[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

THE MECHANISM OF CARBOHYDRATE OXIDATION. XVIII.* THE OXIDATION OF CERTAIN SUGARS WITH SILVER OXIDE IN THE PRESENCE OF POTASSIUM HYDROXIDE

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A clearer understanding of the molecular reaction mechanism involved in the oxidation of various carbohydrates may be obtained through an experimental study of the behavior of these important compounds towards reagents that will yield oxidation products differing respectively both in kind and in number. Glucose may be oxidized completely by alkaline potassium permanganate solutions[1] to carbon dioxide, and oxalic and traces of acetic acids, while with silver oxide under the same conditions, carbon dioxide, and oxalic, glycolic, and formic acids are the final reaction products. In the acid medium of copper acetate solutions containing an excess of this salt, glucose may be oxidized to glucosone, carbon dioxide, and formic, oxalic, and glyoxylic acids.[2] A comparative study of the data obtained through the use of reagents[3] of differing oxidation potential on the sugars and their various theoretical degradation and oxidation intermediates seems to offer a fruitful method of attack on this important oxidation problem.

The reagent chosen for the studies reported in this paper was silver oxide, both alone and in the presence of added alkali. Kiliani,[4] Nef,[5] Behrend and Dreyer,[6] Denis[7] and Witzemann[8] are among those who have studied the action of this reagent on various sugars and their intermediate degradation compounds. The use of silver oxide in the study of carbohydrate oxidation offers certain unique advantages. The oxidation products formed are carbon dioxide, and oxalic, formic and glycolic

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* Contribution XVII of this series, *J. Am. Chem. Soc.*, **57**, 200 (1935). This article was submitted in response to the invitation of the editors.

[1] EVANS AND COLLABORATORS, *J. Am. Chem. Soc.*, **47**, 3085, 3098, 3102 (1925).

[2] EVANS, NICOLL, STROUSE AND WARING, *ibid.*, **50**, 2543 (1928).

[3] KARRER AND PFAEHLER, *Helv. Chim. Acta*, **17**, 363, 766 (1935).

[4] KILIANI, *Ber.*, **13**, 2703 (1880); *Ann.*, **205**, 187, 191 (1880).

[5] NEF, *Ann.*, **357**, 287 (1907).

[6] BEHREND AND DREYER, *Ann.*, **416**, 203 (1918).

[7] DENIS, *Am. Chem. J.*, **38**, 578 (1907).

[8] WITZEMAN, Ph.D. dissertation, The Ohio State University, (1912).

acids, all of which can be determined quantitatively. The silver remaining after oxidation may be easily separated from the unchanged silver oxide, and from its weight the oxygen consumed may be calculated. The reaction is comparatively rapid and hence does not necessitate a long time for its completion. The main objective of these experiments was to study the behavior of mannose, fructose, arabinose and compounds related to these carbohydrates towards silver oxide in the presence and absence of alkalies under carefully controlled conditions for the purpose of obtaining accurate quantitative data which might shed more light on the mechanism involved in the oxidation reaction.

EXPERIMENTAL

Reagents.—All the reagents used in these experiments were examined for their purity by the usual well-known laboratory procedures.

Carbohydrates.—The carbohydrates used were of the highest obtainable purity. Their identities were verified by determinations of their specific rotations, and by other means when necessary.

Silver Oxide.—A solution of 400 g. of $AgNO_3$ in 1200 cc. of distilled water was vigorously stirred and a solution of 150 g. of KOH in 800 cc. of water was added at the rate of 100 cc. per minute. The size of the batch was later increased to as much as 2000 g. of $AgNO_3$ but the same concentrations were always maintained. The brown Ag_2O thus precipitated was washed with water by decantation until the wash water was free of Ag^+ and a 100-cc. sample required less than 0.3 cc. of 0.1N HCl to neutralize the alkali present. This usually required about ten washings. The Ag_2O was then dried at 110°C. under vacuum. When dried at this temperature, it was changed from the chocolate-brown color of the freshly precipitated oxide to a dark purplish-brown. If dried at 85°C., the original brown color was retained. After drying, the oxide was passed through a 100-mesh sieve, placed in brown bottles and stored in the dark. It was believed at first that different lots of silver oxide would give slightly different results, but it was later shown that when the above directions were carefully followed, uniform results were always obtained. Ag_2O was analyzed before using for total silver, ammonia-insoluble matter and carbon dioxide. The analysis of three typical batches of the Ag_2O thus prepared and labeled (a), (b), and (c) was as follows: Silver, (a) 92.6%; (b) 92.20%; (c) 92.95%; theoretical 93.1%: CO_2, (a) 0.10%; (b) 0.05%; (c) 0.03%: Ammonia-insoluble, (a) 0.07%; (b) 0.09%; (c) 0.12%.

Apparatus and Analytical Procedures.—Seven grams of silver oxide was added to 100 cc. of 1.0N KOH contained in a 150-cc. carbon dioxide flask, fitted with a stopper carrying a thermometer and a small stopcock. The flask was then placed in the thermostat maintained at 50° and the reagent was allowed to come to temperature, after which one four-hundredth of a mole of the sugar (*e.g.*, 0.45 g. of mannose, glucose, or fructose, or 0.375 g. of arabinose) was added, the stopper was inserted in the flask and the stopcock closed. By closing the stopcock after inserting the stopper, any pressure effect caused by forcing in the latter was prevented. When this was done, it was found unnecessary to wire on the stoppers to prevent them being blown out, and no loss of carbon dioxide was experienced. In the experiments carried out in the absence of added alkali, the only change made in the above procedures was that of using 11 g. of Ag_2O instead of 7, and carbon-dioxide-free water was used in place of the 1.0*N* alkali. The reaction mixtures were then agitated by a mechanical shaker during the various periods of time indicated in Fig. 1.

This technique was attended by a quick rise in temperature with a maximum of 5°, which rapidly subsided to the thermostatic temperature.

Determination of Consumed Oxygen.—After the reaction flasks were removed from the thermostat they were cooled and the reaction mixture was decanted through a previously weighed and dried Gooch crucible. The silver-silver oxide mixture remaining in the flask was washed several times by decantation and the filtrate and washings were made up to a volume of 250 cc. This solution was used for the determination of oxalic, formic, and glycolic acids. To the residue in the flask was added 50 cc. of dilute NH_4OH (1:3) and the flask was shaken vigorously to hasten solution of the Ag_2O. The undissolved silver was allowed to settle and the liquid was decanted through the Gooch crucible. The ammoniacal solution, thus obtained, was immediately added to a beaker containing an excess of HCl to prevent explosions of the kind reported by previous workers.

The silver residue was washed with two more 50-cc. portions of the NH_4OH, the final washing being tested with HCl to make certain that all the silver oxide was removed. The Ag residue was now transferred to the Gooch crucible, washed with water, dried in a vacuum oven at 110°C., and weighed. The oxygen consumed in the oxidation was calculated from the weight of silver thus obtained after correcting for ammonia-insoluble impurities.

Carbon Dioxide.—The determination of carbon dioxide was made on a second sample obtained in exactly the same manner as the sample used for the determination of the acids. The flask was cooled to a temperature below 40°C. as soon as it was removed from the thermostat and was then connected to a carbon dioxide apparatus which was essentially the same as that described by Foulk.[9]

Oxalic Acid.—Oxalic acid was determined by precipitating as calcium oxalate with calcium acetate in the presence of acetic acid and then titrating the calcium oxalate with potassium permanganate in the usual manner. The calcium content was verified by conversion of the oxalate to the sulfate.

Formic Acid.—Two-fifths of the filtrate from the oxidation mixture was placed in a 500-cc. round-bottom flask fitted with a dropping funnel, capillary tube, and Kjeldahl bulb. The latter was connected, with an adapter, to a spiral water condenser, the end of which extended to the bottom of a 500-cc. suction flask. Sufficient 6.0*M* phosphoric acid was added both to neutralize the alkali present in the oxidation mixture and to form the monopotassium salt. The suction flask was then connected to a water pump and the mixture was distilled under vacuum, the round-bottom flask being placed in a water bath kept at 50°C. Two successive 50-cc. portions of water were added and distillation was carried to dryness each time to insure the presence of all the formic acid in the distillate. The distillate was titrated first with standard alkali, using thymol blue as the indicator, and then by the Jones[10, 11] method. Usually, the two determinations gave very nearly the same result, but when the temperature at which the distillation was carried out was allowed to rise above 55°, or when large amounts of glycolic acid were present, the permanganate value was sometimes higher than that given by the alkali titration. This was found to be due to the distillation of small amounts of glycolic acid with the formic acid. Appropriate corrections were made in each case.

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[9] FOULKS "Notes on Quantitative Analysis," McGraw-Hill Book Co., **1928**, p. 220.

[10] JONES, *Am. Chem. J.*, **17**, 539 (1895).

[11] EVANS, EDGAR AND HOFF, *J. Am. Chem. Soc.*, **48**, 2665 (1926).

Glycolic Acid.—The residue remaining after the formic acid distillation was titrated for glycolic acid by the Jones method. Any glycolic acid that had distilled over with the formic acid was calculated and added to that found in the residue. This method leaves much to be desired, since it is essentially a determination by difference, but a search through the literature failed to offer a better procedure. An attempt was made to precipitate glycolic acid with basic lead acetate, but the precipitation was found to be quantitative only within a very narrow range of conditions which could not be duplicated when using the oxidation mixture. That the compound measured by difference was glycolic acid was proved by using larger quantities of the sugar and isolating the pure acid, which was identified by the method of mixed melting points.

THEORETICAL PART

When aqueous solutions of mannose, glucose, fructose, arabinose, erythritol, glyceraldehyde, or glycolaldehyde are oxidized with silver oxide in the presence and absence of 1.0 N KOH at 50°C., the final reaction products in each case are carbon dioxide and oxalic, formic and glycolic acids. The experimental data presented in this paper will be interpreted, as in other papers of this series, from the standpoint of Nef's[12] enediolic conception of the chemical behavior of the carbohydrates. His views were founded on and are an extension of those of Fischer,[13] and Wohl and Neuberg[14] concerning the presence of hexose enediolic forms of the carbohydrates in alkaline solutions. Some of the recent work in this field, and points of view having a bearing on this theory are herewith summarized.

The existence of the enediolic functional group, $-C(OH){=}C(OH)-$, is now an accepted fact, as is evidenced by the following instances. (a) Fenton[15] obtained dihydroxymaleic acid by the oxidation of tartaric acid. (b) More recently its presence has been established in the molecular structure of *l*-ascorbic acid (vitamin C) and related substances. (c) The isolation by Euler and Martius[16] of *Redukton*, $C_3H_4O_3$, from an aqueous alkaline solution of glucose which had been heated to 90° under a stream of nitrogen is a discovery of the first importance in this connection. These investigators regarded *Redukton* (II) as an enediol of tartronic aldehyde (I). It should be noted that *Redukton* may be considered as the enediol of hydroxymethyl glyoxal (III), discovered by Evans and Waring.[17] It was later isolated by Norrish and Griffiths[17a] in the photochemical decomposition of methyl glyoxal. These workers also pointed out that the

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[12] Nef, *Ann.*, **335**, 191 (1904); **357**, 214 (1907); **376**, 1 (1910); **403**, 204 (1913).

[13] Fischer, *Ber.*, **28**, 1145 (1895).

[14] Wohl and Neuberg, *ibid.*, **33**, 3095 (1900).

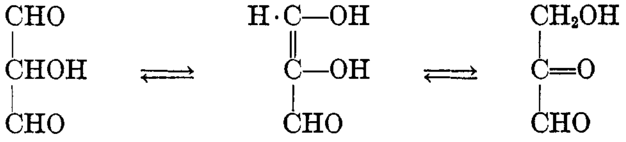
[15] Fenton, *J. Chem. Soc.*, **87**, 804 (1905).

[16] Euler and Martius, *Ann.*, **505**, 73 (1933).

[17] Evans and Waring, *J. Am. Chem. Soc.*, **48**, 2678 (1926).

[17a] Norrish and Griffiths, *J.C.S.*, **1928**, 28–29.

aqueous solutions of hydroxy pyruvic aldehyde must contain its tautomeric form, the tartronic aldehyde enediol. The interrelationship of these three compounds may be shown as follows:



(I) (II) (III)

$$\begin{array}{l} \mathrm{CHO} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CHO} \end{array} \rightleftharpoons \begin{array}{l} \mathrm{H\cdot C{-}OH} \\ \quad \| \\ \quad \mathrm{C{-}OH} \\ \quad | \\ \quad \mathrm{CHO} \end{array} \rightleftharpoons \begin{array}{l} \mathrm{CH_2OH} \\ | \\ \mathrm{C{=}O} \\ | \\ \mathrm{CHO} \end{array}$$

With reference to the chemical character of the hydrogen atoms in the enediolic functional group, Euler and Martius found that *Redukton* possesses the acidity of an organic acid of average strength ($K = 1 \times 10^{-5}$); *i.e.*, it is a little weaker than acetic acid (K 1.8 $\times$ 10^{-5}). Thus it is seen that the enediolic functional group imparts polar properties to the carbohydrate in which it is present.

Winter's[18] "glucic acid," obtained from a solution of invert sugar in lime water, and also isolated by Nelson and Browne[19] from a similar solution of glucose (cerelose), was assigned the molecular formula, $C_3H_4O_3$, by the latter investigators. Like *Redukton* it possessed strong reducing properties, and also absorbed iodine. It was thought by Nelson and Browne to be hydroxyacrylic acid, $CHOH{=}CH{\cdot}COOH$. The properties of "glucic acid" and *Redukton*, compounds possessing the same empirical formula, are strikingly similar.

From their determination of the alkali-fixing capacity of the most important sugars, the conclusion reached by Hirsh and Schlags,[20] would indicate that these compounds are dibasic. The data obtained by Urban and Shaffer[21] appear to indicate that with glucose, fructose and sucrose "a third acidic group begins to function at high alkalinity; but because of large errors in this region the existence of the third group must be regarded as uncertain."

Nef[12] postulated furthermore that the carbohydrate enediols in alkaline solutions would undergo scission at the double bond, thus yielding fragments containing a bivalent carbon atom, a type of compound whose existence was one of the central ideas in his theory of organic chemical behavior. If these fragments were formed in the presence of oxidizing agents, they were oxidized to the corresponding acid, or to compounds having a smaller number of carbon atoms than the fragments themselves. In the

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[18] WINTER, *Z. Ver. Rubenzucker Ind.*, **44** (old series), 1049 (1894).

[19] NELSON AND BROWNE, *J. Am. Chem. Soc.*, **51**, 830 (1929).

[20] HIRSH AND SCHLAGS, *Z. physik. Chem.*, **141**, 387 (1929).

[21] URBAN AND SHAFFER, *J. Biol. Chem.*, **94**, 697 (1931–32).

absence of oxidizing agents, *i.e.* in the presence of alkalies, a scission of the carbohydrates would take place, giving rise to fragments containing a smaller number of carbon atoms than the original carbohydrate. This has been amply evidenced in the literature of this field. Saccharinic acids of the original carbohydrate or of its fragments may form, a reaction which has been experimentally investigated by Kiliani,[22] Nef[12], Shaffer and Friedemann.[23]

The postulate concerning the fragmentation of C=C has met with very definite objections. (a) Such a reaction is not in accord with Schmidt's[24] rule which states that the fragmentation takes place at the C—C in the α-β position to the C=C. It should be pointed out that the data upon which this generalization rests were obtained under much more drastic experimental conditions than have been employed in alkaline solutions of the carbohydrates. The enediolic group is a polar one and is very reactive even at ordinary temperature. (b) The relative values of the well-known bond energies would favor fragmentation at the C—C rather than at C=C.

Hirst[25] and his collaborators have shown that with the usual reaction involving ozonization and subsequent hydrolysis, tetramethylascorbic acid will give 3,4-dimethylthreonic and oxalic acids. Fenton[15] found that dihydroxymaleic dimethyl ester was decomposed in dilute ammonium hydroxide with the formation of oxamide. He suggested that the ester had ruptured at the double bond.

If it is assumed that alkaline solutions of reducing sugars contain enediolic forms, it would seem that the mechanism involving a scission at the double bond in the presence of alkalies and also that taking place in the presence of alkaline oxidizing agents would necessitate one of two points of view; *viz.*, (a) either a scission of the enediolic group followed by oxidation, i. e. Nefs view, or (b) a different mechanism of rupture in the presence of alkalies alone, and still another mechanism for alkaline oxidation in which oxygen plays a part, such as the oxidation of ascorbic acid referred to above. Among the concepts which might offer a simple picture of the mechanism involved in the scission of C=C are those suggested by the electronic theory,[26] and one outlined by Dr. C. L. Bernier of this Laboratory which involves a simple combination of the enediol theory and a reverse aldol condensation.

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[22] *Cf.* TOLLENS, "Handbuch der Kohlenhydrate," 3 Auflage, **1914**, pp. 778–779.

[23] SHAFFER AND FRIEDEMANN, *J. Biol. Chem.*, **86**, 345 (1930).

[24] SCHMIDT, *Chem. Rev.*, **17**, 137 (1935); Ber., **68**, 60, 795 (1935); Cf. Neuberg, ibid, 505.

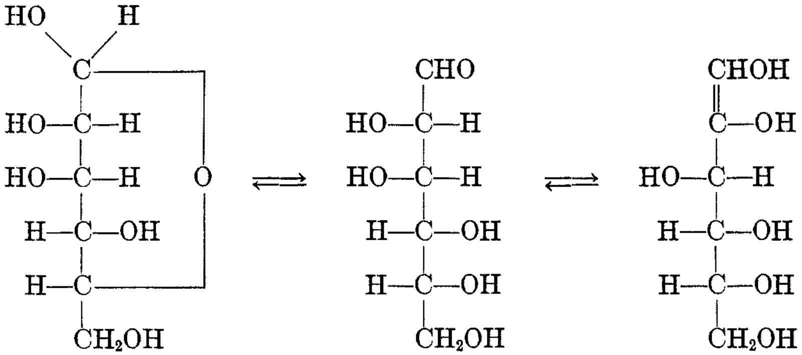
[25] HIRST AND COLLABORATORS, *J. Soc. Chem. Ind.*, **52**, 221, 1270 (1933).

[26] *Cf.* STIEGLITZ, *Proc. Inst. Medicine of Chicago*, **1**, 41 (1916); *Chem. Abstr.*, **17**, 3878 (1923).

The following discussion is concerned primarily with the sources of the four reaction products found in these studies, and the extent of fragmentation which occurs in mannose and fructose under the experimental conditions used.

Mannose and Arabinose.—When an aldohexose like mannose is acted upon by an alkali it may undergo the kind of change indicated in the following reaction:

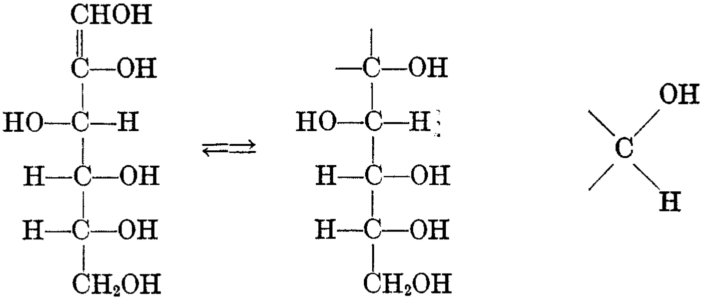
(1)



(*d*-mannose) (aldo-*d*-mannose) (*d*-mannose, 1,2-enediol)

A fragmentation of the mannose 1, 2-enediol between carbon atoms 1 and 2 would yield one molecule of arabinose and one of formaldehyde, *i.e.*,

(2)



(*d*-mannose, 1,2-enediol) (*d*-arabinose,)[27] active form (formaldehyde,)[27] active form

The formaldehyde molecule thus formed would be oxidized to formic acid. It is clear that the arabinose molecule in alkaline solution may in turn undergo the same kind of fragmentation as does mannose, until finally five molecules of formic acid would be formed from the original pentose, provided, however, that it reacts in only one direction. As set forth in Fig. 1, the results of our experiments show that hexoses, such as glucose

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[27] Baly, *Rice Inst. Pamphlet*, **12**, 93 (1925).

and galactose, are oxidized by silver oxide in the absence of potassium hydroxide to carbon dioxide, and oxalic, glycolic and formic acids, and that the ultimate fate of the oxidation products formed is conversion to carbon dioxide. In the presence of added alkali, the salts thus formed tend to become stable towards silver oxide, a fact which confirms Witzemann's observations in this respect with reference to potassium formate, a substance which he found to undergo oxidation slowly when heated.

Our experimental data show that *d*-glucose in the presence of silver oxide and potassium hydroxide reached a maximum production of formic acid at the end of one hour (*i.e.*, 1.5 moles per mole of sugar), mannose 2.74 moles in 24 hours, galactose 2.42 moles in 12 hours and fructose 3.1 moles in 24 hours. The significance of these data lies in the fact that in order to produce yields of formic acid in excess of 1 mole as demanded by equation (2), either the original hexose must undergo a fragmentation between carbon atoms 2 and 3 to give glycolaldehyde and erythrose, between carbon atoms 3 and 4 to give two molecules of glyceraldehyde, or the pentose formed in the fragmentation between carbon atoms 1 and 2 must suffer a further degradation in the manner just outlined for a hexose.

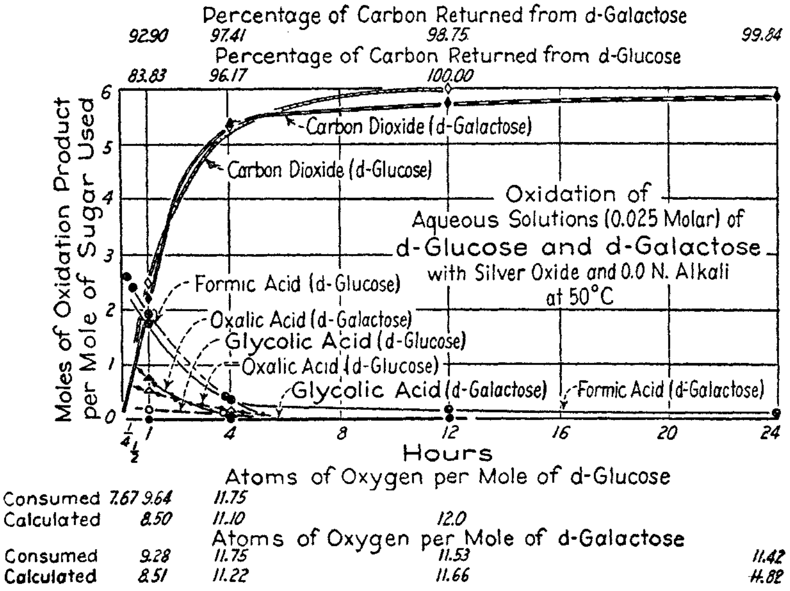

FIG. 1

That the first step in the fragmentation of the *d*-mannose molecule under our experimental conditions would seem to be the formation of arabinose and formaldehyde [equation (2)] follows from an examination of the data obtained at the end of four hours, at which time the total carbon returned in each case is 99.45 per cent for arabinose and 99.33 per cent for mannose.

If the mannose molecule, on fragmentation, yields one molecule of formaldehyde and one of arabinose per mole equivalent of sugar used, then it is clear that the yields of formic acid from these two carbohydrates should differ by 1.0 mole, and the yields of carbon dioxide, and glycolic and oxalic acids should be the same from both sugars. The data in Table I show that these assumptions are approximately true in this case. Hence, it may be safely concluded that *d*-mannose (0.025 molar solution) is de-

TABLE I

DATA EXPRESSED AS MOLES PER GRAM-MOLE EQUIVALENT OF CARBOHYDRATE USED

OXIDATION PRODUCTS	MANNOSE	ARABINOSE	DIFFERENCES
Oxalic Acid	0.98	0.89	+0.09
Formic Acid	2.69	1.64	+1.05
Glycolic Acid	0.56	0.71	−0.15
Carbon Dioxide	0.19	0.13	+0.06
Atoms Oxygen Consumed	6.69	5.46	+1.20

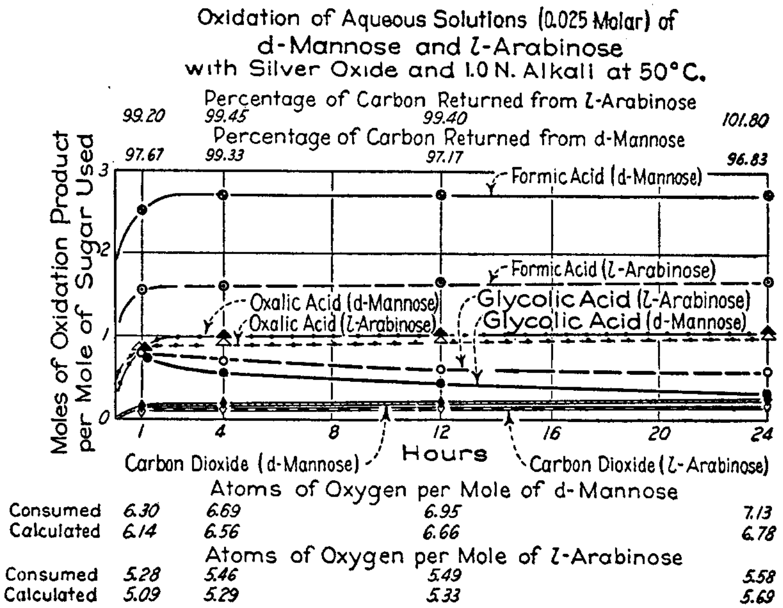

FIG. 2

graded approximately into formaldehyde and arabinose as the first step in its oxidation with silver oxide in the presence of 1.0 *N* alkali at 50°C. P. Fleury and J. Lange[28] obtained one mole of formaldehyde by the oxidation of glucose with periodic acid, which Karrer and Pfaehler, (*loc. cit.*) ascribe to a rupture of glucopyranoside between carbon atoms 5 and 6. The complete data over a period of 24 hours are shown in Fig. 2.

The fate of the arabinose molecule from mannose can be fairly well understood by a comparative study of its oxidation data obtained after 24 hours with those from erythritol, a compound which we had to use instead of the rare sugar erythrose, at this writing known only as a sirup. These are shown in the following table.

TABLE II

DATA EXPRESSED AS MOLES PER GRAM-MOLE EQUIVALENT USED

OXIDATION PRODUCTS	ARABINOSE	ERYTHRITOL	DIFFERENCES
Carbon Dioxide	0.180	0.124	+0.064
Oxalic Acid	1.010	0.594	+0.416
Formic Acid	1.690	1.045	+0.645
Glycolic Acid	0.60	0.803	−0.203

TABLE III

DATA EXPRESSED AS MOLES PER MOLES OF SUBSTANCES USED

OXIDATION PRODUCTS	ONE MOLE ERYTHRITOL	TWO MOLES GLYCOLALDEHYDE	DIFFERENCES
Carbon Dioxide	0.124	0.092	+0.032
Oxalic Acid	0.594	0.648	−0.054
Formic Acid	1.045	1.174	−0.035
Glycolic Acid	0.803	0.720	+0.08

From the differences in the yields of formic and oxalic acids it is clear that the arabinose is not being fragmented into formaldehyde and erythrose, a condition which would cause a difference in the yields of formic acid of one mole per mole of arabinose used. Previous work has shown that a tetrose sugar tends to give two molecules of glycolaldehyde instead of one each of glyceraldehyde and formaldehyde. If this is so, it is conceivable that the erythrose formed from a fragmentation of arabinose might yield oxidation data approximately the same as that for two molecules of glycol aldehyde. Since we do not know the concentration of the erythrose in this reaction, the data used can be assumed to show merely

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[28] FLEURY AND LANGE, *J. pharm. chim.*, [8] **17**, 1 (1933); *Chem. Abstr.*

the *tendency* of the reaction. Such data are given for erythritol and glycolaldehyde after twenty-four hours in Table III. The data for glycolaldehyde are two-thirds of those obtained from a three molar solution, and are used only as an approximation.

Glucose.—Under our experimental conditions glucose and arabinose do not show the same simple relationship with reference to formic acid yields which seems to exist between mannose and arabinose, as is evidenced by the fact that at the end of one hour glucose yielded 1.5 moles of formic acid, and arabinose 1.55 moles per mole equivalent of carbohydrate used. Fig. 3 is a graphic comparison of the data obtained from glucose with those which would have been obtained had this hexose molecule undergone cleavage into two molecules of glyceraldehyde. It is evident from these experimental results that glucose reacts in more than one direction.

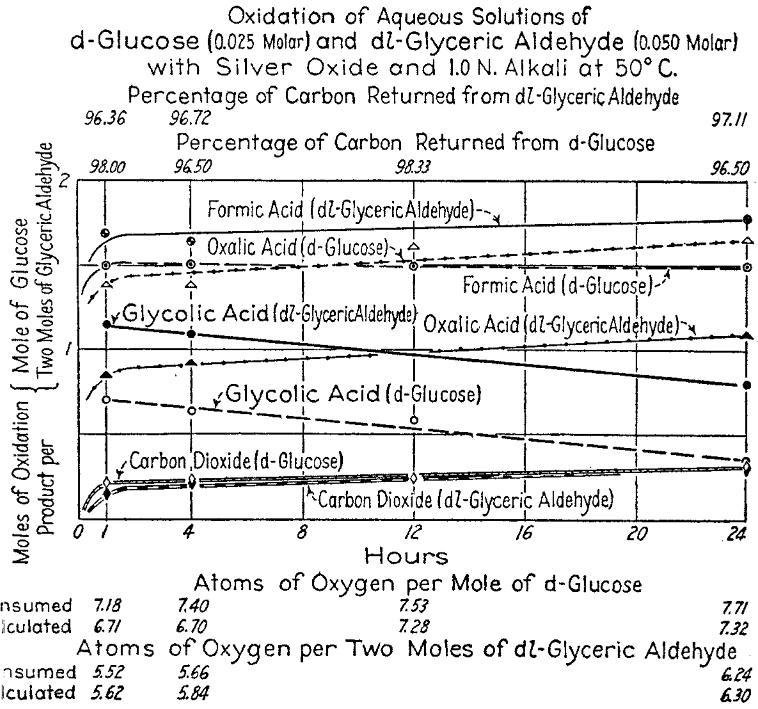
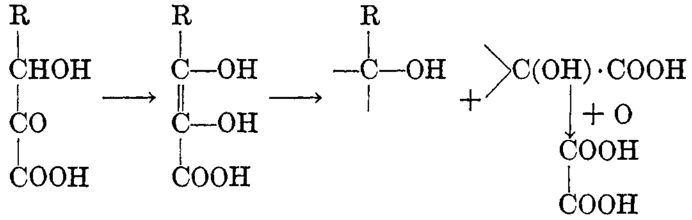


Fig. 3

The formation of oxalic acid from glucose, mannose, galactose, arabinose, fructose, glyceraldehyde and similar compounds may arise from the formation of an α-keto-acid of the hexose as well as of the other theoretically possible keto-acids of fewer carbon atoms. The keto-acid may enolize and then undergo a fragmentation, thus yielding glyoxylic acid, which in turn is oxidized to oxalic acid, in accordance with the following reaction.

(3)



Fructose: Glycolic Acid.—The most plausible source of glycolic acid is glycolaldehyde. From our studies we are led to believe that the primary alcohol group in the sugars studied is only slowly attacked under our conditions and it appears in the oxidation products chiefly as glycolic acid. On the other hand the secondary alcohol groups are rapidly oxidized. Our experiments show that ethylene glycol is stable towards silver oxide and alkalies while glycerol is most readily attacked. Table IV shows the number of moles of glycolic acid formed per mole of compound oxidized after the reaction has proceeded for one hour at 50°. Since the glycolic acid obtained from the aldo-sugars tends to approach, but never exceed, one mole per mole of compound used, and that from fructose and erythritol does exceed one mole, the glycolic acid can be easily accounted for on the basis of glycolaldehyde formation arising in each case from the primary alcohol group and its neighboring carbon atom, formed by the fragmentation of the sugar at that point. The formation of 2,3- and 3,4-enediols would furnish additional primary alcohol groups in the aldo-sugars and hence should furnish more than one mole of glycolic acid per mole of sugar used. From the data tabulated it is seen that this does not take place under our experimental conditions. Dr. Charles L. Bernier of this laboratory has shown that *d*-glucose in aqueous potassium hydroxide solutions at 50° will yield 51.19% of lactic acid, the forerunner of which must be glyceraldehyde.[29]

TABLE IV

MOLES OF GLYCOLIC ACID FORMED PER MOLE OF COMPOUND OXIDIZED

d-Glucose	0.70	*d*-Mannose	0.75	*d*-Galactose	0.76
d-Fructose	1.09	*d*-Arabinose	0.81	*d*-Xylose	0.45
Erythritol	1.18	*dl*-Glyceraldehyde	0.57	Glycolaldehyde	0.52

In view of the data obtained with fructose and erythritol, and more especially the probable facts with reference to glycolic acid formation given

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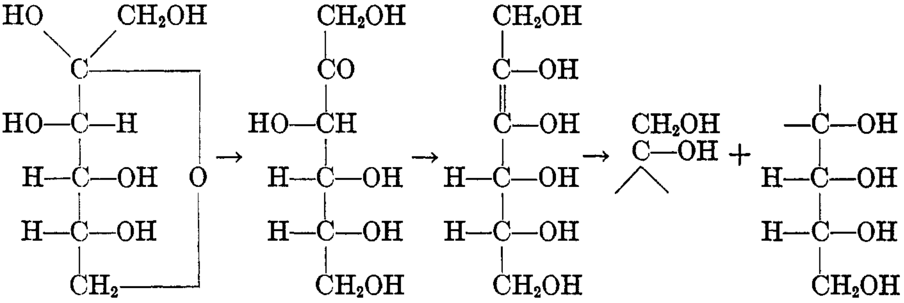
[29] WEISENHEIMER, Ber., **41**, 1009 (1908).

above, it may be assumed that it is the keto-hexose which will undergo a fragmentation to give erythrose and glycolaldehyde according to the following equation:



(*d*-fructose) (*d*-keto-fructose) (*d*-fructose 2,3-enediol) (glycolaldehyde, active form) (erythrose, active form)

That this fragmentation of the fructose molecule probably does take place under these experimental conditions seems to be borne out by the data obtained from erythritol and that obtained by using one-third of the values from glycolaldehyde oxidation as an approximation to the data which we would have obtained had we had sufficient glycolaldehyde for all our experimental purposes. If the keto-hexose undergoes fragmentation in this manner the sum of the products obtained from the tetra-hydric alcohol and the glycolaldehyde should be approximately equal in value to those

TABLE V

Oxidation Products in Moles per Mole of Substance Oxidized

OXIDATION PRODUCTS	ERYTHRITOL	GLYCOL-ALDEHYDE	SUM	FRUCTOSE	DIFFERENCE
Carbon Dioxide	0.124	0.046	0.170	0.18	−0.010
Oxalic Acid	0.594	0.324	0.918	0.85	+0.068
Formic Acid	1.045	0.590	1.635	1.77	−0.135
Glycolic Acid	0.803	0.36	1.163	1.17	−0.007

TABLE VI

Oxygen Consumption—Moles per Mole of Substance Oxidized

	ERYTHRITOL	GLYCOL-ALDEHYDE	SUM	CORRECTED FOR ERYTHROSE	FRUCTOSE
Oxygen, Used	5.07	2.05	7.12	6.12	6.10
Oxygen, Calc'd	4.88	2.01	6.89	5.89	5.86

obtained with fructose. That this is approximately so under the experimental conditions used is seen from Table V. The tetrose formed in this reaction is believed to fragment into two more molecules of glycolaldehyde.

TABLE VII

COMPARISON OF OXIDATION DATA FOR FRUCTOSE (ONE MOLE) AND GLYCOLALDEHYDE (THREE MOLES)

OXIDATION PRODUCTS	GLYCOLALDEHYDE (THREE MOLES)	FRUCTOSE (ONE MOLE)	DIFFERENCE
Carbon Dioxide	0.14	0.18	−0.04
Oxalic Acid	0.97	0.85	+0.12
Formic Acid	1.77	1.77	0.00
Glycolic Acid	1.08	1.17	−0.09
Oxygen Consumed	6.15	6.10	+0.05

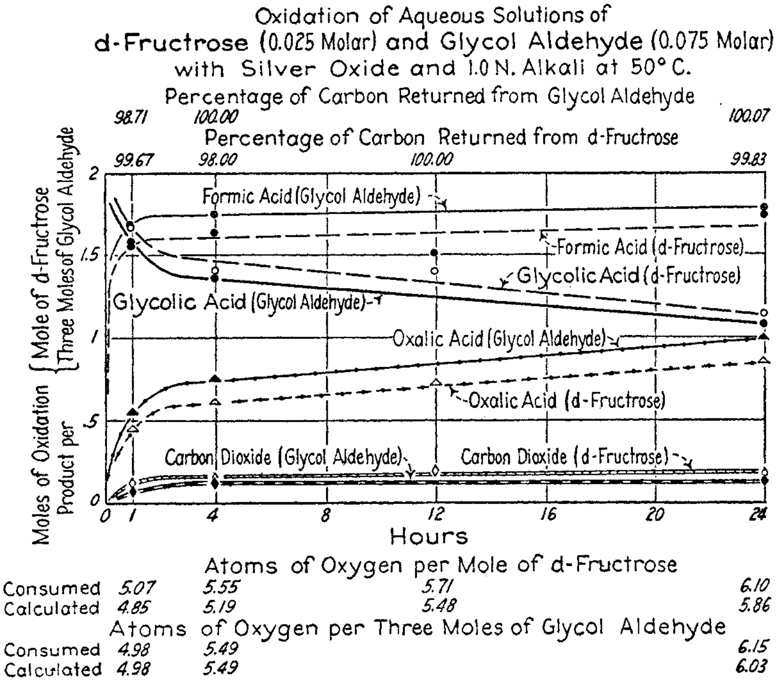


FIG. 4

(See Table IV.) The oxygen relations at this point (Table VI) are of equal interest in this connection.

When the data obtained with fructose at the end of 24 hours are compared with those obtained from a three mole equivalent of glycolaldehyde under the same conditions, the differences are sufficiently small to justify the belief that fructose is oxidized to its final products indicated in Table VII, by way of an erythrose + glycolaldehyde stage, the erythrose thus formed then yielding two more molecules of glycolaldehyde—the total oxidation being, in effect, equivalent to oxidation of three molecules of glycolaldehyde. The complete experimental data for these oxidations are graphically shown in Fig. 4.

Carbon Dioxide.—An examination of the graphical data will show that the yields of carbon dioxide were uniformly low throughout this series of experiments, much to our surprise. Among the possible sources of carbon dioxide are potassium formate, glycolaldehyde, and any possible keto-acids formed as oxidation products in the course of the reaction.

In a separate experiment with glycolic acid (0.57 g.) only 0.29% of the carbon was converted to carbon dioxide. At the end of twenty-four hours, a three molar solution of glycolaldehyde (0.75 molar) gave 2.3% of its carbon as carbon dioxide. Since we had no available keto-acid we oxidized galactonic lactone because, as has been shown, the secondary alcohol group is readily attacked with silver oxide in the presence of potassium hydroxide. Its data are compared at this point with those of galactose at the end of 24 hours, the results in each case being in moles per mole of compound used (Table VIII). It would seem that the chief sources of the carbon dioxide in these experiments are the possible keto-acids formed as intermediate oxidation products, and the slow oxidation of glycolic and formic acids.

TABLE VIII
OXIDATION PRODUCTS OF GALACTOSE AND GALACTONIC LACTONE

	CARBON DIOXIDE	OXALIC ACID	FORMIC ACID	GLYCOLIC ACID
Galactose	0.35	1.44	2.15	0.32
Galactonic Lactone	0.34	1.66	1.79	0.23

SUMMARY

1. Glucose, mannose, galactose, and fructose have been oxidized in .025 molar solutions with silver oxide in the presence of 1.0 *N* potassium hydroxide. The ultimate products in each case were carbon dioxide and oxalic, formic and glycolic acids.

2. Through a similar study of a number of the available theoretically possible intermediate degradation compounds light has been shed upon the oxidation mechanisms of the above hexoses. The following intermediates have been studied in this connection: arabinose, erythritol (for

erythrose), glyceraldehyde, glycolaldehyde, galactonic lactone (for a keto-acid). In all these cases the ultimate products were the same as those obtained with the hexoses.

3. The first stage in the oxidation mechanism of mannose seems to be the fragmentation of this hexose into one molecule each of formaldehyde and arabinose, since its oxidation data differ from those of the pentose by approximately one mole of formic acid.

4. The first stage in the oxidation mechanism of fructose seems to be the fragmentation of this hexose into either one molecule each of glycolaldehyde and erythrose, or into three molecules of glycolaldehyde, since the quantitative data obtained from the fragments in the two cases are practically the same as that obtained from the keto-hexose.

5. The behavior of glucose is best understood on the assumption that it undergoes oxidation in more than one direction.

6. The formaldehyde obtained in the fragmentation of these sugars and related compounds is the source of the oxidation product formic acid. We have indicated that oxalic acid and the chief portion of the carbon dioxide is derived from the fragmentation and subsequent oxidation of keto-acids. Evidence is given for the general stability of the primary alcohol group towards the oxidation medium; hence the presence of this group as glycolic acid in the final reaction products.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

CONTRIBUTIONS FROM THE STUDY OF DIPOLE MOMENTS TO THE PROBLEMS OF ORGANIC CHEMISTRY*

CHARLES P. SMYTH

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During the past ten years the idea of a permanent dipole moment in a molecule has developed from a tentative hypothesis advanced to explain the behavior of dielectric constants to an important tool for the investigation of molecular structure. A dipole consists of two equal electric charges, very close together and opposite in sign. Its magnitude is measured by its moment, which is the product of either charge, e, by the distance between the two charges, r. As the moment acts in the direction of the line joining the two charges, that is, the axis of the dipole, the product, $\mu = er$, is a vector quantity. The moment μ of a molecule can be determined experimentally by measurements of the dielectric constant and density of the substance composed of the molecules in question, and application of the equation of Debye,[1]

$$\frac{\epsilon - 1}{\epsilon + 2} \cdot \frac{M}{d} = a + b/T,$$

in which ϵ is the dielectric constant of the substance, M, the molecular weight, d, the density, T, the absolute temperature, and a and b, constants characteristic of the substance. The quantity on the left of the equation, which is called the molar polarization, P, is evidently a linear function of the reciprocal of the absolute temperature. If P is plotted against $1/T$ or the product PT against T, the values of a and b are obtained as the slopes or intercepts of the resultant lines. As $b = 4\pi N\mu^2/9k$, where N is the Avogadro number, 6.061×10^{23}, and k is the molecular gas constant, 1.372×10^{-16}, the moment is calculated directly from b. The constant, a, which is the induced polarization, is, normally, so little larger than the molar refraction of the substance that the substitution of the latter for a makes possible the calculation of a fairly accurate value of b and, hence, of the moment. Since, in general, the Debye equation applies to polar molecules only in a gas or in very dilute solution in a non-polar solvent, most measurements are carried out in solution, the results extrapolated

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* This review was submitted in response to the invitation of the Editors.

[1] P. DEBYE, *Physik. Z.*, **13**, 97 (1912).

to infinite dilution, and the moment calculated from the extrapolated polarization by subtraction of the molar refraction.[2] The small difference between *a* and the molar refraction introduces, usually, a very small, and often, a negligible error in the moment value. The solvent may alter the moment by as much as 10 or 15%,[3] and even more in the case of some molecules containing two or more movable dipoles,[4] but the differences in the effects of different non-polar solvents upon most moments are, as a rule, little, if any, more than the experimental errors. The values obtained in solution are, therefore, adequate for most purposes, but may be unsatisfactory for the consideration of small effects except for similar molecules in the same or in similar solvents. The number of substances measurable over a sufficiently long temperature range in the gaseous condition is necessarily limited, and the measurements are much more difficult, but a considerable number of precise determinations have yielded values of an absolute accuracy better than 1%.

A rough picture of the existence of a dipole in a molecule may be obtained by regarding the hydrogen chloride molecule as made up electrically of the positive charge of a proton and the negative charge of a chloride ion. If the center of gravity of the electrons lies in the chlorine nucleus, we have effectively a single electronic charge at this point and the equal and opposite charge, 4.774×10^{-10} e.s.u. of the proton separated from it by a distance obtained from infra-red spectra[5] as 1.27×10^{-8} cm. The dipole thus formed by the molecule should have a moment $4.774 \times 10^{-10} \times 1.27 \times 10^{-8} = 6.06 \times 10^{-18}$, while the accurate value determined from dielectric constant measurements on the gas[6] is 1.03×10^{-18}. The writer calculated that the large discrepancy could be approximately accounted for by the attraction of the outer electrons of the chlorine toward the proton[7] and a recent quantum mechanical calculation by Kirkwood[8] gave a more accurate value for this shift of charge and a resultant moment of 1.09×10^{-18}. With increasing size of the halogen atom, the polarizability, which is the moment induced in a molecule by an electric field of unit intensity and is thus the measure of the ease of displacement of the charges, increases to such an extent that the dipole moment falls off to 0.78×10^{-18} for hydrogen bromide and 0.38×10^{-18} for hydrogen iodide in spite of the increasing nuclear separation.

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[2] *Cf.* C. P. Smyth, "Dielectric Constant and Molecular Structure," The Chemical Catalog Co., Inc., New York, **1931**, Chap. I.

[3] H. Müller, *Physik. Z.*, **34**, 689 (1933).

[4] A. E. Stearn and C. P. Smyth, *J. Am. Chem. Soc.*, **56**, 1667 (1934).

[5] M. Czerny, *Z. Physik*, **45**, 476 (1927).

[6] C. T. Zahn, *Phys. Rev.*, **24**, 400 (1924).

[7] C. P. Smyth, *Phil. Mag.*, **47**, 530 (1924).

[8] J. G. Kirkwood, *Physik. Z.*, **33**, 259 (1932).

When the halogen is attached to a carbon atom instead of to hydrogen, a larger moment acts in the direction of the bond. The benzene molecule has no moment,[9] but the chlorobenzene molecule has a moment[10] 1.52×10^{-18} in the direction of the C—Cl bond. When additional chlorines are attached to the ring, new dipoles are formed, the moment of the molecule as a whole being the resultant of the moments of these individual dipoles. Thus, on the basis of the Kekulé model of benzene, the moment of *p*-dichlorobenzene should be zero since the two C—Cl dipoles point in opposite directions, the moment of the *meta* compound should be $2 \times 1.52 \times 10^{-18} \cos 60°$ if the C—Cl dipole is the same as in monochlorobenzene, and the moment of the *ortho* compound should be $2 \times 1.52 \times 10^{-18} \cos 30°$. Table I gives the values calculated in this way for the dichloro- and dinitrobenzenes for comparison with the observed. The agreement is satisfactory for the *para* and *meta* compounds, but the observed *ortho* moments are lower than the calculated, a discrepancy which, according to the calculations of Smallwood and Herzfeld,[11] can be accounted for by the lowering of each of the two moments by the shifts of charge induced by the other. In the *meta* compounds the lowering is much smaller because of the greater separation of the dipoles, while, in the para, the very small lowerings would cancel each other because of the symmetry of the molecule. These results are given as typical of the behavior of all the poly-substituted benzenes in which the moments of the substituents lie in the lines joining them to the ring and are explicable only in terms of a plane hexagonal ring for the structure of benzene, with the external carbon valences in the same plane. This plane regular hexagon may, of course, be instantaneously distorted by oscillation of the carbon atoms or permanently distorted to, at least, a small extent by the mutual repulsion of groups *ortho* to each other.

The moments may be used similarly in the examination of the structure of naphthalene. If the molecule consists of two plane hexagons sharing an edge, two equal dipoles in the 1 and 4 positions should cancel each other and give zero moment, while, in the 1 and 8 positions, they should point in the same direction and give a moment twice that of α-nitronaphthalene. That this is the case is shown by the excellent agreement of the moments calculated on this basis in Table I with those determined by Höjendahl.[12] If the two hexagons did not lie in the same plane, dipoles in the 2 and 6 positions would have component moments which would not cancel. However, Weissberger and Sängewald[13] have found a moment for 2,6-dichloro-

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[9] K. B. McAlpine and C. P. Smyth, *J. Am. Chem. Soc.*, **55**, 453 (1933).

[10] C. P. Smyth and S. O. Morgan, *ibid.*, **50**, 1547 (1928).

[11] H. M. Smallwood and K. F. Herzfeld, *ibid.*, **52**, 1919 (1930).

[12] K. Höjendahl, Thesis, Copenhagen, 1928; *Physik. Z.*, **30**, 391 (1929).

[13] A. Weissberger and R. Sängewald, *Z. physik. Chem.*, **B20**, 145 (1933).

naphthalene indistinguishable from zero. The dipole moments thus give confirmatory evidence of the simple conventional structures assigned by the organic chemist to the benzene and naphthalene molecules.

In diphenyl the two benzene rings are joined by a single C—C bond, the extension of which should lie in the plane of each of the two rings if there is no bending of the bond. The zero moments[14] found by Bretscher for the 4,4′-disubstituted compounds in Table I show that the molecule has this extended structure with the two dipoles pointing in opposite directions in the same line and cancelling one another's moments. In the 2,2′- and 3,3′-disubstituted compounds, it is evident that, if the two rings are coplanar and the two dipoles on opposite sides of the molecule in a sort of *trans* position, the resultant moment is zero, but, if the two dipoles are on the same side, they should give to the molecule a moment, 2 *m* sin 60°, where *m* is the moment of one dipole. If there is freedom of rotation around the single bond between the two rings, one dipole might occupy any position relative to the other which would result from rotation through any angle whatsoever around the bond. If all of these positions are equally probable, the resultant moment observed should be $\sqrt{2}m$ sin 60°.[15] The calculated moments in Table I are obtained by setting *m* in this formula equal to the moment of the mono-substituted benzene, 1.52 × 10^{-18} for chloro- and 3.9 × 10^{-18} for nitrobenzene. The agreement with the values obtained by Bretscher[14] and by Weissberger and Sängewald[13] is rather better than could be expected in view of the fact that the latter investigators found 1.53 × 10^{-18} for *p*-chlorodiphenyl, 1.79 for the *meta* compound and 1.30 for the *ortho*. The results indicate that there is considerable freedom of rotation around the bond between the rings, although it cannot be concluded that all positions are equally probable, and the effect of resonance is uncertain.

TABLE I

MOMENTS (× 10^{18}) OF DISUBSTITUTED BENZENES, NAPHTHALENES AND DIPHENYLS

	OBS.	CALC'D		OBS.	CALC'D
o-$C_6H_4Cl_2$	2.25	2.63	1,8-$C_{10}H_6(NO_2)_2$	7.1	7.2
m-$C_6H_4Cl_2$	1.48	1.52	2,6-$C_{10}H_6Cl_2$	0	0
p-$C_6H_4Cl_2$	0	0	2,2′-$C_{12}H_8Cl_2$	1.73	1.86
o-$C_6H_4(NO_2)_2$	6.03	6.76	3,3′-$C_{12}H_8Cl_2$	1.70	1.86
m-$C_6H_4(NO_2)_2$	3.76	3.9	4,4′-$C_{12}H_8Cl_2$	0	0
p-$C_6H_4(NO_2)_2$	0	0	2,2′-$C_{12}H_8(NO_2)_2$	5.1	4.8
1,5-$C_{10}H_6(NO_2)_2$	0	0	4,4′-$C_{12}H_8(NO_2)_2$	0	0

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[14] E. BRETSCHER, *Helv. Phys. Acta*, **1**, 355 (1928); *ibid.*, **2**, 257 (1929).

[15] *Cf.* J. W. WILLIAMS, *Z. physik. Chem.*, **A138**, 75 (1928).

When, instead of being free to rotate or oscillate around a single bond as in the diphenyls, the two halves of a molecule containing dipoles are fixed relative to one another, the two possible extremes suggested in the case of the diphenyls exist. Errera[16] found 1.85 × 10^{-18} for *cis*-acetylene dichloride, where the two C—Cl dipoles have large components of their moments in the same direction, and 0 for the *trans*-compound in which the two dipoles point in opposite directions, similar relations existing for the other acetylene dihalides. The rigidity of the double bond and the organic chemist's representation of compounds of this type by a plane model are thus supported by the dipole moment results.

These relations are hardly apparent in the case of diethyl maleate and diethyl fumarate,[17] the *cis*-compound having a moment, 2.55, and the *trans* a moment, 2.39 × 10^{-18}. There is a similar lack of difference between the moments of the esters of the *ortho*, *meta*, and *para* acids formed by attaching two carboxyl groups to the benzene ring. Each —$COOC_2H_5$ group contains a large moment in the direction of the C═O and smaller moments in the two C—O bonds. As possible rotation about the first C—O bond in the group would give a variable resultant moment to the group and as rotation of the whole group around its bond to the rest of the molecule would further vary the direction of this resultant moment, the reason for the small effect of the direction of the two group bonds upon the moment of the molecule as a whole becomes apparent.

When two dipoles which can turn relatively to one another are close together, their mutual potential energy makes positions of low resultant moment more probable. This is well illustrated by the moments of the polymethylene bromides, the theoretical values of which are given by the equation,[18] $\mu = m\sqrt{2 - 2(-\cos 110°)^n}$, in which m is the moment due to the movable C—Br dipole and n is the number of carbon atoms in the molecule, freedom of rotation being assumed around all the bonds. With $m = 1.5$, the moment of the ethylene bromide molecule is calculated to be 1.99 as compared to an observed value which increases from 0.8 to 1.05 as the temperature rises from −30° to 70°. The theory of this change of moment with temperature has been developed in detail for ethylene chloride[19] and may be applied equally well to the bromide. The mutual repulsion of the two bromines tends to force them into a *trans* position,

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[16] J. Errera, *Physik. Z.*, **27**, 764 (1926).

[17] C. P. Smyth and W. S. Walls, *J. Am. Chem. Soc.*, **53**, 527 (1931).

[18] C. P. Smyth and W. S. Walls, *ibid.*, **54**, 2261 (1932).

[19] L. Meyer, *Z. physik. Chem.*, **B8**, 27 (1930); C. P. Smyth, R. W. Dornte and E. Bright Wilson, Jr., *J. Am. Chem. Soc.*, **53**, 4242 (1931); L. M. Sturtevant, *ibid.*, **55**, 4478 (1933).

J. E. Lennard-Jones and H. H. M. Pike, *Trans. Faraday Soc.*, **30**, 830 (1934).

W. Altar, *J. Chem. Phys.*, **3**, 460 (1935).

in which the moment of the molecule as a whole would be zero, but the thermal energy of the molecule causes a rotational oscillation about this position of minimum potential energy so that the average location of the dipoles is somewhat out of the *trans* position. Consequently, a moment is observed which increases as the increasing oscillation accompanying rising temperature causes greater departure from the *trans* position. The substance cannot be brought to a sufficiently high temperature to approach the calculated value of the moment. Because of inductive effects, a value 1.7 is assigned to m in trimethylene bromide and 1.9 in the longer chain compounds. The greater separation of the two dipoles in trimethylene bromide so reduces the mutual potential energy that the observed moment rises to 1.98, as compared to a calculated value, 2.36. For decamethylene bromide, the observed value 2.56 differs from the calculated value 2.69 by no more than the probable error introduced by uncertainty in the value assigned to m. If the chain is extended even in the long molecules, a small difference of potential energy may exist between a sort of *cis* position, in which the two dipoles point outward from the same side of the molecule giving a large resultant moment, and an approximate *trans* position, in which the two dipoles largely cancel one another to give a small or zero moment. If the energy difference is appreciable in comparison with the thermal energy kT, the *trans* position is more probable than the *cis*, and the moment of the molecule is less than the calculated. It was calculated[18] that, with an extended carbon chain, the energy difference between the two positions in pentamethylene bromide was about 1/4 kT, a not inappreciable quantity. In accordance with this, the observed value, 2.28, was 0.4 below the calculated. In hexamethylene bromide[20], the energy difference is about 1/7 kT and the observed moment 2.40, still a little low. In nonamethylene bromide the energy difference drops to the negligible value 1/23 kT and the moment rises to 2.56, indistinguishable from that of decamethylene bromide, in which the energy difference is only about 1/32 kT. Although these moments do not decide definitely between an extended carbon chain and one in which free rotation around the C—C bonds gives a great variety of forms to the chain, the results are best explained by the supposition of an extended zig-zag chain which is not infrequently bent by rotation around one or more links in the chain. Many more molecules containing two or more movable dipoles have been studied and equations set up for the calculation of their moments. Among these may be mentioned the chloro-[18,21] and bromohydrins,[18] halogenated ethers,[18] glycols,[18] dicarboxylic acid esters,[17] and chloracetyl chloride.[22]

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[20] C. P. Smyth and W. S. Walls, *J. Chem. Phys.*, **1**, 200 (1933).

[21] C. T. Zahn, *Physik. Z.*, **33**, 529 (1932).

[22] C. T. Zahn, *Phys. Rev.*, **40**, 291 (1932); *Trans. Faraday Soc.*, **30**, 804 (1934).

In order to examine the effects of dipoles upon one another's moments, it is profitable to consider molecules in which they are fixed in close proximity to one another. The fluorine and chlorine substituted methanes[23] in Table II, which have been measured in the vapor state, illustrate this type of molecule. A detailed consideration of the calculation of these inductive effects and of the observed moments is given in the paper just referred to.[23] An exact quantitative consideration of the inductive effect of a dipole upon the rest of the molecule containing it is, at present, impossible. The unsymmetrical distribution of positive and negative electricity which, when regarded at some distance, may be treated as a dipole does not have the field of a dipole when approached too closely. At small distances the precise location of the dipole becomes an important question and one which cannot be settled exactly. Moreover, the averaging of the polarizability of one part of a molecule or electron group over all directions and its assignment to one point in the molecule is a rough approximation. We may, however, calculate the inductive effect on the basis of reasonable assumptions and see whether the calculated effects are comparable in size with the observed differences in moment which may be attributable to induction.

TABLE II

Moments ($\times 10^{18}$) of Substituted Methanes

CH_3Cl	1.86	CH_3F	1.81	CCl_4	0
CH_2Cl_2	1.57	$CHFCl_2$	1.29	CF_2Cl_2	0.51
$CHCl_3$	1.05	CHF_2Cl	1.40	$CFCl_3$	0.45

Consideration of the locations of the centers of gravity of the charges assignable to the carbon-halogen portion of the molecule in the halogenated compounds indicates the most probable location of the principal dipole to be approximately 7/8 of the distance from the carbon nucleus to the halogen nucleus.[19] A moment m thus located in a methyl chloride molecule would induce a moment in each of the three C—H bonds, which, to a very rough approximation, may be calculated in terms of m by use of the equations employed by Smallwood and Herzfeld,[11] the arbitrary assumption being made that the polarizability of the C—H bond acts at its mid-point. If the presumably small intrinsic moment of the C—H bond is neglected, the observed moment, 1.86×10^{-18}, may be regarded as the sum of m and the components of the three induced C—H moments along the extension of the Cl—C line. Thus m is calculated as 1.15×10^{-18} and the sum of the components of the three induced C—H moments in the same direction as 0.7×10^{-18}. The moment, 0.26×10^{-18}, induced in each C—H bond, does not lie in the C—H direction and is not,

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[23] C. P. Smyth and K. B. McAlpine, *J. Chem. Phys.*, **1**, 190 (1933).

therefore, to be added directly to any intrinsic moment in the bond. A similar calculation gave 0.91×10^{-18} for the C—F moment in methyl fluoride with the induced C—H moments having a component of 0.90×10^{-18} in the C—F direction. As these C—Cl and C—F values included the moments induced in the halogens by the C—H moments, it seemed best to lower them to 1.0×10^{-18} and 0.8×10^{-18} to make some allowance for the C—H influence. The use of these values in the calculation of the $CFCl_3$ moment gives a value of 0.44 as compared to the observed 0.45. As the carbon valence angles in the fluorochloromethanes are probably not far from 110°,[24] this value is assumed throughout. In the following equations, the formula of a molecule or of a bond enclosed in parentheses will represent its moment. The different bond moments are exposed to somewhat different inductive effects in the different molecules, but, as the total resultant moments of the molecules are not large, it is evident that the differences in inductive effects, which, in most cases, partially cancel one another, may commonly, as an approximation, be neglected. The moment of $CFCl_3$ lies in the C—F line and is given by

$$\begin{aligned}(CFCl_3) &= (C—F) - 3(C—Cl)\cos 70^\circ \\ &= (C—F) - (C—Cl) = 0.45, \qquad (5)\end{aligned}$$

since $\cos 70^\circ = 1/3$. The moment of CF_2Cl_2 must lie in the line which bisects the F—C—F angle and also the Cl—C—Cl angle and is given by

$$\begin{aligned}(CF_2Cl_2) &= 2(C—F)\cos 55^\circ - 2(C—Cl)\cos 55^\circ \\ &= 1.15\,[(C—F) - (C—Cl)]. \qquad (6)\end{aligned}$$

Substituting for $[(C—F) - (C—Cl)]$ its value given by equation (5),

$$(CF_2Cl_2) = 1.15 \times 0.45 = 0.52, \qquad (7)$$

as compared to an observed value 0.51. The moments of the other fluorochloromethanes have been calculated by similar equations, the agreement with the observed being less satisfactory in some cases because of greater differences in the inductive effects.

Similar methods have been applied recently to other molecules,[25] some of which are illustrated by the following equations:

$$((CH_3)_2CO) - (H_2CCl_2) = (COCl_2),$$

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[24] *Cf.* L. E. Sutton and L. O. Brockway, *J. Am. Chem. Soc.*, **57**, 473 (1935).

[25] C. P. Smyth and K. B. McAlpine, *ibid.*, **56**, 1697 (1934).

or $2.85 - 1.57 = 1.28$, as compared to the observed value 1.18 for phosgene:

$$(HCN) - (HCCl_3) = (CCl_3CN),$$

or $2.93 - 1.05 = 1.88$,
and $(CH_3CN) - (CH_3CCl_3) = (CCl_3CN)$,
or $3.45 - 1.5 = 1.95$, as compared to the observed value 2.0;

$$(CH_3NO_2) - (CH_3CCl_3) = (CCl_3NO_2)$$

or $3.42 - 1.5 = 1.92$ as compared to the observed value 1.88. The agreement here and in the fluorochloromethanes shows that the assumptions and treatment used provide a possible working basis for the attack upon dipole problems.

A further consideration of these moments in a qualitative manner may be helpful. The difference between methyl fluoride and methyl chloride is 0.05×10^{-18}. In the absence of disturbing factors, this should also be the moment of $CFCl_3$, while that of CF_2Cl_2 should be no more than 0.06×10^{-18}. The observed moments, which are approximately nine times as great as these small values, can clearly arise from the fact that the polarizability of fluorine is much smaller than that of chlorine,[26] so that the C—F moment is much less reduced by induction than the C—Cl moment in the molecules containing more than one fluorine or chlorine.

It was shown some time ago[27] that the greater moment of an ethyl halide as compared to a methyl was presumably due to the small moment induced in the second carbon and that the effect of induction beyond this second carbon was practically negligible as far as the moment was concerned, since higher primary alkyl halides were practically indistinguishable in moment from the ethyl compound. This was supported by the fact that a secondary alkyl halide had a larger moment than a primary while a tertiary had one still larger, indicating that, when additional carbons were brought within the effective field of the principal carbon-halogen dipole, measurable moments were induced upon them. A branch farther along the chain, as in an isobutyl halide, did not increase the moment, the field due to the principal dipole being insufficient to induce a detectable moment in these more remote carbons.

Recent precise measurements of the moments of the methyl and ethyl halide vapors[28] indicate that the differences between the changes in moment from the methyl to the ethyl compound for different halides do not conform to what might be expected from the effect of induction alone,

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[26] C. P. Smyth, *Phil. Mag.*, **50**, 361 (1925).

[27] C. P. Smyth and R. W. Dornte, *J. Am. Chem. Soc.*, **53**, 545 (1931).

[28] C. P. Smyth and K. B. McAlpine, *J. Chem. Phys.*, **2**, 499 (1934).

the methyl-ethyl difference increasing regularly from fluoride to iodide while the increasing carbon-halogen distance would lead to the expectation of a reduced inductive effect. Although the direct effects of the induction of the principal dipole of the molecule are evident in the observed moments, it seems that there must be a possibility of, at least, a small shift of charges not immediately calculable from induction. Such shifts of charges are more conspicuous in the case of aromatic and unsaturated compounds. For example, chlorobenzene has a lower moment than methyl chloride although if direct induction by the carbon-halogen dipole were the only cause of difference, the greater polarizability of the adjacent part of the chlorobenzene molecule should give a moment larger than that of methyl chloride, probably not far from 2.1×10^{-18}. The reverse of this effect is seen in the moments of nitromethane[25] and nitrobenzene, for the moment of the aromatic compound is 0.6×10^{-18} higher than that of the aliphatic. It is obvious that the differences cannot be due merely to error in the direct application of the calculation of the effects of induction. Indeed, Sutton[29] has tabulated the differences in moment between corresponding aromatic and aliphatic compounds, termed them the "electromeric effect," and correlated them with the orientating influence of the polar groups in the benzene ring. It appears that, when the aromatic moment is smaller than the corresponding aliphatic, an electron shift has occurred in the direction of the benzene ring, toward which the positive end of the dipole lies, and the substituent is *ortho-para*-directing. When the aromatic moment is larger, the electron shift away from the ring causes a *meta*-directing influence. Although the moments and their differences given in Table III must be regarded as very approximate, they seem to place the groups in a significant order.

The difference found between the vapors of fluorobenzene[30] and ethyl fluoride,[28] which is added to Sutton's data in Table III, locates fluorine about where it should be. A much longer list of groups has been arranged by Svirbely and Warner[31] in the order of ascending moment of the monosubstituted benzene, the groups which give a moment below about 2.07×10^{-18} being *ortho-para*-directing and those which give a moment above 2.07 being *meta*-directing. As this is the point in Table II at which the difference between aromatic and aliphatic changes from positive to negative, the two treatments of the problem yield the same result.

Sutton[29] calculates a similar electromeric effect for ethylene derivatives, but as the data are more limited and less accurate, they are not reproduced here. The double bond in itself is electrically symmetrical as shown by

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[29] L. E. Sutton, *Proc. Roy. Soc.*, **A133**, 668 (1931).

[30] K. B. McAlpine and C. P. Smyth, *J. Chem. Phys.*, **3**, 55 (1935).

[31] W. J. Svirbely and J. C. Warner, *J. Am. Chem. Soc.*, **57**, 655 (1935).

the zero moment of the ethylene molecule,[32] but it may evidently give rise to electronic shifts as evidenced by the moments of propylene[9] and α-butylene[32] as well as by the electromeric effects calculated by Sutton.

The transmission of an electronic shift through a saturated carbon chain was shown to be very small by the absence of a detectable increase of moment in the *n*-alkyl halides when the chain was increased beyond the ethyl compound.[27, 33] This constancy of moment for the longer-chain halides seemed inconsistent with the increase in ionization constant of a fatty acid produced by a halogen even as much as five carbons away from the hydroxyl group until it was pointed out[34] that a logarithmic relation existed between the ionization constant and the distance between the charges, while the inductive effect of the moment depended directly upon the distance and, consequently, varied much less. It is evident that, even in aromatic and ethylenic compounds where the electron shifts or electromeric effects are much larger than in the saturated aliphatic compounds, precisely determined values are necessary for any careful consideration of possible relations between moment and chemical behavior.

TABLE III

Aromatic and Aliphatic Moments (× 10^{18}) and Their Differences

GROUP	AROMATIC	ALIPHATIC	DIFFERENCE
CH_3	+0.45	0.0	+0.45
O	−1.06	−1.29	+0.23
NH_2	+1.55	+1.23	+0.32
F			+0.4
Cl	−1.56	−2.15	+0.59
Br	−1.52	−2.21	+0.69
I	−1.27	−2.13	+0.88
CH_2Cl	−1.82	−2.03	+0.21
$CHCl_2$	−2.03	−2.06	±0.0
CCl_3	−2.07	−1.57	−0.5
$CO\cdot CH_3$	−2.97	−2.79	−0.18
CO	−3.04	−2.76	−0.28
C≡N	−3.89	−3.46	−0.43
NO_2	−3.93	−3.05	−0.88

Consideration of the so-called "bond moment" has been postponed until a foundation has been laid for its brief discussion. In a molecule containing two or more principal dipoles, it is customary to associate each dipole with one bond. By empirical methods a series of bond mo-

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[32] C. P. Smyth and C. T. Zahn, *ibid.*, **47**, 2501 (1925).

[33] C. P. Smyth and K. B. McAlpine, *J. Chem. Phys.*, **3**, 347 (1935).

[34] C. P. Smyth, reference 2, p. 133.

ment values has been built up[35] like the electromotive series of the elements and, as in this series, the absolute values are uncertain, since the moment of a single bond alone can be measured only in diatomic molecules. However, even in so simple a molecule as that of hydrogen chloride, the observed moment depends not only upon the positions of the proton, the chlorine nucleus, and the electrons of the bond, but also upon the shifts toward the proton of the chlorine electrons not involved in the bond. The so-called moment of the C—Cl bond in a molecule involves similar shifts of these chlorine electrons as the result of attraction toward the carbon and of the forces exerted by the rest of the molecule upon these electrons. There is, in addition, the effect of the chlorine upon the rest of the molecule. In other words, a bond moment is merely a measure of the electrical dissymmetry of a certain section of a molecule and is affected by the environment of the section. If the immediate environment of the section in molecules of different compounds is the same, the bond moment remains constant; if it is different, the electrical dissymmetry of the section and its moment change more or less. The term "group moment" is evidently less inaccurate than "bond moment," although it implies no consideration of the effect of the environment of the group.

If the group to which the moment value is assigned is sufficiently large, it will include most of the induction and electromeric effects caused by the principal dipole or dipoles in it, but its moment may not then be particularly significant for structural considerations. If the attempt is made to assign a moment value to one bond alone, the electromeric and induction effects of the bond upon the charges of the adjacent atoms of the molecule and their effects upon the bond under consideration must be evaluated. It is evident that such an evaluation can give no more than a rough magnitude for each effect. However, the association of a moment of definite value with a bond and with the direction of the bond provides the most practical means of using the dipole moment when more than one is present in a molecule. For most purposes, the best results may be obtained by assigning to a dipole the moment value given by it to a simple molecule in which it is the only principal dipole and in which its environment is similar to that in the molecule under consideration. It may be desirable even to lump the moments of two or three principal dipoles into one resultant as was done in the treatment of the phosgene and the trichloromethyl cyanide molecules, which has been outlined.

The use of this method to obtain quantitative results of a different character is illustrated by the determination of valence angles by means of dipole moments. Although the Cl—C—Cl angle in methylene chloride

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[35] A. Eucken and L. Meyer, *Physik. Z.*, **30**, 397 (1929).

could be determined approximately by assigning the methyl chloride moment to each of the two C—Cl bonds, calculating the inductive effects, and determining the angle, θ, between the two vectors, m, which made $2\ m \cos \theta/2$ equal to the observed moment of methylene chloride,[23] uncertainty as to induction and repulsion between the atoms made the result somewhat uncertain. The two principal dipoles were, therefore, separated from one another by using *para*-substituted benzyl compounds with Cl, Br, CN and NO_2 as the substituents. A moment equal to that of the unsubstituted benzyl compound was assigned to the bond connecting the group to the benzyl carbon, and a moment equal to that of the corresponding monosubstituted benzene was assigned to the bond of this carbon to the ring, the extension of which should include the bond of the *para*-substituent.[36] The values of the angle obtained in this way, 114 to 119°, differed from 110° by no more than the possible errors of the method. Similar methods applied to the determination of the oxygen and sulfur valence angles[37] gave 121° for the oxygen angle in 4,4′-dinitrodiphenyl ether, with which the value 118° recently obtained from electron diffraction measurements on 4,4′-diiododiphenyl ether[38] is in excellent agreement, and about 140° for the sulfur angle, but the results for different compounds differed widely, probably, much more because of electromeric effects than of actual variation of the angles.[37, 39]

It should be apparent from what has gone before that the major contribution from the study of dipole moments to organic chemistry has been aid in the determination of the shape of the molecule and the locations of the atoms in the molecule. The indication of the plane hexagonal model for the benzene ring at a time when X-ray analysis pointed to a puckered ring may be cited as a particularly striking example of the way in which dipole moment studies have given physical evidence of the correctness of so many of the conventional spatial formulas of organic chemistry. Even at its initial use little more than ten years ago, the moment proved itself a blunt but effective tool for the investigation of molecular structure. Subsequent years of use and of study of the factors affecting it have so improved its manipulation that it may now be regarded as ready to the hand of the organic chemist for aid in the solution of his special structural problems. The dipole moment does not seem to play an important rôle in chemical activity. In testing theories of the influence of polarity upon

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[36] C. P. Smyth and W. S. Walls, *J. Am. Chem. Soc.*, **54**, 1854 (1932).

[37] C. P. Smyth and W. S. Walls, *ibid.*, **54**, 3230 (1932).

[38] L. R. Maxwell, S. B. Hendricks and V. M. Mosley, *J. Chem. Phys.*, **3**, 699 (1935).

[39] E. Bergmann, L. Engel and S. Sandor, *Z. physik. Chem.*, **B10**, 397 (1930); G. C. Hampson, R. H. Farmer and L. E. Sutton, *Proc. Roy. Soc.*, **143A**, 147 (1933).

chemical behavior, it has shown that many differences in polarity to which differences in chemical behavior were attributed were, if existing at all, too small to be detected. On the other hand, it has given evidence of the so-called electromeric effect in aromatic and ethylenic compounds and it appears probable that small differences in moment may be significant in determining chemical behavior. For the study of these small differences, which may become a very important contribution to organic chemistry, more moment determinations of high accuracy are needed.

[Contribution from the George Herbert Jones Chemical Laboratory, The University of Chicago]

MOLECULAR REARRANGEMENT OF TRIPHENYLMETHYLALKOXYAMINES*

WALTER S. GUTHMANN AND JULIUS STIEGLITZ

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Molecular rearrangements of triarylmethylhydroxylamines, $(Aryl)_3CNHOH$ and $(Aryl)_3CNCH_3(OH)$ were investigated by the one of us and his collaborators.[1] The study of the rearrangement of triarylmethylalkoxyamines, $(Aryl)_3CNH(O\text{-alkyl})$ was undertaken by us with the idea that the greater ease of following the alkoxyl group in —NH(O-alkyl), as compared with the hydroxyl group in —NHOH, might shed further light on the mechanism of rearrangements of this general type.

Triphenylmethylmethoxyamine was first chosen for the study, but the *O*-benzyl ($OCH_2C_6H_5$) derivative was later used as offering greater facility in tracing the fate of the alkoxyl group in the reaction.

Only one other instance of the molecular rearrangement of an alkoxyamine derivative was found in the literature. Semper and Lichtenstadt[2] observed incidentally in 1914 that *O*-methyl benzophenone oxime is rearranged by concentrated sulfuric acid and yields a mixture of benzanilide, benzoic acid, aniline, and methyl benzoate. The triphenylmethyl derivatives have an advantage over ketoximes, aldoximes and acyl derivatives inasmuch as they contain no double bonds or other complicating structural details.

In triphenylmethylalkoxyamines we have the typical electronic molecular instability, or "fault," that is found in other rearranging hydroxylamine

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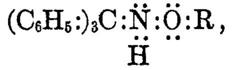
* A portion of the dissertation submitted to the graduate faculty of The University of Chicago by Walter S. Guthmann, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[1] *Cf.* Stieglitz and Leech, *J. Am. Chem. Soc.*, **36**, 272; Stieglitz and Stagner, *ibid.*, **38**, 2047 (1916); Stagner, *ibid.*, **38**, 2069 (1916). For the electronic interpretation of the rearrangements see *ibid.*, **36**, 287 (1914); *Proc. Nat. Acad. Sci.*, **1**, 196 (1915); *J. Am. Chem. Soc.*, **38**, 2046 (1916) and **44**, 1293 (1922).

[2] Semper and Lichtenstadt, *Ber.*, **51**, 930 (1919). Brady and Dunn, *J. Chem. Soc.*, **129**, 2412 (1926), evidently overlooked this report of Semper and Lichenstadt since they claimed that no such rearrangement had ever been observed, although they refer to the above article in another connection. *Cf.* Brady, Dunn and Goldstein, *loc. cit.*, p. 2387.

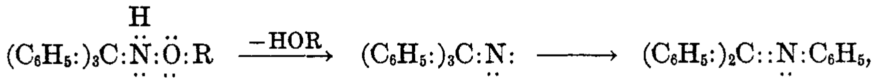
derivatives, chloro- and bromo-amines, hydrazines, azides, etc.[3] The structure,†



$$(C_6H_5:)_3C:\underset{\underset{H}{\cdot\cdot}}{\overset{\cdot\cdot}{N}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}:R,$$

shows that the nitrogen and oxygen atoms together have only fourteen electrons—the electron-saturated atoms require eight each, or sixteen together. The inadequacy of a shared pair of electrons, completing the octets of each, was emphasized by the one of us[4] as characteristic of all the above types of rearranging compounds. There is a shortage of two electrons which creates the "fault" in the molecule. This shortage of two electrons may lead to:

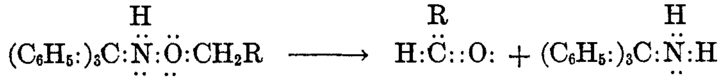
(1) A molecular rearrangement,



$$(C_6H_5:)_3C:\underset{\cdot\cdot}{\overset{\overset{H}{\cdot\cdot}}{N}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}:R \xrightarrow{-HOR} (C_6H_5:)_3C:\underset{\cdot\cdot}{N}: \longrightarrow (C_6H_5:)_2C::\underset{\cdot\cdot}{N}:C_6H_5,$$

with *N*-phenyliminobenzophenone and an alcohol as the products of the action, the nitrogen and the oxygen atoms now having each its own complement of eight electrons.

(2) The capture of two electrons on the part of the oxygen atom[5] by the oxidation of the alkyl group:[6]



$$(C_6H_5:)_3C:\underset{\cdot\cdot}{\overset{\overset{H}{\cdot\cdot}}{N}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}:CH_2R \longrightarrow H:\overset{\overset{R}{\cdot\cdot}}{C}::O: + (C_6H_5:)_3C:\underset{\cdot\cdot}{\overset{\overset{H}{\cdot\cdot}}{N}}:H$$

Triphenylmethylamine and an aldehyde are formed in this reaction.

(3) Hydrolysis, or an equivalent decomposition, of the hydroxylamine derivative:

a. $(C_6H_5)_3C\cdot NHOR + H_2O \rightarrow (C_6H_5)_3COH + NH_2OR$

b. $(C_6H_5)_3C\cdot NHOR + 2\ HCl \rightarrow (C_6H_5)_3CCl + [NH_3OR^+]Cl^-$ (in an anhydrous medium).

The present investigation has shown that molecular rearrangements of the type (1) anticipated do occur. The formation of aniline and of benzophenone, the characteristic products of rearrangement and subsequent

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[3] *Cf.* Stieglitz, *J. Am. Chem. Soc.*, **36**, 287 (1914) and **44**, 1293 (1922).

† $(C_6H_5^-)_3\underset{+}{\overset{+}{\overset{+}{C}}}{}^{+}\ {}^{-}\overset{H^+}{N}{}^{-}_{-}$ $({}^{+}OR)$ represents the same structure with emphasis on the *partial* polarity of the individual atoms.

[4] Stieglitz, *loc. cit.*, p. 1295 (1922).

[5] *Cf.* Stieglitz, *J. Am. Chem. Soc.*, **36**, 279 (1914), on the electron structure of hydroxylamines.

[6] *Cf.* L. W. Jones, *ibid.*, **36**, 1279 (1914), and his references to earlier work.

hydrolysis, was demonstrated. However, only a part of the substance undergoes rearrangement. In the case of the methoxy derivative, it is only a very small part, the predominating reaction leading to a breakdown of the compound to triphenylmethylcarbinol (3*a*) and decomposition products of methoxyamine. *N*-Triphenylmethyl-*O*-benzylhydroxylamine is rearranged much more readily—even by heat alone. The yields indicate a rearrangement of as much as 40 per cent. of the compound. At the same time, the formation of benzaldehyde results, probably from a primary oxidation of the benzyl radical (equation 2), although benzaldehyde might be formed by the oxidation of benzyl alcohol (equation 1), at the high temperature of the rearrangement by heat alone (420°).

It is interesting to note that the rearrangement can occur here even in the *absence of all reagents or salt-forming substances*, heat by itself being effective; but the yield is better when phosphorus pentoxide is used to promote the reaction, and the temperature required is far lower (160° instead of 420°). The free base, in the presence of phosphorus pentoxide, gives a better yield of the rearrangement products than does its hydrochloride under similar conditions.

We may summarize our results: if the hydroxyl group of triarylmethylhydroxylamine is replaced by the more stable methoxyl group, the tendency toward rearrangement is decreased. However, if conditions are made correspondingly more rigorous, rearrangement will again occur. When the *O*-benzyl group is used in place of the methoxyl, rearrangement is again easier. We have further shown that the tendency toward rearrangement exists, apparently residing in the electron deficiency within the hydroxylamino radical; but usually the tendency has to be aided, by the reagent most suitable in each case, toward promoting the primary formation of a rearranging univalent nitrogen derivative.

EXPERIMENTAL

Triphenylmethylmethoxyamine, $(C_6H_5)_3CNHOCH_3$.—Triphenylmethyl chloride (40 g. in 100 cc. of benzene) was rapidly added to methoxyamine* (20 g.), the mixture being well shaken under a reflux condenser. Heat was evolved. After the mixture had stood for twelve hours the precipitate of methoxyamine hydrochloride was removed by filtration; the filtrate, after evaporation of the benzene *in vacuo*, yielded 36 g. of triphenylmethylmethoxyamine (m.p. 89–90°). The product may be purified by recrystallization from ligroïn (b.p., 60–80°), or by precipitation from a saturated benzene solution by ligroïn (b.p., 40–50°). Soluble in ether, acetone, very soluble in benzene, and slightly soluble in ligroïn, the pure compound was obtained in the form of white rhombic crystals, melting at 91.5–.6°. It is quite stable, and may be kept indefinitely in a desiccator.

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* Obtained from Eastman Kodak Co., dried over sodium sulfate and distilled.

Anal. Calc'd for $C_{20}H_{19}NO$: C, 82.88; H, 6.75; N, 4.84.
Found: C, 82.41, 83.17; H, 6.79, 6.79; N, 4.84, 4.76.

All attempts to prepare a benzoyl derivative of triphenylmethylmethoxyamine were unsuccessful.

Triphenylmethylmethoxyamine hydrochloride, $[(C_6H_5)_3CNH_2OCH_3]Cl$.—Dry hydrogen chloride precipitated the hydrochloride from a cooled benzene solution of the pure base as an extremely fine, gleaming white powder. Washed with ethereal hydrogen chloride and ligroïn and dried *in vacuo*, it melts with decomposition at 179–180°.

Anal. Calc'd for $C_{20}H_{20}ClNO$: Cl^-, 10.86.
Found: Cl^-, 10.90, 10.95.

If the salt is allowed to stand *in vacuo* it dissociates into the free base and hydrogen chloride, as do the hydrochlorides of all the other known triphenylmethylhydroxylamines. If allowed to stand for a short time in an ether solution containing dry hydrogen chloride, the salt undergoes dissociation to triphenylmethyl chloride and methoxyamine hydrochloride (equation 3b).

Rearrangement of triphenylmethylmethoxyamine and its hydrochloride.—Twenty separate attempts to rearrange these compounds were made, but only five were successful. The first twelve (unsuccessful) attempts involved the use of ether* as the solvent for the reactants; varying amounts of phosphorus pentachloride, phosphorus pentoxide, thionyl chloride and barium oxide were used as agents. Both the free base and its hydrochloride were tried with these reagents. In all cases the original compound or triphenyl carbinol, or both, were recovered quantitatively. This proved that no migration of a phenyl group had occurred.†

Negative results also attended the reaction when benzene was used as the solvent; but in carbon tetrachloride solutions migration of the phenyl group occurred to some extent. After hydrolysis of the reaction mixture with dilute hydrochloric acid, the carbon tetrachloride layer was separated, the solvent evaporated and the residue found to consist of triphenyl carbinol and benzophenone. The latter was separated as the sodium salt of its oxime. To this end the residue was heated under reflux for 1½ hours with hydroxylamine hydrochloride (1.5 g.) and sodium hydroxide (2 g.) in 20 cc. of dilute alcohol. Upon addition of water (100 cc.) to the solution, triphenyl carbinol was precipitated, collected and weighed. Dilute sulfuric acid precipitated the benzophenone oxime from the filtrate, quantitatively. A solution of triphenylmethylmethoxyamine (3 g.) and phosphorus pentachloride (5 g.) in 30 cc. of carbon tetrachloride yielded 0.2 g. of the oxime, melting at 140–1°. Pure benzophenone oxime melts at 143–4°; a mixture of the oxime obtained and the synthetic product melted at 141–2°. The identification of benzophenone proved that the molecular rearrangement (equation 1) had been effected.

Triphenylmethylmethoxyamine was next heated with phosphorus pentachloride in the absence of all solvents; the yield of benzophenone oxime was comparable to that obtained when carbon tetrachloride was used as solvent. Aniline could not be detected.‡

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* A reaction between phosphorus pentachloride and ether was observed and reported; WALTER S. GUTHMANN, *J. Am. Chem. Soc.*, **54**, 2938 (1932).

† For further details the Dissertation of Guthmann should be consulted.

‡ LEECH, *J. Am. Chem. Soc.*, **35**, 1042 (1913), after confirming that aniline gives the well-known typical purple color with a half-saturated solution of calcium hypo-

When triphenylmethylmethoxyamine hydrochloride was heated with phosphorus pentoxide, only a trace of benzophenone was recovered from the hydrolysis products of the reaction mixture by the method outlined above. Triphenyl carbinol, however, was recovered in almost quantitative amounts.

Pyrolysis does not lead to the rearrangement of triphenylmethylmethoxyamine, which thus differs from *N*-triphenylmethyl-*O*-benzylhydroxylamine, discussed below. When the product of reaction was hydrolyzed and treated as above, no benzophenone and no aniline were found.

N-*Triphenylmethyl*-O-*benzylhydroxylamine*, $(C_6H_5)_3CNHOCH_2C_6H_5$.—A solution of triphenylmethyl chloride (40 g.) in 155 cc. of benzene was added to *O*-benzylhydroxylamine[7] (45 g.), and the mixture was allowed to stand for two days. The reaction was quite slow and no perceptible amount of heat was evolved. The chlorine-free filtrate from the precipitate of *O*-benzylhydroxylamine hydrochloride yielded 45.5 grams of crude *N*-triphenylmethyl-*O*-benzylhydroxylamine (melting point 115–7°). Recrystallized three times from ligroïn (b.p. 60–80°) the pure compound was obtained in the form of hard white rhombic crystals, melting at 118°.

Anal. Calc'd for $C_{26}H_{23}NO$: C, 85.42; H, 6.36; N, 3.84.
Found: C, 85.70, 85.50; H, 6.65, 6.42; N, 3.95, 3.75.

The hydrochloride of *N*-triphenylmethyl-*O*-benzylhydroxylamine is best prepared from a benzene solution of the base, by the addition of dry ethereal hydrogen chloride. The voluminous precipitate was washed with ethereal hydrogen chloride and dried *in vacuo*. It is a gleaming white powder, which softens at 152° and melts at 180–90° with decomposition.

Anal. Calc'd for $C_{26}H_{24}ClON$: Cl^-, 8.82.
Found: Cl^-, 8.11, 8.66.

The low results are probably due to loss of hydrogen chloride by the salt.

Rearrangement of N-*triphenylmethyl*-O-*benzylhydroxylamine and its hydrochloride.*—When *N*-triphenylmethyl-*O*-benzylhydroxylamine, or its hydrochloride, was heated with phosphorus pentachloride in benzene or carbon tetrachloride solution, the reaction followed the same general course as in the case of triphenylmethylmethoxyamine, except that very little color was noted in the hydrolysis product obtained from the reaction mixture.

The free base (3 g.) and phosphorus pentachloride (10 g.) were allowed to stand

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chlorite, showed that methyl aniline gives with the same reagent a *blue* color, which fades in the course of about 15 seconds to a pale yellow color. The two compounds may be distinguished from one another by means of this test, provided they are not present in the same solution. Subsequent work by us on known solutions of aniline has shown that it does not give the hypochlorite color test in the presence of methoxyamine, even when an excess of the reagent is used. [*Cf.* STIEGLITZ AND BROWN, *J. Am. Chem. Soc.*, **44**, 270 (1922) and WEST, Doctorate Dissertation, University of Chicago, 1923, on the interference of ammonium salts with the aniline test.] However, even under these conditions it does give a good test by the method of DE PAOLINI, *Gazz. chim. ital.*, **60**, 859–62 (1930). De Paolini's test is also otherwise quite excellent, especially if carried out in 90% acetic acid; it is nearly as sensitive as the hypochlorite test and like the latter furnishes a means of distinguishing between aniline and methyl aniline, a fact not mentioned by De Paolini. It has the further advantage of functioning also in solvents other than water.

[7] V. MEYER AND JANNY, *Ber.*, **15**, 1324 (1882); JANNY, *Ber.*, **16**, 170 (1883); BEHREND AND LEUCKS, *Ann.*, **257**, 206 (1890).

in carbon tetrachloride (30 cc.) for a day and then the mixture was boiled under reflux for one week. Hydrolysis of the product and subsequent treatment gave 0.3 g. of benzophenone oxime. No aniline was found.

The best yields of rearrangement products were obtained when *N*-triphenylmethyl-*O*-benzylhydroxylamine, or its hydrochloride, was mixed with phosphorus pentachloride and heated in an oil bath at 160°. Benzophenone, recovered from its oxime, synthetic benzophenone and the mixture of the two gave the same melting point, 48°. When bromine water was added to the acid portion of the original product of hydrolysis, tribromoaniline was precipitated. This was sublimed *in vacuo* and identified by its crystal form (needles), its melting point (118°) and by the melting point (118°) of a mixture of the compound and known tribromoaniline (118°).

A mixture of *N*-triphenylmethyl-*O*-benzylhydroxylamine hydrochloride (2.2 g.) and phosphorus pentoxide (3 g.) gave 0.65 g. of tribromoaniline (36% of the theoretical yield) and 0.25 g. of benzophenone oxime (23% of the theoretical yield).

N-triphenylmethyl-*O*-benzylhydroxylamine (2 g.) and phosphorus pentoxide (6 g.), when subjected to the same treatment, yielded 0.95 g. of tribromoaniline (60% of the theoretical yield) and 0.18 g. of benzophenone oxime (19% of the theoretical yield).

A mixture of *N*-triphenylmethyl-*O*-benzylhydroxylamine hydrochloride (3 g.) and phosphorus pentoxide (2 g.) heated to 445° for two minutes in a metal bath gave 0.75 g. of tribromoaniline (31% of the theoretical amount) and 0.18 g. of benzophenone oxime (12% of the theoretical amount). During the heating a few drops of material distilled out of the reaction vessel and were identified as benzaldehyde by the odor and by the formation of its sodium bisulfite addition product, which in turn was converted into benzaldehyde phenylhydrazone (m.p. 154°). A mixture of this product with known benzaldehyde phenylhydrazone (m.p. 156°) melted at 155°.

N-Triphenylmethyl-*O*-benzylhydroxylamine (2 g.) heated alone to 445° for two minutes, yielded 0.015 g. of tribromoaniline and 0.010 g. of benzophenone. The material that distilled during the heating proved to be chiefly benzaldehyde (identified as above) and ammonia.

The gums that remained after the hydrolyses in all the above experiments were not completely identified, but were found to contain small amounts of triphenyl carbinol, which was identified by its own melting point (162°) and the melting point of a mixture of it and known triphenyl carbinol (162°).

All tests for benzyl alcohol, benzoic acid, benzonitrile, and benzhydrol, among the products of the above rearrangements, were negative.

SUMMARY

1. The preparation of triphenylmethylmethoxyamine and of *N*-triphenylmethyl-*O*-benzylhydroxylamine is reported.

2. The rearrangement of triphenylmethylmethoxyamine with phosphorus pentachloride was studied. In benzene and carbon tetrachloride solutions some rearrangement to *N*-phenyliminobenzophenone occurs, but the rearrangement goes very slowly and the yield of rearrangement products is very small. Other decompositions are paramount. These are discussed and demonstrated.

3. The rearrangement of *N*-triphenylmethyl-*O*-benzylhydroxylamine was brought about by phosphorus pentoxide at 160°, and by heat alone at 425°. The yields of rearrangement products, benzophenone and aniline, are very much better than in the case of the methoxyl derivative but not as good as in the rearrangement of triphenylmethylhydroxylamine. Intramolecular oxidation of the *O*-benzyl derivative to benzaldehyde was demonstrated.

4. The experimental results are interpreted on the basis of the Stieglitz theory of molecular rearrangements of this type.

[CONTRIBUTION FROM THE LABORATORIES OF THE DIVISION OF INSECTICIDE INVESTIGATIONS, BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE U. S. DEPARTMENT OF AGRICULTURE, WASHINGTON, D. C.]

CONSTITUENTS OF PYRETHRUM FLOWERS. IV.* THE SEMICARBAZONES OF PYRETHRINS I AND II AND OF PYRETHROLONE†

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The conclusions that have been reached by numerous investigators regarding the relative insecticidal value of the two toxic principles of pyrethrum flowers, pyrethrin I and pyrethrin II, show wide variance.[1] This lack of agreement seems to be due to the fact that the pure pyrethrins have never been available for biological tests. Our investigations in this field have for their object the study of methods by which these pure pyrethrins might be obtained.

A considerable advance toward this accomplishment was made in the improvement in the method of preparing concentrates high in total pyrethrins and the separation of these concentrates into fractions in each of which one of the separate pyrethrins predominates, described in a previous article,[2] to which the reader is referred for complete details.

The preliminary operations whereby the crude starting material, a commerical product consisting of the petroleum-ether extractives of pyrethrum flowers, is freed from fats, waxes, and fatty acids, and which gives a concentrate containing 70 per cent. total pyrethrins, need not be reviewed here.

The process by which this concentrate is separated into fractions in which the separate pyrethrins are concentrated is based on the observation that they have different solubilities in diluted acetic acid and in petroleum ether. When the 70 per cent. concentrate is dissolved in petroleum ether and the solution is agitated with acetic acid containing the proper amount of water, the pyrethrin I and the pyrethrin II are found to be very unequally distributed in the separated liquids, most of the pyrethrin I being

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* For article III of this series see ACREE, SCHAFFER, AND HALLER, *Jour. Econ. Ent.*, in press.

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[1] GNADINGER, C. B., "Pyrethrum Flowers." Minneapolis, **1933**, p. 92.

[2] LAFORGE, F. B., AND HALLER, H. L., *J. Amer. Chem. Soc.*, **57**, 1893 (1935).

in the petroleum-ether solution and most of the pyrethrin II in the acetic acid. Since the impurities present in the concentrate tend to follow the pyrethrin I, the method is more favorable for the purification and concentration of the other toxic principle, pyrethrin II. By repetition of the process just described with the material isolated from the acetic acid solution, a further concentration of pyrethrin II is attained.

As a result of these operations three concentrates are obtained, one that has a content of about 40–45 per cent. pyrethrin I together with 12–14 per cent. pyrethrin II, another containing 80–83 per cent. pyrethrin II with 3–5 per cent. pyrethrin I, and an intermediate fraction that contains both pyrethrins in about equal proportions.*

After many applications of this method we have not found it necessary to make any important changes. Having noticed, however, that in the first separation the impurities tended to go with the fraction in which pyrethrin I predominated, we found it advantageous to keep the intermediate fractions separate for retreatment, because these fractions had a higher total pyrethrin content and, when separated in a new series of operations, yielded concentrates higher in the respective pyrethrins. For instance, the pyrethrin II concentrate obtained from the intermediate fractions contained about 87 per cent. of pyrethrin II, and the corresponding pyrethrin I concentrate about 57 per cent. of pyrethrin I.

As already reported[2] concentrates of 80 per cent. pyrethrin II content can be distilled in the molecular still and yield material which analyses indicate to be substantially 100 per cent. pyrethrin II. For reasons that will be given later, it seems doubtful that the product so obtained represents the natural, unaltered compound. The best available concentrates of pyrethrin I were regarded as too impure to offer promise of satisfactory results by this method of direct distillation.

After we had accomplished an approximate separation of the two pyrethrins, it seemed promising to make a study of their isolation by other means. The investigations of Staudinger and Ruzicka[3] are based on the isolation of the pyrethrins as semicarbazones, which are practically their only known crystalline derivatives. The best starting material available to them for the preparation of the semicarbazones was a concentrate containing 50–60 per cent. of total pyrethrins present in about equal amounts, from which concentrate a mixture of the semicarbazones of both pyrethrins was obtained. The semicarbazone of pyrethrin I proved to be the less soluble, and by repeated recrystallization it was possible, with great loss

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* Pyrethrin I was determined by the method of Seil, *Soap*, **10**, no. 5, 89 (1934); pyrethrin II by the method of Haller and Acree, *Ind. Eng. Chem., Anal. Ed.*, **7**, 343 (1935).

[3] STAUDINGER, H., AND RUZICKA, L., *Helv. Chim. Acta*, **7**, 177 (1924).

of material, to obtain preparations of it which approached the state of purity. When the semicarbazone was hydrolyzed, the free ester, pyrethrin I, was obtained. This product when distilled under reduced pressure, on analysis, agreed fairly well with the formula $C_{21}H_{30}O_3$, but it yielded only 50 per cent. of a semicarbazone apparently identical with the one from which it was obtained. The semicarbazone of pyrethrin II was not obtained in a state even approximating purity.

Staudinger and Ruzicka, in their principal investigations on the structure of the pyrethrins, employed the semicarbazone mixture that had been freed from extraneous material by crystallization. Since the cyclic ketonic alcoholic component, pyrethrolone, was shown to be common to both pyrethrins, its semicarbazone could be obtained by saponification of the mixture of semicarbazones of both the pyrethrins, and the acid components could be isolated and separated subsequently. The pyrethrins themselves were then resynthesized from pyrethrolone and the respective acid components, chrysanthemum acid and chrysanthemum dicarboxylic acid methyl ester. Although these resynthesized pyrethrins possessed high insecticidal properties, they did not yield satisfactory semicarbazones, and it is doubtful that they represent the natural unaltered toxic principles.

As a more careful study of the semicarbazones seemed indicated, the present investigation of their isolation and properties was undertaken with the employment of the concentrates now available in which the pyrethrins had been to a large extent segregated. We first turned our attention to the preparation of the semicarbazone of pyrethrin II from the 80–87 per cent. concentrates.

PYRETHRIN II SEMICARBAZONE

Instead of using sodium acetate, as did Staudinger and Ruzicka, we employed pyridine after we found that better yields of the semicarbazone were obtained with this base. Contrary to what was expected from reports in the literature, the semicarbazone of pyrethrin II was readily obtained in quantitative yield and practically pure from the pyrethrin II concentrate. The same compound is also obtained when sodium acetate is employed. The semicarbazone was easily recrystallized and melted sharply at 165°. Its composition as shown by analysis agreed with the formula $C_{23}H_{33}N_3O_5$ or $C_{23}H_{31}N_3O_5$. On saponification in methyl-alcoholic solution under the conditions prescribed by Staudinger and Ruzicka, it yielded the semicarbazone of pyrethrolone that melted at 208° with decomposition and had the other physical properties described by these authors.

The free ester, pyrethrin II, was obtained from its semicarbazone by hydrolysis with aqueous oxalic acid solution, the method used by Staudinger and Ruzicka to obtain pyrethrin I from its semicarbazone. This method is unsatisfactory, because it involves partial saponification and decomposition, and the yield of crude ester is only 30 per cent. of the theory. Various experiments were made by these authors and also by us, but without discovering a more satisfactory method of hydrolysis. It appears, however, that whatever of the pyrethrin II that survives the treatment, is essentially unaltered, because when the crude product is again converted into the semicarbazone the original compound is regenerated in good yield.

The pyrethrin II that we obtained by molecular distillation of the pyrethrin II concentrate, as mentioned above, had the composition required for pyrethrin II, $C_{23}H_{30}O_5$ or $C_{23}H_{28}O_5$, as shown by analysis, and a preliminary test against flies made by F. L. Campbell, of the Division of Control Investigations of this Bureau, showed it to possess a high order of toxicity. When treated with semicarbazide under the same conditions as those used to prepare pyrethrin semicarbazones, a product was obtained that crystallized only partly on complete removal of the solvent and that was evidently different from the semicarbazone of pyrethrin II described above. It must be concluded that some intramolecular change took place on distillation.

When the semicarbazone preparation was saponified, it yielded only an insignificant amount of pyrethrolone semicarbazone, indicating that some change had taken place in that part of the molecule.

PYRETHRIN I SEMICARBAZONE

The semicarbazone of pyrethrin I was obtained from the pyrethrin I concentrate by the method employed for the preparation of pyrethrin II semicarbazone. This concentrate is of lower total pyrethrin content than that of pyrethrin II and contains, besides a large amount of noncrystalline products, a considerable quantity of the crystalline (nontoxic) pyrethrol. The latter crystallizes on standing and may be removed to a large extent by filtration. After 24 hours the semicarbazone formation was finished and the separation of the crystalline product was completed by cooling in a freezing mixture. The crude product was thus obtained in about quantitative yield, based on the total pyrethrin content of the concentrate. An additional quantity was obtained from the mother liquor as described in the Experimental Part. This material is much less pure and may contain substances other than pyrethrin semicarbazones. The main portion, after washing and drying, melted at 90–100°. The material is difficult to purify. Although it can be readily crystallized from a number of solvents such as acetone, alcohol, and toluene, it is only by repeated recrystallization that a fairly pure product is obtained. After two recrystallizations from acetone and one from alcohol or toluene, it melts not very sharply at about 112–114°. By further recrystallization the melting point can be raised to 118°. We have never obtained a sample entirely free of methoxyl, the quantity found indicating the presence of roughly 10 per cent. pyrethrin II semicarbazone, this in spite of the fact that the latter is very soluble in the solvents employed. The analytical results made on various samples agree only approximately with the formula, $C_{22}H_{33}N_3O_3$.

In an attempt to obtain the semicarbazone of pyrethrin I in pure condition, the material was hydrolyzed with aqueous oxalic acid solution as described in the case of the pyrethrin II semicarbazone. The yield of the free ester in this case was also about 30 per cent. The material was then reconverted into the semicarbazone, which was obtained in good yield, and the properties of the regenerated semicarbazone were the same as those of original material, the melting point being about 115–117°. When the crude pyrethrin I obtained from the semicarbazone in a similar experiment was distilled under a reduced pressure of about 1 mm. and the semicarbazone was prepared from the distillate, a yield of only 50 per cent. was obtained. After recrystallization it melted at about the same temperature as the original semicarbazone. The low yield indicates that pyrethrin I is also to a large degree altered by distillation. However, the fact that the semicarbazone isolated has the same properties as the original semicarbazone indicates that at least part of the pyrethrin I survives the distillation unaltered. The analytical results obtained for these regenerated semicarbazones showed significant divergences from the requirements of the formula $C_{22}H_{33}N_3O_3$. When the semicarbazone of pyrethrin I is dissolved in carbon tetrachloride, it separates in the form of long needles and exhibits physical properties different from those of the original material. The substance has not yet been thoroughly investigated.

SEMICARBAZONE OF PYRETHROLONE

The semicarbazones of pyrethrin II and pyrethrin I give the semicarbazone of pyrethrolone in quantitative yield on saponification in methyl-alcoholic solution with 1 mol of sodium ethylate under the conditions prescribed by Staudinger and Ruzicka. This reaction seems to proceed somewhat more slowly in the case of pyrethrin I. Pyrethrin II semicarbazone yields the semicarbazone of pyrethrolone and a mixture of about equal parts of chrysanthemum dicarboxylic acid and chrysanthemum dicarboxylic acid monomethyl ester in the form of their water-soluble sodium salts and also a considerable quantity of chrysanthemum dicarboxylic acid dimethyl ester. That the saponification of the mixed semicarbazone proceeds in this manner has already been pointed out by Staudinger and Ruzicka.

Pyrethrin I semicarbazone yields, besides pyrethrolone semicarbazone, the monobasic chrysanthemum acid, which is volatile with steam. When large quantities are saponified, a small amount of a nonvolatile acid is obtained which has not yet been identified.

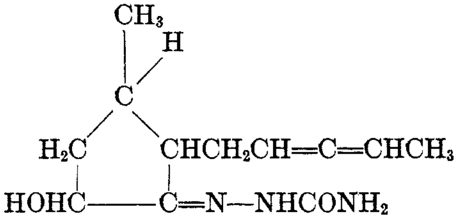
For the isolation and identification of small quantities of chrysanthemum acid and chrysanthemum dicarboxylic acid, it has been found convenient to take advantage of the fact that both form crystalline paraphenylphenacyl esters. A corresponding crystalline derivative of chrysanthemum dicarboxylic acid methyl ester has not been obtained.

Pyrethrolone semicarbazone crystallizes well from acetone, ethyl acetate, or methyl alcohol. It is difficultly soluble in all these solvents, in which it forms supersaturated solutions. The compound is easily purified, and melts at a little above 200° with gas evolution. We have found the decomposition point to be about 208°.

Pyrethrolone semicarbazone has been assigned the formula $C_{12}H_{19}N_3O_2$ by Staudinger and Ruzicka on the basis of three reported analyses. The figures reported by them agree fairly well with this formula, although those for hydrogen are low by more than the limit of error. In our first few analyses of this compound we observed a still lower hydrogen content and a higher carbon content than are required by the above formula. In fact, our own analyses agree within experimental error with a formula with two less hydrogen atoms, *i.e.*, $C_{12}H_{17}N_3O_2$. Having noted the discrepancy, we made a large number of combustions, by both the micro and semimicro methods, on several samples of this compound, all of which confirmed the formula with 17 hydrogen atoms. The theoretical differences between the two formulas in question are 0.39 per cent. for carbon and 0.78 per cent. for hydrogen.

HYDROGENATION OF PYRETHROLONE SEMICARBAZONE

The structural formula of pyrethrolone semicarbazone, according to Staudinger and Ruzicka, is



On hydrogenation four atoms of hydrogen are added to the double bonds, giving tetrahydropyrethrolone semicarbazone. We also prepared this compound by saponification of tetrahydropyrethrin II semicarbazone.

In both hydrogenation experiments the observed volume of hydrogen absorbed corresponded to the addition of four atoms to pyrethrolone and pyrethrin II semicarbazones, respectively. The analyses of the hydrogenated pyrethrolone semicarbazone obtained by both processes indicate that it should be represented by the formula $C_{12}H_{21}N_3O_2$ instead of $C_{12}H_{23}N_3O_2$. The theoretical differences between these formulas are 0.50 per cent. for carbon and 0.76 per cent. for hydrogen. The analyses reported by Staudinger and Ruzicka for this compound agree (except for one hydrogen determination) with the formula $C_{12}H_{21}N_3O_2$ as found by us. We have not yet prepared pyrethrolone itself, but it is apparent that the analyses reported by Staudinger and Ruzicka for this compound agree best with the formula $C_{11}H_{16}O_2$, although even in this case the hydrogen content reported is lower than would be expected.

The discrepancies between the accepted formulas for pyrethrolone semicarbazone and tetrahydropyrethrolone semicarbazone and the observed analytical results seem to be of great importance in their bearing on the structures of these compounds and hence of the pyrethrins themselves. If pyrethrolone contains two hydrogen atoms less than is now supposed, a revision of its formula, possibly by the assumption of the presence of a second ring structure, will be necessary. Such an assumption would disturb the harmony of the conclusions that have been reached with respect to the part of the pyrethrin molecules that is concerned with pyrethrolone.

EXPERIMENTAL

Pyrethrin II semicarbazone has been prepared by us several times with slight variations in the procedure.

Twenty-four grams of pyrethrin II concentrate containing 81 per cent. of pyrethrin II was dissolved in 80 cc. of 95 per cent. alcohol and 35 cc. of pyridine. A solution of 10 grams of semicarbazide hydrochloride in 12 cc. of water was added. After standing 3 days at room temperature, the solution was diluted with about 3 volumes of water and extracted with ether. The ether solution was washed several times with water, then with dilute hydrochloric acid, and again with water. It was then dried and evaporated on the steam bath. Crystallization began when most of the ether had been removed, and was completed by cooling in the ice box. The crystalline material was removed by filtration and washed by suspending in ether and again filtering. The ether washings together with the first mother liquors were evaporated to a syrup, which readily crystallized, and the separated material was filtered from the syrupy mother liquors with suction on silk. The crystals were washed with ether and dried. Both crops melted at 163–164°. The total yield was 16.5 grams, or 75 per cent. of the theory. The pure compound is very difficultly soluble in ether, but it can be recrystallized by dissolving in a large volume of the solvent and evaporating to a smaller volume. It can be crystallized from 95 per cent. alcohol, in which it is much more soluble. It is still more soluble in the other common solvents.

In another experiment the proportions employed were 45 grams of concentrate containing 79.5 per cent. of pyrethrin II, 150 cc. of 95 per cent. alcohol, 65 cc. of pyridine, 18 grams of semicarbazide hydrochloride, and 20 cc. of water. The yield of material with the same melting point as that from the previous experiment was 33.5 grams, or 81 per cent. of the theoretical 41.3 grams.

In a third experiment 49 grams of pyrethrin II concentrate was dissolved in 175 cc. of 95 per cent. alcohol, 75 cc. of pyridine, and 20 grams of semicarbazide hydrochloride in 25 cc. of water was added. After 2 days most of the solvents were removed by distillation under reduced pressure, and the separated crystal mass was suspended in water and filtered off on suction. The material was washed with water and then suspended in ether; the crystals were filtered off and again washed with the same solvent. The yield of practically pure material was 29.5 grams. The ether mother liquor and washings were washed with water, dilute hydrochloric acid, and again with water, dried, and concentrated to a syrup. The syrup was allowed to crystallize, after which the solid material was removed by filtration with suction on silk. An additional quantity of material was thus obtained, which after washing with ether amounted to 8.9 grams. The total yield was therefore 38.4 grams, or 97 per cent. of the theory.

Crystals are seldom obtained directly from the pyridine-alcohol solution. This sometimes occurs, however, when the concentrate employed is of the order of 85–87 per cent. pyrethrin II. One recrystallization gives an analytically pure product melting at 164–165°.

Anal. Calc'd for $C_{23}H_{33}N_3O_5$: C, 64.03; H, 7.66; N, 9.74.
$C_{23}H_{31}N_3O_5$: C, 64.34; H, 7.27; N, 9.79.
Found: C, 64.19, 64.19, 64.46, 64.40, 64.19; H, 7.51, 7.64, 7.37, 7.40, 7.45; N, 9.85, 9.69.

Pyrethrin II semicarbazone is also obtained from the same concentrates with the employment of sodium acetate instead of pyridine, the preparation having been repeated under the conditions employed by Staudinger and Ruzicka to show that pyridine has no influence on the product obtained. The yield, however, is smaller when sodium acetate is used. Two parallel experiments were made with a concentrate containing 84.1 per cent. of pyrethrin II, pyridine being employed in one and sodium acetate in the other.

Three and three-tenths grams of the concentrate was dissolved in 10 cc. of alcohol and 5 cc. of pyridine, and to this solution 1.2 grams of semicarbazide hydrochloride in 1.5 cc. of water was added. After standing 2 days the solution was diluted with water and the separated material was extracted with ether. The solution was washed with water and dilute acid, dried, and the solvent evaporated. The crystalline material was recrystallized from ether. The yield was 1.6 grams, and the melting point 165°.

Three grams of the same concentrate was dissolved in 10 cc. of alcohol, and solutions of 2 grams of sodium acetate in 1.5 cc. of water and 1.2 grams of semicarbazide hydrochloride in 1.5 cc. of water were added. After 2 days the reaction product was isolated as described above and 0.8 gram of recrystallized material was obtained. It melted likewise at 165°.

Hydrolysis of pyrethrin II semicarbazone.—Two and nine-tenths grams of pyrethrin II semicarbazone was shaken at 100° for 7 hours with a solution of 6 grams of oxalic acid in 40 cc. of water. The reaction product, a dark-red oil, was extracted from the aqueous solution with petroleum ether. A large amount of tar remained undissolved. The petroleum-ether solution was washed first with potassium carbonate solution and then with water, dried, and evaporated. The resulting red oil gave a qualitative test for nitrogen. It was reconverted into the semicarbazone by dissolving in 3.5 cc. of alcohol and 1.5 cc. of pyridine and adding 0.4 gram of semicarbazide hydrochloride in 0.5 cc. of water. After 2 days the reaction mixture was worked up in the manner already described, and gave 0.5 gram of recrystallized semicarbazone, m.p. 163°. When mixed with pyrethrin II semicarbazone (m.p. 165°), the melting point was 163°.

Semicarbazone from the pyrethrin II obtained by molecular distillation.—One and eight-tenths grams of a pyrethrin II preparation that had been twice distilled in the Hickman still,* and which from analysis by the methoxyl method contained 97.7 per cent. of pyrethrin II, was dissolved in 20 cc. of alcohol, and 2.7 cc. of pyridine and a solution of 0.7 gram of semicarbazide hydrochloride in 1 cc. of water was added. After 3 days water was added and the reaction product was extracted with ether. The ether solution, after being washed with acid and water, gave on evaporation 1.2 grams of a colorless syrup. After several days this syrup only partly crystallized, but it was not possible to isolate the crystalline material. It was dissolved in 10 cc. of methyl alcohol to which 6 cc. of a 1 per cent. solution of sodium methylate (1 mol) was added. After about 10 days the small quantity of separated crystals was filtered off and recrystallized from acetone. The quantity of pure substance was about 0.1 gram. It melted at 205° with decomposition, in agreement with the melting point of pyrethrolone semicarbazone. Since this compound is obtained in quantitative yield from the semicarbazone of pyrethrin II under the conditions described, it is apparent that some change has taken place in the process of distillation of pyrethrin II.

Hydrogenation of pyrethrin II semicarbazone.—Two grams of pyrethrin II semicarbazone, m.p. 165°, was hydrogenated with platinum oxide catalyst in ethyl acetate solution. After 15 minutes 205 cc. of hydrogen, corresponding to four atoms, had been absorbed and the reaction had stopped. The solvent was removed under reduced pressure and the residue dissolved in ether. The material obtained after evaporation of the ether crystallized on treatment with dilute ethyl alcohol. The crude product was washed with a little cold dilute potassium carbonate solution and, after drying, was recrystallized by dissolving in 20 parts of warm ethyl alcohol, filtering, and slowly adding 8 to 10 parts of warm water. It melted at 139–140°.

Anal. Calc'd for $C_{23}H_{37}N_3O_5$: C, 63.45; H, 8.50.
$C_{23}H_{35}N_3O_5$: C, 63.74; H, 8.08.
Found: C, 63.43, 63.36; H, 8.14, 8.11.

The same compound was obtained from the hydrogenated pyrethrin II concentrate on treatment with semicarbazide in alcohol-pyridine solution. Two and four-tenths grams of a pyrethrin II concentrate with about 82 per cent. pyrethrin II was hydrogenated with platinum oxide catalyst in ethyl acetate solution. After 45 minutes 322 cc. of hydrogen had been absorbed and the reduced material was separated from the solvent. The material was dissolved in 8.5 cc. of alcohol and 3.6 cc. of pyridine to which 1 gram of semicarbazide hydrochloride in 1.5 cc. of water was added. After standing 2 days the semicarbazone was isolated by means of ether and recrystallized from dilute alcohol. It melted at 141–142°. When mixed with the product obtained by direct hydrogenation of pyrethrin II semicarbazone, the mixture melted at 141–142°. The two substances are therefore identical.

Anal. Calc'd for $C_{23}H_{37}N_3O_5$: C, 63.45; H, 8.50.
$C_{23}H_{35}N_3O_5$: C, 63.74; H, 8.08.
Found: C, 63.72, 63.56, 63.50, 63.33, 63.59; H, 8.10, 8.14, 8.09, 8.12, 8.09.

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* See LaForge and Haller[2].

Saponification of hydrogenated pyrethrin II semicarbazone.—One and two-tenths grams of hydrogenated pyrethrin II semicarbazone was dissolved in 30 cc. of methyl alcohol, and 1 cc. of methyl-alcoholic sodium methylate containing 0.01 gram of sodium was added. After being kept for 12 days in the ice box, the solvent was removed under reduced pressure and the residue washed with ether and then with water. It was recrystallized from ethyl acetate and melted with decomposition at 196°.

Anal. Calc'd for $C_{12}H_{23}N_3O_2$: C, 59.75; H, 9.54.
$C_{12}H_{21}N_3O_2$: C, 60.25; H, 8.78.
Found: C, 60.20, 60.05; H, 8.90, 8.76.

Pyrethrin I semicarbazone.—Fifty-five grams of pyrethrin I concentrate from which pyrethrol had been removed by cooling and filtering on silk, and which contained 45 per cent. of pyrethrin I and about 14 per cent. of pyrethrin II, was dissolved in 190 cc. of alcohol and 83 cc. of pyridine. A solution of 22 grams of semicarbazide hydrochloride in 27 cc. of water was added, and the solution was allowed to stand at room temperature for 24 hours. It was placed in the ice box overnight and the crystallization completed by cooling in a freezing mixture. The crystalline material was removed by filtration and washed with cold alcohol, then with dilute acid, and finally with water. The dried material weighed 32 grams. The alcoholic mother liquor and alcoholic washings were concentrated under reduced pressure, after which water was added, causing the separation of an oily product which partly crystallized on cooling. It was agitated with petroleum ether, which dissolved the liquid products, leaving a crystalline material which was removed and washed with petroleum ether. It weighed 12 grams. The first crop of crystals was recrystallized twice from acetone and once from alcohol and melted at about 112°. The material obtained from the mother liquors has a lower melting point and is very soluble in most reagents. It probably is a mixture of pyrethrin I semicarbazone with the semicarbazone of pyrethrin II and other unknown products.

Concentrates of pyrethrin I obtained from the intermediate fractions resulting from the initial separations contain no pyrethrol and are of a higher pyrethrin I content. The material employed for the two preparations described below contained 57 per cent. of pyrethrin I and 14.8 per cent. of pyrethrin II as shown by analysis.

Thirty-two grams of this material was treated with semicarbazide in the same manner as described above, the proportions of the reagents being: alcohol 112 cc., pyridine 40 cc., semicarbazide hydrochloride 12.8 grams, and water 16 cc. After standing at room temperature for 24 hours, crystallization was completed by cooling in a freezing mixture and the crystals were washed with alcohol, acid, and water. The yield was 24 grams, and 5.7 grams of the impure material was obtained from the mother liquor in the manner already described. This impure substance was dissolved in a small volume of alcohol, out of which 1.3 grams crystallized. It melted at about 105°. The alcoholic solution was evaporated under reduced pressure, leaving a product that was easily soluble in ether but could not be made to crystallize from this solvent. On addition of petroleum ether a crystalline precipitate was obtained which melted at about 70°, and a methoxyl determination indicated that it contained 36.7 per cent. of pyrethrin II semicarbazone. Eighteen grams of pyrethrin I concentrate containing 57 per cent. of pyrethrin I obtained from intermediate fractions was converted into the semicarbazone in the manner just described, the proportions of reagents employed being alcohol 60 cc., pyridine 27 cc., semicarbazide hydrochloride 7.2 grams, and water 9 cc. The yield of crystalline material obtained by direct crystallization, washing, and drying was 13.5 grams, and 2.5 grams was obtained from the mother liquors by treatment with water and petroleum ether.

In all these preparations the total yields of semicarbazones were higher than that calculated from the total pyrethrin content of the concentrates as found by analysis. This indicates that substances other than the pyrethrin semicarbazones are present in the crude crystalline products.

For purification only the material obtained by direct crystallization was employed, and recrystallization was accompanied by considerable losses in the first operations. Usually two recrystallizations from acetone and one from alcohol or toluene gave products melting at 112–114°. By further recrystallization it was possible to raise the melting point to 117–118°. Many analyses of the recrystallized products have been made.

Anal. Calc'd for $C_{22}H_{33}N_3O_3$: C, 68.22; H, 8.53.
Found for material with m.p. 114–115°:
C, 68.33, 68.50; H, 8.33, 8.37; for material with m.p. 113–114°:
C, 68.59, 67.98, 68.58; H, 8.42, 8.17, 8.52.

Quantitative saponification of pyrethrin I semicarbazone.—Since pyrethrin I semicarbazone is the ester of a monocarboxylic acid, it should be possible to determine the quantity of pyrethrin II semicarbazone that might be present by quantitative saponification. Many attempts were made to accomplish this determination.

When samples of the purest material available were saponified by boiling for a few minutes with 0.1*N* alkali and back-titrating with standard acid, values close to theoretical were obtained. When it was found that pyrethrin II semicarbazone required 30 minutes boiling with 0.25*N* alkali for complete saponification and the pyrethrin I semicarbazone samples were treated with 0.25*N* alkali under the same conditions, the values obtained indicated the presence of about 15 per cent. of pyrethrin II semicarbazone. Since the results were not sharp, the figures obtained will be omitted. It is possible that the semicarbazone of some compound other than pyrethrin II, difficult to remove by crystallization, is present in the pyrethrin I semicarbazone preparations.

The great difference in solubility between the semicarbazones of pyrethrin I and pyrethrin II indicates that the latter should be easily eliminated.

Hydrolysis of pyrethrin I semicarbazone.—Three grams of pyrethrin I semicarbazone (m.p. 114°), which had been twice recrystallized from acetone and once from alcohol, was agitated with a solution of 6 grams of oxalic acid in 40 cc. of water at 100° for 7 hours. The red oil was extracted from the aqueous solution with petroleum ether, the petroleum ether solution was washed with sodium carbonate, and the solution dried and evaporated. The material obtained weighed 1.4 grams. It was dissolved in 5 cc. of alcohol and 2 cc. of pyridine, and 0.6 gram of semicarbazide hydrochloride in 0.8 cc. of water was added. After 48 hours the solution was cooled and the crystals were removed and washed with cold alcohol. The yield was 0.9 gram. After recrystallization from acetone, 0.7 gram of crystalline material was obtained. It softened at 114° and melted at 117–118°.

Anal. Calc'd for $C_{22}H_{33}N_3O_3$: C, 68.22; H, 8.53.
Found: C, 68.82, 68.66; H, 8.47, 8.45.

Six grams of the purified semicarbazone of pyrethrin I was agitated for 7 hours with a solution of 9 grams of oxalic acid in 60 cc. of water at 100°. The reaction product, which was isolated and separated from acid constituents, weighed 3.1 grams. It was distilled at 2 mm. pressure. The quantity of material that distilled at 175–180° was 1.1 grams. It was converted into semicarbazone, the proportions of reagents being the same as in other preparations. The yield of crude crystalline product was 0.55 gram, melting at 105–110°. It was recrystallized and melted at 111–112°. No crystalline products could be obtained from the mother liquor. The small yield indicates that part of the material was changed on distillation, yielding products that do not form crystalline semicarbazones.

Anal. Calc'd for $C_{22}H_{33}N_3O_3$: C, 68.22; H, 8.53; N, 10.85.
Found: C, 68.50, 68.53; H, 8.47, 8.45; N, 10.61.

Pyrethrolone semicarbazone by saponification of pyrethrin II semicarbazone.— Twenty-five grams of pure pyrethrin II semicarbazone was dissolved in 100 cc. of methyl alcohol, and 120 cc. of 0.5*N* sodium methylate (1 mol) and 6 cc. of water were added to the cooled solution. After standing for 5 days in the ice box, the solution was decanted from the heavy crystalline crust that had formed. The crystalline material was washed with methyl alcohol and, when dry, weighed 9 grams. The alcoholic solution was concentrated to a small volume under reduced pressure, and water was added, causing the separation of a finely divided solid material. The suspension was extracted with petroleum ether and separated from the solvents by filtration. After drying it was combined with the material deposited from the reaction mixture, and all was recrystallized from methyl alcohol. The recrystallization was accomplished by boiling the finely ground material with about 1 liter of methyl alcohol under reflux, filtering from a fraction of a gram of insoluble material, and concentrating the solution to about 200 cc. The yield of pure material melting at 208° with decomposition was 12.5 grams, or about the theoretical yield. Under the given conditions, the substance separates from methyl alcohol in flat prisms which sometimes are half a centimeter long. It can also be recrystallized from acetone or ethyl acetate, and in both these solvents the compound is difficultly soluble and separates on concentration of the solutions.

Anal. Calc'd for $C_{12}H_{19}N_3O_2$: C, 60.77; H, 8.02.
$C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.24.
Found: C, 61.39, 61.08, 61.21; H, 7.62, 7.52, 7.53.

The aqueous solution obtained on dilution of the concentrated mother liquor was acidified with hydrochloric acid, and the separated acid products were dissolved in ether. The ether solution was dried and evaporated, yielding 9 grams of a mixture of chrysanthemum dicarboxylic acid and its monomethyl ester. These were separated by dissolving the syrupy material in a small volume of chloroform and adding petroleum ether. Chrysanthemum dicarboxylic acid crystallized out on standing. After recrystallization and drying under reduced pressure at 60°, it melted at 168°. The petroleum ether-chloroform solution was evaporated, and the residue, consisting of about 40 per cent. of chrysanthemum dicarboxylic acid and 60 per cent. of chrysanthemum dicarboxylic acid methyl ester as calculated from the methoxyl content, was dissolved in ether and shaken out with the quantity of 1*N* alkali calculated to half-neutralize the dicarboxylic acid. The aqueous solution gave a product that contained 1.27 per cent. of methoxyl corresponding to 11.5 per cent. of chrysanthemum dicarboxylic acid methyl ester and, by difference, 88.5 per cent. of chrysanthemum dicarboxylic acid. The ether solution yielded a product that contained 11.55 per cent. of methoxyl, corresponding to 79 per cent. of chrysanthemum dicarboxylic acid monomethyl ester.

The petroleum-ether solution obtained on extraction of the neutral aqueous suspension yielded on evaporation an oil that distilled under 1 mm. pressure at 100–102°. The yield was 3 grams. It was the dimethyl ester of chrysanthemum dicarboxylic acid.

Anal. Calc'd for $C_{12}H_{18}O_4$: $2CH_3O$, 27.3.
Found: CH_3O, 26.6.

Fifteen grams of pure pyrethrin II semicarbazone was dissolved in 60 cc. of methyl alcohol, the solution was cooled, and to it 36 cc. of 0.5*N* (1 cc. = 0.011 gram Na) sodium methylate (0.5 mol) was added. After standing 3 days in the ice box, the separated pyrethrolone semicarbazone was filtered off. The alcoholic solution was concentrated to a small volume under reduced pressure and diluted with water. The solution together with the suspended crystalline material was extracted with petroleum ether, and the crystalline material was filtered from the solvents and added to the substance that had separated from the reaction mixture. The total yield of dry material was 8.4 grams. It was recrystallized from methyl alcohol. The petroleum-ether washings were dried and evaporated, yielding 6.1 grams of chrysanthemum dicarboxylic acid dimethyl ester. One gram of the mixture of chrysanthemum dicarboxylic acid and its monomethyl ester was obtained on acidification and extraction of the aqueous solution.

Paraphenylphenacyl ester of chrysanthemum acid.—An alcoholic solution of chrysanthemum acid was neutralized with 0.25*N* alcoholic potash and the calculated quantity of paraphenylphenacyl bromide[4] was added. The solution was refluxed for 1 hour, cooled, and then diluted with an equal volume of water. The separated crystalline ester was removed by filtration, washed with water, and dried. The yield was quantitative. The ester was recrystallized from methyl alcohol and melted at 65°.

Anal. Calc'd for $C_{24}H_{26}O_3$: C, 79.56; H, 7.18.
Found: C, 79.21, 78.87; H, 7.16, 7.09.

Di-paraphenylphenacyl ester of chrysanthemum dicarboxylic acid.—The procedure for the preparation of this ester was the same as that described for the preparation of the ester of the monocarboxylic acid. The ester was recrystallized from toluene or acetone and melted at 154°.

Anal. Calc'd for $C_{38}H_{34}O_6$: C, 77.82; H, 5.80.
Found: C, 77.16, 77.98; H, 5.88, 5.82.

Pyrethrolone semicarbazone by saponification of pyrethrin I semicarbazone.—Three grams of pyrethrin I semicarbazone, m.p. 117°, was dissolved in 80 cc. of methyl alcohol, the solution was cooled, and 6 cc. of methyl-alcoholic sodium methylate containing 0.06 gram of sodium (1 mol) was added. After being kept in the ice box for about 2 weeks, the crystalline material was removed by filtration, and, when dried, weighed 1.1 grams. It was recrystallized by dissolving in a large volume of acetone and concentrating the solution to about 60 cc. The dried crystals melted with decomposition at 210°. A mixture with an equal part of the product obtained from the semicarbazone of pyrethrin II, showed no depression in the melting point.

Anal. Calc'd for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.24.
Found: C, 61.14, 60.77, 61.21, 60.89, 61.48;
H, 7.26, 7.16, 7.38, 7.35, 7.41.

The alcoholic mother liquor yielded, on dilution with water, an additional small quantity of crystalline material and, on acidification and extraction with petroleum ether, chrysanthemum acid.

Hydrogenation of pyrethrolone semicarbazone.—One gram of pyrethrolone semicarbazone was dissolved in about 100 cc. of a mixture of ethyl acetate and methyl alcohol and reduced with 0.2 gram of platinum oxide catalyst. After 30 minutes 200 cc. of hydrogen had been absorbed, corresponding to the saturation of two double bonds. The solution was filtered and concentrated on the steam bath and readily

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[4] DRAKE, N. L., AND BRONITSKY, J., *J. Am. Chem. Soc.*, **52**, 3715 (1930).

yielded the crystalline reaction product. It melted with decomposition at 196°. It was identical with the compound obtained on saponification of hydrogenated pyrethrin II semicarbazone, as was shown by the mixed melting point 196°. Tetrahydropyrethrolone semicarbazone is reported to melt at 190°. The yield was quantitative.

Anal. Calc'd for $C_{12}H_{23}N_3O_2$: C, 59.75; H, 9.54.
$C_{12}H_{21}N_3O_2$: C, 60.25; H, 8.78.
Found: C, 60.50, 60.65; H, 9.14, 8.69.

SUMMARY

The semicarbazone of pyrethrin II has been prepared from the pyrethrin II concentrate obtained by fractionation with immiscible solvents. It is easily obtained pure and melts at 165°. On hydrogenation it yields tetrahydropyrethrin II semicarbazone, which has the formula $C_{23}H_{35}N_3O_5$.

Pyrethrin II obtained by molecular distillation does not yield this semicarbazone, indicating that distillation produces some intramolecular change.

Hydrolysis of the semicarbazone with oxalic acid solution yields unchanged pyrethrin II, which can be reconverted into the original semicarbazone.

The semicarbazone of pyrethrin I has not been obtained in analytically pure condition. By repeated crystallization a nearly pure preparation melting at 118° is obtained. The semicarbazone of pyrethrin I yields on hydrolysis with oxalic acid substantially unchanged pyrethrin I, which can be reconverted into the original semicarbazone.

Pyrethrin I is in part altered by distillation.

The semicarbazones of both pyrethrins yield the same pyrethrolone semicarbazone on saponification. Pyrethrolone semicarbazone appears from a large number of analyses to have the formula $C_{12}H_{17}N_3O_2$ instead of $C_{12}H_{19}N_3O_2$.

On hydrogenation of pyrethrolone semicarbazone, four atoms of hydrogen are absorbed and the resulting tetrahydropyrethrolone semicarbazone would be represented by the formula $C_{12}H_{21}N_3O_2$. The same compound is obtained by saponification of tetrahydropyrethrin II semicarbazone.

Chrysanthemum monocarboxylic acid and chrysanthemum dicarboxylic acid form crystalline paraphenylphenacyl esters, which serve for their isolation and identification.

[Contribution from the George Herbert Jones Chemical Laboratory, The University of Chicago]

SOME RELATIONS OF CARBON AND ITS COMPOUNDS*

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1. INTRODUCTION

The purpose of this paper is to present a few topics, related to organic chemistry, which have come, more or less intimately, into the work of the author. This has involved the following subjects related to carbon and its compounds: (1) the nuclear chemistry of carbon, (2) free radicals of short life and the organic chemistry of electrical discharges, (3) the synthesis of dyes and explosives, (4) plastics, and (5) the applications of surface chemistry in organic chemistry, and of organic chemistry in surface chemistry.

From these the first, second, and fifth topics have been chosen as illustrating best the applications of physical chemistry.

2. NUCLEUS OF THE CARBON ATOM

Carbon is element six in the periodic system of the electronic region of the atoms, and also in the very different periodic system of atomic nuclei. From the standpoint of theory this is expressed by the statement that there are six negative electrons in the non-nuclear, presumably outer, part of the atom, and an equal, but positive charge, on the nucleus, or massive part, of the atom. Since neutrons are without any outer electronic system, and thus consist of non-charged atomic nuclei, the element, neutron, is designated by the atomic number, zero. Thus carbon is now the seventh element of the system, but with the number six.

Carbon contains two known stable isotopes: about 99.3% of isotopic number zero and atomic mass 12.0035 ± 0.0003 together with about 0.07% of isotopic number 1, and atomic mass 13.0073. In addition there is a radioactive isotope of mass 11.0143, formed by the reaction of a proton with boron of mass 11.0128 and the release of a neutron, or of a deuteron on boron of mass 10, with release of a neutron. The radioactive isotope liberates a positive electron and changes into boron of mass 11.0128.

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* This paper was submitted in response to the invitation of the Editors.

The nucleus of the ordinary carbon atom of mass 12.0035 may be considered to consist of six neutrons and six protons. These are arranged in the form of 3 alpha particles or helium nuclei, which however, lose a part of their identity. This nucleus is one of the most stable of known nuclei, in the sense that it does not readily undergo a nuclear reaction. However, it reacts with deuterium (H^2) to give a neutron and a radioactive species of nitrogen (N^{*13}) as follows:

$$ {}^{0}_{6}C^{12} + {}^{0}_{1}H^{2} \rightarrow {}^{0}_{7}N^{14} \rightarrow {}^{-1}_{7}N^{*13} + {}^{+1}_{0}n^{1} $$

TABLE I

Isotopic Composition of Elements Whose Natural Isotopes Are Found in Organic Compounds

SYMBOL	ATOMIC NUMBER	ISOTOPIC NUMBER	MASS NUMBER	RELATIVE ABUNDANCE	HALF LIFE	ELECTRON EMITTED
H	1	−1	1	99.98		
D		0	2	.02		
T		1	3	7×10^{-8}		
C	6	−1	11	—	20.5 min.	+
		0	12	99.3		
		1	13	0.7		
N	7	−1	13	—	10.7 min.	+
		0	14	99.62		
		1	15	0.38		
		2	16			
O	8	−1	15	—	126 sec.	+
		0	16	99.76		
		1	17	0.04		
		2	18	0.20		
S	16	0	32	*96*		
		1	33	*1*		
		2	34	*3*		
Cl	17	1	35	76		
		2	36	—	35 min.	−
		3	37	24		
Br	35	9	79	50		
		11	81	50	(Note)	
I	53	21	127	100		
			128	—	25 min.	−

Note: Bromine isotopes of half-periods 18 minutes, 4.2 hours, and 30 hours have been described.

This disintegrates, with a half period of 10.5 minutes, to give a positive electron and carbon of mass 13.

$$^{-1}_{\ 7}N^{*13} \rightarrow {}^{+1}_{\ 6}C^{13} + {}^{-2}E^{+}$$

Here the subscript is the atomic number (Z) and the superscripts are the isotopic number (I) and the atomic mass (M). The general formula of any nucleus is $(np)_Z n_I$ in which n is a neutron and p a proton.

The values, $Z = 6, I = 0$, designate the ordinary carbon isotope of mass twelve, while $Z = 6, I = 1$ represents the less abundant isotope of mass 13.

These isotopes differ only very slightly in their chemical properties.

The isotopic composition of a number of elements common in organic compounds is listed in Table I.

3. ISOTOPIC ORGANIC MOLECULES

Since there are two stable isotopes of carbon and three of hydrogen the number of isotopes of organic molecules is very large. Thus for even so simple a compound as methane there are 30 isotopes, though only 10 if merely protium and deuterium are considered. There are 537 isotopes of hexane, or 91 for the two most abundant hydrogen isotopes. The corresponding numbers for benzene are 196 or 49, and for dichloroethane 120 or 45.

If there are e elements in the compound molecules, and n atoms of any element, and i isotopes of the element, then the number of molecular isotopes is given by the formula of Mulliken and Harkins as:

$$\frac{(n' + i' - 1)!\,(n'' + i'' - 1)!\,(n''' + i''' - 1)! \cdots (n^e + i^e - 1)!}{n'!\,n''!\,n'''! \cdots n^e!\,(i' - 1)!\,(i'' - 1)!\,(i''' - 1)! \cdots (i^e - 1)!}$$

This does not include isomerism. It is evident that the number of isomeric-isotopes is extremely large except in the simpler organic molecules.

New optical isomers are possible as a result of isotopism in so far as differences of mass and nuclear spin are able to make the molecule asymmetric.

4. THE ORGANIC CHEMISTRY OF ELECTRICAL DISCHARGES AND ELECTRON BEAMS

By the use of electrical discharges of various types through organic vapors, or of electron beams through vapors, liquids, or solids, it is possible to obtain organic reactions of varied types.

Thus, with electrodeless discharges of 600 kilocycles frequency, it was found that one thousand liters of benzene vapor per hour at 0.25 mm. pressure could be decomposed and resynthesized in a one-liter flask. The product is a reddish-brown solid, insoluble in organic solvents, and evidently of very high molecular weight, with exactly the same elementary composition as benzene $(CH)_n$.

The spectrum of an electrodeless or glow discharge or an electron beam through an organic vapor exhibits a number of emission bands which reveal the presence of diatomic molecules of abnormal valence. Thus, if the organic vapor is a hydrocarbon, molecules, or free radicals of short life, of methine or monohydrocarbon (CH), and dicarbon (C_2), are revealed, together with free atoms of carbon (C), and of hydrogen (H), together with positive ions of carbon (C^+). While the spectrum does not reveal them, both dissociated and ionized forms of the initial organic molecules are also present. Such a gaseous mixture is extremely reactive as is made evident by the experiment with benzene vapor.

If oxygen is present, hydroxyl bands and carbon monoxide bands reveal the presence of these molecules, (OH and CO) and water separates as such, while with nitrogen, inimine (NH), and cyanogen (CN) radicals appear, together with N_2 and N_2^+.

The changes outlined above represent the dissociation of the organic molecules into fragments which are free radicals, atomic or molecular ions, and uncharged atoms.

If the frequency of the electrodeless discharge is increased, the energy lessened, or with electron beams, if the velocity is sufficiently decreased, much milder changes may be induced.

Thus it seems that by electron collisions an electron, a proton, a methyl group, etc. may be removed from a molecule and leave the remainder of the molecule unchanged in composition. In some instances the composition of the whole molecule is not changed but a double bond is shifted from one position to another.

The energy of an electron which could excite a wave-length of 3000 Å is 6.55×10^{-12} ergs or 4.12 electron volts (e.v.) per photon. At 2600 Å the energy would be 4.75 e.v.

The action of electrons on molecules is much less specific than that of a particular wave-length of light. The moving electrons can affect many more electrons in the molecule, and their action is more specifically upon the electrons in the molecule than upon the molecule as a whole, but they may incite a rearrangement of the atoms in the molecule, and it seems that they are efficient in the production of dissociation.

Positive or negative ions produced in the discharge have in impacts a more specific action on the atoms than on the electrons. They possess a potential energy different from that of the neutral atoms, and may give off or receive energy on this account. Ions may affect electronic motions in molecules which they strike but with a very much smaller efficiency than electrons.

The chemical effects of electrodeless and glow discharges between electrodes are different in many respects. Thus benzene in a glow discharge polymerized rapidly to give a white deposit, probably dihydrodiphenyl, approximately 10 molecules of benzene being removed by each equivalent of current. This can be accounted for by a chain mechanism initiated by radicals formed in an amount proportional to the current, although it is not improbable that some of the faster electrons formed more than one radical.

Brewer and Kueck[1] find that ethylene is quantitatively converted into methane and hydrogen in a D.C. glow discharge when the tube is immersed in liquid air. They consider the reaction to be

$$CH_4^+ + CH_4 \rightarrow C_2H_4^+ + 2H_2$$

and that the ethylene ion is subsequently neutralized in a wall reaction.

In the electrodeless discharge there are two electrical fields, one an alternating electrical field, parallel to the axis of the solenoid, and the other an electromagnetic field whose electrical energy is in rings perpendicular to the axis of the solenoid. Both fields may play a part in the discharge reaction, but the electromagnetic field must be most important in the initial ring discharge, and the electrostatic field parallel to the axis most important in the glow which comes later. The pulsating D.C. electrostatic field between the electrodes in the glow discharge is comparable to the field responsible for the glow in the electrodeless discharge.

The differences between the reactions in the two discharges, which are shown by differences in their spectra and products, must depend on the differences in pressure and electrical fields. For instance, it is conceivable that more collisions favorable for the combination of hydrogen atoms into molecules take place at the higher pressure in the glow discharge than in the electrodeless discharge, thus accounting for the appearance of the many-line spectrum of hydrogen in the glow discharge. The Baldet-Johnson high-pressure bands of CO^+ may appear in the one rather than the other, not only on account of the difference of pressure but also because of a difference in electron energy, since energies of the order of one hundred electron volts are required for the appearance of these bands.

Tables II and III give the colors of the discharges and of the solid products for certain electrodeless and glow discharges.

Since many of the intermediate products in electrical discharges are free radicals of short life, the discussion will be continued under this topic.

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[1] BREWER AND KUECK, *J. Phys. Chem.*, **35**, 1293 (1931).

5. FREE RADICALS OF SHORT LIFE

Free radicals were defined by Wieland[2] in 1915 as atomic complexes of abnormal valency which have additive properties, but do not carry an electrical charge and are therefore not free ions.

Most free radicals, which are considered in discussions of the subject, possess one unsatisfied valency.

"In chemistry it is customary to call a structure a free radical only when it saturates its valences with energies of the order of magnitude of that of an ordinary chemical reaction."[3]

Schlenk[4] considers molecules which contain an odd number of electrons (odd molecules) as free radicals. Such a definition is, on the whole, a good one, but there are exceptions such as the CH_2 radical, which may be an "even" molecule, found by positive ray methods. Also many chemists dislike to class odd molecules such as NO, NO_2, ClO_2, H_2PO_3, as free radicals.

The latter definition, however, suggests one of the most important physical methods which may be used in the study of the nature of sufficiently stable free radicals; that is, a determination of the magnetic susceptibility of the material.

The molecular mass susceptibility of a substance, which is not ferromagnetic, may be expressed as the sum of three terms:

$$\chi_M = \chi_d + \chi_\mu + \chi_r,$$

where χ_d is the diamagnetic portion due to the disturbance of the electron orbits by the field, and ranges from -1.88×10^5 for helium to a negative value of a few hundred units for substances which consist of complex organic molecules. For organic molecules in general χ_M is zero, and χ_r is small, so $\chi_\mu \approx \chi_M$.

In the case of odd molecules, however, the molecule possesses a permanent magnetic moment μ which gives rise to a large positive term χ_μ which accompanies paramagnetism. The magnetic moment is determined by the resultant angular momentum of all of the electrons. It has been shown[5] that χ_μ is determined mostly by the net spin S of the molecule, and that the approximate relation is

$$\chi_\mu = 1.242 \times 10^5 \frac{S(S+1)}{T} \qquad (1)$$

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[2] Wieland, *Ber.*, **48**, 1098 (1915).

[3] W. Steiner, "Free Radicals, a General Discussion." The Faraday Society, **1933**, p. 39.

[4] Schlenk, "4th. Cons. Chim. Solvay," **1931**, p. 503.

[5] van Vleck, "The Theory of Electric and Magnetic Susceptibilities." Oxford University Press, **1932**.

In an odd molecule, if only one electron is unbalanced, $S = \frac{1}{2}$ and at 20°C. the value of χ_μ is $+1270$, which is much larger than χ_d, and of the opposite sign. From (1) χ_μ should vary inversely as the absolute temperature as is specified by Curie's law.

The values of χ_μ for a few substances, whose molecules are free radicals, are shown in Table II.

Methine, or monohydrocarbon, CH.—The blue color of an electrical discharge through an organic vapor is due in part to bands at 3900 Å and 4300 Å, found by Mulliken to be due to the neutral CH molecule with an electronic state of the doublet type $^2\Pi$ which indicates that the emitter has an odd electron.

The general appearance of the spectrum given by the decomposition products of benzene in the region of the 4300 band of CH is shown in Fig. 1, which exhibits the double lines characteristic of these bands, and of hydroxyl (OH) bands also. The structure of these bands is very beautiful.

TABLE II

VALUES OF χ_μ THE PARAMAGNETIC TERM, IN THE MAGNETIC SUSCEPTIBILITY OF FREE RADICALS IN UNITS OF 10^5

SUBSTANCE	t	$\chi_\mu \times 10^{-5}$	STATE
α-Naphthlydiphenylmethyl	20	570	In 7% benzene solution
$C_{18}H_{21}O_2N_2$	17	1293	Solid
	17	1109	In 20% benzene solution
Potassium benzophenone	24	1050	In 15% dioxane solution
Potassium phenyl-*p*-biphenylketone	24	1080	In 17% dioxane solution

It is assumed that the CH radical is also formed by the direct photodissociation of acetylene according to the reaction:

$$HC \equiv CH + h\nu \rightarrow 2CH$$

A number of workers have found series of absorption bands in the region between 1900 Å and 2400 Å which they attribute to methine.

According to a summary by Norrish,[6] the dissociation of the first hydrogen atom from CH_4 requires an energy of about 102 kcal., that which involves the change from CH_3 to CH_2 only 55 kcal., from $CH_2 \rightarrow CH \rightarrow C$, a heat for the two steps (Mecke) of 215 kcal., while the average energy of linkage is usually given as about 100 kcal. The accuracy of these values is low.

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[6] NORRISH, "Free Radicals, a General Discussion." The Faraday Society, **1933**, p. 110.

Hydroxyl, OH.—The hydroxyl (OH) molecule, in the doublet $^2\Pi$ state, with an odd electron, is one of the most generally found free radicals of short life, and occurs not only in practically all electrical discharges, where water is present even in minute quantities, but also in flames in which organic substances (or hydrogen) burn in a gas that contains oxygen. In general the hydroxyl bands occur when an electrical discharge is passed through an organic substance whose molecules contain oxygen, but there is some evidence that in some such vapors a mild discharge, presumably one in which the energy of the electrons is low, may pass without an excitation of even the 3064 Å band.

Of all of the water bands, that at 3064 Å is by far the most prominent and the most easily excited but others are found at 3122, 2811, 2875, and 2608 Å. To the eye the bands, like those of CH, seem to consist of double lines. Actually all three of the branches P, Q, and R, are doubled, and for low values of m the doublets are widely separated. This band appears in the emission spectra of both electrical discharges and flames. According to Bonhoeffer and Pearson,[7] the life of this radical is short (of the order of 10^{-3} seconds), much shorter than that of atoms of hydrogen or oxygen. In water vapor the hydroxyl molecules seem to be removed by the reaction

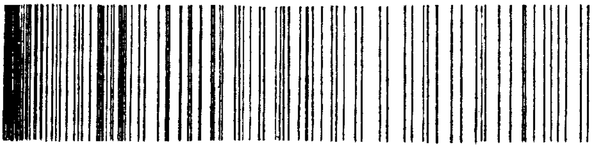

FIG. 1

$$2OH \rightarrow H_2O + O$$

with very little if any production of hydrogen peroxide. The reaction is that found when hydroxyl is discharged at an anode in an aqueous solution.

Cyanogen, CN.—The cyanogen molecule is probably in the doublet state $^2\Sigma^+$ which indicates the presence of an odd electron. The emission bands given off by cyanogen are prominent in electrical discharges through organic vapors that contain nitrogen.

Dicarbon, C_2.—The dicarbon molecule is probably in the triplet state $^3\Pi_\mu$ which indicates a valence of two.

The emission bands given off by C_2 molecules in excited states are in general very prominent indeed in electrical discharges through organic

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[7] BONHOEFFER AND PEARSON, *Z. physik. Chem.*, **139**, 75 (1928).

vapors, though, as mentioned elsewhere, certain discharges of low electronic energy give no emission bands at all that can be detected.

The decomposition spectrum of benzene often shows all five groups of the Swan bands of C_2 very prominently, while the bands of D'Azambuja are present at λ 4102, 4068, 4041, 3852, 3826, 3607, 3593, 3588, 3400, and 3398, though these are faint.

Methylene, CH_2.—The methylene CH_2 molecule gives no emission bands. It is in a singlet state ($^1A_1$) and thus has a zero valence so that it needs to be activated in order to become reactive. Its state is similar to that of the H_2O^{++} ion. The first excited state of methylene is a triplet state ($^3B_1$) which indicates a valence of two. Since methylene in the normal state is not reactive, and is not paramagnetic, it is often considered that it should not be classed as a free radical, but only as a molecule.

Polyatomic Ions as Revealed by Positive Rays.—While, in general, the emission band spectra of organic vapors reveal no radicals more complicated than those that are diatomic, possibly because these are the only ones that are excited in sufficient quantities, the existence of more complicated groups is demonstrated by the positive ray method.

Methyl, CH_3, and Ethyl, C_2H_5.—The methyl molecule is probably in the pyramidal form, and if so is in the doublet ($^2A_1$) state, with an odd electron, so it should be very much more reactive than CH_2.

None of these polyatomic radicals is revealed by emission spectra, but the corresponding positive ions are formed in positive rays.

Either methyl or ethyl is formed easily by heating the appropriate lead tetraälkyl in a stream of hydrogen or nitrogen.[8,9]

The half-life of the methyl radical found experimentally was 5.8×10^{-3} seconds, and that of ethyl 3.9×10^{-3}.

These radicals stick to metals like lead, bismuth, and zinc, and react as follows:

$$Zn + 2CH_3 \rightarrow Zn(CH_3)_2$$

Every radical which strikes a metal surface is held, but only one in a thousand on glass or quartz. On surfaces with which methyl or ethyl do not react, higher hydrocarbons are formed.

The positive ray parabola method as used by Conrad[10] with vapors of benzene, cyclohexane, and hexane, indicates groups with 1, 2, 3, 4, 5, and 6 carbon atoms in each case. In benzene, four lines of about equal intensity appear for C_3, C_3H, C_3H_2, C_3H_3, while C_3H_4 is indicated faintly and the higher hydrides, C_3H_5, C_3H_6, etc. are absent. With hexane and

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[8] F. Paneth and W. Hofditz, *Ber.*, **62**, 1335 (1929).

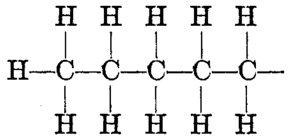
[9] F. Paneth and W. Lautsch, *ibid.*, **64**, 2702 (1931).

[10] Conrad, "Free Radicals, a General Discussion." The Faraday Society, **1933**, p. 215.

cyclohexane, however, the same first four lines are strong, that for C_3H_4 weak, but then there is a strong C_3H_5 line, a weak C_2H_6 line, and finally, in cyclohexane, two weak lines for C_3H_7, and C_3H_8, while for hexane C_3H_7 is strong and C_3H_8 weak. Somewhat similar relations are found for C_4 and C_5.

In the case of the C_5 group from hexane, Conrad assumes that the highest mass, 71, corresponds to a radical formed by breaking CH_3 from hexane, or

71

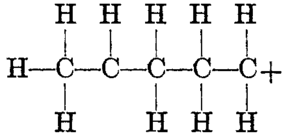


$$H-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-$$

Stable as a positive ion

This is detected, however, as a positive ion; that is, one electron, presumably the valence electron, is missing; the binding electron is gone, and a saturated compound has been formed. If, however, a fourth hydrogen atom is torn out, the ion

70



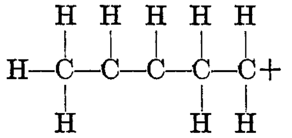
$$H-\underset{H}{\overset{H}{C}}-\overset{H}{C}-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}+$$

Free valency and so a radical and unstable

which is also a radical, is formed. Many particles of mass 71 are found, but only a few of mass 70. That is, 71 remains but 70 is used up.

Mass 69 appears in large quantities, which indicates stability.

69



$$H-\underset{H}{\overset{H}{C}}-\overset{H}{C}-\overset{H}{C}-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}+$$

Stable

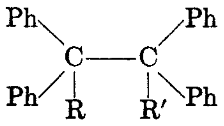
The two valences gained by removing two hydrogen atoms give a double bond.

It is at once seen that the mass 68 is again less stable.

The relations are different with benzene, since, if the ring is broken at one point, no stable configuration is at first possible.

6. FREE RADICALS OF LONG LIFE

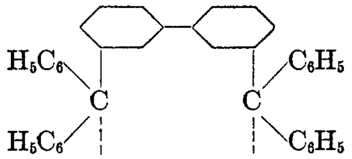
The general discussion of free radicals of long life will be left to the organic chemists. However, a few relations will be mentioned. In the molecule



a splitting into free radicals occurs more readily if R, and R′ are phenyl than if they are ethyl groups. According to Hückel resonance of the free electron of the radical $(C_6H_5)_3C$ with the double bonds of the phenyl groups increases the stability of the radical, since, in a certain sense, the electron disappears in the phenyl groups. According to Ziegler the size of the substituents is extremely important. Thus, very large groups surround the methyl carbon atom and keep it from uniting readily with other radicals.

In recent years a number of organic compounds have been considered as double radicals, on the basis of their high reactivity and intense coloration. These materials exhibit a normal molecular weight instead of the abnormal values of the ordinary free radicals.

This problem has been investigated by Müller and Müller-Rodloff[11] who conclude on the basis of measurements of magnetic susceptibility that Schlenk's hydrocarbon *m,m′*-biphenylene-bis-(diphenylmethyl)



which cannot go over into a valence-tautomeric chinoid system, is a true double radical.

At 74° the molecular magnetic susceptibility of a 9 per cent solution in benzol, $\chi_{\text{mol.}}$ was found to be -320 ± 20 and the difference, $\chi_{\text{mol., calc'd}} - \chi_{\text{mol., exp't'l}}$, *ca.* 290, which is much greater than the limit of error and corresponds to a radical content of 6 ± 2 per cent. The behavior is entirely analogous to that of triphenylmethyl. The color of the solution is light yellow at room temperatures, but dark orange yellow at 74°.

All of the other molecules assumed to be double radicals failed to exhibit this in the magnetic effects.

These investigators consider that true double radicals can exist only if the following conditions are fulfilled:

(1) If there is no possibility of intramolecular stabilization, such as may occur in other derivatives.

(2) If there is no possibility of a change into a valence-tautomeric chinoid system, as in para derivatives.

Schönberg[12] believes, however, that in light the equilibrium is shifted toward the double radical, as in solutions of rubrene, derivatives of anthracene, etc.

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[11] E. Müller and I. Müller-Rodloff, *Ann.*, **517**, 144 (1935).

[12] A. Schönberg, *Trans. Faraday Soc.*, **32**, 514 (1936).

DISCUSSION

The facts presented in this paper indicate that free radicals of short life are formed in great numbers in electrical discharges of all types. It is much more difficult to regulate the discharge in such a way that large molecules are only slightly affected, as by the removal of only one or two hydrogen atoms, and the formation and shift of double bonds, than to produce many diatomic radicals. In silent and semi-corona discharges, Lind and Glockler[13] found that the lower saturated hydrocarbons and ethylene were condensed, with the liberation of hydrogen and ethane, into products which are largely liquid, while the corona discharge yields as much resinous as liquid product. With alpha rays, gaseous, liquid, and solid condensation products were formed. In electrodeless discharges solids alone may be produced with certain types of discharge.

It is often assumed (Bone, Rice, etc.) that many organic substances are dissociated thermally in such a way as to give free radicals, which then react, often by chain mechanisms. Rice assumes that the primary action is a dissociation into two radicals by a rupture of a C—C bond, since this is weaker than a C—H bond. In the range of temperatures between 700 and 1100°C. the chief dissociation product that has been recognized is the methyl radical.

Free methyl and ethyl have been obtained in the gaseous reactions between alkyl halides and sodium vapor (Polyani), and benzyl—as well as methyl and ethyl—has been obtained by Paneth from the metal alkyls by thermal dissociation. With arsenic, antimony, or bismuth, either methyl or ethyl gives a number of different alkyl derivatives. The larger radicals, propyl, butyl, etc. are too short in life to be detected by the means employed up to the present time.

Many photochemically sensitive molecules in gases give continuous absorption spectra; others give a few discontinuous bands on a continuous background, while a few, such as benzene exhibit a discontinuous spectrum. A continuous spectrum indicates that the primary process is one of dissociation into radicals, or into radicals and free atoms. The lapse of time between absorption and dissociation is of the order of 10^{-13} seconds for continuous spectra to 10^{-10} in some predissociation cases. Free radicals and atoms are the most important agencies in the propagation of chain reactions, but excited molecules and atoms also play an important part.[14]

In solution the probability of photochemical reactions resulting from excited particles is increased, and that from free radicals decreased so far as the primary stage is concerned. However, since the excited molecules

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[13] LIND AND GLOCKLER, *J. Am. Chem. Soc.*, **50**, 1767 (1928); **51**, 2811, 3655 (1929).

[14] J. FRANCK AND E. RABINOWITSCH, "Free Radicals, a General Discussion." The Faraday Society, **1933**, p. 120.

are very rapidly deactivated by the molecules of the solvent, free radicals and atoms are almost the only instigators of chain reactions.

It is evident to the student of these subjects that the organic chemistry of electrical discharges, and the chemistry of organic radicals are as yet only in the stage of a preliminary development, and that both of these related fields are fertile for future discoveries by those who are well trained in both physical and organic chemistry. While all possible methods of experiment should be utilized, no established method gives more promise than that of positive rays.

The methods of research utilized by organic chemists are very different from those applied by physical chemists. One of the most urgent needs of organic chemistry at the present time is that some of the workers in this field be first-class scientists in both fields. It may be said that the world is almost entirely without individuals of this class. The universities should be given unfavorable criticism for their failure to train at least a few men, who as organic chemists, are also high-grade physical chemists and physicists.

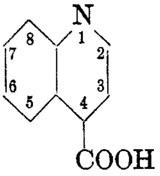
[Contribution from the Chemical Laboratories of Columbia University]

THE SYNTHESIS OF SUBSTITUTED 5,6-BENZOCINCHONINIC ACIDS BY THE DOEBNER AND BY THE PFITZINGER REACTIONS*

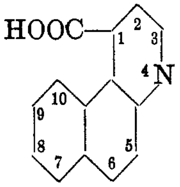
EDWIN ALLIN ROBINSON† and MARSTON TAYLOR BOGERT

Received February 15, 1936

In view of the rather widespread use to which cinchoninic acid (I) derivatives have been put, to increase the excretion of uric acid in the urine in gout and rheumatic fevers, as well as in the treatment of other diseases because of their claimed analgesic, antipyretic, and antiseptic properties, it seemed desirable to study the benzocinchoninic acid group more fully, in the hope that there might be discovered therein some derivatives which retain the beneficial properties of the simple cinchoninic acids and are free from their objectionable ones.



I



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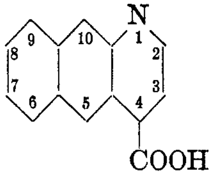

III

For the synthesis of such acids, we had recourse to both the Doebner and the Pfitzinger reactions.

In the familiar Doebner reaction, when a primary aromatic amine, an aldehyde, and a pyruvic acid, interact in a suitable neutral menstruum, the products formed vary not only with the nature of the initial materials, but also with the solvent, its temperature, and the duration of the reaction. Conspicuous among these products are the cinchoninic acids. The mechanism of the reaction has been the topic of many papers and is still under discussion. It is not our purpose to review the subject here.

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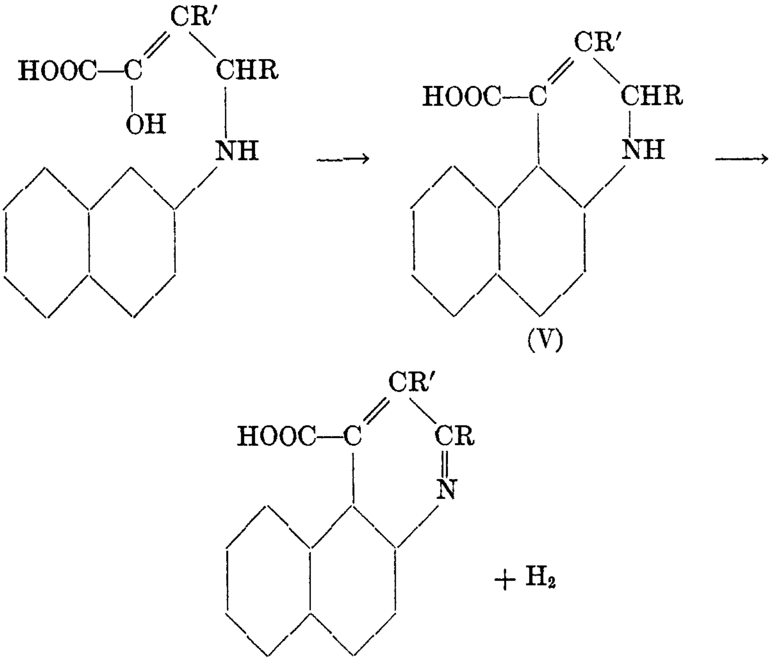
* Based upon the dissertation submitted by Mr. Robinson, May, 1933, for the Ph.D. degree under the Faculty of Pure Science, Columbia University, New York, N. Y., to which dissertation the reader is referred for further experimental details and literature citations.—M. T. B.

† DuPont Fellow at Columbia University, 1932–1933.

In the experiments described beyond, the amine used was 2-naphthylamine; the aldehydes were formaldehyde, acetaldehyde, benzaldehyde, *p*-anisaldehyde, and piperonal; the acids, pyruvic and benzoylpyruvic; and the solvent, boiling ethyl alcohol. The results are in favor of the assumption that, under the conditions employed by us, the principal course of the reaction was probably as follows:

$$C_{10}H_7NH_2 + \underset{\rightarrow}{OCHR} \rightarrow \underset{(IV)}{C_{10}H_7N{=}CHR} + \underset{\rightarrow}{R'CH_2COCOOH}$$

$$C_{10}H_7NHCHRCHR'COCOOH \rightleftarrows$$



(V)

(VI)

$$C_{10}H_7N{=}CHR + H_2 \rightarrow C_{10}C_7NHCH_2R$$

The oxidation of the supposititious intermediate dihydrocinchoninic (V) to the cinchoninic acid (VI) appears to be at the expense of the anil (IV) which is compensatingly reduced to the dihydroanil. Hence, increasing the proportion of anil present increased the yield of the cinchoninic acid. This is in entire agreement with the conclusions of Ciusa and Musajo.[1]

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[1] Ciusa and Musajo, *Gazz. chim. ital.*, **59**, 796 (1929).

It is obvious that, in the application of this reaction to 2-naphthylamine, the cyclization may result in either the 5,6- (II), or the 6,7-benzocinchoninic acids (III).

Previous investigators in this field have shown, mostly by the removal of the carbon dioxide from these benzocinchoninic acids and oxidation of the resultant benzoquinolines, that the acids are evidently of type (II). Our own experiments corroborate this conclusion, for by the simple Pfitzinger reaction, using 2-amino-1-naphthaleneglyoxylic acid (from β-naphthisatin) and substituted acetophenones, we have prepared 3-R-5,6-benzocinchoninic acids identical with those obtained by the Doebner method from pyruvic acid, 2-naphthylamine and the appropriate aldehyde, since both series of products, on decarboxylation, yielded the same 3-R-5,6-benzoquinolines.

Our studies were concerned chiefly with the products of the interaction of benzoylpyruvic acid, 2-naphthylamine and the aldehydes mentioned. The only previous work we found in this field was that of Borsche,[2] who condensed benzoylpyruvic acid and 2-naphthylamine with formaldehyde and with benzaldehyde. His benzocinchoninic acids, however, were neither purified nor analyzed, but were converted directly into the corresponding 2-benzoyl-3-R-5,6-benzoquinolines by heating above their melting points. Further, none of the by-products were isolated.

The 2-benzoyl-3-R-5,6-benzocinchoninic acids prepared by us were purified without difficulty, and were characterized by their properties and analyses, by their conversion into the corresponding 2-benzoyl-3-R-5,6-benzoquinolines when heated alone, and into the 3-R-5,6-benzoquinolines when distilled with caustic soda; by the analysis of the resultant 2-benzoyl-3-R-5,6-benzoquinolines, their picrates and oximes, as well as of the 3-R-5,6-benzoquinolines and their picrates.

The formation of 3-R-5,6-benzoquinolines from the 2-benzoyl-3-R-5,6-benzocinchoninic acids is evidence that the benzoyl group in the latter is attached as a side-chain to the benzocinchoninic acid nucleus, and benzoic acid was separated as the by-product.

Dihydroanils were isolated and identified as by-products in these Doebner reactions, but no tetrahydrobenzocinchoninic acids were encountered.

By the action of thionyl chloride, the benzoyl benzocinchoninic acids were changed to the acid chlorides, and from the latter the esters were prepared.

Attempts to prepare these benzoylbenzocinchoninic acids by the Pfitzinger reaction, from β-naphthisatin and dibenzoylmethane, were defeated by the hydrolysis of the latter during the reaction.

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[2] BORSCHE, *Ber.*, **42**, 4072 (1909).

EXPERIMENTAL

Unless otherwise stated, all the melting points determined by us are corrected and were read while raising the temperature of the bath at the rate of approximately 3° per minute, and the melting points found for previously known compounds agree with those recorded in the literature.

β-Naphthisatin (1,2-β-Naphthazoledione).—*Sym*-Di-2-naphthylthiourea[3,4] was converted into α-(2-naphthylimino)-α-(2-naphthylamino)-acetonitrile according to the process covered by the Dreyfus patent.[5]

Following a modification of this patent, which omitted the isolation of the intermediate anil, a 60% yield of the β-naphthisatin was obtained as follows:

To 200 g. of concentrated sulfuric acid at room temperature, there was added gradually and with vigorous mechanical stirring, 15 g. of the above acetonitrile. After three hours, the solution was dark red. It was left for 12 hours at room temperature, then warmed for an hour at 40°, cooled and poured into ice water. The dark red-brown precipitate crystallized from alcohol in glistening dark red needles, m.p. 249°, in agreement with the literature.[6]

TABLE I

3-R-5,6-BENZOCINCHONINIC ACIDS

R	APPEARANCE	DEC. PT. (°C.)	REF.
H	Tan needles	302 (uncorr.)	
CH_3	Colorless needles	310 (uncorr.)	7
C_6H_5	Colorless needles	296 (uncorr.)	8, 9
p-Anisyl	Pale yellow needles	283	7, 10
Piperonyl	Pale yellow needles	292	7, 10

3-R-5,6-Benzocinchoninic acids, by the Doebner reaction.—This condensation was carried out in practically the same way as described beyond for the synthesis of the analogous 2-benzoyl-3-R-5,6-benzocinchoninic acids, except that pyruvic was substituted for the benzoylpyruvic acid.

The 3-phenyl derivative was the only one which could be purified by crystallization from diluted glacial acetic acid. The others were purified by solution in warm dilute alkali, decolorizing, and precipitating the filtered solution with dilute acetic acid.

5,6-Benzocinchoninic acid was obtained in a yield of 35%.

Anal. Calc'd for $C_{14}H_9NO_2$: C, 75.31; H, 4.07.
Found: C, 75.09; H, 4.09.

All of these acids melted with decomposition. With the exception of 5,6-benzocinchoninic acid itself, they have been described by previous investigators, with whose results our own agreed.

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[3] COSINER, *Ber.*, **14**, 61 (1881).

[4] HUGERSHOFF, *ibid.*, **32**, 2246 (1899).

[5] C. & A. DREYFUS, *Ger. Pat.* 152,019; *Friedländer*, **7**, 276 (1904).

[6] WAHL AND LOBECK, *Ann. chim. phys.* [10], **12**, 166 (1929).

[7] DOEBNER, *Ber.*, **27**, 2020 (1894).

[8] DOEBNER AND KUNTZE, *Ann.*, **249**, 129 (1888).

[9] SIMON AND MAUGUIN, *Compt. rend.*, **143**, 466 (1906).

[10] CIUSA AND ZERBINI, *Gazz. chim. ital.*, **50**, II, 317 (1920).

From the mother-liquors of these benzocinchoninic acids, the dihydroanils were isolated, but no search was made for tetrahydrobenzocinchoninic acids.

3-R-5,6-Benzocinchoninic acids by the Pfitzinger reaction.—By condensing the isatic acid from β-naphthisatin with acetophenone, or with *p*-methoxyacetophenone,[11] the 3-phenyl and 3-*p*-anisyl-5,6-benzocinchoninic acids were prepared as follows:

A mixture of 0.01 mole of β-naphthisatin (1,2-β-naphthazoledione) with 9 cc. of a 30% sodium hydroxide solution was boiled for five minutes. The isatin dissolved to a dark green solution, which changed to a yellow as the sodium salt of the corresponding isatic acid (2-amino-1-naphthaleneglyoxylic acid) was formed. To this solution there was added 0.01 mole of the appropriate acetophenone in 20 cc. of alcohol, and the mixture was refluxed for eight hours. The alcohol was then distilled off, the residue diluted with water and the solution acidified with acetic acid. After four hours' standing, the pale yellow precipitated benzocinchoninic acid was removed, dissolved in warm dilute caustic alkali, the solution decolorized and reprecipitated by dilute acetic acid. The 3-phenyl derivative was further purified by crystallization accomplished by adding two volumes of hot water to its solution in glacial acetic acid.

TABLE II

3-R-5,6-BENZOQUINOLINES

R	APPEARANCE	M.P. (°C.)	SOLVENT	REF.
H	Colorless plates	93.5	H_2O	12
CH_3	Colorless needles	82	Alc. + H_2O	7, 13, 14
C_6H_5	Colorless plates	188	Ether + alc.	8, 9
p-Anisyl	Colorless plates	190–1[a]	EtAc + alc.	7
Piperonyl	Colorless needles	178[b]	Alcohol	7

[a, b] Doebner gave a melting point of 184° for (*a*), but recorded no analysis for either (*a*) or (*b*). Our analytical results were as follows:

	Calc'd	*Found*
$C_{20}H_{15}NO$ (*a*)	C, 84.17; H, 5.30	C, 84.35; H, 5.47
$C_{20}H_{13}NO_2$ (*b*)	C, 80.24; H, 4.38	C, 80.42; H, 4.35

Melting point determinations carried out on mixtures of these products with those prepared by the Doebner Reaction showed no depression. In addition to this, the two sets of acids, when heated above their melting points until the evolution of carbon dioxide ceased, yielded the same benzoquinolines, as shown by mixed melting point determinations and by their other properties.

Table I thus summarizes the results we obtained by the two methods.

The 3-R-5,6-benzoquinolines formed by decarboxylation of the acids listed in Table I are given in Table II, including the solvent used in their recrystallization. The yields were generally about 80%.

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[11] NOLLER AND ADAMS, *J. Am. Chem. Soc.*, **46**, 1889 (1924).

[12] LELLMANN AND SCHMIDT, *Ber.*, **20**, 3154 (1887).

[13] DOEBNER AND V. MILLER, *ibid.*, **17**, 1698 (1884).

[14] SEITZ, *ibid.*, **22**, 254 (1889).

The same benzoquinolines were obtained by debenzoylation of the 2-benzoyl-3-R-5,6-benzoquinolines, or by simultaneous decarboxylation and debenzoylation of the 2-benzoyl-3-R-5,6-benzocinchoninic acids, both of which groups are described beyond.

A mixture of 0.01 mole of the benzoylbenzoquinoline, or benzoylbenzocinchoninic acid, with 12 g. of finely pulverized sodium hydroxide, in a small distilling flask, was treated with 1 cc. of water and then heated gradually. The 3-R-5,6-benzoquinolines formed distilled over gradually, and were purified by crystallization from the solvents noted in Table II; yield, 80–85%. These products melted at the same points as the corresponding compounds prepared by decarboxylation of the 3-R-5,6-benzocinchoninic acids, and mixtures of corresponding compounds from the two sets showed no alteration in the melting point. But when these benzoquinolines were mixed with the analogous 2-benzoyl derivatives, there resulted an immediate and decided drop in the melting point.

These debenzoylation reactions failed with the 3-piperonyl derivatives of both the 2-benzoyl-5,6-benzocinchoninic acid and of the 2-benzoyl-5,6-benzoquinoline, presumably because of hydrolysis of the acetal portion of the piperonyl radical, followed by decomposition.

TABLE III

PICRATES OF 3-R-5,6-BENZOQUINOLINES

R	M.P. (°C.)	REF.
H	251–252[a]	15
CH_3	228–230 (dec.)[b]	14
C_6H_5	250	8
p-Anisyl	224	

[a] Darkens.

[b] Seitz[14] gives 220–221°.

In all of these debenzoylations, there remained in the distilling flask a black mass, from which benzoic acid was isolated and identified by its m.p. (121.5°), by the m.p. of a mixture with an authentic sample of benzoic acid, and by conversion into its anilide.

As additional proof of their identity, the quinolines obtained by these debenzoylation reactions were converted into their picrates, which crystallized from alcohol in yellow needles. Picrates were prepared also from the 3-R-5,6-benzoquinolines resulting from the decarboxylation of the benzocinchoninic acids. The two series were shown to be identical by separate and mixed melting points of corresponding compounds.

Table III shows these melting points, which agree with the literature, except as there indicated.

3-p-Anisyl-5,6-benzoquinoline picrate was not found in the literature. It was therefore analyzed.

Anal. Calc'd for $C_{26}H_{18}N_4O_8$: N, 10.90. Found, 10.99.

Benzoylpyruvic-2-naphthylamide.—A solution of 3 g. of benzoylpyruvic acid[16] in

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[15] SKRAUP AND COBENZL, *Monatsh.*, **4**, 436 (1883).

[16] BRÖMME AND CLAISEN, *Ber.*, **21**, 1131 (1888).

a small quantity of hot alcohol was mixed with a warm alcoholic solution of 2.3 g. of 2-naphthylamine. As the solution cooled, the amide separated in yellow prisms, which, after being recrystallized twice from alcohol, darkened at about 125° and decomposed at 144–146°; yield, 90%. The product was insoluble in dilute alkali.

Anal. Calc'd for $C_{20}H_{15}NO_3$: C, 75.68; H, 4.77.
Found: C, 75.55; H, 4.88.

2-Benzoyl-3-R-5,6-benzocinchoninic acids.—In the case of the aromatic aldehydes, the anil was prepared first with 2-naphthylamine; but with formalin (40%) and acetaldehyde, the aldehyde and naphthylamine were added separately to the benzoylpyruvic acid.

TABLE IV

2-BENZOYL-3-R-5,6-BENZOCINCHONINIC ACIDS

NO.	R	APPEARANCE	YIELD (%)	DEC. (°C.)	H_2SO_4 SOLN.
1	H	Pale yellow	40	247	Green
2	CH_3	Colorless	22	271	Pale yellow
3	C_6H_5	Colorless	62	249	Pale yellow
4	*p*-Anisyl	Pale yellow	51	237	Orange yellow
5	Piperonyl	Pale yellow	56	259	Dark brown-green

ANALYSES

NO.	FORMULA	CALC'D	FOUND
1	$C_{21}H_{13}NO_3$	C, 77.03; H, 4.00	C, 76.67; H, 4.04[a]
2	$C_{22}H_{15}NO_3$	C, 77.39; H, 4.44	C, 77.50; H, 4.55
3	$C_{27}H_{17}NO_3$	C, 80.37; H, 4.21	C, 80.17; H, 4.26[a]
4	$C_{28}H_{19}NO_4$	C, 77.57; H, 4.42	C, 77.29; H, 4.25
5	$C_{28}H_{17}NO_5$	C, 75.14; H, 3.83	C, 75.28; H, 4.01

[a] These two compounds were prepared by Borsche[2] but, as already mentioned, were neither purified, analyzed nor identified, except by their conversion into the corresponding benzoylbenzoquinolines.

When a suspension of 0.1 mole of benzoylpyruvic acid and 0.2 mole of the anil in 250 cc. of 95% ethyl alcohol was refluxed for four hours, the benzocinchoninic acid separated as a crystalline insoluble precipitate, which was filtered out of the hot mixture, washed thoroughly with alcohol and with ether, and dried. From the combined filtrates and washings, after standing for 48 hours at room temperature, the dihydroanils crystallized; except in those reactions where formalin or acetaldehyde was used, when only a tarry oil separated. In the case of formaldehyde, this may have been due to the fact that N-methylene-2-naphthylamine polymerizes rapidly when heated.[17]

The benzoylbenzocinchoninic acids were dissolved in warm dilute alkali, decolorized, and precipitated by the addition of dilute acetic acid. From boiling glacial acetic acid, they crystallized in short needles, when two to three volumes of

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[17] MÖHLAU AND HAASE, *Ber.*, **35**, 4167 (1902).

hot water was added. Dried at 100°, they melted with decomposition, and this decomposition-point was not altered by three to four recrystallizations. They were soluble in dilute caustic alkali and formed mineral salts readily. In concentrated sulfuric acid, they dissolved to colored solutions, from which they were reprecipitated unchanged when water was added. The yields were calculated to the amount of benzoylpyruvic acid employed.

2-Naphthylamine dihydroanils.—As noted above, the mother-liquors and washings from the benzoylbenzocinchoninic acids, on standing, separated crystalline dihydroanils when the aldehydes employed in the reaction were aromatic. As *N*-benzyl-2-naphthylamine is very freely soluble in alcohol, it was frequently necessary to make the dark filtrate alkaline and extract this base with ether.

When the dihydroanils crystallized, additional quantities of the benzocinchoninic acids often were deposited with them. They were freed from these acids by washing with dilute ammonium hydroxide solution. The bases were obtained in yields of 45–50%, and were purified by recrystallization from hot diluted alcohol.

The mother-liquors from the dihydroanils were examined repeatedly for tetrahydrobenzoylbenzocinchoninic acids, but none were found.

TABLE V

2-NAPHTHYLAMINE DIHYDROANILS

R	APPEARANCE	M.P. (°C.)	REF.	HYDROCHLORIDE	
				M.p. (°C.)	Ref.
C_6H_5	Colorless prisms	68	18, 19	219	20
p-Anisyl	Colorless plates	104.5[a]	19	195[c]	21
Piperonyl	Colorless plates[b]	119	10	192	

[a] Ciusa and Zerbini[10] gave the m.p. as 98°.

[b] Ciusa and Zerbini described this compound as existing in red scales.

[c] Steinhart[21] recorded this salt as forming yellow crystals.

The dihydroanils obtained by us are shown in Table V. They agreed in their properties with the literature, except where noted, and were identical with the dihydroanils obtained as by-products when the condensation was carried out with pyruvic acid and the corresponding anil.

Because the melting point of the dihydroanil, in the case of the *p*-anisyl and piperonyl derivatives, was so close to that of the corresponding anil, it seemed desirable to provide additional proof that these by-products were actually the dihydroanils.

Alcoholic suspensions of the carefully purified anils, therefore, were reduced to the dihydroanils with sodium amalgam, following the general method of Steinhart,[21] and the products were crystallized from hot diluted alcohol; yields, 90%. In the case of the reduction product of benzal-2-naphthylamine, it was necessary to add

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[18] KOHLER, *Ann.*, **241**, 358 (1887).

[19] ZECHMEISTER AND TRUKA, *Ber.*, **63B**, 2883 (1930).

[20] CIUSA AND CREMONINI, *Gazz. chim. ital.*, **58**, 153 (1928).

[21] STEINHART, *Ann.*, **241**, 332 (1887).

water to the reaction mixture, in order to isolate it. When these dihydroanils were mixed with the corresponding ones obtained as by-products in the Doebner reaction, no change in melting point occurred; but when the dihydroanils of either origin were mixed with the corresponding anils, there was an immediate and marked lowering of the melting point.

As a further proof of identity, the hydrochlorides of both sets of dihydroanils were prepared by the addition of the calculated amount of concentrated hydrochloric acid to a hot alcohol solution of the base. Recrystallized from alcohol, they formed colorless plates; yield, 95%. The melting points of the corresponding hydrochlorides in the two series were the same, and remained unchanged when the two were mixed. These melting points are recorded in Table V above.

TABLE VI

2-BENZOYL-3-R-5,6-BENZOQUINOLINES

R	M.P. (°C.)	SOLVENT	REF.
H	108–109	Alc.	2
CH_3	132–133	Dil. alc.	
C_6H_5	189[a]	Alc.	2
p-Anisyl	186	EtAc	
Piperonyl	210.5–211	Dil. alc.	
OXIMES			
CH_3	242		
Piperonyl	262 (dec.)		
PICRATES			
CH_3	216–217		
C_6H_5	243–244		
p-Anisyl	199.5–200		

[a] Borsche[2] reported a m.p. of 185° for this compound.

N-*Piperonyl-2-naphthylamine hydrochloride* was not located in the literature. It was therefore analyzed.

Anal. Calc'd for $C_{18}H_{16}ClNO_2$: C, 68.91; H, 5.14.
Found: C, 69.01; H, 5.08.

The basic by-products isolated by Ciusa and Zerbini[10] in the Doebner reaction, were reported by them as dihydroanils, but without the conclusive evidence of their identity which the above experimental facts supply.

2-Benzoyl-3-R-5, 6-benzoquinolines.—Heating the benzoylbenzocinchoninic acids for four or five minutes above their melting points, sufficed to decarboxylate them completely, as evidenced by the cessation of the carbon dioxide evolution, with production of the corresponding benzoylbenzoquinolines. The crude products were purified by adding water carefully to their decolorized hot alcohol solutions. As these solutions cooled, the quinolines separated in colorless needles; yield, 80%. The *oximes* crystallized from alcohol in colorless plates or needles, the *picrates* in yellow needles. The melting points, recrystallization solvents, etc., are recorded in Table VI, and the analytical results in Table VII.

TABLE VII

Analyses of 2-Benzoyl-3-R-5,6-benzoquinolines, their Oximes, and Picrates

R	FORMULA	CALCULATED			FOUND		
		C	H	N	C	H	N
CH_3	$C_{21}H_{15}ON$	84.81	5.09		85.02	5.02	
p-Anisyl	$C_{27}H_{19}O_2N$	83.25	4.92		83.08	5.10	
Piperonyl	$C_{27}H_{17}O_3N$	80.37	4.22		80.15	4.26	
Oximes							
CH_3	$C_{21}H_{16}ON_2$	80.73	5.17	8.98	80.93	5.22	9.07
Piperonyl	$C_{27}H_{18}O_3N_2$	77.48	4.34	6.70	77.65	4.60	6.81
Picrates							
CH_3	$C_{27}H_{18}O_8N_4$			10.65			10.69
C_6H_5	$C_{32}H_{20}O_8N_4$			9.53			9.47
p-Anisyl	$C_{33}H_{22}O_9N_4$			9.06			8.97

TABLE VIII

2-Benzoyl-3-R-5,6-benzocinchoninyl Chlorides

R	APPEARANCE	M.P. (°C.)	FORMULA	Cl, CALC'D	Cl, FOUND
H	Yellow prismatic needles	197–199	$C_{21}H_{12}O_2NCl$	10.26	10.08
C_6H_5	Pale yellow needles	205–206	$C_{27}H_{16}O_2NCl$	8.41	8.47
p-Anisyl	Pale yellow needles	181–183	$C_{28}H_{18}O_3NCl$	7.85	7.91
Piperonyl	Orange yellow needles	188–189	$C_{28}H_{16}O_4NCl$	7.62	7.59

TABLE IX

Ethyl 2-Benzoyl-3-R-5,6-benzocinchoninates

R	APPEARANCE	M.P. (°C.)
H	Short colorless needles	146.5–147
C_6H_5	Pale yellow plates	144[a]
p-Anisyl	Yellow needles	160–161[b]
Piperonyl	Lemon yellow prisms	158–159

Analyses

R	FORMULA	C, CALC'D	C, FOUND	H, CALC'D	H, FOUND
H	$C_{23}H_{17}NO_3$	77.71	77.65	4.82	4.79
C_6H_5	$C_{29}H_{21}NO_3$	80.71	80.68	4.91	4.86
p-Anisyl	$C_{30}H_{23}NO_4$	78.06	78.00	5.02	5.05
Piperonyl	$C_{30}H_{21}NO_5$	75.76	76.00	4.45	4.64

[a] Shrinks at 137–140°.

[b] The methyl ester formed yellow needles, m.p. 175–176°.

As reported in an earlier section of this communication, these benzoyl derivatives can be debenzoylated by caustic alkali, with production of the 3-R-5,6-benzoquinolines.

2-Benzoyl-3-R-5,6-benzocinchoninyl chlorides were prepared from the corresponding acids by the action of thionyl chloride, the crude products being purified by recrystallization from dry benzene; yield, 85%. They dissolved readily in warm dilute sodium hydroxide, with formation of the sodium salts of the acids.

The 2-benzoyl-3-methyl-5,6-benzocinchoninic acid behaved abnormally with thionyl chloride, giving a pale brown solid, which contained nitrogen and sulfur, but no chlorine, decomposed at 199–201°, and did not react with ethyl alcohol.

These melting points were read with the bath temperature rising 5° per minute.

Ethyl 2-Benzoyl-3-R-5,6-benzocinchoninates.—The above acid chlorides were refluxed for 15–20 minutes with absolute ethanol and, as the solutions cooled, the esters crystallized. After treatment with warm dilute sodium hydroxide, to remove any contaminating benzocinchoninic acid, they were recrystallized from 95% ethyl alcohol; yield, 90%. They were insoluble in water, but dissolved in alcohol, ether, or benzene.

SUMMARY

1. From pyruvic and benzoylpyruvic acids, 2-naphthylamine, and various aldehydes, 3-R and 2-benzoyl-3-R-5,6-benzocinchoninic acids have been synthesized.

2. The by-products in these reactions have been shown to be the corresponding dihydroanils of 2-naphthylamine.

3. By utilization of the Pfitzinger reaction, 3-R-5,6-benzocinchoninic acids have been synthesized from acetophenones and β-naphthisatin.

4. By decarboxylation of the 3-R-5,6-benzocinchoninic acids, 3-R-5,6-benzoquinolines have been obtained and their picrates prepared.

5. By decarboxylation of the 2-benzoyl-3-R-5,6-benzocinchoninic acids, the 2-benzoyl-3-R-5,6-benzoquinolines have been obtained and identified also through their oximes and picrates.

6. When the 2-benzoyl-3-R-5,6-benzocinchoninic acids, or the 2-benzoyl-3-R-5,6-benzoquinolines, are heated with caustic alkali, the 3-R-5,6-benzoquinolines result.

7. It is hoped to have some of the new benzocinchoninic acid derivatives examined pharmacologically.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, N. Y.]

OPTICAL ACTIVITY AND CHEMICAL STRUCTURE*

P. A. LEVENE AND ALEXANDRE ROTHEN

Received March 2, 1936

I. HYDROCARBONS

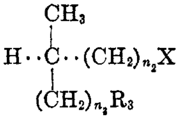
A. Normal Series.
B. Hydrocarbons containing an isopropyl group.
C. Hydrocarbons containing a phenyl or cyclohexyl group.
   1. Phenyl and cyclohexyl series.
   2. Benzyl series.
   3. Methylphenethyl series.

II. CARBINOLS

A. Secondary carbinols of normal series.
B. Primary carbinols of normal series.
C. Carbinols of isopropyl and isobutyl series.
D. Carbinols containing an ethylenic group.
E. Secondary carbinols containing a phenyl or cyclohexyl group.
   1. Phenyl series.
   2. Cyclohexyl series.
   3. Benzyl series.
   4. Phenethyl series.
F. Primary carbinols containing a phenyl group.

III. ACIDS, NITRILES, AND ALDEHYDES

A. Carboxylic acids of the normal series.
B. Carboxylic acids having a phenyl or a cyclohexyl group.
C. Normal aliphatic nitriles.
D. Aliphatic aldehydes.
E. General discussion of observations on substances of the type



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot(CH_2)_{n_2}X \\ | \\ (CH_2)_{n_3}R_3 \end{array}$$

F. A test of the correctness of the configurational relationships assigned to substances discussed in this section.

IV. APPLICATION OF THE RESULTS RECORDED IN THE PRECEDING SECTION

A. Absolute configurations of secondary and primary carbinols.
B. Secondary and primary aliphatic amines.
C. Secondary and primary aliphatic azides.
D. Secondary and primary aliphatic halides.

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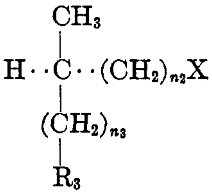
* The present summary was prepared at the request of the Editors.

Given a substance of known configuration of the general type of formula I,

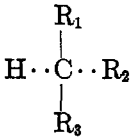


$$\begin{array}{l} \quad CH_3 \\ \quad\ | \\ H\cdot\cdot C\cdot\cdot(CH_2)_{n_2}X \\ \quad\ | \\ \quad (CH_2)_{n_3} \\ \quad\ | \\ \quad R_3 \end{array}$$

I

(where X = a functional group; R_3 = an alkyl or an aryl radical; n_2 and n_3 = 0 or an integer), the configuration of the derivative obtained by substitution of X by Y cannot be predicted when $n_2 = 0$, whereas when n_2 = an integer the substitution cannot produce any change in the original configuration. Similarly, when R_3 is substituted by R_3', it is possible to predict the configuration of the derivative only when n_3 = an integer and not in the case when $n_3 = 0$. The question arises: Is it possible to predict the configurations of the substitution-derivatives in the cases when $n_2 = 0$ or $n_3 = 0$, on the basis of observations on the derivatives when n_2 or n_3 are integers?†

The first requisite for the solution of the problem was to render available series homologous with respect to n_2 and n_3 in which the configurations of all members had been established by methods of classical organic chemistry. When such homologous series were prepared, it was observed that, frequently, members of the same series differed in the direction of their rotation. This phenomenon naturally required an explanation. The modern theory of optical rotation postulates that the optical rotation (even of the simplest organic molecule of the type



$$\begin{array}{l} \quad R_1 \\ \quad\ | \\ H\cdot\cdot C\cdot\cdot R_2 \\ \quad\ | \\ \quad R_3 \end{array}$$

having only one asymmetric center) is the sum of the partial rotations of each of the four substituents, there being an equal number of dextrorotatory and levorotatory partial rotations.[1] Thus, when two members of a homologous series differed in the sign of their rotation, it was evident

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† The present article will summarize work of this laboratory on only one phase of the problem; other work of the laboratory dealing with the problem of the relationship of chemical structure to optical activity will be discussed at a future date.

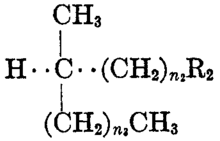
[1] KUHN, W., in FREUDENBERG, "Stereochemie," Franz Deuticke, Berlin and Wien, **1932**, p. 317.

that this difference could be caused either by an inversion in sign of the rotation of one or more of the partial rotations, or by change in the numerical values of one or more of the partial rotations. Hence, for the solution of this problem, information was required as to the partial rotations of the chromophoric groups of each substituent.

The analysis of rotatory dispersion curves extending to the region of the absorption bands (or the greatest proximity to it) offers a method for the solution of the latter problem. Thus the work naturally falls into two parts: one aiming at the building up of homologous series and the other concerned with the direction and relative values of the partial rotations of the significant chromophoric groups.

I. HYDROCARBONS

The simplest group of optically active organic molecules obviously are the trisubstituted methanes of the type



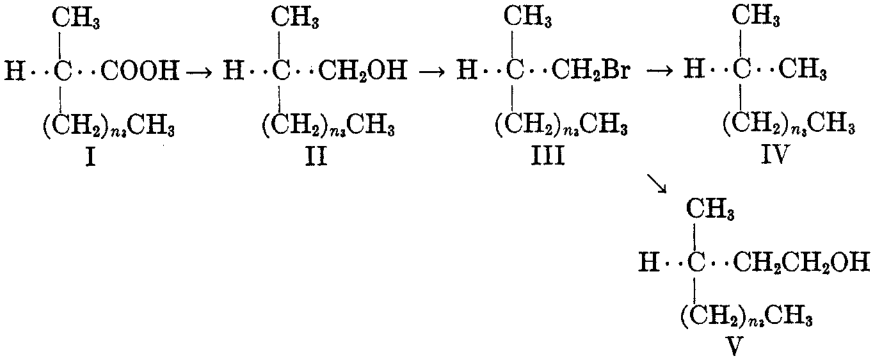
$$\begin{array}{c} \mathrm{CH_3} \\ | \\ \mathrm{H\cdot\cdot C\cdot\cdot(CH_2)_{n_2}R_2} \\ | \\ \mathrm{(CH_2)_{n_3}CH_3} \end{array}$$

(R_2 = CH_3, isopropyl, phenyl or cyclohexyl group).

A. Normal Series

Of these hydrocarbons the simplest are those in which $R_2 = CH_3$.

The building up of a single homologous series of normal hydrocarbons is a comparatively simple task since any number of homologous members may be prepared from a single parent substance under conditions excluding the possibility of Walden Inversion. Thus, starting from a disubstituted acetic acid, it is possible to synthesize all the members of a homologous series by the following set of reactions:



$$\begin{array}{ccccccc} \mathrm{CH_3} & & \mathrm{CH_3} & & \mathrm{CH_3} & & \mathrm{CH_3} \\ | & & | & & | & & | \\ \mathrm{H\cdot\cdot C\cdot\cdot COOH} & \rightarrow & \mathrm{H\cdot\cdot C\cdot\cdot CH_2OH} & \rightarrow & \mathrm{H\cdot\cdot C\cdot\cdot CH_2Br} & \rightarrow & \mathrm{H\cdot\cdot C\cdot\cdot CH_3} \\ | & & | & & | & & | \\ \mathrm{(CH_2)_{n_3}CH_3} & & \mathrm{(CH_2)_{n_3}CH_3} & & \mathrm{(CH_2)_{n_3}CH_3} & & \mathrm{(CH_2)_{n_3}CH_3} \\ \mathrm{I} & & \mathrm{II} & & \mathrm{III} & & \mathrm{IV} \\ & & & & & \searrow & \\ & & & & & & \mathrm{CH_3} \\ & & & & & & | \\ & & & & & & \mathrm{H\cdot\cdot C\cdot\cdot CH_2CH_2OH} \\ & & & & & & | \\ & & & & & & \mathrm{(CH_2)_{n_3}CH_3} \\ & & & & & & \mathrm{V} \end{array}$$

.... continue as in case II→III→IV.

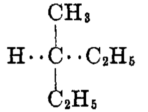
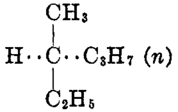
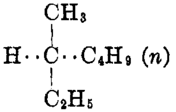
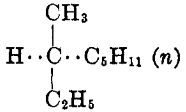
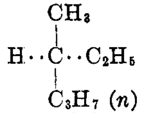
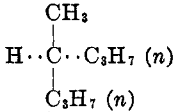
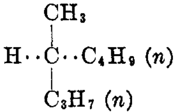
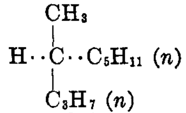
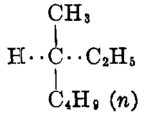
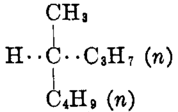
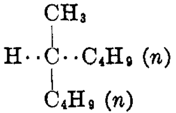
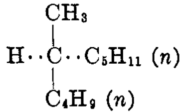
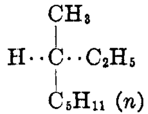
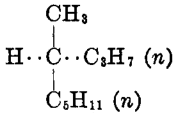
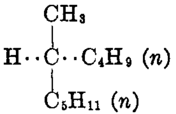
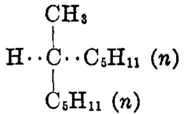
It will be seen later that it is possible to correlate the acids where $n_2 = 0$ with those where $n_2 = 1, 2, 3$ or any higher integer, by methods of classical organic chemistry. Likewise, it is possible to correlate by the same methods, acids varying with respect to n_3. Hence it is possible to build up any desired number of homologous series of hydrocarbons of known configuration. Table I summarizes the results of the observations.

It is evident from Table I that the direction of rotation of the substances of this group depends entirely on clockwise or counter-clockwise arrangement of the substituents. Dextrorotation is assigned to the members in which the groups are arranged in clockwise order (according to descending volumes) when viewed with the largest volume towards the observer—in harmony with the considerations of Boys.[2]

TABLE I

Configurationally Related Normal Hydrocarbons

$[M]^{25}_{D}$ Max. (Homogeneous)

 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_2H_5$ 0	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_3H_7\ (n)$ +9.9	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_4H_9\ (n)$ +11.4	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_5H_{11}\ (n)$ +12.0
 $H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\ (n)}{C}}\cdot\cdot C_2H_5$ −9.9	 $H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\ (n)}{C}}\cdot\cdot C_3H_7\ (n)$ 0	 $H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\ (n)}{C}}\cdot\cdot C_4H_9\ (n)$ +1.7	 $H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\ (n)}{C}}\cdot\cdot C_5H_{11}\ (n)$ +2.4
 $H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\ (n)}{C}}\cdot\cdot C_2H_5$ −11.4	 $H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\ (n)}{C}}\cdot\cdot C_3H_7\ (n)$ −1.7	 $H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\ (n)}{C}}\cdot\cdot C_4H_9\ (n)$ 0	 $H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\ (n)}{C}}\cdot\cdot C_5H_{11}\ (n)$ +0.86
 $H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\ (n)}{C}}\cdot\cdot C_2H_5$ −12.0	 $H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\ (n)}{C}}\cdot\cdot C_3H_7\ (n)$ −2.4	 $H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\ (n)}{C}}\cdot\cdot C_4H_9\ (n)$ −0.86	 $H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\ (n)}{C}}\cdot\cdot C_5H_{11}\ (n)$ 0

The analysis of rotatory dispersion curves of these substances indicates the possibility that the rotation in the visible can be expressed by the sum of two contributions of opposite sign, *i.e.*, by a Drude formula of two terms with opposite signs.[3]

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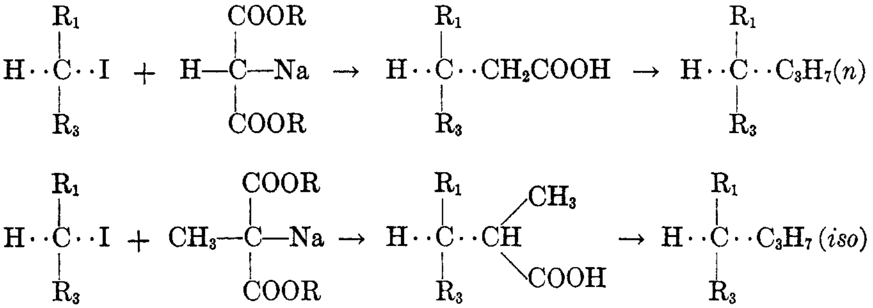
[2] Boys, S. F., *Proc. Roy. Soc.*, **A144,** 655 (1934).

[3] Levene, P. A., and Rothen, Alexandre (unpublished results).

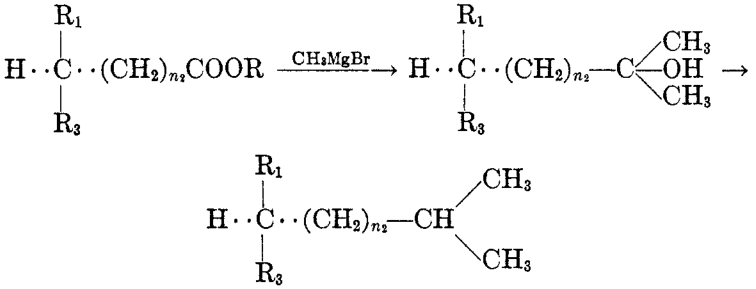
B. Hydrocarbons Containing an Isopropyl Group

In this group of substances $-CH\langle^{CH_3}_{CH_3}$ stands for R_2 and $n_2 = 0, 1$ or 2. The relationship of the configuration of the members of the normal series with that of members of the branched chain series is established by preparing a pair of such hydrocarbons from a halide by the set of reactions given below:[4]



The chances of the occurrence of Walden inversion are identical in both cases; hence the configurations of the two hydrocarbons are identical.

The configurations of the branched-chain hydrocarbons with $n_2 = 1$ or 2 were likewise determined by the method of their preparation. The set of reactions leading to their formation is given below:



The results of the observations on this group of substances are summarized in Table II.

The significant facts recorded in Table II are as follows:

(1). The substitution of the propyl group by an isopropyl group without a Walden inversion brings about a change of sign of the optical rotation of the resulting hydrocarbon. In the hydrocarbons of the normal

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[4] Levene, P. A., and Marker, R. E., *J. Biol. Chem.*, **91**, 405 (1931); **92**, 455 (1931); **95**, 1 (1932); **100**, 769 (1933).

TABLE II

Configurationally Related Hydrocarbons Containing an Isopropyl, Isobutyl or Isoamyl Group

$[M]_D^{25}$ Max. (Homogeneous)

$-(CH_2)_2CH_3$ Series	$-CH{<}^{CH_3}_{CH_3}$ Series	$-(CH_2)_3CH_3$ Series	$-CH_2-CH{<}^{CH_3}_{CH_3}$ Series	$-(CH_2)_4CH_3$ Series	$-(CH_2)_2-CH{<}^{CH_3}_{CH_3}$ Series
$H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_3H_7$ +9.9	$H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_3H_7$ (*iso*) −26.4*	$H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_4H_9$ (*n*) +11.4	$H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_4H_9$ (*iso*) +21.3	$H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_5H_{11}$ (*n*) +12.0	$H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot C_5H_{11}$ (*iso*) +11.9
$H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot C_3H_7$ 0	$H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot C_3H_7$ (*iso*) −5.5*	$H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\ (n)}{C}}\cdot\cdot C_4H_9$ (*n*) +1.7	$H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\ (n)}{C}}\cdot\cdot C_4H_9$ (*iso*) +14.9	$H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\ (n)}{C}}\cdot\cdot C_5H_{11}$ (*n*) +2.4	$H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\ (n)}{C}}\cdot\cdot C_5H_{11}$ (*iso*) +3.5
$H\cdot\cdot\overset{CH_3}{\underset{C_4H_9}{C}}\cdot\cdot C_3H_7$ −1.7		$H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\ (n)}{C}}\cdot\cdot C_4H_9$ (*n*) 0	$H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\ (n)}{C}}\cdot\cdot C_4H_9$ (*iso*) +11.9	$H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\ (n)}{C}}\cdot\cdot C_5H_{11}$ (*n*) +0.86	$H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\ (n)}{C}}\cdot\cdot C_5H_{11}$ (*iso*) +1.5
$H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}}{C}}\cdot\cdot C_3H_7$ −2.4	$H\cdot\cdot\overset{CH_3}{\underset{C_7H_{15}}{C}}\cdot\cdot C_3H_7$ (*iso*) −1.1*	$H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\ (n)}{C}}\cdot\cdot C_4H_9$ (*n*) −0.86	$H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\ (n)}{C}}\cdot\cdot C_4H_9$ (*iso*) +9.3	$H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\ (n)}{C}}\cdot\cdot C_5H_{11}$ (*n*) 0	$H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\ (n)}{C}}\cdot\cdot C_5H_{11}$ (*iso*) +0.2

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* Not maximum rotation.

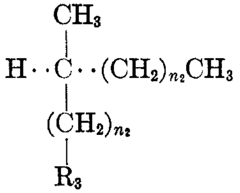
series, the largest group without doubt furnishes the highest partial rotation. It is therefore likely that in the members of the isopropyl series the highest contribution is furnished by the isopropyl group. The alternative assumption would be that this group produces a vicinal effect (inductive effect) on the partial rotations of the other groups in a sense opposite from that of the normal propyl group. In the latter case the rotatory dispersion of the methylethylisopropylmethane should be anomalous. This, however, is not the case.[5]

(2). The increase of the value of n_2 from 0 to 1 or 2 brings about a reversal of the sign of the rotations of the corresponding members of the isobutyl and isoamyl series.

(3). A comparison of the values of the molecular rotations of the members of the isopropyl, isobutyl and isoamyl series (the series with $n_2 > 2$ have not yet been prepared) reveals a periodicity in the shift of rotation of successive (with respect to n_2) members. Thus, from isopropyl to isobutyl the shift is to the left, whereas from isobutyl to isoamyl the shift is to the right.

(4). The maximum rotation of the methylamylisoamylmethane (member in the last column and the last row) is 0.2°, thus showing that at the distance $(CH_2)_2$ from the asymmetric carbon atom the partial contribution of the isopropyl group is nearly equivalent to that of the normal propyl group. It might be expected that the configurationally related methylhexylisoamylmethane would rotate in opposite direction from that of the members of the last column given in Table II.

C. Hydrocarbons Containing a Phenyl or a Cyclohexyl Group



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot(CH_2)_{n_2}CH_3 \\ | \\ (CH_2)_{n_2} \\ | \\ R_3 \end{array}$$

(R_3 = phenyl or cyclohexyl group).

1. *Phenyl and Cyclohexyl Series.*—The rotations of the individual members of the two homologous series have been established by their origin from members of a homologous series of acids.[6]

The relationship of the phenyl to the cyclohexyl series follows from the conversion of the former through catalytic hydrogenation to the latter.

The correlation of the configurations of the phenyl to the normal hexyl

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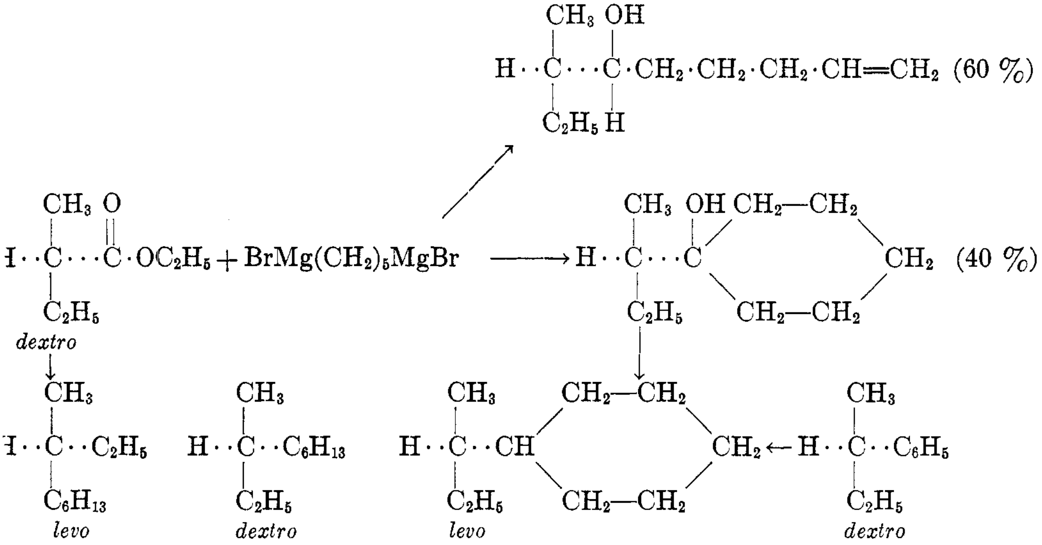
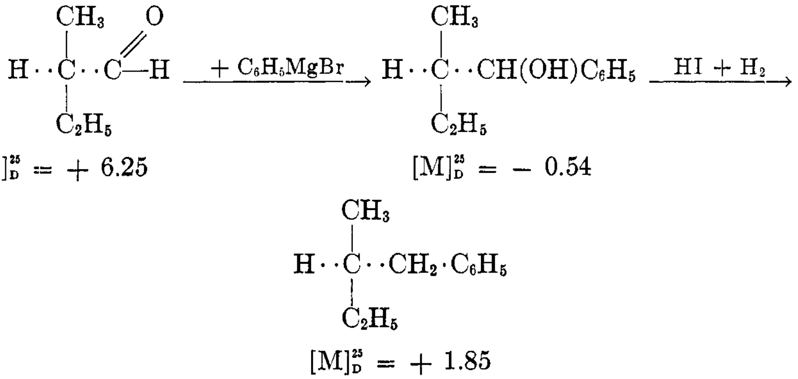
[5] LEVENE, P. A., AND ROTHEN, ALEXANDRE (unpublished results).

[6] LEVENE, P. A., AND MARKER, R. E., *J. Biol. Chem.*, **93**, 749 (1931); **97**, 563 (1932).

series is based on preparation of the members of the two series from the same disubstituted acetic acids of known configuration by the following set of reactions:[7]



2. *Benzyl Series.*—The configurational relationship of methylethylbenzylmethane to methylethylheptylmethane is based on the preparation of the two substances from the identical 2-methylbutyl butanal-1.[8]



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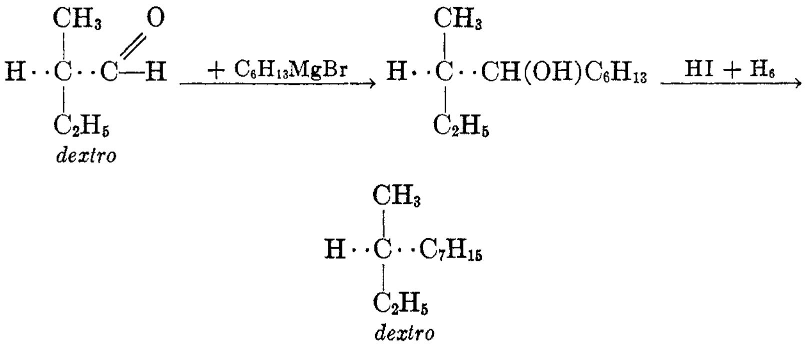
[7] Levene, P. A., and Harris, Stanton A., *ibid.*, **111**, 725 (1935).

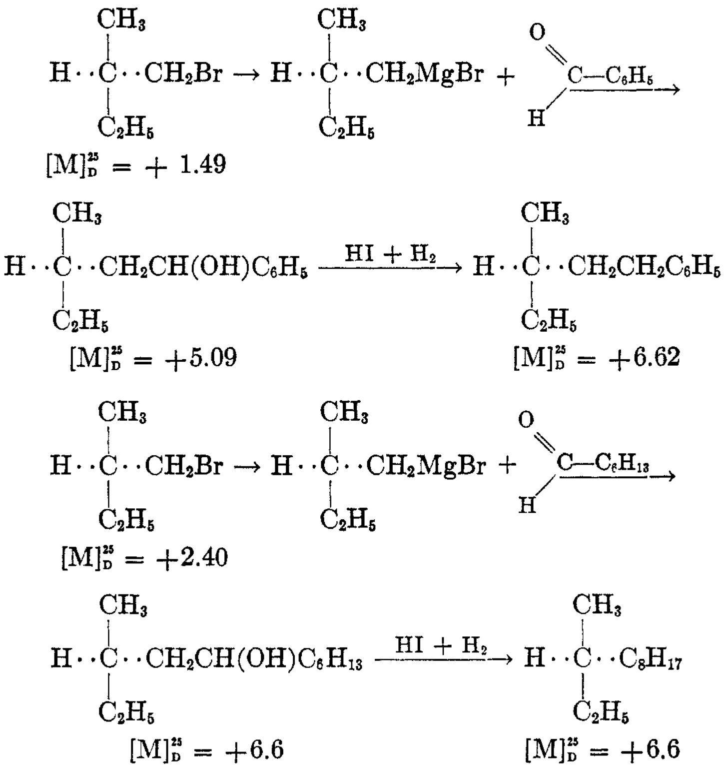
[8] Levene, P. A., *ibid.*, **110**, 323 (1935).



$$\underset{dextro}{H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot\overset{O}{\overset{/\!/}{C}}{-}H} \xrightarrow{+\,C_6H_{13}MgBr} H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot CH(OH)C_6H_{13} \xrightarrow{HI\,+\,H_6}$$

$$\underset{dextro}{H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot C_7H_{15}}$$

3. *Methylphenethyl Series.*—Configurational relationship of methylethylphenethylmethane to methylethyloctylmethane is based on the synthesis of the two hydrocarbons from two 2-methyl-1-bromobutanes[9] of identical configuration as follows:



$$\underset{[M]_D^{25}\,=\,+\,1.49}{H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot CH_2Br} \rightarrow H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot CH_2MgBr + \overset{O}{\underset{H}{\diagdown\!\!\diagup}}C{-}C_6H_5 \longrightarrow$$

$$\underset{[M]_D^{25}\,=\,+5.09}{H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot CH_2CH(OH)C_6H_5} \xrightarrow{HI\,+\,H_2} \underset{[M]_D^{25}\,=\,+6.62}{H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot CH_2CH_2C_6H_5}$$

$$\underset{[M]_D^{25}\,=\,+2.40}{H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot CH_2Br} \rightarrow H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot CH_2MgBr + \overset{O}{\underset{H}{\diagdown\!\!\diagup}}C{-}C_6H_{13} \longrightarrow$$

$$\underset{[M]_D^{25}\,=\,+6.6}{H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot CH_2CH(OH)C_6H_{13}} \xrightarrow{HI\,+\,H_2} \underset{[M]_D^{25}\,=\,+6.6}{H\cdot\cdot\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}\cdot\cdot C_8H_{17}}$$

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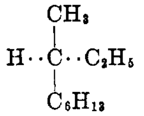
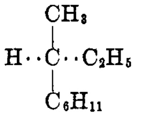
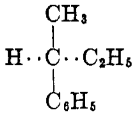
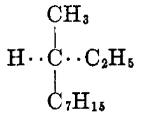
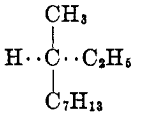
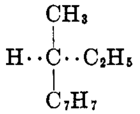
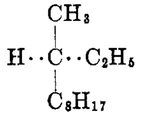
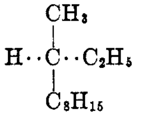
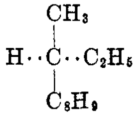
[9] Klages, A., and Sautter, R., *Ber.*, **37**, 649 (1904).
Levene, P. A., and Harris, Stanton A., *J. Biol. Chem.*, **111**, 735 (1935).

The maximum rotations of the three "phenyl," "cyclohexyl" and "normal aliphatic" hydrocarbons have been calculated on the basis of the maximum rotation of the parent substances and the results are summarized in Table III.

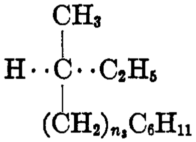
TABLE III

CONFIGURATIONALLY RELATED HYDROCARBONS OF THE NORMAL, CYCLOHEXYL AND PHENYL SERIES

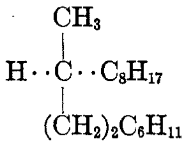
$[M]_D^{25}$ Max. (Homogeneous)

 $H \cdot\cdot \overset{CH_3}{\underset{C_6H_{13}}{C}} \cdot\cdot C_2H_5$ −12.5	 $H \cdot\cdot \overset{CH_3}{\underset{C_6H_{11}}{C}} \cdot\cdot C_2H_5$ +19.5	 $H \cdot\cdot \overset{CH_3}{\underset{C_6H_5}{C}} \cdot\cdot C_2H_5$ −36.5
 $H \cdot\cdot \overset{CH_3}{\underset{C_7H_{15}}{C}} \cdot\cdot C_2H_5$ −12.5 (appr.)	 $H \cdot\cdot \overset{CH_3}{\underset{C_7H_{13}}{C}} \cdot\cdot C_2H_5$ −19.3	 $H \cdot\cdot \overset{CH_3}{\underset{C_7H_7}{C}} \cdot\cdot C_2H_5$ −9.5
 $H \cdot\cdot \overset{CH_3}{\underset{C_8H_{17}}{C}} \cdot\cdot C_2H_5$ −17.4	 $H \cdot\cdot \overset{CH_3}{\underset{C_8H_{15}}{C}} \cdot\cdot C_2H_5$ −16.8	 $H \cdot\cdot \overset{CH_3}{\underset{C_8H_9}{C}} \cdot\cdot C_2H_5$ −35.1

From Table III it may be seen that in the case of the cyclohexyl derivatives of the general type


$$H \cdot\cdot \overset{CH_3}{\underset{(CH_2)_{n_3}C_6H_{11}}{C}} \cdot\cdot C_2H_5$$

with increase in the value of n_3 from 0 to 1 and 2, the events parallel those in the case of the isopropyl series, namely, there is observed a change of sign of rotation when n_3 (n_2 in the "iso" series) changes from 0 to 1 and there is a shift in direction of the rotation in the opposite sense when the value of n_3 (n_2 in the "iso" series) changes from 1 to 2. In a later section of this article other evidence will be presented pointing to the similarity of the cyclohexyl group to the isopropyl group as regards their influence on optical activity. However, the two groups differ with respect to the value of n_3 (n_2 in the "iso" series) at which their effect on optical rotation ceases to have an influence other than that of the corresponding normal alkyl group. It was stated earlier that the maximum rotation of methylamylisoamylmethane (in which the isopropyl group is at a distance $(CH_2)_2$ from the asymmetric center) approaches a zero value whereas the cyclohexyl group at the same distance produces a marked effect on optical rotation as seen from the maximum rotation of methyloctylhexahydrophenethylmethane.[10]

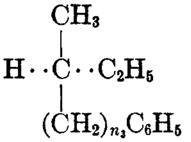


$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot C_8H_{17} \\ | \\ (CH_2)_2C_6H_{11} \end{array}$$

$$[M]^{25}_{D\ \mathrm{Max.}} = -5.27$$

In the light of these observations the *a priori* statement of W. Kuhn[10.5] to the effect that the rotatory contribution of a cyclohexyl group is equivalent to that of a normal hexyl group should be rejected.

In the case of the "phenyl" derivatives of the type

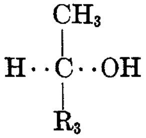


$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot C_2H_5 \\ | \\ (CH_2)_{n_3}C_6H_5 \end{array}$$

there is likewise observed a periodicity in the shift of rotation with the changes of the values of n_3 from 0 to 1 and from 1 to 2. No change in the direction of rotation occurs on passing from the value of $n_3 = 0$ to $n_3 = 1$. Analysis of the rotatory dispersion curve of methylethylphenylmethane, however, revealed the fact that the rotatory dispersion of this substance is anomalous, thus showing that the partial rotation of the nearest active absorption region of the phenyl group is of opposite sign from that of the rotation of the hydrocarbon in the visible region, whereas in the case of the benzyl and phenethyl derivatives, the dispersion curves are normal,[11] indicating that the course of events on change of the value of n_3 from 0 to 1 is similar in the cases of the phenyl derivatives and the cyclohexyl derivatives.

II. CARBINOLS

A. Secondary Carbinols of the Normal Series



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot OH \\ | \\ R_3 \end{array}$$

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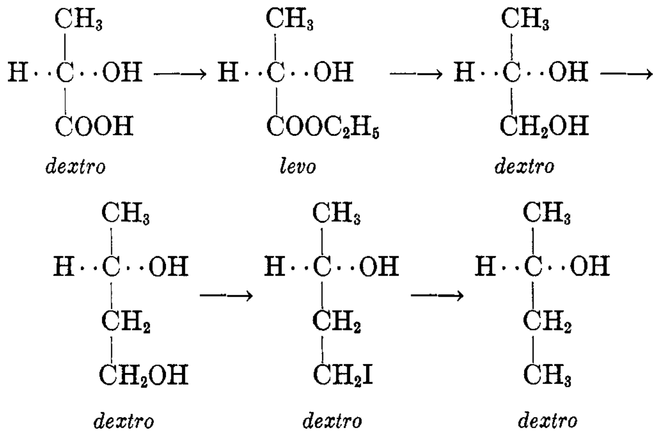
[10] Levene, P. A., and Harris, Stanton A., *J. Biol. Chem.*, **111**, 735 (1935).

[10.5] Kuhn, W., *Z. physik. Chem.*, **B31**, 23 (1935).

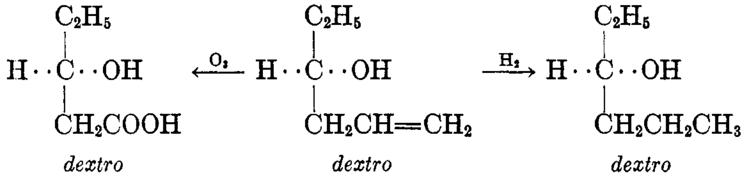
[11] Levene, P. A., and Rothen, Alexandre (unpublished results).

The configuration of these substances has been correlated with that of lactic acid. Three methods have been employed to that end.

1. The first method consists in reducing α-hydroxyacids to the corresponding glycols and converting the glycols into secondary carbinols. Thus the configuration of the simplest carbinol of this series, 2-hydroxybutane, can be arrived at by the following set of reactions:[12]



2. The second method is illustrated by the case of ethylpropylcarbinol. Taking for granted that the configuration of 3-hydroxyvaleric acid is known (it is readily determined by methods of classical organic chemistry), the configuration of the carbinol can be arrived at by the following set of reactions:[13]



3. A third general method is exemplified by condensation of propylene oxide (or any other ethylenic oxide) with a Grignard reagent. This method became available only after the configuration of the lower members of the homologous series of optically active carbinols had been estab-

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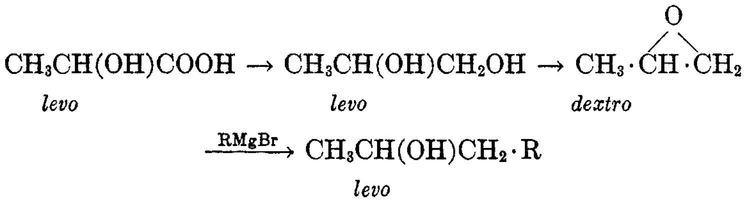
[12] Levene, P. A., and Haller, H. L., *J. Biol. Chem.*, **65**, 49 (1925); **67**, 329 (1926); **69**, 165 (1926); **74**, 343 (1927); **76**, 415 (1928); **77**, 555 (1928).

Levene, P. A., Walti, A., and Haller, H. L., *ibid.*, **71**, 465 (1927).

Levene, P. A., Haller, H. L., and Walti, A., *ibid.*, **72**, 591 (1927).

[13] Levene, P. A., and Haller, H. L., *ibid.*, **79**, 475 (1928); **81**, 425 (1929).

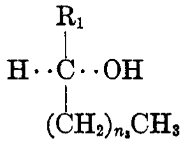
lished by the methods described in (1) and (2). It was then possible to establish the fact that the reaction proceeds without Walden inversion.[14]



$$\underset{levo}{CH_3CH(OH)COOH} \rightarrow \underset{levo}{CH_3CH(OH)CH_2OH} \rightarrow \underset{dextro}{CH_3\cdot \overset{O}{CH\cdot CH_2}}$$

$$\xrightarrow{RMgBr} \underset{levo}{CH_3CH(OH)CH_2\cdot R}$$

Table IV contains a summary of the results of observations on the secondary carbinols of the general type

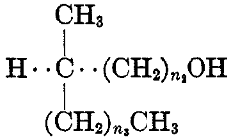


$$\begin{array}{c} R_1 \\ | \\ H\cdot\cdot C\cdot\cdot OH \\ | \\ (CH_2)_{n_3}CH_3 \end{array}$$

(n_3 = 0 or an integer; R_1 = an aliphatic radical).

From Table IV it may be seen that the direction of rotation, in the members of this group of substances, seems to be determined by the position of the radical with the longest carbon chain. Prior to the publication of the work of our laboratory, the question, as to whether or not all members of the ethyl and the propyl series (and series with still higher homologues of R_1) should be of the same sign, was debated.[15] From Table IV it may be seen that in each of these series the rotations of the individual members pass a zero value and then change their direction. Thus it is evident that if it were desired to separate the secondary carbinols into a *d* and *l* series, the dividing line of the two series would be that joining the symmetric carbinols. The series above this line should belong to the *l* series and those below to the *d* series. In other words, each new series should begin with a symmetric member. For practical purposes it is often advantageous to begin each new series with a member having $R_1 = CH_3$.

B. Primary Carbinols of the Normal Series



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot (CH_2)_{n_2}OH \\ | \\ (CH_2)_{n_3}CH_3 \end{array}$$

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[14] LEVENE, P. A., AND WALTI, A., *ibid.*, **71**, 461 (1927).

[15] KENYON, J., *J. Chem. Soc.*, **105**, 2226 (1914).

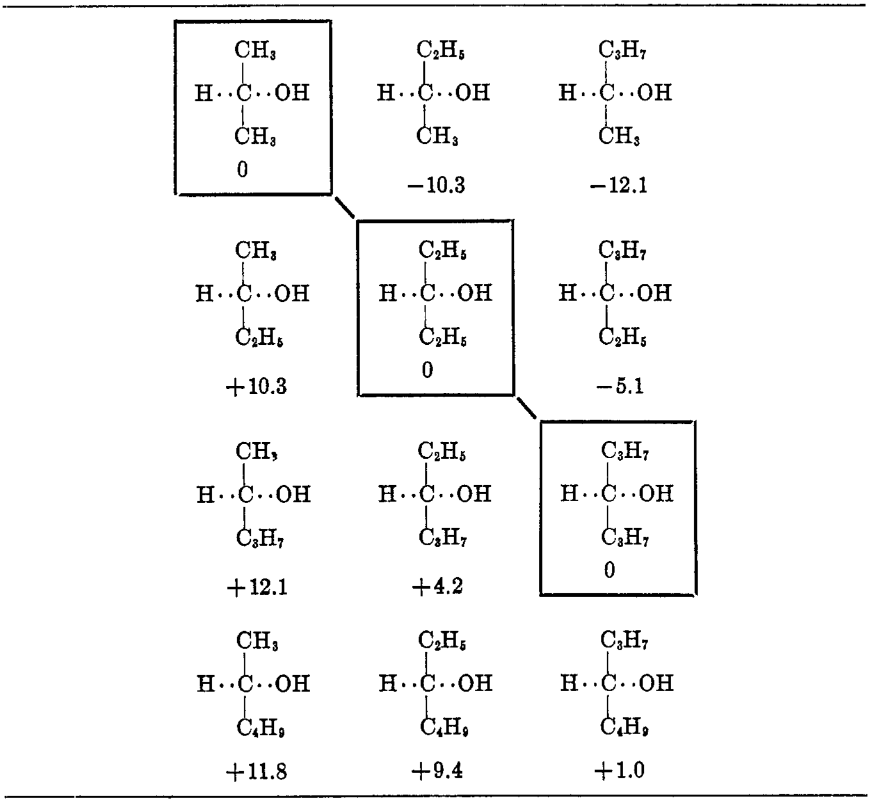
CLOUGH, G. W., *Proc. Chem. Soc.*, **29**, 357 (1913).

Comparatively few optically active primary carbinols of this type had been known prior to the work of our laboratory. The configurations of these carbinols cannot be correlated by methods of classical organic chemistry with those of the corresponding secondary carbinols (those having $n_2 = 0$). However, they can be correlated by such methods between themselves and to the acids of the general type

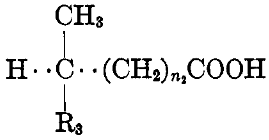
TABLE IV

Configurationally Related Normal Secondary Carbinols.

$[M]_D^{25}$ Max. (Homogeneous)



$H\cdot\cdot\overset{CH_3}{\underset{CH_3}{C}}\cdot\cdot OH$ 0	$H\cdot\cdot\overset{C_2H_5}{\underset{CH_3}{C}}\cdot\cdot OH$ -10.3	$H\cdot\cdot\overset{C_3H_7}{\underset{CH_3}{C}}\cdot\cdot OH$ -12.1
$H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot OH$ $+10.3$	$H\cdot\cdot\overset{C_2H_5}{\underset{C_2H_5}{C}}\cdot\cdot OH$ 0	$H\cdot\cdot\overset{C_3H_7}{\underset{C_2H_5}{C}}\cdot\cdot OH$ -5.1
$H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot OH$ $+12.1$	$H\cdot\cdot\overset{C_2H_5}{\underset{C_3H_7}{C}}\cdot\cdot OH$ $+4.2$	$H\cdot\cdot\overset{C_3H_7}{\underset{C_3H_7}{C}}\cdot\cdot OH$ 0
$H\cdot\cdot\overset{CH_3}{\underset{C_4H_9}{C}}\cdot\cdot OH$ $+11.8$	$H\cdot\cdot\overset{C_2H_5}{\underset{C_4H_9}{C}}\cdot\cdot OH$ $+9.4$	$H\cdot\cdot\overset{C_3H_7}{\underset{C_4H_9}{C}}\cdot\cdot OH$ $+1.0$



$$H\cdot\cdot\overset{CH_3}{\underset{R_3}{C}}\cdot\cdot(CH_2)_{n_2}COOH$$

(where $n_2 = 0$ or an integer, R_3 = normal aliphatic radical).

From the latter they are prepared by reduction of the corresponding ethyl esters. The series of carbinols prepared by this method is given in Table V.[16] For comparison, the hydrocarbons, in which the hydroxyl has been substituted by the group CH_3, are also given.

Table V brings out a great similarity in the rotations of the hydrocarbons and carbinols. The shift of rotation with the increasing value of n_2 is in the same direction in both, and in both cases the value of the optical rotation reaches a zero value. Also, in both cases there is an inversion of sign in the next higher member. It must be emphasized that in the case of the carbinols the zero value does not indicate loss of asymmetry, for the apparently inactive carbinol yields an active halide and an active hydrocarbon with one more carbon atom.

In the case of the hydrocarbons it is clear that the rotation should reach zero value when the radical $(CH_2)_{n_2}CH_3$ reaches identity with R_3; in the case of the carbinols, a minimum value is reached when n_2 is equal to the number of carbon atoms of the radical R_3. Furthermore, at an equal distance from the asymmetric center atom, the CH_3 group seems to introduce a higher contribution to the molecular rotation than the hydroxyl group, save in the case when the hydrocarbon reaches a zero value, thus indicating that at an equal distance from the asymmetric carbon atom the hydroxyl group introduces a smaller partial contribution than the methyl group, or possibly that the hydroxyl group introduces a partial rotation of direction opposite to that of the methyl group.

The dispersion curve of the optically active disubstituted ethanols having $n_2 = 1$ can be expressed by a two-term formula, the terms being of opposite sign and $\lambda_1 \simeq 1600$ Å, thus indicating that the hydroxyl group furnishes a partial rotation of the same direction as that of the substances in the visible region of the spectrum.[17] The substances with $n_2 > 1$ show anomalous dispersion in the lower members of the homologous series and normal dispersion in the higher members, which rotate in opposite direction from the lower. Thus it is evident that in all homologous series of primary carbinols, varying with the values of n_2 and n_3, the hydroxyl groups furnish a partial rotation of the same direction.

It may be pointed out here that for the members with $n_2 = 1$ or 2, the rotations of the carbinols and the corresponding hydrocarbons are of the same sign, yet in each case the rotations in the visible region of the spectrum are determined by groups situated in different parts of the molecule. Thus, in the hydrocarbon (A) the rotation in the visible region is determined by the partial rotation of the C_3H_7 group (which is levorotatory) and that of the carbinol (B) by the group OH or CH_2OH.

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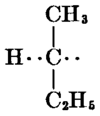
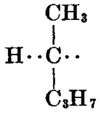
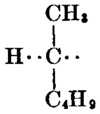
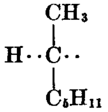
[16] LEVENE, P. A., AND MARKER, R. E., *J. Biol. Chem.*, **103**, 299 (1933).

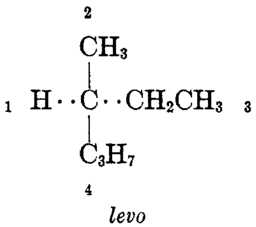
[17] LEVENE, P. A., AND ROTHEN, ALEXANDRE (unpublished results).

TABLE V

CONFIGURATIONALLY RELATED PRIMARY AND SECONDARY CARBINOLS AND HYDROCARBONS

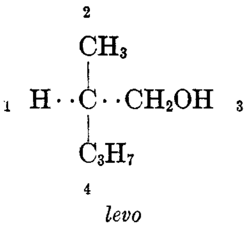
$[M]_D^{25}$ Max. (Homogeneous)

 $\mathrm{H}\cdot\cdot\underset{\substack{\vert \\ \mathrm{C_2H_5}}}{\overset{\substack{\mathrm{CH_3} \\ \vert}}{\mathrm{C}}}\cdot\cdot$	CH_2OH −5.2 CH_2CH_3 0	$(CH_2)_2OH$ +9.1 $(CH_2)_2CH_3$ +9.9	$(CH_2)_3OH$ +11.9 $(CH_2)_3CH_3$ +11.4	$(CH_2)_4OH$ +12.0 $(CH_2)_4CH_3$ +12.0
 $\mathrm{H}\cdot\cdot\underset{\substack{\vert \\ \mathrm{C_3H_7}}}{\overset{\substack{\mathrm{CH_3} \\ \vert}}{\mathrm{C}}}\cdot\cdot$	CH_2OH −6.8 CH_2CH_3 −9.9	$(CH_2)_2OH$ −2.1 $(CH_2)_2CH_3$ 0	$(CH_2)_3OH$ 0 $(CH_2)_3CH_3$ +1.7	$(CH_2)_4OH$ +1.7 $(CH_2)_4CH_3$ +2.4
 $\mathrm{H}\cdot\cdot\underset{\substack{\vert \\ \mathrm{C_4H_9}}}{\overset{\substack{\mathrm{CH_3} \\ \vert}}{\mathrm{C}}}\cdot\cdot$	CH_2OH −7.9 CH_2CH_3 −11.4	$(CH_2)_2OH$ −4.0 $(CH_2)_2CH_3$ −1.7	$(CH_2)_3OH$ −0.7 $(CH_2)_3CH_3$ 0	$(CH_2)_4OH$ 0 $(CH_2)_4CH_3$ +0.86
 $\mathrm{H}\cdot\cdot\underset{\substack{\vert \\ \mathrm{C_5H_{11}}}}{\overset{\substack{\mathrm{CH_3} \\ \vert}}{\mathrm{C}}}\cdot\cdot$	CH_2OH *levo* CH_2CH_3 −12.0	$(CH_2)_2OH$ −6.1 $(CH_2)_2CH_3$ −2.4	$(CH_2)_3OH$ −2.6 $(CH_2)_3CH_3$ −0.86	$(CH_2)_4OH$ −1.9 $(CH_2)_4CH_3$ 0



$${}_1\ H\cdot\cdot\underset{\underset{4}{C_3H_7}}{\overset{\overset{2}{CH_3}}{C}}\cdot\cdot CH_2CH_3\ {}_3$$

levo
A

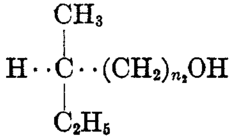


$${}_1\ H\cdot\cdot\underset{\underset{4}{C_3H_7}}{\overset{\overset{2}{CH_3}}{C}}\cdot\cdot CH_2OH\ {}_3$$

levo
B

(The numbers indicate the order of the groups according to their increasing volume.)

The observation that all lower members of the series

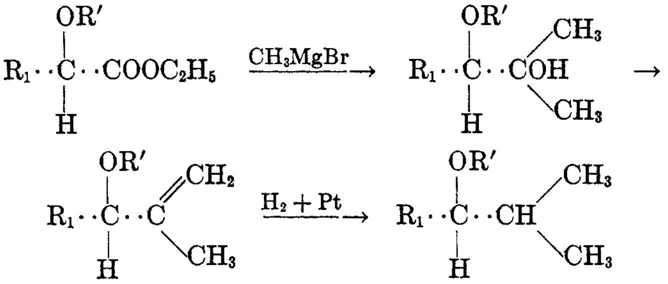


$$H\cdot\cdot\underset{C_2H_5}{\overset{CH_3}{C}}\cdot\cdot(CH_2)_{n_2}OH$$

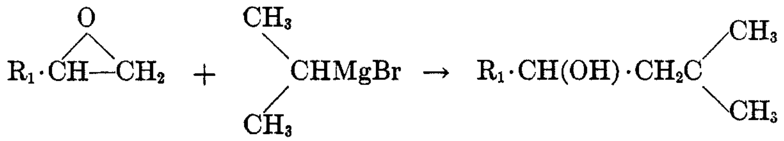
with values of $n_2>1$ are of sign opposite to those with $n_2 = 1$ could be shown to be due to the fact that in the former the partial contribution of the hydroxyl group has a lower numerical value and is of sign opposite to that of the sum of contributions furnished by the rest of the molecule.[17]

C. Carbinols of the Isopropyl and Isobutyl Series

The carbinols of the isopropyl series can be correlated with the normal series by the following set of reactions.[18]



The carbinols of the isobutyl series have been correlated with the normal series in the following manner[19]



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[18] Stevens, P. G., *J. Am. Chem. Soc.*, **54**, 3732 (1932).
Levene, P. A., and Marker, R. E., *J. Biol. Chem.*, **101**, 413 (1933).

[19] Levene, P. A., and Walti, A., *J. Biol. Chem.*, **71**, 461 (1927).

The rotations of the members of the homologous isopropyl and isobutyl series together with the corresponding normal series are given in Table VI. Comparing the rotations of the configurationally related propylisopropyl

TABLE VI

SECONDARY CARBINOLS CONTAINING AN ISOPROPYL OR ISOBUTYL GROUP

$[M]_D^{25}$ Max. (Homogenous)

$(CH_2)_2CH_3$	$-CH(CH_3)_2$	$(CH_2)_3CH_3$	$-CH_2-CH(CH_3)_2$
CH_3 H··C··OH C_3H_7 (*n*) +12.1	CH_3 H··C··OH C_3H_7 (*iso*) +4.7	CH_3 H··C··OH C_4H_9 (*n*) +11.8	CH_3 H··C··OH C_4H_9 (*iso*) +21.1 (?)
C_2H_5 H··C··OH C_3H_7 (*n*) +4.2	C_2H_5 H··C··OH C_3H_7 (*iso*) −16.7	C_2H_5 H··C··OH C_4H_9 (*n*) +9.4	C_2H_5 H··C··OH C_4H_9 (*iso*) +24.6
C_3H_7 (*n*) H··C··OH C_3H_7 (*n*) 0	C_3H_7 (*n*) H··C··OH C_3H_7 (*iso*) −27.1	C_3H_7 (*n*) H··C··OH C_4H_9 (*n*) +0.95	C_3H_7 (*n*) H··C··OH C_4H_9 (*iso*) +16.3
C_4H_9 (*n*) H··C··OH C_3H_7 (*n*) −0.95	C_4H_9 (*n*) H··C··OH C_3H_7 (*iso*) −35.9	C_4H_9 (*n*) H··C··OH C_4H_9 (*n*) 0	C_4H_9 (*n*) H··C··OH C_4H_9 (*iso*) +13.8
C_5H_{11} (*n*) H··C··OH C_3H_7 (*n*) *levo*	C_5H_{11} (*n*) H··C··OH C_3H_7 (*iso*) −38.2	C_5H_{11} (*n*) H··C··OH C_4H_9 (*n*) *levo*	C_5H_{11} (*n*) H··C··OH C_4H_9 (*iso*) +11.3

and butylisobutylcarbinols, it can be seen that the effect of the isopropyl group is opposite in sense to that of the isobutyl group. As with the hydrocarbons, increase of the distance of the isopropyl group from the asymmetric center by one (CH_2) group causes inversion of the sign of the partial rotation of the isopropyl group (or inversion of its vicinal effect on the hydroxyl group).

It may be mentioned here that the configurations of the isopropyl and of the isobutylcarbinols had been correlated at first on the basis of the knowledge of the rotations of the propylisopropyl and butylisobutylcarbinols, combined with information on the progressive changes in rotation of the consecutive members of the two homologous series.

It was argued that when the propylisopropylcarbinol is dextrorotatory, the rotations of the individual members in the homologous series progressively increase to the right and, since the members of the isopropyl series may be regarded as derived from the corresponding members of the normal series by the introduction of an additional dextrorotatory contribution, it follows that the isopropyl series is correlated to that normal series whose consecutive members increased in their rotations to the right.[20] In a similar manner the configurations of the members of the isobutyl series were correlated with those of the normal butyl series. The conclusions reached in this manner were subsequently substantiated by the direct chemical method.

A point of interest regarding the members of the homologous series of isopropylcarbinols is that the rotation of the first member of the series is opposite in sign to that of the higher members. In the course of study of the rotatory dispersions of several other homologous series of substances with a chromophoric group in the near-ultraviolet region of the spectrum, it has been observed that the partial rotations of the corresponding groups always remain of the same sign throughout the homologous series.

In the case of the isopropylcarbinols, the same condition should exist. Hence the rotatory dispersion curves of the lower and the higher members should be anomalous. The anomaly, however, could not be detected.[21] This failure, however, should not be attributed to the exceptional behavior of the members of the isopropylcarbinol series but rather to the fact that the absorption bands of the isopropyl radical and of the hydroxyl group are situated in the distant ultraviolet region of the spectrum so that the dispersion curves could not be extended sufficiently near to the region of absorption. Indeed, in the case of the phthalic esters of the isopropylcarbinols, no difficulty was encountered in the discovery of the anomaly in the rotatory dispersions of the higher members.

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[20] LEVENE, P. A., AND MARKER, R. E., *ibid.*, **90**, 669 (1931); **97**, 379 (1932).
FREUDENBERG, K., *Sitzber. Heidelberg. Akad. Wiss., Math.-Naturw. Klasse*, **1931**, 9.

[21] LEVENE, P. A., AND ROTHEN, ALEXANDRE (unpublished results).

D. Carbinols Containing an Ethylenic Group

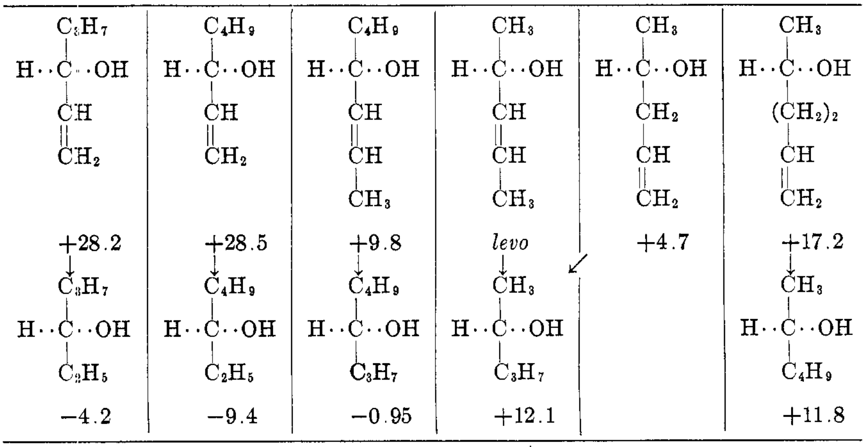
The configurational relationship of carbinols containing an ethylenic group to the saturated carbinols is readily arrived at by catalytic hydrogenation of the former.

The rotations of a number of unsaturated carbinols and the corresponding saturated carbinols are given in Table VII. The significant feature of the table is that the rotations of the unsaturated carbinols are opposite in sign to those of the saturated carbinols in all cases in which the ethylenic group is attached directly to the asymmetric carbon atom but the rotation remains in the same sense when the ethylenic group is removed from the asymmetric center by one (CH_2) group. Thus the rotations of Δ^1-pentenol-4 and Δ^2-pentenol-4 are in opposite directions.

TABLE VII

CONFIGURATIONALLY RELATED CARBINOLS CONTAINING A DOUBLE BOND

$[M]_D^{25}$ Max. (Homogeneous)



$\begin{array}{c} C_3H_7 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ CH \\ \Vert \\ CH_2 \end{array}$	$\begin{array}{c} C_4H_9 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ CH \\ \Vert \\ CH_2 \end{array}$	$\begin{array}{c} C_4H_9 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ CH \\ \Vert \\ CH \\ \vert \\ CH_3 \end{array}$	$\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ CH \\ \Vert \\ CH \\ \vert \\ CH_3 \end{array}$	$\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ CH_2 \\ \vert \\ CH \\ \Vert \\ CH_2 \end{array}$	$\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ (CH_2)_2 \\ \vert \\ CH \\ \Vert \\ CH_2 \end{array}$
$+28.2$ ↓	$+28.5$ ↓	$+9.8$ ↓	*levo* ↓	$+4.7$ ↙	$+17.2$ ↓
$\begin{array}{c} C_3H_7 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ C_2H_5 \end{array}$	$\begin{array}{c} C_4H_9 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ C_2H_5 \end{array}$	$\begin{array}{c} C_4H_9 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ C_3H_7 \end{array}$	$\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ C_3H_7 \end{array}$		$\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ C_4H_9 \end{array}$
-4.2	-9.4	-0.95	$+12.1$		$+11.8$

This change in the rotation of the molecule as a whole is associated with the change of the partial rotation of the ethylenic group. This conclusion emerges clearly from analysis of the rotatory dispersion curves of these substances, which, by virtue of the positions of their chromophoric group, permits one to extend the observations to sufficient proximity to the absorption band and thus to obtain definite information as to the direction of the partial rotation of the double bond.[22]

Thus, again it is seen that with the increase of its distance from the asymmetric center by one (CH_2) group, the chromophoric group changes the sign of its partial rotation. The fact that the influence of the double

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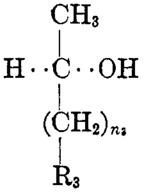
[22] LEVENE, P. A., AND ROTHEN, ALEXANDRE (unpublished results).

bond on the rotation varies with the distance of the bond from the asymmetric center has been noted by previous observers (particularly by Rupe[23]) but the change of sign had not been recognized before.

E. Secondary Carbinols Containing a Phenyl or Cyclohexyl Group

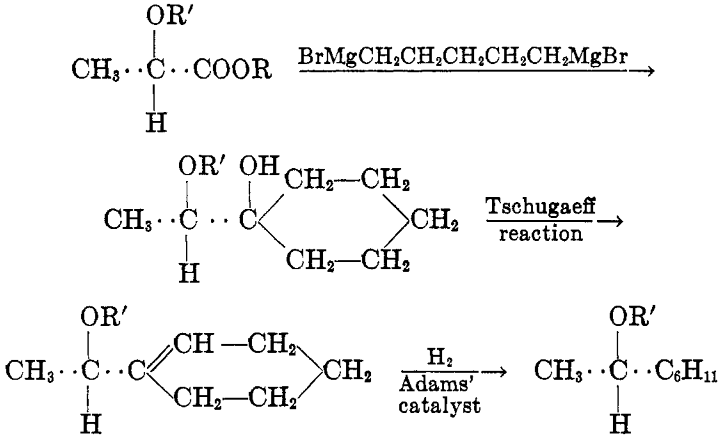


$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot OH \\ | \\ (CH_2)_{n_3} \\ | \\ R_3 \end{array}$$

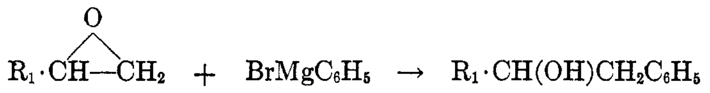
(n_3 = 0,1 or 2; R_3 = phenyl or cyclohexyl)

1. The configurational relationship of the members of the phenyl to the cyclohexyl series can easily be determined by hydrogenation of the former.

2. The configuration of methylcyclohexyl carbinol has been arrived at by methods of classical organic chemistry,[24] starting from the ester of 2-methoxypropionic acid of known configuration. The set of reactions leading to the synthesis are as follows:



3. The configuration of the benzyl series is arrived at through the method of the preparation of its members from the homologous ethylenic oxides of known configuration.[25]



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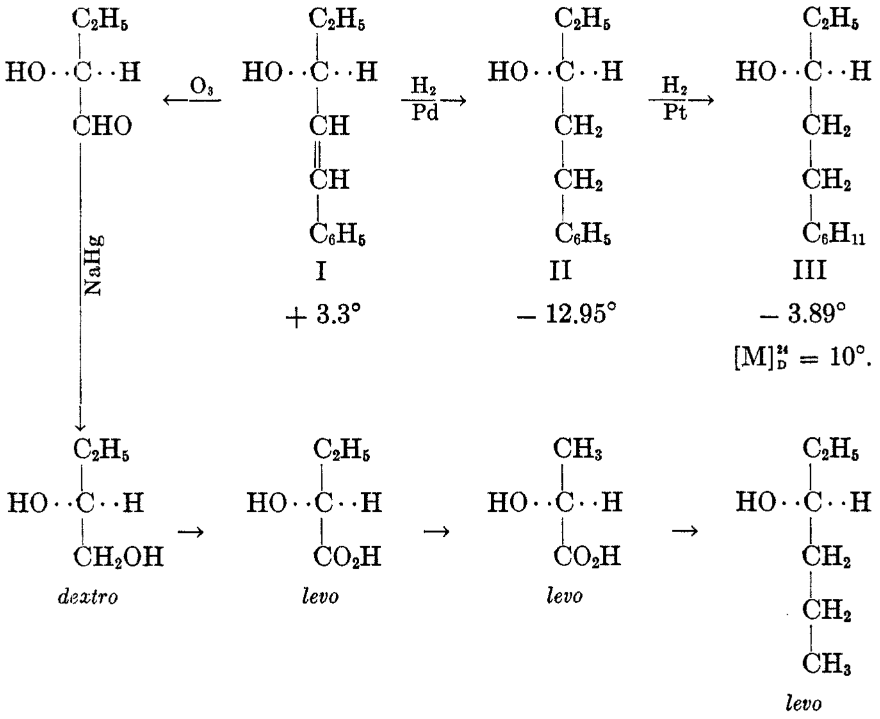
[23] Rupe, H., *Trans. Faraday Soc.*, **10**, 47 (1914).

[24] Levene, P. A., and Harris, Stanton A., *J. Biol. Chem.*, **113**, 55 (1936).

[25] Levene, P. A., and Walti, A., *ibid.*, **90**, 81 (1931).

4. The configuration of the phenethyl series is arrived at through the following set of reactions.[26]



In Table VIII the rotations of the members of the normal, the cyclohexyl and the phenyl series are compared. As in the case of the isopropyl series, the configurations of the cyclohexyl series at first had been arrived at on the basis of the progressive changes in rotation of consecutive members of the normal and the cyclohexyl series. As compared with the hexyl, the cyclohexyl group for the series given in Table VIII introduces a negative partial rotation and the negative rotation increases from member to member. Hence it is evident that in the corresponding normal aliphatic series the rotations of consecutive members likewise should increase towards the left. The conclusions arrived at on the basis of these considerations were later substantiated by the method of synthesis as given above, thus showing the validity of the theoretical speculations.

The effects of the distance from the asymmetric center of the chromophoric groups are recorded in Table IX.

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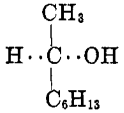
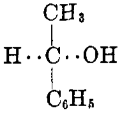
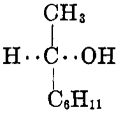
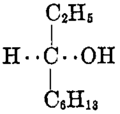
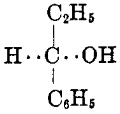
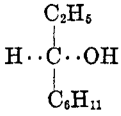
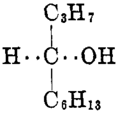
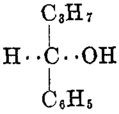
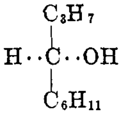
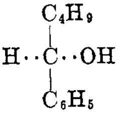
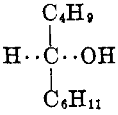
[26] Levene, P. A., and Stevens, P. G., *ibid.*, **87**, 375 (1930).

From Table IX there can be noted a periodicity in the direction of the shift of rotation with the progressive increase in the value of n_3, both in cyclohexyl and phenyl derivatives.

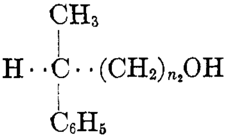
TABLE VIII

Configurationally Related Secondary Carbinols Containing a Phenyl, Cyclohexyl or Hexyl Group

$[M]_D^{25}$ Max. (Homogeneous)

 $H\cdot\cdot\overset{CH_3}{\underset{C_6H_{13}}{C}}\cdot\cdot OH$ +12.7	 $H\cdot\cdot\overset{CH_3}{\underset{C_6H_5}{C}}\cdot\cdot OH$ −52·5	 $H\cdot\cdot\overset{CH_3}{\underset{C_6H_{11}}{C}}\cdot\cdot OH$ +6.5
 $H\cdot\cdot\overset{C_2H_5}{\underset{C_6H_{13}}{C}}\cdot\cdot OH$ +11.6	 $H\cdot\cdot\overset{C_2H_5}{\underset{C_6H_5}{C}}\cdot\cdot OH$ −39.4	 $H\cdot\cdot\overset{C_2H_5}{\underset{C_6H_{11}}{C}}\cdot\cdot OH$ −11.5
 $H\cdot\cdot\overset{C_3H_7}{\underset{C_6H_{13}}{C}}\cdot\cdot OH$ *dextro*	 $H\cdot\cdot\overset{C_3H_7}{\underset{C_6H_5}{C}}\cdot\cdot OH$ −34.9	 $H\cdot\cdot\overset{C_3H_7}{\underset{C_6H_{11}}{C}}\cdot\cdot OH$ −17.0
	 $H\cdot\cdot\overset{C_4H_9}{\underset{C_6H_5}{C}}\cdot\cdot OH$ −28.2	 $H\cdot\cdot\overset{C_4H_9}{\underset{C_6H_{11}}{C}}\cdot\cdot OH$ −21.9

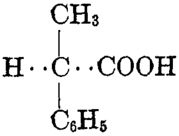
F. Primary Carbinols Containing a Phenyl Group



$$H\cdot\cdot\overset{CH_3}{\underset{C_6H_5}{C}}\cdot\cdot(CH_2)_{n_2}OH$$

(n_2 = 1, 2, 3 and 4)

The configurational relationship of this group of substances follows from their origin from



$$H\cdot\cdot\overset{CH_3}{\underset{C_6H_5}{C}}\cdot\cdot COOH$$

as in the case of primary carbinols of the normal aliphatic series.

TABLE IX

Configurationally Related Secondary Carbinols and Trisubstituted Methanes

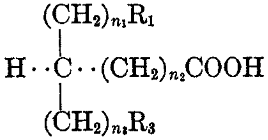
$[M]_D^{25}$ Max. (Homogeneous)

OH $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{C_6H_{13}}$	OH $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{C_6H_{11}}$	OH $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{C_6H_5}$	OH $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{C_6H_{13}}$	OH $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{C_6H_{11}}$	OH $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{C_6H_5}$	OH $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{CH_2}$ $\mathrm{C_6H_{13}}$	OH $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{CH_2}$ $\mathrm{C_6H_{11}}$	OH $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{CH_2}$ $\mathrm{C_6H_5}$
−11.6	+11.5	+39.7	−10.6	−42.0	−51.7	−10.7	−10.0	−31.0
$\mathrm{CH_3}$ $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{C_6H_{13}}$	$\mathrm{CH_3}$ $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{C_6H_{11}}$	$\mathrm{CH_3}$ $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{C_6H_5}$	$\mathrm{CH_3}$ $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{C_6H_{13}}$	$\mathrm{CH_3}$ $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{C_6H_{11}}$	$\mathrm{CH_3}$ $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{C_6H_5}$	$\mathrm{CH_3}$ $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{CH_2}$ $\mathrm{C_6H_{13}}$	$\mathrm{CH_3}$ $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{CH_2}$ $\mathrm{C_6H_{11}}$	$\mathrm{CH_3}$ $\mathrm{H\cdot\cdot C\cdot\cdot C_2H_5}$ $\mathrm{CH_2}$ $\mathrm{CH_2}$ $\mathrm{C_6H_5}$
−12.5	+19.5	−36.5	−12.5 (appr.)	−19.3	−9.25	−17.4	−16.8	−35.1

The rotations of the consecutive members with respect to n_2 are recorded in Table X.[27]

In this case the correlation of the configurations of the secondary carbinols with the primary is to be regarded as tentative and will not be discussed here. Among the members with $n_2 = 1$, 2 and 3 the periodicity in the shift of the direction of rotation with the increase of the value of n_2 is clearly seen.

III. ACIDS, NITRILES, AND ALDEHYDES



$$H\cdot\cdot\overset{(CH_2)_{n_1}R_1}{\underset{(CH_2)_{n_3}R_3}{C}}\cdot\cdot(CH_2)_{n_2}COOH$$

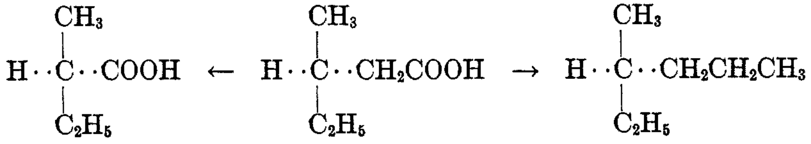
(General Type, Acids)

(n_1, n_2 and n_3 = 0, or an integer; $R_1 = CH_3$; $R_3 = CH_3$, C_6H_{11} or C_6H_5).

A. Configurational Relationships of Carboxylic Acids having R_1 *and* $R_3 = CH_3$ *and* $n_1 = 0$

Two problems presented themselves in connection with this group of substances, one dealing with the direction of rotation in series homologous with respect to n_2 and the other with respect to n_3. The key series of this group of substances is the series having $n_2 = 1$. On one hand, members of this series can (through the Hofmann degradation) be converted into the acid with $n_2 = 0$. On the other hand, they can serve as starting substances for the series having $n_2 > 1$.

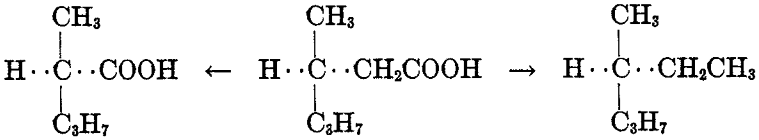
Given two consecutive members of a homologous series, it is evident that they should lead to two enantiomeric hydrocarbons.



$$H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot COOH \leftarrow H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot CH_2COOH \rightarrow H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot CH_2CH_2CH_3$$

dextro *dextro* *dextro*

I II III



$$H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot COOH \leftarrow H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot CH_2COOH \rightarrow H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot CH_2CH_3$$

dextro *levo* *levo*

VI V IV

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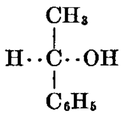
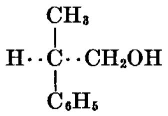
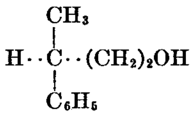
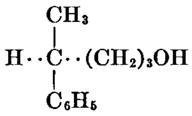
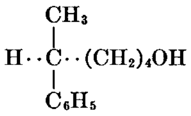
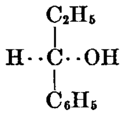
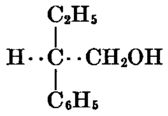
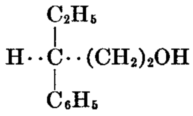
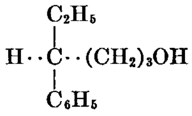
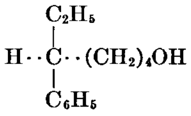
[27] Levene, P. A., and Marker, R. E., *ibid.*, **103**, 299 (1933).

TABLE X

Primary Carbinols Containing a Phenyl Group

$[M]_D^{25}$ Max. (Homogeneous)

 $\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ C_6H_5 \end{array}$ +52.5°(?)	 $\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot CH_2OH \\ \vert \\ C_6H_5 \end{array}$ −20.7°	 $\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot (CH_2)_2OH \\ \vert \\ C_6H_5 \end{array}$ −54.8°	 $\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot (CH_2)_3OH \\ \vert \\ C_6H_5 \end{array}$ −30.8°	 $\begin{array}{c} CH_3 \\ \vert \\ H\cdot\cdot C\cdot\cdot (CH_2)_4OH \\ \vert \\ C_6H_5 \end{array}$ −42.6°
 $\begin{array}{c} C_2H_5 \\ \vert \\ H\cdot\cdot C\cdot\cdot OH \\ \vert \\ C_6H_5 \end{array}$ +39.4°(?)	 $\begin{array}{c} C_2H_5 \\ \vert \\ H\cdot\cdot C\cdot\cdot CH_2OH \\ \vert \\ C_6H_5 \end{array}$ +35.0°	 $\begin{array}{c} C_2H_5 \\ \vert \\ H\cdot\cdot C\cdot\cdot (CH_2)_2OH \\ \vert \\ C_6H_5 \end{array}$ −24.8°	 $\begin{array}{c} C_2H_5 \\ \vert \\ H\cdot\cdot C\cdot\cdot (CH_2)_3OH \\ \vert \\ C_6H_5 \end{array}$ +2.0°	 $\begin{array}{c} C_2H_5 \\ \vert \\ H\cdot\cdot C\cdot\cdot (CH_2)_4OH \\ \vert \\ C_6H_5 \end{array}$ −18.2°

The two hydrocarbons are enantiomeric, inasmuch as one can be derived from the other by a single permutation—it thus follows that the two parent acids (which served for the preparation of the hydrocarbons) are configurationally related. Continuing the same operations with every consecutive pair of acids, the configurational relationship of any number of members of the homologous series can be established.[27, 28]

It may seem surprising that the method of direct conversion of the disubstituted acetic into disubstituted propionic acids was not employed for connecting the configurations of the members of the two homologous series. The method was not used, however, because in this case reduction of the esters of the acids leads to a high degree of racemization. The acids so far analyzed with regard to their configurations are recorded in Table XI.

Analysis of Table XI brings out the following facts:

1. The rotations of the members of the disubstituted acetic acids remain of the same sign and their values progressively increase.
2. In the homologous series of disubstituted propionic acids, the first member differs in the sign of its rotation from the higher members and is of the same sign as the members of the acetic acid series.
3. In this series (propionic) the values of the rotations of the successive members progressively increase.
4. The rotations of the members of the homologous series with $n_2 > 1$ decrease progressively in consecutive members.

On the basis of the theory that the rotation of each substance is the algebraic sum of several partial rotations differing in their sign, the conclusion can be reached at once that in the acetic acid series the values of the *positive* partial rotations increase progressively, whereas in the homologous series of acids with $n_2 > 0$ the values of the *negative* partial rotations increase. Since the carboxyl group is the most polar group possessing absorption bands in the region nearest to the visible, it seemed logical at first to assume that in all substances recorded in Table XI this group furnished the positive partial rotation.

The true meaning of the course of events emerged only from analysis of dispersion curves of this group of substances.[29] At this place it may be expedient to dwell at some length on the method employed for analysis of the rotatory dispersion curves of substances resembling (with respect to the absorption regions of their chromophoric groups) the above carboxylic acids. The group —COOH possesses one absorption band at about 2050 Å. Thus, on one hand, it is situated in a region which is inaccessible to

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[28] Levene, P. A., and Bass, L. W., *ibid.*, **70**, 211 (1926).

[29] Levene, P. A., Rothen, Alexandre and Marker, R. E., *J. Chem. Phys.*, **1**, 662 (1933).

TABLE XI

Configurationally Related Aliphatic Acids Containing a Methyl Group on the Asymmetric Carbon Atom

$[M]_D^{25}$ Max. (Homogeneous)

$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot COOH}$ +18.0	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot CH_2COOH}$ +10.4	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot (CH_2)_2COOH}$ +13.6	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot (CH_2)_3COOH}$ +11.1	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot (CH_2)_4COOH}$ +12.2
$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\,(\mathit{n})}{C}}\cdot\cdot COOH}$ +21.4	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\,(\mathit{n})}{C}}\cdot\cdot CH_2COOH}$ −3.6	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\,(\mathit{n})}{C}}\cdot\cdot (CH_2)_2COOH}$ +6.9	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_3H_7\,(\mathit{n})}{C}}\cdot\cdot (CH_2)_3COOH}$ +3.7	
$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\,(\mathit{n})}{C}}\cdot\cdot COOH}$ +24.3	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\,(\mathit{n})}{C}}\cdot\cdot CH_2COOH}$ −6.1	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\,(\mathit{n})}{C}}\cdot\cdot (CH_2)_2COOH}$ +4.1	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_4H_9\,(\mathit{n})}{C}}\cdot\cdot (CH_2)_3COOH}$ +1.7	
$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_7H_{15}\,(\mathit{n})}{C}}\cdot\cdot COOH}$ +27.3	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\,(\mathit{n})}{C}}\cdot\cdot CH_2COOH}$ −8.1	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\,(\mathit{n})}{C}}\cdot\cdot (CH_2)_2COOH}$ +1.9	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}\,(\mathit{n})}{C}}\cdot\cdot (CH_2)_3COOH}$ +0.6	
$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_{10}H_{21}\,(\mathit{n})}{C}}\cdot\cdot COOH}$ +27.5				

polarimetric measurements with the present-day technique, but, on the other hand, is near enough to render the extrapolation method sufficiently reliable.

The method of analysis is based on the following theoretical considerations.

The assumption is made that, as a first approximation, the dispersion curve at some distance from an absorption band can be expressed by two simple Drude terms. Under the dispersion curve in this instance is understood the graph of the function $((1/\alpha), \lambda^2)$.

The curvature of this graph varies in a definite manner depending upon the relationship of the term $A_1/(\lambda^2 - \lambda_1^2)$ to $A_2/(\lambda^2 - \lambda_2^2)$ (members of the two Drude term equation) as was definitely shown by Hunter.[30] It is evident that for very small intervals of the dispersion curve it is possible to find an expression $A_0/(\lambda^2 - \lambda_0^2)$ which can very nearly satisfy the right-hand term of the expression

$$[M] = A_1/(\lambda^2 - \lambda_1^2) \pm A_2/(\lambda^2 - \lambda_2^2).$$

The value of λ_0 and its variation with successive small wave-length intervals will provide the required information on the relative values of the four constants of the two-Drude-term formula.

Four combinations have to be considered in the discussion of the relationship of the dispersion curves to the relative values of the two terms. They are as follows:

Two terms of same sign (for long wave-lengths).

(1) $\lambda_1 > \lambda_2 [A_1/(\lambda^2 - \lambda_1^2)] > A_2/(\lambda^2 - \lambda_2^2)$

(2) $\lambda_1 > \lambda_2 [A_1/(\lambda^2 - \lambda_1^2)] < A_2/(\lambda^2 - \lambda_2^2)$.

Two terms of opposite sign (for long wave-lengths).

(3) $\lambda_1 > \lambda_2 [A_1/(\lambda^2 - \lambda_1^2)] > A_2/(\lambda^2 - \lambda_2^2)$

(4) $\lambda_1 > \lambda_2 [A_1/(\lambda^2 - \lambda_1^2)] < A_2/(\lambda^2 - \lambda_2^2)$.

Case 1.—The resulting curve is practically a straight line for the long wave-lengths, the curvature becoming more pronounced for λ approaching λ_1. The values of λ_0 lie in between λ_1 and $\lambda_2 (\lambda_2 < \lambda_0 < \lambda_1)$ and are progressively shifted towards λ_1 for smaller wave-lengths.

Case 2.—This is similar to 1 but the curvature is accentuated. The displacements of λ_0 are greater but we still have the condition $\lambda_2 < \lambda_0 < \lambda_1$.

Case 3.—We have here the condition $\lambda_2 < \lambda_1 < \lambda_0$. On the small wave-lengths side we observe a displacement of λ_0 towards λ_1. The curve in general will deviate from a straight line more than in cases 1 and 2. The

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[30] HUNTER, H., *J. Chem. Soc.*, **125**, 1198 (1924).

apparent shift of λ_0 may be considerable when the whole spectrum is considered. Rotations in the visible region may lead to λ_0 values 1500 Å higher than that obtained from rotation in the ultraviolet. (The more so, the more nearly A_1 and A_2 approach the same magnitude.)

Case 4.—With decreasing wave-lengths, the curve shows first a minimum at $\lambda_m(\lambda_2<\lambda_1<\lambda_m)$, then increases to $+\infty$, reappears at $-\infty$ and approaches zero for the smaller wave-lengths. (The rotation goes through a maximum, decreases, reaches a zero value and increases in the opposite direction.) The λ_0 values calculated from measurements in the long wave-lengths region are smaller than $\lambda_2(\lambda_0<\lambda_2<\lambda_1)$ and become negative for λ values approaching λ_m. The dispersion is said to be anomalous.

From this analysis it follows that the graph $((1/\alpha), \lambda^2)$ leads to information as to the direction of rotation of each of the two contributions and of their relative values.

Results of the Analysis of the Dispersion Curves

1. *Homologous Series of Acetic Acids* (n_2 = 0).—The curves could be expressed within a considerable wave-length interval, for all members, by a single Drude term where $\lambda_0 \simeq 1850$ Å, thus showing that the curve indicates a condition corresponding to case (1) or (2).

$$\left([M]^{25}_{\text{Max.}} = \frac{5.8110}{\lambda^2 - 0.03526} \text{ for 2-methylbutyric acid}\right).$$

These observations lead to the conclusion that the direction of the partial rotation of the carboxyl group is the same as that of the rotation of the substance in the visible region of the spectrum. The fact that $\lambda_0 \simeq 1850$ Å and not 2050 Å warrants the conclusion that the longer wave-length absorption band is either entirely inactive or contributes very little to the total partial rotation of the carboxyl group.

2. *Homologous Series of Disubstituted Propionic Acids* (n_2 = 1).—Experience has taught that (in the majority of cases) when, in a homologous series, rotations of the consecutive members at a certain value of n_3 change their direction, the course of rotatory dispersion is anomalous, either in the lower or in the higher members. Thus, in the case of disubstituted propionic acids, it is to be expected that either the first or the higher members should display anomaly.

It was found that the course of the rotatory dispersion of the first member is anomalous as represented in Fig. 1 and in Fig. 2 (curve 1).

The curve is expressed by the two-term Drude formula,

$$[M]^{25}_{\text{Max.}} = -\frac{8.088}{\lambda^2 - 0.042} + \frac{11.63}{\lambda^2 - 0.034},$$

Hence in this case $\lambda_1 \simeq 2050$ Å and $\lambda_2 \simeq 1850$ Å.

Thus it is evident that the longer wave-length absorption band (at λ 2050) of the carboxyl group furnishes the levorotatory and the rest of the molecule furnishes the dextrorotatory partial rotation. The value of λ_2 = 1850 Å may indicate that the second absorption band of the carboxyl group also contributes essentially to the dextrorotatory contribution. In other words, the more distant absorption region of the carboxyl group furnishes a partial rotation of the same sign in both the series of disubstituted acetic and propionic acids, whereas the partial rotation of the carboxyl group as a whole has a different direction in the acetic acid series from that in the propionic acid series.

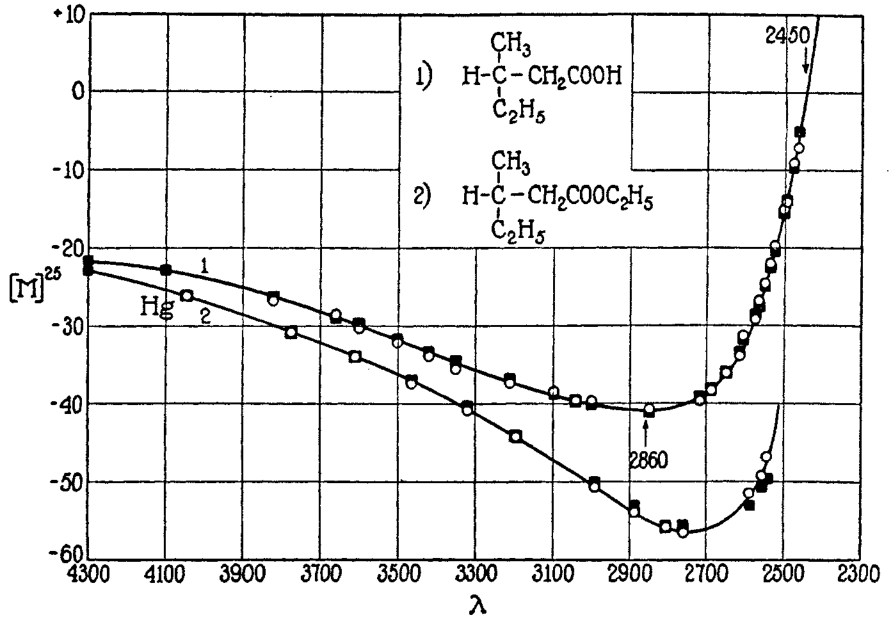


FIG. 1.—DISPERSIONS OF TWO COMPOUNDS EXHIBITING TYPICAL ABNORMALITY

Circles represent experimental values, solid squares, values calculated from a two-Drude-term formula.

This phenomenon is emphasized at this place since it may be of importance for the correlation of configurations by indirect methods.

In the higher members of this homologous series the dispersion curve runs a normal course. Hence, condition (4) is excluded. In this case the presence of two contributions of opposite sign is better seen in the esters, whose dispersion curve can be expressed by a two-term Drude formula.

Thus it appears that the partial contribution of the first band of the carboxyl group is of the same sign in the first and the higher members of this series, notwithstanding the fact that in the visible region the first member rotates in a direction opposite from that of higher members.

Homologous Series of Acids with n_2 = 2.—The progress of change of the numerical values of consecutive members alone (Table XI) indicates that, in this case likewise, the rotations in the visible region are each the sum of two contributions of opposite sign. Were the series extended to members higher with respect to n_2 the direction of rotation of those members might be opposite that given in Table XI.

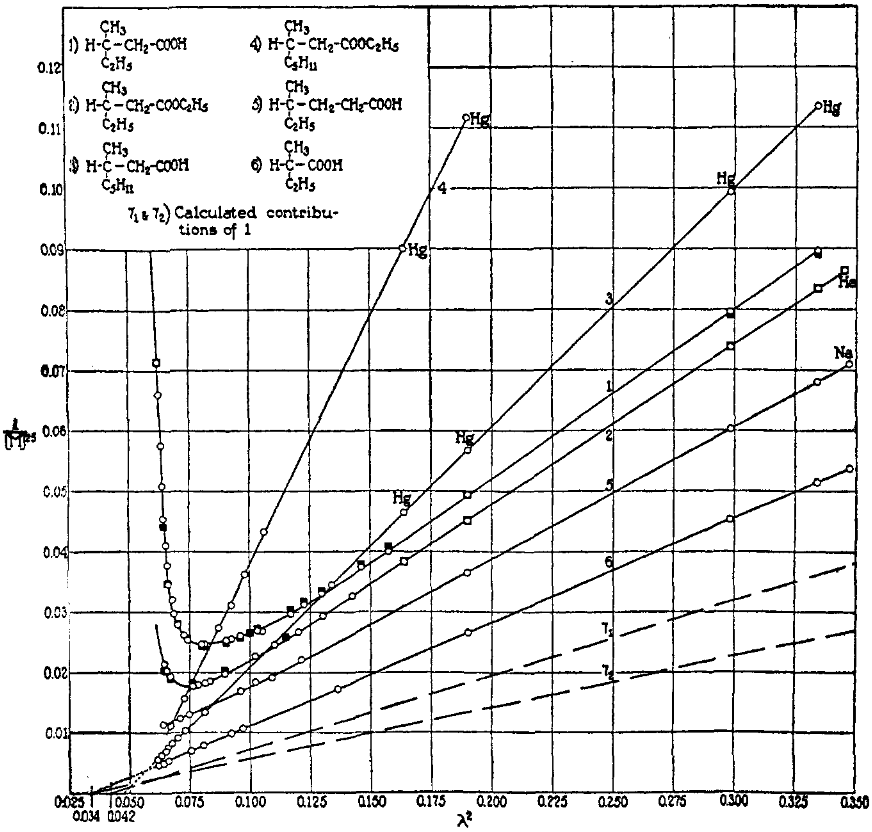


FIG. 2.—EXAMPLES OF THE MOST CHARACTERISTIC DISPERSION CURVES

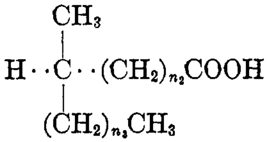
Circles represent experimental values, solid squares, calculated.

The rotatory dispersion curve of the first member of this series has been found to be similar to that of the first member of the disubstituted propionic acid series and similarly it can be expressed by a two-term Drude formula, the terms being of opposite sign.

$$[M]^{25}_{\text{Max.}} = -\frac{3.825}{\lambda^2 - 0.042} + \frac{8.395}{\lambda^2 - 0.032}$$

Thus the active absorption regions in the series with $n_2 = 1$ and in that with $n_2 = 2$ are identical.

To sum up, the analysis of the rotatory dispersion curves of carboxylic acids of the type



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot(CH_2)_{n_2}COOH \\ | \\ (CH_2)_{n_3}CH_3 \end{array}$$

leads to the following conclusions:

1. The directions of the corresponding partial rotations in every series homologous with respect to n_3 are identical for all members.

TABLE XII

ROTATION IN THE VISIBLE REGION AND PARTIAL ROTATIONS IN THE SERIES OF ALIPHATIC CARBOXYLIC ACIDS

SERIES	ROTATION IN VISIBLE REGION	DIRECTION OF PARTIAL ROTATION	
		2050 Å	1850 Å
Acetic	dextro	0	dextro
Propionic	levo (1st member excepted)	levo	dextro
Butyric	dextro	levo	dextro
Valeric	dextro	levo	dextro

2. There is a change of sign of the partial rotation of the carboxyl group when n_2 is changed in value from 0 to 1.

3. There is a periodic change in the shift of rotations with consecutive changes in the value n_2.

For convenience of survey, the partial rotations of the acids varying with respect to n_2 are presented in Table XII.

B. Configurational Relationship of Carboxylic Acids with R_3 = *a Phenyl or Cyclohexyl Group*

Five problems of importance presented themselves in connection with this group of substances.

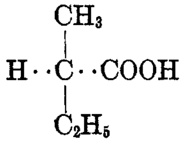
1. *The correlation of the members in homologous series with respect to* n_1.—This was solved in a manner analogous to that employed in the case of normal aliphatic acids, namely, through the comparison of the hydrocarbons of identical composition derived from two consecutive (with

respect to n_1) acids. The hydrocarbons should be enantiomeric if derived from two consecutive configurationally related acids.

2. *The correlation of the acids which differ from one another in their value of* n_2.—All acids with $n_2 > 0$ can be derived directly from those with $n_2 = 0$.

3. *The correlation of the acids varying with respect to* n_3.—This problem is solved by correlating the acids of each series with those of the corresponding normal series. (See 4).

4. *The correlation of the acids containing a phenyl group with those of the corresponding normal aliphatic series.*—This problem was solved by correlating the hydrocarbons derived from the acids containing a phenyl group with those derived from the acid



$$\mathrm{H}\cdot\cdot\overset{\displaystyle \mathrm{CH_3}}{\underset{\displaystyle \mathrm{C_2H_5}}{\mathrm{C}}}\cdot\cdot\mathrm{COOH}$$

by the two methods previously discussed in the section dealing with the correlation of the configurations of hydrocarbons containing a phenyl group.

5. *The correlation of the acids containing a phenyl group with those containing a cyclohexyl group.*—This task was accomplished by hydrogenation of the former.

Thus, it suffices in this place to record the rotations of the acids in the visible regions[31] (depending on the variations of n_2 and of n_3) and the analysis of their rotatory dispersion curves.

From Table XIII it may be seen that:

1. As in the case of carboxylic acids of the normal aliphatic series, there is in all phenyl acids a change of sign of rotation with increase of n_2 from 0 to 1.

2. There is a periodicity in the direction of the shift of rotation with the progressive increase in the value of n_2.

3. The direction of rotation of the acids is not influenced by the value of n_3.

The only striking difference between the acids of this series and those of the aliphatic series is the high values of the maximum rotations of all the phenyl acids with $n_2 = 0$, and of some of them with higher values of n_2.

The absorption curves of the acids are given in Fig. 3, and the partial rotations of each absorption region are recorded in Table XIII.[32]

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[31] Levene, P. A., and Marker, R. E., *J. Biol. Chem.*, **100**, 769 (1933).

[32] Levene, P. A., and Rothen, Alexandre (unpublished results).

TABLE XIII

Carboxylic Acids Containing a Phenyl Group

$[M]_D^{25}$ Max. (Homogeneous)*

	1st part. rot. + 2nd part. rot. −	1st part. rot. − 2nd part. rot. +	1st part. rot. − 2nd part. rot. +	1st part. rot. − 2nd part. rot. +
$H\cdot\cdot\underset{C_6H_{13}}{\overset{CH_3}{C}}\cdot\cdot COOH$ ≃+26.0	$H\cdot\cdot\underset{C_6H_5}{\overset{CH_3}{C}}\cdot\cdot COOH$ +111.6	$H\cdot\cdot\underset{C_6H_5}{\overset{CH_3}{C}}\cdot\cdot CH_2COOH$ −81.2	$H\cdot\cdot\underset{C_6H_5}{\overset{CH_3}{C}}\cdot\cdot (CH_2)_2COOH$ −39.3	$H\cdot\cdot\underset{C_6H_5}{\overset{CH_3}{C}}\cdot\cdot (CH_2)_3COOH$ −47.5
$H\cdot\cdot\underset{C_6H_{13}}{\overset{C_2H_5}{C}}\cdot\cdot COOH$ *dextro*	$H\cdot\cdot\underset{C_6H_5}{\overset{C_2H_5}{C}}\cdot\cdot COOH$ +140.	$H\cdot\cdot\underset{C_6H_5}{\overset{C_2H_5}{C}}\cdot\cdot CH_2COOH$ −83.3	$H\cdot\cdot\underset{C_6H_5}{\overset{C_2H_5}{C}}\cdot\cdot (CH_2)_2COOH$ −6.6	$H\cdot\cdot\underset{C_6H_5}{\overset{C_2H_5}{C}}\cdot\cdot (CH_2)_3COOH$ −22.1
$H\cdot\cdot\underset{C_7H_{15}}{\overset{CH_3}{C}}\cdot\cdot COOH$ +27.3	$H\cdot\cdot\underset{CH_2C_6H_5}{\overset{CH_3}{C}}\cdot\cdot COOH$ +31	$H\cdot\cdot\underset{CH_2C_6H_5}{\overset{CH_3}{C}}\cdot\cdot CH_2COOH$ −3.43	$H\cdot\cdot\underset{CH_2C_6H_5}{\overset{CH_3}{C}}\cdot\cdot (CH_2)_2COOH$ not prepared	$H\cdot\cdot\underset{CH_2C_6H_5}{\overset{CH_3}{C}}\cdot\cdot (CH_2)_3COOH$ not prepared
$H\cdot\cdot\underset{C_8H_{17}}{\overset{CH_3}{C}}\cdot\cdot COOH$ ≃+28	$H\cdot\cdot\underset{(CH_2)_2C_6H_5}{\overset{CH_3}{C}}\cdot\cdot COOH$ +51.2	$H\cdot\cdot\underset{(CH_2)_2C_6H_5}{\overset{CH_3}{C}}\cdot\cdot CH_2COOH$ −52.7	$H\cdot\cdot\underset{(CH_2)_2C_6H_5}{\overset{CH_3}{C}}\cdot\cdot (CH_2)_2COOH$ −6.52	$H\cdot\cdot\underset{(CH_2)_2C_6H_5}{\overset{CH_3}{C}}\cdot\cdot (CH_2)_3COOH$ −14.3

* For all these phenyl acids, the first absorption region (λ2700 to λ2500) [see Fig. 3] is inactive.

From Table XIII it will be seen that the first absorption region of the phenyl group does not furnish a partial rotation, which means that this region is not coupled with the absorption regions of shorter wave-lengths. The second absorption region of these acids is in the neighborhood of the second absorption region of the phenyl group as well as that of the first absorption region of the carboxyl group (which is probably slightly shifted towards the visible region). Inasmuch as in the normal aliphatic acetic series the acids rotate in opposite direction to the corresponding hydro-

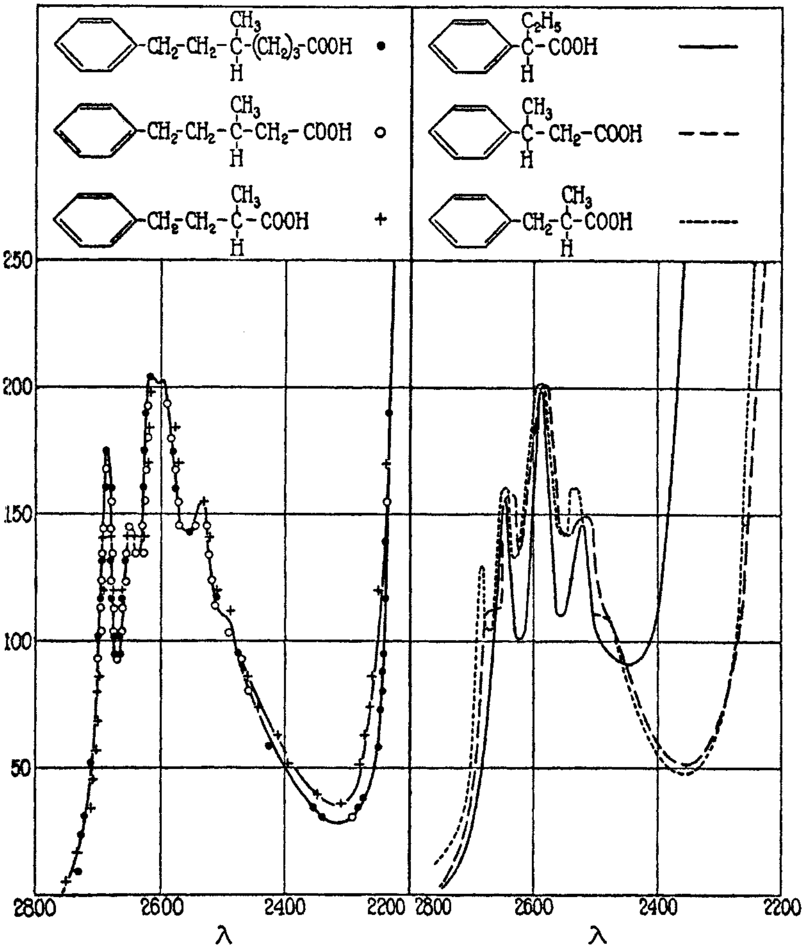


FIG. 3.—ABSORPTION CURVES OF PHENYL ACIDS IN HEPTANE SOLUTION

It is interesting to note how the distance between the aromatic ring and the carboxyl group affects the different absorption bands.

carbons (derived from the acids by the conversion of the carboxyl group into an ethyl group) and inasmuch as the same phenomenon is observed in the case of the phenyl series, it may be assumed that the partial rotation of the second absorption region is furnished in the latter series by the carboxyl group. Thus it follows that the partial rotation of the carboxyl group changes its direction with the change of n_2 from 0 to 1 and stays constant for all members with $n_2 > 1$.

The second partial rotation (of the third absorption region) represents the sum of the remaining contributions (including the shorter wavelengths absorption region of the phenyl group). This partial rotation likewise changes sign with the change of n_2 from 0 to 1. In this respect the acids of the phenyl series differ from those of the normal aliphatic series. Whether or not there is an inversion of the sign of the partial rotation of the phenyl group with the change of n_2 from 0 to 1 it is not possible to ascertain.

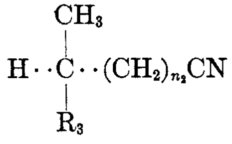
The high rotations of the members of the phenyl series may be attributed, not to the high partial rotation of the phenyl group, but rather to the vicinal effect of this group on the carboxyl. This assumption, however, has not been rigorously proved.

Thus the significant features of the observations in this series of acids are:

(1) the inversion of the sign of the partial rotation of the carboxyl group with the change of n_2 from 0 to 1,

(2) the periodicity, in the direction of the shift, of the partial rotation of the carboxyl group with the progressive increase in the value of n_2.

C. Normal Aliphatic Nitriles



$$H\cdot\cdot\underset{\displaystyle R_3}{\overset{\displaystyle CH_3}{C}}\cdot\cdot(CH_2)_{n_2}CN$$

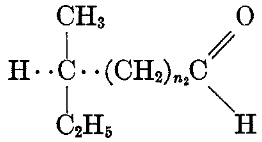
(n_2 = 0, 1, 2, 3 or 4).

Only one series of nitriles will be discussed here, namely that with $R_3 = C_4H_9$, the reasons being, first, that a greater number of members of this series has been prepared than of any other series and, second, that it has been established that the signs of the partial rotation of the chromophoric group R_2 (in this case CN stands for R_2) do not change in members of series homologous with respect to R_3. The interest attached to this group of substances lies in the position of the absorption band of the $—C{\equiv}N$ group, which lies farther in the distant ultraviolet region than that of the OH group: hence these derivatives offered an opportunity for appraising the effect on the rotation in the visible region of an absorption band situated in the distant ultraviolet region when the band differs in nature from that of a hydroxyl or a normal aliphatic radical.

The rotations of the nitriles in the visible region of the spectrum are presented in Table XIV. The configurational relationship of these acids is established on the basis of the method of preparation, namely, either from acids or from halides of known configuration.

From a survey of the rotations in the visible region it would seem that on passing from $n_2 = 0$ to $n_2 = 1$ no change of sign of the partial rotation takes place, and, furthermore, that the shift of rotation from the first to the second member and from the second to the third is in the same direction, namely, to the right. However, by analysis of the dispersion curves, an entirely different state of affairs was discovered. The dispersion curves of the second and third members were found anomalous, indicating that in these two members the second partial rotation furnishes the major contribution to the rotation in the visible region. Thus, there is a change of the partial rotation of the first absorption region with change of n_2 from 0 to 1. There is a second change of direction on passing from the substance having $n_2 = 1$ to that with $n_2 = 2$. In the shorter wave-length region a periodicity in the direction of the shift of rotation with progressive increase in the value of n_2 is observed.[33]

D. Aliphatic Aldehydes



($n_2 = 0, 1, 2$ or 3).

Analysis of this group of substances is simpler, owing to the position and the properties of the absorption bands of the aldehydic group. The first band at λ 2950 is weak ($\epsilon \simeq 20$), well isolated, and free from overlapping, thus permitting calculation of its partial rotation from the experimental dispersion curve within the region of the absorption band.

The rotations of the members of this group of substances are recorded in Table XV.

The configurational relationship of the members of this group of substances is evident from the method of their preparation,[34] which consisted in oxidation of the corresponding carbinols of known configuration or in synthesis from halides of known configuration by the method of Tschitschibabin.

[33] Levene, P. A., and Rothen, Alexandre (unpublished results).

[34] Levene, P. A., and Rothen, Alexandre, *J. Biol. Chem.*, **111**, 739 (1935).

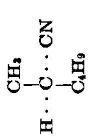
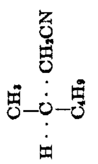
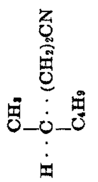
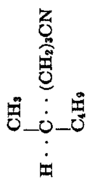
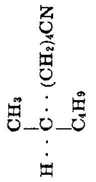
A reversal of sign is observed on passing from $n_2 = 0$ to $n_2 = 1$ and from $n_2 = 1$ to $n_2 = 2$. Analysis of the dispersion curves, however, brought out the fact that the dispersions of the members with $n_2 = 2$ or 3 are anomalous and it can be clearly seen that there is a periodic change in the shift of the partial rotation of the band λ 2950 and in all four members.[35]

In Fig. 4 are given the absorption curves of the four aldehydes and in Fig. 5, the dispersion curves of two of them. From the latter it is obvious that the sign of the partial rotation of the band λ 2950 changes with the change of n_2 from 0 to 1.

TABLE XIV

Configurationally Related Nitriles

$[M]_D^{25}$ Max. (Homogeneous)

	 $\mathrm{H}\cdots\overset{\mathrm{CH_3}}{\underset{\mathrm{C_4H_9}}{\mathrm{C}}}\cdots\mathrm{CN}$	 $\mathrm{H}\cdots\overset{\mathrm{CH_3}}{\underset{\mathrm{C_4H_9}}{\mathrm{C}}}\cdots\mathrm{CH_2CN}$	 $\mathrm{H}\cdots\overset{\mathrm{CH_3}}{\underset{\mathrm{C_4H_9}}{\mathrm{C}}}\cdots(\mathrm{CH_2})_2\mathrm{CN}$	 $\mathrm{H}\cdots\overset{\mathrm{CH_3}}{\underset{\mathrm{C_4H_9}}{\mathrm{C}}}\cdots(\mathrm{CH_2})_3\mathrm{CN}$	 $\mathrm{H}\cdots\overset{\mathrm{CH_3}}{\underset{\mathrm{C_4H_9}}{\mathrm{C}}}\cdots(\mathrm{CH_2})_4\mathrm{CN}$
$[M]_D^{25}$ Max.	−50.0	−5.9	+1.6	−5.2	−2.0
* First contribution	− −	+	− −	− −	−
Second contribution	+	− −	++	+	+

* The relative magnitudes are indicated by the number of (+) or (−) signs.

The mathematical expressions for the dispersion curves of the four substances in heptane solution are as follows:

$$\text{2-Methylbutanal-1 } [M]^{25}_{\text{Max.}} = + \frac{5.104}{\lambda^2 - 0.932}$$

$$\text{3-Methylpentanal-1 } [M]^{25}_{\text{Max.}} = - \frac{7.569}{\lambda^2 - 0.093} + \frac{6.693}{\lambda^2 - 0.032}$$

$$\text{4-Methylhexanal-1 } [M]^{25}_{\text{Max.}} = - \frac{0.371}{\lambda^2 - 0.087} + \frac{4.114}{\lambda^2 - 0.036}$$

$$\text{5-Methylheptanal-1 } [M]^{25}_{\text{Max.}} = - \frac{0.8158}{\lambda^2 - 0.087} + \frac{4.9102}{\lambda^2 - 0.036}$$

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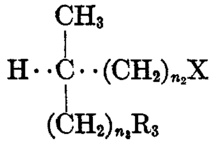
[35] Levene, P. A., and Rothen, Alexandre, *J. Chem. Phy.*, **4**, 48 (1936).

E. General Discussion of the Results of the Observations on Substances of the Type



$$H\cdot\cdot\overset{CH_3}{\underset{(CH_2)_{n_3}R_3}{C}}\cdot\cdot(CH_2)_{n_2}X$$

(where n_2 and n_3 = 0 or an integer; X = a functional group; R_3 = an alkyl or aryl group).

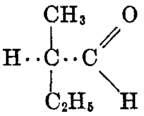
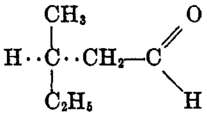
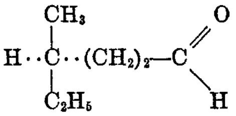
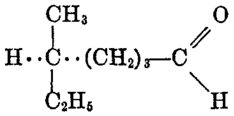
The most significant results obtained by changing the value of n_2 are the following:

(1) The partial rotations of the corresponding groups X in substances varying with respect to n_3 (having n_2 constant) remain of the same direction but change in magnitude relative to the sum of the remaining partial rotations.

TABLE XV

CONFIGURATIONALLY RELATED ALIPHATIC ALDEHYDES

$[M]^{25}_{D}$ Max. (in heptane)

			
+20.3°	−8.7°	+12.0°	+12.8°

(2) There is a change in the direction of the partial rotations of X with the change of n_2 from 0 to 1.

(3) There is a periodic change in the direction of the shift of rotation with progressive increase of n_2.

(4) The last two phenomena are associated with the change in the direction of rotation of the chromophoric group as a whole. This is due either to change in direction of the contribution of the identical absorption region (as in the case of CHO,+) or to the fact that another absorption band furnishes the dominant partial rotation (as for the carboxylic acids).

(5) No explanation can as yet be given for phenomena (2) (3) and (4) on the basis of present-day physical theories of optical rotation. Inasmuch as the phenomena are observed in substances in which X = a polar group, it is suggested that they are due to the alternating induced polarity of the carbon atoms of the chain $(CH_2)_{n_2}X$,—an effect transmitted to the central atom.

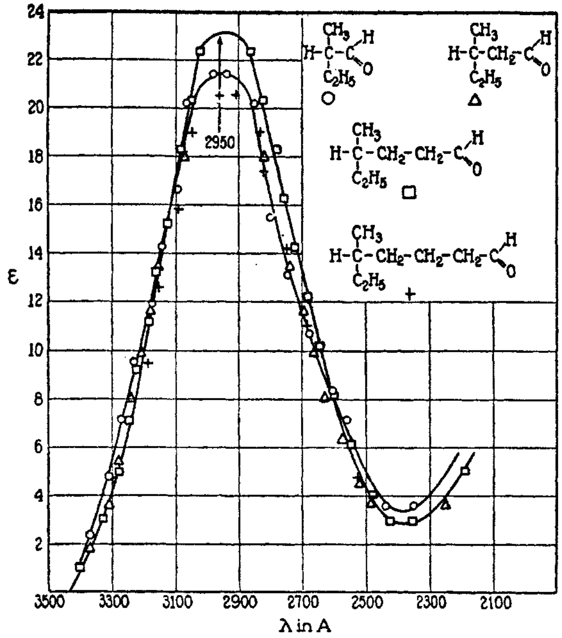

ε
24
22
20
18
16
14
12
10
8
6
4
2
3500
3300
3100
2900
2700
2500
2300
2100
λ in A
2950
CH3 H-C-C(H)(O) C2H5 ○
CH3 H-C-CH2-C(H)(O) C2H5 △
CH3 H-C-CH2-CH2-C(H)(O) C2H5 □
CH3 H-C-CH2-CH2-CH2-C(H)(O) C2H5 +

FIG. 4

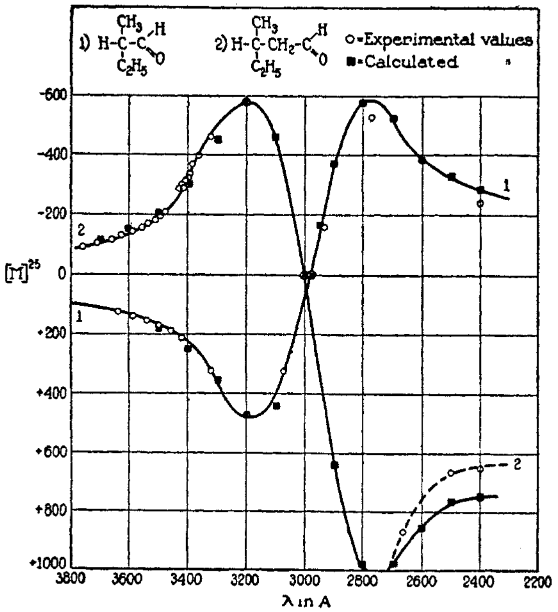
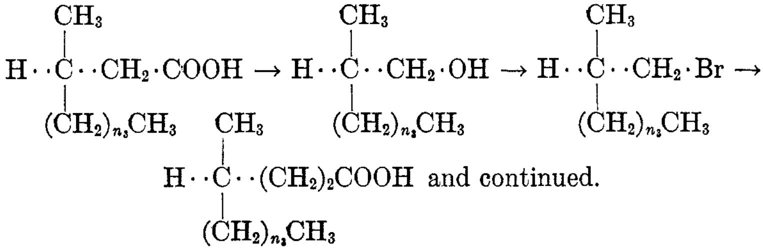

1) CH3 H-C-C(H)(O) C2H5
2) CH3 H-C-CH2-C(H)(O) C2H5
○-Experimental values
■-Calculated "
[M]25
-600
-400
-200
0
+200
+400
+600
+800
+1000
3800
3600
3400
3200
3000
2800
2600
2400
2200
λ in A
1
2
1
2

FIG. 5

F. A Test of the Correctness of the Configurational Relationships Assigned to the Substances Discussed in this Section

Throughout the discussion in this section configurational relationships have been postulated on the basis of the configurational relationships of the acids from which the substances were derived. The arguments by which this relationship was arrived at may be exemplified by the following set of reactions:



$$H\cdot\cdot\underset{(CH_2)_{n_3}CH_3}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}\cdot\cdot CH_2\cdot COOH \rightarrow H\cdot\cdot\underset{(CH_2)_{n_3}CH_3}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}\cdot\cdot CH_2\cdot OH \rightarrow H\cdot\cdot\underset{(CH_2)_{n_3}CH_3}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}\cdot\cdot CH_2\cdot Br \rightarrow$$

$$H\cdot\cdot\underset{(CH_2)_{n_3}CH_3}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}\cdot\cdot(CH_2)_2COOH \text{ and continued.}$$

When $n_2 = 0$ a rearrangement might have occurred in the process of bromination. Were this actually the case then the two acetates, one of which was derived from the carbinol directly and the other from the bromide, should have been of opposite sign. This, however, was not found to be the case.

When n_2 = an integer, the migration of the bromine atom might have taken place on one of the carbon atoms of $(CH_2)_{n_2}$. When n_3 was equal to $(n_2 + 1)$ and the bromine atom was substituted by a CH_3, an optically active hydrocarbon should have resulted. On the other hand, if rearrangement did not occur, then the hydrocarbon should be inactive. This test has been performed,[36] and the results indicated the absence of rearrangement in the course of the above reactions, hence proving the correctness of the configurational relationships arrived at in this section.

IV. APPLICATION OF THE RESULTS RECORDED IN THE PRECEDING SECTION

In preceding sections were discussed substances whose configurations could be determined by methods of classical organic chemistry. The present section will be devoted to groups of substances in which the configurations of the members with $n_2 = 0$ cannot be correlated with those with $n_2 = 1$ by this means. An attempt will be made to correlate their configurations on the basis of the experience gained through observations

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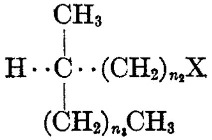
[36] LEVENE, P. A., AND MARKER, R. E., *J. Biol. Chem.*, **106**, 173 (1934); **108**, 409 (1935).

reported in the preceding sections. The substances belonging to this group are of the same general type,

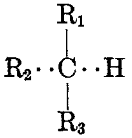


$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot(CH_2)_{n_2}X \\ | \\ (CH_2)_{n_3}CH_3 \end{array}$$

(where $X = OH$, NH_2, N_3 or a halogen atom; n_2 and $n_3 = 0$ or an integer).

A. Primary and Secondary Carbinols

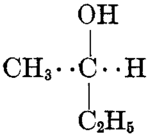
Correlation of the configurations of these two groups of substances is closely connected with the concept of absolute configuration. The configurations of primary carbinols are readily determined by reason of the fact that they are convertible into normal aliphatic hydrocarbons. The latter may be regarded (according to Boys) as dextrorotatory when the groups are arranged in space in such a manner that, viewed with the group of largest volume towards the observer, the remaining groups are arranged in a clockwise order according to decreasing volumes:



$$\begin{array}{c} R_1 \\ | \\ R_2\cdot\cdot C\cdot\cdot H \\ | \\ R_3 \end{array} \qquad (R_3 > R_2 > R_1 > H)$$

dextro

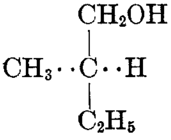
The configurations of the secondary carbinols would be correlated with those of corresponding hydrocarbons if the problem of the absolute configurations of the former could be solved with the same certainty as in the case of hydrocarbons. Within recent years two attempts have been made to solve this problem—one by Boys,[2] who suggested that the absolute configuration of simple substances such as secondary normal aliphatic carbinols can be determined on the basis of the arrangement in space of the individual groups (in the same manner as for hydrocarbons), taking the following order for the volumes of the groups: $H < OH < CH_3 < CH_2OH < (CH_2)_nCH_3$ (where $n = 1$ or a higher integer). On the basis of this assumption the absolute configurations of carbinols A and B are as given below, and the rotations (in the visible region) of the two carbinols are of opposite sign when the hydroxyl groups are in similar positions.



$$\begin{array}{c} OH \\ | \\ CH_3\cdot\cdot C\cdot\cdot H \\ | \\ C_2H_5 \end{array}$$

dextro

A



$$\begin{array}{c} CH_2OH \\ | \\ CH_3\cdot\cdot C\cdot\cdot H \\ | \\ C_2H_5 \end{array}$$

levo

B

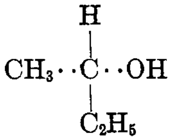
Boys evolved the following mathematical formula:

$$[\alpha] = \frac{16.62\ (n^2+2)\ (n^2+5)\ R_A R_B R_C R_D}{\lambda^2\ M}\ I\ ,$$

(where M = molecular weight of the substance, n = the observed refractive index of the medium, $R_A R_B R_C R_D$ = refractivities of the four groups, and I = a function of the radii of the groups which determines the sign of the rotation) by which he evaluated the expected rotation of two carbinols and obtained values of the order of magnitude of the experimental values.

It may be added that the theory of Boys fails entirely when a slight change is introduced into the structure of the simple secondary carbinol (*e.g.*, substitution of a propyl by an isopropyl group).

The conclusions of Boys were recently challenged by W. Kuhn.[10.5] This author devised an imaginary model whose direction of rotation is determined by the electric moment of the polar group $\equiv \mathrm{C}-\mathrm{O}{\diagup}^{\mathrm{H}}$ and by its position with respect to the clockwise or counterclockwise arrangement of the other three groups. Kuhn then attributed levorotation to the methylethylcarbinol of the following configuration:



$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{CH_3}\cdots & \mathrm{C} & \cdots\mathrm{OH} \\ & | & \\ & \mathrm{C_2H_5} & \end{array}$$

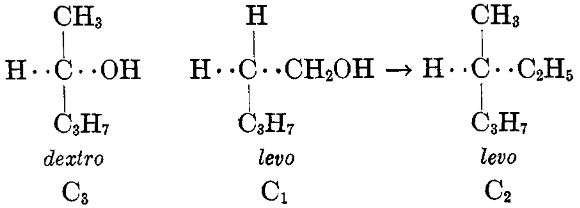
levo

According to this theory primary and corresponding secondary carbinols should rotate in the same direction in the visible region.

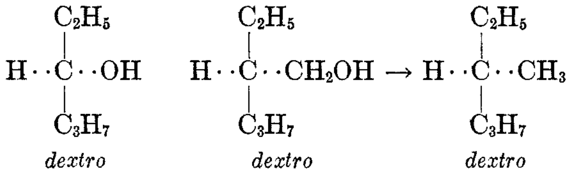
Both theories are based on theoretical physico-mathematical considerations; neither suffices to explain all the experimental observations.

The theory of Boys considers the rotation of the molecule as a whole and fails to take into account the partial rotation of either the hydroxyl or the other groups.

Deductions from the behavior of the model of Kuhn failed to predict the possibility of the carbinols A and B rotating in opposite directions.



$$\begin{array}{ccc} \mathrm{CH_3} & \mathrm{H} & \mathrm{CH_3} \\ | & | & | \\ \mathrm{H}\cdots\mathrm{C}\cdots\mathrm{OH} & \mathrm{H}\cdots\mathrm{C}\cdots\mathrm{CH_2OH} \rightarrow & \mathrm{H}\cdots\mathrm{C}\cdots\mathrm{C_2H_5} \\ | & | & | \\ \mathrm{C_3H_7} & \mathrm{C_3H_7} & \mathrm{C_3H_7} \\ \textit{dextro} & \textit{levo} & \textit{levo} \\ \mathrm{C_3} & \mathrm{C_1} & \mathrm{C_2} \end{array}$$

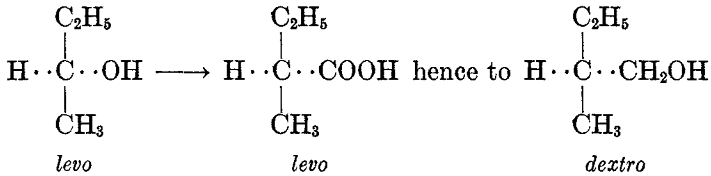


$$\begin{array}{ccc} C_2H_5 & C_2H_5 & C_2H_5 \\ | & | & | \\ H\cdot\cdot C\cdot\cdot OH & H\cdot\cdot C\cdot\cdot CH_2OH \rightarrow & H\cdot\cdot C\cdot\cdot CH_3 \\ | & | & | \\ C_3H_7 & C_3H_7 & C_3H_7 \\ \textit{dextro} & \textit{dextro} & \textit{dextro} \end{array}$$

D_3 D_1 D_2

From the above formulae (C_1 and D_1) it is evident that the two primary carbinols are configurationally related. It has also been found that their rotatory dispersions are normal.[37] Hence it follows that in both cases the direction of rotation in the visible is determined by the partial rotation of the hydroxyl group. It is evident then that one of the primary carbinols rotates in the same direction as the corresponding secondary carbinol whereas the other rotates in the opposite direction. The question naturally arises as to which primary carbinol rotates in the same direction as the corresponding secondary. The difference in the primary carbinols lies in their reverse order of spatial distribution of the four groups (in order of decreasing or increasing volumes). In the carbinol D_1 the order is the same as in the secondary carbinols, whereas in carbinol C_1 the order is reversed. Hence it may be assumed that carbinol D_1 should rotate in the same direction as the secondary D_3, whereas carbinol C_1 should rotate in the opposite direction. Thus the dextrorotatory secondary carbinols of type C_3 should be regarded as configurationally related to the levorotatory carbinol C_1.

It may here be added that Kenyon, Phillips and Pittman[38] correlated a levorotatory secondary carbinol with a levorotatory disubstituted acetic acid as follows:



$$\begin{array}{ccccc} C_2H_5 & & C_2H_5 & & C_2H_5 \\ | & & | & & | \\ H\cdot\cdot C\cdot\cdot OH & \longrightarrow & H\cdot\cdot C\cdot\cdot COOH & \text{hence to} & H\cdot\cdot C\cdot\cdot CH_2OH \\ | & & | & & | \\ CH_3 & & CH_3 & & CH_3 \\ \textit{levo} & & \textit{levo} & & \textit{dextro} \end{array}$$

Accepting this assumption, one observes a change of sign of rotation with the change of n_2 = from 0 to 1, in harmony with that observed in the substances discussed in the preceding sections.

It is therefore proposed to modify the rule of Boys to postulate that *the direction of rotation of the normal aliphatic carbinols is determined by the dissymmetry of the molecule as a whole. Molecules whose groups are*

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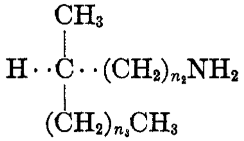
[37] Levene, P. A., and Rothen, Alexandre (unpublished results).

[38] Kenyon, J., Phillips, H., and Pittman, V. P., *J. Chem. Soc.*, **1935**, 1072.

arranged, as in the dextrorotatory hydrocarbons—according to the order of their volume—induce in the hydroxyl a partial rotation to the right, and vice versa.

B. Normal Aliphatic Amines



$$\begin{array}{l} \quad CH_3 \\ \quad\ | \\ H\cdot\cdot C\cdot\cdot(CH_2)_{n_2}NH_2 \\ \quad\ | \\ \ (CH_2)_{n_3}CH_3 \end{array}$$

(n_2 and n_3 = 0 or an integer).

Primary Amines.—In Table XVI are recorded the rotations of the amines of the above type together with those of the corresponding carbinols and hydrocarbons. The configurations of the amines follow from their method of preparation from the corresponding configurationally related nitriles or halides.[39]

Three facts emerge from a survey of Table XVI.

(1) The maximum rotations of the corresponding members of the three groups of substances are of the same order of magnitude.

(2) The values of the molecular rotations progressively decline, and the sign of rotation changes when $n_2 \geq n_3 + 1$. (The zero value in the case of the carbinol does not indicate loss of asymmetry since the same substance on halogenation yields an optically active halide, and an optically active carbinol results when the value of n_2 is changed from 4 to 5.) Thus it follows that with respect to optical activity the NH_2 group functions similarly to the group OH.

(3) When, instead of the rotation of the free amines, that of their ions is considered, then there is observed a periodic change in the direction of the shift of rotation with the progressive increase in the value of n_2.

Secondary Amines (n_2 = 0).—Rigorous correlation of the configurations of primary with those of secondary carbinols is of fundamental importance for the correlation of primary with secondary azides, inasmuch as the latter are readily reduced to the corresponding amines. It would thus be possible to correlate the configurations of primary with those of secondary azides and this correlation might then be made the basis for the correlation of primary with secondary halides.

However, the primary and secondary amines cannot as yet be correlated by the arguments employed in the case of the carbinols. It may, however, be warranted to correlate the configurations of secondary amines with those of secondary carbinols.

A basis for this correlation may be found in a comparison of the partial

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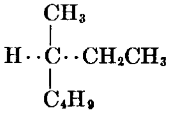
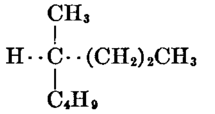
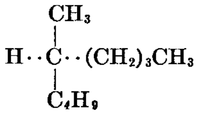
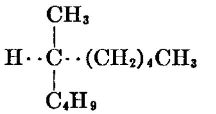
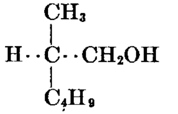
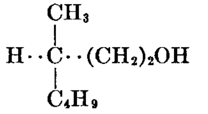
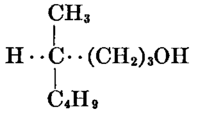
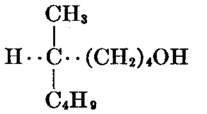
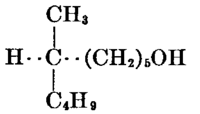
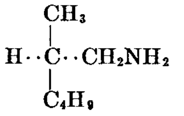
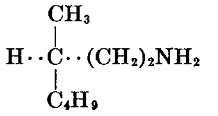
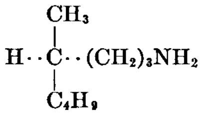
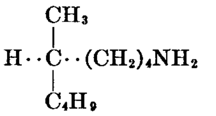
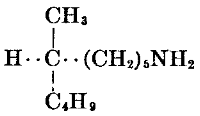
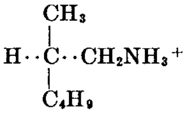
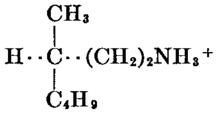
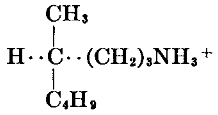
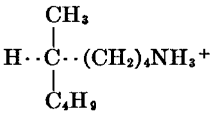
[39] LEVENE, P. A., ROTHEN, ALEXANDRE AND MARKER, R. E. (unpublished results).

TABLE XVI

ROTATIONS OF CONFIGURATIONALLY RELATED HYDROCARBONS, CARBINOLS AND AMINES

$[M]^{25}_{D}$ Max. (Homogeneous)*

$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{CH_2CH_3}$ −11.4	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_2CH_3}$ −1.7	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_3CH_3}$ 0	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_4CH_3}$ +0.86	
$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{CH_2OH}$ −7.9	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_2OH}$ −4.0	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_3OH}$ −0.7	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_4OH}$ 0	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_5OH}$ *dextro*
$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{CH_2NH_2}$ −16.	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_2NH_2}$ −1.7	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_3NH_2}$ −0.8	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_4NH_2}$ +0.5	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_5NH_2}$ +2.4
$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{CH_2NH_3}^{+}$ −13.	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_2NH_3}^{+}$ +2.1	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_3NH_3}^{+}$ −0.64	$\mathrm{H}\cdot\cdot\underset{\mathrm{C_4H_9}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\cdot\cdot\mathrm{(CH_2)_4NH_3}^{+}$ +1.1	

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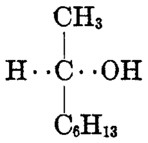
* The rotations of the hydrochlorides of the amines were measured in aqueous solution.

rotations of the hydroxyl and of the amino groups in primary carbinols and primary amines. In these the partial rotations of the amino and the hydroxyl groups are of the same direction. Thus it may be assumed that a similar relationship exists in the case of secondary carbinols and secondary amines. Granting the validity of this assumption, the correlation of the configurations of secondary carbinols with those of the secondary amines will follow from a knowledge of the direction of the partial rotation of the NH_2 group in the secondary amines.

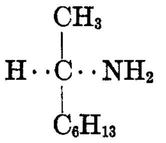
The rotatory dispersion curve of similar aliphatic amines has been found to be anomalous,[40] showing that the optical rotation of the amines in the visible region is the algebraic sum of two partial rotations of opposite sign, the contribution of the nearer anisotropic band of the amino group furnishing the contribution of lower numerical value. Hence in a dextrorotatory amine the nearest active absorption band of the amino group is levorotatory. In the case of the ion $R\cdot NH_3^+$ the anomaly disappears and the amino group then furnishes (in the visible region) the major contribution, which is in the same direction as that of the first contribution in the free amines. Thus, in the form of its hydrochloride, the dextrorotatory amine is levorotatory.

On the assumption that the partial rotation of the amino group is of the same direction as that of the hydroxyl, the following correlation is suggested:



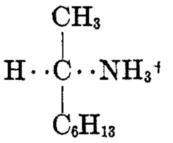
$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot OH \\ | \\ C_6H_{13} \end{array}$$

dextro



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot NH_2 \\ | \\ C_6H_{13} \end{array}$$

levo



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot NH_3^+ \\ | \\ C_6H_{13} \end{array}$$

dexto

It may be mentioned that a similar relationship has been suggested by Kenyon, Phillips and Pittman.[38] The probability of this conclusion would be enhanced if it were possible to obtain more accurate information as to the origin of the second partial contribution of the amines. In order that the above assumption might be justified, the sign of the second contribution should be furnished by the sum of the partial rotations of the groups other than the NH_2 group. Unfortunately, the opacity (and the low molecular rotation) of the amines does not permit rotatory measurements sufficiently far into the ultraviolet region.

The following information now is available for correlation of the primary to the secondary amines:

(1) The partial rotations of the amino and of the hydroxyl groups in corresponding primary amines and carbinols are of the same sign.

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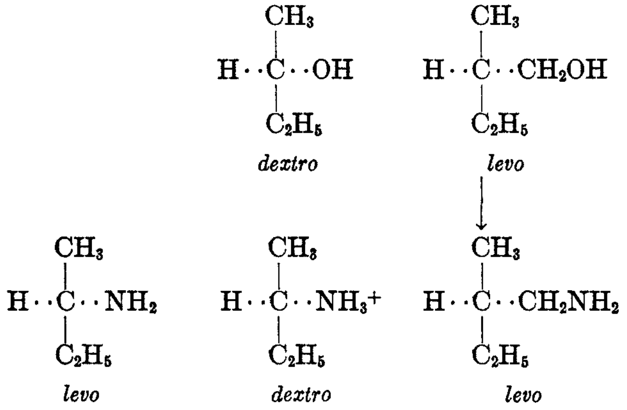
[40] LEVENE, P. A., AND ROTHEN, ALEXANDRE (unpublished results).

(2) The hydroxyl groups of the primary and secondary carbinols rotate in opposite directions (on the basis of the assumed absolute configurations of the two groups of substances).

(3) The secondary carbinols and amines rotate in opposite directions; the carbinols and the salts of the secondary amines rotate in the same direction.

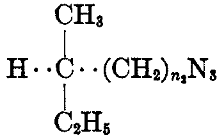
On the basis of these premises, it may be permissible to postulate that *primary and secondary amines rotate in the same direction in the visible region; and that primary amines and the salts of secondary amines rotate in opposite directions.* (This applied to the substances having $R_1 = CH_3$).



$$\begin{array}{ccc} & \begin{array}{c}CH_3\\ |\\ H\cdot\cdot C\cdot\cdot OH\\ |\\ C_2H_5\\ \textit{dextro}\end{array} & \begin{array}{c}CH_3\\ |\\ H\cdot\cdot C\cdot\cdot CH_2OH\\ |\\ C_2H_5\\ \textit{levo}\end{array}\\ & & \downarrow\\ \begin{array}{c}CH_3\\ |\\ H\cdot\cdot C\cdot\cdot NH_2\\ |\\ C_2H_5\\ \textit{levo}\end{array} & \begin{array}{c}CH_3\\ |\\ H\cdot\cdot C\cdot\cdot NH_3^+\\ |\\ C_2H_5\\ \textit{dextro}\end{array} & \begin{array}{c}CH_3\\ |\\ H\cdot\cdot C\cdot\cdot CH_2NH_2\\ |\\ C_2H_5\\ \textit{levo}\end{array}\end{array}$$

In favor of this correlation may be cited the fact that the change of n_2 from 0 to 1 brings about a change in the direction of the partial rotation of the amino group, an event in harmony with observations in the series of substances discussed in sections I, II, and III.

C. Azides



$$\begin{array}{c}CH_3\\ |\\ H\cdot\cdot C\cdot\cdot (CH_2)_{n_2}N_3\\ |\\ C_2H_5\end{array}$$

(where $n_2 = 0, 1, 2$ and 3).

The configurational relationship of the members of this group of substances (with $n_2 = 1, 2,$ or 3) follows from their preparation (through the iodides) from carbinols of known configuration.

In Table XVII are recorded the rotations for the sodium D line of the members of this series,[41] and also the equations expressing the rotatory dispersions.

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[41] LEVENE, P. A., AND ROTHEN, ALEXANDRE (unpublished results).

In the azido group two absorption regions can be distinguished; one weak band at λ 2880 and a strong absorption from λ 2200 down.

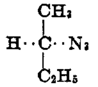
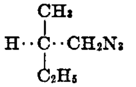
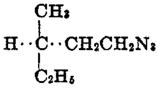
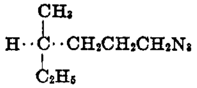
Analysis of the rotatory dispersion curves of this group of substances brings out the fact that in none of these members does the first absorption band furnish a contribution to the optical activity.[42] The distant part of the second region is anisotropic. In the three primary azides given in Table XVII, the major part of the rotation in the visible is furnished by the azido group. (It should be mentioned, however, that the higher members of the series with $n_2 = 1$ are of opposite sign, the rotatory dispersion being anomalous—showing convincingly that the rotations in the visible region are the resultants of two contributions of opposite sign.)

The configuration of the members with $n_2 = 0$ cannot be determined by methods of classical organic chemistry. However, the secondary azides can be converted by catalytic reduction into amines having the same sign of rotation in the visible region as the parent substance. Hence, granting the validity of the correlation of the amines having $n_2 = 0$ with those having $n_2 = 1$, the correlations of the azides should be given as in Table XVII.

TABLE XVII

CONFIGURATIONALLY RELATED AZIDES

$[M]^{25}_{D}$ Max. (in heptane)

	 $\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot N_3}$	 $\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot CH_2N_3}$	 $\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot CH_2CH_2N_3}$	 $\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot CH_2CH_2CH_2N_3}$
$[M]^{25}_{D}$ Max.........	−16	+10	+26	+17
$[M]^{25}$ Max.........		$+\frac{3.211}{\lambda^2-0.03625}$	$+\frac{8.300}{\lambda^2-0.0352}$	$+\frac{5.338}{\lambda^2-0.0314}$

Comparing the course of events following the progressive increase in the value of n_2 in this series of compounds with that observed in the various series of substances discussed in the preceding sections (of which the aldehydes were the most representative example), it emerges that change of n_2 from 0 to 1 brings about the same phenomenon in both series, namely, a change in the direction of the partial rotation of the active chromophoric group nearest to the visible region.

On the other hand, periodic change in the shift of rotation with the progressive increase in the value of n_2 begins in the case of the azides with the member having $n_2 = 1$.

[42] LEVENE, P. A., AND ROTHEN, ALEXANDRE (unpublished results).

TABLE XVIII

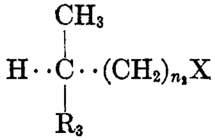
Configurationally Related Bromides

$[M]_D^{25}$ (Homogeneous)

$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot CH_2Br}$ +7.9	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot (CH_2)_2Br}$ +38.8	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot (CH_2)_3Br}$ +21.9	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot (CH_2)_4Br}$ +14.9	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot (CH_2)_5Br}$ +14.0
$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot CH_2Br}$ *low dextro*	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot (CH_2)_2Br}$ +21.0	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot (CH_2)_3Br}$ +14.5	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_3H_7}{C}}\cdot\cdot (CH_2)_4Br}$ +7.8	
$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_4H_9}{C}}\cdot\cdot CH_2Br}$ *low dextro*	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_4H_9}{C}}\cdot\cdot (CH_2)_2Br}$ +16.8	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_4H_9}{C}}\cdot\cdot (CH_2)_3Br}$ +8.3	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_4H_9}{C}}\cdot\cdot (CH_2)_4Br}$ +5.3	
$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}}{C}}\cdot\cdot CH_2Br}$ *low dextro*	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}}{C}}\cdot\cdot (CH_2)_2Br}$ +14.7	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}}{C}}\cdot\cdot (CH_2)_3Br}$ +6.2	$\mathrm{H\cdot\cdot\overset{CH_3}{\underset{C_5H_{11}}{C}}\cdot\cdot (CH_2)_4Br}$ +4.0	

A periodicity beginning with the first member would have existed if the secondary azide with $[M]_D^{25} = -16°$ had been substituted for that with $[M]_D^{25} = +16°$. In this case, however, no change in the partial rotation of the azido group would have taken place on increasing n_2 from 0 to 1. Thus, in neither case is the course of events in the series of azides identical with that found for the aldehydes.

D. Halides



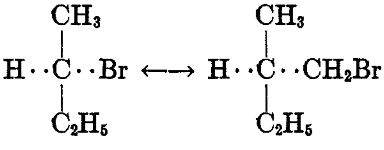
$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot(CH_2)_{n_2}X \\ | \\ R_3 \end{array}$$

(n_2 = 0 or an integer; X = a halogen atom; R_3 = an alkyl group).

In Table XVIII are recorded the maximum rotations for the D line of members of several homologous series of alkyl bromides, each series differing from the other in the value of n_2.[27] From the table it can be seen that with the progressive increase of the value of n_2 (from 1 to 2 to 3) there is associated a periodic change in the direction of the shift of rotation.

The direction of rotation of the corresponding secondary bromides is not known and cannot be arrived at by the classical methods of organic chemistry nor can the configurations of the secondary halides be correlated to those of corresponding secondary carbinols by any direct chemical method.

An attempt may be made to correlate the configurations of these substances by using the experience gained from the observations recorded in the preceding sections. In the series previously discussed the most significant event is the inversion of the direction of rotation of the individual members with increase of n_2 from 0 to 1. Granting that this phenomenon holds also for the series of the alkyl bromides the following correlation would follow:



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot Br \\ | \\ C_2H_5 \end{array} \longleftrightarrow \begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot CH_2Br \\ | \\ C_2H_5 \end{array}$$

levo *dextro*

This assumption, however, can only be made provided the sign of rotation given in Table XVIII could be shown to be due, in each case, to the partial rotation of the bromine atom. More accurate information as to the origin of the rotations of the halides in the visible region can be obtained only

TABLE XIX

EQUATIONS REPRESENTING THE MAXIMUM MOLECULAR ROTATIONS OF THE IODIDES, BROMIDES AND CHLORIDES (IN HOMOGENEOUS STATE) VALID IN THE VISIBLE AND THE NEAR-ULTRAVIOLET SPECTRUM

Levo 2-Iodobutane

$$[M]^{25}_{\text{Max.}} = -\frac{9.8023}{\lambda^2 - 0.0685} - \frac{7.2490}{\lambda^2 - 0.040}$$

Levo 2-Iodoöctane

$$[M]^{25}_{\text{Max.}} = -\frac{13.312}{\lambda^2 - 0.069} - \frac{15.162}{\lambda^2 - 0.040}$$

$$[M]^{25}_{\text{Max.}} = -\frac{12.226}{\lambda^2 - 0.069} - \frac{18.175}{\lambda^2 - 0.040} \text{ (in heptane)}$$

Dextro Iodo-2-Methylbutane

$$[M]^{25}_{\text{Max.}} = -\frac{4.7539}{\lambda^2 - 0.043} + \frac{8.5535}{\lambda^2 - 0.028}$$

Dextro 1-Iodo-2-Methylheptane

$$[M]^{25}_{\text{Max.}} = -\frac{4.4216}{\lambda^2 - 0.046} + \frac{6.2033}{\lambda^2 - 0.032}$$

Dextro 1-Iodo-2-Methylnonane

$$[M]^{25}_{\text{Max.}} = -\frac{5.707}{\lambda^2 - 0.040} + \frac{7.527}{\lambda^2 - 0.018}$$

Dextro 1-Iodo-3-Methylpentane

$$[M]^{25}_{\text{Max.}} = +\frac{14.133}{\lambda^2 - 0.0466}$$

Dextro 1-Iodo-4-Methylhexane

$$[M]^{25}_{\text{Max.}} = +\frac{8.377}{\lambda^2 - 0.0336}$$

Levo 2-Bromobutane

$$[M]^{25}_{\text{Max.}} = -\frac{12.614}{\lambda^2 - 0.032} + \frac{3.482}{\lambda^2}$$

Levo 2-Bromoöctane

$$[M]^{25}_{\text{Max.}} = -\frac{22.159}{\lambda^2 - 0.034} - \frac{2.540}{\lambda^2 - 0.025} + \frac{5.434}{\lambda^2 - 0.010}$$

Dextro 1-Bromo-2-Methylbutane

$$[M]^{25}_{\text{Max.}} = -\frac{9.4151}{\lambda^2 - 0.032} + \frac{12.169}{\lambda^2 - 0.025}$$

TABLE XIX—*Continued*

Dextro 1-Bromo-3-Methylpentane

$$[M]^{25}_{\text{Max.}} = +\frac{12.243}{\lambda^2 - 0.0317}$$

Levo 2-Chlorooöctane

$$[M]^{25}_{\text{Max.}} = -\frac{15.966}{\lambda^2 - 0.024} - \frac{7.329}{\lambda^2 - 0.020} + \frac{10.820}{\lambda^2 - 0.012}$$

Dextro 1-Chloro-2-Methylbutane

$$[M]^{25}_{\text{Max.}} = -\frac{3.667}{\lambda^2 - 0.030} + \frac{4.352}{\lambda^2 - 0.020}$$

Dextro 1-Chloro-3-Methylheptane

$$[M]^{25}_{\text{Max.}} = +\frac{4.6373}{\lambda^2 - 0.025} - \frac{2.1879}{\lambda^2 - 0.015}$$

Dextro 1-Chloro-5-Methylnonane

$$[M]^{25}_{\text{Max.}} = +\frac{1.763}{\lambda^2 - 0.025} - \frac{1.059}{\lambda^2 - 0.015}$$

through the study of the dispersion curves of these substances. It was soon discovered that analysis of the dispersion curves of the bromides alone does not suffice to furnish the required information, because of the position of the absorption bands of the bromine atom with a first continuum (λ1990) relatively close to the second region of absorption, which can be resolved into terms fitting two Rydberg series starting at λ1786.[43] Observations could not be extended to wave-lengths <λ2500 on account of the opacity of the substance.

Hence it seemed advantageous to supplement the observations on the bromides with those on the iodides and chlorides. The *iodides* offered the advantage of having one absorption region (continuum) in the near ultraviolet widely separated from the second region of absorption, and the *chlorides* that of relatively great transparency, which permitted extension of the observations farther into the ultraviolet region.

In Table XIX the equations expressing the maximum molecular rotations of the iodides, bromides and chlorides, valid for the visible and the near-ultraviolet region of the spectrum, are given.[44]

---

[43] Price, W. C., *Phys. Rev.*, **47**, 510 (1935).

[44] Levene, P. A., and Rothen, Alexandre, *Science*, **81**, 623 (1935) [details unpublished].

From Table XIX the following conclusions can be reached:

1. In all the halides the major part of the rotation in the visible is furnished by the partial rotation of the halogen atom as a whole.

2. The anomalous course of the dispersion curves of the series with $n_2 = 1$ is due to the fact that the value of the partial rotation of the third absorption region of the halides is of opposite sign and greater than that of the second absorption region.

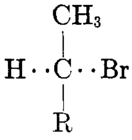
3. The first absorption band of the iodine atom is appreciably anisotropic only in the members with $n_2 = 0$.

TABLE XX

Directions of the Partial Rotations of the Absorption Regions of the Configurationally Correlated Halides

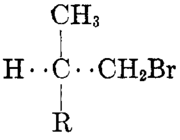
n_2	0	1	2	3
First Band	−	0	0	0
Second Band	−−	−	++	+
Third Band	−	++	−	++
Fourth Band (In the main furnished by the rest of the molecule)	++	?	?	?

4. If the levorotatory members of the series with $n_2 = 0$ are taken to be correlated with the dextrorotatory members of the primary halides with $n_2 = 1$,



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot Br \\ | \\ R \end{array}$$

levo



$$\begin{array}{c} CH_3 \\ | \\ H\cdot\cdot C\cdot\cdot CH_2Br \\ | \\ R \end{array}$$

dextro

then the relative values of the partial rotations of each band of the halides would be as given in Table XX.

A periodicity in the direction of the shift of rotation of the third absorption region may be noted. For the second region the periodicity begins after n_2 reaches the value of 1. The partial contributions of the halogen atom as a whole show periodicity of shift of rotation only for $n_2 > 0$.

A periodicity is observed in the dispersive power of the chlorides with successive values of n_2, as can be seen from Table XXI, in which the values of λ_0 obtained from a one-Drude-term formula—calculated for each compound from the corresponding rotations α^{25}_{5780} and α^{25}_{4358}—are presented.

The shifts in rotation resulting from the change of the value of n_2 are similar in the halides and in the corresponding azides, as can be seen from Table XXII.

In each of these two series the rotations in the visible region are conditioned by the partial rotation of the functional group as a whole; in each case the shifts of rotation are caused by changes in the partial rotations of the polar group or element. In attempting to correlate the members with $n_2 = 0$ to those with $n_2 = 1$, one is confronted with the same dilemma in both series.

TABLE XXI

Dispersive Power of Configurationally Related Chlorides

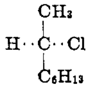
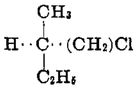
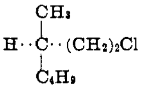
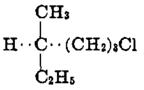
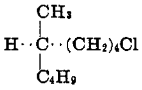
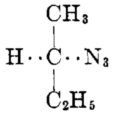
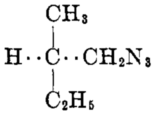
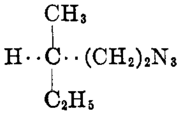
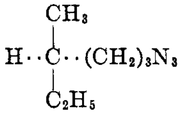
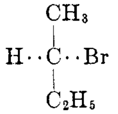
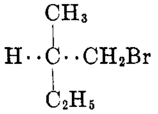
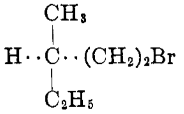
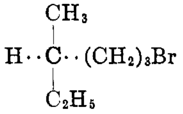
COMPOUNDS	 $H\cdot\cdot\overset{CH_3}{\underset{C_6H_{13}}{C}}\cdot\cdot Cl$	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot(CH_2)Cl$	 $H\cdot\cdot\overset{CH_3}{\underset{C_4H_9}{C}}\cdot\cdot(CH_2)_2Cl$	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot(CH_2)_3Cl$	 $H\cdot\cdot\overset{CH_3}{\underset{C_4H_9}{C}}\cdot\cdot(CH_2)_4Cl$
λ_0 in Å	1753	−3262 (anomalous dispersion)	1893	1666	1950

TABLE XXII

Rotations of Configurationally Related Azides and Halides

[M]$^{25}_{D}$ Max.

 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot N_3$	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot CH_2N_3$	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot(CH_2)_2N_3$	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot(CH_2)_3N_3$
−16.0	+10.0	+26.0	+17.0
 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot Br$	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot CH_2Br$	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot(CH_2)_2Br$	 $H\cdot\cdot\overset{CH_3}{\underset{C_2H_5}{C}}\cdot\cdot(CH_2)_3Br$
−30.0	+7.9	+38.8	+21.9

If the correlation be accepted as given in Table XXII, then the shift of rotation between the members with $n_2 = 0$ and those with $n_2 = 1$ is in harmony with the events in the substances discussed in the previous section, but differs in that the periodicity in the direction of shift of rotation is evident only in members having $n_2 > 0$.

If the alternative correlation of the halide having $n_2 = 0$ with that having $n_2 = 1$ be accepted, then the periodicity in the shift in rotation with the increase of n_2 would be similar to that observed among the members of the series discussed in the preceding sections. On the other hand, in passing from $n_2 = 0$ to $n_2 = 1$, change of sign of the partial rotation of the absorption band nearest to the visible region would be lacking.

Thus, whichever correlation be chosen, the series of azides and halides compared with the substances discussed in preceding sections will present an exceptional position following the increase of the value of n_2. We are inclined to give preference to the correlation as given in Table XXII. Kenyon, Phillips and Pittman,[38] however, have chosen the alternative correlation, on the basis of observations by Rule[45] on the effect on rotation of change in polarity of a substituent. It must be remarked, however, that these authors themselves have found exceptions to this rule. Our laboratory was among the first, if not the first, to study the effect on rotation of the change in polarity of the functional group and has found that the method cannot be regarded as fully reliable, particularly when the rotations are measured in the visible region only.

CONCLUSION

Thus, the problem of choosing between the two competitive views regarding the correlation of the configurations of substances with $n_2 = 0$ to those with $n_2 = 1$ (discussed in Section IV) as yet cannot be answered with a sufficient degree of certainty.

Further progress towards the solution of this problem depends on progress in the domain of the physics of optical rotation. Until there is developed a theoretical model, or a mathematical theory capable of describing and predicting all the events described in the preceding sections, the present problem will remain without a definite solution. To date the physicist has been handicapped by the lack of satisfactory material on which to test a physical theory of optical rotation of organic substances. The need for such material was pointed out many years ago by workers interested in the problem of chemical structure and optical activity (Pickard and Kenyon[46] and Armstrong[47]).

The problem should eventually find its solution, since large groups of substances whose members are configurationally correlated to a single reference hydrocarbon (Sections I and III) and another group whose members are configurationally correlated to a single secondary carbinol, have now been made available, and since the configurations of the hydrocarbons are tentatively correlated to those of the secondary carbinols.

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[45] RULE, H. G., *J. Chem. Soc.*, **125**, 1121 (1924).

[46] PICKARD, R. H., AND KENYON, J., *J. Chem. Soc.*, **99**, 45 (1911); **103**, 1923 (1913).

[47] ARMSTRONG, H. E., *Trans. Faraday Soc.*, **10**, 44 (1910).

Born[48] has already suggested a model which predicts a periodic change in the value of optical rotation of a set of coupled oscillators with change of the distance separating them. The latter model, however, does not predict a change of sign with the change by one CH_2 group of the distance of the chromophoric group from the asymmetric carbon atom.

The authors wish to express their appreciation to Dr. R. Stuart Tipson for reading the manuscript.

[48] Born, M., *Proc. Roy. Soc. (London)*, **A150**, 84 (1935).

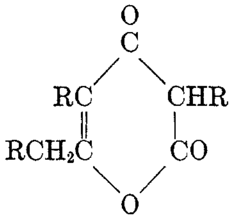
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

THE STRUCTURE OF WEDEKIND'S KETENIUM COMPOUNDS*

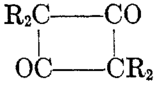
LEON L. MILLER AND JOHN R. JOHNSON

Received February 18, 1936

About thirty years ago Wedekind[1] and his collaborators investigated the action of aliphatic tertiary amines on the acid chlorides of mono- and di-substituted acetic acids. Their studies led to the generalization that typical acid chlorides of the form RCH_2-COCl give rise to 2,4-pyronones (I), and those of the form $R_2CH-COCl$ to 1,3-cyclobutanediones (II). The ketenes (III) were assumed to be intermediate products but were not isolated by Wedekind.



I



II

$$RCH{=}C{=}O$$
$$R_2C{=}C{=}O$$

III

From isobutyryl chloride and triethylamine they obtained the crystalline dimethylketene dimer[2] (mp. 115–116°) in 18–20 per cent. yields, along with a small quantity of a colorless liquid (b.p. 192–193°). They concluded that this accessory product was composed of one molecule of dimethylketene and one of triethylamine, although their analytical data did not agree accurately with this composition. The compound was named dimethylketene-triethylium[3] and two structures (IV and V) were suggested for it.†

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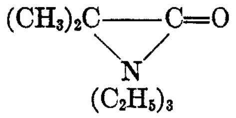
* This article is an abstract of a portion of a doctoral dissertation submitted to the Faculty of the Graduate School of Cornell University by Leon L. Miller.

[1] WEDEKIND *et al.*, *Ann.*, **323**, 246 (1902); **378**, 264 (1910).

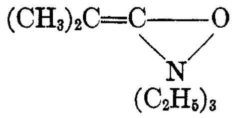
[2] WEDEKIND AND WEISWANGE, *Ber.*, **39**, 1631 (1906).

[3] WEDEKIND AND MILLER, *Ber.*, **42**, 1269 (1909).

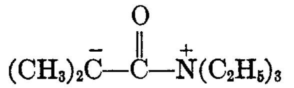
† A meaningless coördination formula, $(CH_3)_2C = CO \cdots N(C_2H_5)_3$, was proposed subsequently by WEDEKIND AND WEINAND, *Ber.*, **55**, 64 (1922).



IV

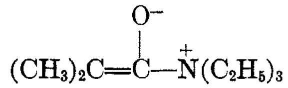


V



$(CH_3)_2\overset{-}{C}-\overset{\overset{O}{\|}}{C}-\overset{+}{N}(C_2H_5)_3$

VI



$(CH_3)_2C=\overset{\overset{O^-}{|}}{C}-\overset{+}{N}(C_2H_5)_3$

VII

Dimethylketene-triethylium was the first of a series of five similar substances which were obtained by Wedekind and were regarded as a new class of ketene derivatives.[4] These were given the general name ketenium compounds, to distinguish them from Staudinger's ketene bases,[4] formed by combination of two molecules of a ketene and one of a pyridine base. The latter differ very markedly from the ketenium compounds in their chemical behavior.

It is now recognized that nitrogen cannot exceed a covalence of four, and the modern equivalents of Wedekind's original formulæ would be electromeric (resonating) forms (VI and VII) of an addition complex. Since these systems are structurally analogous to enolate anions they should be extremely reactive, but actually the ketenium compounds are remarkably inert. Wedekind observed that dimethylketene-triethylium is unaffected by strong aqueous alkalies and is hydrolyzed only by prolonged heating with concentrated hydrochloric acid. He reported the formation of isobutyric acid and triethylamine hydrochloride by hydrolysis, and obtained isobutyraldehyde and triethylamine by catalytic reduction. The stability of the ketenium compounds cannot be reconciled with the structures VI and VII, which probably represent the labile intermediate products that are responsible for the catalytic effect of tertiary amines in certain ketene reactions. Furthermore, Staudinger[4] observed that the ketenium compound is not formed by direct combination of dimethyl ketene and triethylamine, and the present investigation disclosed the fact that it is not formed by heating dimethylketene dimer and triethylamine for 150 hours at 140°.

Since the ketenium compounds cannot be formulated upon any rational basis,* it seemed of interest to investigate their properties more fully. Repetition of Wedekind's procedure, with slight modifications, increased

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[4] *Cf.* STAUDINGER, "Die Ketene," **1912**, pp. 19, 87; STEWART, "Recent Advances in Organic Chemistry," **1927**, I, p. 95.

* The rational formula, $(CH_3)_2C = C(OC_2H_5)N(C_2H_5)_2$, appears to be excluded by the chemical behavior of the compound.

the yield of dimethyl ketene dimer to 60 per cent. of the theoretical; nevertheless, there was obtained a small quantity (3–5 per cent. yield) of the ketenium compound, which agreed in physical and chemical properties with that of Wedekind. However, the basic product resulting from its hydrolysis proved to be diethylamine instead of triethylamine (as reported by Wedekind). This result suggested that the alleged dimethylketene-triethylium is merely the diethylamide of isobutyric acid. This conclusion was confirmed by the fact that an authentic specimen of this amide (synthesized from diethylamine and isobutyric anhydride) was found to be identical in all respects with the supposed ketenium compound.

TABLE

PHYSICAL CONSTANTS OF DIETHYLAMIDES COMPARED WITH THOSE OF WEDEKIND'S KETENIUM COMPOUNDS

ACID CHLORIDES $R-CO-Cl$	PHYSICAL CONSTANT	TRIETHYLIUM[a] COMPOUNDS	DIETHYLAMIDES $R-CO-N(C_2H_5)_2$
$(CH_3)_2CH-$	n_D^{20}	1.440	1.4382
	sp.gr.	0.892 (18°)	0.891 (24°)
	b.p.	192–193°/740 mm.	192–193°/740 mm.
C_6H_5CHCl-	b.p.	150–155°/0.5 mm.	156–158°/4 mm.
	m.p.	51°	51–51.5°
$ClCH_2-$	b.p.	120–125°/10 mm.	109–110°/9 mm.
Cl_2CH-	b.p.	142–145°/18 mm.	124–126°/19 mm.[b]
$BrCH_2-$	b.p.	128–129.5°/18 mm.	114–117°/9 mm.

[a] Physical constants in this column are those of Wedekind and Miller.[3]

[b] This specimen contained some of the monochloro compound.

Specimens of the appropriate diethylamides were synthesized for comparison with the four other ketenium compounds reported by Wedekind, and the results are shown in the table. The diethylamide of phenylchloroacetic acid was found to melt at 51–51.5°, in close agreement with the value 51° reported for the supposed ketenium compound. In general, the boiling-points of the authentic diethylamides are lower than the values reported for the ketenium compounds; these discrepancies are due to the fact that Wedekind's determinations were made with exceedingly small specimens. There can be no doubt that dimethylketene- and phenylchloroketene-triethylium are identical with the diethylamides of the corresponding acids, and it is extremely probable that the same is true for the remainder of the list.

The diethylamides appear to arise from the presence of small quantities of diethylamine as an impurity in the triethylamine. Owing to the use of a considerable excess of the latter, a quantity of only 1–3 per cent. of secondary amine would account for the observed results. It is unlikely that the diethylamides arise by the interaction of triethylamine with the acid chloride; a reaction of this type has been found to occur with trimethylamine and benzene sulfonyl chloride but not with benzoyl chloride.[5]

$$(CH_3)_2CH{-}COCl + 2\ N(C_2H_5)_3 \rightarrow (CH_3)_2CH{-}CO{-}N(C_2H_5)_2 + N(C_2H_5)_4Cl$$

This possibility appears to be excluded in the present instance, since an examination of the amine salt produced in the reaction failed to reveal any tetraethylammonium chloride.

EXPERIMENTAL

Isobutyryl chloride and triethylamine.—(a) A solution of 100 g. (0.94 mole) of pure isobutyryl chloride in 100 cc. of pure, dry carbon disulfide was added dropwise with shaking, but without external cooling, to 97 g. (0.96 mole) of dry triethylamine (Kahlbaum) in 200 cc. of carbon disulfide. The reaction mixture was warmed gently for several hours, and after standing overnight the precipitate of amine hydrochloride was removed by suction filtration. The procedure of Wedekind was followed except that the reaction was not carried out in a constant stream of dry hydrogen. The products obtained were: 113 g. of triethylamine hydrochloride (86% of the theoretical), 22 g. of dimethylketene dimer (33% yield), and 4 g. of a light-yellow liquid (b.p. 192–194; n_D^{20} 1.443) corresponding to Wedekind's dimethyl ketenetriethylium (b.p. 192–194°, n_D^{20} 1.440). The supposed triethylium compound had a disagreeable odor and gave a positive test for sulfur. From a similar experiment Wedekind obtained 123 g. of triethylamine hydrochloride (95% yield), 12 g. of dimethyl ketene dimer (18% yield) and 17 g. of crude triethylium compound.

(b) Since Staudinger[6] has shown that dimethyl ketene combines with carbon disulfide in the presence of tertiary amines it is evident that this solvent is inappropriate. Wedekind had observed that anhydrous ether was superior but failed to note that carbon disulfide actually reacted with the ketenes. Our experiments showed that the yields of dimethylketene dimer were increased threefold by using anhydrous ether or ligroïn (60–80°) as solvent and effecting the reaction at room temperature. In a typical preparation, 53 g. (0.5 mole) of isobutyryl chloride in 100 cc. of anhydrous ether was added to 86 g. (0.85 mole) of triethylamine in 150 cc. of the same solvent, and the reaction mixture was allowed to stand at 20–25° for 10–15 days. The products were 65 g. (95% of the theoretical) of triethylamine hydrochloride, 20 g. (57% yield) of dimethylketene dimer, and about 2 g. of a *colorless* liquid, b.p. 192–194°, n_D^{20} 1.438. This product had a pleasant terpene-like odor, instead of the disagreeable odor of the specimens obtained from carbon disulfide solutions.

Wedekind and Miller[3] state that their specimen gave a 95% yield of triethylamine

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[5] JONES AND WHALEY, *J. Am. Chem. Soc.*, **47**, 1343 (1925).

[6] STAUDINGER, *Helv. Chim. Acta*, **8**, 320 (1925).

hydrochloride, m.p. 253°, upon hydrolysis with concentrated hydrochloric acid in a sealed tube. The identity of the amine was not confirmed by further tests. Our specimen of the liquid boiling at 192–193° gave a 60% yield of diethylamine hydrochloride, m.p. 214–217°. No melting-point depression was observed when this salt was mixed with authentic diethylamine hydrochloride, m.p. 218–219°. The free amine from our specimen gave an acid-oxalate, m.p. 207–210°, which showed no melting-point depression on mixture with authentic diethylamine acid-oxalate, m.p. 208–210°.

Authentic diethylamides.—(a) Isobutyrodiethylamide was prepared by treating 25 g. (0.16 mole) of isobutyric anhydride with 10 g. (0.14 mole) of diethylamine, and refluxing gently for one-half hour. Fractionation of the mixture gave 17.5 g. (90% yield) of the diethylamide; b.p. 192–194°/740 mm., n_D^{20} 1.4382, sp. gr. (24°) 0.892.

Anal. Calc'd for $C_8H_{17}NO$: N, 9.78. Found: N, 9.61, 9.68.

(b) Phenylchloracetodiethylamide was obtained in 40% yield by adding a solution of 4 g. (0.02 mole) of phenylchloroacetyl chloride in ligroïn (60–80°) to 3 g. (0.04 mole) of diethylamine in the same solvent. The general method of Jacobs and Heidelberger[7] gave a similar yield. A cold aqueous solution of 17 g. (0.16 mole) of diethylamine hydrochloride, containing 0.33 mole of sodium hydroxide, was treated with 25 g. (0.13 mole) of phenylchloroacetyl chloride. There was obtained 12 g. of the diethylamide; colorless, viscous liquid, b.p. 156–158°/4 mm. On cooling and scratching the oil solidified, and after crystallization from methyl alcohol melted at 51–51.5°.

Anal. Calc'd for $C_{12}H_6ClNO$: Cl, 15.72. Found: Cl, 15.68, 15.70.

(c) Chloroacetodiethylamide has been described by Jacobs and Heidelberger[7] who reported its boiling point as 125.5–130.5° (mainly 126.5–128.5°)/21–22 mm. Our specimen, prepared from chloroacetyl chloride according to their directions, distilled at 109–110°/9 mm.

(d) Dichloroacetodiethylamide was prepared from the middle fraction (b.p. 84–85°/9 mm.) of a commercial specimen of "pure" dichloroacetic acid, by conversion to the acid chloride and treatment with diethylamine according to the general method of Jacobs and Heidelberger. The diethylamide (50% yield) distilled at 124–126°/19 mm., but chlorine analyses indicated that this product contained about 90% of the desired amide and 10% of the monochloro compound.

Anal. Calc'd for $C_6H_{11}Cl_2NO$: Cl, 38.53. Found: Cl, 36.92, 36.80, 36.99.
Calc'd for $C_6H_{12}ClNO$: Cl, 23.72.

As we were interested merely in knowing roughly the boiling-point of this amide, the preparation was not repeated with pure dichloroacetic acid. It is evident that the diethylamides of chloroacetic and dichloroacetic acids (like the free acids and acid chlorides) have almost exactly the same boiling-points and cannot be separated by ordinary fractional distillation methods.

(e) Bromoacetodiethylamide was obtained in 20% yield by treating 14 g. of diethylamine, in aqueous alkaline solution, with 38 g. of bromoacetyl bromide. This amide is a colorless liquid, b.p. 114–117°/9 mm., possessing powerful lachrymatory and sternutative properties.

Anal. Calc'd for $C_6H_{12}BrNO$: Br, 41.38. Found: Br, 41.45, 41.80, 41.87.

A preliminary attempt to obtain this amide from bromoacetic acid by way of bromoacetyl chloride, gave an impure product containing an appreciable amount of the chloro amide.

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[7] JACOBS AND HEIDELBERGER, *J. Biol. Chem.*, **21**, 148 (1915).

SUMMARY

The reaction between isobutyryl chloride and triethylamine, in the presence of organic solvents, has been investigated. The principal product was found to be dimethylketene dimer, which can be isolated in 60 per cent. yield by slight modifications of Wedekind's procedure.

It has been shown that Wedekind's ketenium compounds, such as dimethylketene- and phenylchloroketene-triethylium, are merely dialkylamides of the corresponding acids and are not to be regarded as a general class of ketene derivatives. Apparently these amides owe their origin to the presence of a small amount of secondary amine as an impurity in the usual samples of aliphatic tertiary amines.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

THE OZONIZATION OF TRIPLE BONDS

CHARLES D. HURD AND ROBERT E. CHRIST

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In 1907, Molinari[1] stated that aliphatic compounds add one molecule of ozone quantitatively for each double bond, while compounds with triple bonds in general added no ozone. This generalization was severely criticized by Harries,[2] but Molinari[3] maintained his stand. The discussion brought out the fact that ozonized air, giving rise to less than 1% of ozone in the gas stream, was important in Molinari's procedure. With ozonized oxygen, Harries was able to add ozone to the triple bonds of such compounds as stearolic or phenylpropiolic acids.

Acetylene itself reacts[4] with ozone. Formic acid is one of the products. That glyoxal is the other major product is interesting, for it demonstrates non-cleavage during ozonization, but this is apparently the only case of its kind on record. The rate of absorption of ozone by 1-heptyne has been studied,[5] but without attention to the nature of the products of ozonolysis. Recently, ozonization has been employed[6] to prove the positions of the triple bonds in 6,10-hexadecadiyne, and in 6,9-pentadecadiyne. Caproic and succinic acids were formed from the latter; caproic and malonic acids from the former.

The quantitative extent of ozonization has been practically disregarded in the above work. The present work was undertaken to obtain evidence on this point and to test the generality of ozonolysis of acetylenes. Ozone concentrations of 5% and 10% were employed. The solvent used was carbon tetrachloride. Six compounds were included: phenylpropiolic acid, 1-ethynyl-1-cyclohexanol, 1-hexyne, 1-heptyne, phenylacetylene and ethynylfenchyl alcohol. In all cases, reaction with ozone occurred. Acids were formed as predicted, in percentage yields, respectively, of 42, 52, 51,

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[1] MOLINARI, *Ber.*, **40**, 454 (1907).

[2] HARRIES, *ibid.*, **40**, 4905 (1907); **41**, 1227 (1908).

[3] MOLINARI, *ibid.*, **41**, 585, 2782 (1908).

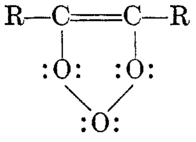
[4] WOHL AND BRAUNIG, *Chem.-Ztg.*, **44**, 157 (1920); BRINER AND WUNENBURGER, *Helv. Chim. Acta*, **12**, 786 (1929).

[5] BRUS AND PEYRESBLANQUES, *Compt. rend.*, **190**, 685 (1930).

[6] LAI, *Bull. soc. chim.*, **53**, 1537, 1543 (1933).

59, 59 and 61. It is significant that the ozonolysis never gave rise to a quantitative yield of acids even though an excess of ozone was employed.

Regarding the structures of the acetylene ozonides, formulæ I, II, III, which are analogous to formulæ IV, V, VI for olefin ozonides, should be



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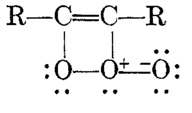

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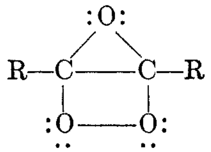
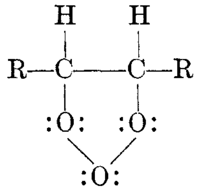
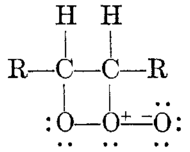


III

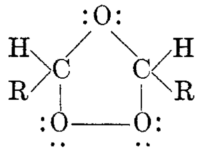
considered. Formula IV is the conventional formula of Harries, whereas V and VI are supported by Staudinger,[7] V being the unstable form which



IV



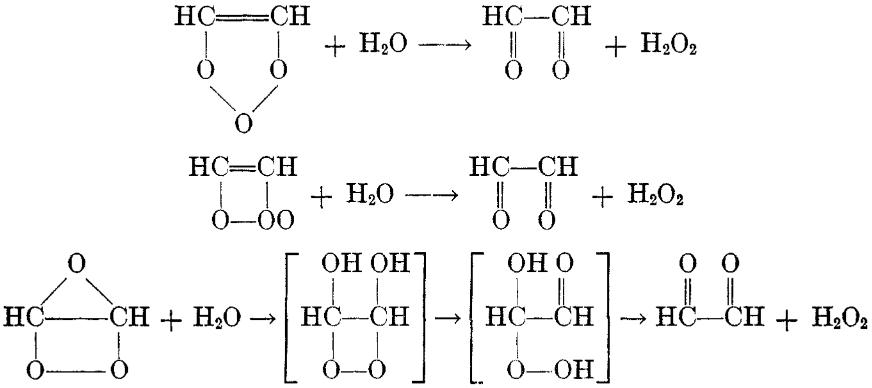
V



VI

is considered to rearrange into the stable, hydrolyzable "isozonide," VI.

All of the various formulæ lend themselves satisfactorily to the interpretation of the evidence of hydrolysis. All three forms (I, II, III) would give rise to acids (RCOOH) on hydrolysis, *via* α-diketones (RCOCOR, or glyoxals if R = H) and hydrogen peroxide. The following equations may be used to illustrate the formation of glyoxal from acetylene ozonide by each of the formulæ in question.



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[7] STAUDINGER, *Ber.*, **58**, 1088 (1925); RIECHE, "Alkylperoxide und Ozonide." Theo. Steinkopff, Dresden and Leipzig, **1931**, pp. 133, 155.

In all cases, the subsequent reaction is: HCOCHO + HOOH → 2HCOOH. Hence the present evidence cannot be used to decide between the various possibilities. As Rieche points out, however, the evidence for V is better than that for IV. On this basis, II is preferred as the structure for the initial addition product of ozone to the acetylene.

EXPERIMENTAL

Materials.—1-Ethynyl-1-cyclohexanol was prepared according to the directions of Rupe, Messner and Kambli, as modified by Hurd and Jones.[8] The directions for the synthesis of ethynylfenchyl alcohol will be presented in another paper. The phenylacetylene was redistilled before use; b.p., 139°. The phenylpropiolic acid (m.p., 136°) was synthesized from pure phenylacetylene. Modifications of the method of Lebeau and Picon[9] were adopted for the preparation of 1-hexyne and 1-heptyne. Alkyl bromides were used instead of alkyl iodides. After considerable preliminary experimentation, the following conditions were developed for a large-scale run, and for hexyne of high purity.

1-Hexyne.—A 5-l. three-necked, round-bottomed flask, fitted with a mercury-sealed stirrer, an inlet tube reaching to the bottom of the flask, and an exit tube of large bore leading into a hood, was immersed in a crock wrapped with one layer of 6-mm. asbestos paper and cooled with a mixture of "dry ice" (1.4 kg.) and acetone. The air in the flask was replaced by hydrogen, after which 161 g. (7 moles) of sliced sodium was inserted. Ammonia was then condensed in the flask with constant stirring until it was three-fourths full. A current of acetylene was then passed in until the blue color (sodium) had disappeared. A dropping funnel was inserted in place of the inlet tube and 959 g. (7 moles) of *n*-butyl bromide was run in slowly.

The flask was then allowed to warm up to room temperature over a period of six hours, to permit the ammonia to distill off slowly. Enough water was then added to dissolve the sodium bromide, with care to allow for the heating effect caused by any unused sodamide. The insoluble layer was separated, washed with dilute sulfuric acid and dried over calcium chloride. After this, it was carefully fractionated through a Davis column. A 406-g. fraction boiling at 71–72° was collected. Analysis of this material by the method of Hill and Tyson[10] gave corrected values for 1-hexyne of 93.4 and 94.2%. This corresponds to a 64% yield of pure 1-hexyne.

Purification.—Some of the hexyne was treated with alcoholic silver nitrate. The precipitate was collected, washed with alcohol, and dried. Thirty-nine grams of this salt ($C_4H_9C{\equiv}CAg\cdot AgNO_3$) was mixed in a distilling flask with 39 g. of ammonium thiocyanate and 200 cc. of water. 1-Hexyne was liberated on distillation. This was separated, washed with dilute sulfuric acid, dried over calcium chloride, and distilled. The yield was 3.9 g. (40%) but the loss was largely mechanical. In larger duplicate runs, a total of 60 g. of pure 1-hexyne was collected; b.p., 71°; n_D^{19}, 1.400. Analysis as before gave uncorrected values of 97.0 and 97.4%. Since this was pure 1-hexyne, a correction factor of 2.8% was placed on the analytical method, this factor being applied on the first analysis of the crude hexyne. The pure hexyne was taken for ozonolysis.

1-Heptyne.—The general procedure was the same as that given for hexyne, except that a mixture of about equal parts of *n*-pentyl bromide and *n*-pentyl chloride was

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[8] Hurd and Jones, *J. Am. Chem. Soc.*, **56**, 1924 (1934).

[9] Lebeau and Picon, *Compt. rend.*, **156**, 1077 (1913); Picon, *ibid.*, **169**, 32 (1919).

[10] Hill and Tyson, *J. Am. Chem. Soc.*, **50**, 172 (1928).

used, rather than the bromide alone. The crude heptyne fraction contained only 33% of 1-heptyne by analysis. The purification by silver nitrate gave pure 1-heptyne which, as with the pure hexyne, required the correction factor in the analysis. The uncorrected analytical value was 98%. A total of 82 g. of this pure 1-heptyne was obtained; b.p., 98.5°; n_D^{20} 1.417.

General Method of Ozonization.—An ozonizer of the Henne[11] type was used. A stream of dry oxygen was employed. The ozone concentration in the ozonized gas was determined by the potassium iodide method of Smith[12]; *e.g.*, with a rate of flow of 4.7 l. per hour, the O_3-concentration was 8–10%. In general, from 1 to 4 g. of the acetylene to be ozonized was dissolved in dry carbon tetrachloride (50–80 cc.) and the solution was kept ice-cold during the ozonization. A considerable excess of ozone was employed in all cases. The excess became apparent when the solution assumed a faint blue color.

To hydrolyze the ozonides, it was only necessary to add water (75–100 cc.) and distill from a steam bath. The distillate (of carbon tetrachloride) was shaken with water and titrated with standard alkali to determine the small amount of acids which distilled also. In most cases this figure was almost negligible, but it was included in the total amount of acids formed. In the cases of the ozonides of hexyne and heptyne the solvent was distilled off before adding the water. In all cases, the aqueous solutions were titrated to determine the acid content. The details of characteristic experiments are collected in Table I.

TABLE I

DATA CONCERNING OZONIZATIONS

SUBSTANCE		CCl_4 cc.	OZONE		NaOH CONSUMED BY ACIDS FORMED		YIELD OF ACIDS, %
Name	g.		Vol., l.	Concn. %	cc.	Normality	
Phenylpropiolic Acid........	4.00	80	223	5	85.30	0.4096	42.4
Phenylacetylene.............	2.00	80	95.2	5	56.40	0.4096	59.1
1-Hexyne....................	1.07	60	67.6	5	32.20	0.4170	51.1
1-Heptyne...................	1.84	100	31.8	5	207.5	0.1089	59.4
Ethynylcyclohexanol........	2.00	85	93.5	9	41.00	0.4096	52.2
Ethynylfenchyl alcohol......	3.00	75	113	9	50.20	0.4096	61.3

Indentification of acids from phenylpropiolic acid (A), phenylacetylene (B), ethynylcyclohexanol (C), and ethynylfenchyl alcohol (D).—After titration of the acids, the neutral solutions of the sodium salts were evaporated to small volume, treated with decolorizing charcoal, and extracted with ether to remove any organic impurities. Traces of ether were removed by further evaporation. Oxalic acid (from A) and formic acid (from B, C, D) were indicated by the decolorization of potassium permanganate solution by test portions. The remainder of the solution was acidified with sulfuric acid. Benzoic acid (from A) separated as a heavy white precipitate; m.p. and mixture m.p., 120°. The benzoic acid from B melted at 121° and weighed 1.22 g. When mixed with authentic benzoic acid, it melted also at 121°. After

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[11] HENNE, *ibid.*, **51**, 2676 (1929).

[12] SMITH, *ibid.*, **47**, 1844 (1925).

acidification, the solution from C gradually yielded a small quantity of 1-hydroxy-1-cyclohexanecarboxylic acid. This, after recrystallization from alcohol, gave the correct[13] melting point of 106–107°. The acid produced from D, after two crystallizations from alcohol, appeared as white flakes which melted at 92°. That this was *dl-α*-fenchocarboxylic acid,[14] m.p. 92°, was confirmed by its neutralization equivalent of 195: 0.0840 g. required 3.80 cc. of 0.1132 *N* alkali for neutralization (calc'd neutral. equ., 198).

Identification of acids from 1-hexyne.—After hydrolysis of the ozonide, the volume of the aqueous solution was made up to 110 cc. and analyzed by the Duclaux method.[15] Exactly 10.0 cc. of the solution required 23.6 cc. of the alkali used. Of the remaining 100 cc., 30.0 cc. was distilled. It required 90.17 cc. of the same alkali. From these data, the percentage ratio of formic to valeric acids was 48.5:51.5, or about 1:1.

Identification of acids from 1-heptyne.—In this case, the solution of acids was neutralized and evaporated to dryness. One g. of the salts was dissolved in water and the formate content determined by permanganate titration. A total of 0.0048 equivalent, or 0.326 g. of sodium formate, was found. By difference, the weight of sodium caproate must have been 0.674 g. or 0.0049 equivalent. Here again, the ratio of 1:1 (0.0048:0.0049) was found.

The caproic acid was identified by treating the solution from the permanganate titration with sulfuric acid and distilling. The distillate, made up to 110 cc., was analyzed by the Duclaux method. The 10.0 cc. portion required 7.31 cc. of alkali. The first, second, and third 10-cc. portions of distillate (from the 100 cc., which represented 73.10 cc. of alkali) required 23.90, 16.80 and 13.20 cc. of the same alkali. Thus, the Duclaux values were 32.6, 23.0 and 18.2, which are those for caproic acid. Confirmatory evidence was obtained by evaporating this solution of sodium caproate to dryness and treating it with *p*-bromophenacyl bromide. The m.p. (and mixture m.p.) of the *p*-bromophenacyl caproate thus obtained was 71°.

SUMMARY

The ozonolysis of triple bonds has been studied with these six acetylene representatives: phenylpropiolic acid, phenylacetylene, 1-hexyne, 1-heptyne, ethynylcyclohexanol, ethynylfenchyl alcohol. With the ozone concentrations used, namely, 5 or 10%, ozonization was satisfactory in all cases. The acids which resulted from cleavage of the triple bonds were formed in 42–61% yields. Methods for the identification of these acids are given. Details are included for the synthesis of pure 1-hexyne in quantity.

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[13] Bucherer, *Ber.*, **27**, 1231 (1894).

[14] Wallach, *Ann.*, **259**, 326 (1890).

[15] Calculated by method of Virtanen and Pulkki, *J. Am. Chem. Soc.*, **50**, 3138 (1928).

[Contribution from the Chemical Laboratory of Iowa State College]

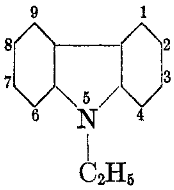
CARBAZOLE. I. SELECTIVE METALATION

HENRY GILMAN and ROBERT H. KIRBY

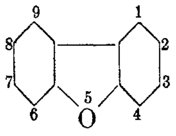
Received March 24, 1936

INTRODUCTION

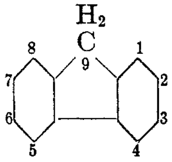
The hydrogen of an aromatic nucleus (in a parent or unsubstituted aromatic cycle) which is replaceable by metal appears to be independent of the metal and of the metalating agent. For example, metalation of dibenzofuran (II) gives a 4-metallo derivative



I



II



III

when the metal is lithium, sodium, potassium, calcium or mercury, or when the metalating agent is an organometallic compound, an inorganic salt like mercuric acetate, or a metal.[1] However, we have found that in the metalation of 5-ethylcarbazole (I) the hydrogen replaced depends on the metal which is introduced. Metalation by means of organoälkali compounds introduces the alkali metal in the 4-position; but metalation by mercuric acetate introduces the mercuri group in the 2-position. With the somewhat related cycle, fluorene (III), mercuration in acetic acid takes place in the 4-position and mercuration with no solvent involves both the 3- and the 4-positions.[2]

The structures of 5-ethylcarbazole-4-carboxylic acid and carbazole-4-carboxylic acid obtained by carbonation of the alkali-metalated 5-ethyl-

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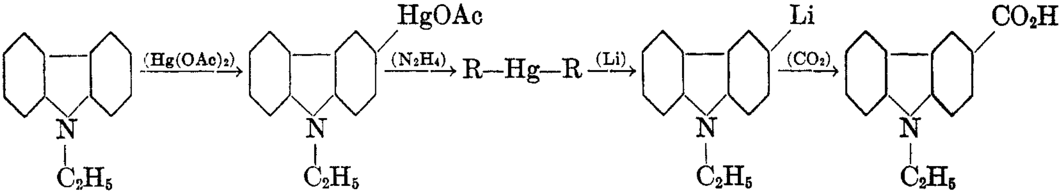
[1] Gilman and Young, *J. Am. Chem. Soc.*, **56**, 1415 (1934) and *ibid.*, **57**, 1121 (1935). See Gilman and co-workers, *Rec. trav. chim.*, **55**, 79 (1936) for metalation by means of phenylcalcium iodide.

[2] Miller and Bachman, *J. Am. Chem. Soc.*, **57**, 2447 (1935).

carbazole and carbazole, respectively, were established by comparison with authentic specimens of the acids. Carbazole-4-carboxylic acid was prepared by the procedure of Ciamician and Silber[3] from carbazole, potassium hydroxide and carbon dioxide. This acid was 5-ethylated[4] to give an acid identical with that obtained by alkali-metalation of 5-ethylcarbazole.

5-Ethylcarbazole was mercurated by mercuric acetate in ethanol and by fusion with mercuric acetate. In each case a mixture of mono- and dimercurials was obtained. The constitution of the monomercurial was established by replacing the mercuri group by iodine to give the known 5-ethyl-2-iodocarbazole.[4,5] The apparently anomalous site of mercuration suggested the desirability of ruling out the possibility that replacement of the mercuri group by iodine may have involved two separate and, in a sense, conflicting reactions: (1) replacement of the mercuri group by hydrogen; and (2) iodination of the resulting non-mercurated carbazole. It is known that direct iodination of 5-ethylcarbazole gives 5-ethyl-2-iodocarbazole;[5] accordingly, if reaction (1) occurred, the position of iodine would have no necessary bearing on the position of the initial mercuri group. With this difficulty in view, the mercurial was converted smoothly and in excellent yield by the hydrazine hydrate method[6] to the bis-mercurial, which with lithium gave the corresponding organolithium compound; and this organometallic compound when carbonated yielded 5-ethylcarbazole-2-carboxylic acid:



The constitution of the 2-carboxylic acid was established by three methods. (1) 5-Ethyl-2-iodocarbazole[5] was converted to the corresponding Grignard reagent which was carbonated; (2) the organolithium compound from

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[3] Ciamician and Silber, *Gazz. chim. ital.*, **12**, 272 (1882). The structure of this acid was established subsequently by Briscoe and Plant, *J. Chem. Soc.*, **1928**, 1990, by sulfur-dehydrogenation of 1,2,3,4-tetrahydrocarbazole-6-carboxylic acid, which was obtained by ring closure.

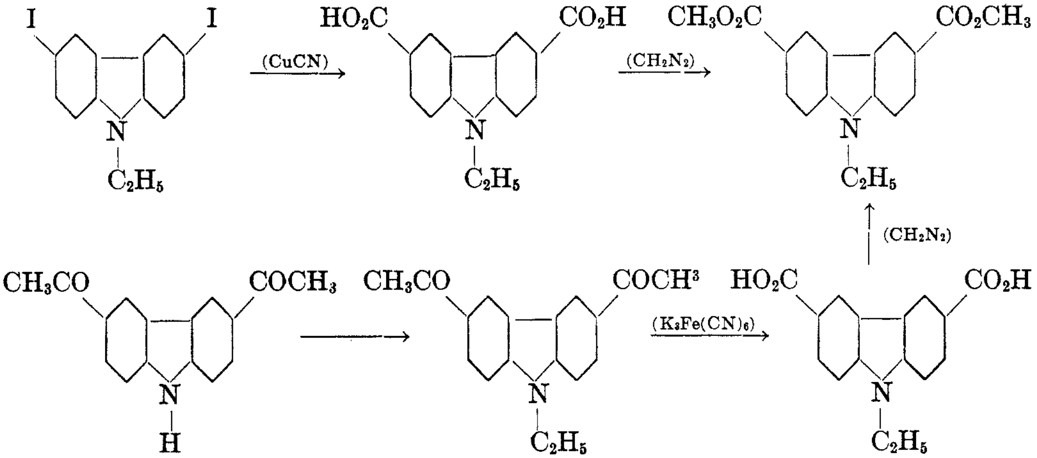
[4] In accordance with the procedure of Stevens and Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

[5] Tucker, *ibid.*, **1926**, 546.

[6] Gilman and Barnett, *Rec. trav. chim.*, **55**, (July, 1936).

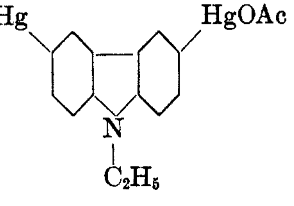
5-ethyl-2-bromocarbazole* was carbonated; and (3) carbazole-2-carboxylic acid[7] was ethylated to 5-ethylcarbazole-2-carboxylic acid.

The dimercurial was shown to have mercuri groups in the 2- and 8-positions, for on replacement of the mercuri groups by iodine there resulted 5-ethyl-2,8-diïodocarbazole. This diïodo compound was prepared earlier by Tucker[5] who correctly assumed the positions of the iodines. The constitution of the diïodo compound was established by the following sequence of reactions, the structure of the 5-ethyl-2,8-diacetylcarbazole having been proved recently by Plant and co-workers[8] by means of ring closure.

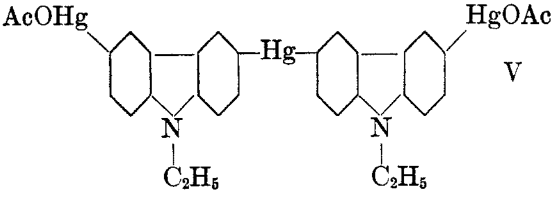


Because of difficulties in the purification of the dimercurial it is not known whether the diïodo compound was obtained from either or both of the following possible compounds:

IV



V



Cechetti and Sarti[9] were the first to mercurate carbazole, and although

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* 5-Ethyl-2-bromocarbazole was prepared by the bromination of 5-ethyl-carbazole. The structure of 2-bromocarbazole was established by Tucker, *J. Chem. Soc.*, **125**, 1144 (1924), and although this compound was known to give 5-ethyl-2-bromocarbazole, it had not been established hitherto that bromination of 5-ethylcarbazole gave 5-ethyl-2-bromocarbazole.

[7] Prepared in accordance with the directions of Plant and Williams, *J. Chem. Soc.*, **1934,** 1142, by oxidation of 2-acetylcarbazole.

[8] Plant, Rogers and Williams, *J. Chem. Soc.*, **1935,** 741.

[9] Cechetti and Sarti, *Gazz. chim. ital.*, **60,** 189 (1930); [*C. A.*, **24,** 3787 (1930)].

they did not establish the structures of their compounds they indicate that the dimercurated compound may have a bis-mercurial constitution.

DISCUSSION OF RESULTS

If we confine consideration to metalation of one aromatic cycle of a polynuclear type it is clear that metalation can be selective in some cases and that the same hydrogen is not always replaced by any metal or its equivalent. Accordingly, there is no justification for using metalation as a criterion of the so-called acidity of aromatic hydrogens. It may be that some specific metalating agents can be used for this purpose. There are now available three chief classes of metalating agents: (1) organometallic compounds; (2) inorganic compounds like mercuric acetate; and (3) metals.

The rate of metalation depends, among other factors, on the carbon-hydrogen linkage and on the metalating agent. First, if we omit non-aromatic hydrogens like those attached to oxygen, nitrogen, sulfur, and true acetylenes, and activated hydrogens like those in the 9-position of fluorene (all of which react moderately rapidly to violently) we observe that the decreasing order of metalation is: dibenzofuran, 5-ethylcarbazole, 5-lithiumcarbazole. Second, the rate of metalation by means of organometallic compounds depends on both the R group and the metal, and appears to follow the general order of relative reactivity of organometallic compounds: the probable order of decreasing activity being RK, RNa, RLi, RCaI, RMgX.[10] Third, the rates of metalation of a series of aromatic compounds by inorganic salts do not follow the rates of metalation of the same series by organometallic compounds: for example, 5-ethylcarbazole is mercurated more readily than dibenzofuran. Also, the rates of metalation by metals appear to parallel the rates of metalation by organometallic compounds, but there is not now available sufficient evidence to warrant any definite conclusion. Fourth, not only do supposedly related polynuclear types metalate in different positions, but a selected polynuclear type may metalate in different positions depending upon nuclear substituents. For example, all types of metalating agents react in the 4-position of dibenzofuran; however, metalation of 2-methoxydibenzofuran, by means of RLi compounds, involves the 1- and the 3-positions.[11]

EXPERIMENTAL

Metalation of carbazole.—A clear, yellow solution containing 3.9 g. (0.02 mole) of carbazole in ether and 0.055 mole of *n*-butyllithium was refluxed for 20 hours and

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[10] Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

[11] Studies by R. L. Bebb.

then carbonated with solid carbon dioxide. There was isolated 0.05 g. of carbazole-4-carboxylic acid. The recovery of 2 g. of carbazole and the pronounced odor of *n*-valeric acid indicated a highly restricted reaction. Actually, the 4-acid may have come in part, at least, from a rearrangement reaction of the 5-lithium compound during carbonation.

Metalation of 5-ethylcarbazole.—To a clear ether solution (125 cc.) containing 0.06 mole of *n*-butyllithium (prepared from *n*-butyl chloride) was added 9.75 g. (0.05 mole) of 5-ethylcarbazole. After refluxing for 18 hours, the mixture was carbonated by solid carbon dioxide to give 2.2 g., or 23%, of acid, which is soluble in benzene, ethanol and carbon tetrachloride. The product was purified by crystallization from carbon tetrachloride-petroleum ether mixtures and finally from carbon tetrachloride alone, and melted at 165°.

Neutralization equivalent: Calc'd, 239; Found, 241.

Anal. Calc'd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.44; N, 5.86.
Found: C, 75.1; H, 5.50; N, 6.03.

When the above experiment was repeated with the use of a larger excess of *n*-butyllithium (0.085 mole, and 0.03 mole of 5-ethylcarbazole), the yield of 5-ethylcarbazole-4-carboxylic acid was 22%, and no dicarboxylic acid was isolated.

No acid was isolated in an experiment involving 0.095 mole of ethylmagnesium bromide and 0.02 mole of 5-ethylcarbazole. Prior to carbonation the ether-toluene solution was heated at 85° for 20 hours. Ninety per cent. of the 5-ethylcarbazole was recovered.

Although no metalation occurred under the stated conditions with ethylmagnesium bromide, it does appear that the more reactive phenylcalcium iodide is somewhat effective. The acidic fraction (other than the benzoic acid from excess phenylcalcium iodide) has not yet been resolved. The 85% recovery of 5-ethylcarbazole is remindful of the definitely established but highly restricted metalation of dibenzofuran by phenylcalcium iodide.[1]

The acidic fractions obtained by metalating 5-ethylcarbazole by means of the ethyl- and *n*-butylsodium and -potassium compounds have not been identified as yet. In some of these cases there is evidence of dimetalation. The organolithium compounds are superior to the organosodium and -potassium compounds for monometalation of both 5-ethylcarbazole and dibenzofuran.

It is interesting to note in connection with relative acidities that after refluxing a suspension of 0.05 mole of 4-dibenzofurylpotassium with 0.05 mole of 5-ethylcarbazole for 24 hours, and then cooling to −5° and carbonating with carbon dioxide gas, there was isolated dibenzofuran-4-carboxylic acid free of carbazole acid. The experiment just described is perhaps as one might have predicted; however, the following experiment which indicates that benzene has a more acidic hydrogen than 5-ethylcarbazole is not as one might have predicted. To a solution of 0.03 mole of di-*n*-butylmercury in 100 cc. of benzene was added 2.1 g. (0.09 g. atom) of sodium, and the mixture was stirred at room temperature for 16 hours. 5-Ethylcarbazole (0.05 mole) was added to the resulting suspension, and the mixture was stirred for 8 hours, after which it was carbonated at 0°. There was isolated a 77% yield of benzoic acid, but no carbazole acid; and there must have been some unused *n*-butylsodium, as evidenced by the odor of valeric acid. It is quite possible in this latter experiment that the *n*-butylsodium had metalated the benzene prior to addition of the 5-ethylcarbazole; if this be the case, one might still have expected the phenylsodium to have metalated the 5-ethylcarbazole.

Constitution of 5-ethylcarbazole-4-carboxylic acid.—Two-tenths g. (0.001 mole) of carbazole-4-carboxylic acid was ethylated in acetone by means of diethyl sulfate and potassium hydroxide[4] (followed by hydrolysis) to give an 84% yield of crude 5-ethylcarbazole-4-carboxylic acid melting at 156–158°. Crystallization from carbon tetrachloride raised the melting point to 165°, and there was no depression in the melting point of a mixture of this product with the acid obtained from 5-ethylcarbazole and *n*-butyllithium.

Inasmuch as acids other than carbazole-4-carboxylic acid have been obtained from the carbonation of 5-potassiumcarbazole, the carbazole-4-carboxylic acid used in the above experiment (m.p., 271°) was admixed with the carbazole-2-carboxylic of Plant and Williams[7] (m.p., 276–278°), and the melting point of the mixture was 230–235°. The carbazole-3-carboxylic acid is ruled out, for it melts at 320°. Incidentally, a melting-point determination of a mixture of ethyl carbazole-2-carboxylate (m.p., 165°) and 5-ethylcarbazole-4-carboxylic acid (m.p., 165°) was 145–150°.

Mercuration of 5-ethylcarbazole.—To 19.5 g. (0.1 mole) of 5-ethylcarbazole dissolved in 500 cc. of hot 95% ethanol was added a solution of 31.9 g. (0.1 mole) of mercuric acetate in 500 cc. warm ethanol to which 10 cc. of acetic acid had been added. The mixture was boiled for one and one-half hours, a white crystalline solid separating at the end of one-half hour. After standing for 24 hours, the mixture was filtered and the solid washed with 500 cc. of ethanol. The solid which weighed 13.5 g.* decomposed at 240° with gas evolution but without darkening, and analyzed for 51.7 and 51.4% Hg. When 5.3 g. of the 240° material was extracted with ethanol for 8 hours, the 3.5 g. which remained melted at 242°. This residue, insoluble in the lower alcohols, benzene, acetone and chloroform, analyzed for 53.6, 53.8 and 54.6% Hg. The theoretical value for mercury in 5-ethyl-2,8-diacetoxymercuricarbazole (IV) is 56.3%; and for the bis-(5-ethyl-2-acetoxymercuri-8-carbazyl-) mercury (V) the theoretical percentage of mercury is 54.4.

The alcoholic solution from the mercuration yielded 5-ethyl-2-acetoxymercuricarbazole. This compound was obtained by evaporating the ethanol, and dissolving most of the residue (one g. melting with decomposition at 235° remained) in 600 cc. of warm benzene. The benzene solution yielded 13.8 g. (30.4%) of compound melting at 153°; crystallization from methyl alcohol and benzene raised the melting point to 156°.

Anal. Calc'd for $C_{16}H_{15}NHgO_2$: Hg, 44.2. Found: Hg, 44.7, 44.5.

In a mercuration experiment without solvent, a melt of 0.03 mole of 5-ethylcarbazole and 0.02 mole of mercuric acetate was heated for three hours, and then extracted with 200 cc. of boiling ethanol. The residue (2.9 g.) was the 240°-melting material. To the alcoholic solution was added an excess of an alcoholic solution of calcium chloride in ethanol to give 2 g. of 5-ethyl-2-chloromercuricarbazole, which, after recrystallization from *n*-butyl alcohol, melted at 212° (mixture with known sample), and which gave with iodine and potassium iodide the 5-ethyl-2-iodocarbazole (identified by melting point of mixture with known sample).

5-Ethyl-2-acetoxymercuricarbazole.—The mercurial gave a 75% yield of 5-ethylcarbazole on warming with 10% alcoholic hydrochloric acid.

An 88% yield of 5-ethyl-2-iodocarbazole (m.p. and mixture m.p., 82°) was obtained in the customary manner by treatment with iodine and potassium iodide.

A 93% yield of 5-ethyl-2-chloromercuricarbazole was obtained from the acetoxymercuri compound and calcium chloride. The compound melted at 212–213° after crystallization from *n*-butyl alcohol.

Anal. Calc'd for $C_{14}H_{12}ClHgN$: Hg, 46.6 Found: Hg, 47.1, 47.1.

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*If the reaction is run at a lower temperature and with a lesser volume of ethanol, a greater quantity of the 240° material separates.

A 90% yield of bis-(5-ethylcarbazyl-2-)mercury was obtained from the acetoxymercuri compound and hydrazine hydrate.[6] The bis-mercurial was crystallized from a benzene-petroleum ether mixture and melted at 217°. It was cleaved by alcoholic hydrochloric acid to give 5-ethylcarbazole.

Anal. Calc'd for $C_{28}H_{24}HgN_2$: Hg, 34.1. Found: Hg, 34.4, 34.0.

5-Ethylcarbazole-2-carboxylic acid.—(1) A Schlenk tube containing 0.5 g. of bis-(5-ethylcarbazyl-2-)mercury, 1 g. of lithium shavings and 20 cc. of ether was filled with nitrogen and shaken for 12 hours. Carbonation by solid carbon dioxide gave a 50% yield of 5-ethylcarbazole-2-carboxylic acid, which melted at 226° after crystallization from benzene and ethanol.

Neutralization equivalent: Calc'd, 239; Found, 242.

Anal. Calc'd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.44; N, 5.86.
Found: C, 75.2; H, 5.40; N, 6.00.

(2) The Grignard reagent of 5-ethyl-2-iodocarbazole (prepared by iodination of 5-ethylcarbazole)[5] was carbonated with solid carbon dioxide to give a 20% yield of 5-ethylcarbazole-2-carboxylic acid. The acid may be sublimed under reduced pressure without decomposition.

(3) 5-Ethylcarbazole (0.075 mole) in acetic acid was brominated by 0.05 mole potassium bromide and 0.056 mole of potassium bromate, to give a 54% yield of pure 5-ethyl-2-bromocarbazole melting at 83° and shown to be identical with the compound obtained by ethylating 2-bromocarbazole.[4] The position of the bromine in the compound prepared by these two procedures is established by the fact that 5-ethyl-2-iodocarbazole (of determined structure) and our bromo compound give 5-ethylcarbazole-2-carboxylic acid *via* carbonation of the respective organometallic compounds.

5-Ethyl-2-bromocarbazole was converted to the corresponding organolithium compound in a customary manner, and the organolithium compound was carbonated by solid carbon dioxide to give a 34% yield of 5-ethylcarbazole-2-carboxylic acid.

(4) Ethyl carbazole-2-carboxylate in acetone was ethylated by means of diethyl sulfate. Hydrolysis of the 5-ethyl ethyl ester gave 5-ethylcarbazole-2-carboxylic acid.

Mixture melting points showed the acids obtained from procedures (1), (2), (3) and (4) to be identical.

5-Ethyl-2,8-diïodocarbazole.—The dimercurial obtained by mercurating 5-ethylcarbazole was treated with iodine and potassium iodide to replace the mercuri groups by iodine. From 10 g. of the dimercurial there was isolated 4 g. of 5-ethyl-2,8-diïodocarbazole which was shown to be identical with the compound obtained by the direct iodination of 5-ethylcarbazole.[5] From the filtrates of the diïodo compound, there was isolated 0.5 g. of 5-ethyl-2-iodocarbazole. No 5-ethyl-triïodocarbazole was isolated.

Dimethyl 5-ethylcarbazole-2,8-dicarboxylate.—A mixture of 3.1 g. of 5-ethyl-2,8-diïodocarbazole, 3 g. of cuprous cyanide, 3 g. of potassium cyanide, 7 cc. of water and 5 cc. of ethanol was heated for 20 hours at 230° in a sealed tube.* The mixture was extracted with sodium hydroxide; the organic acids were precipitated by 15% hydrochloric acid; the precipitate was extracted first with boiling alcohol and then with hot acetic acid; and the residue, which melted above 320°, was ground finely and treated with an excess of diazomethane in ether to give 0.5 g., or a 23%

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* This is in essential accordance with the procedure of ROSENMUND AND STRUCH, *Ber.*, **52B**, 1749 (1919), for the conversion of halides to acids.

yield, of dimethyl 5-ethylcarbazole-2,8-dicarboxylate. The ester melts at 187° after crystallization from benzene-petroleum ether (b.p., 60–68°) and methanol.

Anal. Calc'd for $C_{18}H_{17}NO_4$; C, 69.5; H, 5.47.
Found: C, 69.3; H, 5.55.

Saponification of the ester by 10% potassium hydroxide in 50% ethanol gave 5-ethylcarbazole-2,8-dicarboxylic acid which did not melt at 320°.

Neutralization equivalent: Calc'd, 142; Found, 139.

An authentic specimen of 5-ethylcarbazole-2,8-dicarboxylic acid was synthesized by first ethylating 2,8-diacetylcarbazole and then oxidizing the 5-ethyl-2,8-diacetylcarbazole. The 2,8-diacetylcarbazole in acetone was ethylated by means of diethyl sulfate and sodium hydroxide. The 5-ethyl-2,8-diacetylcarbazole was obtained in 97% yield and melted at 182° after crystallization from methanol and benzene.

Anal. Calc'd for $C_{18}H_{17}NO_2$; C, 77.4; H, 6.09.
Found: C, 77.3; H, 6.05.

To a solution of 150 g. of potassium ferricyanide and 23 g. of potassium hydroxide in 600 cc. of hot water was added 1 g. of 5-ethyl-2,8-diacetylcarbazole. The mixture was refluxed with stirring for one hour and then warmed on a steam bath for 16 hours; cooled; filtered and acidified with 15% hydrochloric acid. Then the acid was again dissolved in alkali, the solution was filtered, and the acid was reprecipitated by hydrochloric acid, after which, it was dried, pulverized and treated with an ether solution of diazomethane. The dimethyl 5-ethylcarbazole-2,8-dicarboxylate obtained in this manner (in 45% yield) melted at 187° after crystallization from methanol, and was shown to be identical with the dimethyl ester obtained from 5-ethyl-2,8-diïodocarbazole.

SUMMARY

Metalation of 5-ethylcarbazole by an organometallic compound like *n*-butyllithium takes place in the 4-position. Mercuration, however, occurs in the 2-position. With dibenzofuran, all varieties of metalating agents so far examined involve the 4-position.

Generalizations are proposed on the metalation of the aromatic nucleus of some related polynuclear types.

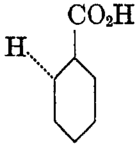
[Contribution from the Chemical Laboratory of Howard University]

THE PRINCIPLE OF VINYLOGY AND THE EFFECT OF *ORTHO* SUBSTITUENTS ON THE REACTIVITY OF BENZENE DERIVATIVES

A. H. BLATT

Received January 23, 1936

In a recent article, Oskar Zwecker[1] has discussed in considerable detail the occurrence of steric hindrance in *ortho*-substituted benzene derivatives. His point of view may be illustrated by reference to benzoic acid. The effect on the reactivity of the carboxyl group in benzoic acid of the introduction of any substituent in the *ortho* position will be comparable with the effect on the reactivity of the carboxyl group in formic acid caused by the replacement of the hydrogen atom in that acid by the same substituent. Taking a methyl group as the substituent the following pairs are to be compared:



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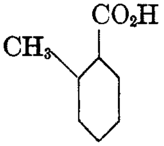

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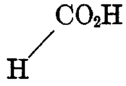

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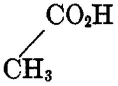

In other terms, any monosubstituted benzene derivative is comparable with the hydrogen compound of the substituent and the effect of introducing a substituent in the position *ortho* to the first substituent is similar to the effect of introducing this same substituent into the hydrogen compound of the first substituent. It is not the purpose of this paper to challenge the validity of Zwecker's point of view but rather to show that this point of view is simply a special case of a much wider generalization —the principle of vinylogy as formulated by Fuson.[2]

More specifically Zwecker's comparisons are valid because they form a special case of an extension of the principle of vinylogy. As stated by Fuson, the principle of vinylogy deals with the effect of an unsaturated group on substituents attached to that group and shows that this effect

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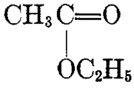
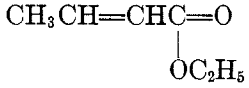
[1] Oskar Zwecker, *Ber.*, **68**, 1289 (1935).

[2] Fuson, *Chem. Rev.*, **16**, 1 (1935). Zwecker's analogies may also be considered as following from Angeli's rule. See Angeli, *Ahren's Sammlung*, **28**, 1 (1926).

may be transmitted through intervening vinylene groups. Thus the hydrogen atoms of the methyl group in ethyl acetate are activated sufficiently to condense with esters. If a vinylene group is interposed, as in ethyl crotonate, the hydrogen atoms in the terminal methyl group are still sufficiently active to undergo ester condensations.



$$\begin{array}{l}\mathrm{CH_3C{=}O}\\ \quad\;|\\ \quad\mathrm{OC_2H_5}\end{array}$$



$$\begin{array}{r}\mathrm{CH_3CH{=}CHC{=}O}\\ |\quad\;\;\\ \mathrm{OC_2H_5}\end{array}$$

We are dealing with the effects of saturated substituents on the reactivity of a functional group, usually unsaturated, and we shall show that *when a given effect on the reactivity of a functional group is produced by a saturated substituent attached directly to that functional group, a similar effect may be produced by the same substituent when it is separated from the functional group by an intervening vinylene group.* Thus, if one compares formic, acetic, and propionic acids, it is seen (Table I) that the replacement of the hydrogen atom of formic acid by a methyl or an ethyl group results in a decrease in the rate of esterification. The vinylogs of these three acids are acrylic, crotonic, and β-ethylacrylic acids, and a comparison of their esterification velocities (Table II) shows the similar effect resulting from

TABLE I*

ESTERIFICATION WITH METHANOL (T = 15°C.)

SUBSTANCE	k
$\mathrm{HCO_2H}$	1224
$\mathrm{CH_3CO_2H}$	104
$\mathrm{C_2H_5CO_2H}$	91

TABLE II

ESTERIFICATION WITH METHANOL (T = 15°C.)

SUBSTANCE	k
$\mathrm{CH_2{=}CH\ CO_2H}$	3.09[3]
$\mathrm{CH_3CH{=}CH\ CO_2H}$	1.26[3]
$\mathrm{C_2H_5CH{=}CH\ CO_2H}$	1.5[4]
$\mathrm{C_6H_5CH{=}CH\ CO_2H}$	0.937[4]

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* Reference 1, p. 1293. To facilitate comparisons reference is made whenever possible to Zwecker's article rather than to the original sources.

[3] SUDBOROUGH AND DAVIS, *J. Chem. Soc.*, **95**, 976 (1909).

[4] SUDBOROUGH AND GITTINS, *ibid.*, **95**, 315 (1909).

the introduction of a methyl or ethyl group separated from the carboxyl group by an intervening vinylene residue.

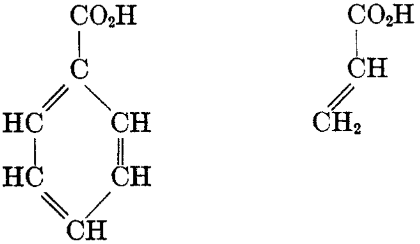
To these illustrations we shall add but one other—a case in which the reactivity of the functional group is enhanced rather than decreased by the introduction of a substituent. Ethyl chloride is hydrolyzed more rapidly than methyl chloride and the same relationship holds true for the corresponding bromides.† The vinylogs of these halides are found in allyl bromide and crotonyl bromide and the data of Table III show that a methyl group introduced into allyl bromide, even though separated from the halogen atom by an intervening vinylene group, has an effect similar to that brought about by the introduction of a methyl group into methyl chloride or bromide.

The application of this extension of the principle of vinylogy to the *ortho*-substituted benzene derivatives requires but little explanation. When benzoic acid is used as an illustration and a developed Kekule formula is written, it is obvious that a vinylene group intervenes between the *ortho* position and the carboxyl group (and three vinylene groups between the *ortho'* position and the carboxyl group). The open-chain analog of benzoic acid is, therefore, not formic acid but acrylic acid.

TABLE III[5]

REACTION WITH POTASSIUM IODIDE (T = 15°C.)

SUBSTANCE	k
$CH_2{=}CH\ CH_2Br$	126
$CH_3CH{=}CH\ CH_2Br$	519



Zwecker's comparison between benzoic and toluic acids on the one hand and formic and acetic acids on the other is valid because the effect of the *ortho* substituent on the reactivity of the functional group is transmitted *qualitatively unchanged* by the intervening vinylene group. In other words

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† Reference 1, pp. 1301–2.

[5] JUVALA, *Ber.*, **63**, 2001 (1930).

it is a direct consequence of the extension of the principle of vinylogy as stated and illustrated in the preceding paragraphs.

TABLE IV[6]

Esterification with Methanol ($T = 15°C.$)

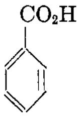
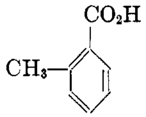
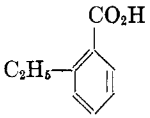
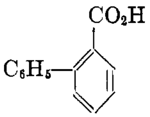
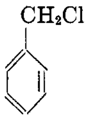
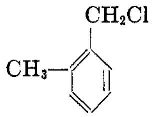
SUBSTANCE	k
	0.283
	0.092
	0.056
	0.051

TABLE V[7]

Hydrolysis ($T = 30°C.$)

SUBSTANCE	k
	1
	4.95

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[6] Sudborough and Turner, *J. Chem. Soc.*, **101**, 238 (1912).

[7] Olivier, *Rec. trav. chim.*, **41**, 648 (1922). In the case of the substituted benzyl halides there is an indication that the influence of a substituent can be transmitted through two intervening vinylene groups, for the hydrolysis velocity of *p*-tolylmethyl chloride is 9.4 in the units given in Table V. However, the inclusion of *para* substituents would unduly extend the length of the present discussion.

Two sets of examples may be given to show the application of the principle. We may compare the series of *ortho*-substituted benzoic acids (Table IV) with the β-substituted acrylic acids (Table II), and the pair, benzyl chloride and *o*-tolylmethyl chloride (Table V), with the pair, allyl bromide and crotonyl bromide (Table III). In each case the effect of the saturated substituent on the reactivity of the functional group is transmitted qualitatively unchanged through the intervening vinylene group. Since this discussion is not intended to be exhaustive, further illustrations are omitted. Doubtless other cases will occur to the reader, and it may be stated that the application of this extension of the principle of vinylogy leads to many interesting predictions.

Zwecker has used his results and those of others as the basis for a criticism of the common concept of hindrance as a spatial phenomenon. Without entering into a discussion of this point it seems advisable to point out that most organic chemists will agree both that hindrance is effective only in reactions involving addition and that hindrance is not the sole factor that determines the occurrence and rate of chemical transformations. It is unfortunate that in the usual illustrations of hindrance, *e.g.*, the nonesterification of 2,4,6-trisubstituted benzoic acids, the steric effects are so predominant that other influences are masked completely. This, and the failure to recognize the qualification that hindrance affects addition reactions only, are responsible for much of the confusion regarding those borderline cases where at least two effects—hindrance to reaction by a substituent and activation of the reacting group by the same substituent—may be nearly balanced. In such cases the effect of the substituent may be either to retard or to accelerate the reaction. A more detailed study of hindrance in just such borderline cases would be of value in clarifying the issue.

SUMMARY

It has been pointed out that the effects of saturated substituents on a functional group may be transmitted qualitatively unchanged through an intervening vinylene group. This extension of the principle of vinylogy has been used to correlate the effects of *ortho* substituents on the reactivities of various benzene derivatives with the behavior of the analogous open-chain compounds.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

A PROPOSED MECHANISM FOR MERCURY CATALYSIS IN ACETYLENE ADDITION REACTIONS*

G. F. HENNION, R. R. VOGT AND J. A. NIEUWLAND†

Received March 27, 1936

DISCUSSION

The many well-known reactions of acetylene with water, alcohols, glycols, carboxylic acids, oxy-acids, phenols, etc., which yield acetaldehyde, acetals, vinyl and ethylidene esters, and the like, are too numerous to permit of review here. Some corresponding reactions with alkylacetylenes have recently been described in publications from our laboratory.[1]

These reactions are similar in that they all proceed quite readily when carried out in an appropriate acid medium in the presence of mercuric oxide or a suitable mercuric salt. Considerable interest attaches to the rôles played by the mercury and acid in these reactions. The amounts of mercuric salt and acid required are so small that these substances must undoubtedly undergo a definite cycle of reactions which may be repeated until the mercuric salt is reduced by secondary reactions. Such recurring reactions may well explain the nature of the so-called "mercury catalysis" in acetylene chemistry. The mercuric salt must presumably be ionized since slightly ionizable salts and conditions which depress ionization are, in general, not suitable.

A small quantity of boron fluoride, when used with an alcohol, forms a strongly acidic medium. Boron fluoride has been found to be an extremely effective acid-forming catalyst. Nieuwland, Vogt and Foohey[2] showed

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* Paper XIII on the chemistry of the alkylacetylenes and their addition compounds; previous paper, *J. Am. Chem. Soc.*, **58**, 892 (1936).

† *Editorial note:* Dr. Nieuwland, a member of the Board of Editors of THIS JOURNAL, died suddenly of a heart attack on June 11th [*Ind. Eng. Chem., News Ed.*, **14**, 248 (June 20, 1936)]. His many friends will welcome this outline of his views on a reaction to the knowledge of which he was an outstanding contributor.

[1] HENNION, NIEUWLAND AND COWORKERS, *J. Am. Chem. Soc.*, (*a*) **56**, 1130 (1934); (*b*) **56**, 1384 (1934); (*c*) **56**, 1786 (1934); (*d*) **56**, 1802 (1934); (*e*) **57**, 2006 (1935); (*f*) **58**, 80 (1936).

[2] NIEUWLAND, VOGT AND FOOHEY, *ibid.*, **52**, 1021 (1930).

that 0.142 grams of boron fluoride was sufficient to catalyze the conversion of 250 grams of glycerol to the ethylidene acetal. Later Vaughn[3] pointed out that $(50 \pm 2) \times 10^{-6}$ grams of boron fluoride per milliliter of glycol is sufficient to catalyze the formation of glycol acetal. In other cases[1c,f] a small amount of a strong acid, such as trichloroacetic acid, promotes the catalytic effect of boron fluoride. The lower limit of the quantity of required mercuric oxide (or salt) has not been determined but is known to be largely dependent upon experimental conditions.

A great deal of work concerning mercury-acetylene addition compounds —much of which is questionable or indefinite—has been reported in the literature. Kutscheroff[4] was probably the first to recognize the existence and catalytic effect of complex mercury-acetylene addition compounds; nevertheless in many subsequent discussions the rôle of either the mercuric salt or acid has been unjustifiably ignored.

A consideration of these catalytic effects should, in the light of present experimental experience, include the following points.

1. Both a mercuric salt (or mercuric oxide which, no doubt, forms the salt) and a strong acid are required. A notable exception to this rule is the hydration of the acetylenic triple bond. Some acetaldehyde is formed, for example, by passing acetylene through boiling 20% sulfuric acid. Certain alkylacetylenes may be converted to ketones[5] by dissolving in strong sulfuric acid followed by dilution with water. Even in these instances, however, the reactions are certainly more advantageously carried out with the aid of a mercuric salt and a more dilute acid.

2. Acetylenic hydrogen cannot be concerned, or is at least unnecessary for catalysis. It has been shown that the dialkylacetylenes form typical derivatives by addition. For example, methylamylacetylene yields, with methanol, 3,3-dimethoxyoctane[1e].

3. It is logical to believe that the catalytic mercury salt reacts with the acetylene *by addition*, being subsequently replaced by the adding molecule. It is quite probable that the mercury content of the catalytic intermediate may depend upon whether acetylene, a monosubstituted acetylene or a disubstituted acetylene is used. The authors are of the opinion that replacement of acetylenic hydrogen by mercury may be of secondary importance and not immediately concerned with the catalytic mechanism.

4. Vinyl ethers add alcohols to form ketals (acetals) with extreme ease when catalyzed by a trace of strong acid only.[6] It is significant that mercuric compounds are not required in this step.

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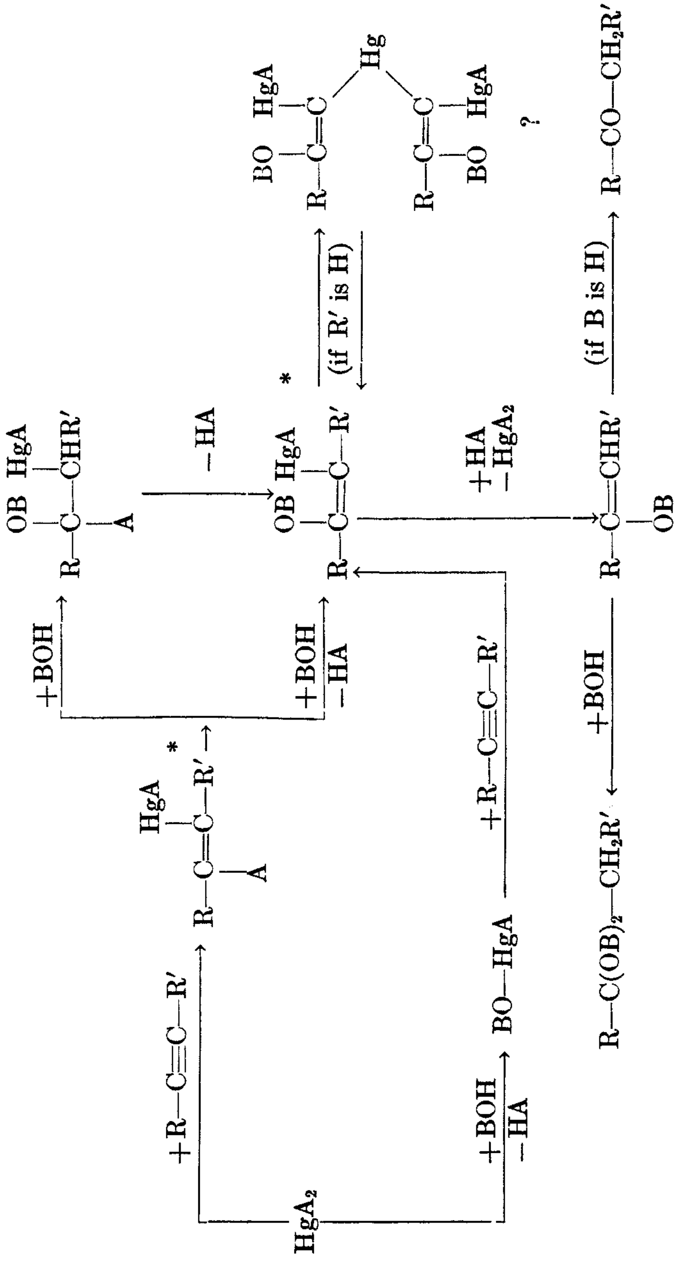
[3] VAUGHN, *Proc. Ind. Acad. Sci.*, **42**, 129 (1933).

[4] KUTSCHEROFF, *Ber.*, **17**, 13 (1884).

[5] BEHAL, *Ann. chim.*, [6], **15**, 270 (1888).

[6] KILLIAN, HENNION AND NIEUWLAND, *J. Am. Chem. Soc.*, **57**, 544 (1935).



* Cis or trans compounds?

5. The alkylacetylenes react with acetic acid to form monoäddition compounds, *e.g.*, 2-acetoxy-1-heptene from amylacetylene[1d]. With acetylene either mono- or diäddition compounds may be obtained.

6. The small amount of catalyst needed seems to indicate that its addition product is extremely reactive and easily decomposed.

7. It is logical to believe that the mechanism of this catalysis is, *in its essential features*, independent of the nature of the acetylene and the type of hydroxylated compound being added.

The authors have formulated and here present a mechanism consistent with these points, plausible, and useful as working tool.

Nomenclature.—R and R′ are independently hydrogen atoms or alkyl groups originating in the acetylene used. A represents the acid radical contained in the mercuric salt and (or) the acid used. For example when boron trifluoride and methyl alcohol are employed A becomes $^{-}OCH_3 \cdot BF_3$. The existence of the salt $Hg(OCH_3 \cdot BF_3)_2$ was established by O'Leary and Wenzke.[7] B represents the group attached to the hydroxyl group of the adding molecule such as hydrogen (in the case of water), alkyl groups (in the case of alcohols), or acyl groups (in the case of acids).

We are fully aware of the fact that such a mechanism is incapable of rigid proof; hence none is offered. In fact the extreme reactivity of the intermediate mercury compounds and their susceptibility to reduction (not infrequently to metallic mercury) argues against the possibility of their isolation and characterization.

It is readily seen that the proposed scheme of reactions is generally applicable to the addition of any hydroxy compound to any type of acetylene. In the event that the acetylene in question is a conjugate enyne or diyne, where there is a possibility that reagents may add in the 1,4 positions, it is only necessary to assume that the catalytic mercuric salt previously added in that fashion.

SUMMARY

A mechanism for mercury catalysis in acetylene addition reactions is offered. The proposed scheme of reactions is plausible, consistent with experimental results, and useful as a working tool.

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[7] O'Leary and Wenzke, *ibid.*, **55**, 2118 (1933).

[Contribution from the Chemical Laboratories of the University of Notre Dame]

THE ADDITION OF ACETYL CHLORIDE TO ALKYLACETYLENES*

JOHN W. KROEGER, FRANK J. SOWA, and JULIUS A. NIEUWLAND†

Received February 14, 1936

INTRODUCTION

A number of reports concerning the reactions of acyl halides with olefins[1,2,3] have been presented in the literature, but none on the analogous addition to acetylenic hydrocarbons. Acetyl chloride has been reported to add to olefins to form saturated chloro ketones which lose hydrogen chloride on distillation. The chloro ketones from acetylenic compounds were found to distill undecomposed and lost hydrogen chloride only to a slight extent even after standing for rather long periods of time.

Krapivin,[2] in his report on the condensation of olefins with acid chlorides in the presence of aluminum chloride, mentioned as by-products "halogen-substituted, saturated hydrocarbons of the series $C_nH_{2n+1}X$", which obviously are formed by the addition of hydrogen chloride to the double bond in a manner analogous to the formation of the chloro olefins herein described.

Darzens[3] carried out a very careful investigation along similar lines and found that, of all the catalysts tried, anhydrous stannic chloride gave the best results. His conclusions were verified in the present investigation, and stannic chloride was selected from a number of covalent metal chlorides which were found to catalyze the reaction. These included zinc chloride, aluminum chloride, antimony pentachloride, phosphorus tri- and penta-

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* Paper VIII on the addition reactions of alkyl acetylenes. Previous paper, *J. Am. Chem. Soc.*, **58**, 80 (1936).

† Dr. Nieuwland, a member of the Board of Editors of This Journal, died suddenly of a heart attack on June 11th [*Ind. Eng. Chem.*, *News Ed.*, **14**, 248 (June 20, 1936)].

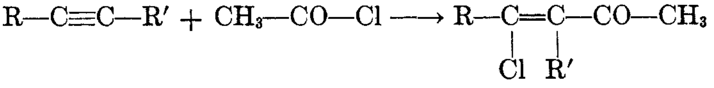
[1] Kondakow, *Bull. soc. chim.*, **7**, 576 (1892); Zelinski, *J. Russ. Phys. Chem. Soc.*, **31**, 402 (1899); Blanc, *Bull. soc. chim.*, **19**, 699 (1890); Norris and Couch, *J. Am. Chem. Soc.*, **42**, 2329 (1930); Wieland and Bettag, *Ber.*, **55**, 2246 (1922); Schoeller and Zöllner, *U. S. Patent* 1,737,203 (Nov. 1929).

[2] Krapivin, *Bull. Soc. Imp. Nat. Moscow*, **1**, (1908); *Chem. Abstr.*; **5**, 1281 (1911).

[3] Darzens, *Compt. rend.*, **150**, 707 (1910).

chlorides, phosphorus oxychloride, mercuric chloride, and cuprous chloride. Stannic chloride in amounts greater than 4% caused an immediate violent reaction. In addition it had the advantage of being completely soluble in the reaction mixture.

We found that acetyl chloride reacts with alkylacetylenes in the presence of catalysts to form, mainly, chloro-olefinic ketones together with smaller amounts of 2-chloro-1-olefins and traces of alkyl acetates. The principle reaction is:



$$R\text{—}C{\equiv}C\text{—}R' + CH_3\text{—}CO\text{—}Cl \longrightarrow R\text{—}\underset{\displaystyle Cl}{\underset{|}{C}}{=}\underset{\displaystyle R'}{\underset{|}{C}}\text{—}CO\text{—}CH_3 \qquad \text{(A)}$$

(R′ = hydrogen or R)

The chloro-olefinic ketones are pleasant-smelling liquids, and have a light yellow color when freshly distilled, but darken slightly on standing. They decompose readily in the presence of traces of acid but can be kept indefinitely by the addition of a small amount of anhydrous potassium carbonate. They have a slight vesicant and lachrymatory action which decreases with increase in the molecular weight of the compound. They were found to be oxidized to some extent by air—especially the lower members of the series. In the case of the lowest member of the group, 4-chloro-3-hexene-2-one, a temperature of 75° was reached by bubbling air through the pure substance.

The *cis* and *trans* isomers of these ketones were found to be rather readily separable and were isolated in certain cases. On standing for a few weeks the pure isomers reverted completely to an equilibrium mixture. By analogy to the known pairs of liquid *cis-trans* isomers, the higher-boiling fraction has been designated *cis* and the lower-boiling, *trans*. This assignment is supported by the fact that an alcoholic solution of sodium acetate gives an almost immediate precipitation of sodium chloride with the *trans* isomers of the normal ketones, while several days are required for the precipitate to form from the *cis* isomers; moreover when hydrogen chloride is added to an acetylenic ketone the product is mainly the *trans* isomer. Hydrogen chloride is generally conceded to add to and split out from the *trans* positions.

By keeping the amount of catalyst low, usually 2 to 4% of the mixture, the reaction was prevented from going to completion. In spite of this precaution the reaction was always accompanied by the formation of some tarry polymerized products. The yields were usually from 20 to 35% of the chloro olefin and from 25 to 40% of the ketone. The larger yields of chloro olefin were obtained in the case of the dialkylacetylenes. Traces of alkyl acetates were also formed, and could not be accounted for.

Both hexyne-1 and decyne-5 formed about 1% of *n*-butyl acetate, which was identified by fractionation and saponification.

A satisfactory explanation for the formation of the chloro olefin, as yet, has not been advanced. The following mechanism might be considered plausible:

$$CH_3{-}CO{-}Cl \xrightarrow{SnCl_4} CH_2{=}C{=}O + HCl \qquad (B)$$

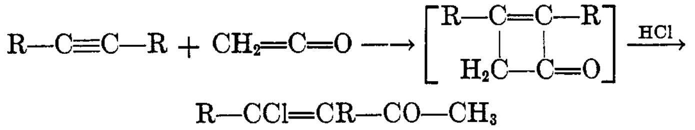
Hydrogen chloride and ketene might then react with the alkylacetylene as follows:

$$R{-}C{\equiv}CH + HCl \longrightarrow R{-}CCl{=}CH_2 \qquad (C)$$

$$\begin{gathered} R{-}C{\equiv}CH + CH_2{=}C{=}O \longrightarrow R{-}C{\equiv}C{-}CO{-}CH_3 \xrightarrow{HCl} \\ R{-}CCl{=}CH{-}CO{-}CH_3 \end{gathered} \qquad (D)$$

And in the case of dialkylacetylenes:

$$R{-}C{\equiv}C{-}R + HCl \longrightarrow R{-}CCl{=}CH{-}R \qquad (E)$$



(F)

Direct addition of acetyl chloride to the triple bond might also take place as written previously (A).

The acetylenic ketones were found to add hydrogen chloride very readily, which may explain the fact that no such ketones, nor those of the cyclobutenone type, were isolated.

EXPERIMENTAL

Materials.—The monoalkylacetylenes were prepared from the corresponding alkyl bromides and sodium acetylide in liquid ammonia. The *sym.*-dialkylacetylenes were prepared in a similar manner from the sodium compound of the monoalkylacetylenes. Commercial acetyl chloride was fractionated and the fraction boiling from 50.0 to 50.5° was saved. Stannic chloride, anhydrous, was used after redistillation.

The procedures for the preparation of the ketones were all quite similar and a description of one such preparation will be sufficient.

Addition of acetyl chloride to hexyne-1.—In a three-liter, three-necked flask, equipped with a reflux condenser, dropping funnel and mercury-sealed stirrer, was placed 850 g. (10.4 moles) of hexyne-1, b.p. 70.0 to 70.5°, and 820 g. (10.4 moles) of acetyl chloride. To this mixture, which was stirred vigorously, a solution of 40 g. of anhydrous stannic chloride in 100 g. of acetyl chloride was added dropwise. The addition was carried on rapidly enough to keep the reaction mixture refluxing slowly. The color of the solution changed rapidly from yellow to dark-red. The mixture was then refluxed for one hour.

TABLE

PHYSICAL CONSTANTS AND ANALYSES OF ADDITION COMPOUNDS

	COMPOUND	b.p.	n_D^{25}	d_4^{25}	MOL. WT.		CHLORINE (%)		
					Calc'd	Found	Calc'd	Found	
I	4-chloro-3-ethyl-3-hexene-2-one (*trans*)	89–91°/30 mm.	1.4611	0.9993	160.6	159	22.1	22.1	21.5
II	4-chloro-3-ethyl-3-hexene-2-one (*cis*)	97–99°/30 mm.	1.4596	1.0029	160.6	163	22.1	21.6	21.2
III	4-chloro-3-*n*-propyl-3-heptene-2-one (*trans*)	112-113°/28 mm.	1.4601	0.9592	188.6	178	18.8	18.6	18.6
IV	4-chloro-3-*n*-propyl-3-heptene-2-one (*cis*)	117–118°/28 mm.	1.4587	0.9680	188.6	185	18.8	18.8	18.7
V	4-chloro-3-*n*-butyl-3-octene-2-one	140–146°/28 mm.	1.4612	0.9459	216.7	214	16.4	16.1	16.2
VI	4-chloro-3-*n*-amyl-3-nonene-2-one	115–121°/5 mm.	1.4626	0.9348	244.7	245	14.5	14.3	14.4
VII	4-chloro-3-hexene-2-one	46–53°/10 mm.	1.4906	1.0973	—	—	—	—	—
VIII	4-chloro-3-heptene-2-one (*trans*)	54.5–55.5°/10 mm.	1.4702 (23°)	1.0134 (23°)	—	—	—	—	—
IX	4-chloro-3-heptene-2-one (*cis*)	62–63°/10 mm.	1.4602 (23°)	1.0321 (23°)	—	—	—	—	—
X	4-chloro-3-octene-2-one (*trans*)	69°/10 mm.	1.4657	0.9705	160.6	163	22.1	22.5	22.7
XI	4-chloro-3-octene-2-one (*cis*)	80°/10 mm.	1.4721	0.9984	160.6	160	22.1	22.0	22.6
XII	4-chloro-3-nonene-2-one (*trans*)	89°/10 mm.	1.4665	0.9752	174.6	171	20.3	20.7	20.5
XIII	4-chloro-3-nonene-2-one (*cis*)	99°/10 mm.	1.4607	0.9830	174.6	178	20.3	20.3	20.1
XIV	3-chloro-3-hexene	113.0–113.5°/748 mm.	1.4320	0.8898	119.6	119	30.0	29.8	29.5

TABLE—*Concluded*

	COMPOUND	b.p.	n_D^{25}	d_4^{25}	MOL. WT.		CHLORINE (%)		
					Calc'd	Found	Calc'd	Found	
XV	4-chloro-4-octene	157.5–159.5°/750 mm.	1.4394	0.8788	146.6	143	24.2	23.4	23.6
XVI	5-chloro-5-decene	99–100°/28 mm.	1.4448	0.8753	174.7	175	20.3	19.4	20.0
XVII	6-chloro-6-dodecene	128–129°/28 mm.	1.4493	0.8760	202.7	196	17.5	17.0	17.5
XVIII	2-chloro-1-butene	57–59°/748 mm.[a]	1.4115 (21°)	0.8950 (21°)	—	—	—	—	—
XIX	2-chloro-1-hexene	109.5–110.5°/735 mm.	1.4187	0.8872	—	—	—	—	—
XX	2-chloro-1-heptene	138–139°/748 mm.[b] 71–72°/75 mm.	1.4302 (24°)	0.8788 (24°)	—	—	—	—	—

[a] Constants reported[5]: b.p. 61–62°, n_D 1.4168.

[b] Constants reported[6]: b.p. 71°/75 mm., d_4^{20} 0.8895, n_D^{20} 1.4349.

In the case of the dialkylacetylenes, the mixture was hydrolyzed at this point. Considerable time could be saved, when large quantities of ketone were desired, by using the following procedure. This was particularly applicable where the acetylene was low-boiling.

The unchanged acetyl chloride and hexyne-1 were distilled off with continued stirring until the temperature reached 80°. The residue was then washed with water, 10% sodium carbonate, then again with water, and finally was steam-distilled.

The mixture of acetyl chloride and hexyne-1, amounting to 1040 g. was replaced in the three-necked flask and 25 g. of stannic chloride was added. After refluxing for one hour the unchanged reactants were again distilled off and the residue was washed and steam-distilled as before.

This procedure was repeated twice more and the product of the fourth reaction was hydrolyzed immediately after refluxing, then washed and steam-distilled. The products after steam distillation were combined, dried over calcium chloride and fractionated. Two hundred sixty grams (3.2 moles) of hexyne-1 was recovered. Yields: 2-chloro-1-hexene (b.p. 107–111°), 130 g. (1.1 moles), 15%; 4-chloro-3-octene-2-one (b.p. 75–95°/20 mm.), 430 g. (2.7 moles), 37%.

The crude ketone was further fractionated* in an all-glass apparatus with a Widmer column with a packed section 35 cm. long.

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* This fractionation could be carried out only with quantities less than 200 g. Attempts to fractionate larger quantities resulted in complete conversion to a polymer, b.p. 174°/10 mm., n_D^{20} 1.4705. Treatment of the simple ketone with 0.2% of concentrated hydrochloric acid caused a quantitative conversion to this polymer on standing for 24 hours. If distilled immediately the boiling point of the polymer could be duplicated. On standing for three days over potassium carbonate in diffused sunlight the polymer reverted completely to the monomer. This compound is obviously not a condensation product and it is possible that the formula may be analogous to those of the truxillic acids.

(I) *Trans* isomer: b.p. 69°/10 mm., n_D^{25} 1.4657, d_4^{25} 0.9705.

(II) *Cis* isomer: b.p. 80°/10 mm., n_D^{25} 1.4721, d_4^{25} 0.9984.

(I) gave a semicarbazone which, after recrystallization from aqueous alcohol, melted at 109–110°. The semicarbazone of (II) melted at 121.0–121.5°.

In the reaction with butyne-1, b.p. 8°, liquid ammonia, rather than water, was circulated through the reflux condenser.

The Widmer column was used to fractionate the compounds from hexyne-1 and heptyne-1 only. The other pairs of *cis-trans* isomers were fractionated through a Vigreux type column 20 cm. long and of 10 mm. outside diameter, and consequently were not quite as pure.

The semicarbazones of 4-chloro-3-nonene-2-one, the compound from heptyne-1, were also prepared. *Trans* isomer, m.p. 127°; *cis* isomer, m.p. 137–138°. An indication of the rapidity with which the *cis-trans* equilibrium mixture is formed from the individual isomers was obtained from the fact that the semicarbazones of 4-chloro-3-ethyl-3-hexene-2-one, the compound from hexyne-3, which were prepared after the pure isomers had been standing for two weeks, both melted at 161°.

Proof of Structure.—3-Hexyne-2-one (b.p. 76°/15 mm., n_D^{25} 1.4460, d_4^{25} 0.8622) and 3-heptyne-2-one (b.p. 89–91°/15 mm., n_D^{24} 1.4461, d_4^{24} 0.8780; reported, b.p. 91–95°/18 mm., n_D^{24} 1.4453, d^0 0.8893) were prepared by a modification of the procedure of Moureu and Delange[4] using the following reaction:

$$R-C\equiv C-MgCl + O(CO-CH_3)_2 \rightarrow R-C\equiv C-CO-CH_3 + MgCl(O-CO-CH_3) \quad (G)$$

Hydrogen chloride was added to these compounds in the following manner. The acetylenic ketones were dissolved in chloroform, and the solution was cooled in a bath of liquid ammonia. Dry hydrogen chloride was passed into the cold solution in the presence of a trace of cuprous chloride. The absorption were quite rapid, and after an hour the chloroform solution was removed, was washed first with water, then with sodium carbonate solution, and was dried over calcium chloride. The chloroform was distilled off, and the residue was again washed with sodium carbonate solution, since at this point large amounts of hydrogen chloride were evolved. The material was then dissolved in benzene and dried over calcium chloride. The liquid remaining after the benzene was removed, distilled, in the case of hexynyl methyl ketone, at 67–70°/10 mm.; n_D^{23} 1.4625; d^{25} 0.9720. The addition compound of heptynyl methyl ketone had the following properties: b.p. 89–95°/10 mm.; n_D^{25} 1.4640; d_4^{25} 0.9824. The yields were quantitative. It may be noted that these physical constants compare favorably with those of the *trans* isomers given previously. (See Table.)

The analyses for chlorine were conducted according to the method of Vaughn and Nieuwland.[7] The molecular weights of all compounds except 4-chloro-3-octene-2-one and 4-chloro-3-nonene-2-one were determined cryoscopically in benzene. The molecular weights of the latter compounds were determined in camphor by the method of Rast.[8]

In the reaction of acetyl chloride with pentyne-1, no chloro olefin was obtained. Other acid chlorides, such as alkyl and aryl chlorocarbonates and aryl sulfone-

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[4] MOUREU AND DELANGE, *ibid.*, **131**, 710 (1900).

[5] DUPONT, *ibid.*, **148**, 1522 (1909).

[6] BACHMANN AND HILL, *J. Am. Chem. Soc.*, **56**, 2730 (1934).

[7] VAUGHN AND NIEUWLAND, *Ind. Eng. Chem.*, *Anal. Ed.*, **3**, 247 (1931).

[8] RAST, *Ber.*, **55**, 1051, 3727 (1922).

chlorides were found to react with acetylenes and will be discussed in a future contribution.

Acknowledgement is made to Mr. G. M. Wolf for the preparation of the acetylenic ketones.

SUMMARY

1. The addition of acetyl chloride to alkylacetylenes has been effected with the aid of catalysts.

2. Several members of a new series of ketones and some new chloro olefins have been prepared.

3. A mechanism has been proposed for the formation of the chloro olefin.

[Contribution from the Chemical Laboratory of Stanford University]

THE ACTION OF BASES ON ORGANIC HALOGEN COMPOUNDS. I. THE REACTION OF ARYL HALIDES WITH POTASSIUM AMIDE

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It has long been known that halogen directly attached to the benzene nucleus is not readily replaced by a hydroxyl, amino, or alkoxyl group, unless its activity is enhanced by other groups present in the proper positions within the molecule. Thus, a nitro group will labilize *ortho* and *para* halogen atoms in a manner perhaps best explained by current electrochemical theories of substitution in the aromatic nucleus.[1] The effect of conventional "*ortho-para*-directing" groups—such as methyl—upon the mobility of aromatically bound halogen is on the other hand much more difficult to determine, because, in the majority of cases, the halogen is even less reactive than if attached to an unsubstituted benzene nucleus. It was thought that these difficulties could be satisfactorily overcome by carrying the replacement reactions out in a dissociating solvent—liquid ammonia—using potassium amide, a base of the ammonia system, in place of the less reactive alkali hydroxides or alcoholates. Since the reactions in liquid ammonia were found to be extremely rapid, there is available a method for determining the effects of various groups on the mobility of aromatically bound halogen. In the present paper, we have reported at length only on the reaction between potassium amide and the phenyl halides in liquid ammonia.

DISCUSSION

Liquid ammonia solutions of potassium amide at $-33°$ react very rapidly with phenyl chloride, bromide or iodide to give aniline, diphenylamine, small quantities of *p*-aminobiphenyl, and occasional traces of triphenylamine. Tarry products are formed at the same time, and the solutions acquire a red or reddish-brown color. In harmony with its known inert-

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[1] Ingold, *Rec. trav. chim.*, **48**, 810 (1929); Robinson, *J. Soc. Dyers and Colourists*, Jubilee Journal, **1934**, p. 74.

ness, phenyl fluoride fails to react with potassium amide under the same conditions, and even at room temperature the reaction is extremely slow. Sodium amide fails to react with phenyl chloride or bromide in boiling diethyl ether or in boiling benzene (three hours' refluxing), although the reaction occurs readily in liquid ammonia.[1a]

Horning*, working in this laboratory has found that lithium diethylamide, $(C_2H_5)_2NLi$, reacts with phenyl bromide in ether at room temperature to give diethylaniline in good yield. Since the formation of by-products has been decreased, in comparison with the potassium amide reactions described in this article, there is perhaps available a still better reagent for determining the relative reactivities of aryl halides.

α-Chloronaphthalene, *o*-, *m*- and *p*-chlorotoluene, *o*- and *p*-chlorobiphenyl, and *o*-chloroaniline are all rapidly attacked by potassium amide solution at −33°; α-fluoronaphthalene reacts slowly at this temperature, but more rapidly at room temperatures, while the fluorotoluenes appear to be unattacked at −33°. A detailed discussion of the reactions mentioned in this paragraph will be reserved for the future.

Calcium amide and barium amide react with phenyl bromide in ammonia at room temperature to give a mixture of mono- and diphenylamines, with some tar. Apparently the formation of secondary amine cannot be avoided by using an amide of low ammonia solubility.

The following equations express the reactions that occur when an aryl halide is treated with a solution of potassium amide in ammonia.

(1) $C_6H_5X + KNH_2 = C_6H_5NH_2 + KX$

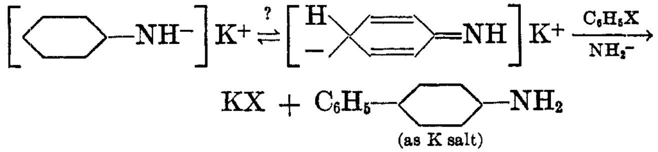
(2) $C_6H_5NH_2 + KNH_2 = C_6H_5NHK + NH_3$

(3) $C_6H_5NHK + C_6H_5X \xrightarrow{NH_2^-} (C_6H_5)_2NH + NH_3$

(4) $(C_6H_5)_2NH + KNH_2 = (C_6H_5)_2NK + NH_3$

(5) $(C_6H_5)_2NK + C_6H_5X \xrightarrow{NH_2^-} (C_6H_5)_3N + KX$

(6)



Halogen is removed almost quantitatively from phenyl chloride, bromide or iodide by a liquid ammonia solution of an excess of potassium amide. However, when potassium amide is added to a considerable excess of phenyl halide in liquid ammonia, potassium halide is formed in yields of

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[1a] Cf. Titherley, J. Chem. Soc. **71**, 460 (1897); Sachs, Ber. **39**, 3011 (1906).

* Unpublished work.

fifty to sixty per cent. of the theoretical, as calculated from equation (1) alone. This can only mean that reaction (2)—in which potassium anilide is produced—is more rapid than the primary reaction expressed by equation (1). Since the yield of halide ion (*i.e.*, of potassium halide) is slightly greater than the fifty per cent. calculated from the combined equations (1) and (2), potassium anilide and potassium diphenylamide must further react, in the sense of equations (3), (5), and (6), although it is possible that the aniline has not been completely converted to potassium anilide in accordance with (2). The amide ion was found to be an essential catalyst for reactions (3), (5), and (6), which otherwise did not take place under the conditions of the present experiments. A more complete discussion is reserved for the second paper of this series.

Competition experiments, in which an ammonia solution of potassium amide is added to an excess of a mixture of aryl halides in the same solvent, indicate the following order of decreasing reactivity, as judged by relative yields of the respective potassium halides.

$$\mathrm{Br} > \mathrm{I} > \mathrm{Cl} > \quad (>>>\mathrm{F})$$

The same order is found when potassium amide is added to a mixed aryl dihalide of the type of *p*-chlorobromobenzene, although the results are a little more difficult of strict theoretical interpretation. Bromine appears in both cases to be more readily removed from the aromatic nucleus than iodine, although the difference in reactivity is not great.

EXPERIMENTAL

The apparatus used in the present investigation (see Figure 1) consists essentially of pyrex cells, *1* and *2*, the first being cooled by a liquid ammonia bath, the second being fitted snugly into a large Dewar vessel to hinder evaporation of the solvent.* Vessel *1* is connected at *A* to a source of ammonia gas (from a tank of the commercial liquid containing sodium) and to vessel *2* through the siphon *B*, which allows one quantitatively to transfer a solution from *1* to *2*. With the use of stopcocks *C*, *D*, and *E*, *1* could be connected to a mercury bubbler, or to the waste. Vessel *2* is connected to *1* in the manner described, to the waste ammonia line at *E* and to an adjustable mercury bubbler, *H*, which has at its upper end, *G*, a three-way stopcock, so that gases (coming from *2*) can be diverted to the waste, or to a gas collector, *K*, containing water. The contents of vessel *2* are agitated by a motor-driven stirrer, *L*, whose shaft passes through a packed joint.

The manipulation will be understood from the following description of the reaction between a known amount of potassium amide and an excess of chlorobenzene.

Cells *1* and *2* are cleaned, thoroughly dried, and air in them is displaced by ammonia. (Air in *1* is swept out when stopcocks *A*, *C*, *D* and *E* are opened and stopcock *B* is closed; air in *2* is displaced when stopcocks *A*, *B* and *E* are opened and

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* From our experience, it is recommended that this second cell likewise be cooled by an ammonia bath.

stopcock *C* is closed.) With ammonia gas passing through about 20 cm. of mercury in the bubbler (stopcocks *A* and *C* open, stopcocks *B* and *D* closed) and with liquid ammonia in the Dewar liquid readily condenses in *1*. When this is about two-thirds full, stopcocks *C* and *A* are closed, *B* is opened, and about half of the liquid is forced over into *2*, applying ammonia pressure through *A′* if necessary. (It is convenient to have a stopcock sealed to the cap closing *A′*.) *B* is then closed, the ground-glass joint *A′* is cautiously removed and a previously broken capsule containing a weighed amount of potassium is introduced,[2] together with some clean iron wire. (A slow stream of ammonia passes through *A* and out at *M* to prevent access of air during these manipulations. The ammonia must, of course, first bubble through the condensed liquid in *1*.) In the meanwhile, the stirrer in *2* is started and an excess of chlorobenzene is introduced (through *J*) from a weight pipet. After the disappearance of the blue potassium solution in *1*, the potassium amide is slowly forced over into the liquid ammonia solution of the chlorobenzene in *2* according to the method described above. An opaque red solution results immediately with evolution of enough heat to cause ebullition of the ammonia. Twenty or twenty-five cc. of fresh ammonia is condensed in *1* and forced into *2*, the process being repeated twice to insure complete transference of the potassium amide. Shortly thereafter, cell *2* is disconnected and removed from the Dewar, in order to facilitate evaporation of the

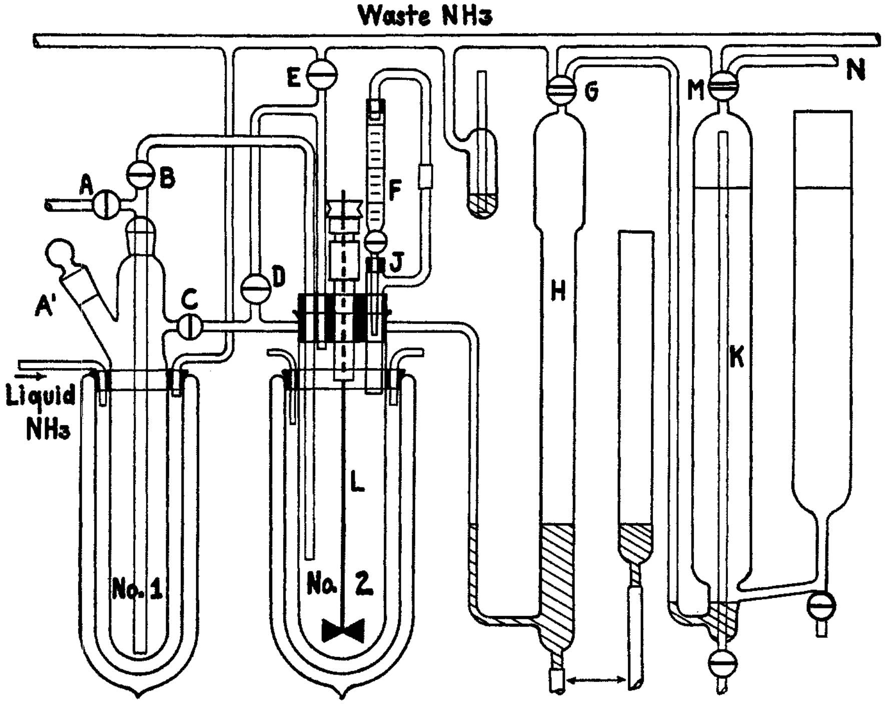

Fig. 1

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[2] Peck, *J. Am. Chem. Soc.*, **40**, 338 (1918); Kraus and Chiu, *ibid.*, **44**, 2001 (1922).

ammonia, which generally consumes two to three hours. (Vessel *2* may, if desired, be dipped in a large volume of water.) The solvent-free residue is then covered with benzene, and water is slowly added to effect hydrolysis.

The treatment of the hydrolysate varied with the experiment. In the preliminary runs—where larger and less accurately weighed quantities of reagents were used, and where the phenyl halide was often added (from buret *F*) to a large excess of potassium amide, the hydrolysate was acidified and the benzene layer extracted twice with 1:1 hydrochloric acid. The acidic aqueous solution was distilled with steam, diphenylamine passing over, and aniline hydrochloride remaining behind. The latter was made basic and steam-distilled to remove aniline, which was identified by conversion to acetanilide. Diphenylamine was identified by the melting point of a mixture with a specimen of authentic origin.

In the smaller-scale runs, in which halide ion was to be determined quantitatively, the following procedure was adopted.

To the residue left after evaporation of the ammonia was added about 75 cc. benzene, followed by about 50 cc. water. The benzene layer was extracted three times with very dilute sodium hydroxide, and halide ion was determined gravimetrically as silver halide in the total aqueous extract. Aniline was extracted from the benzene with 3*N* hydrochloric acid, and determined in an aliquot portion by bromine titration,[3] after first filtering off a small precipitate of *p*-aminobiphenyl hydrochloride. Diphenylamine was then extracted from the benzene with concentrated sulfuric acid (4/5 H_2SO_4 by vol.), either being weighed directly after precipitation from solution, or being determined by bromine titration. (Extraction with concentrated hydrochloric acid gave a somewhat better separation, for the sulfuric acid dissolved a small quantity of triphenylamine and tar. The reported yields of diphenylamine are nevertheless sufficiently accurate for comparative purposes.)

Evaporation of the benzene yielded a viscous, sweet-smelling, tarry oil, from which small quantities of triphenylamine could often be isolated by repeated crystallizations from petroleum ether (identification by mixture melting point).

p-Aminobiphenyl, prepared by addition of sodium hydroxide to its hydrochloride, melted at 53–54.5° uncorr., and at the same temperature after mixture with authentic *p*-aminobiphenyl (prepared by reduction of *p*-nitrobiphenyl).

The results of these runs are summarized in Table I.

Competitive Runs

Two phenyl halides were introduced separately from weighing burets into vessel *2* (see figure), which contained 50–75 cc. ammonia. Potassium amide, in known amount, dissolved in 50–75 cc. of ammonia in vessel *1*, was very slowly forced into *2* with mechanical stirring. Vessel *1* was finally washed with two or three 25-cc. portions of solvent, to transfer all amide to *2*. Necessarily, the phenyl halides must be in excess.

Halide ion in the hydrolysate was determined both gravimetrically and volumetrically (Mohr titration) in aliquot portions of the water extract. The apparent molecular weight of the precipitated silver halide may be calculated from the data thus obtained. The mol fraction, *F*, of the heavier silver halide in the precipitate is equal to $(A\text{-}B)/(C\text{-}B)$, where *A* is the apparent molecular weight of the silver

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[3] KOLTHOFF AND FURMAN, "Volumetric Analysis," John Wiley and Sons, New York, **1928**, vol. I, p. 212.

halide precipitated, *B* is the molecular weight of the lighter silver halide, AgX, and *C* is the molecular weight of the heavier halide, AgY.

The ratio, (moles AgX)/(moles AgY) can be regarded as the ratio of the relative reactivities of X and Y only if the average molar concentration of each of the two phenyl halides is the same in a given run. Since this is not usually the case, it is necessary to correct the observed ratio, (moles AgX)/(moles AgY), multiplying it by the factor, (av'ge conc. C_6H_5Y)/(av'ge conc. C_6H_5X), the "average concentration" being equal to ½ (twice the initial conc. phenyl halide minus the halide consumed). The halide consumed is the product of the mole fraction of AgX (or AgY) and the equivalents of halide ion, the latter having been determined by the Mohr titration.

TABLE I

REACTION OF INDIVIDUAL ARYL HALIDES WITH POTASSIUM AMIDE

HALIDE	MOLES KNH_2	MOLES HALIDE	YIELD OF HALIDE ION	YIELD OF ANILINE[c]	YIELD OF DIPHENYLAMINE[c]	NOTES
C_6H_5Cl	0.0160	0.0210	55.8%	24.5 (43)	12.8 (23)	(*a*)
	0.0263	0.0256	53.0	25.4 (48)	10.8 (20)	(*b*, *d*)
	0.0305	0.0141	99.0[i]	52.3 (53)	15.5 (15.6)	(*b*)
	0.0261	0.15	56.4	24.2 (43)	12.4 (22)	(*a*)
C_6H_5Br	0.0314	0.0352	56.1	22.8 (41)		(*b*)
	0.0312	0.0337	58.2	22.0 (40)		
	0.0383	0.287	56.8	21.7 (38)	17.6 (31)	(*a*, *e*)
	0.0505	0.0255	99.1[i]	42.1 (43)	24 (24)	(*b*)
	0.0383	0.0470	60.9	18 (30)	16 (28)	(*b*)
	0.0235	0.0242	57.0	25.8 (46)	15 (26)	(*b*)
C_6H_5I	0.0289	0.0448	55.3	21.4 (39)	Tr	(*a*)
	0.0296	0.0357	54.8	22.5 (47)	8.1 (15)	(*b*, *f*)
	0.0424	0.0190	96.2[i]	50.7 (52)	20.4 (21)	(*b*)
p-$CH_3C_6H_4Cl$	0.0230	0.0240	58.7	(*g*)		
	0.0136	0.0116	53.9	(*g*)		

(*a*) Potassium amide solution added to a solution of the halide.

(*b*) Solution of halide added to potassium amide solution. In the fifth experiment liquid C_6H_5Br was added to the KNH_2 solution.

(*c*) Calculated on the basis of potassium in the equations, $C_6H_5Cl + KNH_2 = C_6H_5NH_2 + KCl$ or $2C_6H_5Cl + 2KNH_2 = (C_6H_5)_2NH + 2KCl + NH_3$. The figures in parentheses are yields calculated on the basis of the halide ion (= yield, as calculated above ×100/yield of halide ion).

(*d*) 0.018 g. *p*-aminobiphenyl hydrochloride isolated (0.3% of theory).

(*e*) 0.05 g. *p*-aminobiphenyl hydrochloride isolated (1.3% of theory). (See equation 6.)

(*f*) Diphenylamine not pure.

(*g*) *p*-Toluidine is the chief product formed, other than tar.

(*i*) Calculated on the basis of the halide; in all other experiments yields are calculated on the basis of the potassium amide.

It has been assumed that within reasonable limits the relative reactivities of the phenyl halides are independent of the concentration.

As the volumetric determination may be in error by as much as one per cent., and as the conditions for such a rapid reaction cannot be perfectly controlled, the following results give more the orders of magnitude than the absolute values of the relative reactivities of the phenyl halides toward potassium amide:

$$Br/Cl = 20\ (\pm 5)/1;\ I/Cl = (8.3 \pm 0.3)/1;\ I/Br = 0.40\ (\pm 0.10)/1$$

TABLE II

COMPETITIVE REACTIONS OF PAIRS OF PHENYL HALIDES WITH POTASSIUM AMIDE

ATOMS K	HALIDES	MOLES	EQUIVALENT HALIDE ION	AV'GE MOL. WT. AgX	WT. MIXED AgX	MOLE FRACTIONS AS FOUND	CORRECTED RATIO
0.02306	C_6H_5Cl	0.0259	0.01324	223.6	2.961	AgCl 0.121	I/Cl
	C_6H_5I	0.0267				AgI 0.879	8.6/1.0
0.02364	C_6H_5Cl	0.0276	0.01343	223.1	2.996	AgCl 0.128	I/Cl
	C_6H_5I	0.0286				AgI 0.872	8.0/1.0
0.02426	C_6H_5Br	0.0312	0.01375	200.2	2.773	AgBr 0.737	I/Br
	C_6H_5I	0.0266				AgI 0.264	0.35/1.0
0.02401	C_6H_5Br	0.0293	0.01326	201.4	2.680	AgBr 0.711	I/Br
	C_6H_5I	0.0250				AgI 0.289	0.38/1.0
0.02814	C_6H_5Cl	0.0404	0.01603	184.4	2.957	AgCl 0.077	Br/Cl
	C_6H_5Br	0.0261				AgBr 0.923	25/1.0
0.02756	C_6H_5Cl	0.0318	0.01580	184.0	2.905	AgCl 0.085	Br/Cl
	C_6H_5Br	0.0261				AgBr 0.915	18/1.0
0.01593	C_6H_5Cl	0.0156	0.01723	185.3	3.192	AgCl 0.056	Br/Cl
	C_6H_5Br	0.0145				AgBr 0.944	23/1.0
0.02469	C_6H_5Cl	0.0571	0.01421	181.3	2.577	AgCl 0.146	Br/Cl
	C_6H_5Br	0.0270				AgBr 0.854	16/1.0
0.02525	C_6H_5Cl	0.0559	0.01419	182.9	2.596	AgCl 0.110	Br/Cl
	C_6H_5Br	0.0258				AgBr 0.890	23/1.0

A typical calculation follows (first run, Table II):

KNH_2 0.02306 mole (= atoms of K used)

C_6H_5Cl 0.0259 mole $\left(100 \times \frac{0.0259}{0.02306} = 112\% \text{ of K.}\right)$

C_6H_5I 0.0267 mole (116% of K)

Wt. Ag. halides (×0.1) = 0.2961; cc. 0.0498*N* $AgNO_3$, 26.59 (in 0.1 aliquot)

Equivalents halide ion, 0.01324; theoretical equivalents halide ion, calculated from equation (1) = moles KNH_2 = 0.02306.

Yield of halide ion, calc'd on basis of equation (1), $= 57.4\% = 100 \times \frac{0.01324}{0.02306}$
Av'ge mol. wt. halide 0.2961/0.001324 = 223.6.
Mole % AgI = (223.6 − 143.3)/(234.8 − 143.3) = 87.8
Mole % AgCl = 100.0 − 87.9 = 12.1
Ratio, (moles AgI)/(moles AgCl) = 87.9/12.1 = 7.3/1.0
Av'ge conc. of $C_6H_5I = \frac{1}{2}\,[(2 \times 116) - (57.4 \times 0.879)] = 90.8\%$ of K.
Av'ge conc. of $C_6H_5Cl = \frac{1}{2}[(2 \times 112) - (57.4 \times 0.121)] = 109.1\%$ of K.
For convenience the concentrations have been expressed in terms of the potassium concentration.
Corrected ratio, I^-/Cl^- (= ratio of reactivities of C_6H_5I/C_6H_5Cl) = 7.2 × 109.1/90.8 = 8.6/1.0.

TABLE III

REACTION OF PHENYL DIHALIDES WITH POTASSIUM AMIDE

ATOMS K	HALIDE[a]	EQUIVALENTS OF HALIDE ION	CORRECTED RATIO REACTIVITIES[b]
0.00761	C_6H_4BrCl	Br 0.00303 Cl 0.00048	Br/Cl 7.6/1
0.01684	C_6H_4BrCl	Br 0.00868 Cl 0.00133	Br/Cl 8.4/1
0.01731	C_6H_4BrCl	Br 0.00708 Cl 0.00150	Br/Cl 5.7/1
0.01300	C_6H_4BrI	Br 0.00442 I 0.00230	I/Br 0.48/1
0.01901	C_6H_4BrI	Br 0.00648 I 0.00333	I/Br 0.47/1

(*a*) All dihalides were *para* compounds, obtained from the Eastman Kodak Co. (best grade). No. moles used = No. atoms of K.

(*b*) The observed ratios, $\frac{\text{Equivalents of halide ion (1)}}{\text{Equivalents of halide ion (2)}}$, were multiplied by the inverse ratios of the average concentrations of the two un-ionized halogens during the run, to obtain the corrected figures in this paragraph. The calculations were made as in the preceding section. At the beginning of a reaction, the concentrations of un-ionized halogen were necessarily the same, altering because the rates of removal of halogen were different.

The Action of Potassium Amide on the Phenyl Dihalides

A known amount of potassium amide was added to an excess of a phenyl dihalide of the type of *p*-chlorobromobenzene, using the manipulations described in the preceding section. The mixed halides in the hydrolysate were determined indirectly by weighing the mixed silver halides, which were subsequently converted to silver chloride by heating in a stream of chlorine.[4] The experimental data are recorded in Table III, and, although admittedly incomplete, indicate the following relative reactivities of the halogens X and Y in compounds of the type, $X \cdot C_6H_4 \cdot Y$-*p*. Br/Cl = 7/1; I/Br = 0.5/1. Obviously, the results are not as amenable to exact theoretical treatment as those previously discussed, since we are concerned also with the replacement of halogen from the intermediate compounds of the type, $NH_2 \cdot C_6H_4 \cdot Y$.

SUMMARY

(1) Chloro-, bromo-, and iodobenzenes react very rapidly with a liquid ammonia solution of potassium amide at −33° to give aniline and diphenylamine, with smaller quantities of triphenylamine and *p*-aminobiphenyl. The relative proportions of the reaction products depend upon experimental conditions. Under similar conditions, fluorobenzene does not react with potassium amide. A number of substituted chloro-, bromo- and iodobenzenes have been shown to react with solutions of the alkali amides in liquid ammonia. In boiling ether or benzene, the above reactions do not occur, on else are very slow.

(2) The reaction, $C_6H_5NH_2 + KNH_2 = C_6H_5NHK + NH_3$, is very rapid in comparison with the primary replacement of halogen, $C_6H_5X + KNH_2 = C_6H_5NH_2 + KX$. Consequently, the yield of halogen ion obtained when potassium amide is added to an excess of phenyl halide lies between 50 and 60% of the theoretical, as calculated from the second equation. Divergence from the theoretical value of 50% is accounted for by the occurrence of the reactions that yield di- and triphenylamine, and perhaps also by the incompleteness of formation of potassium anilide in accordance with the first equation above.

(3) Competition reactions indicate the following order of ease of replacement of the halogen atoms in the unsubstituted phenyl halides Br > I > Cl, (F not replaced in NH_3 at −33°). The same order is found for replacements involving the phenyl dihalides of the type *p*-C_6H_4XY.

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[4] Treadwell-Hall, "Analytical Chemistry," John Wiley and Sons, New York, 4th ed., **1915**, vol. II, p. 334.

[Contribution from the Chemical Laboratories of Stanford University]

THE ACTION OF BASES ON ORGANIC HALOGEN COMPOUNDS. II. BASIC CATALYSIS IN THE DEHALOGENATION OF THE PHENYL HALIDES*

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The authors, with Chandler and Gilkey, have shown in the preceding paper[1] that potassium amide reacts rapidly with chlorobenzene, bromobenzene and iodobenzene in liquid ammonia solution at −33° to give aniline and diphenylamine, together with smaller amounts of triphenylamine and *p*-aminobiphenyl. The present paper reports experiments designed to afford an explanation of the formation of the three last-named products.

It is known from the work of White, Morrison and Anderson[2] and Eatough[3] that the reactions expressed by the equations,

$$C_6H_5NHK + C_6H_5X = (C_6H_5)_2NH + KX \quad (1)$$

$$(C_6H_5)_2NK + C_6H_5X = (C_6H_5)_3N + KX \quad (2)$$

do not take place in liquid ammonia at −33°, a conclusion that we have verified. However, a fair yield of diphenylamine may be obtained by adding potassium amide to a solution of potassium anilide and chlorobenzene, and of triphenylamine by adding potassium amide to a solution of potassium diphenylamide and chlorobenzene, both reactions being carried out in liquid ammonia at −33°. Since the yields are much better than that obtained by treating chlorobenzene with potassium amide alone, one must conclude that the amide ion, NH_2^-, catalyzes the reactions of equations (1) and (2), although the mechanism by which this is accomplished is at present not definitely known.†

That such a catalysis occurs is shown also by determining the halide

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* From the Ph.D. Thesis of Richard E. Wright, October, 1935.

[1] Bergstrom, Wright, Chandler and Gilkey, This Journal, **1**, 170–178 (1936).

[2] White, Morrison and Anderson, *J. Am. Chem. Soc.*, **46**, 967 (1924).

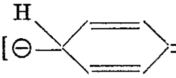
[3] Eatough, *Thesis*, Brown University, **1927**.

† It is assumed, in using the term "catalysis," that reactions (1) and (2) proceed normally at an extremely slow rate in the absence of NH_2^-.

ion formed in reactions where potassium amide is added to a mixture of phenyl halide and potassium anilide (or potassium diphenylamide) in liquid ammonia. Yields of 70–90% of halide ion, calculated from the equation

$$C_6H_5X + KNH_2 = C_6H_5NH_2 + KX \tag{3}$$

are obtained, whereas, when potassium amide is added to a phenyl halide alone, the yield of halide ion is only 50–60% of the theoretical, the remainder having therefore been formed in the reactions of equations (1) and (2). [Yield of halide ion = (100 × equivalents halide ion)/(atoms K used).]

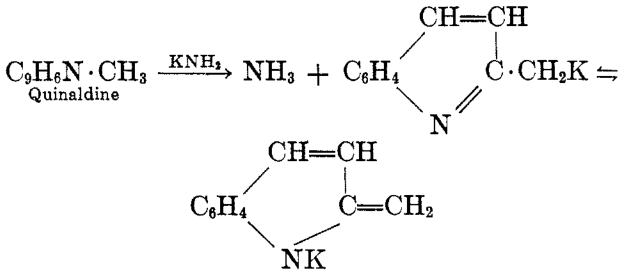
p-Aminobiphenyl is possibly formed from a phenyl halide and a *p*-quinoid form of potassium anilide, K^+ [⊖—  =NH], in the presence of NH_2^- ions.

The catalytic effect of the amide ion may be demonstrated for a number of reactions of the type,

$$C_6H_5Cl + K\cdot R \xrightarrow{NH_2^-} C_6H_5\cdot R + KCl \tag{4}$$

when R·H is a sufficiently weak "acid" in liquid ammonia. Thus, quinaldyl potassium, which will not alone react with chlorobenzene[4] in liquid ammonia solution at −33°, does so when potassium amide is added, to give 2-benzylquinoline, 2-benzohydrylquinoline (?), and 2-triphenylmethylquinoline (?). The following equations express the reactions.

(5)



$$C_9H_6N\cdot CH_2K + C_6H_5Cl \xrightarrow{NH_2^-} C_9H_6N\cdot CH_2C_6H_5 + KCl \tag{6}$$

$$C_9H_6N\cdot CH_2C_6H_5 + KNH_2 = C_9H_6N\cdot CHKC_6H_5 + NH_3 \tag{7}$$

$$\text{or, } C_9H_6N\cdot CH_2C_6H_5 + C_9H_6N\cdot CH_2K \rightleftharpoons C_9H_6N\cdot CHKC_6H_5 + C_9H_6N\cdot CH_3$$

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[4] Bergstrom, *J. Am. Chem. Soc.*, **53**, 3034 (1931).

$$(8)\quad C_9H_6N\cdot CHKC_6H_5 + C_6H_5Cl \xrightarrow{NH_2^-} C_9H_6N\cdot CH(C_6H_5)_2 + KCl$$

$$(9)\quad C_9H_6N\cdot CH(C_6H_5)_2 \xrightarrow{KNH_2} C_9H_6N\cdot CK(C_6H_5)_2 \xrightarrow[NH_2^-]{C_6H_5Cl} C_9H_6N\cdot C(C_6H_5)_3$$

Triphenylmethylpotassium, which reacts very slowly with chlorobenzene in liquid ammonia at $-33°$, reacts much more rapidly in the presence of potassium amide to give a 46% yield of tetraphenylmethane—the best that has so far been obtained by any reaction.

$$(10)\quad (C_6H_5)_3C\cdot K + C_6H_5Cl \xrightarrow{NH_2^-} (C_6H_5)_4C + KCl$$

On the other hand, potassium phenoxide, the salt of an acid stronger than any of those treated above, does not appear to react with chlorobenzene or bromobenzene, even in the presence of potassium amide. The following reaction, involving the salt of a very strong acid, does not take place, although bromobenzene is twenty times as reactive toward potassium amide as is chlorobenzene.[1]

$$(11)\quad C_6H_5Br + KCl \xrightarrow{NH_2^-} C_6H_5Cl + KBr$$

Preliminary experiments indicate that diphenylmethylpotassium, which reacts slowly with chlorobenzene to give triphenylmethane and tetraphenylmethane, catalyzes the formation of triphenylamine according to the reaction of equation (2). There is, however, indication that diphenylmethylpotassium may be slightly ammonolyzed at room temperatures in liquid ammonia, and the possibility remains that these results are occasioned in part by a low concentration of amide ions, rather than by diphenylmethyl ions exclusively. Thus

$$(12)\qquad (C_6H_5)_2CH^- + NH_3 \rightleftharpoons (C_6H_5)_2CH_2 + NH_2^-$$

DISCUSSION

Because of the lack of experimental proof, we shall for the present forego an extended discussion of the mechanisms of the reactions treated in this paper, satisfying ourselves with a few generalizations from the point of view of Brønsted's theory of acids and bases. It will be recalled that Brønsted[5] defined an acid as any substance regardless of charge which can, under the conditions of the reaction, yield a proton, and a base as any substance which can accept a proton. Therefore, all of the anions which have been found in the present work to replace aromatically bound halogen may in this sense be regarded as bases. These may be arranged in a series of decreasing reactivity toward the phenyl halides.

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[5] BRØNSTED, *Chem. Rev.*, **5**, 231 *ff.* (1928).

Base	NH_2^-	$(C_6H_5)_2CH^-$	$(C_6H_5)_3C^-$	$C_6H_5NH^-$	$(C_6H_5)_2N^-$	$C_6H_5O^-$
Rate of reaction with C_6H_5X in NH_3.....	rapid	slow	slow	do not react at −33°		
Activity as a catalyst in NH_3............	high	slight	?	?	?	?
		React with C_6H_5X in the presence of NH_2^-				Does not react with C_6H_5X + NH_2^-

The position of the quinaldyl ion is unknown. The relative activities of the anions are, at least qualitatively, directly related to their strengths as bases in the above sense, or to their proton affinities.[6] Catalytic activity is shown definitely by the strongest base (NH_2^-) and probably to a lesser extent by the diphenylmethyl anion. It is reasonable to assume that all bases approaching or exceeding the amide ion in strength will be active as catalysts. Possibly the almost exclusive formation of triphenylamine in the reaction of the phenyl halides with sodium in liquid ammonia[7] is connected with the catalytic activity of the negative electron, which is present in solutions of the alkali metals.[8]

EXPERIMENTAL

The technique for carrying out reactions in liquid ammonia, for the determination of halide ion, and for the separation of aniline from diphenylamine has been described in the first article of this series.[1] All organic compounds used in the present work, although supplied by the Eastman Kodak Company, Kahlbaum, or the Gesellschaft für Teerverwertung in a state of high commercial purity, were fractionated, the middle fractions being retained.

Potassium anilide and phenyl chloride.—Potassium amide was made in vessel *1*, and transferred quantitatively to vessel *2* by the method of the previous article.[1] Slightly more than one equivalent of aniline was introduced into *2* from a weighing pipet, followed after the lapse of five or ten minutes by chlorobenzene, the reaction mixture being stirred mechanically throughout. Solvent was evaporated from the reaction vessel during the next two to three hours. Benzene was added, and hydrolysis was effected by the slow addition of water. Chloride ion was determined in the combined aqueous extracts of the benzene layer.

(Two expts.) Atoms K, 0.02085, 0.01595; moles $C_6H_5NH_2$, 0.02414, 0.02194; moles C_6H_5Cl, 0.0204, 0.0171; Cl^-, 3.7%, 0.8%, calculated on the basis of potassium [equation (1)]. It is thought that the chloride ion results in part, at least, from the reaction between chlorobenzene and potassium amide which has spattered on the walls of vessel *2* above the liquid level.

Potassium diphenylamide and phenyl chloride.—The reactions were carried out

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[6] Bennet, *Annual Reports on the Progress of Chemistry*, **26**, 136 (1929), has stressed the importance of the proton affinity of the reagent in reactions involving the replacement of halogen in substituted phenyl halides.

[7] White, *J. Am. Chem. Soc.*, **45**, 779 (1923).

[8] Kraus, *ibid.*, **43**, 749–70 (1921), and previous articles.

as described in the preceding paragraph, except that diphenylamine was used in place of aniline. In the third run especial pains were taken to avoid spattering of the potassium amide solution.

ATOMS K	MOLES $(C_6H_5)_2NH$	MOLES C_6H_5Cl	CHLORIDE ION (%)
0.01402	0.02373	0.0165	2.2
0.0130	0.0163	0.0193	1.3
0.01846	0.01843	excess	0.6

Chloride ion was calculated on the basis of the potassium [see equation (2)].

The Catalytic Effect of the Amide Ion: Chlorobenzene, potassium anilide (or diphenylamide) and NH_2^-.—The description of a typical run follows. 100 cc. of liquid ammonia was condensed in vessel *1*, as previously described,[1] a weighed amount of potassium was introduced in a broken glass capsule, and converted to amide by the catalytic action of clean iron wire (Table I, column 1). The solution was transferred quantitatively to vessel *2*, the last portions being washed over with fresh solvent. To this was added an approximately equivalent amount of aniline or diphenylamine, with vigorous mechanical stirring, the chlorobenzene being introduced after five or ten minutes. With the stopcock connecting the two containers closed, another 100 cc. of liquid ammonia was condensed in *1*, and potassium was introduced in weighed amount, this being converted to amide under the influence of the iron wire already in the vessel (Table I, column 2). The potassium amide in vessel *1* was slowly siphoned over into vessel *2*, with continuous stirring. A rapid reaction ensued, with the formation of an opaque reddish-brown solution. After the lapse of ten or fifteen minutes, the reaction vessel was removed from the insulating Dewar to hasten the evaporation of the ammonia, which generally consumed two or three hours. The solvent-free residue was worked up and reaction products were determined in the manner described in the first article.

From the preceding article[1] it is known that a 53–58% yield of chloride ion is obtained when potassium amide is added to an excess of chlorobenzene in liquid ammonia. The yields of chloride ion in Table I, calculated on the basis of the same equation, are much higher, indicating that the potassium anilide or potassium diphenylamide is taking part in the reaction, thus demonstrating the catalytic effect of the amide ion. The results further show that *p*-aminobiphenyl is formed from potassium anilide, and that the reaction,

$$(C_6H_5)_2N^- + NH_2^- \rightleftharpoons 2C_6H_5NH^- \tag{13}$$

does not occur, for otherwise the yields of aniline (column 7, last two entries) would be much greater.

Quinaldylpotassium, chlorobenzene and potassium amide.—Quinaldine, (0.0196 mole), was added to 0.0304 mole of potassium amide in 100 cc. of ammonia in vessel *2*, followed in a few moments by 0.0476 mole of chlorobenzene. To this deep-red mixture was added 0.0257 mole of potassium amide, which had been prepared in vessel *1*. Solvent was evaporated during the next three hours, and the mixture was hydrolyzed after it had first been covered with a layer of benzene. The benzene solution, after successive extractions with water, dilute hydrochloric acid and 18 *N* sulfuric acid, was evaporated to dryness under reduced pressure, leaving a solid (Solid II), which melted at 190.5-191.5° uncorr. after crystallization from alcohol.

A viscous tar separated when the benzene solution was extracted with hydrochloric acid. The petroleum ether extract of the tar was evaporated, and the solid formed was treated with cold alcohol, to dissolve most of the tar. After filtration, the white, solid residue was crystallized from 80% alcohol; m.p., 110.5–112.0°, uncorr. (Solid I). The hydrochloric-acid-soluble portion was brought to the methyl red endpoint with dilute sodium hydroxide and extracted with benzene. The benzene solution was distilled to remove solvent, then distilled under reduced pressure (about 20 mm.), quinaldine first passing over, followed by a dark viscous oil at 210–

TABLE I

VESSEL *1*	VESSEL *2*			YIELDS				
Atoms K	Atoms K	Moles Amine	Moles C_6H_5Cl	Cl^-[b]	$PhNH_2$	Ph_2NH[a]	Ph_3N[a,c]	*p*-$C_6H_5C_6H_4NH_2$[g]
				%	*% Recovered*	*% Theoretical*		%
0.04109	0.02849	0.03811 $PhNH_2$	0.060	78.2	70.5[d]	57.0	present	5.9
0.04114	0.02886	0.04741 $PhNH_2$	0.062	75.5	68.0[d]	58.4	present	7.1
					% Theoretical	*% Recovered*		
0.03644	0.03435	0.03178 Ph_2NH	0.0518	85.6	20.9	77[f]	79	trace
0.03673	0.03299	0.03312 Ph_2NH	0.0518	89.4	21.2[e]	78[f]	59	trace

(*a*) Theoretical yield of di- or triphenylamine = 100 (moles amine obtained)/(total atoms K in both vessels minus moles aniline or diphenylamine, column 3). The aniline or diphenylamine in II reacts with an equivalent of KNH_2. The equations, $2\ C_6H_5Cl + KNH_2 = (C_6H_5)_2NH + NH_3 + 2KCl$ and $3C_6H_5Cl + 3KNH_2 = (C_6H_5)_3N + 3KCl + 2NH_3$ have been assumed, but since the yields of amines total over 100% in one experiment (#3) it is evident that potassium anilide, C_6H_5NHK, or potassium diphenylamide, $(C_6H_5)_2NK$, are not inert, but react with the chlorobenzene in the presence of NH_2^-.

(*b*) The chloride ion was determined as silver chloride in the aqueous part of the hydrolysate of the reaction mixture. The yield of chloride ion was calculated on the basis of the potassium amide in excess of an equivalent amount of amine, assuming the reaction, $C_6H_5Cl + KNH_2 = C_6H_5NH_2 + KCl$. Yield $Cl^- = 100$ [equivalents Cl^-/atoms K (column 1)].

(*c*) Crude; m.p., after cryst. from alc., 124–5°; m.p. of mixture with authentic triphenylamine the same. A small amount of triphenylamine could not be separated from another solid with which it formed a mixture melting at about 118–9°. A portion of the triphenylamine in experiment 4 was lost.

(*d*) Expressed as per cent. of the aniline in column 3.

(*e*) Expressed as the per cent. of the theoretical aniline, assuming the equation, $C_6H_5Cl + KNH_2 = C_6H_5NH_2 + KCl$, and calculated on the basis of the potassium in excess of the amount necessary to form potassium diphenylamide. Moles $C_6H_5NH_2$, theoretical = total atoms K (columns 1 + 2) minus moles Ph_2NH (column 3).

(*f*) Expressed as per cent. of the diphenylamine in column 3.

(*g*) Theoretical yield of *p*-aminobiphenyl, in mols = 1/2 (total atoms K, columns 1 and 2, minus moles aniline) × 169.1. [Mol. wt. *p*-$C_6H_5C_6H_4NH_2$ = 169.1.]

280°. This was converted in alcoholic solution to a picrate; m.p., 155–6°. M.p. of mixture with the picrate of 2-benzylquinoline, 155–6°.[9] In the reaction a chloride ion yield of 93.3% of the theoretical was obtained, indicating again the catalytic effect of the NH_2^- ion. [*Cf.* note (*b*), Table I.]

In a repetition of this run, ammonium bromide was added to the ammonia solution to destroy reactive potassium salts and minimize the formation of tar. Yield: 2.01 g. Solid I (0.0068 mole); 0.97 g. Solid II (0.0026 mole); and some 2-benzylquinoline. (Starting with 0.038 mole KNH_2 in vessel *1*, 0.0293 mole quinaldine and 0.132 mole chlorobenzene in vessel *2*, and an additional 0.077 mole KNH_2 in vessel *1*.)

Mol. Wts.—Solid I: Solute (g.), 0.2784, 0.2001; C_6H_6 (g.), 17.23, 17.23; lowering of f.p., 0.280°, 0.200°. Mol. wt. found, 283, 284. Calc'd for $C_{22}H_{17}N$, 295. *Solid* II: Solute (g.), 0.2857, 0.2443; C_6H_6 (g.), 19.82, 19.81; lowering of f.p. 0.182°, 0.160°. Mol. wt. found, 388, 378. Calc'd for $C_{28}H_{21}N$, 371.

Anal. Solid I Found: C, 89.43; H, 5.78; N, 4.96.

Calc'd for $C_{22}H_{17}N$ (2-benzohydrylquinoline): C, 89.44; H, 5.81; N, 4.75.

Solid II Found: C, 90.13; H, 6.03; N, 4.52.

Calc'd for $C_{28}H_{21}N$: C, 90.5; H, 5.7; N, 3.8. The analysis is unsatisfactory, but indicates 2-triphenylmethylquinoline.

Potassium amide, potassium phenolate and chlorobenzene.—Potassium amide, in vessel *1*, was added to a solution of potassium phenolate (prepared from potassium amide and phenol) and an equivalent of chlorobenzene in vessel *2*. Following the customary treatment, attempts were made to isolate diphenyl ether from the hydrolysate, but without success, although the small residue left after evaporation of the benzene extract had an odor like that of the expected compound. Two experiments gave the following results. Atoms K, 0.0319, 0.0424; moles phenol, 0.0183, 0.0252; moles C_6H_5Cl, 0.052, 0.054; yield of halide ion (theoretical yield in equivalents = atoms of K minus moles of phenol) = 55.9%, 58.6%; yield of aniline, 31.2%, 29.8% [see Table I, note (*e*)]; yield of diphenylamine, 7.8%, 11.4%.

Since approximately a 55% yield of chloride ion is obtained by adding potassium amide to an excess of chlorobenzene in ammonia[1] it may be concluded that potassium phenolate and chlorobenzene do not react appreciably in the presence of amide ions.

A portion of the aniline could result from the reaction,

$$(C_6H_5)_2O + 2KNH_2 = C_6H_5OK + C_6H_5NHK + NH_3, \tag{14}$$

but this was found not to proceed at a measurable rate under the present experimental conditions.

Potassium triphenylmethyl, chlorobenzene and potassium amide.—Triphenylmethane (0.0241 mole) was added to potassium amide (0.0296 mole) in vessel *2*, followed after an hour by chlorobenzene (0.0714 mole). To this mixture was added potassium amide (0.0420 mole) solution from vessel *1*, the solvent being slowly evaporated over a period of about 3 hours. The hydrolysate was extracted several times with benzene, and this in turn was extracted with dilute hydrochloric acid to remove amines. The benzene solution was evaporated, and the residue was crystallized from the same solvent; m.p., 277–8° uncorr. M.p. of mixture with known tetraphenylmethane,[10] 277–8°, showing their identity.

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[9] Prepared by the method of BERGMANN AND ROSENTHAL, *Jour. prakt. Chem.*, **135**, 275 (1932).

[10] Prepared by the method of KRAUS AND KAWAMURA, *J. Am. Chem. Soc.*, **45**, 2760 (1923).

Aniline, 13.9%, calculated on basis of KNH_2 in excess of the quantity equivalent to the $(C_6H_5)_3CH$. Diphenylamine, 20%, calculated as above. Tetraphenylmethane, calculated on basis of $(C_6H_5)_3CH$, 46% (3.53 g.).

Potassium triphenylmethyl and chlorobenzene.—Potassium triphenylmethyl was prepared in vessel *2* by adding triphenylmethane to two equivalents of potassium amide (from potassium solution and iron wire). To this was added an excess of phenyl chloride, the solution standing for one hour, three hours more being required for the forced evaporation of the solvent. Tetraphenylmethane was isolated and identified, although not determined quantitatively, in the benzene extract of the hydrolysate. Since aniline was not found among the reaction products, it may be concluded that triphenylmethylpotassium is not appreciably ammonolyzed to potassium amide and triphenylmethane under the experimental conditions.

Atoms of K, 0.02430; mole $(C_6H_5)_3CH$, 0.02398; mole C_6H_5Cl, 0.029; chloride ion, 28.5% of theoretical; aniline, none.

TABLE II

K ATOM	$(C_6H_5)_2CH_2$ MOLE	C_6H_5Cl MOLE	Cl^-, % THEORETICAL	$C_6H_5NH_2$, % THEORETICAL	DURATION OF RUN
0.02567	0.02514	0.052	84.7	0.5	2 hrs.
0.01361	0.01372	0.0174	40.3	1.9	6 hrs.

TABLE III

K ATOM	$(C_6H_5)_2CH_2$ MOLE	$(C_6H_5)_2NH$ MOLE	Cl^{-a} %	ANILINE[b] %	$(C_6H_5)_2NH$ RECOVERED	$(C_6H_5)_3N$ %
0.02342	0.01146	0.01160	111	1.1	61%	39
0.03273	0.01626	0.01592	63	2.8	86	10

(*a*) Calculated on the basis of the potassium in excess of the amount required to form $(C_6H_5)_2N \cdot K$.

(*b*) Calculated on the basis of the potassium. ($1K \approx 1C_6H_5NH_2$.)

Potassium diphenylmethyl and phenyl chloride.—Potassium diphenylmethyl was prepared from potassium amide and diphenylmethane, and treated with chlorobenzene, in the manner of the preceding experiment. The results appear to depend upon the purity of the diphenylmethane, which, for the first runs (both tables), was redistilled Eastman material, boiling range 2°, and for the second run the same, distilled again, boiling range, 1.5°.

Triphenylmethane and tetraphenylmethane were not determined quantitatively but were isolated and identified in the benzene extract of the hydrolysate. (The benzene had been extracted with dilute HCl to remove amines.)

In the following runs, a mixture of diphenylmethane and diphenylamine was added to potassium amide in vessel *2*; then phenyl chloride was introduced. Duration of runs, 5.5–7 hours. Mole C_6H_5Cl, 0.0568 in first run; an excess in the second. $\%Cl^- = 100 \times [Cl^- \text{obtained}/(\text{atoms } K - \text{moles } (C_6H_5)_2NH)]$. Yield of $(C_6H_5)_3N = 100 \times [\text{moles } (C_6H_5)_3N/\text{moles } (C_6H_5)_2NH \text{ used}]$. M.p. $(C_6H_5)_3N$, cryst. alc., 123–4°.

Tetraphenylmethane and triphenylmethane were also identified as reaction products. The small quantities of aniline reported are doubtless formed by the action of potassium amide on chlorobenzene. The potassium amide may have been left in slight excess because of imperfect introduction of the diphenylmethane and diphenylamine, or it may have been formed by ammonolysis of the diphenylmethylpotassium.

Since the yields of chloride ion are higher than that obtained when chlorobenzene reacts with potassium amide alone,[1] and since considerable triphenylamine is formed, it is evident that potassium diphenylamine and phenyl chloride are reacting under the catalytic influence of the diphenylmethyl ion. It may of course be argued that amide ions, formed in accordance with the equation,

$$(C_6H_5)_2CHK + NH_3 \rightleftharpoons (C_6H_5)_2CH_2 + KNH_2 \qquad (15)$$

are actually responsible for the effects observed. While we have no data concerning the occurrence of this reaction in liquid ammonia at −33°, the following experiments indicate that there is some ammonolysis at higher temperatures.

Expt. 1.—Potassium (0.3318 g.) was converted to KNH_2 in a two-legged liquid ammonia weighing tube[11] (20°, Fe catalyst) and allowed to react with 1.51 g. diphenylmethane (an excess). An orange-colored solution was formed. After two hours' reaction, solvent was evaporated, the tube was evacuated to a few tenths of a mm. at 90° and weighed. Loss in weight, 0.1384 g. or 96% of that calculated from equation (15) read from right to left. The ammonolysis of potassium diphenylmethyl under these conditions is therefore slight.

Expt. 2.—In a two-legged liquid ammonia reaction tube, 1.03 grams of diphenylmethane was allowed to react with the sodium amide from 0.34 g. sodium (2.4 moles). A deep-red solution was formed, which was concentrated to a few cc. over the excess amide and allowed to stand over night. A portion of the solution was then decanted into the clean leg of the reaction tube, the solvent was evaporated, and the substance was analyzed in the customary manner. The specimen tube was heated in a vacuum at 20°, and at 52°, there being no further loss at the latter temperature. The solid was a pale yellow, indicating extensive ammonolysis.

Found: Na, 11.5%. Calc'd for $(C_6H_5)_2CHNa$: Na, 12.1%.

Bromobenzene, sodium chloride and potassium amide.—To a solution of 0.0413 mole bromobenzene and 0.0232 mole sodium chloride in vessel *2* was added 0.0314 mole potassium amide (prepared in vessel *1*). After evaporation of the solvent, the chloride ion in the residue was found to correspond exactly with the sodium chloride used. The yield of bromide ion (57.8% theoretical) is the same as would be obtained without the addition of sodium chloride.

SUMMARY

(1) Potassium amide, or rather the amide ion, catalyzes the following reactions, which do not take place, or which proceed very slowly in the absence of a catalyst in liquid ammonia at −33°.

$$C_6H_5NHK + C_6H_5X = (C_6H_5)_2NH + KX$$
$$C_6H_5NHK + C_6H_5X = p\text{-}C_6H_5\cdot C_6H_4NH_2 + KX$$
$$(C_6H_5)_2NK + C_6H_5X = (C_6H_5)_3N + KX \; (X = Cl, Br, I)$$

The amide ion also accelerates the following reaction, which is otherwise very slow in ammonia at −33°.

$$(C_6H_5)_3CK + C_6H_5Cl \rightarrow KCl + (C_6H_5)_4C$$

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[11] Bergstrom, *J. Am. Chem. Soc.*, **53**, 4068–9 (1931).

Chlorobenzene and potassium phenolate do not react, either alone, or in the presence of potassium amide in ammonia at −33°.

(2) Diphenylmethylpotassium reacts slowly with chlorobenzene in the absence of potassium amide, and apparently catalyzes the reaction of potassium diphenylamide with chlorobenzene. The diphenylmethyl anion (a base in Brønsted's sense) is presumably the actual catalyst.

(3) The strongest bases (in the Brønsted sense) react most readily with the phenyl halides, and only the very strongest (NH_2^- and $(C_6H_5)_2CH^-$) catalyze reactions between the phenyl halides and salts of the type of potassium anilide, potassium diphenylamide, potassium quinaldyl, and potassium triphenylmethyl. The degree of dissociation of these salts seems to be of minor importance in their reactivity.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

HYDROLYSIS OF SOME HALOBENZENESULFONIC ACIDS WITH ALKALI

C. M. SUTER AND PAUL H. SCRUTCHFIELD

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A survey of various possible procedures for obtaining the 3,5-dihydroxybenzenesulfonic acid needed in the synthesis of a series of 3,5-dihydroxyphenyl alkyl sulfides indicated that the partial hydrolysis of *sym.*-benzenetrisulfonic acid would be most satisfactory.[1] However, preliminary experiments upon the trisulfonation of benzene by the methods described in the literature[2] showed that securing the quantities of the trisulfonic acid desired would offer some difficulty.* Our attention was then directed to the work of Olivier[3] who found that *sym.*-chloro- and bromobenzenedisulfonic acids are readily obtained by the action of oleum upon chloro- and bromobenzene at high temperatures. It seemed of interest to determine if these compounds, upon treatment with fused or concentrated alkali, would yield hydroxysulfonic acids. For purposes of comparison the hydrolysis of a number of other related compounds was also investigated.

Little is known concerning the relative lability of halogen and sulfo groups in the benzene ring when these are meta to each other. 2,5-Dichlorobenzenesulfonic acid[4,5] with alkali at 170–190° loses the chlorine ortho to the sulfo group first. Both chlorines are removed from 3,4-

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[1] SENHOFER, *Sitzber. Akad. Wiss. Wien, Math.-naturw. Klasse, Abt. IIb*, **78**, 678 (1879).

[2] SENHOFER, *Ann.*, **174**, 243 (1874); JACKSON AND WING, *Ber.*, **19**, 898 (1886); *Am. Chem. J.*, **9**, 329 (1887); LAMBERTS, *German Pat.* 113,784; *Chem. Zentr.*, **1900**, II, 883; BEHREND AND MERTELSMAN, *Ann.*, **378**, 352 (1910).

* More recently Mr. Harrington of this laboratory has worked out the details of a method of sulfonation which gives good results. This will be described later in connection with other work.

[3] OLIVIER, *Rec. trav. chim.*, **37**, 307 (1918); OLIVIER AND KLEERMAEKER, *ibid.*, **39**, 640 (1920).

[4] BAD. ANILIN- UND SODA-FABRIK., *German Pat.* 132,423; *Chem. Zentr.*, **1902**, II, 170.

[5] BOEHRINGER AND SÖHNE, *German Pat.* 286,266; *Frdl.* **12**, 158; *German Pat.* 284, 533, *ibid.*, **12**, 157.

dichlorobenzenesulfonic acid[5,6] without loss of the sulfo group by heating at a somewhat higher temperature with an alkali solution in a copper bomb. 2-Chlorophenol-4,6-disulfonic acid is converted into the catechol-disulfonic acid with aqueous sodium hydroxide[7] at 180–190°.

TABLE I

HYDROLYSIS WITH 60% POTASSIUM HYDROXIDE

TIME, HRS.	TEMP., °C., ±2	EXTENT OF HYDROLYSIS	
		Hal., %	One sulfo group, %
A. Potassium 1-bromobenzene-3,5-disulfonate			
3	130	11	2.2
3	130	21	3.1 (trace $CuSO_4$)
2.5	152	61	11.9
0.25	166	35	6.7
1	166	complete	18.0
2	166	complete	19.6
3	166	complete	19.8
1	166	complete	14.3 (Cu powder)
B. Potassium 1-chlorobenzene-3,5-disulfonate			
2	166	95.0	43.3
6	166	complete	47.7
C. Potassium 1-chlorobenzene-2,4-disulfonate			
0.6	166	82.0	27.5
3	135	80.0	29.2
D. Potassium 1-iodobenzene-3-sulfonate			
1	166	10.3	0.4
2	166	30.8	2.9
E. Sodium 1-iodobenzene-3,5-disulfonate			
2	166	95.0	29.0
3	130	9.8	2.3
F. Sodium benzene-1,3-disulfonate tetrahydrate			
1	166	—	19.5

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[6] CHEM. FABR. GRIESHEIM ELEKTRON, *German Pat.* 137,119; *Chem. Zentr.*, **1903,** I, 112; ZOLLINGER AND ROEHLING, *U. S. Pat.* 1,321,271; *Chem. Abstr.*, **14,** 186 (1920).

[7] SACCHARINFABR. A.-G. VORM FAHLBERG, LIST AND CO., *German Pat.* 276,273; *Frdl.* **12,** 162.

In this investigation the manner in which the halobenzenesulfonic acids underwent hydrolysis was determined by analysis of the reaction mixtures for ionizable halogen and sulfite. To prevent oxidation of the sulfite and the occurrence of side reactions[8] the alkali treatment was carried out in an atmosphere of nitrogen. Two sets of experiments were performed. In the first, the results of which are shown in Table I, the hydrolyzing agent was 10 g. of 60% potassium hydroxide for 1 g. of the potassium sulfonate.

A number of important facts are brought out under A. (1) The removal of a sulfo group is much more difficult after the bromine has been exchanged for hydroxyl than before, while there is no apparent stabilization of the bromine by the hydrolysis of a sulfo group. (2) The bromine hydrolyzes approximately five times as rapidly as a sulfo group, or ten times as rapidly if we consider the presence of two of the latter. (3) The presence of copper or cupric ions apparently increases the hydrolysis rate for the halogen, although the data are too limited to be certain of this. Comparing B with A it is evident that the chlorine hydrolyzes more slowly than bromine since over 40% of one sulfo group is removed before the chlorine is lost. No attempt was made to determine for C which sulfo group was lost the more rapidly. The somewhat anomalous results obtained with the iodine compounds were probably due to non-homogeneity of the reaction mixtures; with the other compounds they were either homogeneous at the start or became so within a few minutes, except for the bromobenzenedisulfonate at 130°. In D the solubility of the iodobenzenedisulfonate apparently increased as the hydrolysis products accumulated in the mixture. In preliminary experiments not included in Table I it was found that refluxing potassium *sym.*-chlorobenzenedisulfonate with 15% potassium hydroxide for 1.5 hours brought about no appreciable amount of hydrolysis. With 30% alkali, three hours' refluxing hydrolyzed 1.4% of the chlorine, while with 40% alkali this increased to 59%.

The reactions carried out with fused potassium hydroxide gave results somewhat analogous to those of Table I except that at the higher temperatures hydrolysis of the halogen was always complete. The reaction mixtures of Table II contained 6 g. of potassium hydroxide and 1 g. of the potassium sulfonate. The presence of small amounts of water and potassium carbonate in the C.P. potassium hydroxide used made possible the obtaining of homogeneous reaction mixtures at 200°, considerably below the melting point of the pure base.

It is apparent under A that at 200° only the sulfo group that hydrolyzes before removal of the bromine is affected by alkali at this temperature.

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[8] BOSWELL AND DICKSON, *J. Am. Chem. Soc.*, **40**, 1786 (1918).

It is also apparent that the relative rate of hydrolysis of the sulfo group is much more rapid here than with 60% potassium hydroxide. These results are in general agreement with the claims of the patents already cited,[4,5,6] which specify aqueous alkali for the preferential hydrolysis of halogen. The second sulfo group is not hydrolyzed appreciably until temperatures in the neighborhood of 300° are attained.

It is obvious from these experiments that the preparation of *sym.*-hydroxybenzenedisulfonic acid can be accomplished by hydrolysis of the bromodisulfonic acid but that the product would contain considerable amounts of the dihydroxybenzenesulfonic acids. On the other hand, preparation of the *sym.*-dihydroxybenzenesulfonic acid from either the chloro- or bromodisulfonic acid is entirely feasible. Preliminary fusion reactions on a preparative scale verified this latter conclusion. A more complete account of the preparation of the dihydroxysulfonic acid will be published in connection with another investigation.

TABLE II

HYDROLYSIS WITH FUSED POTASSIUM HYDROXIDE

TIME, HRS.	TEMP., °C.,±5	HYDROLYSIS OF ONE SULFO GROUP, %
A. Potassium 1-bromobenzene-3,5-disulfonate		
1	200	57.5
3	200	58.2 59.8
3	255	98
3	300	110
B. Potassium 1-chlorobenzene-3,5-disulfonate		
3	200	76
3	260	103
3	310	131

EXPERIMENTAL

Materials.—The potassium *sym.*-chloro- and -bromobenzenedisulfonates were prepared by sulfonation of the halobenzenes according to the directions of Olivier.[3] The potassium 1-chlorobenzene-2,4-disulfonate was obtained as a by-product in the preparation of the symmetrical compound. Potassium 1-iodobenzene-3-sulfonate was obtained from metanilic acid according to the method of Langmuir.[9] The iodobenzene-3,5-disulfonate was obtained from the 1-nitrobenzene-3,5-disulfonic acid of Heinzelmann[10] by reduction with ammonium sulfide, diazotization of

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[9] LANGMUIR, *Ber.*, **28**, 93 (1895).

[10] HEINZELMANN, *Ann.*, **188**, 161 (1877).

the resulting aminosulfonic acid (without isolation) and treatment of the diazonium salt with sodium iodide. The sodium 1-iodobenzene-3,5-disulfonate was recrystallized from 95% alcohol and dried at 120°.

Anal. Calc'd for $C_6H_3INa_2O_6S_2$: I, 31.11. Found: I, 31.00.

Procedure.—An 80-cc. pyrex side-arm test-tube was fitted with a mechanical stirrer, with a glass tube bearing which extended to just above the reaction mixture of alkali and alkali sulfonate. During reactions a slow stream of dry nitrogen was passed in through the side-arm of the test-tube and escaped through the bearing of the stirrer. In the test-tube were placed 6 g. of potassium hydroxide (or 10 g. of a 60% solution) and a 1 g. sample of the alkali sulfonate. The test-tube was then partially immersed in an electrically heated salt bath for a specified time at a given temperature. The fusion mixture was dissolved in a 5% aqueous solution of glycerol and made up to a volume of 250 cc. The glycerol was necessary to prevent oxidation of the sulfite by oxygen.[11] Aliquot portions of the solution were analyzed for halogen by the Volhard method, and for sulfite by titration with standard iodine. The results which have been listed in Tables I and II are typical of those obtained.

SUMMARY

A study of the hydrolysis reactions for a number of halobenzenesulfonic acids with potassium hydroxide has shown that: (1) the halogens are more easily hydrolyzed than the sulfo groups; (2) the ratio of the hydrolysis rates for the halogen and sulfo groups is greater in 60% alkali than in fusion reactions; (3) the rate of removal of a sulfo group is much slower after the halogen has been hydrolyzed than before.

From the results it was concluded that it is feasible to prepare 3,5-dihydroxybenzenesulfonic acid from chloro- or bromobenzene-3,5-disulfonic acid by alkaline hydrolysis.

[11] HALLER, *J. Soc. Chem. Ind.*, **38**, 52 (1919).

[Contribution from the Cobb Chemical Laboratory, University of Virginia]

ETHERS AND HETERO-ETHERS OF MORPHINE AND ITS ISOMERS*

BURT F. FARIS† and LYNDON SMALL

Received February 18, 1936

It has long been known that the pharmacodynamic result of methylation of the phenolic hydroxyl group of morphine is an increase in toxicity and convulsant action, accompanied by a marked decrease in analgesic, depressant, and other effects. The comparison of a long series of morphine derivatives with their methylated analogs which has been made in recent years[1] shows that with occasional exceptions (principally among hydrogenated derivatives) the change in physiological action produced by inactivation of the phenolic hydroxyl through methyl ether formation is quite uniform.[2] Although numerous other phenol ethers of morphine have been described,[3] with the exception of the ethyl and benzyl ethers, little is known of their pharmacology. Of the isomers of morphine, only the phenol methyl ethers (*i.e.*, the codeine isomers) have been previously prepared, and only recently have any extensive studies been made of the physiological action of this series of ethers.[4]

It is possible to etherify the secondary alcoholic hydroxyl of morphine, while leaving the phenolic hydroxyl intact, by utilizing the ingenious device

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* The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

† Squibb Fellow in Alkaloid Chemistry, 1933-35; Mallinckrodt Fellow in Alkaloid Chemistry, 1935-36.

[1] By the pharmacological unit associated with us at the University of Michigan; Eddy, *J. Pharmacol.*, **49**, 319 (1933); Eddy and Ried, *ibid.*, **52**, 468 (1934).

[2] Edmunds, Eddy, and Small, *J. Am. Med. Assoc.*, **103**, 1417 (1934).

[3] Small and Lutz, "Chemistry of the Opium Alkaloids," Supplement 103 to the Public Health Reports, **1932**, p. 156.

[4] Eddy, *J. Pharmacol.*, **45**, 361 (1932); **51**, 35 (1934); Eddy and Ahrens, *Am. J. Psychol.*, **47**, 614 (1935); Foster, *J. Pharmacol.*, **51**, 153, 170 (1934); Wright, *ibid.*, **51**, 327, 343 (1934); Krueger, *ibid.*, **50**, 254 (1934); Krueger, Howes, and Gay, *ibid.*, **55**, 288 (1935).

of Mannich.[5] Heterocodeine (I, R = CH_3) is the only ether of this type known. As we were led to predict from the extraordinary increase in activity (especially in respect to analgesia and depression) observed in other morphine types where the alcoholic hydroxyl is masked or removed (codeine methyl ether, monoacetylmorphine, desoxymorphine-C, dihydrodesoxymorphine-D[6]), heterocodeine is much more effective in the animal body than morphine.[7] Dihydroheterocodeine, which we have prepared not only by hydrogenation of heterocodeine but also by methylation of dihydromorphine, is approximately as potent a narcotic in man as dihydrodesoxymorphine-D, although open to the same objections in respect to habituation and brevity of action as the latter drug.[8]

It is evident from the above-cited examples that the phenolic and alcoholic hydroxyl groups in the morphine series exert a profound influence on physiological action, and we regard it as important to extend our pharmacological knowledge of the phenolic and especially of the alcoholic ethers not only of morphine but of its isomers and related compounds. We have, accordingly, prepared the series of derivatives listed in Table I, which is arranged with respect to the type of morphine isomer and type of etherification. Several previously known ethers, listed here to indicate the extent of the comparative studies being conducted by the pharmacological unit, are designated by literature references.

Comparison of the physiological action of the numerous phenol ethyl ethers with the unalkylated morphines and with the codeines should yield information on the effect of ethylation in a series where thus far only morphine, codeine, and ethylmorphine have been studied. The methoxymethyl and benzyl ethers represent interesting types in which the phenolic hydroxyl is covered with groups easily removed (especially the methoxymethyl) by hydrolytic processes, and which may liberate the phenolic base at the site of hydrolysis in the body. In the case of benzyldihydrodesoxymorphine-D, it was believed that by benzylation the powerful but disadvantageously evanescent analgesic action of dihydrodesoxymorphine-D might be prolonged, an expectation which has been realized to some extent. Similarly, benzylmorphine methyl ether may be expected to liberate heterocodeine slowly in the body, as it does on hydrolysis *in vitro*.

The alcoholic methyl and ethyl ethers of the morphine isomers are important because of striking observations already reported for γ-isomor-

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[5] Mannich, *Arch. Pharm.*, **254**, 349 (1916).

[6] Edmunds, Eddy, and Small, *J. Am. Med. Assoc.*, **103**, 1417 (1934); Eddy and Howes, *J. Pharmacol.*, **53**, 430 (1935); **55**, 257 (1935); Wright and Barbour, *ibid.*, **54**, 25 (1935).

[7] Eddy, *ibid.*, **55**, 127 (1935).

[8] C. K. Himmelsbach, unpublished results.

TABLE I

MORPHINE ISOMER DERIVATIVES PREPARED

PHENOLIC ETHER	ALCOHOLIC ETHER
Morphine	
Codeine[9]	Heterocodeine[5]
Ethylmorphine[9]	Heteroethylmorphine
Benzylmorphine[9]	Heterodihydrocodeine
Methoxymethylmorphine[6]	Heteroethyldihydromorphine
Dihydrocodeine[9]	
Ethyldihydromorphine	
Benzyldihydromorphine	
Methoxymethyldihydromorphine	
α-Isomorphine	
Isocodeine[10]	Heteroisocodeine
Ethyl-α-isomorphine	Heteroethyl-α-isomorphine
Dihydroisocodeine[11]	Heterodihydroisocodeine
Ethyldihydro-α-isomorphine	Heteroethyldihydro-α-isomorphine
β-Isomorphine	
Allopseudocodeine[10]	Heteroethyl-β-isomorphine(?)
Ethyl-β-isomorphine	
Dihydroallopseudocodeine[12]	
Ethyldihydro-β-isomorphine	
γ-Isomorphine	
Pseudocodeine[10]	Heteropseudocodeine
Ethyl-γ-isomorphine	Heteroethyl-γ-isomorphine
Dihydropseudocodeine[13]	Heterodihydropseudocodeine
Ethyldihydro-γ-isomorphine	Heteroethyldihydro-γ-isomorphine
Miscellaneous	
Benzyldihydrodesoxymorphine-D	Benzylmorphine methyl ether
	Benzyldihydromorphine methyl ether

phine and pseudocodeine, and their respective dihydro derivatives.[14] These four substances exert moderate analgesic action, with low toxicity and complete lack of any convulsant action, even in fatal doses. If the

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[9] Literature abundant. See SMALL AND LUTZ, "Chemistry of the Opium Alkaloids," pp. 156, 174.

[10] SPEYER AND KRAUSS, *Ann.*, **432**, 233 (1923).

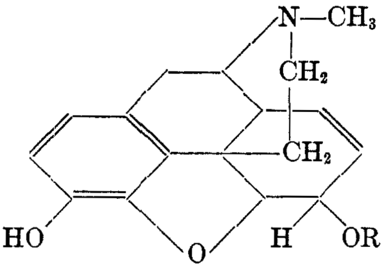
[11] SPEYER AND WIETERS, *Ber.*, **54**, 2647 (1921).

[12] LUTZ AND SMALL, *J. Am. Chem. Soc.*, **54**, 4715 (1932).

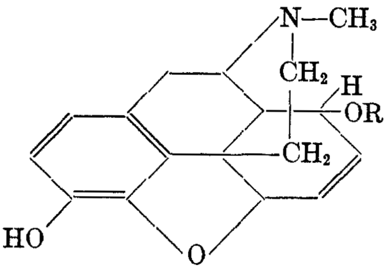
[13] LUTZ AND SMALL, *ibid.*, **56**, 2466 (1934).

[14] EDDY, *J. Pharmacol.*, in press.

analgesic action of this series can be heightened by alkylation of the alcoholic hydroxyl group (formula II) to a degree comparable with that reported for heterocodeine and dihydroheterocodeine, a group of valuable narcotics may be obtained. The same considerations apply to some extent to the compounds of the α-isomorphine series.

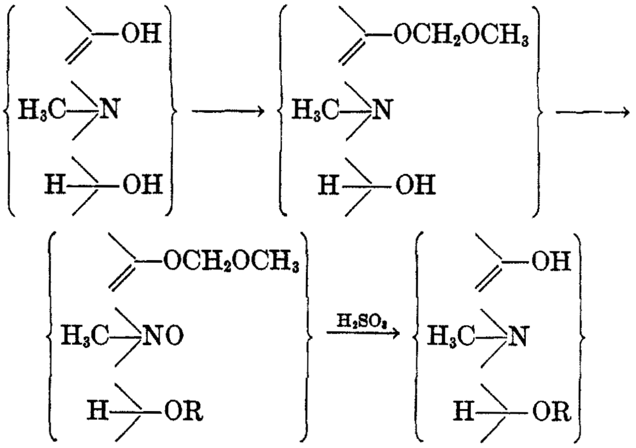


I. Morphine hetero-ethers



II. γ-Isomorphine hetero-ethers

The ethylation of the phenolic hydroxyl group throughout the series (with the exception of ethylmorphine) was accomplished by the use of diazoethane; methoxymethylation and benzylation, by the usual procedures. Alkylation of the alcoholic hydroxyl was carried out by the method of Mannich,[5] through the methoxymethyl ether, methoxymethyl ether-*N*-oxide alcoholic alkyl ether, followed by simultaneous reduction at the *N*-oxide group and hydrolysis at the methoxymethyl ether group by means of sulfurous acid. The operation may be represented by the following equations, in which the three principal functional groups of morphine (the phenolic hydroxyl, the basic nitrogen, and the secondary alcoholic hydroxyl) are joined by brackets:



For the heteromethyl- and heteroethyl-γ-isomorphine types, we were able to spare effort by applying an alcoholysis of the type discovered by

Knorr and Hartmann[15] for the conversion of α-chlorocodide to pseudocodeine methyl ether by heating with methanol. In the cases under discussion, heteropseudocodeine (γ-isomorphine alcoholic methyl ether) was first synthesized on a small scale by the Mannich method, in order that we might be certain of the structure of our alcoholysis product. The compound obtained in good yield by comparatively large scale methyl alcoholysis of α-chloromorphide was found identical with the substance obtained by Mannich's procedure. Heteroethyl-γ-isomorphine, from ethyl alcoholysis of α-chloromorphide is assumed, without further proof, to have the same structure.

An attempt to prepare the heteromethyl and heteroethyl ethers of β-isomorphine by prolonged alkylation of methoxymethyl-β-isomorphine-*N*-oxide resulted only in unchanged material. Hydrolysis of bromomorphide results, to a large extent, in formation of β-isomorphine, and by analogy, alcoholysis of bromomorphide might be expected to yield the desired 8-alkyl ether. We have obtained in fact from ethyl alcoholysis of bromomorphide a new ethyl ether which we believe to be heteroethyl-β-isomorphine, but the structural proof is as yet not complete.

The preparation of the hydrogenated β- and γ-isomorphine ethers involves overcoming the well known tendency shown by all pseudocodeine types to undergo scission of the ether linkage with formation of 4-phenolic tetrahydro derivatives. In the cases of ethyldihydro-β- and ethyldihydro-γ-isomorphines the most convenient method lay in the ethylation of the already available dihydro-β-[16] and dihydro-γ-isomorphines.[17] For heterodihydropseudocodeine and heteroethyldihydro-γ-isomorphine, the respective unhydrogenated hetero-alkyl derivatives were first prepared and then hydrogenated according to the Lutz and Small technique,[12] establishing two more cases in which this method has been successfully applied to the preparation of otherwise inaccessible derivatives.

EXPERIMENTAL

I. Morphine Series

Ethyldihydromorphine.—Ethylmorphine[18] in dilute hydrochloric acid with platinum oxide, absorbed one mole of hydrogen. The product was a colorless oil, which was distilled in a high vacuum at 170°. In absolute alcohol $[\alpha]_D^{24}$ −135.9° (c = 1.004).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99.
Found: C, 72.13; H, 8.22.

The only crystalline salt obtainable was the acid tartrate, of m.p. 167° (sinters

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[15] Knorr and Hartmann, *Ber.*, **45**, 1354 (1912).

[16] Small and Faris, *J. Am. Chem. Soc.*, **57**, 364 (1935).

[17] Small and Lutz, *ibid.*, **56**, 1928 (1934).

[18] Prepared by the method of Mering, U. S. Patent 629,264 (July 18, 1899).

with loss of water at 93°) and $[\alpha]_D^{25}$ −59.4° (water, $c = 1.095$), which gave inconsistent analyses.

The methiodide crystallizes from ethanol and has the m.p. 260° (evac. tube); $[\alpha]_D^{25}$ −66.9° (water, $c = 1.001$).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 27.92.

Benzyldihydromorphine.—Hydrogenation of benzylmorphine in dilute acetic acid solution (faintly acid) resulted in considerable hydrolysis, as evidenced by the appearance of much dihydromorphine. A solution of 13.4 g. of benzylmorphine (m.p. 126–128°, prepared by the method of Mering[19]) in methanol with 50 mg. of platinum oxide absorbed one mole of hydrogen in 3 hours. The yield was 13 g.; the product crystallizes best from its own weight of ethyl acetate as a monohydrate of m.p. 95–97°. In alcohol $[\alpha]_D^{24}$ −88.1° ($c = 1.028$).

Anal. Calc'd for $C_{24}H_{27}NO_3 + H_2O$: C, 72.87; H, 7.40; H_2O, 4.5.
Found: C, 73.20; H, 7.67; H_2O, 4.1.

The hydrochloride monohydrate (dihydroperonin), prepared with 3 *N* hydrochloric acid, avoiding any excess, can be recrystallized from water without hydrolysis; it is soluble to the extent of 4% at 25°. The salt melts at 233–235° (evac. tube); $[\alpha]_D^{20}$ −52.1° (water, $c = 0.960$).

Anal. Calc'd for $C_{24}H_{28}ClNO_3 + H_2O$: H_2O, 4.2; Cl, 8.21.
Found: H_2O, 3.8; Cl, 7.90.

The hydrobromide monohydrate (from water) melts at 193–195° (evac. tube); $[\alpha]_D^{24}$ −44° (water, $c = 0.981$).

Anal. Calc'd for $C_{24}H_{28}BrNO_3 + H_2O$: H_2O, 3.8; Br, 16.78.
Found: H_2O, 3.8; Br, 16.75.

The hydriodide can be recrystallized from water with very slow cooling, and melts at 215–217° (evac. tube, gas); $[\alpha]_D^{24}$ −45.3° (water, $c = 1.036$).

Anal. Calc'd for $C_{24}H_{28}INO_3$: I, 25.13. Found: I, 25.22.

The perchlorate crystallizes from water containing 20% alcohol. It melts at 188–192° and has $[\alpha]_D^{23}$ −59.5° (alcohol, $c = 1.008$).

Anal. Calc'd for $C_{24}H_{28}ClNO_7$: Cl, 7.42. Found: Cl, 7.23.

The methiodide crystallizes in beautiful flakes from methanol (very sparingly soluble). It melts at 242–244° (evac. tube, gas); $[\alpha]_D^{24}$ −43.2° (methanol, $c = 1.041$).

Anal. Calc'd for $C_{25}H_{30}INO_3$: I, 24.45. Found: I, 24.40.

Methoxymethyldihydromorphine.—Hydrogenation of methoxymethylmorphine in alcohol with platinum (oxide) yielded a low-melting base which was best purified from acetone (very soluble). It melts at 99–101°; $[\alpha]_D^{24}$ −154.5° (alcohol, $c = 1.133$).

Anal. Calc'd for $C_{19}H_{25}NO_4$: C, 68.84; H, 7.61.
Found: C, 68.99; H, 7.89.

Methoxymethyldihydromorphine is exceedingly sensitive to hydrolysis in the presence of acids, but salts can be prepared by working slightly on the basic side. The hydrochloride was prepared in absolute alcohol by adding an insufficient quantity of alcoholic hydrogen chloride and precipitating the salt with absolute ether. It was purified in similar fashion. M.p. 124–126° (gas evolution); $[\alpha]_D^{24}$ −71.8° (water, $c = 1.020$).

Anal. Calc'd for $C_{19}H_{26}ClNO_4 + H_2O$: H_2O, 4.6. Found: H_2O, 4.6.
Calc'd for $C_{19}H_{26}ClNO_4$: Cl, 9.64. Found: Cl, 9.81.

The sulfate was prepared in alcohol with insufficient 10% sulfuric acid, and precipitated crystalline when absolute ether was added. It was purified by reprecipitation. It melts at 49° (gas evolution at 118°); $[\alpha]_D^{24}$ −72.8° (water, $c = 1.098$).

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[19] MERING, U. S. Patent, 584,388 (June 15, 1897).

Anal. Calc'd for $C_{38}H_{52}N_2O_{12}S + 5H_2O$: H_2O, 10.6. Found: H_2O, 10.8.
Calc'd for $C_{38}H_{52}N_2O_{12}S$: SO_4, 12.63. Found: SO_4, 12.91.

The methiodide was purified by crystallization from ethanol. It melted at 201–203° (evac. tube, gas); $[\alpha]_D^{24}$ −61.8° (water, c = 1.020).

Anal. Calc'd for $C_{20}H_{28}INO_4$: I, 26.83. Found: I, 26.43.

Heterodihydrocodeine (*Dihydromorphine alcoholic methyl ether*).—A solution of 43.5 g. of heterocodeine[5] in 95 cc. of 10% acetic acid was made up with water to 150 cc. and hydrogenated in the presence of 2 g. of palladium-barium sulfate. In 3 days 3480 cc. of hydrogen was absorbed, and the solution was made ammoniacal and extracted with 2.5 liters of ether; crystallization of the new base from the ether causes some difficulty at this point. The yield is nearly quantitative. After recrystallization from alcohol, the base melts at 216.5–217° (evac. tube); $[\alpha]_D^{26}$ −178.0° (alcohol, c = 1.000).

In the preparation from dihydromorphine, the crystalline sodium salt of dihydromorphine was converted to methoxymethyldihydromorphine (*q. v.*); the latter was converted to the *N*-oxide in the usual way, and the *N*-oxide was methylated as previously described.[5] The product from hydrolysis and reduction was identical with the above heterodihydrocodeine, but the over-all yield was only about 10% of the calculated amount, chiefly because of losses (incomplete etherification) in the preparation of methoxymethyldihydromorphine.

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.70.
Found: C, 71.68; H, 7.93.

The hydrochloride was prepared in absolute alcohol with alcoholic hydrogen chloride; m.p. 299–299.5° (evac. tube, gas); $[\alpha]_D^{26}$ −136.5° (water, c = 1.000).

Anal. Calc'd for $C_{18}H_{24}ClNO_3$: Cl, 10.50. Found: Cl, 10.75.

The hydriodide, prepared in the usual way, crystallized after several weeks. It was purified from water; m.p. 269° (evac. tube); $[\alpha]_D^{25}$ −98.9° (water, c = 1.001).

Anal. Calc'd for $C_{18}H_{24}INO_3$: I, 29.58. Found: I, 29.73.

The perchlorate, prepared with 25% perchloric acid, crystallized from water; m.p. 258–260° (evac. tube, decomp.); $[\alpha]_D^{28}$ −110.0° (water, c = 1.042).

Anal. Calc'd for $C_{18}H_{24}ClNO_7$: Cl, 8.83. Found: Cl, 8.80.

The acid fumarate was prepared with alcoholic fumaric acid and recrystallized from 95% alcohol; m.p. 215–216° (evac. tube, gas); $[\alpha]_D^{28}$ −110.0° (water, c = 1.046).

Anal. Calc'd for $C_{22}H_{27}NO_7$: C, 63.28; H, 6.52.
Found: C, 63.37; H, 6.91.

The methiodide crystallizes from methanol; m.p. 260–261° (evac. tube, gas); $[\alpha]_D^{28}$ −91.4° (methanol, c = 1.023).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.64. Found: I, 28.93.

Heteroethylmorphine (*Morphine alcoholic ethyl ether*).—Treatment of 108 g. of methoxymethylmorphine with 65 cc. of 30% hydrogen peroxide as described by Mannich gave a viscous yellow oil, which on treatment with hot acetone yielded 116 g. of the hitherto unknown crystalline form of methoxymethylmorphine-*N*-oxide, containing a molecule of acetone. This material was alkylated with 180 cc. of ethyl sulfate and 180 cc. of 10 *N* sodium hydroxide during 10 hours. After hydrolysis and reduction, the residue from the ether extracts was most advantageously converted to the very insoluble salicylate; the base was liberated, and transformed to the hydrochloride with 3 *N* hydrochloric acid. Yield of hydrochloride, 55 g. Heteroethylmorphine crystallizes best from ethyl acetate, as the monohydrate; m.p. 110–112°; $[\alpha]_D^{23}$ −178.8° (alcohol, c = 1.012).

Anal. Calc'd for $C_{19}H_{23}NO_3 + H_2O$: C, 68.84; H, 7.61; OC_2H_5, 13.6; H_2O, 5.4.
Found: C, 68.68; H, 7.60; OC_2H_5, 13.3; H_2O, 4.8.

The hydrochloride (heterodionin), prepared as above and recrystallized from water contains 3 molecules of hydrate water and melts at 241–243° (evac. tube); $[\alpha]_{\mathrm{D}}^{24}$ −134.9° (water, $c = 1.004$).

Anal. Calc'd for $C_{19}H_{24}ClNO_3 + 3H_2O$: H_2O, 13.4. Found: H_2O, 13.4.
Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.22.

The hydrobromide dihydrate was prepared with 20% hydrobromic acid and recrystallized from water; m.p. 285–287° (evac. tube, sintering at 170–180°); $[\alpha]_{\mathrm{D}}^{23}$ −119.2° (water, $c = 1.081$).

Anal. Calc'd for $C_{19}H_{24}BrNO_3 + 2H_2O$: H_2O, 8.3; Br, 18.58.
Found: H_2O, 8.3; Br, 18.53.

The hydriodide crystallizes from water as the dihydrate, melts at 171–174°, solidifies, and remelts at 282° (evac. tube, decomp.); $[\alpha]_{\mathrm{D}}^{24}$ −115.8° (water, $c = 1.027$).

Anal. Calc'd for $C_{19}H_{24}INO_3 + 2H_2O$: H_2O, 7.6; I, 26.60.
Found: H_2O, 7.6; I, 26.60.

The perchlorate, prepared with 25% perchloric acid and purified from water, melts at 249–250° (evac. tube, decomp.); $[\alpha]_{\mathrm{D}}^{24}$ −126° (alcohol, $c = 1.103$).

Anal. Calc'd for $C_{19}H_{24}ClNO_7$: Cl, 8.57. Found: Cl, 8.63.

The methiodide was recrystallized from water; it melts with decomp. at 255–265° (evac. tube); $[\alpha]_{\mathrm{D}}^{24}$ −104.6° (water, $c = 1.060$). It lost 2.5% in weight on drying, but does not appear to be hydrated.

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 27.75.

Heteroethyldihydromorphine.—A solution of 17 g. of heteroethylmorphine in 200 cc. of water with 1 g. of palladium-barium sulfate took up 1150 cc. of hydrogen in one hour. By evaporation of the solvent under diminished pressure the new hydrochloride was obtained in nearly quantitative yield. The base was precipitated crystalline by ammonia in the presence of a little ether (in which it is practically insoluble) and purified from ethyl acetate. It melts at 189–190°; $[\alpha]_{\mathrm{D}}^{23}$ −164.8° (alcohol, $c = 1.017$).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 7.99.
Found: C, 72.48; H, 8.04.

The hydrochloride trihydrate (dihydroheterodionin) was prepared with 3 *N* hydrochloric acid and purified from water, in which it is very soluble. It melts in an open tube at 95–110° (gas), in an evacuated tube at 165–170°, solidifies and remelts at 274–276°; $[\alpha]_{\mathrm{D}}^{24}$ −121.7° (water, $c = 1.00$).

Anal. Calc'd for $C_{19}H_{26}ClNO_3 + 3H_2O$: H_2O, 13.3. Found: H_2O, 13.2.
Calc'd for $C_{19}H_{26}ClNO_3$: Cl, 10.08. Found: Cl, 10.02.

The hydrobromide crystallizes from water, probably as the dihydrate, but appears to lose part of its hydrate water readily (calc'd for $2H_2O$, 8.3; found, 7.5). It melts in a vacuum at 282–284°; $[\alpha]_{\mathrm{D}}^{25}$ −125.1° (water, $c = 1.00$).

Anal. Calc'd for $C_{19}H_{26}BrNO_3$: Br, 20.18. Found: Br, 20.37.

The hydriodide crystallizes from water, and melts at 291–293° (evac. tube); $[\alpha]_{\mathrm{D}}^{25}$ −110.6° (water, $c = 1.066$).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.65. Found: I, 28.75.

The perchlorate crystallizes from water, and melts in a vacuum at 234–235°; $[\alpha]_{\mathrm{D}}^{23}$ −98° (alcohol, $c = 1.020$).

Anal. Calc'd for $C_{19}H_{26}ClNO_7$: Cl, 8.53. Found: Cl, 8.18.

The methiodide was prepared by heating the base in methanol with methyl iodide under reflux for 20 minutes, precipitated crystalline with ether, and was purified from methanol by addition of ether. It melts at 250–251° (evac. tube); $[\alpha]_{\mathrm{D}}^{25}$ −79.4° (methanol, $c = 1.026$).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 27.76.

II. *α-Isomorphine Series*

Ethyl-α-isomorphine (α-Codethylin).—Pure α-isomorphine base (from hydrolysis of bromomorphide) was suspended in a mixture of 3 parts of absolute ether with 1 part of absolute ethanol, and diazoethane in 100% excess of the calculated amount was distilled into the suspension. After the reaction mixture had stood for 24 hours in the dark, the solvent was distilled off, the residue dissolved in normal hydrochloric acid, made alkaline with excess of normal sodium hydroxide, and the ethylated base was extracted into ether. The material obtained after removal of the ether was best purified by conversion to the hydrobromide and recrystallization of the salt from water after decolorizing with Norit. The base regenerated from the hydrobromide was finally purified by distillation in a high vacuum at 140°. The yield of crystalline ethyl-α-isomorphine of m.p. 128–130° was 40% of the calculated amount. The compound shows in alcohol $[\alpha]_D^{23}$ −143.7° (c = 1.030).

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40: OC_2H_5, 14.7.
Found: C, 72.75; H, 7.46; OC_2H_5, 13.6.

The salts of ethyl-α-isomorphine with the common acids were not crystalline. The methiodide, prepared in the usual way and recrystallized from absolute alcohol has the m.p. 243° (evac. tube), and $[\alpha]_D^{21}$ −91.6° (water, c = 0.999).

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 27.73.

Ethyldihydro-α-isomorphine.—An ethereal suspension of dihydro-α-isomorphine[16] was treated with excess of diazoethane. After 24 hours the solution was washed with dilute sodium hydroxide and the ether was removed. The resulting pale yellow oil crystallized when ethyl acetate was added, and could be purified from this solvent, in which it is quite soluble; the yield is 90% of the calculated amount. The base crystallizes with one molecule of water; m.p. 86–91° (gas evolution at 105°); $[\alpha]_D^{24}$ −110° (methanol, c = 0.970). It distills in a high vacuum at 130°, yielding the anhydrous crystalline form of m.p. 104°.

Anal. Calc'd for $C_{19}H_{25}NO_3 + H_2O$: H_2O, 5.44. Found: H_2O, 5.38.
Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 8.00.
Found: C, 72.15; H, 8.23.

Of the salts, only the acid tartrate could be obtained crystalline. This crystallized after several days from a solution of the base in excess of alcoholic tartaric acid, and was purified from acetone, yield 70%. It is very soluble in water or alcohol. The hydrated salt has the m.p. 109–112° (gas evolution), and $[\alpha]_D^{23}$ −66° (water, c = 0.932).

Anal. Calc'd for $C_{23}H_{31}NO_9 + H_2O$: H_2O, 3.73. Found: H_2O, 3.55.
Calc'd for $C_{23}H_{31}NO_9$: C, 59.32; H, 6.72.
Found: C, 59.22; H, 6.52.

The methiodide, prepared in the usual way, is very soluble in water, nearly insoluble in alcohol, and was crystallized from 80% alcohol. It melts at 277° (evac. tube) with gas evolution; $[\alpha]_D^{23}$ −76.2° (water, c = 1.233).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 27.56.

Heteroisocodeine (α-Isomorphine alcoholic methyl ether).—Twenty grams of α-isomorphine were added to a cold solution of 1.5 g. of sodium in 50 cc. of absolute alcohol. A crystalline sodium salt could not be obtained by precipitation with ether; the solution was evaporated to dryness at 60° under diminished pressure, and the residue was converted to the methoxymethyl ether by treatment with chloromethyl ether in absolute chloroform, as described by Mannich.[5] Methoxymethyl-α-isomorphine was obtained as a viscous oil, as was its *N*-oxide. The latter compound, in 20 cc. of water, was methylated under vigorous stirring and ice-cooling by dropwise addition of 30 cc. of dimethyl sulfate and 30 cc. of 10 *N* sodium hydroxide over a period of 6 hours. The mixture was acidified with sulfuric acid, and sulfur dioxide was bubbled through it at 40° until the odor no longer disappeared after an hour's standing. The solution was made alkaline with ammonia, and extracted with ether. Heteroisocodeine was purified by crystallization from absolute alcohol, followed by high-vacuum sublimation at 155°; m.p. 206.5–207° (evac. tube); $[\alpha]_D^{22}$ −185.5° (methanol, c = 0.973).

Anal. Calc'd for $C_{18}H_{21}NO_3$: C, 72.19; H, 7.08; OCH_3, 10.4.
Found: C, 72.01; H, 7.17; OCH_3, 11.1.

Heteroisocodeine methiodide crystallizes from absolute alcohol, and has the m.p. 227–228° (evac. tube, gas evolution); $[\alpha]_D^{22}$ −105.4° (water, c = 1.110).

Anal. Calc'd for $C_{19}H_{24}INO_3$: I, 28.78. Found: I, 28.65.

Heterodihydroisocodeine (*Dihydro-α-isomorphine alcoholic methyl ether*).—Five grams of heteroisocodeine dissolved to neutral solution in 200 cc. of very dilute hydrochloric acid, with 50 mg. of platinum oxide, took up one mole of hydrogen in two hours. The new base precipitated crystalline when ammonia was added, and was purified from absolute alcohol; m.p. 198–200°; $[\alpha]_D^{25}$ −118.1° (alcohol, c = 1.004).

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.70.
Found: C, 71.69; H, 7.88.

The hydrochloride was prepared with 3 *N* hydrochloric acid, purified from water; m.p. 273–275° (evac. tube); $[\alpha]_D^{24}$ −111.1° (water, c = 1.026).

Anal. Calc'd for $C_{18}H_{24}ClNO_3$: Cl, 10.50. Found: Cl, 10.72.

The hydriodide was prepared in 10% acetic acid with potassium iodide, purified from water; m.p. 287–288° (evac. tube, gas evolution); $[\alpha]_D^{24}$ −85.2° (water, c = 0.416).

Anal. Calc'd for $C_{18}H_{24}INO_3$: I, 29.58. Found: I, 29.52.

The methiodide, crystallized from ethanol, melts at 245–248° (evac. tube, sintering at 170–180°); $[\alpha]_D^{24}$ −77.9° (water, c = 1.078).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.64. Found: I, 28.93.

Heteroethyl-α-isomorphine.—The ethylation of methoxymethyl-α-isomorphine-*N*-oxide was carried out like the methylation, but with ethyl sulfate at room temperature, and the product was isolated in the same way. The yield was 6 g. from 20 g. of α-isomorphine; the base was obtained crystalline by high vacuum distillation at 170°. It melts at 161–162° (evac. tube); $[\alpha]_D^{22}$ −205.1° (methanol, c = 0.946).

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40; OC_2H_5, 14.4.
Found: C, 72.77; H, 7.43; OC_2H_5, 14.0.

The hydrochloride (heteroisodionin) was prepared with alcoholic hydrogen chloride and washed with absolute alcohol; m.p. 247–248° (evac. tube, decomp.); $[\alpha]_D^{24}$ −164.2° (water, c = 1.102).

Anal. Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.15.

The hydriodide (from acetic acid and potassium iodide) crystallizes from water; m.p. 264° (evac. tube, decomp.); $[\alpha]_D^{24}$ −132.7° (water, c = 1.168).

Anal. Calc'd for $C_{19}H_{24}INO_3$: I, 28.77. Found: I, 28.70.

The hydrobromide, prepared with 20% hydrobromic acid, crystallizes from water; m.p. 255–258° (evac. tube, decomp.); $[\alpha]_D^{24}$ −150.2° (water, c = 1.051).

Anal. Calc'd for $C_{19}H_{24}BrNO_3$: Br, 20.28. Found: Br, 20.67.

The methiodide crystallizes from alcohol and has the m.p. 229–231° (evac. tube, gas); $[\alpha]_D^{24}$ −131.3° (water, c = 1.050).

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 28.10.

Heteroethyldihydro-α-isomorphine.—The preparation of this base by hydrogenation of heteroethyl-α-isomorphine is parallel to that of heterodihydroisocodeine. It crystallizes from absolute alcohol; m.p. 210–212°; $[\alpha]_D^{24}$ −128° (alcohol, c = 1.031).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 7.99.
Found: C, 72.07; H, 8.20.

The hydrochloride (dihydroheteroisodionin), prepared with alcoholic hydrogen chloride and washed with absolute alcohol, melts at 300° (evac. tube, gas); $[\alpha]_D^{24}$ −125.7° (water, c = 1.034).

Anal. Calc'd for $C_{19}H_{26}ClNO_3$: Cl, 10.08. Found: Cl, 10.04.

The hydriodide was prepared by adding potassium iodide solution to a saturated aqueous solution of the hydrochloride, and was recrystallized from water; m.p. 287° (evac. tube, gas); $[\alpha]_D^{24}$ −99.5° (water, c = 0.467).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.65. Found: I, 28.59.

The methiodide, crystallized from absolute ethanol, has the m.p. 256–258° (evac. tube) and shows $[\alpha]_D^{24}$ −86.1° (water, c = 1.034).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 27.82.

III. β-Isomorphine Series

Ethyl-β-isomorphine (β-Codethylin).—Ethylation of β-isomorphine with diazoethane was carried out as for α-isomorphine. The resulting base was a viscous oil, which was purified by distillation in a high vacuum at 170°. It was brought to analysis in the form of its salts.

The acid sulfate was prepared with 20% sulfuric acid, and was recrystallized from water; m.p. 195–198° (evac. tube); $[\alpha]_D^{24}$ −136.3° (water, c = 1.027).

Anal. Calc'd for $C_{19}H_{25}NO_7S$: C, 55.44; H, 6.27; SO_4, 23.36.
Found: C, 55.20; H, 6.37; SO_4, 23.53.

The perchlorate crystallizes from water, in which it is only sparingly soluble; m.p. 264–266° (evac. tube, decomp.); $[\alpha]_D^{25}$ −113.2° (40% alcohol, c = 0.733).

Anal. Calc'd for $C_{19}H_{24}ClNO_7$: Cl, 8.57. Found: Cl, 8.26.

The fumarate, of m.p. 172–175° (evac. tube) and $[\alpha]_D^{24}$ −100.3° (alcohol, c = 0.723) was exceedingly difficult to burn, and gave inconsistent analyses.

Ethyldihydro-β-isomorphine.—Ethylation of dihydro-β-isomorphine with diazoethane gave an 80% yield of glass-like solid, which was distilled in a high vacuum at 210°.

The perchlorate crystallizes from water; m.p. 231–234° (evac. tube); $[\alpha]_D^{25}$ −64.3° (water, c = 1.057).

Anal. Calc'd for $C_{19}H_{26}ClNO_7$: C, 57.43; H, 6.31; Cl, 8.53.
Found: C, 57.26; H, 6.62; Cl, 8.37.

The picrate was prepared with alcoholic picric acid, and recrystallized from 50% alcohol; m.p. 187–189° (evac. tube); $[\alpha]_D^{25}$ −64.8° (alcohol, c = 0.617).

Anal. Calc'd for $C_{25}H_{28}N_4O_{10}$: N, 10.29. Found: N, 10.39.

Heteroethyl-β-isomorphine (?).—Five grams of bromomorphide in 100 cc. of absolute ethanol was heated in a pressure bottle at 100° for 6 hours. The solution was evaporated to dryness, the residue was dissolved in dilute acid, ammonia was added, and the precipitate was extracted into ether. The product was found to contain halogen; it was brought into ether, and extracted with tenth-normal hydrochloric acid in six fractions. The base obtained from the first two fractions was halogen-free, and was purified by crystallization from alcohol; yield 20%; m.p. 209–211° (evac. tube); $[\alpha]_D^{24}$ −60.1° (abs. alcohol, c = 1.015).

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40; OC_2H_5, 13.6.
Found: C, 72.69; H, 7.74; OC_2H_5, 14.1.

The new base is different from heteroethyl-α-isomorphine and from heteroethyl-γ-isomorphine, and reasoning from the course taken by hydrolysis of bromomorphide, we believe it to be the desired heteroethyl-β-isomorphine.

IV. γ-Isomorphine Series

Ethyl-γ-isomorphine (*γ-Codethylin*).—Ten grams of γ-isomorphine suspended in 100 cc. of absolute ether and 100 cc. of absolute alcohol was ethylated with diazoethane and the product isolated as described for the α-series. The product, 7 g., was purified from absolute alcohol; m.p. 183–184°; $[\alpha]_D^{22}$ −75° (methanol, $c = 0.967$).

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40; OC_2H_5, 14.3.
Found: C, 72.64; H, 7.53; OC_2H_5, 14.2.

The hydrochloride (γ-isodionin) was prepared with alcoholic hydrogen chloride and washed with absolute alcohol; m.p. 298–300° (evac. tube, decomp.); $[\alpha]_D^{24}$ −62.7° (water, $c = 1.005$).

Anal. Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.24.

The methiodide, recrystallized from 70% alcohol, melts at 252–253° (evac. tube, gas); $[\alpha]_D^{21}$ −40.8° (water, $c = 1.005$).

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 27.43.

Ethyldihydro-γ-isomorphine.—Dihydro-γ-isomorphine,[17] suspended in absolute ether was ethylated with diazoethane and the product was isolated as described above; it crystallized best from ethyl acetate. Yield 80%; m.p. 158–159°; $[\alpha]_D^{23}$ −36.2° (methanol, $c = 0.985$).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.16; H, 7.98.
Found: C, 72.33; H, 8.00.

The neutral fumarate was the only salt which could be obtained crystalline; it was prepared with absolute alcoholic fumaric acid and recrystallized from absolute alcohol; m.p. 180–192° (evac. tube. In open tube it develops an intense magenta color before melting); $[\alpha]_D^{23}$ −23.7° (water, $c = 0.992$).

Anal. Calc'd for $C_{40}H_{46}N_2O_{10}$: C, 67.52; H, 7.29.
Found: C, 67.04; H, 7.23.

The methiodide, prepared as usual and crystallized from 70% alcohol has the m.p. 252–253° (evac. tube, gas); $[\alpha]_D^{21}$ −40.8° (water, $c = 1.005$).

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 27.43.

Heteropseudocodeine (*γ-Isomorphine alcoholic methyl ether*).—Twenty grams of γ-isomorphine was dissolved in 50 cc. of alcohol containing 1.5 g. of dissolved sodium; addition of 100 cc. of ether caused precipitation of the crystalline sodium salt. This salt was converted to the methoxymethyl ether, which was likewise crystalline. Methoxymethyl-γ-isomorphine-*N*-oxide crystallized when acetone was added to the resinous mass resulting from vacuum evaporation of the hydrogen peroxide solution. The methylation was carried out as described for heteroisocodeine, and the product was crystallized from absolute alcohol; yield 8 g.; m.p. 239–241° (evac. tube); $[\alpha]_D^{23}$ −79.5° (methanol, $c = 0.880$).

Anal. Calc'd for $C_{18}H_{21}NO_3$: C, 72.19; H, 7.08; OCH_3, 10.4.
Found: C, 72.02; H, 6.88; OCH_3, 9.3.

The same compound was obtained when 15 g. of α-chloromorphide in 100 cc. of absolute methanol was heated in a pressure bottle at 100° for 6 hours. The methanol was removed in a vacuum, the residue dissolved in a liter of water, decolorized with Norit, made ammoniacal, and extracted; yield about 40%.

The hydrochloride was prepared with 3 *N* hydrochloric acid and purified from water, in which it is very soluble. It melts at 274–276° (evac. tube, decomp.); $[\alpha]_D^{22}$ −48.6° (water, $c = 1.161$).

Anal. Calc'd for $C_{18}H_{22}ClNO_3$: Cl, 10.56. Found: Cl, 10.37.

The hydriodide crystallizes from water and melts at 185–188° (decomp.); $[\alpha]_D^{21}$ −48.7° (water, $c = 1.036$).

Anal. Calc'd for $C_{18}H_{22}INO_3$: I, 29.72. Found: I, 29.63.

Heterodihydropseudocodeine (*Dihydro-γ-isomorphine alcoholic methyl ether*).—A suspension of 5 g. of heteropseudocodeine with 0.1 g. of platinum oxide in 200 cc. of glacial acetic acid took up 1.3 moles of hydrogen. Enough water was added to dissolve the new hydrochlorides, catalyst was removed, and the solution was distilled to dryness at 40° under diminished pressure. The residue, in water, was made ammoniacal and extracted into ether. The residue from the ether was dissolved in dilute hydrochloric acid, made ammoniacal and again extracted. The tetrahydro derivative is not appreciably dissolved by the ether. The dihydro base was recrystallized from absolute alcohol and sublimed at 175° in a high vacuum; yield 40%. Heterodihydropseudocodeine has the m.p. 235–237° (evac. tube); $[\alpha]_D^{25}$ −83.4° (alcohol, $c = 0.857$).

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.70.
Found: C, 71.96; H, 7.89.

The hydrobromide (from 20% hydrobromic acid) was purified from water; m.p. 256–258° (evac. tube); $[\alpha]_D^{25}$ −55.4° (water, $c = 0.884$).

Anal. Calc'd for $C_{18}H_{24}BrNO_3$: Br, 21.71. Found: Br, 21.45.

The hydriodide, prepared as usual, and purified from water, melts at 185–187° (evac. tube); $[\alpha]_D^{25}$ −52.8° (water, $c = 0.776$).

Anal. Calc'd for $C_{18}H_{24}INO_3$: I, 29.58. Found: I, 29.86.

Heteroethyl-γ-isomorphine.—Ten grams of α-chloromorphide in 100 cc. of absolute alcohol was heated in a pressure bottle at 100° for 6 hours. The product was isolated as in the methyl alcoholysis of α-chloromorphide and crystallized from absolute ethanol; yield, 30%. The compound melts at 215–220° (evac. tube, decomp.); $[\alpha]_D^{23}$ −43.5° (methanol, $c = 0.827$).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.80; H, 7.40; OC_2H_5, 14.4.
Found: C, 72.56; H, 7.56; OC_2H_5, 13.5.

The hydrochloride dihydrate (heteropseudodionin) was prepared with 3 *N* hydrochloric acid and recrystallized from water in which it is very soluble; m.p. 287–290° (evac. tube, decomp.); $[\alpha]_D^{23}$ −30.5° (water, $c = 1.114$).

Anal. Calc'd for $C_{19}H_{24}ClNO_3 + 2H_2O$: H_2O, 9.3. Found: H_2O, 8.8.
Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.25.

The hydriodide monohydrate was prepared in the usual way and purified from water; m.p. 276–277° (evac. tube, decomp.); $[\alpha]_D^{22}$ −23.2° (water, $c = 0.906$).

Anal. Calc'd for $C_{20}H_{24}INO_3 + H_2O$: H_2O, 3.9. Found: H_2O, 3.6.
Calc'd for $C_{20}H_{24}INO_3$: I, 26.60. Found: I, 26.44.

Heteroethyldihydro-γ-isomorphine.—Six grams of heteroethyl-γ-isomorphine in 200 cc. of 1.5 *N* hydrochloric acid with 50 mg. of platinum oxide absorbed 1.54 moles of hydrogen. The catalyst was removed, and the crystalline mixed hydrochlorides obtained by concentration under diminished pressure. The hydrochlorides of the mixed dihydro and tetrahydro derivatives could not be separated, but the free heteroethyldihydro-γ-isomorphine proved to be much more soluble in ether than the tetrahydro base, and was separated from the latter by this means. It crystallized in contact with absolute ethanol, and was sublimed in a high vacuum at 175°; yield 30%. It melts at 220–223° (evac. tube); $[\alpha]_D^{25}$ −20.2° (ethanol, $c = 0.692$).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 7.99.
Found: C, 72.25; H, 7.85.

The hydrochloride and sulfate are not crystalline. The hydriodide, prepared in the usual way and recrystallized from water, melts at 277–281° (evac. tube) and has $[\alpha]_D^{25}$ −9.1° (water, $c = 0.551$).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.65. Found: I, 28.45.

The methiodide crystallizes from 80% alcohol, and melts at 250–252° (evac. tube); $[\alpha]_D^{25}$ −7.2° (water, $c = 0.552$).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 28.04.

V. Miscellaneous

Benzylmethylmorphine (*Benzylmorphine alcoholic methyl ether*).—Benzylmorphine (100 g.) was warmed with 100 cc. of 30% hydrogen peroxide; the vigorous reaction was controlled with ice. The clear yellow solution crystallized rapidly when water was added, and the sparingly soluble *N*-oxide separated as a white mass of short thick prisms; yield, 84 g. The product can be recrystallized from alcohol; m.p. 236–238° (evac. tube, decomp.); $[\alpha]_D^{23}$ −53.2° (alcohol, $c = 0.2112$).

Anal. Calc'd for $C_{24}H_{25}NO_4$: C, 73.62; H, 6.44.
Found: C, 73.55; H, 6.73.

This product, suspended in water, was methylated by the Mannich procedure for 24 hours, but, due to the extremely slight solubility of the *N*-oxide, methylation was incomplete. The unchanged oxide was filtered out, and the mother liquor was acidified and treated with sulfur dioxide. Sodium hydroxide and ether yielded about 10% of the calculated amount of an oily base, which was purified as the hydrochloride.

Because of these difficulties, the preparation from heterocodeine is to be preferred. Five grams of heterocodeine and 2.1 g. of benzyl chloride were added to a solution of 0.4 g. of sodium in 50 cc. of absolute alcohol. This was heated under reflux for an hour, sodium chloride was filtered out, and the alcohol was removed under diminished pressure. An oily base was obtained and was converted to the hydrochloride with 3 *N* hydrochloric acid, after distillation in a high vacuum at 180°. The salt crystallizes from water; m.p. 233–236° (evac. tube); $[\alpha]_D^{28}$ −88.9° (water, $c = 1.080$).

Anal. Calc'd for $C_{25}H_{28}ClNO_3$: Cl, 8.33. Found: Cl, 8.50.

The acid sulfate forms with 20% sulfuric acid, and crystallizes well from water; m.p. 247–249° (evac. tube); $[\alpha]_D^{25}$ −90.1° (water, $c = 0.910$).

Anal. Calc'd for $C_{25}H_{29}NO_7S$: C, 61.57; H, 6.00; SO_4, 19.72.
Found: C, 61.78; H, 6.33; SO_4, 19.45.

The methiodide crystallizes from 50% alcohol, and has the m.p. 155–157° (evac. tube); $[\alpha]_D^{24}$ −75.8° (50% alcohol, $c = 0.448$).

Anal. Calc'd for $C_{26}H_{30}INO_3$: I, 23.90. Found: I, 23.69.

Benzylmethyldihydromorphine.—This derivative was prepared by benzylation of heterodihydrocodeine as described above for benzylmethylmorphine. The base is not crystalline, nor does it yield crystalline salts. It was purified by distillation in a high vacuum at 210°. In alcohol it shows $[\alpha]_D^{25}$ −89.1° ($c = 0.942$).

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.68; H, 7.47.
Found: C, 76.45; H, 7.72.

The methiodide crystallizes readily from ethanol and has the m.p. 155–157° (evac. tube); $[\alpha]_D^{24}$ −54.60° (water, $c = 1.034$).

Anal. Calc'd for $C_{26}H_{32}INO_3$: I, 23.81. Found: I, 23.72.

Benzyldihydrodesoxymorphine-D.—To a solution of 1.1 g. of sodium in 100 cc. of absolute alcohol, 12.7 g. of dihydrodesoxymorphine-D[20] was added under hy-

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[20] Prepared by the method of SMALL, YUEN, AND EILERS, *J. Am. Chem. Soc.*, **55**, 3863 (1933), and *U. S. Patent* 1,980,972 (Nov. 13, 1934); we are indebted to Merck and Co., Rahway, N. J. for the quantity preparation of this material.

drogen, and the red solution was then treated with 6.05 g. of benzyl chloride. The mixture was heated under reflux (hydrogen stream) for 2 hours, sodium chloride was filtered out, and alcohol was removed by distillation. The residue was taken up in 10% acetic acid, excess of dilute sodium hydroxide was added, and the precipitated base was extracted into ether. The aqueous layer, with ammonium chloride, gave 2.3 g. of unchanged dihydrodesoxymorphine-D. The ether yielded a pale yellow oil which could not be induced to crystallize. It was taken up in absolute alcohol, and treated with alcoholic hydrogen chloride to faint acidity. The yield of white crystalline hydrochloride was 11 g. It was recrystallized from 35 cc. of alcohol; m.p. 249° (evac. tube, gas); $[\alpha]_D^{23}$ −34.4° (alcohol, $c = 1.060$).

Anal. Calc'd for $C_{24}H_{28}ClNO_2$: Cl, 8.92. Found: Cl, 8.94.

The hydrobromide was prepared in 10% acetic acid with potassium bromide, and recrystallized from alcohol; m.p. 226–227° (evac. tube); $[\alpha]_D^{23}$ −29.8° (alcohol, $c =$ 1.074).

Anal. Calc'd for $C_{24}H_{28}BrNO_2$: C, 65.13; H, 6.38; Br, 18.07.
Found: C, 64.92; H, 6.65; Br, 17.85.

The perchlorate crystallizes in sparkling flakes from alcohol and melts at 223–224° (evac. tube, gas); $[\alpha]_D^{24}$ −51.5° (alcohol, $c = 1.068$).

Anal. Calc'd for $C_{24}H_{28}ClNO_6$: Cl, 7.68. Found: Cl, 7.71.

The methiodide, prepared in the usual way, separates from methanol in brilliant yellow crystals having a decomposition point at about 70°; $[\alpha]_D^{24}$ −25.8° (methanol, $c = 1.00$). It is so unstable that it had largely decomposed before it could be brought to analysis.

SUMMARY

As part of an investigation on the relationship between constitution and physiological action, a series of 21 new ethers of morphine, of α-, β-, and γ-isomorphines, and of their dihydro derivatives has been synthesized. This series includes both phenolic and alcoholic ethers (heteroethers). New ethers of benzylmorphine, benzyldihydromorphine, and of dihydrodesoxymorphine-D are described.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

GRIGNARD REAGENTS—THEIR REDUCING ACTION AND RATES OF ADDITION*

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INTRODUCTION

Although the reducing property of Grignard reagents first observed by Grignard[1] in 1901, has been the object of numerous subsequent investigations, relatively little progress has been made hitherto toward the formulation of a reaction mechanism, or the correlation of structure with reducing activity. In view of the widespread utilization of organomagnesium compounds in synthetic chemistry further study of this reaction appeared desirable. In the investigation reported the writers had the following objectives in view: first, determination of the effect of experimental conditions (such as temperature, solvent, concentration, etc.) upon the amount of reduction observed; second, evolution of a satisfactory mechanism for the reduction process; third, establishment of a correlation, of predictive value, between the relative reducing activity of a Grignard reagent and some property of its organic radical.

Reduction by Grignard reagents is a very common phenomenon. The rôle of reduction is not always obvious, and interpretations of reactions that take an "abnormal" course often ignore it.†

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* Abstracted from a dissertation submitted by S. Weinhouse to the Faculty of the Division of the Physical Sciences of The University of Chicago in August, 1935, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[1] GRIGNARD, *Ann. chim. phys.*, [7], **24**, 468 (1901).

† Thus, the interaction of alkyl halides, such as ethyl chloride, with ethylmagnesium halides to yield ethylene and ethane may be, though seldom is, regarded as a typical Grignard reduction. In other cases, the reducing action of Grignard reagents is well recognized, as, *e.g.*, in the reduction of azobenzene and azotoluene to the respective hydrazo compounds: *cf.* FRANTZEN AND DIEBEL, *Ber.*, **38**, 2716 (1905); KIRBERG, *J. prakt. Chem.*, [2] **118**, 1, (1928). See also WIELAND AND KOGL, *Ber.*, **55**, 1798 (1922), regarding the reduction of nitroso compounds to the corresponding azo compounds. HOFFMAN, *ibid.*, **56**, 125 (1928), cites the reduction of manganous chloride to metallic manganese by means of ethylmagnesium bromide, and BUYLLA AND OLAY, *Anal. soc. españ. fís. quím.*, **20**, 599 (1922); *C. A.*, **17**, 2412

This paper is limited to a study of the reducing action of Grignard reagents on aldehydes and ketones. The authors believe, however, that the interpretation here offered can be extended to the elucidation of the reducing action of Grignard reagents in other systems.

PREVIOUS WORK

Grignard,[1] in his pioneer paper on reactions of organomagnesium compounds, reported the formation of a small amount of benzyl alcohol (in addition to 56% of 1-phenylisohexanol) when benzaldehyde was treated with isoämylmagnesium bromide. Sabatier and Maihle[2] noted considerable evolution of gas when cyclohexanone was treated with isopropyl- or isobutylmagnesium bromide. Later these investigators[3] found that cyclohexylmagnesium chloride reduces benzophenone to benzhydrol.

The relative effectiveness of a series of alkylmagnesium bromides in the reduction of cyclohexanone and 4-methylcyclohexanone has been evaluated.[4] The following yields of the cyclohexanols were obtained from the cyclohexanones (the respective reagents are identified by their alkyl radicals); propyl, 50%; isoämyl, 20%; isopropyl, 75%; *sec.*-octyl, 20%. Aromatic Grignard reagents had no reducing effect on the two ketones.

Konovalov, Miller, and Timtschenko[5] have reported the formation of 38% of benzhydrol in the reaction between *tert.*-butylmagnesium bromide and benzophenone. Klages and Heilmann[6] erroneously report the preparation of isopropyldiphenylcarbinol by the treatment of benzophenone with isopropylmagnesium bromide, since the physical constants of the product correspond with those of benzhydrol. Letellier[7] has observed reduction when ethyl hydroxypivalate is treated with ethylmagnesium bromide. It is quite likely that the Grignard reagent first adds to the carbonyl group of the ester and that the ketone thus formed is reduced to the secondary alcohol. Gorskin[8] records the reduction of benzopinacolone to benzopinacolyl alcohol by means of propylmagnesium iodide. Faworsky[9] states that a 50% reduction of the aldehyde takes place in the reaction between isobutyraldehyde and *tert.*-butylmagnesium chloride.

(1922), report the formation of hydrocarbons (methane and pentane) by the reduction of sodium methylate and sodium amylate with ethylmagnesium bromide, ethylene being formed as the oxidation product.

[2] Sabatier and Maihle, *Compt. rend.*, **138**, 1321 (1903).

[3] Sabatier and Maihle, *ibid.*, **139**, 345 (1904).

[4] Sabatier and Maihle, *ibid.*, **141**, 301 (1905).

[5] Konovalov, Miller, and Timtschenko, *Chem. Zentr.*, **1906**, II, 312.

[6] Klages and Heilmann, *Ber.*, **37**, 1451 (1904).

[7] Letellier, *Compt. rend.*, **146**, 343 (1908).

[8] Gorskin, *J. Russ. Phys. Chem. Soc.*, **45**, 163 (1913).

[9] Faworsky, *J. prakt. Chem.*, [2], **88**, 652 (1913).

Schmidlin[10] obtained benzopinacol from the reaction between benzophenone and triphenylmethylmagnesium chloride. Leroide[11] obtained, from propylmagnesium chloride and pinacolone, a 20% yield of pinacolyl alcohol, together with propane and propylene. His data on the reducing action of several Grignard reagents on terpenic ketones and ethyl pivalate are summarized in Table I.

Hess and Wustrow[12] obtained 35–40% yields of crotonyl alcohol and cinnamic (cinnamyl) alcohol by treatment of crotonaldehyde and cinnamaldehyde, respectively, with isobutylmagnesium bromide. An ether-free coördination compound, which contained one molecule of aldehyde for each molecule of Grignard reagent, was isolated. When the coördination compound is hydrolyzed without previous heating a good yield of secondary alcohol results, but warming gives rise to evolution of isobutylene, and the residue yields only the primary alcohol. It was proved that this unusual behavior was not due to the instability of the secondary alcohol. The same authors obtained a 60% yield of benzyl alcohol on refluxing the reaction product of benzaldehyde and ethylmagnesium bromide for some time in benzene. Without heating, however, only the normal product, 1-phenylpropanol, was obtained.

TABLE I

REDUCTION OF TERPENIC KETONES AND ETHYL PIVALATE (LEROIDE[11])

CARBONYL COMPOUND	GRIGNARD REAGENT	REDUCTION (%)
Camphenylone	n-C_3H_7MgCl	100
Fenchone	n-C_3H_7MgCl	100
Camphor	n-C_3H_7MgCl	100
Ethyl pivalate	C_2H_5MgI	13
Ethyl pivalate	n-C_3H_7MgCl	48
Ethyl pivalate	n-C_3H_7MgBr	Reduction; yield not stated
Ethyl pivalate	n-C_3H_7MgI	
Ethyl pivalate	n-C_4H_9MgI	

Rheinbolt and Roleff[13] obtained a 56% yield of benzyl alcohol from the reaction between benzaldehyde and isobutylmagnesium bromide. Through a series of carefully planned experiments these investigators proved conclusively that the reductions observed do not result from decomposition of the normal addition products. Rheinbolt and Roleff[14] extended their investigation to a number of other reactions and studied the effect of

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[10] SCHMIDLIN, *Ber.*, **39**, 4198 (1906).

[11] LEROIDE, *Ann. chim.*, [9], **16**, 354 (1921).

[12] HESS AND WUSTROW, *Ann.*, **437**, 256 (1924).

[13] RHEINBOLT AND ROLEFF, *Ber.*, **57**, 1921 (1924).

[14] RHEINBOLT AND ROLEFF, *J. prakt. Chem.*, [2], **109**, 175 (1925).

temperature and of order of addition upon the extent of reduction. In some cases reduction proceeds quantitatively in the cold; in other cases, reduction is not complete at room temperature, but is somewhat increased at higher temperatures. Order of addition appeared to have no effect

TABLE II

REDUCTION OF BENZALDEHYDE AND KETONES (RHEINBOLT AND ROLEFF[14])

ORIGINAL REACTANTS	YIELDS OF REDUCTION PRODUCTS AFTER 1 HR. REFLUXING (%)	
	In ether	In benzene
Benzaldehyde + C_2H_5MgBr	11	22
Benzaldehyde + *cyclo*-$C_6H_{11}MgCl$	18	23*
Benzaldehyde + *i*-C_4H_9MgBr	55	57
Benzophenone + *i*-C_4H_9MgBr	Quantitative reduction in the cold	
Phenyl isobutyl ketone + *i*-C_4H_9MgBr	Quantitative reduction in the cold	
Benzopinacolone + *i*-C_4H_9MgBr	72	73

* In boiling anisole.

TABLE III

GRIGNARD ADDITION TO AND REDUCTION OF KETONES (STAS[15])

KETONE	ALKYLMAGNESIUM BROMIDE	YIELDS (%)	
		Addition Product	Reduction Product
Diïsopropyl	*i*-C_3H_7	0	100
Diïsopropyl	*n*-C_3H_7	30	30
Diïsopropyl	C_2H_5	54	21
Ethyl isopropyl	*i*-C_3H_7	51	30
Ethyl isopropyl	*n*-C_3H_7	100	0
Ethyl isopropyl	C_2H_5	100	0
Dipropyl	*i*-C_3H_7	100	0
Dipropyl	*n*-C_3H_7	60	20
Dipropyl	C_2H_5	100	0
Methyl isopropyl	*i*-C_3H_7	78	14
Methyl isopropyl	*n*-C_3H_7	100	0
Diethyl	*i*-C_3H_7	100	0
Diethyl	C_2H_5	100	0
Dimethyl (Acetone)	*i*-C_3H_7	100	0

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[15] STAS, *Bull. soc. chim. Belg.*, **34**, 188 (1925); **35**, 379 (1926).

on the amount of reduction in the reactions investigated. The results are summarized in Table II.

J. Stas[15] found some unchanged ketone (an indication of enolization) in addition to the normal and reduction products, in the reaction between aliphatic ketones and Grignard reagents. His data are summarized in Table III. The reduction product was always accompanied by an equivalent amount of the corresponding unsaturated hydrocarbon.† Methyl- and phenylmagnesium bromides showed no reduction in any case.

Conant and co-workers[16] have studied the effect of branching of the chains of alkylmagnesium halides on the yields of reduction products obtained from aldehydes, ketones, and esters, and have reached the conclusion that there is some correlation between structure and reducing activity. Conant considers that, besides the normal addition of Grignard reagents to carbonyl compounds, there are three other reactions namely, enolization, condensation of the aldol type, and reduction. The "abnormal" reactions, however, are slow, and come into play only when addition is hindered, presumably by steric effects. Table IV summarizes the observations of Conant and previous workers. The letters A, R, E, and C

TABLE IV

REACTIONS OF CARBONYL COMPOUNDS WITH GRIGNARD REAGENTS (CONANT[16] AND OTHER WORKERS)

CARBONYL COMPOUND	GRIGNARD REAGENT			
	CH_3MgI	C_4H_9MgBr	$(CH_3)_2CHMgBr$	$(CH_3)_3CMgBr$
CH_3CHO	AA	. . .	A	AA
$(CH_3)_2CHCHO$	A	. . .	AA	AR
$(CH_3)_3CCHO$	. . .	AA	AR	RR
CH_3COCH_3	AA	. . .	AA	A
$C_2H_5COC_2H_5$	AA	AA	AA	C
$CH_3COCH(CH_3)_2$	AA	. . .	. . .	. . .
$CH_3COC(CH_3)_3$	AA	AR	EC	EC
$(CH_3)_2CHCOCH(CH_3)_2$	AA	. . .	RR	RR
$(CH_3)_2CHCOC(CH_3)_3$	AA	. . .	RR	RR
$(CH_3)_3CCOC(CH_3)_3$	AA	. . .	R	RR
$(CH_3)_2CHCO_2C_2H_5$	. . .	. . .	RR	. . .
$(CH_3)_3CCO_2C_2H_5$	. . .	. . .	. . .	. . .
$C_6H_5CH_2CO_2C_2H_5$	. . .	. . .	EE, CC	. . .

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† NOLLER, GREBE, AND KNOX, *J. Am. Chem. Soc.*, **54**, 4690 (1932), have proved that equivalent amounts of isobutylene and benzhydrol are formed in the reaction of isobutylmagnesium bromide with benzophenone.

[16] CONANT AND BLATT, *J. Am. Chem. Soc.*, **51**, 1227 (1929); CONANT, WEBB, AND MENDUM, *ibid.*, **51**, 1246 (1929).

refer to normal addition, reduction, enolization, and condensation, respectively. Yields are not given, for the data of different investigators are not strictly comparable. However, an approximate idea of the extent of the reaction is conveyed by doubling the letters for reported yields greater than 50%.

The work of Blatt and Stone,[17] however, throws some doubt upon the validity of the hypothesis that the complexity of the alkyl group and the reducing activity of the reagent are directly related. Their data are summarized in Table V. Blicke and Powers[18] have made a study of the reducing action of several Grignard reagents on benzophenone and related ketones (see Table VI).

TABLE V

GRIGNARD ADDITION TO AND REDUCTION OF KETONES (BLATT AND STONE[17])

KETONE	GRIGNARD REAGENT	ADDITION (%)	REDUCTION (%)	ENOLIZATION (%)
Dipropyl	n-C_3H_7MgBr	54	24	—
Dipropyl	i-C_3H_7MgBr	44	5	15
Propyl isopropyl	n-C_3H_7MgBr	63	17	—
Propyl isopropyl	i-C_3H_7MgBr	17	49	—
Diïsopropyl	n-C_3H_7MgBr	43	34	—
Diïsopropyl	i-C_3H_7MgBr	0	80	—

TABLE VI

GRIGNARD REDUCTION OF BENZOPHENONE AND RELATED KETONES (BLICKE AND POWERS[18])

KETONE	GRIGNARD REAGENT	REDUCTION (%)
Benzophenone	CH_3MgI	0
Benzophenone	C_2H_5MgBr	0
Benzophenone	n-C_3H_7MgBr	50
Benzophenone	i-C_3H_7MgBr	22
Benzophenone	n-C_4H_9MgBr	27
Benzophenone	i-C_4H_9MgBr	74
Benzophenone	i-$C_5H_{11}MgBr$	30
p-Bromobenzophenone	n-C_3H_7MgBr	24
Phenyl naphthyl ketone	n-C_3H_7MgBr	65
Phenyl biphenyl ketone	n-C_3H_7MgBr	48
Phenyl benzyl ketone	n-C_3H_7MgBr	9

Noller[19] has found that isobutylmagnesium bromide, as well as diïso-

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[17] BLATT AND STONE, *ibid.*, **54**, 1495 (1932).

[18] BLICKE AND POWERS, *ibid.*, **51**, 3378 (1929).

[19] NOLLER, *ibid.*, **53**, 635 (1931).

butylmagnesium, reduces benzophenone to the extent of about 80%. Later[20] he extended his study to other aliphatic Grignard reagents. (See Table IV.)

Sherwood and Wallace[21] have observed that a terpenic Grignard reagent such as bornylmagnesium chloride, reduces isovaleraldehyde to isoämyl alcohol, citral (geranial) to geraniol, and piperitone to phellandrene.

Gomberg, Bachmann, and co-workers[22] have made an extensive study of the reduction of aromatic ketones to pinacols by the system Mg-MgI_2. While this is not a strictly typical case of Grignard reduction it has been used to interpret the results of the latter reaction. The reduction of a ketone to a pinacol by the system Mg-MgI_2 is presumed to take place through the momentary formation of magnesious iodide, which may add to the carbonyl group to form a free ketyl radical in a manner analogous to the formation of ketyls by the addition of alkali metals to ketones.[23]

TABLE VII

GRIGNARD REDUCTION OF BENZOPHENONE (NOLLER[20])

GRIGNARD REAGENT	REDUCTION (%)
tert.-C_4H_9MgBr	0
C_2H_5MgBr	2
i-C_3H_7MgBr	13
sec.-C_4H_9MgBr	40
n-C_3H_7MgBr	58
n-C_4H_9MgBr	59
i-C_4H_9MgBr	86

Only an infinitesimal amount of magnesious iodide is supposed to be present at any time, and in fact no weighable quantity could ever be detected; but the authors offer considerable evidence in support of the existence of this subhalide. The reduction proceeds at 0°, and is very fast at 25° (55 grams of benzophenone is reduced in five minutes to give a 99.5% yield of benzopinacol). Similar results were obtained with the system Mg-$MgBr_2$, but no reduction was observed with Mg-$MgCl_2$.

The work of Gomberg and Bachmann emphasizes the necessity of using filtered solutions free of metallic magnesium, and serves to explain the observations of Schmidlin,[10] Lagrave,[24] and Arbuzov,[25] who obtained benzo-

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[20] NOLLER AND HILMER, *ibid.*, **54**, 2503 (1932).

[21] SHERWOOD AND WALLACE, *J. Chem. Soc.*, **1931**, 3340.

[22] GOMBERG, BACHMANN, *et al.*, *J. Am. Chem. Soc.*, **49**, 236, 2584 (1927); **50**, 2762 (1928); **51**, 308, 2238 (1929); **52**, 2455, 3287, 3290, 4412, 4967 (1930); **53**, 1524, 2762 (1931).

[23] SCHLENK AND WEICKEL, *Ber.*, **44**, 1182 (1911).

[24] LAGRAVE, *Ann. chim.*, [10], **8**, 363 (1927).

[25] ARBUZOV AND ARBUZOVA, *J. Gen. Chem.* (U. S. S. R.), **2**, 388 (1932).

pinacol in the reaction between various Grignard reagents and benzophenone in the presence of excess magnesium. Barnett, Cook, and Nixon[26] and Hatt[27] have reduced a number of esters to the corresponding pinacols by Grignard reagents in the presence of excess magnesium, but no pinacols were obtained when the solutions were carefully filtered. Davies, Dixon, and Jones[28] have made identical observations regarding the reaction between benzophenone and *n*-amyl-, isoämyl-, and 1-methylbutylmagnesium bromides.

One case of similar reduction by a Grignard reagent in the absence of excess magnesium is reported by Bachmann,[29] who found that triphenylmethylmagnesium bromide reduces aromatic ketones to the corresponding pinacols. The reaction proceeds through the intermediate formation of free radicals, as shown by the intense coloration of the reaction mixture, and the isolation of triphenylmethyl as the oxidation product in the form of the peroxide. His results are summarized in Table VIII.

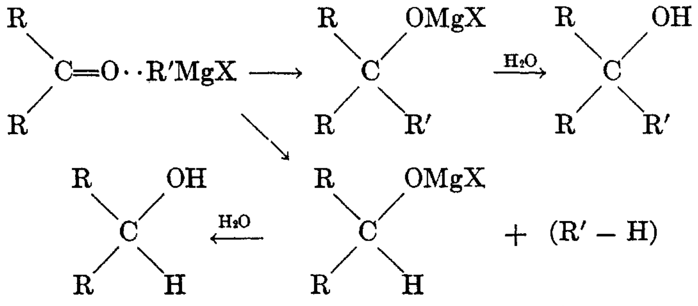
TABLE VIII

REDUCTION OF KETONES BY TRIPHENYLMETHYLMAGNESIUM BROMIDE (BACHMANN[29])

KETONE	REDUCTION (%)
Benzophenone	93
4-Chlorobenzophenone	78
4-Phenylbenzophenone	86
4,4′-Diphenylbenzophenone	98
Fluorenone	80
Xanthone	84

DISCUSSION

A brief discussion of some of the hypotheses which have been advanced to explain the reducing action of Grignard reagents is in order. Hess and Rheinbolt[30] postulate the following "mechanism":



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[26] BARNETT, COOK, AND NIXON, *J. Chem. Soc.*, **1927**, 505.

[27] HATT, *ibid.*, **1927**, 898; **1929**, 1623.

[28] DAVIES, DIXON AND JONES, *ibid.*, **1930**, 1916.

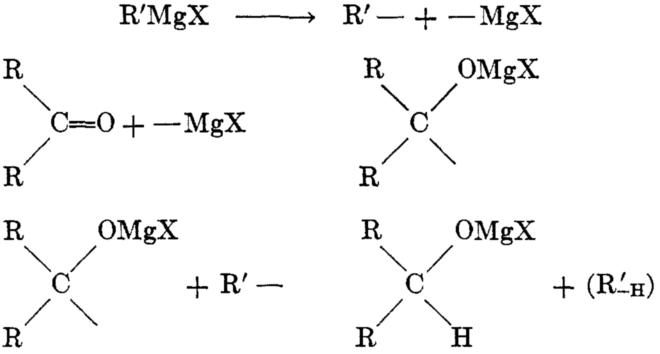
[29] BACHMANN, *J. Am. Chem. Soc.*, **53**, 2758 (1931).

[30] HESS AND RHEINBOLT, *Ber.*, **54**, 2043 (1921).

This of course is nothing more than a graphic record of the reaction. Furthermore, the formation of addition compounds is not a unique characteristic of those systems which exhibit the phenomenon of reduction, but is also observed in reactions which follow a normal course.[31]

Conant's[16] postulate of the reduction process as a slow one, coming into play only when the normal addition reaction is impeded because of steric influences, is illuminating and suggestive. However, it needs further elaboration, for as is demonstrated later, many reduction reactions are extremely rapid (in some cases they are practically instantaneous), while some additions are quite slow—in fact, slower than the reduction reactions.

Blicke and Powers[18] base their interpretation of the reducing action of a Grignard reagent upon the assumption that the reagent dissociates into a free organic radical and magnesium subhalide. The latter is assumed to behave like an alkali metal, and to yield, with carbonyl compounds, the corresponding ketyls. The last step in the mechanism involves intermolecular disproportionation (oxidation-reduction) of the free organic radical and the ketyl; an olefin and a secondary alcohol are thus the natural products of the reaction.



In support of this mechanism Blicke and Powers cite the observation[32] that triphenylmethylmagnesium chloride is dissociated into free radicals, and furthermore that it reduces benzophenone to benzopinacol.

There are some observations, however, which are difficult to reconcile with the above mechanism of the reducing action of Grignard reagents Thus, it would be reasonable to expect some benzopinacol when benzophenone is treated with an aliphatic Grignard reagent. Noller[20] records an unsuccessful search for the substance, an experience repeated by the present authors in numerous experiments. Furthermore, when a solution

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[31] MEISENHEIMER, *Ber.*, **54**, 1655 (1921); *Ann.*, **442**, 180 (1925).

[32] GILMAN AND FOTHERGILL, *J. Am. Chem. Soc.*, **51**, 3149 (1929).

of bromomagnesium ketyl* was treated with an excess of butylmagnesium bromide it gave no benzhydrol; recovery of the benzopinacol was quantitative. This experiment has an important bearing upon the mechanism under discussion, for it demonstrates that the absence of benzopinacol is not due to the rapid interaction of the ketyl with the Grignard reagent to yield benzhydrol. This result raises considerable doubt as to the validity of the ketyl mechanism in reduction by Grignard reagents. Furthermore, in the absence of any experimental evidence for the dissociation of Grignard reagents into free radicals, except in organomagnesium compounds of the triarylmethyl type† there appears to be little justification for such an assumption. On the other hand, a mechanism for the reduction process based on a type of dissociation which has been adequately demonstrated experimentally, namely, dissociation into a negative organic ion and a positive halomagnesium ion, is in the authors' estimation, more defensible, for it is in full accord with the experimental facts.

This mode of dissociation of the Grignard reagent may lead to a normal addition reaction, or, if other factors tend to hinder addition, the negative ion may stabilize itself in a manner characteristic of all organic oxidation-reductions namely, through the loss of a pair of electrons to the acceptor molecule. The detailed steps involved in this transfer need not concern us at this time.

This picture of the reduction process implies a relationship between the reducing activity of the Grignard reagent and the affinity of the organic radical for electrons, *i.e.*, its electronegativity.[33] From an inspection of the data collected by previous workers it can be seen that only Grignard reagents containing radicals of intermediate electronegativity cause reduction; no reduction appears to be exhibited with the strongly electronegative (aromatic) or the weakly electronegative radicals, with the exception of the very weakly electronegative triphenylmethyl radical. In the last case free-radical dissociation probably takes place, and the reduction product is, as might be expected, exclusively benzopinacol.

It is difficult, however, to draw unqualified conclusions from the available data for several reasons, most important of which is the difference in the experimental techniques employed by various investigators. Thus,

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* Gomberg and Bachmann, *op. cit.*, have shown that halomagnesium pinacolate, as evidenced by its intense red color, and its reduction with iodine, oxygen, etc., is dissociated to a large extent into the ketyl. The pinacolate was prepared by adding the equivalent amount of *n*-butylmagnesium bromide to a solution of benzopinacol in ether.

† Theoretically, triarylmethyl Grignard reagents, as contrasted with aliphatic and aromatic, would be expected to dissociate into free radicals.

[33] Kharasch and Reinmuth, *J. Chem. Educ.*, **5**, 404 (1928); **8**, 1703 (1931); Kharasch, Reinmuth, and Mayo, *ibid.*, **11**, 82 (1934); **13**, 7 (1936).

for the purpose of testing the hypothesis advanced, it was necessary to study the behavior of a wide variety of Grignard reagents toward a typical ketone under carefully controlled experimental conditions. Benzophenone was chosen for the following reasons: first, a considerable amount of work had already been done on this compound; second, it does not enolize; and third, the product of reduction, the halomagnesium salt of benzhydrol, is insoluble in ether. Before proceeding with this study it was necessary to determine the effect of variations in the experimental conditions upon the yield of the reduction product.

Temperature appears to exert no great influence on the yield of benzhydrol in the reaction between benzophenone and *n*-butylmagnesium bromide. Even at −80° the reaction is very fast, and a 48.5% yield of benzhydrol was obtained. At 0° and at 20° the yields of benzhydrol were 58.0 and 58.6% respectively. This is in agreement with Noller's[20] experiments in which a 59% yield of benzhydrol was obtained at 0 to 5°. Rheinbolt and Roleff[14] have noted a slight temperature effect in the reactions between several Grignard reagents and benzaldehyde.

Order of addition likewise appeared to have little effect on the reduction. In all experiments here reported the procedure of Noller[20] was followed. The benzophenone, dissolved in dry benzene, was added at a uniform rate to an approximately 10% excess of a standardized solution of the Grignard reagent at such a rate that the temperature remained between 10° and 20°. When the order of addition was reversed in the reaction between *n*-butylmagnesium and benzophenone, a 63.6% yield of benzhydrol was obtained. Meisenheimer[34] and Marshall[35] have shown that reaction between aldehydes and Grignard reagents leads to reduction if an excess of the aldehyde is used, but the reduction follows a different course. The halomagnesium alcoholate, which is formed by addition of the Grignard reagent to the aldehyde, reduces the excess of aldehyde to the corresponding primary alcohol, and is simultaneously oxidized to the corresponding ketone. However, the treatment of *n*-butylmagnesium bromide with an excess (10%) of benzophenone resulted in no significant increase in reduction to benzhydrol.

The effect of solvents other than the usual benzene-ether mixture, was determined in the following way. The ether was distilled from a filtered solution of *n*-butylmagnesium bromide, and the residue was heated at 100° *in vacuo* for four hours to remove the last traces of ether. The hard, gray residual mass was broken up as well as possible, suspended in dry benzene, in which it is insoluble, and the calculated amount of benzophenone, dissolved in benzene, was added in the usual manner. A 64.5%

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[34] MEISENHEIMER, *Ann.*, **446**, 76 (1925).

[35] MARSHALL, *J. Chem. Soc.*, **1925**, 2184.

yield of benzhydrol was obtained. To a similarly prepared "anhydrous" reagent pyridine was added. Considerable heat was evolved, and a yellow pyridine complex separated. Addition of solid benzophenone, in small portions, resulted in an 80% yield of benzhydrol.

In our usual procedure the concentration of Grignard reagent varied between one and two molar. In order to determine the effect of varying concentration benzophenone was added to a solution of *n*-butylmagnesium bromide of about one-tenth the usual concentration (0.141 *N*). After correction for the slight solubility of the bromomagnesium alcoholate in ether a yield of 38–45% benzhydrol was obtained.

The results in a study of benzophenone with a series of Grignard reagents ranging in the electronegativities of their radicals from phenyl to tertiary butyl are shown in Table IX. The Grignard reagents were prepared in the ordinary manner, but no catalyst was used in initiating the reaction. For details of the experimental procedure see the experimental part.

TABLE IX

ACTION OF VARIOUS GRIGNARD REAGENTS ON BENZOPHENONE

GRIGNARD REAGENT	NORMALITY	REDUCTION (%)	ADDITION (%)
C_6H_5MgBr	1.98	0	90
$C_6H_5CH_2MgCl$	1.04	0	95
$C_6H_5CH_2MgBr$	1.54	0	52
p-$ClC_6H_4CH_2MgCl$	0.475	0	74
tert.-C_4H_9MgCl	0.880	0	63
$CH_2:CHCH_2MgBr$	1.32	5	72
cyclo-$C_6H_{11}MgBr$	1.44	7.1	—
$C_6H_5(CH_2)_3MgBr$	1.28	20.0	38.5
$C_6H_5(CH_2)_2MgBr$	1.66	32.6	43.2
n-C_4H_9MgBr	1.41	58.6	—
n-C_4H_9MgCl	1.83	76.2	—
i-C_4H_9MgBr	1.86	91.0	—
cyclo-C_5H_9MgBr	1.86	94.0	—

These results have confirmed our previous observation that reduction occurs only with radicals of intermediate electronegativity. While, superficially, these data might seem to indicate that no correlation between the reducing action and the electronegativity of a group exists, it must be borne in mind that the normal addition reaction is proceeding simultaneously with the reduction, and therefore that the relative reaction velocities must be considered. From a theoretical standpoint it would be expected that weakly electronegative radicals, in consequence of their relatively great electron-sharing tendency, would add with relatively high velocity. Thus, while the reducing tendency is enhanced with decreasing electron affinity, the increase in addition velocity may be even greater, proportionately, with the result in the cases of very weakly electronegative radicals, of the complete overshadowing of the reducing tendency by the relatively greater addition speed.

A search of the literature reveals only two studies of reaction rates in the addition of Grignard reagents. Gilman[36] and collaborators have determined the time required for complete addition of a series of Grignard reagents to azobenzene by means of the color test devised by Gilman and Schulze.[37] More recently Vavon[38] has determined the velocities of addition of several Grignard reagents to butyl benzoate. Both of these investigations point to correlation between the addition speed of a Grignard reagent and its electronegativity. Because ordinary reaction-rate studies are experimentally impossible in the reactions between Grignard reagents and ketones on account of their relatively high velocity, the authors have resorted to competition experiments in which an equimolar mixture of two Grignard reagents is allowed to react with one mole of benzophenone. The hypothesis outlined leads to the conclusion that the reagent containing the less electronegative organic radical should react with the larger proportion of the ketone. The results of these experiments have confirmed the prediction.

When one equivalent of benzophenone was added to a solution containing one equivalent each of *n*-butylmagnesium bromide and benzylmagnesium chloride no reduction occurred and a 65% yield of benzyldiphenylcarbinol was obtained. No benzhydrol was isolated in spite of the fact that the experimental method is capable of detecting as little as a few per cent. In a similar experiment with *n*-butylmagnesium bromide and phenylmagnesium bromide reduction occurred to the extent of 43%, and no triphenylcarbinol could be isolated. With an equimolar mixture of phenylmagnesium bromide and benzylmagnesium chloride, benzyldiphenylcarbinol was obtained in greater than 75% yield, but no triphenylcarbinol could be detected. Whereas isobutylmagnesium bromide itself reduces benzophenone to the extent of 91%, a mixture of the former with *tert.*-butylmagnesium chloride yielded only *tert.*-butyldiphenylcarbinol, and no reduction was observed. In another experiment, after the addition of benzophenone to a mixture of phenylmagnesium bromide and *tert.*-butylmagnesium chloride, carbon dioxide was passed into the solution. A yield of 91% of benzoic acid, calculated on the basis of the phenylmagnesium bromide used, was obtained. This indicates that little, if any, of the phenyl Grignard reagent added to the benzophenone in the presence

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[36] Gilman, Heck, and St. John, *Rec. trav. chim.*, **49**, 212 (1930).

[37] Gilman and Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

[38] Vavon, Barbier, and Thiebaut, *Bull. soc. chim.*, [5], **1**, 806 (1934).

of *tert.*-butylmagnesium chloride. Finally, benzophenone was treated with a mixture of phenylmagnesium bromide and a Grignard reagent of a more electronegative radical, namely, α-naphthylmagnesium bromide. In this experiment, a 76% yield of triphenylcarbinol was obtained, and steam-distillation of the reaction mixture after hydrolysis yielded 71% of naphthalene.

These competition experiments clearly indicate a definite relationship between the electronegativity of a group and its speed of addition in the Grignard reaction. Indeed the apparent one-sidedness of these reactions is all the more striking, since the more reactive of the two reagents is constantly being used up through addition to the ketone, thus leaving a preponderance of the less reactive reagent in solution. If the radicals studied in these orientation experiments are arranged in the order of their addition velocities the following series is obtained: *tert.*-butyl > benzyl > isobutyl > *n*-butyl > phenyl > α-naphthyl. This order is without exception the same as the order obtained when the radicals are arranged according to increasing electronegativity. The striking agreement between the two properties could hardly be considered a result of pure chance.

TABLE X

CORRELATION BETWEEN ELECTRONEGATIVITY AND REDUCING ACTIVITY OF GRIGNARD RADICALS

(Alkylmagnesium Halides + Benzophenone)

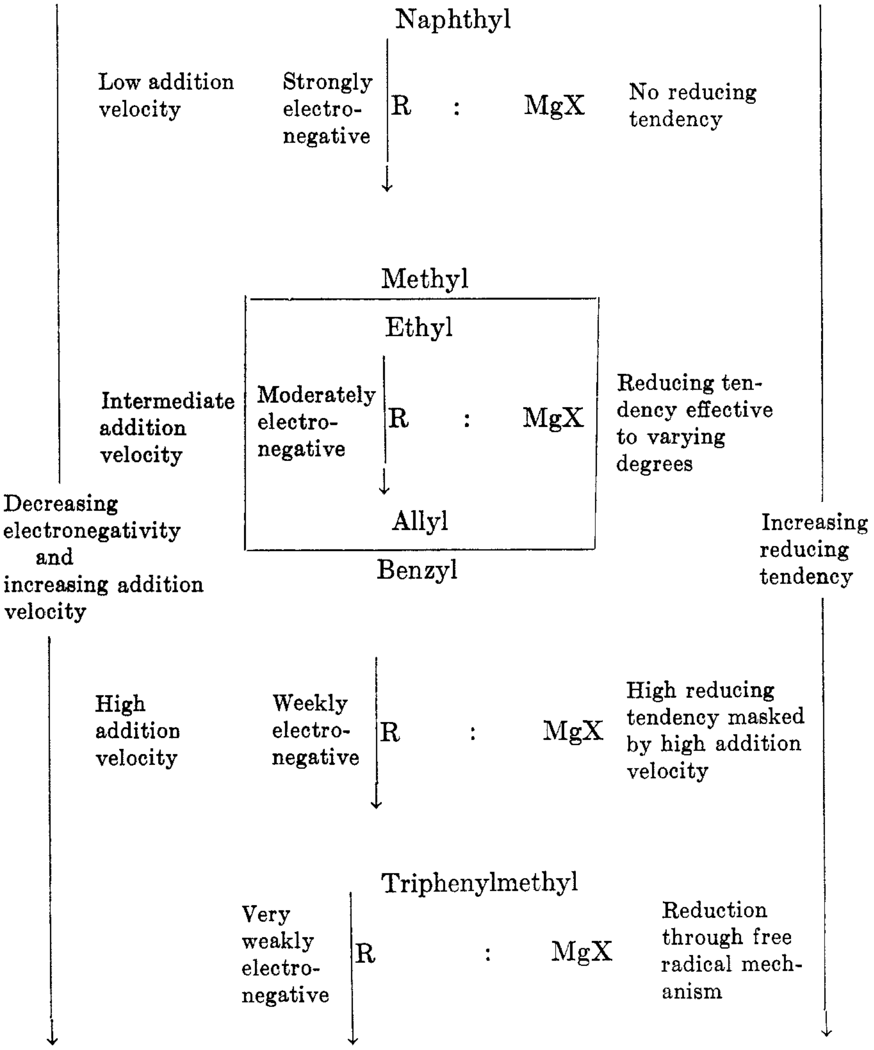
RADICAL	REDUCTION (%)
C_2H_5-	2
n-C_3H_7-	58
n-C_4H_9-	59
i-C_4H_9-	91
cyclo-C_5H_9-	94
sec.-C_4H_9-	40
i-$C_5H_{11}-$	30
$C_6H_5(CH_2)_2-$	33
$C_6H_5(CH_2)_3-$	20
cyclo-$C_6H_{11}-$	7
$CH_2{:}CHCH_2-$	*ca.* 5

With the results of these orientation experiments in mind, the reader will see more clearly in Table X the interesting relationship between the relative electronegativity of a group and its reducing tendency.

It will be noticed upon inspection of the table that as the electronegativity is decreased, the percentage of reduction increases to a certain point and then progressively falls off. This behavior is ascribed, not to a reducing tendency which increases and then decreases, but to a constantly increasing reducing tendency, on which is superimposed a more rapidly increasing addition velocity.

FIGURE 1

Schematic Correlation of Radical Electronegativities with Addition-Reduction Tendencies of Grignard Reagents as Exhibited toward Benzophenone



As a basis for predicting the behavior of a particular Grignard reagent, we may establish four classifications:

One: Those reagents containing strongly electronegative radicals, for which the addition velocity is small, but in which the reducing tendency is absent.

Two: Those reagents containing radicals of intermediate electronegativity, which add and reduce in varying proportions.

Three: Those reagents containing weakly electronegative radicals with strong reducing tendencies, which are, however, completely masked by very great addition velocities.

Four: Those reagents containing very weakly electronegative radicals which exhibit the phenomenon of free-radical dissociation and give rise to a somewhat different type of reduction.

Only radicals which fall into groups two and four will cause reduction. If the triarylmethyl Grignard reagents are excluded it may be said that that reagents containing radicals either more electronegative than ethyl, or less electronegative than allyl, will not exhibit this property. Although this study has been restricted to only one ketone, the foregoing literature survey indicates that the above predictive generalizations would hold in the reactions of Grignard reagents with other ketones, except for the possibility of minor shifts in the dividing lines between the various groups.

EXPERIMENTAL PART

The Grignard reagents were prepared in a special three-necked flask, into the bottom of which was sealed a sintered glass disc and a vertical tube which could be closed by means of a stopcock. The design of the flask allowed easy, quick filtration of the reagent by means of dry nitrogen pressure through the sintered glass filter.

The anhydrous ether was prepared by washing the commercial product with dilute potassium permanganate solution until there was no further decolorization; then with water. The ether was dried successively with calcium chloride and sodium, and distilled from the sodium into a dark stock bottle, in which it was kept over sodium wire. Unless otherwise indicated, the chemicals used were obtained from the Eastman Kodak Co., and purified by distillation or crystallization immediately before using.

Approximately six moles of ether was used for each mole of halide, and the following procedure was adopted. One-third the required quantity of ether was poured into the flask onto about a 10% excess of magnesium turnings (commercial variety), the rest of the ether being used to dissolve the halide. A few cubic centimeters of the halide solution was added dropwise from a dropping funnel, and when the reaction was slow in starting the solution was warmed gently with a micro burner. When reaction began the remainder of the halide, dissolved in ether, was added at such a rate that the ether was kept gently refluxing without external application of heat.

After addition of the halide was completed, the solution was refluxed with continued stirring for a half-hour, and then allowed to cool. The Grignard reagent was filtered through the sintered glass disc by means of dry nitrogen pressure into a graduated Erlenmeyer flask and a 2-cc. aliquot was removed for titration. The flask was then fitted with a thermometer and dropping funnel. The required amount of benzophenone, dissolved in approximately twice its weight of dry benzene, was placed in the dropping funnel and the flask was cooled in ice. When the temperature reached 10° the ketone was added dropwise at such a rate that the temperature remained between 10 and 20°. During addition the contents of the flask were stirred by swirling the flask vigorously.

Addition of benzopinacol to n-*butylmagnesium bromide.*—To 100 cc. of a 1.77 *N* solution of *n*-butylmagnesium bromide was added 16.0 g. (.044 mole) of benzopinacol with stirring. The deep violet color of the "ketyl" appeared, and part of the salt separated, but redissolved on the addition of 25 cc. of benzene. After the clear violet solution had stood for four hours it was hydrolyzed by pouring into dilute hydrochloric acid, and the mixture was extracted four times with 25-cc. portions of ether. The colorless residue left after evaporation of the solvent was extracted twice with 10-cc. portions of cold alcohol to remove any benzhydrol. The residue, melting at 175–178°, weighed 13.3 g. Evaporation of the alcohol extract yielded 0.1 g. of residue melting at 168°. No benzhydrol was isolated.

Effect of temperature in the addition of benzophenone to n-*butylmagnesium bromide.*—A 1.77 *N* solution of *n*-butylmagnesium bromide was divided into three 100-cc. portions which were treated in the following ways.

(1) Eighteen grams of benzophenone was added in the usual manner while the temperature was kept between 10 and 20°. Immediately upon addition of the ketone a violet-red color appeared, and before addition was complete, the insoluble bromomagnesium alcoholate began to precipitate. When addition was complete, the mixture was allowed to stand for about a half-hour at room temperature, and then filtered quickly through a 7.5-cm. Buchner funnel. The precipitate was washed with three 10-cc. portions of anhydrous benzene, then transferred quickly back to the flask and hydrolyzed with dilute hydrochloric acid. The hydrolysate was then extracted three times with ether, and the combined ether extracts were evaporated to dryness on the steam bath. The solid residue was dried in a vacuum desiccator. Yield of benzhydrol (m.p., 64–65°), 10.6 g., 58.6%.

(2) The procedure followed was exactly the same as for (1), except that the temperature during addition was kept between −5° and 0° by means of an ice-salt mixture. Yield of benzhydrol (m.p. 63–65°), 10.5 g., 58.0%.

(3) The procedure was the same as for (1) and (2) except that the temperature was kept at −80° with solid carbon dioxide. In this case, the mixture was not allowed to warm up to room temperature, but was filtered immediately after addition. Yield of benzhydrol (m.p. 64–65°), 8.8 g., 48.5%.

Effect of reversal of addition.—A 100-cc. portion of a 1.77 *N* solution of *n*-butylmagnesium bromide was filtered directly into a dropping funnel and added in the usual manner to a solution of 18.0 g. of benzophenone in 40 cc. of dry benzene. Working up of the precipitate in the above-described manner yielded 11.5 g. (63.6%) of benzhydrol (m.p. 62–64°).

Effect of excess benzophenone.—To 50 cc. of a 1.41 *N* solution of *n*-butylmagnesium bromide was added 14.3 g. (0.079 mole) of benzophenone in 30 cc. dry benzene. Working up in the usual way, 9.3 g. of benzhydrol (m.p. 62–64°) was obtained. Yield, 64.3%.

Effect of concentration of the Grignard reagent.—Ten cubic centimeters of a 1.41 *N* solution of *n*-butylmagnesium bromide was diluted to 100 cc. and 2.1 g. of benzophenone dissolved in 5 cc. of benzene was added in the usual way. A total of 0.8 g. of benzhydrol (m.p. 63–65°) was isolated. After correction for the slight solubility of the bromomagnesium salt of benzhydrol in ether, the yield was estimated to be between 38 and 45%.

Addition of benzophenone to n-*butylmagnesium bromide in benzene.*—After several unsuccessful attempts to prepare the Grignard reagent in benzene, the following method was finally adopted to obtain an ether-free Grignard reagent. A 1.70 *N* solution of *n*-butylmagnesium bromide in ether (75 cc.) was transferred to a 200-cc. round-bottomed flask, and the ether was evaporated under reduced pressure. The last traces of ether were then removed by heating the flask for four hours at 100° *in vacuo*. The gray amorphous residue showed some tendency to sublime during heating. The flask was then cooled, 75 cc. of anhydrous benzene was added, and the hard mass was broken up as well as possible with a stirring rod. While the flask was cooled in ice, 15.0 g. of benzophenone, dissolved in 30 cc. of dry benzene, was added at a slow, regular rate. The usual red color appeared and a heavy, white precipitate formed. The mixture was allowed to stand one hour, then filtered, and the residue was hydrolyzed with dilute acid. After extraction with ether and working up of the extract as usual, 9.80 g. of benzhydrol (m.p. 64–65°) was obtained. Yield, 64.5%.

Addition of benzophenone to n-*butylmagnesium bromide in pyridine.*—To a similarly prepared "anhydrous" reagent was added 75 cc. of dry pyridine. A great deal of heat was liberated in this process and considerable care was required to prevent the reagent from becoming too hot. This was accomplished by adding the pyridine slowly in small portions with continuous cooling and stirring. The solution took on a deep yellow color and a lemon-yellow pyridine complex separated. To this well-stirred suspension was added 15.0 g. of benzophenone in small portions, while ice-bath cooling was continued. A momentary green coloration developed on the addition of each portion of benzophenone. After about an hour's standing the mixture was hydrolyzed with dilute sulfuric acid, enough acid being added to give a red color when tested with methyl orange. Extraction with ether and evaporation of the solvent yielded 12.2 g. (80.0%) of benzhydrol (m.p. 64–65°).

Addition of benzophenone to benzylmagnesium chloride.—Benzophenone (45.5 g.) was added to 300 cc. of a 1.04 *N* solution of benzylmagnesium chloride. A momentary violet coloration developed after each addition of benzophenone, but after completion of addition no precipitate had formed and the solution was a faint green in color. After standing a half-hour, the solution was hydrolyzed, extracted with ether, and the ether was evaporated. The residue was crystallized from 95% alcohol. The first crop yielded 57 g. of colorless crystals; m.p. 87.5–88.5°. Upon working up the mother liquor an additional lot of 6.1 g. (m.p. 85–87°) was isolated. Total yield of benzyldiphenylcarbinol, 95%.

Addition of benzophenone to benzylmagnesium bromide.—The procedure followed was the same as for the chloride. No precipitate of the bromomagnesium benzhydrylate appeared, and a 52% yield of benzyldiphenylcarbinol was obtained; m.p. 85–87°.

Addition of benzophenone to p-*chlorobenzylmagnesium chloride.*—Benzophenone (7.0 g.) in 15 cc. of dry benzene was added to .038 moles of a 0.475 *M* solution of *p*-chlorobenzylmagnesium chloride. The usual momentary red color was exhibited and a white precipitate formed. This was filtered and worked up as usual. The solid product obtained was recrystallized from hot 95% alcohol. Yield 8.8 g.; m.p. 116.5–117.5°. One recrystallization from alcohol raised the melting point to 117.5–118.5°, at which point it remained constant upon further recrystallization.

Analysis for Cl: Found, 11.25%, Calc'd for *p*-chlorobenzyldiphenylcarbinol, 11.49%.

Addition of benzophenone to tert.-*butylmagnesium chloride.*—Because of the abnormally low yield of Grignard reagent obtainable by the use of *tert.*-butyl bromide (about 25%), the chloride was used. Average yields of 60% were obtained with this reagent. To 185 cc. of a 0.880 *N* solution of *tert.*-butylmagnesium chloride 30 g.

of benzophenone was added in the usual manner. The usual red coloration appeared, but no precipitate formed. After a half-hour's standing the clear solution was hydrolyzed and worked up in the usual way. The product obtained was a viscous yellow oil, which distilled at 160–162° under a pressure of 5 mm. After a second distillation 23.8 g. of a colorless oil having a refractive index of 1.5722 was obtained. (*tert.*-Butyldiphenylcarbinol: b.p. 178–180°/11 mm.; n_D^{15} 1.5731.)[39] Yield, 63%.

Addition of benzophenone to allylmagnesium bromide.—Benzophenone (18.2 g.) was added in the usual way to 100 cc. of a 1.32 *N* solution of allylmagnesium bromide. No precipitate formed. The red solution was hydrolyzed, and after working up, the oily product was distilled under reduced pressure. Yield of allyldiphenylcarbinol (b.p. 150–155°/3 mm.), 72%. A small amount of yellow, gummy matter remained in the flask after distillation. This was washed out with acetone, and the acetone was evaporated. The gum was taken up in hot alcohol and on cooling 0.6 g. of white crystals was obtained; m.p. 105–106°. Recrystallization from alcohol raised the melting point to 107–109°. This substance was shown by means of a mixture melting-point determination to be dibenzhydryl ether;[40] m.p. 108–109°.

Oxidation of allyldiphenylcarbinol.—A sample (2.2 g.) of the product obtained in the above reaction was refluxed with 4.2 g. of potassium permanganate in 80 cc. of water until the color of the permanganate was discharged. The solution was filtered from manganese dioxide and the filtrate was extracted with ether. Acidification of the aqueous portion yielded a flocculent white precipitate which was filtered, washed with water, and dried; m.p. 208–209°. (Melting point of β-hydroxy-ββ-diphenylpropionic acid, 212°.)[41]

Addition of benzophenone to cyclohexylmagnesium bromide.—Benzophenone (21.0 g.) dissolved in 40 cc. of anhydrous benzene was added to 110 cc. of a 1.44 *N* solution of cyclohexylmagnesium bromide in the usual manner. The usual red coloration appeared, and near the end of the addition a small amount of precipitate formed. After a half-hour's standing the solution was filtered, and the precipitate and the filtrate were hydrolyzed and worked up separately. The precipitate yielded 1.70 g. (7.1%) of benzhydrol (m.p. 59–61°). The filtrate yielded a colorless oil with a pronounced camphor-like odor. On distillation under reduced pressure a considerable quantity of water was given off and 21.5 g. of distillate was collected, over a range of 150 to 220° at 8 mm. All attempts to crystallize this product were unsuccessful.

Preparation of γ-phenylpropyl bromide.—Cinnamic (cinnamyl) alcohol (134 g.) was treated with hydrogen under a pressure of three atmospheres in the presence of a Raney nickel catalyst. Absorption of hydrogen was very rapid. The reduction was continued until hydrogen absorption ceased (about four and a half hours). The product was then distilled under reduced pressure, the fraction boiling at 124–125°/15 mm. being collected. Yield, 118 g., 87%.

A 68-g. lot of the hydrocinnamic alcohol so obtained was refluxed for two hours with 170 g. (2 moles) of a 48% aqueous solution of hydrogen bromide. After cooling, the two layers were separated; the bromide layer was washed with concentrated hydrochloric acid, then with cold water, and finally was dried with anhydrous sodium sulfate. The product was then fractionated under reduced pressure; b.p. 108–109°/11 mm.; yield, 69.6 g. (70%).

Addition of benzophenone to γ-phenylpropylmagnesium bromide.—To 100 cc. of a

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[39] Ramart-Lucas, *Compt. rend.*, **154**, 1088 (1912).

[40] Knoevenagel and Heckel, *Ber.*, **36**, 2827 (1903).

[41] Rupe and Busolt, *ibid.*, **40**, 4538 (1907).

1.28 *N* solution of γ-phenylpropylmagnesium bromide (obtained in 86% yield) was added 18.0 g. of benzophenone. The precipitate was filtered, and the precipitate and filtrate were hydrolyzed separately. The precipitate yielded 3.60 g. (20.0%) of benzhydrol; m.p. 59–61°. The filtrate yielded 11.5 g. of a crystalline product melting at 68–72°. Recrystallization from alcohol, and then from ligroïn, raised the melting point to 74–75°. Yield of γ-phenylpropyldiphenylcarbinol, 38.5%.

Dehydration of γ-phenylpropyldiphenylcarbinol.—A 1.0 g. lot of the product was dissolved in 50 cc. of dry benzene, and an excess of phosphoric anhydride was added. The mixture was heated to its boiling point on the water bath for 30 minutes and then allowed to cool. The solution was then filtered from the P_2O_5 and the benzene was evaporated. The colorless dehydration product melted at 122–123° (1,1,4-Triphenylbutene-1, m.p. 122–124°).[42]

Preparation of phenethyl (β-phenylethyl) bromide.—Phenethyl (β-phenylethyl) alcohol (75 g.) was refluxed for two hours with 285 cc. of 48% hydrobromic acid (mol. ratio, 1:4). After cooling, the upper bromide layer was washed with cold water, dried with anhydrous sodium sulfate, and fractionated; b.p. 109–110°/24 mm. Yield, 86 g. (76%).

Addition of benzophenone to phenethylmagnesium bromide.—Addition of 25 g. of benzophenone to 110 cc. of a 1.66 *N* solution of phenethylmagnesium bromide (obtained in 92% yield) resulted in the isolation of 8.2 g. of benzhydrol (m.p. 58–61°); yield 32.6%.

Hydrolysis of the filtrate yielded 14.5 g. of a solid crystalline product, which after recrystallization from alcohol melted at 85–86°. (Phenethyldiphenylcarbinol, m.p. 85–87°.)[43]

Addition of benzophenone to n*-butylmagnesium chloride.*—A 25 g. lot of benzophenone in 40 cc. of dry benzene was added to 80 cc. of a 1.46 *N* solution of *n*-butylmagnesium chloride. The usual red coloration appeared, and precipitation began immediately. Recovery in the usual way yielded 20.6 g. of benzhydrol (m.p. 62–64°); 76%.

Addition of benzophenone to isobutylmagnesium bromide.—Benzophenone (13.0 g. in 20 cc. dry benzene) was added to 36 cc. of a 1.86 *N* solution of isobutylmagnesium bromide. The precipitate yielded 12.0 g. (91%) of benzhydrol; m.p. 62–64°.

Addition of benzophenone to cyclopentylmagnesium bromide.—The cyclopentylmagnesium bromide was prepared by the usual Grignard procedure, which resulted in a 93.5% yield of the reagent. The cyclopentyl bromide was prepared by the following series of reactions, according to the method of Adams:[44] cyclohexanol → adipic acid → cyclopentanone → cyclopentanol → cyclopentyl bromide. To 100 cc. of a 1.86 *N* solution of the reagent was added 25 g. of benzophenone in 40 cc. of dry benzene. The usual procedure for working up the reduction product yielded 23.5 g. (91%) of benzhydrol; m.p. 61–63°.

Addition of benzophenone to a mixture of n*-butylmagnesium bromide and benzylmagnesium chloride.*—A solution containing 0.084 mole of each of the two Grignard reagents was made up to 100 cc. with ether, and 14.0 g. of benzophenone (0.077 mole) in 30 cc. of dry benzene was added at a slow, uniform rate. Although the usual red coloration appeared, no precipitate formed. After standing a half-hour, the solution was hydrolyzed, extracted with ether, and the ether was evaporated. The

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[42] WOOSTER AND RYAN, *J. Am. Chem. Soc.*, **54**, 2419 (1932).

[43] PATERNO AND CHIEFFI, *Gazz. chim. ital.*, **39**, II, 423 (1909).

[44] ADAMS AND NOLLER, *J. Am. Chem. Soc.*, **48**, 1080 (1926).

crystalline residue was recrystallized from 95% alcohol, yielding 11.9 g. of a colorless product melting at 82–84°. Recrystallization from ligroïn raised the melting point to 87–88°. Yield of benzyldiphenylcarbinol, 56%. No benzhydrol could be isolated.

Addition of benzophenone to a mixture of phenyl- and n-*butylmagnesium bromides.*—To 100 cc. of a solution containing 0.084 mole of each of the two Grignard reagents was added 14.0 g. of benzophenone in 30 cc. dry benzene. After standing one-half hour, the solution was filtered, and the precipitate and filtrate were hydrolyzed and worked up separately. The precipitate yielded 4.6 g. (33%) of benzhydrol (m.p. 61–64°). No triphenylcarbinol could be isolated from the hydrolysis products of the filtrate.

Addition of benzophenone to a mixture of phenylmagnesium bromide and benzylmagnesium chloride.—A 14.0 g. lot of benzophenone in 30 cc. dry benzene was added to 100 cc. of a solution containing .084 mole of each Grignard reagent. After exhaustive fractional crystallization of the reaction product, 16.7 g. (a 79% yield) of benzyldiphenylcarbinol (m.p. 88.0–88.5°) was obtained. No triphenylcarbinol could be isolated.

Addition of benzophenone to a mixture of isobutylmagnesium bromide and tert.-*butylmagnesium chloride.*—Thirteen grams (.072 mole) of benzophenone in 25 cc. of benzene was added to 100 cc. of a solution containing .080 mole of each of the two Grignard reagents. The usual red coloration appeared during addition, but no precipitate formed, indicating that no reduction had occurred.

Addition of benzophenone to a mixture of phenylmagnesium bromide and tert.-*butylmagnesium chloride.*—Eleven grams of benzophenone in 20 cc. of dry benzene was added to 100 cc. of a mixture containing .069 mole of each Grignard reagent. After completion of addition the clear red solution was carbonated with powdered solid carbon dioxide. After standing one hour the solution was hydrolyzed with dilute hydrochloric acid, and extracted with four portions of ether. The ether extract was then shaken with three 25-cc. portions of dilute sodium hydroxide solution, and the aqueous extract was acidified by the addition of dilute hydrochloric acid. The white precipitate was filtered and dried; m.p. 118–120°; weight 6.0 g. Concentration of the mother liquor yielded another crop of crystals weighing 1.9 g.—a total of 7.9 gms. of benzoic acid, corresponding to a yield of 94%.

Addition of benzophenone to a mixture of phenyl- and α-naphthylmagnesium bromides.—Benzophenone (16.4 g. in 30 cc. of dry benzene) was added to 110 cc. of a mixture containing 0.100 mole of each Grignard reagent. The semi-solid residue obtained by the usual method of recovery was steam-distilled. After cooling, the solid residue from the steam-distillation was extracted and the extract was allowed to crystallize from a mixture of benzene and ligroïn; 13.3 g. of triphenylcarbinol, (m.p. 159–160°) was obtained. Fractional crystallization of the mother liquor yielded an additional 4.5 g. of triphenylcarbinol—a total yield of 76%. Further fractionation of the mother liquor yielded 0.7 g. of α-naphthyldiphenylcarbinol (m.p. 135–136°). From the distillate, 9.1 g. (a yield of 71%) of naphthalene was obtained.

SUMMARY

1. The literature pertaining to the reducing action of Grignard reagents has been reviewed.

2. A study of the behavior of a series of Grignard reagents containing

radicals of a considerable electronegativity range (from α-naphthyl to *tert.*-butyl) reveals that reduction is caused only by radicals of intermediate electronegativity.

3. The effect of experimental conditions upon the reducing action of Grignard reagents has been evaluated.

4. A study of the velocities of addition of a series of Grignard reagents to benzophenone shows that rate of addition increases with decreasing electronegativity of the radical.

[Contribution from the Laboratories of the University of Buffalo]

THE REACTION OF BENZOYL CHLORIDE WITH CERTAIN ALIPHATIC ORTHO ESTERS AND ACETALS

HOWARD W. POST

Received March 5, 1936

The literature already contains the report of work on the action of benzoyl chloride on several orthoformates and acetals.[1] The products of the reaction were ethyl formate, ethyl benzoate and an ethyl halide when ethyl orthoformate was used, and analogous products were obtained from the acetal. The reactions were carried out, not with the pure ortho compounds, but with these compounds in the presence of magnesium or zinc iodide and the resultant alkyl halide was not the chloride but rather the iodide. The mechanism which was assumed for the reaction as well as the structure which the author assigned to the double compound seemed out of agreement with more recent work and it was therefore considered worth while to reopen the question and if possible to study the course of the reaction in more detail.

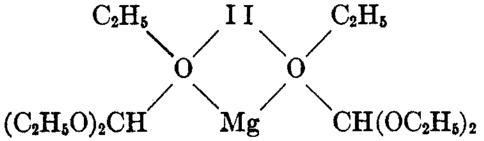
Blaise[1] assumed a direct action of benzoyl chloride on the double compound of magnesium iodide and ortho ester, a third-order reaction as written, by which seven molecules of products were formed.

$$[HC(OC_2H_5)_3]_2[MgI_2] + 2C_6H_5COCl = MgCl_2 + 2C_2H_5I + 2C_6H_5COOC_2H_5 + 2HCOOC_2H_5$$

$$[CH_2(OC_2H_5)_2]_2[ZnI_2] + 2C_6H_5COCl = ZnCl_2 + 2C_6H_5COOC_2H_5 + 2C_2H_5OCH_2I$$

Furthermore this mechanism did not take into account the possibility of a reaction taking place between benzoyl chloride and the zinc or magnesium iodide, as shown by Kishner.[2]

The double compound which he postulated contained tetravalent oxygen in a sense that would in all probability not be approved by modern proponents of the electronic theories of molecular structure:



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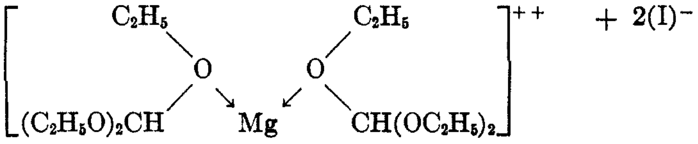
[1] E. E. Blaise, *Compt. rend.*, **139**, 1211 (1904); **140**, 661 (1905).

[2] Kishner, *Chem. Zentr.*, **1909**, II, 1132; Beilstein, Prager, Jacobson, "Handbuch der organischen Chemie," 4th Ed., Vol. IX, p. 195.

It would seem much more logical in view of the more modern concepts to write the formula of the above compound, if indeed it exists at all, as:



It was decided to study the action of benzoyl chloride on an alkyl orthoformate and on an acetal in the absence of inorganic salt.

When benzoyl chloride was refluxed with *n*-propyl or *n*-amyl orthoformate the reaction which took place was analogous to that already mentioned—

$$HC(OC_3H_7\text{-}n)_3 + C_6H_5COCl = n\text{-}C_3H_7Cl + HCOOC_3H_7\text{-}n + C_6H_5COOC_3H_7\text{-}n$$

$$HC(OC_5H_{11}\text{-}n)_3 + C_6H_5COCl = n\text{-}C_5H_{11}Cl + HCOOC_5H_{11}\text{-}n + C_6H_5COOC_5H_{11}\text{-}n$$

Data were collected on the extent of the reaction of benzoyl chloride with *n*-propyl orthoformate with time by determining the amount of *n*-propyl benzoate which was formed. Then the maximum yield from this reaction was compared with that using different orthoformates. In working up the reaction mixtures, no benzoyl chloride or ortho ester were found, even though the yield of alkyl benzoate never exceeded 74%. The alkyl benzoate was separated by fractional distillation of the products of the reaction and its volume determined. The errors in the determination of alkyl benzoate were estimated at 5 to 10 per cent. Alkyl halides and formates could not be satisfactorily isolated and were not determined quantitatively. However the separation was sufficiently good to make certain that these compounds were present in the reaction mixtures.

As shown in Table I, the yield of alkyl benzoate was found to drop quite distinctly as the molecular weight of the orthoformate increased, or in other words with rise of weight of the alkyl radical used in the orthoformate.

The identity of each alkyl benzoate was determined at the end of the run during which it was first isolated (see experimental part). At the end of subsequent runs identification was limited to a determination of the boiling point and in a few cases to the refractive index in addition. In no case was any appreciable deviation in values detected.

As regards the reaction between *n*-propyl orthoformate and benzoyl chloride in the presence of magnesium iodide the results of Blaise[1] were qualitatively sustained. Large quantities of hydrohalogen gases were evolved, so much in fact that no attempt was made to evaluate the reaction or separate the products. No hydrohalogen acid was set free when magnesium iodide was omitted. Blaise makes no mention of the evolution of hydrohalogen gases.

Magnesium iodide dissolves exothermally in *n*-propyl orthoformate to a heavy red oil, quite stable at room temperatures. This oil reacted with benzoyl chloride exactly as did the mixture described in the preceding paragraph. It may be that the reaction between orthoformate, inorganic salt and benzoyl halide does proceed through the preliminary formation of an addition compound from salt and orthoformate.

Diethyl acetal reacts with benzoyl chloride as described by Blaise.[1] Di-*n*-propyl acetal has been found here to react in the same manner. Considerable polymerization was detected when formaldehyde diethyl acetal was used. Blaise stated that formaldehyde was set free by the action of water, and this might have happened to a certain extent:

TABLE I

C_6H_5COCl + ORTHOFORMATES

NO.	TIME (MIN.)	AM'T TAKEN (MOLES)	COMPOUND USED	YIELD OF BENZOATE (PER CENT.)
1	30	0.46	$HC(OC_3H_7\text{-}n)_3$	20
2	30	0.46	$HC(OC_3H_7\text{-}n)_3$	20
3	60	0.46	$HC(OC_3H_7\text{-}n)_3$	30
4	60	0.46	$HC(OC_3H_7\text{-}n)_3$	33
5	60	0.46	$HC(OC_3H_7\text{-}n)_3$	30
6	90	0.46	$HC(OC_3H_7\text{-}n)_3$	74
7	90	1.00	$HC(OC_3H_7\text{-}n)_3$	74
8	90	0.23	$HC(OC_4H_9\text{-}n)_3$	56
9	90	0.24	$HC(OC_4H_9\text{-}i)_3$	50
10	90	1.00	$HC(OC_5H_{11}\text{-}n)_3$	29

$$CH_3CH(OC_2H_5)_2 + C_6H_5COCl = C_6H_5COOC_2H_5 + CH_3CHClOC_2H_5$$

$$CH_3CH(OC_3H_7\text{-}n)_2 + C_6H_5COCl = C_6H_5COOC_3H_7\text{-}n + CH_3CHClOC_3H_7\text{-}n$$

$$CH_2(OC_2H_5)_2 + C_6H_5COCl = C_6H_5COOC_2H_5 + C_2H_5OCH_2Cl$$

$$C_2H_5OCH_2Cl + HOH = HCl + HCHO + C_2H_5OH(?)$$

A caustic soda trap was set up to catch any hydrochloric acid evolved and to provide for quantitative determination, but none was so detected, although a slight odor was evident when the trap was removed.

As will be seen from Table II, the difference in yields from diethyl and di-*n*-propyl acetals was not significant, but both of these compounds gave more satisfactory yields than did the diethyl acetal of formaldehyde.

The runs were made with an apparatus consisting of a reflux condenser leading from a three-liter flask and fitted with an outlet tube leading down into a distilling flask. The distilling flask was immersed in a bath of crystalline calcium chloride and ice by means of which a constant temperature of −5°C. was maintained. This device was used for the purpose of catching any olefinic compounds which might have been formed. The side-arm of the distilling flask led to and beneath the surface of a solution of standard sodium hydroxide of known volume for the purpose of trapping any hydrochloric acid. All stoppers were of cork, previously soaked in water-glass. No olefines were detected in quantities sufficient for analysis.

TABLE II

C_6H_5COCl + ACETALS

NO.	TIME (MIN.)	AM'T TAKEN (MOLES)	COMPOUND USED	YIELD OF BENZOATE (PER CENT.)
11	90	1.00	$CH_3CH(OC_2H_5)_2$	76*
12	90	0.46	$CH_3CH(OC_3H_7\text{-}n)_2$	71
13	90	0.46	$CH_3CH(OC_3H_7\text{-}n)_2$	72
14	60	0.46	$CH_3CH(OC_3H_7\text{-}n)_2$	75
15	90	0.46	$CH_3CH(OC_3H_7\text{-}n)_2$	77*
16	90	1.00	$CH_2(OC_2H_5)_2$	61*

* Indicates titration for HCl—none detected.

EXPERIMENTAL

The orthoformates were prepared according to the method outlined in the literature.[3]

The diethyl and di-*n*-propyl acetals of acetaldehyde were prepared by the calcium chloride method.[4]

n-*Butyl orthoformate* was prepared after the method[3] employed for the propyl orthoformate; b. p., 145°/32 mm., 148–9°/40 mm.; n_D^{22}, 1.4177; n_D^{27}, 1.4163; $d_4^{23.5}$, 0.865.

Diethyl acetal of formaldehyde (*diethoxymethane*) was purchased from the Eastman Kodak Co.; b. p., 85°.

Benzoyl chloride was purchased; b.p., 190–1°.

Ethyl benzoate was identified. Constants found: b. p., 204–7°; n_D^{22}, 1.4949; d_4^{25}, 1.0685. Literature constants: b. p., 212.6°; $n_D^{17.3}$, 1.5068; d_0^{15}, 1.0509.

n-*Propyl benzoate* was identified. Constants found: $n_D^{23.5}$, 149.30; d_4^{22}, 1.017; b.p., 231°/747.6 mm. (corr.); M. W., 162. Literature and calculated constants: n_D^{15}, 1.5014; d_4^{22}, 1.027; b.p., 229–31° (corr.); M.W., 164.

Anal. Calc'd for $C_{10}H_{12}O_2$: C, 73.1; H, 7.3.
Found: C, 73.2, 73.3, 73.3; H, 7.3, 7.5, 7.4.

n-*Butyl benzoate* was identified; b.p., 129°/21 mm. (literature, 250°/760 mm.); n_D^{2}, 1.4874; d_{20}^{20}, 0.991.

i-*Butyl benzoate* was identified; b.p., 155°/73 mm.; $n_D^{25.5}$, 1.4918; d_4^{23}, 1.023.

n-*Amyl benzoate* was identified; b.p., 167°/44 mm.; n_D^{22}, 1.4815; d_4^{22}, 0.9520.

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[3] POST AND ERICKSON, *J. Am. Chem. Soc.*, **55**, 3851 (1933).

[4] ADKINS AND NISSEN, *Organic Syntheses*, **3**, 1 (1923).

SUMMARY

1. The reaction between benzoyl chloride and certain alkyl orthoformates has been studied and has been found to proceed with net interchange of alkyl radical for halogen, and with production of alkyl formate, halide and benzoate. The presence of inorganic salts is not necessary. The yield of alkyl benzoate falls with rise of radical weight.

2. Acetals react with benzoyl chloride in the same general way, with the production of alkyl benzoate and chloroether. Inorganic salts are not necessary in this reaction either. No significant difference was found between the yields from ethyl and *n*-propyl acetals but the diethyl acetal of formaldehyde gave a much less satisfactory yield of benzoate.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

RESEARCHES ON THIAZINES. III. THE SYNTHESIS OF CYANINE DYES OF THE *PERI*-NAPHTHOMETATHIAZINE SERIES*†

HOMER VAN BEUREN JOY AND MARSTON TAYLOR BOGERT

Received May 5, 1936

Cyanine dyes containing the thiazole nucleus are well known and many of them are useful photographic sensitizers. Analogous dyes carrying the thiazine nucleus, however, have not been described. It was, therefore, the object of this research to synthesize such dyes from the 2-methyl-*peri*-naphthometathiazine (I) of Bogert and Bartlett,[1] in order to contribute to the elucidation of the problem of the relation between chemical constitution and photosensitizing properties. One reason for the choice of this particular thiazine was that the isomeric cyanines from methyl-*alpha*- and *beta*-naphthothiazoles (II and III) were already known and could thus be used for comparison.

The thiazine (I) was treated with both methyl and ethyl iodides. With the former, the reaction proceeded normally, with formation of the methiodide (IV); but with ethyl iodide it followed an abnormal course, which yielded the hydriodide as the main product, with but small amounts of the desired ethiodide.

From the methiodide (IV), a thiazinocarbocyanine (VII) was obtained by the action of ethyl orthoformate in pyridine solution. The ethiodide, which could not be isolated, yielded the corresponding thiazinocarbocyanine only when treated with ethyl orthoformate and potassium acetate in acetic anhydride solution. Condensed with *p*-dimethylaminobenzaldehyde, in absolute ethanol solution, the methiodide and hydriodide (IV) gave the *p*-dimethylaminostyryl derivatives (VI).

Digestion of the methiodide (IV), in alcoholic solution, with silver chlo-

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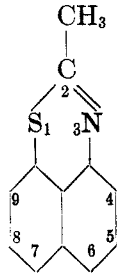
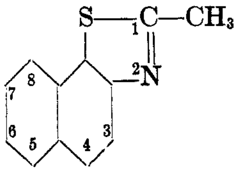
* Based upon the dissertation submitted by Mr. Joy, May, 1934, for the Ph.D. degree, under the Faculty of Pure Science, Columbia University, New York, N. Y., to which the reader is referred for further experimental details and literature citations.—M. T. B.

† Presented in abstract before the Division of Dye Chemistry, at the Washington Meeting of the American Chemical Society, March 27, 1933.

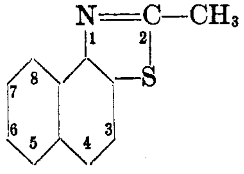
[1] BOGERT AND BARTLETT, *J. Am. Chem. Soc.*, **53**, 4046 (1931).



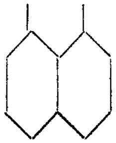
I

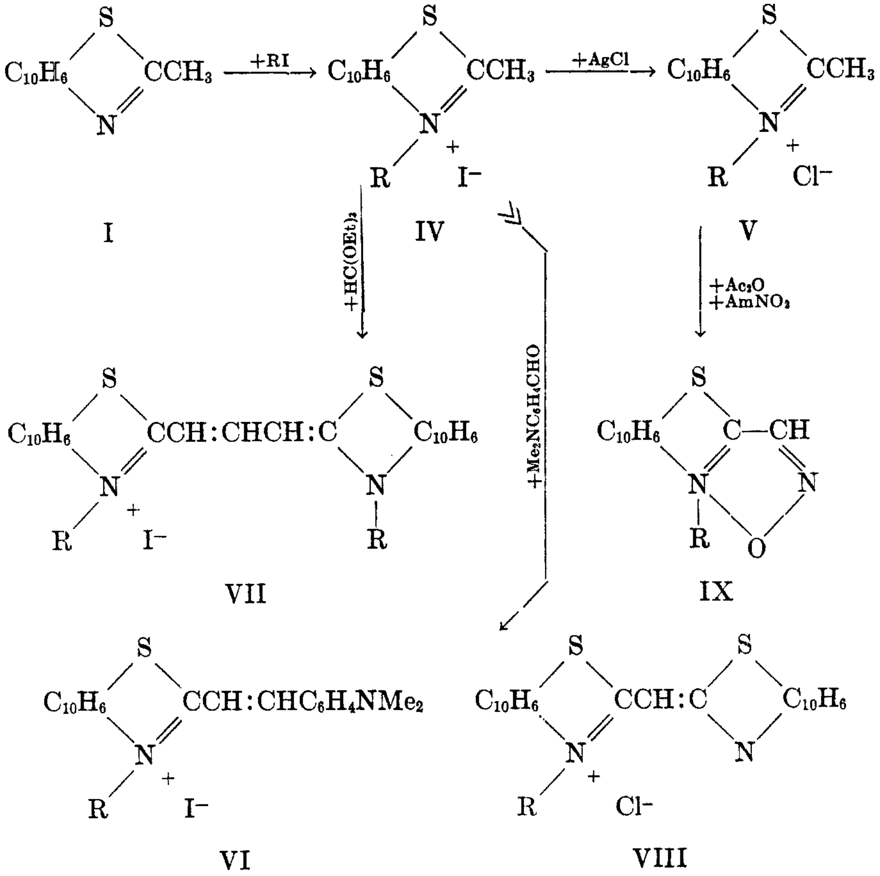


II (*alpha-*)



III (*beta-*)

In the following structural formulae, $C_{10}H_6$ =  and R = H, Me or Et.



ride, changed it to the corresponding methochloride which, when heated in acetic anhydride solution with amyl nitrite, following the method used by Fisher and Hamer[2] for the preparation of thiocyanines, did not yield the expected dye (VIII), but bright yellow needles with a metallic lustre, which melted with decomposition at 236°, and on analysis gave figures corresponding to the empirical formula, $C_{13}H_{10}N_2OS$. Of the several constitutions which might be suggested for this product, we think that the furazan structure (IX) is the most probable. The hydriodide (IV) formed a similar compound.

The process of Beattie, Heilbron, and Irving[3] applied to the thiazine methiodide (IV), yielded what appeared to be the expected thiazinodicarbocyanine, but which we were unable to obtain analytically pure.

The various dyes secured were tested for both absorption spectra and photosensitizing properties, since the sensitization maximum lies in the vicinity of the absorption maximum and usually somewhat farther towards the red, this displacement often amounting to about 200 Å. The details are given in the experimental part. The results did not indicate any outstanding photosensitizing action for the *peri*-naphthometathiazine nucleus. Further, these thiazinocarbocyanines showed only a single absorption maximum, whereas the analogous carbocyanines of the thiazole series show two.

It is hoped to determine also whether these dyes possess any selective bacteriostatic or bactericidal properties.

The nomenclature and numbering used throughout this paper are those of *Chemical Abstracts.*

Acknowledgments.—We are indebted to Professor H. W. Webb and Dr. L. J. Hayner, of the Columbia University Department of Physics, for assistance in the preliminary examination of certain of the dyes. The sensitization tests and absorption spectra of the styryls (VI) and the sensitization tests of the thiazinocarbocyanines (VII) were determined by the Eastman Kodak Co. laboratories, through the courtesy of Dr. C. E. K. Mees, Vice President; the absorption spectra of the thiazinocarbocyanines, by Dr. R. S. Este, of the Electrical Testing Laboratories, New York City.

EXPERIMENTAL

Unless otherwise stated, all melting points recorded are "corrected." Those below 150°, were taken while the temperature was being raised at the rate of 3° per minute; those above 150°, at 8° per minute.

1,8-Nitronaphthalenesulfonyl chloride.—The method used by Bogert and Bartlett[1] was simplified and improved as follows.

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[2] FISHER AND HAMER, *J. Chem. Soc.*, **1930**, 2502.

[3] BEATTIE, HEILBRON, AND IRVING, *ibid.*, **1932**, 260.

To 1000 g. of technical sodium 1-naphthalenesulfonate, dried at 120°, there was added 600 g. of phosphorus pentachloride, and the mixture was heated cautiously at 100°, with occasional stirring, until it became homogeneous (about 30 minutes) when it was poured upon cracked ice with rapid mechanical stirring. The crude sulfonyl chloride was collected by filtration, ground with ice, to hydrolyze any remaining phosphorus halides, and dried on porous plates; m.p., 42°; yield, 920 g., or 93%. Crystallized five times from ligroïn, it melted at 66–67°, as reported by Bogert and Bartlett.

To 300 cc. of nitric acid (sp. gr., 1.5), there was added with stirring 200 g. of the crude 1-naphthalenesulfonyl chloride (m.p., 42°) suspended in 80 cc. of acetic anhydride, at a temperature of 0–12°. After all the chloride had been added the stirring was continued for ten minutes. The solution was then poured upon cracked ice with vigorous mechanical stirring which was continued for about 45 minutes. The nitrated sulfonyl chloride was removed, triturated with ether, to remove gummy impurities, and dried; yield, 150 g. This crude product was dissolved in rather more than three times its weight of warm benzene, the solution was filtered and the 1,8-nitronaphthalenesulfonyl chloride was precipitated from the filtrate by the addition of two volumes of gasolene; yield, 38 g.; m.p. 154°. A single recrystallization from benzene and gasolene, raised this m.p. to 161–162°, which is that recorded in the literature.

*2-Methyl-*peri*-naphthometathiazine* (I).—The chlorostannate of *peri*-aminonaphthylmercaptan, prepared as reported by Bogert and Bartlett, was used, instead of the tin chloride addition product, for cyclization to the thiazine, and the yield was improved by the addition of metallic tin, whose reducing action inhibited disulfide formation. The thiazine was obtained nearly pure and in high yield, by making use of its selective solubility in petroleum ether.

In detail, this improved technic was as follows. After dissolving 50 g. of fused sodium acetate in 500 cc. of boiling glacial acetic acid and adding 20 g. of tin, 50 g. of *peri*-aminonaphthylmercaptan chlorostannate was introduced in one lot with vigorous stirring. When all lumps had been broken up, 65 g. of acetic anhydride was poured into the hot solution, and the mixture was allowed to cool to room temperature. It was then neutralized with ammonium hydroxide solution; the yellow precipitate was filtered out, dried, and extracted with petroleum ether in the extraction apparatus described by Bogert and Conklin.[4] Evaporation of the petroleum ether extract, left 21 g., or a yield of 57%, of the naphthothiazine, m.p. 93°, sufficiently pure for the preparation of the alkyl halides described beyond. Recrystallized from acetone, the m.p. was raised to 96.5–97.5°, the figure found by Bogert and Bartlett.

Methiodide (IV).—A mixture of 30 g. of the thiazine (I), 25.6 g. of methyl iodide, and 0.05 g. of hydroquinone, was heated for 12 hours at 100° in a sealed tube. The hard brown product was extracted with cold chloroform, to remove unidentified dark, gummy impurities. It then melted at 190° and was sufficiently pure for use in subsequent condensations; yield, 32 g., or 62%. Omission of the hydroquinone, reduced the yield to 54%. The crude methiodide, when crystallized rapidly from absolute ethanol, formed short yellow needles, which were slightly soluble in water. Introduced into the bath at 197°, they shrank at 204°, and melted gradually with decomposition at 222–230°.

Anal. Calc'd for $C_{13}H_{12}INS$: C, 45.75; H, 3.55; I, 37.21.
Found: C, 45.77; H, 3.57; I, 36.71.

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[4] BOGERT AND CONKLIN, *J. Am. Chem. Soc.*, **55**, 1705 (1933).

The methiodides of the isomeric naphthothiazoles (II and III) have been described by Hamer[5] as nearly colorless, and as crystallizable from 95% ethanol, whereas our product suffered considerable decomposition when an attempt was made to crystallize it from that solvent.

Hydriodide and Ethiodide.—A mixture of 20 g. of the thiazine (I) with 8.1 cc. (1.2 moles) of ethyl iodide was heated for 24 hours at 100° in a sealed tube. The viscous brown product, containing some crystals, was extracted with cold chloroform, and there remained 14 g., or 39%, of a yellow-brown crystalline solid. From the chloroform extract, there was recovered, by extraction with hydrochloric acid, 7 g. of the original thiazine.

The crystalline solid, insoluble in chloroform, was believed at first to be the desired ethiodide, inasmuch as a small quantity of 3,3′-diethyl-*peri*-naphthothiazinocarbocyanine iodide (VII) was obtained from it by the usual reaction; but further crystallizations from absolute ethanol, together with analyses, proved that it consisted chiefly of the hydriodide, apparently formed by the breakdown of the ethyl iodide. Introduced into the bath at 255°, it decomposed at 259°. Treated with ammonium hydroxide solution, it gave a product which was identical in m.p. and mixed m.p. with the original thiazine.

Anal. Calc'd for $C_{12}H_{10}INS$: C, 44.03; H, 3.08; I, 38.81.
Found: C, 44.22; H, 3.17; I, 39.48.

As further proof of this identification, a benzene solution of the original thiazine (I) was treated with dry hydrogen iodide. A yellow hydriodide was obtained, in practically 100% yield which, when heated alone or mixed with the hydriodide formed in the ethyl iodide reaction, decomposed at the same temperature as the latter. Further, the two products exhibited exactly the same behavior when reacted with *p*-dimethylaminobenzaldehyde.

It is worth noting that Hamer[5] obtained less than 1% of *beta*-naphthothiazole ethiodide by the use of ethyl iodide, but a 31% yield when she employed ethyl *p*-toluenesulfonate and potassium iodide. Our attempts to utilize the latter method for the preparation of the thiazine ethiodide, however, were unsuccessful, as too much tar was formed.

Methochloride.—A solution of 5 g. of the methiodide (IV) in 250 cc. of alcohol was boiled for 45 minutes with an excess of freshly prepared and well washed silver chloride. The silver iodide was filtered out and the filtrate concentrated rapidly to a small volume. As it cooled, the methochloride separated in yellow needles, free from iodine, melting with decomposition at 230°; yield, 2 g., or 55%. Rapidly recrystallized from absolute ethanol, the decomposition point was raised to 234–235° when the crystals were introduced into the bath at 227°.

Anal. Calc'd for $C_{13}H_{12}ClNS$: C, 62.51; H, 4.85; Cl, 14.20.
Found: C, 62.18; H, 4.80; Cl, 14.67.

Hydrochloride.—Prepared from the corresponding hydriodide by the method used above for the methochloride, the crude product separated in yellow needles which melted with decomposition at 230°; yield, 2.9 g., or 78%. This decomposition point was raised to 233–234° (introduced into bath at 225°) by rapid recrystallization from absolute ethanol.

Anal. Calc'd for $C_{14}H_{14}ClNS$: Cl, 15.05. Found: Cl, 14.99.

*Reactions of 2-Methyl-*peri*-naphthometathiazine Methochloride and Hydrochloride with Acetic Anhydride and Amyl Nitrite.*—This was an attempt to apply to the *peri*-

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[5] Hamer, *J. Chem. Soc.*, **1929**, 2598.

naphthometathiazine group the thiocyanine reaction of Fisher and Hamer.[2] A mixture of 0.5 g. of the thiazine methochloride with 15 cc. of acetic anhydride was heated to 80°, and 0.23 g. of amyl nitrite (b.p., 96–106°) was added with stirring. A gas was evolved and the mixture turned an intense yellow. It was allowed to cool to 65°, and was then thoroughly chilled. The precipitate was removed, washed with ethyl acetate, and dried; yield of crude crystals, 0.3 g., or 58%, m.p. 230°. Recrystallized from absolute alcohol, the product was obtained in bright yellow needles, with a metallic lustre, which decomposed at 236° when introduced into the bath at 226°.

This compound was not the expected dye of thiocyanine type (VIII), but was halogen-free, and insoluble in either dilute sodium hydroxide or dilute hydrochloric acid.

Anal. Calc'd for $C_{13}H_{10}N_2OS$: C, 64.45; H, 4.16; N, 11.57; S, 12.23.
Found: C, 64.36; H, 4.08; N, 12.10; S, 12.22.

When the thiazine hydrochloride was used instead of the methochloride, in this reaction, the results were entirely similar, the crystalline product having the empirical formula $(C_{12}H_8N_2OS)_n$; yield, 62%. It decomposed at 237–238° when inserted in the bath at 228°.

Anal. Calc'd for $C_{12}H_8N_2OS$: C, 63.13; H, 3.53.
Found: C, 62.79; H, 3.65.

It is our belief that these products were *peri*-naphthometathiazinofurazans (IX), but not enough material was available for further study.

*3,3'-Dimethyl-*peri*-naphthometathiazinocarbocyanine Iodide* (VII).—The carbocyanine method of Hamer[6] was used for the preparation of this compound. A mixture of 2 g. of the thiazine methiodide (IV), 2 cc. of ethyl orthoformate and 10 cc. of dry pyridine, was heated just below the boiling point. An intense purplish red color developed immediately and at the end of 5 minutes long green needles separated in large amount. When these were filtered out and the filtrate was heated again, another crop of crystals resulted, and this treatment was repeated as long as additional crops were obtained. This piecemeal separation of the product was necessary, because when the crystals were heated for any length of time in the reaction mixture, they suffered some decomposition. The speed of the reaction was surprising, the total time required to throw out all the crystals, even in this stepwise manner, was only about 15 minutes; whereas in most other similar cases recorded in the literature, the reaction has required from 1 to 6 hours for completion.

The various lots of crystals were combined, and washed thoroughly with cold alcohol and then with ethyl acetate; yield, 0.7 g., or 43%; melting with decomposition at 221°; insoluble in water, slightly soluble in alcohol. The product dyed silk a purplish red. Recrystallized from chloroform, in the extractor mentioned previously, it was obtained in dark green needles, of metallic lustre, which melted with decomposition at 222° when introduced into the bath at 214°. These crystals carried chloroform of crystallization, which was held so tenaciously that the crystals lost but little weight when heated for 45 minutes *in vacuo* at 110–120°. The formation of stable solvates of cyanine dyes has been noted by others also. For analysis the compound was heated for an hour at 80°.

Anal. Calc'd for $C_{27}H_{21}IN_2S_2 \cdot CHCl_3$: C, 49.16; H, 3.24; N, 4.10; Ag halide, 97.23.
Found: C, 49.73; H, 3.35; N, 4.56; Ag halide, 91.40.

The analysis of such solvates is generally unsatisfactory. It is manifest that the loss of even a small quantity of the chloroform would throw the silver halide deter-

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[6] HAMER, *ibid.*, **1927**, 2796.

mination far out, since each molecule of the former gives three of the latter. The halide determination, however, does indicate the presence of chloroform.

The dye had no sensitizing power, and its single absorption maximum was found to lie at 5350 Å. In the case of carbocyanines of other types, it often happens that the *N*-methyl dyes have a much feebler sensitizing action than the corresponding ethyl derivatives. The *N*-methyl carbocyanines prepared from the *alpha-* and *beta*-naphthothiazoles are likewise but weak sensitizers, and the chief absorption maxima for both lie at about 6000 Å. This shift towards the blue in the case of the naphthothiazine dye was unexpected, because of the fact that the thiazine methiodide is yellow, while the thiazole methiodides are nearly colorless. Mills[7] has expressed the opinion that, since quinoline methiodides are yellow, and benzothiazole methiodides nearly colorless, it was to be expected that cyanine dyes containing the quinoline nucleus should have absorption maxima lying farther towards the red than those of the corresponding dyes containing a benzothiazole nucleus.

3,3'-Diethyl-peri-*naphthometathiazinocarbocyanine Iodide.*—On heating the mixture of hydriodide and ethiodide obtained by the action of ethyl iodide upon the thiazine (I), with ethyl orthoformate and pyridine (or acetic anhydride), a decided purplish red color developed, but no crystals separated. The dye was finally secured as follows.

A solution of 0.08 g. of anhydrous potassium acetate and 0.5 cc. of ethyl orthoformate in 4.5 cc. of acetic anhydride was heated to boiling. The heating was then discontinued and there was stirred in quickly 0.5 g. of the crude product resulting from the interaction of ethyl iodide and the thiazine (I). The color of the solution changed immediately to an intense reddish purple and, after a minute or two, when the temperature of the mixture had fallen to 120°, it was chilled, two volumes of ethyl acetate were added, and the crystals which separated were removed. The combined crops of crystals from seven such runs were ground up carefully with water and further purified by treatment with 15 cc. of boiling methanol; yield, 0.25 g. The product formed lustrous green needles, which melted at 243° with decomposition when introduced into the bath at 235°. Its formation from the crude reaction product of ethyl iodide and the thiazine proves clearly the presence therein of the thiazine ethiodide (IV). It dyed silk a reddish purple, similar to that produced by the above-mentioned methyl homolog. Its absorption spectrum also resembled the latter, its single absorption maximum being at 5400 Å, with a slight shift towards the red, as has been noted by other investigators in analogous cases. The fact that the absorption spectra of these two dyes showed but a single maximum was surprising, since most carbocyanines exhibit two such maxima.

Further, the dye possessed no sensitizing action whatever, although the analogous *N*-ethyl dyes containing the closely related naphthothiazole nuclei are powerful sensitizers.

From chloroform, this compound, like its methyl homolog, separated with solvent of crystallization.

Anal. Calc'd for $C_{29}H_{25}IN_2S_2CH\cdot{}_2Cl_3$: C, 50.61, H, 3.68.
Found: C, 51.50; H, 3.76.

In as much as solvates do not always crystallize with exactly one molecule of the solvent, these analytical results are submitted as fairly satisfactory.

2-p-*Dimethylaminostyryl*-peri-*naphthometathiazine Methiodide* (VI).—A mixture of 1 g. of the thiazine methiodide (IV) and 0.42 g. (1.2 moles) of *p*-dimethylamino-

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[7] MILLS, *ibid.*, **121**, 455 (1922).

benzaldehyde, in absolute ethanol (or acetic anhydride) solution, was boiled for ten minutes. An intense reddish purple color appeared almost immediately, soon followed by a separation of purple needles. After standing for an hour at room temperature, the mixture was filtered, the crystals washed with absolute ethanol, then with ethyl acetate, and dried; yield, 0.87 g., or 63%; m.p. 228°. These crystals were purified for analysis by recrystallization by extraction from methanol. Introduced into the bath at 230°, the crystals melted with decomposition at 235°.

Anal. Calc'd for $C_{22}H_{21}IN_2S$: C, 55.92; H, 4.48; N, 5.93.
Found: C, 55.39; H, 4.62; N, 6.13.

The compound was soluble in chloroform or acetone. It did not dye silk. As a sensitizer, it proved to be of a weak benzothiazole type. Its broad absorption band showed a single poorly defined maximum at about 4700 Å. Both *alpha*- and *beta*-naphthothiazole ethiodides form *p*-dimethylaminostyryl derivatives with fairly powerful sensitizing action.

In carrying out the above reaction, the addition of a few drops of piperidine completely inhibited the condensation. This was unexpected, because in other cases piperidine has been found to be a useful catalyst in promoting aldol formation.

The researches of Mills and Raper[8] have shown that in the formation of these styryls, the methiodide first loses hydrogen iodide, giving a methylene base which then condenses with the aldehyde to an allene base, with which the hydrogen iodide then recombines.

*2-*p*-Dimethylaminostyryl-*peri*-naphthometathiazine Hydriodide*, prepared like the above methiodide, from the corresponding thiazine hydriodide, also formed purple needles which, in the crude state, melted with decomposition at 239°; yield, 1.1 g., or 79%. Purified as described for the methiodide, and introduced into the bath at 238°, it darkened and emitted vapors at 243°, melting with decomposition and swelling at 250°. Like the methiodide it was devoid of tinctorial properties, but proved to be a feeble sensitizer of benzothiazole type. Its broad absorption band possessed a single poorly defined maximum at about 4500 Å.

Anal. Calc'd for $C_{24}H_{25}IN_2S$: C, 55.00; H, 4.18; N, 6.11.
Found: C, 54.94; H, 4.50; N, 5.96.

*3,3'-Dimethyl-12-chloro-*peri*-naphthometathiazinodicarbocyanine Iodide.*—The dicarbocyanine method of Beattie, Heilbron and Irving[3] was tried.

Mucochloric acid, prepared as described by them, was converted into the *alpha*-chloro-*beta*-anilinoacraldehyde anil hydrochloride, $C_6H_5NHCH{:}\ CClCH{:}NC_6H_5$, by the method of Dieckmann and Platz.[9]

A mixture of 0.22 g. of this anil hydrochloride, 0.15 g. of anhydrous potassium acetate and 10 cc. of acetic anhydride, was heated to boiling. The heating was then stopped and 0.5 g. of the thiazine methiodide (IV) was added immediately with stirring. The mixture turned an intense blue. When it had cooled to 120°, it was chilled and an equal volume of ethyl acetate added. The dark crystals were removed and freed from acetic anhydride by washing with ethyl acetate. The product from four such runs was washed thoroughly with water and extracted with boiling methanol until the filtrate was blue. This left a residue of 0.55 g., equivalent to a yield of 30%. Introduced into the bath at 211°, it melted with decomposition at 221°. It dyed silk blue. It was so difficultly soluble in all solvents tried that we were unable to purify it satisfactorily, and the analytic results, therefore, differed by several per cent from the figures calculated.

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[8] Mills and Raper, *ibid.*, **127**, 2466 (1925).

[9] Dieckmann and Platz, *Ber.*, **37**, 4638 (1904).

Since its solutions were blue, while those of the monocarbocyanine iodide (VII) were reddish purple, it seems that the increase of two methine groups in the side chain has caused the expected shift of the absorption towards the red.

*Attempts to Prepare other Dyes from 2-Methyl-*peri*-naphthometathiazine*

Pseudocyanine.—The thiazine methiodide (IV) failed to condense with 2-iodoquinoline methiodide in absolute ethanol solution, in the presence of sodium hydroxide. No cyanine color developed and no crystals separated. This failure was foreshadowed by the sensitivity to piperidine of the thiazine methiodide in the *p*-dimethylaminostyryl condensation, as noted already.

Other types.—Attempts to produce a desensitizer, by condensing thiazine methiodide with *p*-nitrosodimethylaniline in absolute ethanol, with or without piperidine as catalyst, resulted only in tars. A similar lack of success attended our experiments for the production of a tricarbocyanine by the methods of Hamer and Fisher.[10]

SUMMARY

1. 2-Methyl-*peri*-naphthometathiazine has been converted into quaternary halides and these, in turn, into cyanine dyes.

2. In photosensitizing power, these thiazine dyes appear to be much weaker than the corresponding naphthothiazole or benzothiazole derivatives.

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[10] Hamer and Fisher, *J. Chem. Soc.*, **1933**, 189.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

THE ERGOT ALKALOIDS. X.* ON ERGOTAMINE AND ERGOCLAVINE

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Ergotinine, for which the empirical formula $C_{35}H_{39}N_5O_5$ was derived by Barger and Carr,[1] has been shown by us[2] to be composed of lysergic acid, ammonia, isobutyrylformic acid, *d*-proline, and *l*-phenylalanine, joined in amide linkages, a fact in agreement with such a formulation. Similarly, the simpler ergot alkaloid, ergometrine, now accepted as possessing the formula $C_{19}H_{23}N_3O_2$,[3] we have shown to yield lysergic acid and 2-aminopropanol-1 on hydrolysis, and is therefore the hydroxyisopropylamide of lysergic acid.[4] Preliminary notes have also been presented on the results of similar hydrolytic studies with ergotamine[5] and ergoclavine.[6] Our examination, from this standpoint, of these alkaloids as well as that of ergotoxine has since been carried farther.

The ergotamine employed in these studies was purchased as the tartrate from the Sandoz Chemical Works. The free base was separated from the salt and was then submitted to alkaline hydrolysis as described in the experimental part. The formula for ergotamine (and ergotaminine) has been well established by its discoverer, Stoll,[7] to be $C_{33}H_{35}N_5O_5$. This formula differs from that of ergotinine by C_2H_4. Since in our first experiments no evidence of the formation of isobutyrylformic acid from ergotamine on alkaline hydrolysis could be obtained, it appeared possible that pyruvic acid, which differs from the first acid by C_2H_4, might be in question. Unfortunately, the instability of pyruvic acid under the conditions of

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* For paper IX of this series see *J. Biol. Chem.*, **113**, 767 (1936).

[1] G. BARGER AND F. H. CARR, *J. Chem. Soc.*, **91**, 337 (1907).

[2] W. A. JACOBS AND L. C. CRAIG, *J. Biol. Chem.*, **110**, 521 (1935).

[3] A. STOLL AND E. BURCKHARDT, *Compt. rend.*, **200**, 1680 (1935); W. A. JACOBS AND L. C. CRAIG, *Science*, **82**, 16 (1935); H. W. DUDLEY, *J. Am. Chem. Soc.*, **57**, 2009 (1935).

[4] W. A. JACOBS AND L. C. CRAIG, *Science*, **82**, 16 (1935).

[5] W. A. JACOBS AND L. C. CRAIG, *ibid.*, **81**, 256 (1935).

[6] W. A. JACOBS AND L. C. CRAIG, *J. Am. Chem. Soc.*, **57**, 960 (1935).

[7] *Swiss Patents*, No. 79879 (1918) and No. 86321 (1919). A. STOLL, *Schweiz. Apoth. Ztg.*, Nos. 26–28, pp. 134, 136–138 (1922).

hydrolysis makes its detection more difficult than that of isobutyrylformic acid in the case of ergotinine. If ergotamine is heated for a short time in alkaline solution the resulting mixture gives a red color with nitroprusside similar to that given by pyruvic acid, and a color which changes after addition of ammonium chloride through purple to blue. Such a reaction is not given by ergotinine where isobutyrylformic acid is in question. This experience with ergotamine was confirmed by the preparation of a phenylhydrazone, although in extremely poor yield, which proved to be identical with that of pyruvic acid. This was prepared by acidification and extraction of the mixture obtained after short alkaline hydrolysis. During the latter, partial evolution of ammonia was readily detected. On resumption of the alkaline hydrolysis, the cleavage was completed and from the reaction mixture lysergic acid was readily obtained.

Paralleling our earlier experience with ergotinine, an appreciable amorphous, amphoteric fraction was recovered which was further hydrolyzed by hydrochloric acid. Phenylalanine (almost entirely racemized) was readily isolated from this hydrolysate after removal of Cl ions. The mother liquor from phenylalanine was desiccated and the residue was esterified with methyl alcohol and hydrochloric acid. A basic amino acid ester fraction was obtained in the usual manner, which on fractionation in a micro still gave a distillate at the proper temperature and pressure for proline methyl ester. This was identified by conversion into the double gold salt $C_6H_{11}NO_2 \cdot HAuCl_4$. Thus, ergotamine and therefore its isomer ergotaminine consist of lysergic acid, ammonia, proline, phenylalanine, and pyruvic acid combined in amide linkage.

In order to determine the optical character of the amino acids present in ergotamine, the latter was then hydrolyzed directly with hydrochloric acid. After removal of the deeply colored products arising from the decomposition of lysergic acid, it was a comparatively simple matter to obtain phenylalanine which, as in the case of ergotinine, proved to be *l*-phenylalanine, although partly racemized ($[\alpha]_D^{25} = -23°$). From the filtrate of the latter, the methyl ester was prepared as usual and the fraction corresponding to proline methyl ester was obtained in the micro still. Unfortunately, the amount was insufficient to redistill for analysis. However, its rotation, $[\alpha]_D^{25} = +20°$, indicated, as in the case of ergotinine, that we were again dealing with the unnatural form of an amino acid, *i.e.*, *d*-proline.

The occurrence of the unnatural form of an amino acid is so unique that at one stage of our studies we sought for a possible explanation of its formation in the process of isomerization of the alkaloids, such as ergotoxine into ergotinine and ergotamine into ergotaminine. The possibility was considered that such isomerization might involve enolization with participation of the hydrogen atom on the asymmetric α-carbon atom of proline, with racemization of the latter. And since other asymmetric centers are still present elsewhere in the large molecule, the resulting substances would be epimers and not true enantiomorphs. Hence, ergotinine could be one of these easily crystallizing epimers and so yield *d*-proline on hydrolysis. If this theory were valid, ergotoxine should then yield *l*-proline. Ergotoxine (the ethane sulfonate of Burroughs Wellcome and Company), however, on acid hydrolysis also yielded *d*-proline methyl ester of $[\alpha]_D^{25} = +34°$ (c = 0.570). Therefore, such an explanation of the occurrence of *d*-proline in these alkaloids must be discarded. Although this observation is of interest in confirming our experiences with ergotinine and ergotamine in regard to the optical character of the proline constituent, we now know that another explanation is necessary for the isomerization noted in the cases of the pairs of alkaloids. As we are presenting elsewhere, the center of such isomerization is to be found in lysergic acid itself and the evidence at hand indicates that the shift of the double bond of the latter is responsible.

We have similarly attempted the study of ergoclavine which was first described by Küssner.[8] Our experience with this alkaloid has convinced us that it is a difficult matter to obtain it in homogeneous form. When prepared by the method given by Küssner, it was readily isolated from the crude alkaloid mixture and agreed in general properties with those described by him. In Küssner's report a formulation for the alkaloid of $C_{31}H_{37}N_5O_5 \cdot H_2O$ was derived, or $C_{31}H_{37}N_5O_5$ for the anhydrous substance (dried at 80° and 1–2 mm.). Our experience has shown that such a formulation requires revision. Our analytical data with the anhydrous substance, as given in the experimental part, are in excellent agreement with the figures of Küssner. However, the results of our hydrolytic studies indicate that the formulation of ergoclavine should be more properly $C_{25}H_{30}N_4O_4$. When ergoclavine was hydrolyzed by alkali, lysergic acid was obtained by the usual procedure, and its identity was confirmed by the preparation of the methyl ester. Ammonia was also collected as the hydrochloride during the hydrolysis. When the attempt was made to isolate isobutyrylformic acid by the method used in the case of ergotinine, only a few milligrams of a phenylhydrazone of doubtful homogeneity could be obtained. The conclusion appears warranted that pure ergoclavine does not contain this component. The statement in our preliminary note, based on results obtained with an impure alkaloid, that it contains isobutyrylformic acid is therefore withdrawn. When ergoclavine is hydrolyzed for a short time with alkali, it is possible to obtain a positive red color test for pyruvic acid with nitroprusside, which changes on addition of ammonium chloride through purple to blue. However, we were not able to isolate a

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[8] W. Küssner, *E. Merck's Jahresbericht*, **47**, 5 (1933).

pure phenylhydrazone of pyruvic acid. The very small amount of phenylhydrazone which was obtained as stated above proved to be nonhomogeneous, and there is a suggestion that it consisted of a mixture of the phenylhydrazones of pyruvic acid and isobutyrylformic acid. The latter probably has its origin in a small amount of ergotinine which contaminates the ergoclavine and which was difficult to remove by repeated recrystallization. This was also suggested by the investigation of the amino acid fraction.

When the amphoteric fraction which remained after separation of lysergic acid was further hydrolyzed by acid, an amino acid was readily isolated, and gave analytical figures required by leucine. It was optically inactive. No phenylalanine could be obtained, and, although the leucine mother liquor after concentration gave an appreciable pyrrole reaction, it was not possible to isolate either proline or hydroxyproline. The pyrrole test, we believe, was probably caused by the presence of a small amount of proline having its origin in a small amount of contaminating ergotinine. Acid hydrolysis confirmed the results of the alkaline hydrolysis. Lysergic acid was destroyed as usual by the process, and after removal of chloride ions an amino acid was readily obtained, which from the analysis and rotation proved to be *l*-leucine. Its optical activity indicated partial racemization; $[\alpha]_D^{25} = -7°$ ($c = 1.0$ in water), which changed to $[\alpha]_D^{25} = +10°$ on acidification with hydrochloric acid. This change of the rotation sign excludes isoleucine. No phenylalanine and no proline could be isolated from the material which remained in the leucine mother liquors.

If it is accepted that ergoclavine consists of lysergic acid, ammonia, *l*-leucine, and pyruvic acid in amide linkages, its formula should be $C_{25}H_{30}N_4O_4$. Our analytical figures obtained with the alkaloid, as well as those reported by Küssner, are in excellent agreement with the requirements of such a formulation.

On repeated recrystallization from alcohol not only the analytical figures but the optical activity of ergoclavine appeared to remain constant. Nevertheless, such apparent constancy of the rotation does not entirely exclude the possibility that it may be a mixture of isomers. According to Kreitmair,[9] ergoclavine possesses a specific biological action quantitatively indistinguishable from that of ergotoxine. However, contrary to the other active ergot alkaloids which are levorotatory in chloroform solution, ergoclavine is strongly dextrorotatory. We have observed for the air-dry alkaloid +104° ($c = 0.5$ in chloroform), and Küssner reported +115° ($c = 0.5$ in chloroform). This might suggest a mixture of isomeric ergoclavines of the ergotinine and ergotoxine types. Another possibility also comes to

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[9] H. Kreitmair, *ibid.*, **47**, 13 (1933).

mind: namely, that ergoclavine may belong in a third isomeric group (ψ ergotinine of Smith and Timmis?[10]). This point, however, will be discussed at greater length elsewhere in connection with the discussion of isomeric lysergic acids and derivatives. The above formulation for ergoclavine must be advanced, however, with necessary reservations until at least the work can be repeated with unquestionably homogeneous material.

EXPERIMENTAL

Alkaline hydrolysis of ergotamine.—A solution of 0.6 g. of ergotamine tartrate (Sandoz Chemical Works) was treated with excess sodium carbonate solution, and extracted with warm chloroform. After drying of the extract, the chloroform was removed *in vacuo.* The residue was dissolved in methyl alcohol and the solution was again concentrated to remove any chloroform. The amorphous residue was treated with a solution containing 3 cc. of water, 3 cc. of methyl alcohol, and 0.18 g. of potassium hydroxide. The solution was refluxed in a current of hydrogen for 15 minutes during which ammonia was evolved. Water (3 cc.) was then added to the mixture, and methyl alcohol was quickly removed under reduced pressure. The remaining solution, about 5 cc. in volume, was cooled in ice and treated with dilute sulfuric acid until acid to Congo red. It was then extracted with 10 cc. of ether. The aqueous layer was further treated as described below.

The clear ether extract was carefully concentrated to a small oily residue which was treated with a few milligrams of phenylhydrazine. The mass partially crystallized. It was taken up in a very small volume of dilute acetic acid and the crystals were collected. The crystalline material was combined with the same fraction from a previous 0.3-g. run. The combined weight was 4.2 mg. It was recrystallized from a drop of glacial acetic acid; 2.6 mg. was thus obtained, which melted at 191° and was indistinguishable from the phenylhydrazone of synthetic pyruvic acid melting at 191.5°. A mixture melting point showed no depression.

Anal. Calc'd for $C_9H_{10}N_2O_2$. C, 60.68; H, 5.67.
Found: C, 61.27; H, 5.70.

The acid aqueous solution which remained after the above ether extraction was treated with excess sodium carbonate solution and then evaporated to dryness *in vacuo.* To the residue was added a solution containing 5 cc. of water, 5 cc. of methyl alcohol, and 1.4 g. of potassium hydroxide. The solution was refluxed in an atmosphere of hydrogen for 45 minutes. Water was added and the volume was then reduced to about 10 cc. *in vacuo* in order to remove the methyl alcohol. After cooling, the solution was made slightly acid to Congo red with sulfuric acid. The solid material was collected and the filtrate was set aside to be treated further as described below.

The solid material was extracted with ammoniacal methyl alcohol and the undissolved inorganic material was filtered off. The somewhat colored filtrate was evaporated to dryness. The residue was treated with 5 cc. of methyl alcohol, heated to boiling, and then cooled; 0.12 g. of crystalline lysergic acid was collected with methyl alcohol. Recrystallization from water gave 0.09 g. of substance crystallizing in leaves. It showed a decomposition point of about 228° depending on the rate of heating.

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.69; H, 6.00; N, 10.45.
Found: C, 71.56; H, 5.83; N, 10.48.

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[10] S. Smith and G. M. Timmis, *J. Chem. Soc.*, **1931**, 1888.

For further characterization, the lysergic acid was esterified by treating its suspension in dry acetone with excess diazomethane. The solid material soon dissolved. After evaporation to dryness, the residue was treated with ether. The ether solution was filtered from a small amount of amorphous material, and again concentrated. After recrystallization twice from benzene, it melted at 168°. The melting point of a mixture with the methyl ester of lysergic acid showed no depression.

The filtrate from the crude lysergic acid fraction was combined with a similar fraction from a previous 0.3-g. run. After treating with an excess of sodium carbonate, the solution was evaporated to dryness *in vacuo*. The residue was extracted with hot ethyl alcohol which removed most of the inorganic material. The extract was evaporated to dryness, and the residue was treated with 25 cc. of concentrated hydrochloric acid. After digesting on the steam bath overnight, the mixture was evaporated to dryness. The residue was dissolved in water and treated several times with boneblack in order to remove the dark-colored, amorphous material. The filtrate remained very dark-colored. It was treated with excess ammonia and then boiled down to a volume of about 2 cc. Upon cooling, crystallization occurred; 80 mg. of crystalline material was collected with a small volume of water. After boneblacking and recrystallization, colorless leaves were obtained which had all the properties of phenylalanine. The material decomposed at about 258° depending somewhat on the rate of heating.

Anal. Calc'd for $C_9H_{11}NO_2$: C, 65.45; H, 6.72; N, 8.48.
Found: C, 65.41; H, 6.60; N, 8.27.

The filtrate from the crude phenylalanine was evaporated to thorough dryness *in vacuo*. The residue was treated with 10 cc. of absolute methyl alcohol and saturated with dry hydrogen chloride. After standing at room temperature for 2 hours, the solution was evaporated to dryness. The residue was treated with several cc. of absolute methyl alcohol and evaporated to dryness again. The residue was dissolved in 2 cc. of methyl alcohol and treated with excess powdered potassium carbonate. The solid was filtered off and washed with a few drops of methyl alcohol. The filtrate was then treated with powdered calcium oxide and filtered. The filtrate was concentrated *in vacuo* to a syrup at a low temperature, and 10 cc. of anhydrous ether was added. The somewhat sticky, insoluble material was ground with a stirring rod in order to extract all the ether-soluble ester. The clear ether filtrate was concentrated to a syrup which weighed 100 mg. This was promptly fractionated in a micro still; 50 mg. of colorless oil distilled at the proper temperature for the methyl ester of proline, *i.e.*, 85–90° at 15 mm. A 15-mg. portion of the oil was dissolved with chilling in a few drops of 10 per cent. hydrochloric acid. A small volume of gold chloride was added and the crystals were collected with dilute hydrochloric acid. The product weighed 20 mg. and melted at 152°.

Anal. Calc'd for $C_6H_{11}NO_2 \cdot HAuCl_4$: C, 15.35; H, 2.57; Au, 42.04.
Found: C, 15.69; H, 2.67; Au, 42.14.

Acid hydrolysis of ergotamine.—The free amorphous alkaloid obtained, as in the previous case, from 1 g. of ergotamine tartrate was treated with 25 cc. of hydrochloric acid (sp. gr., 1.19) and digested on the steam bath overnight. The dark-colored solution was evaporated to dryness. The residue was treated with a small volume of water, and then with a saturated solution of silver sulfate until no more silver chloride was precipitated. The filtrate was saturated with hydrogen sulfide. After removal of excess hydrogen sulfide, the filtrate was carefully treated with barium hydroxide solution until all sulfate ion was just removed. The clear, somewhat colored filtrate was concentrated to a smaller volume and boneblacked. Not all the color was removed by boneblack. The filtrate was again boiled down until crystals began to appear and the mixture was then chilled. The crystalline material was collected with a few drops of water, and the filtrate was set aside to be treated for the proline fraction as described below. The crystals weighed 80 mg. The material was dissolved in water and boneblacked. The colorless filtrate, on concentration, yielded colorless leaves which were collected with a few drops of water; 45 mg. of material was thus obtained, which decomposed at 260°.

$$[\alpha]_D^{25} = -23° \ (c = 0.6 \text{ in water})$$

Anal. Calc'd for $C_9H_{11}NO_2$: C, 65.41; H, 6.72.
Found: C, 65.47; H, 6.45.

The above filtrate from the crude, partly racemized phenylalanine was concentrated to dryness and esterified with methyl alcohol and hydrogen chloride exactly as described for the isolation of the methyl ester of proline under the alkaline hydrolysis. Upon fractionation, the fraction corresponding to the methyl ester of proline was too small to get satisfactory analytical figures, although a rotation was obtained; $[\alpha]_D^{25} = +20°$ ($c = 0.45$ in methyl alcohol).

Ergoclavine.—For the preparation of this alkaloid from the crude alkaloid mixture, the directions of Küssner[8] were essentially followed. The crude alkaloid was recrystallized from 90 per cent. alcohol. It formed microscopic platelets as described by Küssner. It began to soften at 175° and slowly melted at 176–177° to a resin which cleared only on heating a few degrees higher. (Küssner gives 170–171°.)

$$[\alpha]_D^{25} = +104° \ (c = 0.54 \text{ in chloroform for the air-dry substance})$$

For analysis the substance was dried at 120° and 15 mm.

Anal. Calc'd for $C_{25}H_{30}N_4O_4$: C, 66.63; H, 6.71; N, 12.44.
Found: C, 66.43; H, 6.57; N, 12.47.

After recrystallization from 90 per cent. alcohol.

$$[\alpha]_D^{25} = +104.5° \ (c = 0.535 \text{ in chloroform})$$

Anal. Found: C, 66.58; H, 6.70.

Other samples gave similar figures.

Küssner reported the following analyses for his substance which was dried at 20° and therefore still contained solvent (H_2O ?).

Anal. Calc'd for $C_{25}H_{30}N_4O_4 \cdot H_2O$: C, 64.07; H, 6.89; N, 11.97.
Found: C, 64.19, 64.30; H, 6.75, 6.77; N, 11.74, 12.16.

Küssner found that his substance lost 3.17 per cent. (apparently water) at 80° and 1–2 mm. Calculated for 1 mole H_2O, 3.84.

Alkaline hydrolysis of ergoclavine.—A 0.2-g. portion of ergoclavine was treated with 4 cc. of a solution containing 2 cc. of methyl alcohol, 2 cc. of water, and 0.56 g. of potassium hydroxide. It was refluxed in an atmosphere of hydrogen for 45 minutes. The methyl alcohol was removed under reduced pressure, and 2 cc. of water was added. The chilled mixture was made slightly acid to Congo red with sulfuric acid and extracted with 10 cc. of ether. The acid aqueous layer was treated for the lysergic acid fraction as described below. The ether solution was carefully concentrated to a syrup which was fractionated in a micro still. Approximately 2.5 mg. of colorless oil distilled. It was treated with an equivalent of phenylhydrazine. The crystalline product was recrystallized from glacial acetic acid. A small amount of crystals was thus obtained; melting point, 152–154°. This suggested the derivative of isobutyrylformic acid, but the amount obtained was too small for identification and, at any rate, negligible when compared with the yield of this substance obtained under similar conditions from ergotinine.

The acid aqueous layer was filtered and the collected solid was treated with ammoniacal methyl alcohol. The undissolved inorganic salts were filtered off and the filtrate was evaporated to dryness. The residue was treated with 5 cc. of methyl alcohol and heated to boiling, leaving crystalline lysergic acid, which was collected, and recrystallized from water (50 mg. of broad leaves); decomposition on rapid heating at about 238°.

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.69; H, 6.00.
Found: C, 71.85; H, 6.02.

A portion of the above-mentioned acid was converted into the ester with diazomethane. It was recrystallized from benzene and melted at 168°. A mixture melting point with the ester of lysergic acid showed no depression.

$$[\alpha]_D^{25} = +86° \text{ (}c = 0.3\text{ in methyl alcohol)}$$

During the above alkaline hydrolysis the hydrogen which bubbled through the boiling mixture was passed through dilute hydrochloric acid. This, on concentration, gave 15 mg. of ammonium chloride. Calculated, 23 mg.

The above-mentioned acid aqueous mother liquor from the crude lysergic acid and salts was treated with alcohol to remove salts, and filtered. The filtrate was concentrated to dryness and then hydrolyzed, as in the case of ergotamine, with concentrated hydrochloric acid. A dark-colored solution resulted which, after boneblacking and removal of chloride ions, gave a crystalline amino acid on concentration to a few cc., and addition of alcohol. Successive fractions were obtained and combined for recrystallization. The product melted above 290° and was optically inactive. Analysis showed it to be *d,l*-leucine.

Anal. Calc'd for $C_6H_{13}NO_2$: C, 54.93; H, 9.99.
Found: C, 55.58, 54.92; H, 10.16, 9.77.

Acid hydrolysis of ergoclavine.—Ergoclavine (0.8 g.) was treated with 25 cc. of concentrated hydrochloric acid (sp. gr., 1.19) and heated on the steam bath overnight. The acid solution was concentrated to dryness *in vacuo*. The residue was then taken up in water and filtered through boneblack. The deeply colored filtrate was treated with an excess of silver sulfate. The filtrate was saturated with hydrogen sulfide and after removal of excess reagent was filtered. The filtrate was carefully treated with the exact amount of barium hydroxide to remove all sulfate ions, and after filtration was concentrated to 10 cc. and boneblacked. The still somewhat colored solution was brought to about 2 cc. and treated with 2 cc. of ethyl alcohol. After cooling, 80 mg. of broad, thin leaves were collected. The mother liquor on further concentration yielded a second crop of crystals which weighed 10 mg. The combined fractions were recrystallized with boneblacking from 50 per cent. ethyl alcohol. The substance had all the properties of leucine. It melted at 297–300°.

Anal. Calc'd for $C_6H_{13}NO_2$: C, 54.93; H, 9.99.
Found: C, 55.04; H, 10.14.

The rotation showed it to be partially racemized *l*-leucine. $[\alpha]_D^{25} = -7°$ ($c = 1.0$ in water). Upon acidifying with hydrochloric acid, the rotation became $[\alpha]_D^{25} = +10°$. The mother liquor from leucine gave a positive pyrrole test, and the presence of proline was therefore suggested. However, an attempt to isolate it as the methyl ester, as described for the degradation of ergotamine, gave an oil which proved on distillation to be a mixture. The results obtained in the attempt to fractionate this mixture were not of a conclusive, clear-cut nature. The total methyl ester fraction weighed 0.27 g.

To determine whether the pyrrole test might have had its origin in hydroxyproline, the residue obtained after extraction of the above-mentioned free methyl ester was examined for this amino acid by the method of Lang, as modified by Waldschmidt-Leitz and Akabori.[11] This proved to be definitely negative.

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[11] K. LANG, *Z. physiol. Chem.*, **219**, 148 (1933); E. WALDSCHMIDT-LEITZ AND S. AKABORI, *ibid.*, **224**, 187 (1934).

[CONTRIBUTION FROM GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

SOME ASPECTS OF MOLECULAR SYMMETRY

JAMES K. SENIOR

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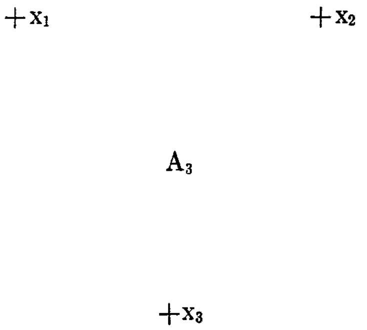
A fundamental problem in organic chemistry is the following: Consider a set *A* of *n* isomeric compounds and a set *B* of *n* structural or steric formulae. Assuming that *A* corresponds to *B*, how may a one-to-one correspondence between the individual compounds and the individual formulae be established? It is well known that the molecular symmetries of the various substances in question are often of great aid in solving this problem. Molecular symmetries may be investigated in various ways, and two of the methods most readily applicable to substances in the fluid states are the determinations of the optical activity and of the electric dipole moment. The purpose of the present paper is to consider certain inferences which may be drawn from the presence or absence of these two symmetry effects. The magnitudes of the two properties will not enter into the discussion.

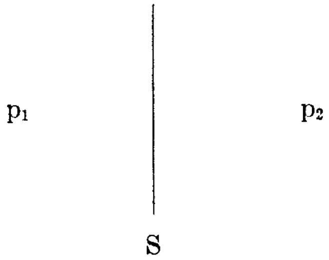
In approaching this subject, it is convenient first to solve one geometrical and electrostatic problem, and thus to obtain a general theorem which may then be applied chemically. This problem is: Given an assembly of electric point charges finite in number and relatively fixed in space, what are the symmetry and other conditions on the distribution of these charges necessary and sufficient to give the assembly a definite non-zero dipole moment? As is well known, the first condition is that the net charge on the assembly must be zero. Chemically speaking, this means that the rules to be developed apply only to neutral molecules and not to positive or negative ions. There remain to be considered the symmetry conditions, but before these can be discussed, a preliminary definition must be adopted in order to fix what is meant by the rotation or reflection of an electric charge.

Concerning the rotation there can be little question. In the assembly, an axis of rotation symmetry A_n (of period n) means that a point charge x_1 not located on this axis implies the presence of $n - 1$ other point charges $(x_2 \ldots\ldots x_n)$ equal in magnitude and sign to x_1. The n point charges thus defined lie on the vertices of a regular n-sided polygon at the center of which the symmetry axis A_n is erected as a perpendicular.



Where $n = 3$

In regard to a plane of reflection symmetry (S), on the other hand, two definitions are possible. The presence of a charge at the point p_1 (not on S) implies the presence of a charge of like absolute magnitude at the point p_2.



But is the sign of the charge at p_2 to be the same as that of the charge at p_1 or its negative? Although either of these alternatives leads to a self-coherent system, for chemical purposes the first alone comes into serious consideration. Reflection of a unit negative into a unit positive charge would mean the transformation by reflection of an electron into a positron —a theoretical operation which seems to have no connection with present experimental methods of molecular chemistry.

Assuming, then, that reflection alters the position but not the sign or magnitude of an electric charge, the following fundamental theorem may be proved. *If the symmetry of a finite assembly of point charges includes at least one homopolar axis, the assembly has no dipole moment.** Now the

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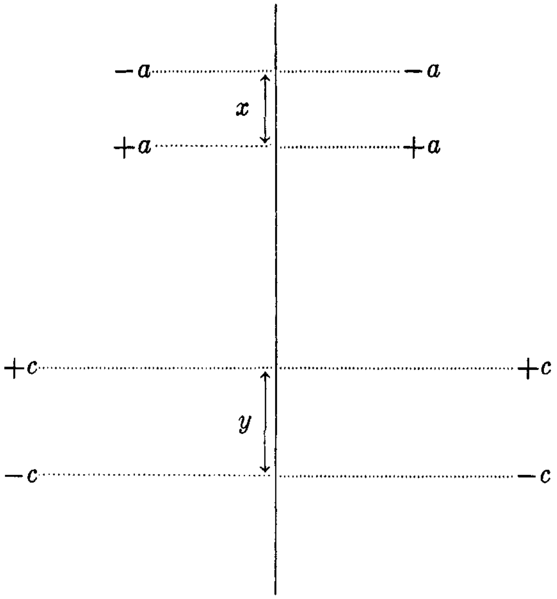
* For the proof (see appendix) of this theorem the author is greatly indebted to Dr. A. C. Lunn.

theory of the symmetry of finite rigid assemblies of points shows that every such assembly must have a symmetry completely defined by one of fourteen symbols.*

(*a*) $C_n, C_n^V, \bar{C}_{2n}, C_n^H, D_n, D_n^D, D_n^H$
(*b*) $T, T^D, T^H, K, K^H, P, P^I$

The first seven of these (*a*) refer to infinite classes, since the subscript n may have any finite positive integral value for the symbols in C and any finite positive integral value >1 for the symbols in D. The second seven (*b*) refer to individual cases. Of the fourteen, all but the first two in (*a*) indicate the presence of a homopolar axis among the symmetry elements. Consequently, if an assembly of point charges has any symmetry other than C_n or C_n^V, it can have no dipole moment.

There remains the question: if the assembly has the symmetry C_n or C_n^V, must it always have a dipole moment? That such is not the fact is illustrated by the following diagram.



A_2

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* $C_1^V = C_1^H = S$. $\bar{C}_2 = I$ (inversion). The fourteen symbols are essentially those developed by Schönflies. Their meaning is explained in most texts on symmetry, *e.g.*, F. M. Jaeger, "Lectures on the Principle of Symmetry" (Elsevier, Amsterdam, **1920**). To meet the special case of a linear distribution of points the symbols C_∞^V

A_2 is a binary axis of rotation; *a* and *c* represent the absolute magnitudes of the various point charges. The symmetry of the assembly is C_2^V. But, as may be seen from the diagram, if $ax = cy$ the "center of gravity" of the negative charges and the "center of gravity" of the positive charges coincide, and the assembly has no dipole moment. An exactly analogous argument holds for any symmetry C_n or C_n^V.

Physically, however, such a distribution of charges represents an unstable state. Destroying the equality of *ax* and *cy* without changing the symmetry would produce a dipole moment in the system. There is no obvious reason why a set of point charges should take on so special a configuration in the first place, and if by chance such a configuration were assumed, there is little probability that it would be maintained under varying conditions. Speaking chemically, if a substance with the molecular symmetry C_n or C_n^V chanced to show no dipole moment in benzene solution, it would almost certainly show a dipole moment when dissolved in carbon tetrachloride. The probability of the occurrence of a molecule with a symmetry C_n or C_n^V but no dipole moment may thus be regarded as negligible. At all events, the uncertainty introduced by this possibility into the experimental situation is far less than that caused by the imperfections in the methods of measuring the dipole moments. Hence, for practical purposes, a homopolar axis in the symmetry of an assembly of point charges is not only a sufficient but also a necessary condition for the absence of a dipole moment. That is to say, for practical purposes, if the symmetry is C_n or C_n^V, the dipole moment is not zero; if the symmetry is anything else, the dipole moment is zero.

TABLE I

OPTICAL ACTIVITY

DIPOLE MOMENT		+ or −	0
	+	C_n	C_n^V
	0	D_n T, K, P	$\bar{C}_{2n}$, $C_n^H (n \neq 1)$, D_n^D, D_n^H T^D, T^H, K^H, P^I

In the chemical application of this principle, the first question to be considered is the legitimacy of regarding the charged particles supposed to compose a molecule as an assembly of point charges rigidly fixed with re-

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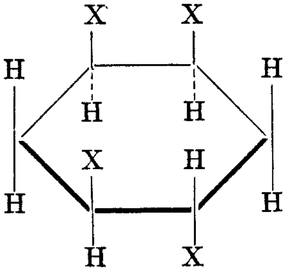
and D_∞^H should be added to the above list. These geometrically degenerate cases, however, add no complications to the theory here developed, and for the sake of brevity are not further considered.

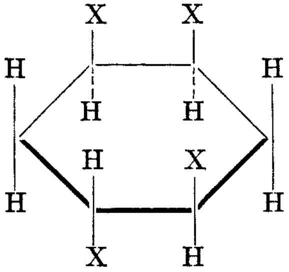
spect to one another. Atoms and electrons are not generally believed to be so rigidly fixed, but, at least where so-called "free rotation" in the molecules is absent, the periods and amplitudes of intramolecular vibrations are usually supposed to be such that the (time) average positions occupied by the various particles may (with close enough approximation) be considered as rigidly fixed relative to one another.

Confining attention for the moment to those molecules where free rotation is absent, the classic theory of stereochemistry furnishes one distinction between the various types of molecular symmetry. It distinguishes between those symmetries which include reflections and those which do not. If and only if a molecule has a symmetry of the latter class, is it optically active. In other words, optical activity divides the fourteen symmetry symbols into one set of five and one set of nine. The introduction of a new method of discrimination (namely the presence or absence of a dipole moment) serves to further divide these sets so that the final result can be graphed as in Table I.

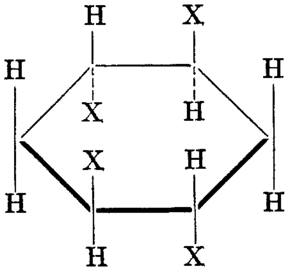
How useful such a double classification may be is well illustrated by the formulae for a set of stereoisomeric tetrasubstitution derivatives of cyclohexane.



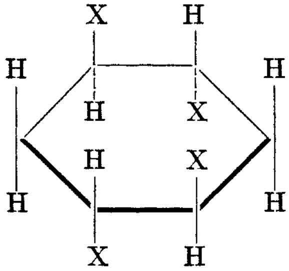
Ia (*d*)
C_1



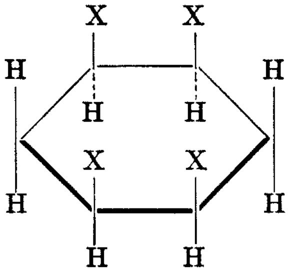
Ib (*l*)
C_1

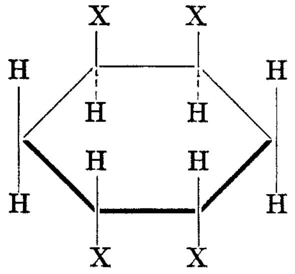


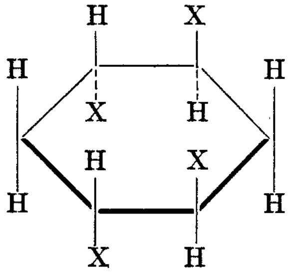
IIa (*d*)
D_2



IIb (*l*)
D_2


III
C_2^V


IV
C_2^H


V
C_2^H

The pairs I (a and b) and II (a and b) are enantiomorphic, and the symbols (*d*) and (*l*) have only a relative significance. Hence, so long as such a pair of compounds is considered by itself, there can be no means of assigning one formula to each substance. This portion of stereochemical theory is not changed by the introduction of considerations dealing with dipole moments. But further, the polariscope by itself furnishes no method of distinguishing between the I pair and the II pair. And here the usefulness of the dipole moment at once appears. The members of the I pair have dipole moments; those of the II pair do not. Among the optically inactive compounds, III has a dipole moment and is thus identified; IV and V have no dipole moments, but since the symbol in either case is C_2^H, mere considerations of symmetry are insufficient to distinguish between the two.*

In current stereochemical theory, the univalent substituents designated by X are, for the purpose of the argument, regarded as single points, and experiment has shown that, so long as the univalent substituents are not themselves dissymmetric (optically active), this assumption leads to

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* They may however be identified by other methods; *e.g.*, their genetic relations with pentasubstitution derivatives of formula $C_6H_7X_5$.

verifiable results. With regard to dipole moments, the situation is not so simple. A univalent substituent which produces a dipole moment in the molecule can be considered as a point only when no component of the internal moment of that substituent is perpendicular to the line of the valence bond uniting the substituent with the rest of the molecule. Whether or not a substituent X meets this condition, may be decided by the behavior of the *para*-disubstituted benzene derivative XC_6H_4X. If this derivative has no dipole moment, the substituent X may be safely used in the solution of problems of the kind indicated in the previous paragraph; otherwise it may not. Some of the most common substituents are thus classified in Table II.*

Note that among the substituents of type I there is not one with good compound-forming properties. It is therefore very difficult to combine the dipole moment method of investigation with the ordinary methods of optical resolution so long as only substituents of type I are used. Substituents of type II might also be used if there were available a method of resolving the dipole moment produced by such a substituent into two components—one along the line of union with the molecule, and one perpendicular to this line. Only the first of these components is important for the problem in hand. Various combination procedures are also conceivable. For example, the dipole moments in the above set of isomers might be determined where X is $-NO_2$. The tetranitro compounds might then be reduced to tetra-amino compounds, and the optical resolutions carried out in the usual way. But in any case rather cumbersome and indirect methods would have to be employed.

TABLE II

TYPE I DIPOLE MOMENT OF X  X IS ZERO	TYPE II DIPOLE MOMENT OF X  X IS NOT ZERO
X = H, F, Cl, Br, I $-CH_3$, $-NO_2$ −CN (?), $-C_6H_5$ (?)	X = −OH, $-OCH_3$, $-NH_2$, $-N(CH_3)_2$ −COOR, $-O-\underset{\underset{O}{\|}}{C}R$, $-\overset{H}{C}{=}O$

Where more than one sort of univalent substituent is used, there is

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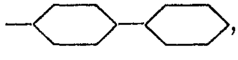
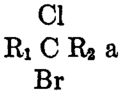
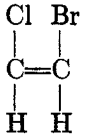
* The dipole moment data here quoted are taken from the table in Freudenberg's "Stereochemie" (Deuticke, Leipzig, **1933**, pp. 232 *et seq.*) Obviously other substituents of type I may be manufactured by combining the above listed substituents of this type; *e.g.*,

Cl, , $-CCl_3$, $-C(CH_3)_3$ etc.

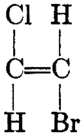
another serious limitation on the dipole moment method. The polariscope clearly distinguishes between chlorine and bromine. For instance, compounds of the type  $R_1\overset{Cl}{\underset{Br}{C}}R_2$ are not known to be particularly resistant to resolution. But the limit of accuracy of the dipole moment method is such that this distinction is sometimes obscured. Take for example the pair of isomers I and II.

I



(S)

II



(S)

I shows a positive dipole moment, but II does not, although both have the symmetry (S) of a single plane. In II, the dipole moments associated with the chlorine and bromine atoms are exerted in opposite directions along the same line. The difference in their magnitudes is apparently too small to be experimentally detected. Consequently, where bromine and chlorine atoms are used as univalent substituents, the absence of a detectable dipole moment in the resulting compound does not always permit the inference that the molecular symmetry of this substance involves a homopolar axis. And the same uncertainty might possibly in some cases adhere to the pairs fluorine and chlorine or bromine and iodine.

When molecules which permit free rotation are considered, the situation becomes more complex. Such a molecule cannot be said to have any fixed symmetry in the sense in which this property is ascribed to a rigid object. The situation usually encountered is that, in all but certain special phases of the rotation, the molecular model exhibits a definite minimal symmetry; in passing through certain special phases, it acquires momentarily higher symmetries which include the lower symmetry already referred to. If these lower and higher symmetry forms are either all in the class which calls for a dipole moment or all in the class which calls for no dipole moment, then no complications arise. (See cases 1–4, Table III). But case 5 is different. Here the presence or absence of a measurable dipole moment presumably depends upon the statistical distribution of the molecules among the various phases. If all forms were equally frequent, the effect of the single C^{H}_{2} form would be negligible compared with the net effect of the very large number of C_2 forms. From considerations of electric repulsion, the C^{H}_{2} form should be statistically preferred, but experiment shows that there is still enough material in the C_2 and C_2^V forms to give rise to a considerable dipole moment.

Paraxylylene dichloride ($ClCH_2C_6H_4CH_2Cl$), is still more complex, as there are two bonds about which free rotation can occur. The minimum symmetry is C_1, but in various special positions the symmetries C_2, S, $\bar{C}_2$, C_2^V and C_2^H are all attained. Of these C_1, C_2, S and C_2^V call for a dipole moment; $\bar{C}_2$ and C_2^H call for none. Experimentally, the net result is again an easily detectable dipole moment.

In all cases known to the author, the dipole moment actually found for a given non-rigid compound is the one compatible with the low symmetry of that compound in the general (not special) form. The optical rotation on the other hand indicates one of the higher symmetries.* In other words, the polariscope seems to detect the highest possible molecular symmetry; the results obtained by the dipole moment method seem to depend on the lowest possible symmetry. The reason for this divergence probably lies in the fact that optical rotation may be either positive or negative, whereas a negative dipole moment is an absurdity. Suppose a molecule to be in a highly symmetric form in which both its optical activity and its dipole moment are zero. Disturbing forces which distort the system from this initial position may in certain cases, by lowering the symmetry, produce both optical rotation and a dipole moment. But if the molecules are isotropically distributed relative to such disturbing forces, one half of the optical rotation is positive, the other half negative, and the net rotation zero. Moreover if the vibrations set up by the disturbing forces are of high frequency (as is usually assumed), rapid autoracemization prevents the optical resolution of the fifty-fifty mixture. The final result is thus

TABLE III

CASE	COMPOUND	LOWER SYMMETRY	HIGHER SYMMETRIES	DIPOLE MOMENT
1	$CH_3 - CH_3$	D_3	D^D D_3^H	0 in all phases
2	$CH_3 - CH_2Cl$	C_1	S	+ in all phases
3	$CH_3 - CHCl_2$	C_1	S	+ in all phases
4	$CH_3 - CCl_3$	C_3	C_3^V	+ in all phases
5	$ClCH_2 - CH_2Cl$	C_2	C_2^V, C_2^H	+ in C_2 and C_2^V phases 0 in C_2^H phase

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* The ideas here developed for "free rotations" apply equally well to other types of vibration. For example, the polarimetric results for ammonia and its univalent substitution derivatives indicate the highest symmetry D_3^H for the ammonia molecule. The dipole moment reveals a lower symmetry—probably C_3^V.

just what would have been found if the molecule had remained in its original, undistorted, highly symmetric and optically inactive form. On the other hand, the dipole moments in the distorted forms are all positive, and thus the resultant (time) average dipole moment is not zero—the same result which would have been found if the molecule had never been in its undistorted and highly symmetric form.

There is nothing satisfactory in the cumbersome sort of development which appears to be necessary in order to connect optical activity and dipole moment with symmetry in systems which are not supposed to be (even approximately) rigid. Nor need this state of affairs occasion surprise. The attempt to apply a symmetry system designed for rigid objects to collections of objects in motion with respect to one another could scarcely be expected to lead to esthetic solutions. The appropriate mathematical tool for the treatment of such non-rigid systems is a comprehensive theory of four- (three space and one time) dimensional symmetry. Such a theory is greatly needed for the solution of various chemical problems, and the dipole moment situation merely emphasizes a long-felt want.

APPENDIX

In an assembly of point charges which is as a whole electrically neutral, the dipole moment is independent of the point from which the position vectors of the individual point charges are reckoned. If the number of points is finite, the assembly, under its group of symmetry, has at least one invariant point O, here taken as origin, through which pass all axes and planes of symmetry. This point is also the center of symmetry if such a center is present.

Let the points be classified into "sets of transitivity" relative to the cyclic group of rotations associated with any axis of rotation A. Any single such subset is composed of equal charges at the vertices of a regular polygon perpendicular to A with center on A. It is understood that the half-turn case of a pair of points is no exception to this rule. The vector moment of such a polygon of equal charges is $e\ \Sigma\rho_i$ where e is the individual charge and ρ_i the position vector of the i-th vertex. On account of symmetry, this moment reduces to $ne\beta$ where n is the number of vertices and β the vector from O to the center of the polygon.

If the plane of the polygon contains O, then β is zero, so that the dipole moment of the subset by itself is zero. If the plane of the polygon does not contain O, and the axis A is homopolar, then there is another like polygon in a parallel plane so situated that the centers of the two polygons are inverse points relative to O. In this case the two β's are opposite vectors and the dipole moment of the two subsets together is zero. The moment of the whole assembly may thus be exhibited as a sum of zeros whenever a homopolar axis is present.

This proof supposes that the conjugate of a charge under any operation of symmetry is an algebraically equal charge. If the conjugate under an operation of the "second kind" were supposed to be an opposite charge, the zero value of the dipole moment would not follow, if the homopolarity of the axis were only of the second kind.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE HYDROLYTIC INSTABILITY OF THE CARBON-TO-CARBON BOND

M. S. KHARASCH AND JULIUS PORSCHE

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INTRODUCTION

Kharasch and co-workers have postulated[1,2] that the substitution of a strongly electronegative* group for a hydrogen atom in methane decreases the electronegativity of the methane carbon atom. It is a logical consequence of this concept that, beyond a certain liminal value of decreased electronegativity of the methane carbon atom, the bonds linking the methane carbon atom to strongly electronegative substituents should be distinctly polar† in character. An investigation was undertaken to determine whether or not such a threshold may be reached among carbon-to-carbon bonds.

The literature contains but little evidence for the existence of markedly polar carbon-to-carbon bonds.[3] The necessary search for a molecule or group containing a powerfully electronegative carbon atom was simplified by a clue obtained from the work of Kharasch and Howard.[4] Their study of the stability of the carbon-to-nitrogen bond demonstrated that the 1 carbon atom of 2-naphthol is very strongly electronegative—a conclusion supported by the chemical behavior of 2-naphthol. The molecular

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[1] KHARASCH AND MARKER, *J. Am. Chem. Soc.*, **48**, 3130 (1926).

[2] KHARASCH AND REINMUTH, *J. Chem. Educ.*, **5**, 409 (1928).

* Electronegative is here used in the sense defined by Kharasch and co-workers, *loc. cit.*

† Electrovalence is not here implied, although that would be the extreme type of the phenomenon under consideration. This paper, however, deals with what the authors believe to be unsymmetrical covalences.

[3] (*a*) KOSTANECKI AND ZIBELL, *Ber.*, **24**, 1695 (1895).

(*b*) NIETZKI AND GUITERMAN, *ibid.*, **20**, 1274 (1887).

(*c*) MOEHLAU AND STROBACH, *ibid.*, **33**, 804 (1900).

(*d*) BOEHM, *Ann.*, **318**, 259 (1901).

(*e*) BRASS AND FIEDLER, *Ber.*, **65B**, 1654 (1932).

The foregoing references cite some of the more important instances of marked polarity of carbon-to-carbon bonds.

[4] KHARASCH AND HOWARD, *J. Am. Chem. Soc.*, **56**, 1370 (1934).

types

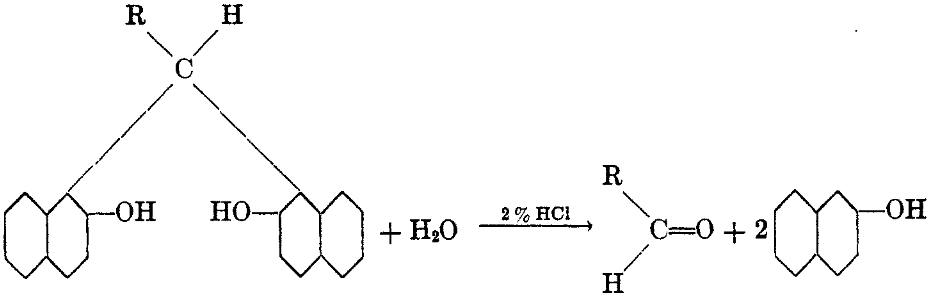
and ϕ_3C-phenol suggest themselves because of the possibility of wide variation in the electronegativity of R and of the phenol.

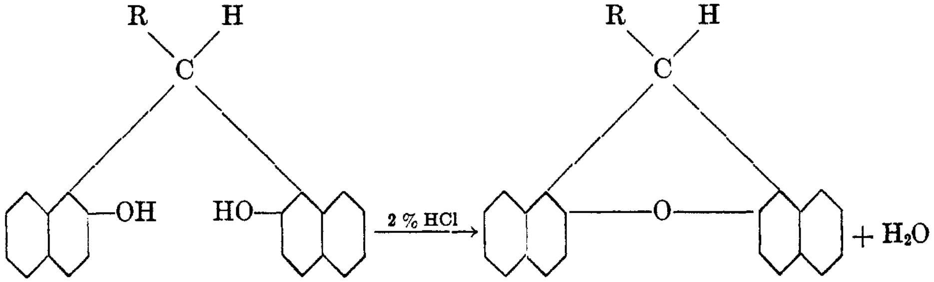
One of the criteria of bond polarity adopted was susceptibility to acid hydrolysis under comparatively mild experimental conditions. Hydrochloric acid was chosen as the hydrolytic agent because of its strongly acid and exceedingly feeble reducing properties. Acetic acid has been used as a solvent for convenience in manipulation and in the isolation of the compounds studied and their decomposition products.

RESULTS

The series of compounds listed in the accompanying tables has been synthesized and the various members have been subjected to treatment with two per cent. hydrochloric acid in boiling glacial acetic acid.

Two distinct reactions indicated by the following equations, occur almost instantaneously.





The chief reaction is that involving scission of the carbon-to-carbon bond. The results obtained are summarized in Table I. 1-Benzyl-2-naphthol, submitted to this treatment, was recovered unchanged.

With a view to preventing dibenzoxanthene formation, the corresponding methoxynaphthyl compounds have been prepared and subjected to the same treatment. Rupture of the carbon-to-carbon bond was again observed with consequent formation of an aldehyde and 2-methoxynaphthalene. The extent of formation of 2-methoxynaphthalene, corresponding to variations in the group R is recorded in Table I.

TABLE I

EXTENT OF HYDROLYSIS OF THE DI-1-(2-HYDROXYNAPHTHYL)METHANES AND THEIR DIMETHYL ETHERS

R	SUBSTITUTED DI-1-(2-HYDROXYNAPHTHYL) METHANES			DIMETHYL ETHERS
	C-C Scission in Mole %	Xanthene Formation	Unchanged Material	C-C Scission in Mole %
p-Dimethylaminophenyl*	15	?	?	Not prepared
p-Anisyl	35	?	?	45
Phenyl	50	20	30	45
m-Nitrophenyl	30	10	40	10
o-Nitrophenyl	5	5	85	Trace
Phenethyl	35	?	?	35
Hydrogen	5	15	80	5
Trichloromethyl	Not prepared			None

* Under the experimental conditions employed it is actually the hydrochloride of this compound that is investigated.

TABLE II

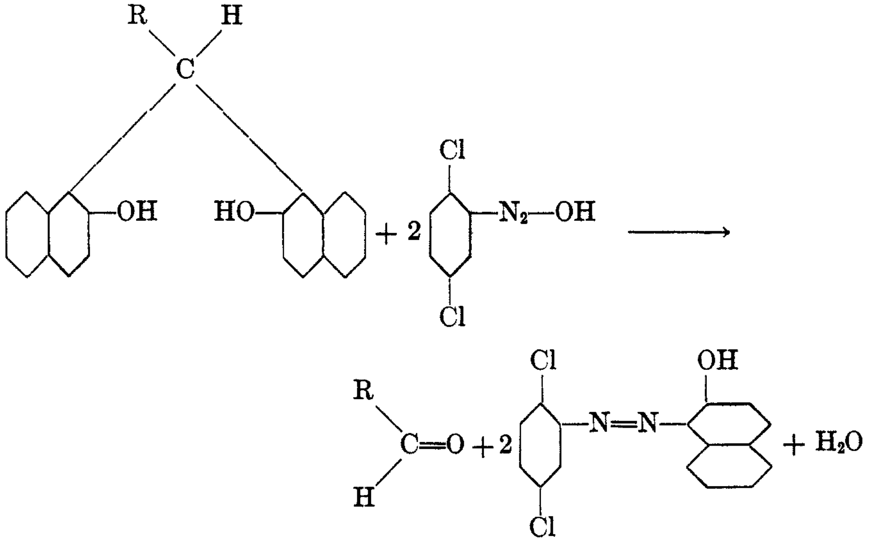
YIELDS OF 2,5-DICHLOROBENZENEAZO-2-NAPHTHOL OBTAINED FROM THE DI-1-(2-HYDROXYNAPHTHYL)METHANES

R	% YIELD	M.P.
p-Anisyl	80	170–3°
Phenyl	48	171–4°
Hydrogen	47	155–65°
Phenethyl	64	170–5°
m-Nitrophenyl	49	160–5°
o-Nitrophenyl	0	
p-Dimethylaminophenyl	(0.75 g.)	125–35°
1-(2-Hydroxynaphthyl)	96	177–9°

The dibenzoxanthenes were not affected by two per cent. hydrochloric acid.

Nuclear triphenylmethyl derivatives of phenol, resorcinol, resorcinol dimethyl ether and 2-naphthol have been subjected to the same treatment without evidence of decomposition.

Further evidence for the marked polarity of the dinaphthol methane derivatives has been obtained by treating them in acetic acid solution at room temperature, with the *anti*-diazotate of 2,5-dichloroaniline. They are found to react with the resultant diazo reagent at varying rates, depending on the nature of the group R, in accordance with the following equation.



1-Triphenylmethyl-2-naphthol does not undergo decomposition under these conditions, but couples, as a unit, with the diazo compound. The results of the experiments performed are presented in Table II.

DISCUSSION

The results obtained demonstrate strikingly the necessity of passing a certain threshold* of decreased electronegativity of the methane carbon atom before it is possible to obtain perceptible evidence of marked polarity. The stability of the tetraärylmethanes seems to indicate that three phenyl groups and one 4-hydroxyphenyl or one 2,4-dihydroxyphenyl group are insufficient to induce the liminal degree of electronic displacement. Similarly one phenyl and one naphthol group are insufficient, as evidenced by the stability of 1-benzyl-2-naphthol toward the reagents employed. One might conclude further, from the stability of 1-triphenylmethyl-2-naphthol to two per cent. hydrochloric acid, that three phenyl groups and one naphthol group are also insufficient were it not for the observation that

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* This concept is discussed in greater detail by KHARASCH, REINMUTH AND MAYO, *J. Chem. Educ.*, **11**, 82 (1934).

the molecule couples, as a whole, with the diazo reagent. This reaction suggests the possibility that the 1 position of the naphthol group is free and that the structure is not 1-triphenylmethyl-2-naphthol as proposed by Hardy.[5] Two naphthol groups and two hydrogen atoms, however, as in di-1-(2-hydroxynaphthyl)methane, are just sufficient to exceed the liminal degree of electron displacement. Two per cent. hydrochloric acid effects a scission of the carbon-to-carbon bond that is just perceptible, as indicated in Table I, and a more striking indication is obtained by removing 2-naphthol as 2,5-dichlorobenzeneazo-2-naphthol and displacing the equilibrium as shown in Table II. Further decrease in the electronegativity of the methane carbon atom through the substitution of a strongly electronegative group for one of the remaining hydrogen atoms in di-1-(2-hydroxynaphthyl)methane results in augmented hydrolytic instability of the bonds between the naphthol groups and the methane carbon atoms. The very weakly electronegative *o*-nitrophenyl and trichloromethyl groups were the only substituents employed which did not enhance the polarity of the molecule.

Examination of the data reveals a correlation, although not an exact parallelism between the relative electronegativities of the R groups and the rates of carbon-to-carbon scission. However, consideration of the side reactions which might occur simultaneously with the scission of the carbon-to-carbon bond makes it evident that the electronegativity of the radicals is the dominant although not the sole factor determining the rate of scission. Some of the complications introduced by side reactions are avoided by methylation of the reactive naphtholic hydroxyl groups, or by the removal of 2-naphthol as an insoluble azo compound, and it is clear from the results tabulated that when this is done a much closer correlation may be obtained between the relative electronegativity of R and the relative rate of carbon-to-carbon bond scission.

In order to demonstrate that the carbon-to-carbon bond scission is hydrolytic rather than thermal in nature, two grams of 1,1′-benzalbis-2-naphthol was subjected to the same treatment that led to fifty per cent. decomposition, except that the hydrochloric acid addition was omitted, and was recovered without change. Similarly, 1,1′-*p*-anisalbis-2-naphthol was unchanged after heating in benzene solution at 150° for five hours.

EXPERIMENTAL

Preparations

*1,1′-(*p*-Dimethylaminobenzal)bis-2-naphthol.*—The method of Hewitt, Turner and Bradley[6] for the preparation of the hydrochloride was employed with but slight

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[5] HARDY, *J. Chem. Soc.*, **1929**, 1000.

[6] HEWITT, TURNER AND BRADLEY, *ibid.*, **81**, 1207 (1902).

modification.[7] The hydrochloride was made into a paste with acetone and treated with an excess of sodium bicarbonate solution. The free base was extracted with an ether-acetone mixture. Evaporation of the dry (sodium sulfate) solution yielded a brown solid from which a snow-white crystalline solid was obtained by repeated crystallizations from alcohol. Yield, 50–60%; m.p., 175–6° (dec.)

Anal. Calc'd for $C_{29}H_{25}NO_2$: C, 83.01; H, 6.01.

Found: H, 6.35, 6.29; C, 82.90, 82.89.

1,1'-(p-Anisal)bis-2-naphthol.—Anisaldehyde (13. 6g.) and 28.8 g. of 2-naphthol were dissolved in 120 cc. of glacial acetic acid. The solution was cooled to about 5° and treated with 4 cc. of concentrated hydrochloric acid. The solution was kept at 5° in a tightly stoppered flask. After 48 hours a precipitate separated, and was collected on a filter and washed thoroughly with 70% acetic acid. The product was crystallized twice by the addition of water to its boiling alcoholic solution until crystallization commenced. The substance was completely soluble in 2% NaOH. Yield, 60%; m.p., 190–2° (dec.).

Anal. Calc'd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.46.

Found:* C, 82.40, 82.16; H, 5.74, 5.66.

1,1'-Benzalbis-2-naphthol:—The following modifications of Hewitt and Turner's[8] procedure facilitated the isolation of a pure product. The condensation was allowed to take place at 5° and 0.1% sodium acetate was added to the glacial acetic acid used for crystallization.

The melting point observed was 203–4° (dec.).

1,1'-[o- (and m-) Nitrobenzal]bis-2-naphthols.—Great difficulty was experienced in the isolation of products free from the corresponding nitrophenyldibenzoxanthenes. This difficulty may be obviated by mixing the reagents and permitting the condensation to proceed at a temperature of 5–10°. Furthermore, the rate of addition of the condensing agent must be slow in order to avoid local heating effects. 1,1'-(*o*-Nitrobenzal)bis-2-naphthol is very sensitive to light and must be kept in the dark. Observation of these precautions made it possible to duplicate the results of Dischendorfer.[9] 1,1'-(*o*-Nitrobenzal)bis-2-naphthol, m.p. 205–7° (dec.); 1,1'-(*m*-nitrobenzal)bis-2-naphthol, m.p. 182–3° (dec.).

1,1'-(γ-Phenylpropional)bis-2-naphthol.—All efforts to synthesize this molecule by direct condensation of hydrocinnamaldehyde with 2-naphthol led almost exclusively to products insoluble in alkali. The following procedure, however, gives a satisfactory yield of the pure compound.

γ-Phenyl-α-1-(2-hydroxynaphthyl)propyl-γ-phenylpropylidenamine (26.2 g.) and 40 g. of 2-naphthol were dissolved in a minimum quantity of boiling benzene. The temperature of the mixture was kept at 90°–100° for ten hours. Completion of the reaction was recognized by triturating a sample of the gum with cold alcohol. The Schiff base is very insoluble in cold alcohol and separates in the form of white needles if present in appreciable quantities.

When the reaction was complete, the brown gum was extracted four times with one-liter portions of boiling water. The residue was dissolved in about 250 cc. of cold acetone, and treated with 750 cc. of two per cent. sodium hydroxide solution. A small amount of insoluble material was removed by filtration. Acidification of

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[7] PORSCHE, Doctorate Dissertation, University of Chicago (1933).

* Considerable difficulty was experienced in burning many of the di-2-naphthol methanes.

[8] HEWITT AND TURNER, *Ber.*, **34**, 202 (1901).

[9] DISCHENDORFER, *Monatsh.*, **48**, 543 (1927); **49**, 137 (1928).

the filtrate precipitated an oil which solidified on standing for a short time. The latter was subjected to three crystallizations from alcohol by the addition of sufficient water to produce a permanent turbidity at the boiling point. This treatment yielded a tan-colored crystalline substance. Two crystallizations from toluene were sufficient to remove all the color from the compound. The product was completely soluble in dilute NaOH. Yield, 60–65%; m.p., 172–3°.

Anal. Calc'd for $C_{29}H_{24}O_2$: C, 86.10, H, 5.98.
Found: C, 85.82, 86.08; H, 6.45, 6.23.

The Di-1-(2-methoxynaphthyl)methanes (1,1'-formalbis-2-methoxynaphthalenes).—With the exception of 1,1'-trichloroacetalbis-2-methoxynaphthalene, all the dimethyl ethers were prepared in the following manner.

A ten per cent. solution of di-1-(2-hydroxynaphthyl)methane in acetone was stirred vigorously. Two per cent. sodium hydroxide and methyl sulfate (four moles of each) were added from dropping funnels in such a way that the solution remained faintly alkaline. The resulting mixtures were stirred for one hour to permit completion of the reaction. The products were precipitated by addition of water and redissolved in acetone. Four more moles of sodium hydroxide and methyl sulfate were added, and the products were precipitated completely with water. These substances were invariably very pure, although not always obviously crystalline.

1,1'-(p-*Anisal)bis-2-methoxynaphthalene.*—The product was crystallized from glacial acetic acid; m.p. 194–5°.

Anal. Calc'd for $C_{30}H_{26}O_3$: C, 82.90, H, 6.04.
Found: C, 82.89, 82.66; H, 6.12, 6.14.

1,1'-Benzalbis-2-methoxynaphthalene.—The product was crystallized from glacial acetic acid; m.p. 184°.

Anal. Calc'd for $C_{29}H_{24}O_2$: C, 86.10; H, 5.98.
Found: C, 86.00, 85.89; H, 5.97, 5.90.

1,1'-(m-*Nitrobenzal)bis-2-methoxynaphthalene.*—Dilute acetic acid was used to crystallize this compound. The observed melting point was 172–3°, whereas Dischendorfer[9] reported 216°.

Anal. Calc'd for $C_{29}H_{23}NO_4$: C, 77.47; H, 5.16.
Found: C, 77.69, 77.39; H, 5.92, 5.97.

1,1'-(o-*Nitrobenzal)bis-2-methoxynaphthalene.*—The solvent used for crystallization was again dilute acetic acid. The observed m.p. was 196–7°, whereas Dischendorfer[9] reported 191°.

1,1'-(γ-Phenylpropional)bis-2-methoxynaphthalene.—The product was crystallized from alcohol; m.p., 146–7°.

Anal. Calc'd for $C_{31}H_{28}O_2$: C, 86.09; H, 6.53.
Found: C, 86.00, 86.05; H, 6.60.

Di-1-(2-methoxynaphthyl)methane (1,1'-formalbis-2-methoxynaphthalene).—The observed melting point was 146–7°, whereas Kohn and Ostersetzer[10] report 144–5°.

Hydrolyses

The following method has been adopted for a comparative study of the extent of carbon-to-carbon scission in the presence of two per cent. hydrochloric acid.

Two grams of each compound was dissolved in 50 cc. of boiling glacial acetic acid. The source of heat was removed, and when ebullition ceased, 2.4 cc. of hydrochloric acid (sp. gr. 1.18) was added with agitation of the solution. The resulting mixture

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[10] Kohn and Ostersetzer, *ibid.*, **38**, 402 (1918).

was dropped into 150 cc. of boiling water through which a rapid current of steam was passing. The rate of addition was such that three to five minute were required for its completion. Distillation was continued for ten to fifteen minutes.

1,1'-Benzalbis-2-naphthol.—The steam distillate was collected in a flask containing one cc. of phenylhydrazine dissolved in a little glacial acetic acid. After two hours, 0.49 g. of benzaldehyde phenylhydrazone (m.p., 154–5°) was obtained by filtration of the distillate.

The suspension remaining in the distillation flask was removed by filtration while the mixture was hot, and dissolved in acetone. The addition of an excess of two per cent. sodium hydroxide to the acetone solution precipitated 0.40 g. of a crystalline substance which was identified as 14-phenyldibenzo(*aj*)xanthene. Acidification of the alkaline solution yielded 0.52 g. of 1,1'-benzalbis-2-naphthol. Neutralization of the dilute acetic acid from the distillation flask and subsequent saturation with sodium chloride precipitated 0.77 g. of nearly colorless crystals (m.p. 117–20°) which were identified as 2-naphthol.

1,1'-(p-Dimethylaminobenzal)bis-2-naphthol.—None of the starting material or the corresponding dibenzoxanthene could be isolated from the brown gum which remained in the distillation flask.

Neutralization of the supernatant dilute acetic acid solution and saturation with salt yielded a small quantity of a green gum from which 0.20 g. of 2-naphthol was obtained by extraction with boiling water containing Norite.

1,1'-(p-Anisal)bis-2-naphthol.—None of the starting material could be isolated from the red gum that remained in the distillation flask. It was possible, however, to obtain 0.18 g. of colorless needles which were identified as 14-*p*-anisaldibenzo(*aj*)-xanthene.

The dilute acetic acid solution yielded 0.60 g. of a red-brown crystalline substance; m.p., 114–19°. Extraction of the solid with ten per cent. sodium hydroxide left 0.05 g. of a light-brown solid of unknown constitution; m.p., 240–3°. Acidification of the alkaline extract precipitated 0.45 g. of 2-naphthol; m.p., 118–20°.

1,1'-(m-Nitrobenzal)bis-2-naphthol.—The alkali-insoluble fraction of the gum remaining in the distillation flask weighed 0.23 g. and was identified as 14-*m*-nitrophenyldibenzo(*aj*)xanthene. The alkali-soluble portion yielded 0.90 g. of the starting material and a small quantity of gum that resisted all efforts at purification.

2-Naphthol (0.42 g.) was recovered in the manner previously described.

1,1'-(o-Nitrobenzal)bis-2-naphthol.—14-*o*-Nitrophenyldibenzo(*aj*)xanthene (0.07 g.) was obtained by the usual technique from the red-brown gum in the distillation flask. The alkali-soluble fraction contained 1.70 g. of the starting material contaminated with a dark, tarry impurity which could be removed only by repeated crystallization from acetic acid.

A small amount of red gum was obtained from the hot solution in the distilling flask. Two crystallizations from water (Norite) resulted in the isolation of 0.01 g. of 2-naphthol; m.p., 118–20°.

1,1'-(γ-Phenylpropional)bis-2-naphthol.—Repeated crystallizations of the alkali-insoluble fraction of the residual yellow gum from benzene-alcohol yielded 0.07 g. of a white crystalline substance (m.p., 173°) which was assumed to be 14-phenethyldibenzo(*aj*)xanthene.

Anal. Calc'd for $C_{29}H_{22}O$: C, 90.11; H, 5.74.
Found: C, 89.51, 89.86; H, 6.07, 6.13.

It was impossible to separate the alkali-soluble fraction into its constituents.

The usual treatment of the dilute acetic acid solution yielded 0.48 g. of 2-naphthol.

Di-1-(2-hydroxynaphthyl)methane (1,1'-formalbis-2-naphthol).—Alkali-insoluble material (0.29 g.; m.p., 183–90°) was obtained from the residue in the distillation flask. It was identified as dibenzo(*aj*)xanthene. Of the starting material, 1.48 g. was recovered. Semicrystalline material (0.15 g.) was obtained upon neutralization of the dilute acetic acid. Extraction with hot water yielded .055 g. of 2-naphthol, and recrystallization of the residue from alcohol-water left .08 g. of the original material.

1-Benzyl-2-naphthol.—1-Benzyl-2-naphthol (1.97 g.; m.p. 112–13°) was recovered. Treatment with an aqueous solution of the anti-diazotate of 2,5-dichloroaniline proved the absence of 2-naphthol in the distillate and in the distilling flask.

The Di-1-(2-methoxynaphthyl)methanes (1,1'-formalbis-2-methoxynaphthalenes).—The same hydrolytic procedure was followed as in the case of the di-1-(2-hydroxynaphthyl)methanes except that steam distillation was continued until no more methoxynaphthalene appeared in the distillate. Two grams of material was used in each experiment.

1,1'-Benzalbis-2-methoxynaphthalene.—Extraction of the residual tar with ether yielded 0.26 g. of crystalline material; m.p., 170–6°. This was identified as the starting material. All attempts to separate the remaining resinous substance into its constituents failed.

2-Methoxynaphthalene (0.70 g.) was obtained from the distillate.

*1,1'-(*p*-Anisal)bis-2-methoxynaphthalene.*—None of the starting material could be recovered from the residual gum.

The distillate yielded 0.65 g. of 2-methoxynaphthalene.

*1,1'-(*m*-Nitrobenzal)bis-2-methoxynaphthalene.*—Fractional crystallization of the residual material from acetone-water mixtures resulted in the recovery of 1.35 g. of the starting material. The remainder of the residue was a brown oil containing a small amount of *m*-nitrobenzaldehyde.

The distillate yielded 0.13 g. of 2-methoxynaphthalene.

*1,1'-(*o*-Nitrobenzal)bis-2-methoxynaphthalene.*—A residue (1.95 g.; m.p., 194–6°) was obtained. Only a faint odor of 2-methoxynaphthalene could be detected.

1,1'-(γ-Phenylpropional)bis-2-methoxynaphthalene.—A yellow resinous substance, which was not purified, remained in the distillation flask. 2-Methoxynaphthalene (0.52 g.) was isolated from the distillate.

Di-1(2-methoxynaphthyl)methane (1,1'-formalbis-2-methoxynaphthalene).—The crystalline residue weighed 1.86 g.; m.p., 136–42°. After several crystallizations from alcohol, the mixture was shown to consist chiefly of the starting material.

The distillate contained 0.10 g. of 2-methoxynaphthalene.

1,1'-Trichloroacetalbis-2-methoxynaphthalene.—A half-gram of the substance was subjected to the treatment previously described; 0.47 g. was recovered. No 2-methoxynaphthalene could be detected.

The dibenzoxanthenes.—Half-gram portions of 14-phenyl- (and 14-*p*-anisyl-) dibenzo(*aj*)xanthenes were recovered quantitatively after treatment with two per cent. hydrochloric acid.

The tetraärylmethanes.—No triphenylcarbinol could be isolated, following the previously described treatment with two per cent. hydrochloric acid of any of the four substances examined.

Reactions with Diazo Reagent.—A 0.5 g. portion of each substance investigated was dissolved in 50 cc. of glacial acid, and the solutions were cooled to room temperature. Twenty cc. of water, containing four moles of the *anti*-diazotate of 2,5-dichloroaniline for each mole of compound, was added dropwise to each of the solutions, with agitation. After five to seven minutes, the red precipitates were collected on filters washed with 50% acetic acid and water. The weights and melting points of the products have been recorded in Table II.

One gram of 1-triphenylmethyl-2-naphthol yielded 1.50 g. of a red substance, (m.p., 265–73°). After crystallization from pyridine-methyl alcohol, the m.p. 275–7° was obtained.

Anal. Calc'd for $C_{35}H_{24}Cl_2N_2O$: N, 5.01.
Found: N, 5.00.

SUMMARY

1. The validity of the general theory of the stability of the carbon-to-carbon bond[1,2] has received further experimental confirmation in the case of markedly polar carbon-to-carbon bonds.

2. Carbon-to-carbon bonds which possess the remarkable property of undergoing hydrolytic scission in the presence of dilute mineral acids have been investigated.

3. The following new compounds have been prepared:
   - (a) 1,1′-(*p*-anisal)bis-2-naphthol,
     p-$CH_3O \cdot C_6H_4 \cdot CH:(C_{10}H_6OH)_2$;
   - (b) 1,1′-(*p*-anisal)bis-2-methoxynaphthalene,
     p-$CH_3O \cdot C_6H_4 \cdot CH:(C_{10}H_6OCH_3)_2$;
   - (c) 1,1′-benzalbis-2-methoxynaphthalene,
     $C_6H_5 \cdot CH:(C_{10}H_6OCH_3)_2$;
   - (d) 1,1′-(γ-phenylpropional)bis-2-methoxynaphthalene,
     $C_6H_5 \cdot C_2H_4 \cdot CH:(C_{10}H_6OCH_3)_2$;
   - (e) 1,1′-(γ-phenylpropional)bis-2-naphthol,
     $C_6H_5 \cdot C_2H_4 \cdot CH:(C_{10}H_6OH)_2$;
   - (f) 14-phenethyldibenzo(*aj*)xanthene,
     $C_6H_5 \cdot C_2H_4 \cdot CH:(C_{10}H_6)_2O$;
   - (g) 1,1′-(*p*-dimethylaminobenzal)bis-2-naphthol,
     p-$(CH_3)_2N \cdot C_6H_4 \cdot CH:(C_6H_{10}OH)_2$;
   - (h) 1,1′-trichloroäcetalbis-2-methoxynaphthalene,
     $Cl_3C \cdot CH:(C_6H_{10}OCH_3)_2$;
   - (i) 2,5-dichlorobenzeneazo-1-triphenylmethyl-2-naphthol,
     $(2\text{-}5\text{-}Cl_2C_6H_3 \cdot N_2) \cdot ((C_6H_5)_3C \cdot C_{10}H_6OH)$.

[Contribution from the Laboratories of the Mount Sinai Hospital, New York, N. Y.]

CHOLEIC ACIDS. VI. ISOMERISM AND COÖRDINATIVE VALENCE; COLORED CHOLEIC ACIDS

WALTER MARX* AND HARRY SOBOTKA

Received July 20, 1936

In the preceding papers of this series[1–5] the coördination compounds of desoxycholic acid with a number of organic substances were studied. The influence of structural and steric isomerism on the molecular ratio and stability of coördination compounds was discussed. The coördinative affinity for desoxycholic acid was found to vary for optical antipodes, thus affording a means for the resolution of certain racemates.[5] The tendency of enol forms to combine with the bile acid led to complete enolization of tautomeric substances when they formed choleic acids.[4]

In the present investigation these studies were extended to the choleic acids of *cis-trans* isomers. We prepared the choleic acids of the pairs, oleic-elaidic and erucic-brassidic acids, and determined the coördination number, which was invariably eight. This was the value previously found for the corresponding saturated acids. The acholic components could be recovered unaltered, no *cis-trans* rearrangements occurring.

The effect of angular as against straight annulation was tested in the case of phenanthrene and anthracene. Phenanthrene combines with three molecules of desoxycholic acid, as has also been observed by Fieser and Newman,[6] while the isomeric, but longer, anthracene molecule forms a tetra-choleic acid. This finding parallels the observation that normal-chain aliphatic acids possess higher coördinative valence than their less symmetrical isomers.[3,7] 1,2-Benzanthrene, with a coördination number of three,[6] behaves, therefore, like phenanthrene of which it is the 2,3-benzo derivative.

The question as to the stability of organic coördination compounds in

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* Isidore Hernsheim Research Fellow.

[1] H. Sobotka and A. Goldberg, *Biochem. J.*, **26**, 555 (1932).

[2] H. Sobotka and A. Goldberg, *ibid.*, **26**, 557 (1932).

[3] H. Sobotka and A. Goldberg, *ibid.*, **26**, 566 (1932).

[4] H. Sobotka and J. Kahn, *ibid.*, **26**, 898 (1932).

[5] H. Sobotka and A. Goldberg, *ibid.*, **26**, 905 (1932).

[6] L. F. Fieser and M. S. Newman, *J. Am. Chem. Soc.*, **57**, 1602 (1935).

[7] E. Chargaff and G. Abel, *Biochem. J.*, **28**, 1901 (1934).

solution, especially of choleic acids, is still open and the answer will have a bearing on the physiological significance of the choleic acid principle. Molecular weight determinations[8] and enol titrations[4,9] indicate practically complete dissociation upon solution. However, confirmation of these results is desirable by methods, preferably optical, which do not affect association when the coördination compound is dissolved. The color of certain diketones, such as di-(3-methoxy-4-hydroxycinnamoyl)methane (curcumin), is known to deepen when the second carbonyl group becomes enolized with an excess of alkali. The progress of enolization during formation of choleic acids, and their degree of association in various solvents, may be observed directly with the choleic acids of such colored diketones. At the same time, the formation of such colored choleic acids, as slightly soluble as the related colorless benzoylacetone-choleic acid,[4] might be put to analytical use.

Thus, choleic acids of the following compounds were prepared: dibenzoylmethane, cinnamoylacetone, dicinnamoylacetone and dicinnamoylmethane. The coördination number of dibenzoylmethane was three, of the monocinnamoyl derivative four, whereas six molecules of desoxycholic acid were found associated with each molecule of the dicinnamoyl compounds. The crystals of the two latter choleic acids are greenish yellow, yet lighter in appearance than the dark yellow crystals of their acholic components. Nevertheless, when compared to physical mixtures of their respective components in proportionate amounts, the colors of the choleic acids are decidedly deeper in the solid state. These differences, however, disappear in solution, where corresponding concentrations of choleic acids and acholic components cannot be distinguished by colorimetric or spectroscopic observation thus indicating practically complete dissociation in solution.

EXPERIMENTAL

Preparation of Substances.—Desoxycholic acid was prepared and purified according to Sobotka and Goldberg;[2] m.p. 176°. (All melting points corrected.)

Oleic acid, free of linolic acid, was redistilled *in vacuo* under N_2 and recrystallized from alcohol.

Elaidic acid was obtained from oleic acid[10] and recrystallized from alcohol and ether; m.p. 45–46°.

Erucic acid was recrystallized from alcohol and petroleum ether; m.p. 34–35°.

Brassidic acid was prepared from erucic acid,[10] and recrystallized from alcohol-petroleum ether solution, then from alcohol; m.p. 58–5–59.5°.

Phenanthrene and anthracene were recrystallized from benzene-alcohol (1:1); m.p. 99° and 217–217.5°, respectively.

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[8] H. Sobotka, *Chem. Rev.*, **15**, 311, 364 (1934).

[9] H. Sobotka and J. Kahn, *Ber.*, **65**, 227 (1932).

[10] A. Gruen, "Analyse der Fette und Wachse," J. Springer, Berlin, **1925**, vol. I, p. 240.

Cinnamoylacetone (1-phenyl-1-hexene-3,5-dione) was obtained from methyl cinnamate plus acetone according to Ryan and Dunlea,[11] as the preparation from cinnamoyl acetoacetate proved unsatisfactory;[12] m.p. 84–85°.

Dicinnamoylacetone (1,9-diphenyl-1,8-nonadiene-3,5,7-trione) was derived from the monocinnamoyl compound by condensation with sodium amide;[12] m.p. 112.5–113.5°.

Dicinnamoylmethane (1,7-diphenyl-1,6-heptadiene-3,5-dione), in turn, from the preceding substance by boiling with 50 per cent. acetic acid;[12] m.p. 143°.

TABLE I

Choleic Acids of *Cis-Trans* and Structural Isomers

CHOLEIC ACID FROM:	M.P. (CORR.)	ANALYSIS			PER CENT. ACHOLIC COMPONENT		COÖRDINATION NUMBER n
		Mg. Substance	Cc. $N/10$ Alkali Used				
			Acholic Component	Desoxycholic Acid	Found	Calculated	
Oleic acid*	188°	440.2	1.505	10.41	8.50†	8.25‡	8
Elaidic acid	187–188°	433.4	—	10.16	8.04	8.25	8
		441.3	—	10.35	8.02	8.25	8
Erucic acid	193.5–194.5°	421.6	1.267	9.82	9.41†	9.73**	8
		452.7	1.273	10.32	10.12†	9.73	8
Brassidic acid	193–194°	415.3	—	9.59	9.52	9.73	8
		433.0	1.16	—	9.07	9.73	8
					ACID EQUIVALENT		
					Found	Calculated	
Phenanthrene	186–187°	219.7	—	4.85	453	451	3
		221.4	—	4.95	448	451	3
Anthracene	193°	314.9	—	7.24	435	437	4
		194.6	—	4.45	437	437	4

* Cf. reference 12.

† Mean value of both determinations.

‡ Percentage for $n = 7$: 9.32; $n = 9$: 7.40.

** Percentage for $n = 7$: 10.96; $n = 9$: 8.74.

All three cinnamoyl derivatives, as well as dibenzoylmethane (1,3-diphenylpropane-1,3-dione), m.p. 79°, were purified by recrystallization from alcohol.

Choleic Acids.—When desoxycholic acid and a small excess of the fatty acid were dissolved in hot methyl alcohol under nitrogen, the coördination compounds of the

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[11] H. Ryan and I. M. Dunlea, *Proc. Roy. Irish Acad.*, **32B**, 1 (1913).

[12] V. Lampe and J. Milobedzka, *Ber.*, **46**, 2235 (1913).

fatty acids crystallized readily upon cooling. In the case of phenanthrene and anthracene, the low solubility in alcohol of the acholic component necessitated the addition of benzene. The choleic acids of the three yellow cinnamoyl derivatives and of dibenzoylmethane were synthesized in concentrated hot methyl alcoholic solution, yielding well-formed prismatic crystals. Dibenzoylmethane-choleic acid is distinguished by its very slight solubility.

Recrystallization of choleic acid from alcohol, especially from ethyl alcohol, always entails the danger of dissociation and subsequent contamination of the choleic acid with ethyl alcohol-choleic acid, as indicated by lower and less sharply defined melting points. This should be taken into account in any study of the physical or chemical properties of these compounds (see, *e.g.*, footnote 13).

The analysis of the fatty acid-choleic acids was done by the xylene method of Wieland and Sorge[14] under nitrogen. The xylene was removed by steam distillation in a nitrogen atmosphere under reduced pressure. The titrations of the separated desoxycholic acid and fatty acid were carried out with $N/10$ alcoholic alkali and naphtholphthalein as indicator. The presence of desoxycholic acid interfered with the determination of the iodine number of the unsaturated acid. The coördination numbers of anthracene, phenanthrene and of dibenzoylmethane were determined by direct titration of the choleic acids in hot alcohol with $N/10$ alcoholic alkali and naphtholphthalein as indicator. The acidity of the enol group of the diketone was negligible. The colored cinnamoyl derivatives were analysed by the xylene method, as the color and the enolic character of the acholic components prevented direct titration.

TABLE II

COLORED CHOLEIC ACIDS

CHOLEIC ACID FROM:	M.P. (CORR.)	ANALYSIS		ACID EQUIVALENT		COÖRDINATION NUMBER
		Mg. Substance	Cc. $N/10$ Alkali Used for Desoxycholic Acid	Found	Calculated	
Dibenzoylmethane	199.5–200.5°	259.7	5.65	467	467	3
		191.8	4.15	470	467	3
Cinnamoylacetone	190.5–191.5°	97.8	2.22	441	439	4
		170.3	3.88	439	439	4
Dicinnamoylacetone	191.5°	166.4	3.73	446	442	6
		175.0	3.93	445	442	6
Dicinnamoylmethane	195–196°	95.5	2.15	444	438	6
		163.4	3.72	439	438	6

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[13] Y. GO AND O. KRATKY, *Z. phys. Chem.*, **B26**, 439 (1934).

[14] H. WIELAND AND H. SORGE, *Z. physiol. Chem.*, **97**, 1, (1916).

SUMMARY

1. The choleic acids of *cis-trans* isomers of unsaturated aliphatic acids have coördination numbers equal to each other and to that of their corresponding saturated acids.

2. Phenanthrene combines with three molecules, anthracene with four molecules of desoxycholic acid.

3. Various aromatic diketones form colored, slightly soluble coördination compounds with desoxycholic acid. These choleic acids are apparently completely dissociated when dissolved.

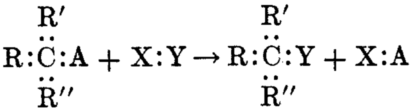
[Contribution from the Chemical Laboratory of the University of Illinois]

OPTICALLY ACTIVE QUATERNARY AMMONIUM SALTS FROM *d*- AND *l*-2-OCTYL *p*-BROMOBENZENESULFONATE AND TERTIARY AMINES

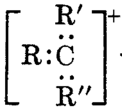
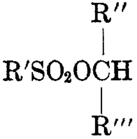
R. C. CARY, J. F. VITCHA and R. L. SHRINER

Received July 30, 1936

Numerous reactions of optically active compounds which involve the replacement of a group attached to the asymmetric carbon atom are known. If, in a reaction of the following type, an exchange of anions is involved (*i.e.*, the group A takes with it the shared pair of electrons),



$$\mathrm{R{:}\underset{\underset{R''}{\cdot\cdot}}{\overset{\overset{R'}{\cdot\cdot}}{C}}{:}A + X{:}Y \rightarrow R{:}\underset{\underset{R''}{\cdot\cdot}}{\overset{\overset{R'}{\cdot\cdot}}{C}}{:}Y + X{:}A}$$

the residue would be a carbonium ion  $\left[\mathrm{R{:}\underset{\underset{R''}{\cdot\cdot}}{\overset{\overset{R'}{\cdot\cdot}}{C}}}\right]^{+}$ which would immediately combine with the anion (:Y) to form the reaction product. Such a replacement may result in racemization or in the formation of an optically active product with or without a Walden inversion. The optically active esters of sulfonic acids constitute one class of compounds which are especially suited to the study of such reactions. Phillips, Kenyon and their co-workers,[1] by treatment of an optically active ester of a sulfonic acid of the type  $\mathrm{R'SO_2O\underset{\underset{R'''}{|}}{\overset{\overset{R''}{|}}{C}}H}$ with ionic reagents, such as potassium acetate, have shown the sulfonate radical may be replaced by another anion without racemization. Ammonia and primary and secondary amines were also found to react with such esters to produce optically active amines.

In the present communication it is shown that the sulfonate radical of an optically active ester may be supplanted by a tertiary amino group

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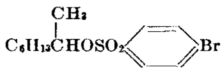
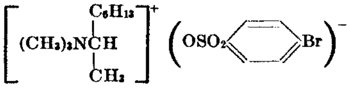
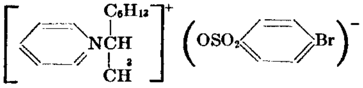
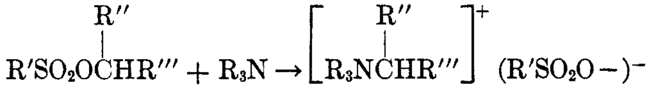
[1] Phillips, *J. Chem. Soc.*, **123**, 44 (1923); *ibid.*, **125**, 399 (1925); *ibid.*, **127**, 2552 (1927); Kenyon and Phillips, *ibid.*, **1930**, 1676; *Trans. Faraday Soc.*, **26**, 451 (1930); Kenyon, Phillips and Pittman, *J. Chem. Soc.*, **1935**, 1072; Kenyon, Phillips and Shutt, *ibid.*, **1935**, 1663.

TABLE I

						
	M. P.	$[\alpha]_D^{25}$ (Ethanol)	M. P.	$[\alpha]_D^{25}$ (Ethanol)	M. P.	$[\alpha]_D^{25}$ (Ethanol)
dl-	40–41°	—	204–205°	—	111–112°	—
d-	30	+7.06	208–209	+14.72	88–96	−6.95
l-	30	−6.70	208–210	−14.95	94–96	+6.95

leading to the formation of quaternary ammonium salts without destruction of optical activity.



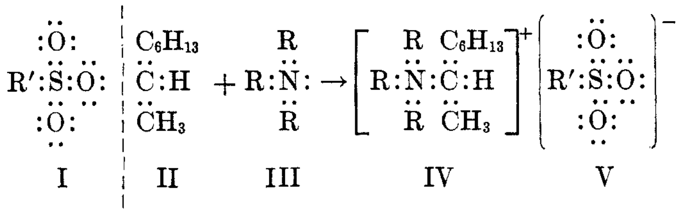
$$R'SO_2O\overset{\overset{R''}{|}}{C}HR''' + R_3N \rightarrow \left[R_3N\overset{\overset{R''}{|}}{C}HR'''\right]^+ (R'SO_2O-)^-$$

The particular esters used were those obtained by treatment of *d*- and *l*-2-octanol with *p*-bromobenzenesulfonyl chloride in the presence of a limited amount of pyridine. The *d*- and *l*-2-octyl *p*-bromobenzenesulfonates were solids which could be purified by recrystallization, and it was for this reason that the *p*-bromo derivative was used. The two tertiary amines used, trimethyl amine and pyridine, combined readily with the optically active sulfonates to form quaternary ammonium salts, which were found to be optically active. The racemic forms were also prepared for comparison; the formulas, melting points and rotations of the compounds are summarized in Table I.

Considerable experimental difficulties were encountered in the preparation of these compounds. The 2-octyl *p*-bromobenzenesulfonates were very sensitive to moisture and were easily hydrolyzed. The quaternary ammonium salts readily decomposed to give the amine salts of *p*-bromobenzenesulfonic acid and the unsaturated hydrocarbon. The analytical data indicate that the salt from trimethylamine is pure, whereas the active pyridine salt always contained some of the pyridinium *p*-bromobenzenesulfonate and some of the racemic salt. All attempts to purify the pyridinium salt caused further racemization or decomposition.

From the data in Table I, it will be noted that the *dextro* ester produced a *dextro* quaternary salt with trimethylamine, but a *levo* pyridinium salt. Also, the *levo* ester produced a *levo* trimethyl-2-octyl ammonium *p*-bromobenzenesulfonate, but a *dextro* pyridinium salt. Whether or not a Walden inversion occurred cannot be stated, since there is no direct means of determining the configurations of the two quaternary salts.

The most interesting point to be noted is that these salts were *optically active* and *not* racemic forms. If the reaction is written electronically,



it is evident that the sulfonic ester (I + II) in forming the sulfonate ion (V) leaves the octyl radical (II) with the asymmetric carbon atom carrying only a sextet of electrons (the cleavage is indicated by the dashes). The latter combines with the tertiary amine (III), which has an unshared pair of electrons, to form the quaternary ammonium ion (IV). During these transformations the 2-octyl carbonium ion (II) retains its configuration and does not undergo racemization. This equation, however, only represents the completed process and does not prove that the carbonium ion (II) existed for any finite interval of time actually detached from the electron donor groups (I) or (III). Thus the reaction probably involves simultaneous addition of (III) and dissociation of (I), since immediate racemization appears to occur if the carbonium ion is formed in reactions[2] or conditions where it is not stabilized by an electron donor.

One of the best pictures indicating how such a substitution process can occur without racemization has been suggested by Lewis[3] and elaborated by Olson.[4] According to this mechanism, the entering group approaches the face of the tetrahedron opposite the group which is being displaced.

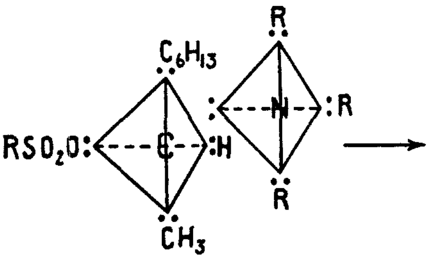


FIG. 1

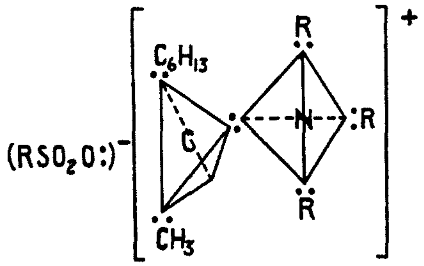


FIG. 2

By a slight shift of the kernel, the asymmetric carbon atom then becomes the center of a new tetrahedron. A one-step reaction thus leads to an inversion of the configuration. Applied to the present compounds this means that the tertiary amine approaches the ester in an oriented position, such that the unshared pair of electrons at one apex is opposite that face of the asymmetric carbon atom which, in turn, is opposite the sulfonate group (Fig. 1).

The kernel of the carbon atom shifts its position and a new tetrahedron is formed, attached to the tetrahedron of the nitrogen atom, thus constituting the quaternary ammonium ion and simultaneously the sulfonate anion (Fig. 2). If the amine approaches the face indicated, then an inversion

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[2] For example, reaction of magnesium with *d*-2-bromoöctane produces an optically inactive Grignard reagent; PORTER, *J. Am. Chem. Soc.*, **57**, 1436 (1935).

[3] LEWIS, "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., New York, **1923**, p. 113.

[4] OLSON, *J. Chem. Phys.*, **1**, 418 (1933).

in configuration takes place. This appears to be the preferred line of approach.[5] If, however, the amine approached any of the other three faces, the sulfonate ion might be displaced without inversion. This picture, admittedly speculative, does offer a working hypothesis for replacement reactions.

EXPERIMENTAL

dl-*2-Octyl* p-*bromobenzenesulfonate.*—Thirteen grams (0.1 mole) of *dl*-2-octanol was placed in a dry 200-cc., three-necked, round-bottomed flask equipped with a dropping funnel, a mercury-sealed stirrer and a calcium chloride drying tube. Thirty-one and two-tenths grams (0.125 mole) of *p*-bromobenzenesulfonyl chloride was then added. An ice-salt bath was applied, the stirrer started and, after the temperature had fallen to 0°, 31.6 g. (0.4 mole) of dry pyridine was added dropwise over a period of three hours. Stirring was continued for four hours more, the temperature being kept below 0°. The reaction mixture, while stirred vigorously, was made acid to litmus by the addition of about 100 cc. of cold, 4 *N* hydrochloric acid. The ester was extracted with ether, and the ether extract washed twice with cold water and dried with sodium sulfate. The ether was removed by vacuum distillation at room temperature, the ester recrystallized by dissolving it in three times its volume of methanol and then cooling in a mixture of solid carbon dioxide and acetone. The yield of colorless crystals melting at 40–41° was 29 g. (83 per cent. theoretical). The ester is rather unstable and decomposes slowly on standing. Moisture causes hydrolysis and must be excluded during all manipulations involving the preparation and use of the ester.

Anal. Calc'd for $C_{14}H_{21}BrO_3S$: Br, 22.90. Found: Br, 22.76.

l-*2-Octyl* p-*bromobenzenesulfonate.*—The procedure described above was followed, using *l*-2-octanol ($[\alpha]_D^{25}$ in ethanol, −10.00°). The yield of product was 27 g. (77 per cent. theoretical). It melted at 30°, and had a specific rotation in ethanol at 25° of −6.70° ($c = 4.62$). It was less stable and more difficult to crystallize than the inactive product. It turned tan in four weeks, and its melting point dropped to 26°, while its specific rotation increased to −7.67°, due to the formation of *l*-2-octanol by hydrolysis.

Anal. Calc'd for $C_{14}H_{21}BrO_3S$: Br, 22.9. Found: Br, 22.8.

d-*2-Octyl* p-*bromobenzenesulfonate.*—This ester was prepared from *d*-2-octanol ($[\alpha]_D^{25}$ in ethanol, +10.00°) by the same procedure. Yield, 24 g. (70 per cent. theoretical), m.p., 30°. Specific rotation in absolute ethanol at 25°, +7.06 ($c = 1.84$).

Anal. Calc'd for $C_{14}H_{21}BrO_3S$: Br, 22.9. Found: Br, 22.79.

l-*Trimethyl-2-octylammonium* p-*bromobenzenesulfonate.*—One gram of *l*-2-octyl *p*-bromobenzenesulfonate was placed in a bomb tube and cooled to −10°. Three cubic centimeters of dry, liquid trimethylamine was then added, the tube sealed, and allowed to stand at room temperature for two days. It was again cooled, opened, and the excess amine removed by a water pump. The salt was washed with dry ether, then dissolved in 7 cc. of absolute ethanol and, while the alcohol solution was warm (35°), dry ether was added until the solution became slightly cloudy. Upon cooling to −10°, 1 g. of plates precipitated; m.p., 206–208°. Upon recrystallization from alcohol-ether mixture, a constant melting point of 208–210° was obtained.

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[5] PAULING, *J. Am. Chem. Soc.*, **53**, 1367 (1931); SLATER, *Phys. Rev.*, **37**, 481 (1931).

Specific rotation in absolute ethanol at 25° = −14.95° (c = 1.54).

Anal. Calc'd for $C_{17}H_{30}BrNO_3S$: S, 7.83; N, 3.42; Br, 19.60.
Found: S, 7.71; N, 3.41; Br, 19.36.

d-*Trimethyl-2-octylammonium* p-*bromobenzenesulfonate.*—The above procedure was followed, using *d*-2-octyl *p*-bromobenzenesulfonate and trimethylamine; m.p., 208–209°. Rotation in absolute ethanol at 25° = +14.72° (c = 1.29).

Anal. Calc'd for $C_{17}H_{30}BrNO_3S$: N, 3.42. Found: N, 3.39.

dl-*Trimethyl-2-octylammonium* p-*bromobenzenesulfonate.*—The above procedure was followed, using *dl*-2-octyl *p*-bromobenzenesulfonate. This racemic form melted at 204°.

Anal. Calc'd for $C_{17}H_{30}BrNO_3S$: N, 3.42. Found: N, 3.60.

Trimethylammonium p-*bromobenzenesulfonate.*—This salt was prepared for comparison with the above-discussed compounds. Dry trimethylamine gas was passed slowly into an absolute ether solution of one gram of *d*-2-octyl *p*-bromobenzenesulfonate. By refluxing this mixture for three hours the quaternary salt was decomposed into octene and the salt of trimethylamine. The crystals which separated were removed and recrystallized from absolute ethanol-ether mixture. Yield, 0.5 g.; m.p., 112–114°.

Anal. Calc'd for $C_9H_{14}BrNO_3S$: N, 4.73. Found: N, 4.96.

dl-*2-Octylpyridinium* p-*bromobenzenesulfonate.*—Two grams of *dl*-2-octyl *p*-bromobenzenesulfonate, 2 cc. of dry pyridine and 5 cc. of absolute ether were refluxed under anhydrous conditions for thirty-five minutes, cooled and 25 cc. of absolute ether added. The salt was filtered, washed with absolute ether and recrystallized from dry acetone until the melting point was constant; m. p., 111–112°; yield, 2 g.

Anal. Calc'd for $C_{19}H_{26}BrNO_3S$: Br, 18.7. Found: Br, 18.65.

l-*2-Octylpyridinium* p-*bromobenzenesulfonate.*—The above-described procedure was followed, using *d*-2-octyl *p*-bromobenzenesulfonate. The product was recrystallized seven times from dry acetone at the end of which time it melted at 88–96°. Two series of fractional crystallizations were made from this product and from the product recovered from the combined filtrates. Each series was recrystallized four times from dry ethyl acetate, then six times from absolute ethanol-dry ether mixture. This yielded four fractions.

(a) A white crystalline solid, melting at 133–134° which was shown to be pyridinium *p*-bromobenzenesulfonate by melting point of a mixture with a sample of this compound prepared as described below.

(b) A solid melting at 112°, which was optically inactive, and which was the *dl*-pyridinium salt described above.

(c) A fraction which melted at 110–112°; $[\alpha]_D^{25}$ in ethanol of −2.37° (c = 1.69).
Anal. Calc'd for $C_{19}H_{26}BrNO_3S$: N, 3.27. Found: N, 3.30.
This was evidently a mixture of the *l* quaternary salt with some of the *dl* salt.

(d) A fraction melting at 78–96°. This was a mixture of the *dl* quaternary salt with the pyridinium *p*-bromobenzenesulfonate. It was optically inactive.

The preparation was repeated except that the reaction time was shortened to 15 minutes, and the precipitate which resulted upon addition of the dry ether was filtered, washed with dry ether and dried *in vacuo* for five minutes. The rotation was taken immediately and found to be −6.95°. The product was not homogeneous; it melted over a range of 74–105°, and the analyses indicate that it contained some of the pyridinium *p*-bromobenzenesulfonate.

Anal. Calc'd for $C_{19}H_{26}BrNO_3S$: Br, 18.70; N, 3.27; S, 7.46.
Found: Br, 19.08; N, 3.39; S, 7.81.

d-*2-Octylpyridinium* p-*bromobenzenesulfonate*.—Two grams of *l*-2-octyl *p*-bromobenzenesulfonate was placed in 10 cc. of dry pyridine. The flask was stoppered and allowed to stand at room temperature for twenty-seven hours. Then 100 cc. of dry ether was added, and the precipitate was filtered and washed with dry ether. The product, which melted at 74–98°, was then fractionally crystallized from absolute alcohol-ether mixture (1:1) and two samples, melting at 88–94° and 90–94°, were obtained. They were combined and dissolved in 50 cc. of the same mixed solvent, an additional 50 cc. of dry ether added and the solution placed in the refrigerator. After two weeks, another 100 cc. of dry ether was added. After standing a total of eight weeks, the fine needles were filtered and recrystallized once from dry alcohol-ether mixture. The product consisted of colorless plates which had a melting point of 94–96°, and had a specific rotation at 25° in absolute ethanol of +6.95° (c = 0.65).

Anal. Calc'd for $C_{19}H_{26}BrNO_3S$: N, 3.34. Found: N, 3.40.

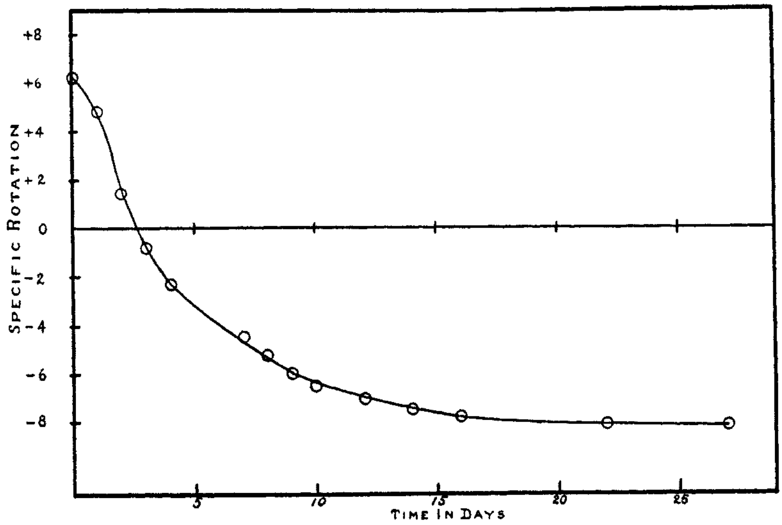

FIG. 3

The reaction with pyridine was followed polarimetrically. A sample of 0.45 g. of *d*-2-octyl *p*-bromobenzenesulfonate was treated with 0.4 g. of dry pyridine, and the mixture was diluted to 15 cc. in a volumetric flask. The rotation was taken immediately and at intervals for twenty-seven days. The change in specific rotation is shown in Fig. 3.

Pyridinium p-*bromobenzenesulfonate*.—In 10 cc. of dry ethanol 2.59 g. (0.01 mole) of dry sodium *p*-bromobenzenesulfonate was added to 1.155 g. (0.01 mole) of dry pyridine hydrochloride prepared from dry hydrogen chloride and dry pyridine. After standing overnight, the sodium chloride was filtered off, and the pyridine *p*-bromobenzenesulfonate precipitated by adding about 5e cc. of dry ether. The melting point was constant after five recrystallizations from a mixture of absolute ethanol and dry ether; yield, 1.2 g.; m. p., 134–135°.

Anal. Calc'd for $C_{11}H_{10}BrNO_3S$: N, 4.4. Found: N, 4.3.

SUMMARY

The reaction between *d*- and *l*-2-octyl *p*-bromobenzenesulfonate and trimethylamine and pyridine produced optically active quaternary ammonium salts. The salts obtained from trimethylamine had the same direction of rotation as the original esters whereas those prepared from pyridine had rotations in the opposite directions.

It is pointed out that the reaction probably involves simultaneous addition of the tertiary amine and expulsion of the sulfonate anion.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE SYNTHESIS OF PHENANTHRENES FROM HYDROXYL DERIVATIVES OF *beta*-PHENYLETHYLCYCLOHEXANES AND THE NATURE OF THE BY-PRODUCT*

DAVID PERLMAN, DAVID DAVIDSON, AND MARSTON TAYLOR BOGERT

Received July 31, 1936

Since our preliminary announcement[1] of the synthesis of phenanthrene by the dehydration of 1-*beta*-phenylethylcyclohexanol-1 (III), followed by dehydrogenation of the *as*-octahydrophenanthrene so produced, we have been studying the reactions involved, especially from the standpoint of their mechanism and the structure of the by-product, and this has delayed publication of the details much longer than we had anticipated. In the meantime, other investigators also have found the method of service.[2]

This research is a sequel to our recent studies in the ionene,[3] irene,[4] and indane[5] fields, and has resulted in a synthetic process which we believe offers certain advantages over those used previously for the preparation of many phenanthrene derivatives.

The alcohols used in our experiments were the phenylhexahydrobenzylcarbinol (I), benzylcyclohexylcarbinol (II), 1-*beta*-phenylethylcyclohexanol-1 (III), and 1-*beta*-phenylethyl-2-methylcyclohexanol-1 (IV). They were obtained by appropriate Grignard reactions, as described in the experimental part of this paper. As the dehydrating agent, we employed

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* Based upon the Dissertation submitted by David Perlman, May, 1936, for the degree of Ph.D., under the Faculty of Pure Science, Columbia University, New York, N. Y., to which Dissertation the reader is referred for further experimental details and literature citations. Presented in abstract before the Division of Organic Chemistry, at the Washington Meeting of the American Chemical Society, March 29, 1933.—M. T. B.

[1] BOGERT, *Science*, **77**, 289 (March 17, 1933).

[2] (*a*) COOK AND HEWETT, *J. Chem. Soc.*, **1933**, 451; (*b*) COOK AND HEWETT, *ibid.*, **1933**, 1098; (*c*) FULTON AND ROBINSON, *ibid.*, **1933**, 1463; (*d*) HARPER, KON, AND RUZICKA, *ibid.*, **1934**, 124; (*e*) COHEN, COOK, HEWETT, AND GIRARD, *ibid.*, **1934**, 653; (*f*) COOK, HEWETT, MAYNEORD, AND ROE, *ibid.*, **1934**, 1727; (*g*) VAN DE KAMP AND MOSETTIG, *J. Am. Chem. Soc.*, **58**, 1062 (1936).

[3] (*a*) BOGERT, *Science*, **76**, 475 (1932); (*b*) BOGERT, *ibid.*, **77**, 197 (1933); (*c*) BOGERT, DAVIDSON, AND APFELBAUM, *J. Am. Chem. Soc.*, **56**, 959 (1934).

[4] BOGERT AND APFELBAUM, *Science*, **79**, 280 (1934).

[5] (*a*) BOGERT AND DAVIDSON, *J. Am. Chem. Soc.*, **56**, 185 (1934); (*b*) ROBLIN, DAVIDSON, AND BOGERT, *ibid.*, **56**, 248 (1934).

sulfuric acid, 90% for the secondary alcohols (I and II), and 85% for the tertiary ones (III and IV), for reasons explained in our previous communications.[5]

The first of these alcohols (I), subjected to the action of 90% sulfuric acid, yielded a thermoplastic resin, which was apparently a polymer of the olefin formed by the dehydration. This result was similar to that observed by us in the dehydration of 1-phenylpentanol-1[5b], when only a polymer was obtained, and gives additional support to our hypothesis that whenever there is a hydroxyl on the *alpha* carbon, or an olefin bond in the *alpha, beta* position, with respect to the benzene nucleus, treatment with sulfuric acid will yield only a polymer of the olefin.

Our experience in the tetralin and indane fields would suggest that the alcohols II and III should each give rise to two isomeric hydrocarbons when dehydrated by sulfuric acid, since there is a branched carbon chain, in the form of a cyclohexane ring, on the carbon *gamma* to the benzene nucleus. When the reactions were actually carried out, the results confirmed this deduction. Each alcohol yielded not only two isomeric hydrocarbons, but the same two, namely the *as*-octahydrophenanthrene (V) and the spirocyclohexane-1,1-indane (VII).

On working up the crude product from II, there were obtained a hydrocarbon fraction (65%), b.p. 135–150° at 10 mm., and an appreciable quantity of a very viscous polymer (b.p. 220° at 2 mm.). An attempt to separate the components of the hydrocarbon mixture by repeated fractionation, following the progress of the separation by the refractive indices, showed quite clearly that we were dealing with a two-component system and that, with the amount of material at our command, the separation of the components by distillation alone was likely to prove both laborious and unsatisfactory. Recourse was had, therefore, to a combination of fractionation and oxidation. The first runnings of the first fraction, with the lowest index of refraction, and the later runnings of the higher-boiling fraction, with the highest index, were separately oxidized by alkaline permanganate. The first fraction yielded *alpha,alpha*-pentamethylenehomophthalic and some phthalic acids (VIII), the other one only phthalic acid. Oxidation of the original mixture, gave both acids. Using the refractive indices and density data of the first few drops and of the last fraction, and assuming the specific refraction of the homogeneous mixture of isomers to have the mean value of those of its components, calculations by the Lorenz-Lorentz equation showed that it consisted of approximately 14.6% of the spirane (VII) and 85.4% of *as*-octahydrophenanthrene (V). It is appreciated that this is at best only a rough estimate, since neither the first few drops nor the last fraction of the distillate was a chemically pure compound.

The dehydration product from alcohol (III) consisted practically exclusively of a mixture of V and VII, which distilled over a 2°-range, with but little residue. Calculations similar to those mentioned in the case of the hydrocarbon mixture from alcohol II, indicated the composition of this mixture from III to be approximately 4% of VII to 96% of V.

In a recent communication, van de Kamp and Mosettig[2c] report the dehydration of alcohol III by phosphorus pentoxide, and the separation of the product into two main hydrocarbon fractions: *A* (20%), b.p. 135.5–135.7° at 10.5–10.8 mm.; and *B* (70%), b.p. 142.6–142.8° at 9.2 mm. *A* is obviously identical with the fraction which we believe to consist mainly of the spirane (VII), and *B* the *as*-octahydrophenanthrene (V). The proportions of the two differ somewhat from our calculations, but this may be due to the fact that their dehydrating agent was not the same as ours. These two fractions, they suggest, represent the two stereoisomeric forms of *as*-octahydrophenanthrene, and assign to *A* the *trans* and to *B* the *cis* configuration.

As yet, we have not succeeded in isolating this putative spirane (VII) in analytical purity. The proof of its presence, therefore, rests upon the nature of the oxidation product of the lower-boiling (and lower index) hydrocarbon fraction, and the close resemblance of its properties to those of certain other spiranes which we have synthesized in analytical purity and studied more fully. The synthesis of spirane (VII) is now being attempted.[6]

That the oxidation product of the lower-boiling hydrocarbon constituent has the structure assigned (VIII) is supported by the following facts.

(1) Indanes and tetralins carrying *gem*-dialkyl groups on an *alpha* carbon can be oxidized to the corresponding *alpha*, *alpha*-dialkylhomophthalic acids[3c,5]. In the case of the *gem*-dialkylindanes, alkaline permanganate oxidizes them directly to the crystalline dialkylhomophthalic acids. The *gem*-dialkyltetralins, however, under similar conditions, generally first yield oils, which are apparently the intermediate *alpha*-keto acids, for they dissolve in alkali and are readily oxidized by 30% hydrogen dioxide to the expected homophthalic acids, with elimination of carbon dioxide. The spirane (VII) under discussion was easily oxidized by alkaline permanganate directly to the crystalline pentamethylenehomophthalic acid (VIII).

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[6] Cook, Hewett, and Lawrence (*J. Chem. Soc.*, **1936**, 73, 78), on oxidation of crude *as*-octahydrophenanthrene by chromic oxide in acetic acid solution, isolated in addition to a hexahydrophenanthrone another ketone which they thought might be derived from the above spirane (VII), but the analysis of whose oxime (m.p. 187°) gave figures which, they state, "are in much better agreement with a compound containing two hydrogen atoms less." M. T. B.

(2) Spirocyclohexane-1,1-tetralin, and spirocyclopentane-1,1-tetralin, whose syntheses will be described in another paper, when oxidized by alkaline permanganate, followed by 30% hydrogen dioxide, gave the corresponding *alpha,alpha*-pentamethylene (VIII) and *alpha,alpha*-tetramethylene homophthalic acids. The former was identical with the oxidation product of the spirane VII.

Inasmuch as the *as*-octahydrophenanthrene (V) is the main product of the dehydration of benzylcyclohexylcarbinol (II), 1-*beta*-phenylethylcyclohexanol-1 (III), or 1-*beta*-phenylethylcyclohexanol-2,[7] it is manifest that, with the exception of the last compound, this cyclization cannot be due to a simple direct condensation between the hydroxyl of the side chain and the ortho-hydrogen of the benzene nucleus. Rather, as in the case of ionene,[3] is the evidence all in favor of our hypothesis that these reactions generally proceed through the preliminary formation of an olefin, which then isomerizes to one or two cyclic hydrocarbons, the products varying with the structure and loading of the side chain. Were the cyclodehydration direct, alcohol III should give only the spirane (VII), whereas the major product is the *as*-octahydrophenanthrene (V). Further, when the alcohol III was heated for one minute with 50% sulfuric acid, or was distilled with a crystal of iodine, an olefin resulted which was promptly and smoothly rearranged by 85% sulfuric acid to the same *as*-octahydrophenanthrene (V) as was obtained by the action of this 85% sulfuric acid upon the alcohol itself. The formation of V from the alcohol II, necessitates a shift in the position of the double bond of the intermediate olefin from the side chain into the cyclohexane nucleus, a migration which is not at variance with experimental observations previously reported from these laboratories.[5b]

Wallach,[8] and Signaigo and Cramer,[9] have shown that 1-alkylcyclohexanols-1, when dehydrated by sulfuric acid, give alkylcyclohexenes, with a little alkenecyclohexane. In our own previous experiments[5b] with 1-phenyl-3-methylpentanols and sulfuric acid, the ratio of indane to tetralin in the product was 3:1 when the hydroxyl was *beta* to the benzene nucleus, and 1:4 when it was in the *gamma* position. It was to be expected, therefore, that the yield of spirane from alcohol II would be greater than that from alcohol III and, as noted above, this proved to be the fact. It follows also that some of this same spirane is likely to be found in the dehydration product of 1-*beta*-phenylethylcyclohexanol-2.[7]

This synthesis of *as*-octahydrophenanthrenes is simpler than that of Bardhan and Sengupta in that the initial materials are generally more

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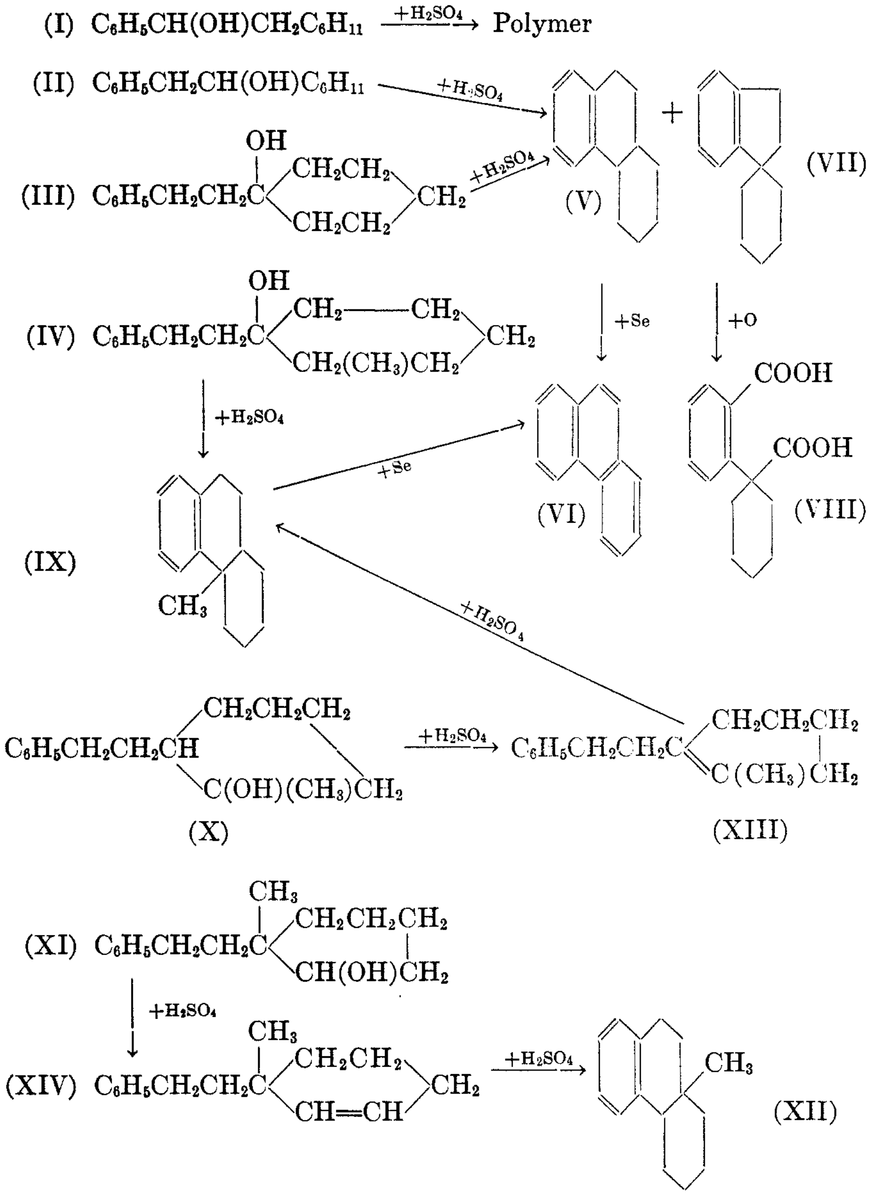
[7] Bardhan and Sengupta, *J. Chem. Soc.*, **1932**, 2520.

[8] Wallach, *Ann.*, **396**, 264 (1913).

[9] Signaigo and Cramer, *J. Am. Chem. Soc.*, **55**, 3326 (1933).

FLOW SHEET


(I) $C_6H_5CH(OH)CH_2C_6H_{11}$ $\xrightarrow{+H_2SO_4}$ Polymer
(II) $C_6H_5CH_2CH(OH)C_6H_{11}$
+H₂SO₄
(III)
OH
$C_6H_5CH_2CH_2C$
CH_2CH_2
CH_2
CH_2CH_2
+H₂SO₄
(V)
+
(VII)
(IV)
OH
$C_6H_5CH_2CH_2C$
CH_2
CH_2
CH_2
$CH_2(CH_3)CH_2$
+Se
+O
COOH
COOH
+H₂SO₄
+Se
(VI)
(VIII)
(IX)
CH_3
+H₂SO₄
$C_6H_5CH_2CH_2CH$
$CH_2CH_2CH_2$
$C(OH)(CH_3)CH_2$
(X)
+H₂SO₄
$C_6H_5CH_2CH_2C$
$CH_2CH_2CH_2$
$C(CH_3)CH_2$
(XIII)
(XI)
CH_3
$C_6H_5CH_2CH_2C$
$CH_2CH_2CH_2$
$CH(OH)CH_2$
+H₂SO₄
(XIV)
CH_3
$C_6H_5CH_2CH_2C$
CH_2CH_2
CH_2
$CH{=}CH$
+H₂SO₄
CH_3
(XII)

easily obtainable, and fewer steps are involved. The fusion with selenium of the hydrocarbon mixtures thus produced from alcohols II or III, gave large yields of phenanthrene.

Direct cyclodehydration of 1-*beta*-phenylethyl-2-methylcyclohexanol-1 (IV) should result in the formation of the 2-methyl-spirocyclohexane-1,1-indane, but no such spirane could be detected in the hydrocarbon product, which gave an 89% yield of phenanthrene when fused with selenium. This result indicates that the $C_{15}H_{20}$ hydrocarbon obtained was the 12-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (IX), the angular methyl group, as usual,[2d,2e,2f,10] having been eliminated in the dehydrogenation. Here too, then, is evidence of the formation of an olefin prior to cyclization. Kon[10] also reported that the 2-*beta*-phenylethyl-1-methylcyclohexanol-1 (X), on dehydration yielded the same 12-methyloctahydrophenanthrene (IX), whereas the 2-*beta*-phenylethyl-2-methylcyclohexanol-1 (XI) gave the isomeric 11-methyl derivative (XII). Loss of water from either IV or X should give preferably[8,9] the olefin XIII, which would then rearrange to IX. The absence of 1-methylphenanthrene from the dehydrogenation product of IX, shows that no cyclization occurred between the benzene nucleus and the carbon in position No. 6 of the cyclohexane nucleus. The course of the cyclization is doubtless influenced by the methyl group, for such an effect has been observed in other cases[2d,2e,2f].

The formation of the 11-methyl isomer (XII) may be explained either as the result of a direct cyclodehydration, or as due to the cyclization of the olefin XIV.

In general, the presence of a saturated cycle upon the alkyl side-chain appears to exert much the same effect as that of a *gem*-dimethyl group upon the course of the cyclodehydration.[3c,4,5a] (See page 292.)

EXPERIMENTAL

General

Distillations were performed under reduced pressure with a barostat[11] which controlled the pressure to ±0.1 mm.

Thermometers used for distillations and melting points were calibrated against a total-immersion thermometer calibrated by the U. S. Bureau of Standards. The melting points were observed while raising the temperature of a Fisher melting-point apparatus about 3° per minute.

Density determinations were made with a Sprengel-type pycnometer and were precise to ±0.0003.

Refractive indices were taken with an Abbé refractometer kept at 25° ± 0.01°C. by circulating water from a thermostat through the thermoregulator[12] by means of a gear pump. Precision of readings was ±0.0002.

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[10] Kon, *J. Chem. Soc.*, **1933**, 1081.

[11] Ellis, *Ind. Eng. Chem.*, *Anal. Ed.*, **4**, 318 (1932).

[12] Heisig and Cameron, *Ind. Eng. Chem.*, *Anal. Ed.*, **6**, 419 (1934).

Grignard reactions were carried out in an all-glass apparatus equipped with a three-necked flask, reflux condenser, stirrer with mercury seal, dropping funnel, and thermometer.

Fractionation of mixtures containing isomeric hydrocarbons was accomplished by means of an all-glass outfit carrying a Widmer column.

Halides

beta-*Phenylethyl bromide*, prepared according to the general method of Kamm and Marvel,[13] from phenylethylalcohol, hydrobromic acid and sulfuric acid, was obtained in a yield of 76%; b.p. 96.5–97.5° at 13–14 mm.; n_D^{25} 1.5543; d_4^{25} 1.3535; $R_L^{obs.}$ 43.81, $R_L^{calc.}$ 43.31. B.p. in the literature,[14] 96.5–98.5° at 13 mm.

Cyclohexyl chloride.—Following the general procedure of Norris, Watt and Thomas,[15] using cyclohexanol, concentrated hydrochloric acid and anhydrous zinc chloride, the yield was 69%, and the b.p. 46–48° at 26 mm.

We found it more convenient to reflux for three hours a mixture of one volume of cyclohexanol with three of concentrated hydrochloric acid, then to separate the upper layer of halide, dry it over calcium chloride, transfer to a Claisen flask, reduce the pressure and pass a current of dry air through the filtered halide for an hour and a half, to remove all hydrogen chloride gas, and distill under reduced pressure with a Vigreux column. It can be distilled also at atmospheric pressure, b.p. 142–143°, without appreciable decomposition, if the distillation be conducted very slowly; yield, 70%; n_D^{25} 1.4600; d_4^{25} 0.9854; $R_L^{obs.}$ 32.95, $R_L^{calc.}$ 32.58. B.p. in the literature, 142° at atmospheric pressure,[16] 46–48° at 22 mm.[17]

Cyclohexylmethyl bromide was prepared from cyclohexylcarbinol and phosphorus tribromide, by the method of Hiers and Adams;[18] yield, 78%; b.p. 82–83° at 26 mm.; n_D^{25} 1.4906; d_4^{25} 1.2763; $R_L^{obs.}$ 40.14, $R_L^{calc.}$ 40.09; b.p. in the literature, 76–77° at 26 mm.,[18] 86–87° at 28–29 mm.[19]

Alcohols

Cyclohexylcarbinol, from cyclohexylmagnesium chloride and paraformaldehyde;[20] yield, 52.5%; b.p. 182–183°; b.p. in literature[21] 181–183°.

Phenylhexahydrobenzylcarbinol (I).—To a mixture of 90.4 g. (0.535 mole) of cyclohexylmethylbromide, 13.2 g. (0.55 mole) of magnesium turnings, and 300 ml. of anhydrous ether, there was added a crystal of iodine and some magnesium turnings activated by ethyl bromide in ether, to initiate the reaction. Completion of the reaction was accomplished by refluxing the mixture for 30 minutes. It was then cooled to 0°, and 58 g. (0.55 mole) of freshly distilled benzaldehyde in 100 cc. of dry ether was added at such a rate that the temperature of the mixture did not rise above 10°. After refluxing for 30 minutes, the addition compound was hydrolyzed

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[13] Kamm and Marvel, *Organic Syntheses*, Collective Vol. I, p. 23 (1932).

[14] Schroeter, Lichtenstadt, and Irineu, *Ber.*, **51**, 1599 (1918).

[15] Norris, Watt, and Thomas, *J. Am. Chem. Soc.*, **38**, 1078 (1916).

[16] Krause and Pohland, *Ber.*, **57**, 534 (1924).

[17] Markownikoff, *Ann.*, **302**, 1 (1898).

[18] Hiers and Adams, *J. Am. Chem. Soc.*, **48**, 2389 (1926).

[19] Freundler, *Bull. soc. chim.*, [3], **35**, 544 (1906).

[20] Norris and Catlin, *Organic Syntheses*, Collective Vol. I, p. 182 (1932).

[21] Zelinsky, *Bull. soc. chim.*, [3], **32**, 574 (1904).

by the careful addition of ice and water, and sufficient 20% sulfuric acid to make the mixture acid to Congo Red. The ether layer was removed, washed with water, then with a 10% sodium carbonate solution, dried over anhydrous potassium carbonate and distilled. The distilled carbinol congealed as it cooled, and was crystallized either from petroleum ether (b.p. 30–60°) or from methanol and water. It formed an amorphous white solid; m.p. 54–56°; b.p. 142–143° at 3 mm.; yield, 60%.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.29; H, 9.87.
Found: C, 81.76; H, 10.09.

Prepared similarly, were the following:

Benzylcyclohexylcarbinol (II), from cyclohexyl chloride and phenylacetaldehyde, colorless needles (from petroleum ether); m.p. 57.5°; b.p. 139–143° at 2 mm.; yield, 61%.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.29; H, 9.87.
Found: C, 82.56; H, 10.15.

1-beta-*Phenylethylcyclohexanol-1* (III), from phenylethyl bromide and cyclohexanone, was crystallized by making a saturated solution in warm petroleum ether and chilling it with an ice-salt or solid carbon dioxide-alcohol mixture. It was thus obtained in white needles; m.p. 57°, b.p. 145° at 2–3 mm.; yield, 54%. Cook and Hewett[2b] reported the m.p. as 55–56°, and the b.p. as 165° at 10 mm.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.29; H, 9.87.
Found: C, 82.04; H, 9.93.

1-beta-*Phenylethyl-2-methylcyclohexanol-1* (IV), from phenylethyl bromide and *o*-methylcyclohexanone, was a viscous oil of agreeable odor; b.p. 150–151° at 5–6 mm.; n_D^{25} 1.5287; d_4^{2} 0.9997; $R_L^{obs.}$ 67.27, $R_L^{calc.}$ 67.19; yield, 46%.

Anal. Calc'd for $C_{15}H_{22}O$: C, 82.50, H 10.16.
Found: C, 82.74; H, 10.41.

Phenylurethanes

ALCOHOL	M.P.	FORMULA	N CALC'D	N FOUND
I	91–92°	$C_{21}H_{25}NO_2$	4.34	4.36
II	83.5–84.5°	$C_{21}H_{25}NO_2$	4.34	4.56
III	125–126°	$C_{21}H_{25}NO_2$	4.34	4.47
IV	132–133°	$C_{22}H_{27}NO_2$	4.12	4.27

Equimolecular quantities of the alcohol and phenyl isocyanate were left at room temperature, in a well-stoppered bottle, until the contents solidified (generally 2–3 days). Excess of isocyanate was removed by washing with cold petroleum ether (b.p. 30–60°). The residual solid was then extracted in a Soxhlet apparatus with petroleum ether, which dissolved out the urethanes, but not the carbanilide. The urethanes were then purified by recrystallization to constant m.p. from methanol-water mixtures; yields, 35–80%.

Dehydration of the Alcohols

This was effected with 90% sulfuric acid for the secondary alcohols (I and II), and 85% for the tertiary ones (III and IV).

The alcohol was added slowly with stirring to two volumes of the acid cooled by an ice pack. When all the alcohol had been added, the stirring was continued for 15–20 minutes at room temperature, and the mixture was then extracted with petroleum ether. The extract was agitated vigorously twice or thrice with cold 85% sulfuric acid, until the ether layer was a pale lemon-yellow, when it was washed with a 10% sodium carbonate followed by a 10% sodium sulfate solution, dried over anhydrous potassium carbonate and fractioned under diminished pressure.

Dehydration of Phenylhexahydrobenzylcarbinol (I).—The reaction product from 24 g. of the carbinol and 50 ml. of 90% sulfuric acid became more and more viscous as the stirring continued, and the result was a thermoplastic resin from which no pure compounds were isolated.

Dehydration of Benzylcyclohexylcarbinol (II).—The hydrocarbon product was a colorless liquid, of musty odor; yield, 65%; b.p. 135–150° at 10 mm.; n_D^{25} 1.5486; d_4^{25} 1.0005; $R_L^{obs.}$ 59.14, $R_L^{calc.}$ 58.85. There was also formed (8 g. from 32.5 g. of the carbinol) a very viscous polymer, b.p. 220° at 2 mm.

Attempts were made to separate the fraction of b.p. 135–150° at 10 mm. by distillation in an all-glass apparatus equipped with a Widmer column, following the progress of the separation by the refractive indices of the fractions, and there were thus obtained fractions whose indices ranged from 1.5270 to 1.5527. These results indicated that, although separation was actually being achieved, it was unlikely that it could be carried to a successful conclusion with the amount of material available. However, it was definitely established that the first and last fractions contained different isomers, since on oxidation the former yielded *alpha, alpha*-pentamethylenehomophthalic (VIII), and the latter phthalic acid.

An approximate calculation of the two components of the hydrocarbon fraction was made by assuming the specific refraction of the mixture (n_D^{25} 1.5486) to be the mean of that of its constituents, taking the lowest index (1.5270), that of the first runnings of the first fraction, as that of the spirane (VII), and the highest index (1.5528), that of the last runnings of the higher-boiling fraction, for the *as*-octahydrophenanthrene. The densities of the individual constituents and of their mixtures, were taken as 1.00, as shown by determinations on the original mixtures and on the higher-boiling fraction. In this way, the approximate composition of the original hydrocarbon mixture (b.p. 135–150° at 10 mm.) was computed as 14.6% spirane (VII) and 85.4% octahydrophenanthrene.

Dehydration of 1-beta-*Phenylethylcyclohexanol-1* (III).—The yield of crude hydrocarbon mixture was 90%, and its b.p. 135–137° at 10 mm.; n_D^{25} 1.5510; d_4^{25} 1.0049; $R_L^{obs.}$ 59.11, $R_L^{calc.}$ 58.85.

Repeated distillations of this product, yielded two fractions, with indices of refraction of 1.5468 and 1.5528, and b.p. at 10 mm. of 135.5–137.5° and 146–147°.

The higher-boiling fraction (b.p., 146–147° at 10 mm.; n_D^{25} 1.5528; d_4^{25} 1.0067; $R_L^{obs.}$ 59.15, $R_L^{calc.}$ 58.85) was analyzed with the following results.

Anal. Calc'd for $C_{14}H_{18}$: C, 90.25; H, 9.75.
Found: C, 90.15; H, 9.98.

Cook and Hewett[2b], from the same alcohol (III) and concentrated sulfuric acid, obtained a product; b.p. 159° at 15 mm.; $n_D^{19.2}$ 1.5527. Van de Kamp and Mosettig[2a] used phosphorus pentoxide, instead of sulfuric acid, and by repeated fractionation of their crude product isolated an *as*-octahydrophenanthrene (their "Fraction B"), in a yield of 70%; b.p. 142.6–142.8° at 9.2 mm.; $n_D^{10.6}$ 1.5592; d_4^{25} 1.0053.

Bardhan and Sengupta[7], from 1-*beta*-phenylethylcyclohexanol-2, obtained an octahydrophenanthrene; b.p. 135° at 9 mm.; n_D^{32} 1.548575; d_4^{25} 0.997325.

1-beta-*Phenylethylcyclohexene-1*.—A crystal of iodine was added to the 1-*beta*-phenylethylcyclohexanol-1 (III) and the mixture distilled. About 1 ml. of water was collected in the first runnings, whereas the theory required 1.3 ml. Repeated fractionation of the residue gave a cut, b.p. 134–137° at 9–10 mm., of characteristic odor, which immediately discharged the color of a carbon tetrachloride solution of bromine; yield 88%.

In another set of experiments, the cyclohexanol was heated for about a minute with 50% sulfuric acid, the solution diluted with water, extracted with ether, the ether extracts washed with sodium carbonate solution, then with water, dried over calcium chloride, and distilled under diminished pressure, collecting the fraction boiling at 135–138° at 10 mm., apparently identical with the product obtained by the action of iodine upon the alcohol.

When this unsaturated hydrocarbon was treated with concentrated sulfuric acid, the odor of *as*-octahydrophenanthrene was immediately detected.

Cook and Hewett[2b] have since obtained similar results in the preparation of this olefin and its conversion into the *as*-octahydrophenanthrene; and Fulton and Robinson[2c] have described a similar unsaturated hydrocarbon, prepared by the action of zinc chloride, acetic anhydride, or phenylisocyanate, upon the same alcohol (III).

*Dehydration of 1-*beta-*Phenylethyl-2-methylcyclohexanol-1* (IV).—A yield of 92% of 12-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (IX) was obtained; b.p. 145–147° at 10 mm.; n_D^{25} 1.5508; d_4^{25} 1.0045; $R_L^{obs.}$ 63.56, $R_L^{calc.}$ 63.47.

Anal. Calc'd for $C_{15}H_{20}$: C, 89.92; H, 10.07.
Found: C, 90.27; H, 10.25.

Kon[10] has also prepared this compound, using phosphorus pentoxide as the dehydrating agent, and gave its constants as b.p. 157° at 16 mm.; $n_D^{18.2}$ 1.5543; $d_4^{18.2}$ 1.0082.

Dehydrogenation of the Hydrocarbons by Selenium

The mixture of hydrocarbon (1 part) and selenium (1.5–2 parts) in a pyrex test-tube, fused to a long pyrex tube which functioned as an air condenser, was heated in a potassium nitrate-sodium nitrate (55:45) bath at 290°–320° for 14–15 hours. The dehydrogenation product was extracted with benzene, the benzene extract distilled at atmospheric pressure, the residual hydrocarbon crystallized to constant m.p., and identified as phenanthrene by its m.p. (99.5°), the m.p. (144–145°) of its picrate, and by mixed melting points with authentic samples of other origin. The results are given in the following table; in which A is the hydrocarbon mixture, b.p. at 10 mm., 135–137°; n_D^{25} 1.5510, from alcohol III; B is the analogous mixture, b.p. 135–150° at 10 mm., n_D^{25} 1.5486, obtained by the dehydration of alcohol II; and C, the methyloctahydrophenanthrene (IX) from the alcohol IV.

Dehydrogenation Experiments

	A	*B*	*C*
Hydrocarbon (g.)	6.6	8.6	6.4
Selenium (g.)	12.	15.	11.
Yield of phenanthrene (g.)	5.8	6.7	5.1
Yield of phenanthrene (%)	91.	81.	89.

Phenanthrene has been obtained also by others, from this octahydro derivative, by dehydrogenation with selenium[7] or with sulfur[2c].

Oxidation of the Dehydration Products

In a 3-necked flask equipped with a mercury-sealed stirrer and reflux condenser, a mixture of 0.01 mole (about 2 g.) of the hydrocarbon, 0.16 mole (25 g.) of potassium permanganate and 5 drops of a 10% potassium hydroxide solution, was refluxed with vigorous stirring (to prevent bumping) until the color of the permanganate was discharged (8–24 hours). Some (0.5–1.0 g.) of the hydrocarbon remained unattacked, partly because of its slight solubility in water and partly because it was carried up into the reflux by the steam. The mixture was filtered hot, the filtrate concentrated to 30 ml., and 50% sulfuric acid added until the solution was acid to Congo Red. At this point, the oxidation product of the spirane (VII) separated in crystalline form; the others, as heavy viscous oils, from which no crystals could be obtained either on long standing, or by the use of solvents. These oils, therefore, were treated with 1 g. of sodium hydroxide and 10 ml. of 30% hydrogen dioxide,[22] boiled for 10 minutes, cooled and the solution made acid to Congo Red with 50% sulfuric acid. The precipitated organic acid was then purified by crystallization from a suitable solvent.

The results obtained by this method were the following:

1. From 2 g. of the original hydrocarbon mixture (n_D^{25} 1.5486) from II, 0.2 g. of *alpha,alpha*-pentamethylenehomophthalic acid and 0.1 g. of phthalic acid.

Although the octahydrophenanthrene is present in the initial hydrocarbon mixture in much larger proportion than the spirane, the latter is easily oxidized to the difficultly soluble pentamethylenehomophthalic acid, whereas the former is much harder to oxidize to the readily soluble phthalic acid. This accounts for the relatively better recovery of the spirane oxidation product, especially when working with small quantities of material.

2. From 1 g. of the first fraction (n_D^{25} 1.5302) of the same crude as the foregoing, 0.1 g. of the *alpha,alpha*-pentamethylenehomophthalic acid, and a trace of phthalic acid as detected by the Breithut and Apfelbaum[23] test.

3. From 2 g. of the crude octahydrophenanthrene (n_D^{25} 1.5510) from III, 0.7 g. of phthalic acid, identified through its anhydride (m.p. 130–131°).

4. From 0.8 g. of the first fraction (n_D^{25} 1.5468) of this same crude, 0.12 g. of white crystals, very slightly soluble in hot water. Recrystallized from methanol and water, this acid melted at 154.5–155.5°, and was identical with the *alpha,alpha*-pentamethylenehomophthalic acid (VIII) which will be described more fully in a subsequent paper.

5. From 2 g. of 12-methyloctahydrophenanthrene (IX), 0.8 g. of phthalic acid (m.p. of anhydride, 131°).

SUMMARY

1. Several new hydroxyl derivatives of *beta*-phenylethylcyclohexane have been prepared and described.

2. When dehydrated by sulfuric acid, the products vary with the location of the hydroxyl group. If this group is on the carbon directly attached to the benzene nucleus, as in phenylhexahydrobenzylcarbinol, the unsaturated hydrocarbon first formed immediately undergoes polymerization. When the hydroxyl is on the second or third carbon from the aromatic nucleus, as in benzylcyclohexylcarbinol and *beta*-phenylethylcyclohexanol-1, the main product is the *as*-octahydrophenanthrene, with the spirane (spirocyclohexane-1,1-indane) as the by-product; except in the

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[22] Holleman, *Rec. trav. chim.*, **23**, 169 (1904).

[23] Breithut and Apfelbaum, *Ind. Eng. Chem.*, **17**, 534 (1925).

case of *beta*-phenylethyl-2-methylcyclohexanol-1, when the methyl group directs the cyclization practically exclusively to the formation of the 12-methyloctahydrophenanthrene. The presence of a saturated cycle upon the third carbon of the aromatic side chain seems to exert much the same influence as the *gem*-dimethyl group upon the course of the cyclization.

3. Fusion of the *as*-octahydrophenanthrene, or of its 12-methyl (angular) derivative, with selenium, yields phenanthrene.

4. Oxidation of spirocyclohexane-1,1-indane gives *alpha,alpha*-pentamethylenehomophthalic acid.

5. Further evidence is presented in support of the hypothesis that these cyclizations proceed chiefly through the formation of an intermediate olefin, which then rearranges to the cycle.

[Contribution from the Chemical Laboratories of Columbia University]

THE SYNTHESIS AND PROPERTIES OF CERTAIN SPIRANES FROM PHENYLPROPYLCYCLANOLS*

David Perlman, David Davidson, and Marston Taylor Bogert

Received July 31, 1936

In the preceding paper,[1] evidence was submitted that in the dehydration of some hydroxylated *beta*-phenylethylcyclohexanes by sulfuric acid spiranes were formed, as well as *as*-octahydrophenanthrene.

The present paper describes two new spiranes, the spirocyclohexane-1,1-tetralin (III) and the spirocyclopentane-1,1-tetralin (IV), prepared respectively from the 1-gamma-phenylpropylcyclohexanol-1 (I) and the 1-gamma-phenylpropylcyclopentanol-1 (II), by the action of 85 per cent. sulfuric acid. The yields in both cases were over 90 per cent., and no other hydrocarbons were found in the crude products. Like the *gem*-dimethyl group,[1] a cyclane in a suitable position on the side chain thus appears to favor cyclization to a six-membered ring.

These spiranes were subjected to the action of selenium at high temperatures (320–350°). Depending upon the duration of the heating (15–40 hours), they were either recovered unaltered, or yielded fluorescent oils from which no crystalline picrates could be obtained. It has been reported in a number of instances that high-temperature fusions of spiranes with selenium caused molecular rearrangements;[2] although in other cases,[3] no such isomerizations were observed.

Determination of constitution by dehydrogenation with selenium at high temperature may therefore be misleading, and we have preferred,

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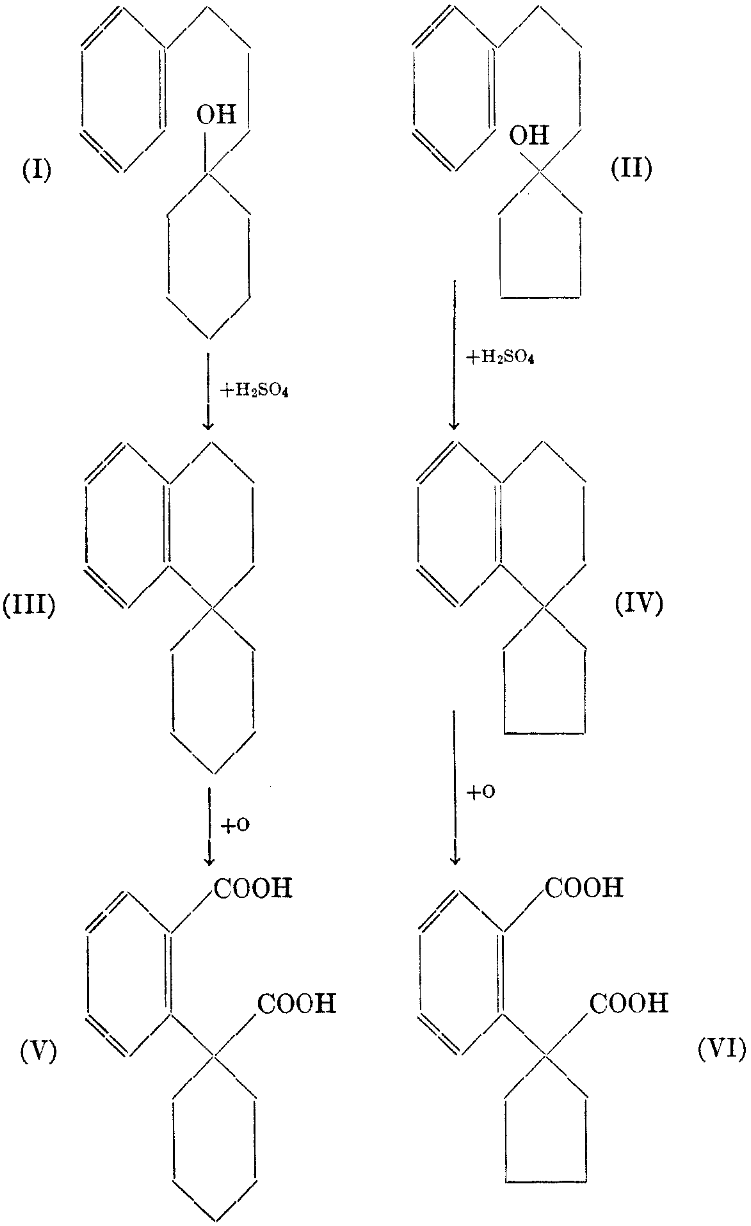
* Based upon the Dissertation submitted by David Perlman, May, 1936, for the degree of Ph.D., under the Faculty of Pure Science, Columbia University, New York, N. Y., to which Dissertation the reader is referred for further experimental details and literature citations.

[1] Perlman, Davidson, and Bogert, This Journal, **1**, 288–99 (1936).

[2] (*a*) Clemo and Ormston, *J. Chem. Soc.*, **1933**, 352; (*b*) Sengupta, *J. Indian Chem. Soc.*, **11**, 389 (1934); (*c*) Cook and Hewett, *J. Chem. Soc.*, **1934**, 365; (*d*) Barry, Cook, *et al.*, *Proc. Royal Soc.* (London), **B117**, 321, footnote (1935); (*e*) Ruzicka and Peyer, *Helv. Chim. Acta*, **18**, 676 (1935); (*f*) Cook, Hewett, and Lawrence, *J. Chem. Soc.*, **1936**, 72, 80.

[3] (*a*) Cook, Hewett, Mayneord and Roe, *J. Chem. Soc.*, **1934**, 1727; (*b*) Cohen, Cook and Hewett, *Ibid.*, **1935**, 1633.


OH
(I)
OH
(II)
+H₂SO₄
+H₂SO₄
(III)
(IV)
+O
+O
COOH
COOH
COOH
COOH
(V)
(VI)

when possible, to base our deductions upon the nature of the products obtained by oxidative degradation.

These oxidations were conducted both with alkaline potassium permanganate, followed by 30 per cent. hydrogen dioxide, and with chromic anhydride in glacial acetic acid solution.* The final product was the same in the two cases. Spirane III yielded the *alpha, alpha*-pentamethylenehomophthalic acid (V), identical with the oxidation product of spirocyclohexane-1,1-indane;[1] and spirane IV, the corresponding tetramethylene derivative (VI). (See page 301.)

EXPERIMENTAL

In general, the manipulative technique was that described in our previous communication,[1] of which this paper is a continuation.

gamma-*Phenylpropylbromide* was prepared from the corresponding alcohol by treatment with either hydrobromic acid[4] or phosphorus tribromide;[5] yield, in each case, approximately 68%; b.p. 109° at 10 mm., 120–122° at 20 mm.; n_D^{25} 1.5540; d_4^{25} 1.3106; $R_L^{obs.}$ 47.93, $R_L^{calc.}$ 47.93; b.p. in literature, 109° at 11 mm.,[5] 128–129° at 29 mm.[4]

1-gamma-*Phenylpropylcyclohexanol-1* (I) was obtained by the action of phenylpropylmagnesium bromide upon cyclohexanone; yield, 66%; b.p. 139–140° at 3–4 mm.; n_D^{25} 1.5278; d_4^{25} 0.9976; $R_L^{obs.}$ 67.31, $R_L^{calc.}$ 67.19. Above 5 mm. pressure this alcohol lost water when distilled, with formation of a hydrocarbon which instantly decolorized a carbon tetrachloride solution of bromine.

Anal. Calc'd for $C_{15}H_{22}O$: C, 82.50; H, 10.16.
Found: C, 83.07; H, 10.35.

1-gamma-*Phenylpropylcyclopentanol-1* (II).—Phenylpropylmagnesium bromide, from 100 g. (0.5 mole) of phenylpropylbromide and 12.2 g. (0.51 mole) of magnesium turnings, was treated with 43 g. (0.51 mole) of freshly distilled cyclopentanone. At the close of the reaction, the addition compound solidified. It was filtered out, washed with ether, decomposed in the usual manner, extracted with ether, the ether extracts washed, dried over anhydrous potassium carbonate, and fractioned at low pressure. There was thus obtained a colorless oily liquid, b.p. 136–137° at 2–3 mm., n_D^{25} 1.5255; d_4^{25} 0.9996; $R_L^{obs.}$ 62.64, $R_L^{calc.}$ 62.58; yield, 50%.

Distilled at pressures above 5 mm., it tended to split out water, with formation of a hydrocarbon unsaturated to a carbon tetrachloride solution of bromine.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.29; H, 9.87.
Found: C, 82.66; H, 10.01.

Phenylurethanes

ALCOHOL	FORMULA	M.P.	N CALC.	N FOUND
I	$C_{22}H_{27}O_2N$	106–106.5°	4.12	4.31
II	$C_{21}H_{25}O_2N$	90–91°	4.34	4.51

These, and the following two hydrocarbons, were prepared and purified as described for analogous compounds in our earlier communication.[1]

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* Compare also Kohler's work [*Am. Chem. J.*, **40,** 217 (1908)] in the indene field.

[4] NORRIS, WATT AND THOMAS, *J. Am. Chem. Soc.*, **38,** 1078 (1916).

[5] RUPE AND BÜRGIN, *Ber.*, **43,** 178 (1910).

Spiranes

	SPIRANE III	SPIRANE IV
Yield (%)	93.	91.
Appearance	Colorless crystals	Colorless liquid of faint musty odor
M. p.	40–41°	
B.p.	153–154° at 10 mm.	137–138° at 10 mm.
n_D^{25}	1.5535	1.5533
d_4^{25}	1.0088	1.0095
$R_L^{calc.}$	63.57	58.85
$R_L^{obs.}$	63.47	59.03
Formula	$C_{15}H_{20}$	$C_{14}H_{18}$
Compos. calc'd	C, 89.92; H, 10.07	C, 90.25; H, 9.75
Compos. found	C, 90.14; H, 9.86[a]	C, 90.51; H, 9.83
	C, 89.57; H, 9.87[b]	

[a] On the liquid; [b] on the solid hydrocarbon.

The Spirocyclohexane-1,1-tetralin (III), when freshly prepared, was a colorless liquid but, after standing for a month, solidified in colorless crystals. The two forms were proven identical by their analysis and oxidation products (see beyond).

Fusion of the Spiranes with Selenium.—A mixture of 4 g. of spirane III with 6 g. of selenium was heated at 330–350° for 42 hours. There resulted 2 g. of a fluorescent liquid from which no phenanthrene could be isolated via the picrate.

When a mixture of 5 g. of spirane IV with 8 g. of selenium was heated at 290–320° for 40 hours, most of the spirane was recovered unchanged. Another run, with 5.5 g. of the spirane and 11 g. of selenium, heated at 330–350° for 42 hours, resulted in considerable carbonization and the formation of 2 g. of a fluorescent oil, like that from spirane III, and in which no phenanthrene could be detected. In view of the extensive decomposition at 350°, the use of higher temperatures seemed inadvisable.

Oxidation Products

The spiranes were oxidized either by alkaline permanganate followed by hydrogen dioxide,[1] or by chromic anhydride in glacial acetic acid solution. The latter oxidation was carried out as follows.

A solution of 0.005 mole (about 1 g.) of the hydrocarbon in 20 ml. of glacial acetic acid was heated to incipient boiling and, after 10 g. (0.1 mole) of chromic anhydride had been added in small portions, most of the acetic acid was distilled. In this evaporation, care must be taken not to go too far, or the entire mixture may suddenly ignite. The residue was diluted with 100 cc. of water and boiled for 10 minutes, to effect solution. Occasionally crystals separated on cooling. Without removing any such crystals, the cold mixture was extracted with chloroform, the extract washed with water, to free it from acetic acid, the chloroform evaporated. When the residue was a solid, it was purified by crystallization from an appropriate solvent; when it was an oil, it was further oxidized by 30% hydrogen dioxide, as in the permanganate method.

alpha,alpha-*Pentamethylenehomophthalic Acid* (V).—Oxidation of 2 g. of spirane III by permanganate and hydrogen dioxide, yielded 0.8 g. of this acid, in white crystals, m.p. 154.5–155.5°. This acid forms a liquid anhydride when heated. Its melting point, therefore, varied with the temperature of the bath and rate of heating. The melting point recorded was taken by placing the tube in the bath at 145° and raising the temperature fairly rapidly. Oxidations conducted with chromic anhydride gave the same product (V), the yields from 1 g. of the spirane varying from 0.18 g. to 0.2 g.

alpha, alpha-*Tetramethylenehomophthalic Acid* (VI).—The spirane IV (2 g.), oxidized by permanganate and hydrogen dioxide, yielded the acid (VI) (0.6 g.) in white needles (from water), m.p. 130–130.5°. The same product was obtained when the oxidizing agent was chromic anhydride; yield, 0.15 g. from 1 g. of the spirane.

	ACID V	ACID VI
M.p.	154.5–155.5°	130–130.5°
Formula	$C_{14}H_{16}O_4$	$C_{13}H_{14}O_4$
Compos. calc'd	C, 67.72; H, 6.50	C, 66.63; H, 6.03
Compos. found	C, 68.09; H, 6.71	C, 66.48; H, 6.01
Acid equiv. calc'd	124.6	117.1
Acid equiv. found	124.4	117.4

SUMMARY

1. The syntheses of spirocyclohexane-1,1-tetralin and spirocyclopentane-1,1-tetralin are described.

2. Fusion of these spiranes with selenium at high temperatures does not convert them into phenanthrenes.

3. On oxidation, the spiranes yield respectively *alpha, alpha*-pentamethylene and *alpha, alpha*-tetramethylene homophthalic acids.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

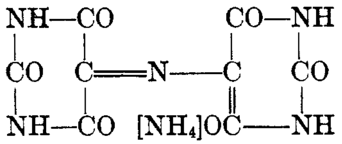
THE MUREXIDE QUESTION

DAVID DAVIDSON AND ELIAS EPSTEIN

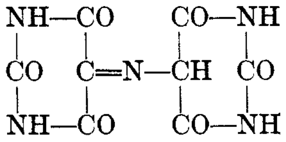
Received August 17, 1936

INTRODUCTION

The current structural formula for murexide (I) represents it as the ammonium salt of an as yet unisolated acid, purpuric acid (II). It was proposed practically simultaneously by Piloty,[1] Möhlau,[2] and Slimmer and Stieglitz.[3]



I



II

This structure serves to explain the formation of murexide by (*a*) the oxidation of uramil (III),[4,8] (*b*) the direct condensation of uramil with alloxan (IV),[2,3,4] (*c*) the action of ammonium salts on alloxantine or a mixture of alloxan and ammonium dialurate,[1,3,5] and (*d*) the action of alloxan on 7-alkyluramils.[1,2] It also accounts for the production of other purpurates by (*e*) metathesis of murexide with salts,[1,3] (*f*) the condensation of alloxan with alkali salts of uramil,[3] (*g*) the oxidation of alkali salts of uramil,[1,4] and (*h*) the action of amines or aminoacids on alloxan or alloxantine,[1,2,6,7] although auxiliary hypotheses are necessary to account for (*d*) and (*h*).

The most conspicuous chemical property of murexide is its hydrolysis by acids, in which uramil (III) and alloxan (IV) are obtained, accompanied by more or less alloxantine (V).[1,2,3,4,8]

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[1] PILOTY, *Ann.*, **333**, 22 (1904).

[2] MÖHLAU, *Ber.*, **37**, 2686 (1904); MÖHLAU AND LITTER, *J. prakt. Chem.*, [2], **73**, 449 (1906).

[3] SLIMMER AND STIEGLITZ, *Am. Chem. J.*, **31**, 661 (1904).

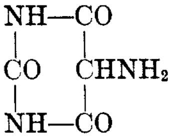
[4] WÖHLER AND LIEBIG, *Ann.*, **26**, 319 (1838).

[5] HARTLEY, *J. Chem. Soc.*, **87**, 1791 (1905).

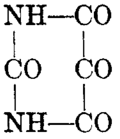
[6] STRECKER, *Ann.*, **123**, 363 (1862).

[7] TRAUBE, *Ber.*, **44**, 3145 (1911).

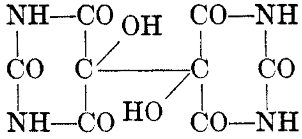
[8] BEILSTEIN, *Ann.*, **107**, 176 (1858).



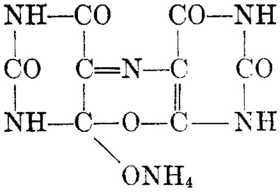
III



IV



V



VI

This occurrence of alloxantine has not been accounted for satisfactorily. Piloty was even inclined to consider alloxantine a primary hydrolytic product although uramil and alloxan are more consistent with the azomethine structure of purpuric acid (II). He favored an alternative formula (VI) for murexide, and ascribed the production of alloxantine and ammonia on the one hand and of uramil and alloxan on the other to concurrent reactions, although the latter formula makes this no more plausible than the former. The unconvincing character of this explanation is reflected in the following statement of Johnson and Hahn:[9]

> "It might be assumed further that the resolution of this complex [purpuric acid] on hydrolysis would serve to define this relation but unfortunately the experimental evidence is confusing." [p. 279]

It thus appears desirable either (1) to suggest a new formula for murexide, which accounts for its close relationship to alloxantine, or (2) to offer a plausible explanation for the formation of alloxantine from the present structure.

ALLOXANTINE

Among the proponents of the azomethine structure for murexide, Piloty, alone, emphasized the close relationship between alloxantine and murexide. Thus, as mentioned above, he considered alloxantine a primary hydrolytic product of murexide. He also implied that the formation of murexide from alloxantine and ammonium salts did not proceed through the intermediary uramil, as was suggested by other writers.[2,3,4] It is well, therefore, to consider the structure of alloxantine before proceeding further.

Alloxantine is characterized by its instability. In aqueous solution it appears to be largely dissociated[10] into alloxan (IV) and dialuric acid (VII). Attempts to form derivatives of it have led to derivatives of its dissociation products.[11] Nevertheless, one may seriously consider the

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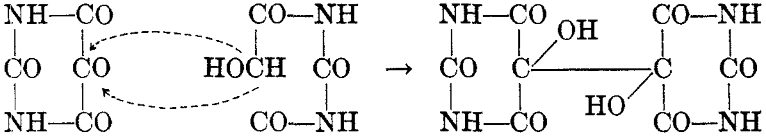
[9] Johnson and Hahn, *Chem. Rev.*, **13**, 193 (1933).

[10] Biilmann and Bentzon, *Ber.*, **51**, 522 (1918).

[11] Biltz and Paetzold, *Ann.*, **433**, 64 (1923).

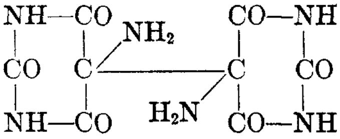
molecular structure of alloxantine, since it yields unique insoluble salts among which may be mentioned the beautiful purple barium salt which is used to detect alloxantine. This unusual salt led Hantzsch and Retinger[12] to revive the old pinacol formula (V) in preference to the hemiacetal formula of Piloty[1] and of Slimmer and Stieglitz.[3] Hantzsch and Retinger compared the barium salt of alloxantine with the metal ketyls.[13] The dissociation of alloxantine into alloxan and dialuric acid may then be considered a disproportionation of the ketyl radicals.[14] Another fact in favor of this view is the formation of analogs of alloxantine from alloxan and acyl derivatives of dialuric acid.[15] In these acylated dialuric acids the hydroxyl group necessary for the formation of a hemiacetal is presumably converted to an ester group. The formation of alloxantine from dialuric acid (VII) and alloxan (IV) may, therefore, be represented as follows:



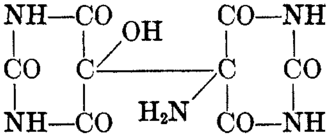
IV VII V

MUREXIDE AN ANALOG OF ALLOXANTINE (?)

The foregoing considerations led to the suggestion of the following formula (VIII) for the structure of murexide.



VIII



IX

All the methods of preparing murexide are readily explained by it. Purpuric acid is then represented as an intermediate between alloxantine and murexide (IX). Formula IX differs from formula II by a mole of water. It is significant that the metallic purpurates described by Piloty[1] and by Slimmer and Stieglitz[2] contain a mole of water (based on II). The formation of murexide from alloxantine would thus be represented by the replacement of two acidic hydroxyls by two amino groups (amide formation). The production of alloxantine on hydrolysis would be represented by the

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[12] HANTZSCH, *Ber.*, **54**, 1271 (1921); RETINGER, *J. Am. Chem. Soc.*, **39**, 1059 (1917).

[13] SCHLENK AND THAL, *Ber.*, **46**, 2840 (1913).

[14] MICHAELIS, *Chem. Rev.*, **16**, 243 (1935).

[15] BEHREND AND FRIEDERICHS, *Ann.*, **344**, 1 (1906).

reverse reaction, the replacement of amide groups by acidic hydroxyls. The production of uramil and alloxan could be accounted for by the disproportionation of the intermediate purpuric acid (IX). This formula would have great advantage in explaining the behavior of the alkyl ammonium purpurates of Möhlau and Litter.[2] It may be noted that the foregoing hypothesis relates murexide to the highly-colored meriquinones.[14]

LEUCOMUREXIDE

An *experimentum crucis* for testing this formula was found in reduction. While Piloty[1] has claimed that reducing agents cause a scission of the murexide molecule, it has recently been found that murexide is readily reduced by sodium hydrosulfite to a colorless leuco compound without disrupting the molecule.[16] Now formula VIII requires the formation of two moles of uramil on reduction, while formula I permits the absorption of two atoms of hydrogen by the azomethine bond. The colorless product obtained from murexide was readily distinguished from uramil by the ease with which it was reconverted to murexide by air or potassium ferricyanide.

THE HYDROLYSIS OF URAMIL

The suggestion of a murexide structure based on analogy with alloxantine having been disposed of, attention was next directed toward explaining the occurrence of alloxantine in the hydrolysis of murexide on the basis of the azomethine structure. Since alloxantine may arise from alloxan and dialuric acid, and alloxan is a recognized hydrolytic product of murexide, the problem reduces itself to tracing the origin of the dialuric acid. Uramil is at once suspected.

In 1904, Piloty wrote relative to the hydrolysis of murexide:[1]

> "Bei diesem Versuche ist eine Einwirkung der geringen Menge verdünnter Säure auf das Uramil and auch auf das Alloxan etwa unter Bildung von Alloxantin—ausgeschlossen. Reines Alloxan unter den gleichen Verhältnissen mit verdünnter Salzsäure behandelt, zeigt selbst nach längerer Zeit keine Veränderung, vor allem werden keine isolierbaren Mengen Alloxantin gebildet." [p. 33]

The conviction that uramil was stable under these conditions was so strong that Piloty does not appear to have troubled to test it. The influence of his dictum may be traced in Möhlau's remark:[2]

> ". . . und da es ausgeschlossen erscheint, dass Uramil unter den Bedingungen dieser Spaltung in Ammoniak und Dialursäure zerfallt. . . . " [p. 2687]

and in Johnson and Hahn's splendid review:[9]

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[16] (*a*) KUHN AND LYMAN, *Ber.*, **69B**, 1547 (1936), and (*b*) DAVIDSON, *J. Am. Chem. Soc.*, **58**, 1821 (1936).

> "Moreover there is again no instance recorded in the literature of an amino group in the 5-position being easily split off from a pyrimidine by hydrolysis." [p. 271]

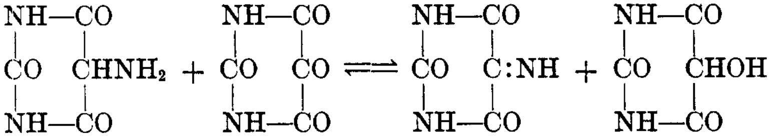
On the other hand, it appears that Liebig and Wöhler[4] found that uramil was decomposed by dilute sulfuric acid yielding "uramilic acid." Piloty and Finckh[17] found "uramilic acid" to be ammonium hydurilate and, concerning the decomposition of ammonium thionurate, a progenitor of uramil, they state:

> "Neben diesen Krystallen tritt stets unverandertes thionursäures Salz und Uramil, zuweilen auch Alloxantin auf."

Furthermore, Techow[18] reported that 1,3-dimethyluramil was completely hydrolyzed by boiling hydrochloric acid to 1,3-dimethyldialuric acid, which, on aerial oxidation, yielded crystalline tetramethylalloxantine. Behrend[19] also claims that 5-aminouracil is converted to isobarbituric acid by hydrochloric acid.

It is now found that the alleged stability of uramil toward hydrolysis is illusory. Actually, treatment for one or two minutes with boiling 6 *N* hydrochloric acid produces sufficient dialuric acid to yield a purple precipitate of barium alloxantinate with barium hydroxide or a colorless precipitate of sodium dialurate with sodium acetate. The behavior of uramil toward barium hydroxide before and after treatment with hydrochloric acid may, in fact, be used as a convenient test for uramil.

Quantitative experiments indicated erratic rates of hydrolysis with different samples of uramil. The hypothesis was proposed that oxidizing agents accelerate the hydrolysis, while reducing agents hinder it. Since uramil may be oxidized to alloxan (in acid medium), the following mechanism seems a plausible explanation for the catalyzed hydrolysis of uramil. Uramil (III) and alloxan (IV) first undergo an oxidation-reduction reaction, yielding alloxan-imine (X) and dialuric acid (VI). The alloxan-imine hydrolyzes readily (as is characteristic of imines) regenerating alloxan, which may go through the cycle again, converting another mole of uramil to dialuric acid and ammonia, and so on.[20]



$$\begin{array}{l}\text{NH—CO}\\ |\quad\ \ |\\ \text{CO}\ \ \text{CHNH}_2\\ |\quad\ \ |\\ \text{NH—CO}\end{array} + \begin{array}{l}\text{NH—CO}\\ |\quad\ \ |\\ \text{CO}\ \ \text{CO}\\ |\quad\ \ |\\ \text{NH—CO}\end{array} \rightleftharpoons \begin{array}{l}\text{NH—CO}\\ |\quad\ \ |\\ \text{CO}\ \ \text{C:NH}\\ |\quad\ \ |\\ \text{NH—CO}\end{array} + \begin{array}{l}\text{NH—CO}\\ |\quad\ \ |\\ \text{CO}\ \ \text{CHOH}\\ |\quad\ \ |\\ \text{NH—CO}\end{array}$$

III IV X VII

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[17] Piloty and Finckh, *Ann.*, **333**, 71 (1904).

[18] (*a*) Techow, *Ber.*, **27**, 3083 (1894). Compare (*b*) Fisher and Johnson, *J. Am. Chem. Soc.*, **54**, 2040 (1932).

[19] Behrend, *Ann.*, **229**, 38 (1885).

[20] Pinck and Hilbert, *J. Am. Chem. Soc.*, **54**, 710 (1932), report a closely related dehydrogenation reaction involving fluorenylamine.

Alloxan thus appears to be a true catalyst for the hydrolysis of uramil. Table I represents the time required for the dissolution of 0.5 g. of uramil by 25 cc. of 2.5 *N* hydrochloric acid at the boiling point in the presence of various proportions of alloxan. Thus, for example, 0.1 g. of alloxan tetrahydrate causes 0.5 g. of uramil to dissolve (*i.e.*, hydrolyze) in seven minutes. Ferric chloride is equally effective in promoting the hydrolysis of uramil.

TABLE I

Time Required for Hydrolysis of 0.5 g. Uramil by 25 cc. of 2.5 *N* HCl in the Presence of Alloxan

ALLOXAN	TIME
0.015 g.	>180 min.
0.025	87
0.050	16
0.075	10
0.100	7

TABLE II

Time Required for Hydrolysis of 0.5 g. Uramil in the Presence of 0.050 g. Alloxan by HCl of Different Strengths

HCl	TIME
1.0 *N*	35 min.
2.5	16
6.0	5

TABLE III

Recovery of Uramil from 1 g. after Refluxing for 2 Hours with 50 cc. 6 *N* HCl in the Presence of Stannous Chloride

$SnCl_2 \cdot 2H_2O$	RECOVERY
0.16 g.	51%
0.32	89
0.50	92
1.08	98

On the other hand, as little as one milligram of stannous chloride greatly retards the reaction. This effect of small amounts of tin or of alloxan explains the variable behavior of different samples of uramil. Larger amounts of stannous chloride protect the uramil almost completely. Thus, 98 per cent. of the uramil employed was recovered after boiling a gram of uramil for two hours with 50 cc. of 6 *N* hydrochloric acid containing one gram of stannous chloride. This result accounts for the success of Hartman and Sheppard's method of preparing uramil.[21] (Table III.)

When *equivalent* quantities of uramil and alloxan are treated with boiling 6 *N* hydrochloric acid, they are immediately converted into alloxantine and ammonia, the intermediate dialuric acid combining with the regenerated alloxan to form alloxantine. It is now possible to explain the results obtained in the hydrolysis of murexide. Assuming that alloxan and uramil are the primary products of the reaction, it becomes clear that more or less alloxantine will be formed from these, according to the mechanism suggested above, depending on the strength of the acid employed, the temperature, and the time of contact. (Tables I, II.)

THE HYDROLYSIS OF DIALURIC ACID

In the hydrolysis experiments just discussed tests for the hydrolytic products (dialuric acid or alloxantine) were obtained except when the hydrolysis was prolonged for several hours. It thus seemed that the dialuric acid appearing in the hydrolysis of uramil was itself undergoing hydrolysis involving the scission of the pyrimidine ring. Accordingly dialuric acid was subjected to boiling with 6 *N* hydrochloric acid. While a test for dialuric acid could still be obtained after 30 minutes, at the end of two hours the test was negative. Tartronic acid was isolated in the form of its barium salt.

THE MECHANISM OF FORMATION OF MUREXIDE

The formation of murexide from alloxantine and ammonium salts has been explained[2,3] as follows. Alloxantine dissociates into alloxan and dialuric acid. Dialuric acid then reacts with the ammonium salt to form uramil which condenses with alloxan to form purpuric acid, the ammonium salt of which is murexide. While dialuric acid is known to be converted to uramil by ammonium salts,[22] this reaction appears to be much slower than the formation of murexide under discussion. This suggests an indirect formation of uramil, which may proceed according to the following suggested scheme. Alloxan condenses with ammonia to form alloxan-imine (hypothetical) which is reduced by the dialuric acid present to uramil. This condenses with alloxan or with alloxan-imine to form purpuric acid. The postulated oxidation-reduction is the reverse of that given above in the mechanism of the hydrolysis of uramil.

In the preparation of murexide by the action of mercuric oxide on uramil, alloxan-imine is undoubtedly the primary product of oxidation. The production of murexide by the action of 7-alkyluramils on alloxan or

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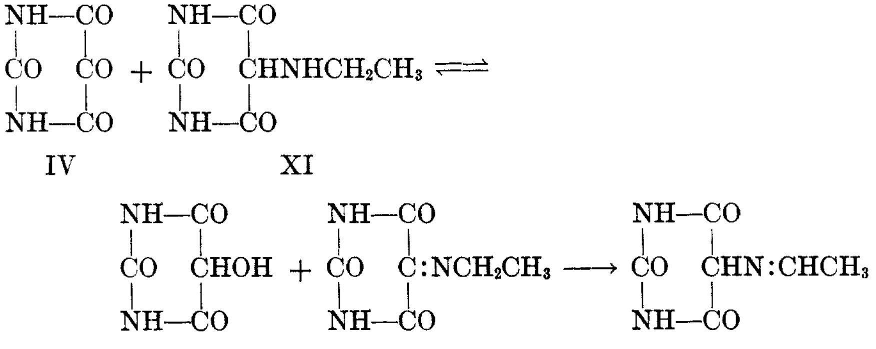
[21] HARTMAN AND SHEPPARD, *Org. Syntheses*, **12**, 84 (1932).

[22] BILTZ AND DAMM, *Ber.*, **46**, 3668 (1913).

alloxantine in the presence of ammonium carbonate[1,2] requires further consideration. It may be supposed that oxidation-reduction plays a rôle here too. For example, with 7-ethyluramil (XI) alloxan may react as follows, being converted to alloxan-ethylimine (XII).



IV XI

VI XII XIII

From this point, two alternatives are possible: (1) since, as a result of the redox reaction, both alloxan and dialuric acid are present, murexide may be formed as outlined above for alloxantine; or (2) alloxan-ethylimine (XII) may isomerize to ethylidene-uramil (XIII)[23] which then reacts with alloxan, eliminating acetaldehyde. Möhlau[2] claims to have detected ethyl alcohol (iodoform test) in this reaction. This test would, of course, apply equally well to acetaldehyde.

The action of amines on alloxan may be explained similarly. Condensation yields alloxan-alkylimines (like XII) which may then be converted to purpuric acid and an aldehyde according to the second mechanism given just above. If ammonia is absent, the amine combines with the purpuric acid to form an alkylammonium purpurate. Traube[7] obtained a good yield of benzaldehyde from the action of benzylamine on alloxan. In the reaction between aminoacids and alloxan, the same mechanism may be applied, if, in addition, decarboxylation is postulated to occur, following the isomerization step.[6,7,24]

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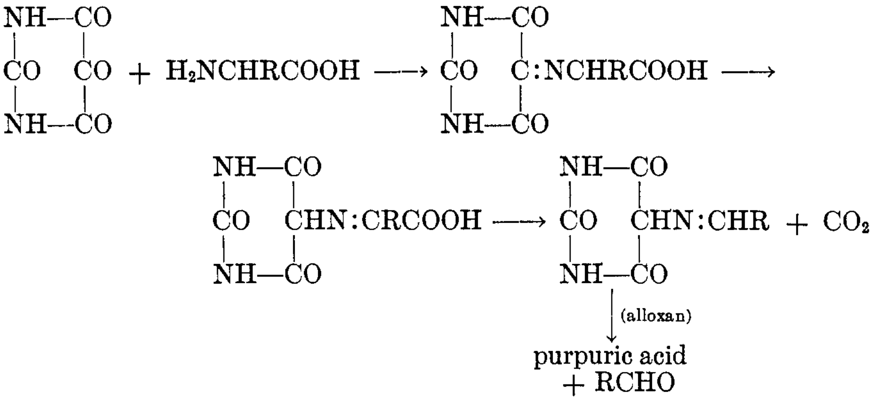
[23] Ingold and Wilson, *J. Chem. Soc.*, **1933**, 1500.

[24] (*a*) Hurtley and Wooton, *ibid.*, **99**, 288 (1911), (*b*) Harding and Warneford, *J. Biol. Chem.*, **25**, 319 (1916), and (*c*) Franke, *Biochem. Z.*, **258**, 297 (1933), offer other mechanisms. Support for the present mechanism will be presented in a forthcoming paper from this laboratory.



EXPERIMENTAL

Uric acid was oxidized with potassium chlorate according to Biltz and Damm.[22] From the resulting alloxan solution, *alloxan tetrahydrate* was obtained by chilling, *alloxantine* by reduction with stannous chloride in the cold,[25] and *dialuric acid* by reduction with stannous chloride in the hot.

Uramil was prepared from dialuric acid by the method of Biltz and Damm[22] and from barbituric acid by the method of Hartman and Sheppard,[21] as well as by the following improved method. A mixture of 12.8 g. (0.10 mole) of barbituric acid, 7.5 g. (0.11 mole) of sodium nitrite, and 500 cc. of water is heated with stirring until the acid dissolves and a deep purple solution of sodium violurate forms. The hot solution is filtered and then heated to boiling in a 3-l. flask. In the meantime a solution of sodium hydrosulfite is prepared by shaking 60 g. of the salt with 400 cc. of water and 100 cc. of concentrated ammonia in a well-stoppered flask. This solution is quickly filtered by suction and added *at once* to the boiling violurate solution. Vigorous boiling is continued for about 30 minutes to remove the ammonia and complete the precipitation of the uramil which appears as snow-white, silky needles. The mixture is then cooled to room temperature and filtered by suction. The product is washed by removing it from the filter, stirring it up to a paste with water and refiltering. This is repeated and the resulting cake washed with water and finally with methanol. After drying at 100°, a yield of 13.6 g. (95% of theory) of uramil is obtained.

Anal. Calc'd for $C_4H_5N_3O_3$: N, 29.4; Found: N, 28.9.

Murexide was prepared from alloxantine by the method of Davidson.[16b]

Hydrolysis of Murexide to Alloxantine.—While previous writers have reported varying amounts of alloxantine to be formed in the hydrolysis of murexide, it is possible to obtain principally alloxantine as follows. To 1.00 g. of murexide was added 50 cc. of dilute hydrochloric acid (1:4). The mixture was boiled for one to two minutes, filtered hot from a small residue, and then cooled rapidly. A nearly colorless, granular precipitate was obtained, which was recognized as alloxantine by its solubility, its purple barium salt, and its conversion to murexide. Yield, 0.68 g. (60% of theory).

Action of Alloxan on Uramil in Acid Solution.—While the action of alloxan on uramil in alkaline solution yields purpurates (see Introduction), their interaction

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[25] Biltz, *Ber.*, **45**, 3673 (1912).

in acid solution has not been reported. A mixture of 1.43 g. of uramil, 2.14 g. of alloxan tetrahydrate, and 25 cc. of dilute hydrochloric acid (1:1) was boiled for two minutes and then diluted with 50 cc. of boiling water. This resulted in complete solution of the reagents. On cooling, 2.32 g. (72% theoretical) of coarse, granular crystals characteristic of alloxantine separated, which was identified as described above.

Hydrolysis of Uramil to Dialuric Acid (Catalyzed by Alloxan).—One g. of uramil and 0.1 g. of alloxan tetrahydrate were refluxed in 50 cc. of 6*N* hydrochloric acid. The uramil dissolved completely in five minutes. The solution was then evaporated to dryness under diminished pressure. The residue was treated with 100 cc. of warm water, and the mixture was filtered from a small insoluble residue (0.02 g.). The clear filtrate was treated with 15 g. of sodium acetate, which precipitated 0.78 g. of sodium dialurate.[15] This was identified by its solubility in dilute hydrochloric acid, the precipitation of a purple barium salt from the acid solution by barium hydroxide, and its blue ferric salt (with ferric chloride and ammonia).

The experiments represented in Tables I, II, and III were performed by refluxing the materials in a 200-cc. flask attached to a condenser to which was fitted a downcomer which dipped into mercury. This served to prevent access of air to the reaction mixture.

Hydrolysis of Dialuric Acid.—One gram of dialuric acid was refluxed with 50 cc. of 6*N* hydrochloric acid for two hours. The solution was then evaporated under diminished pressure and the residue taken up in water. Precipitation with barium acetate solution in the hot yielded 0.3 g. of a dense, white salt which was filtered off, washed with dilute acetic acid and with water, and dried at 120°. It did not melt below 350° and contained no nitrogen.

Anal. Calc'd for $C_3H_2BaO_5$: Ba, 53.9; Found: Ba, 54.0.

SUMMARY

1. The hydrolysis of murexide by acid may yield alloxantine, or a mixture of uramil and alloxan, or all three products, depending on conditions.
2. Alloxan and uramil interact in acid solution to form alloxantine.
3. Uramil is susceptible of hydrolysis to dialuric acid in the presence of alloxan or other oxidizing agents, but resists hydrolysis in the presence of reducing agents.
4. Dialuric acid is readily hydrolyzed to tartronic acid by boiling 6*N* hydrochloric acid.
5. The formation of murexide, the hydrolysis of murexide, and the catalyzed hydrolysis of uramil may be explained by assuming the following reversible redox reaction:

$$\text{Alloxan} + \text{Uramil} \leftrightharpoons \text{Dialuric Acid} + \text{Alloxan-imine}.$$

6. The action of primary amines and of *alpha*-aminoacids on alloxan may be plausibly explained by a mechanism involving (*a*) condensation, (*b*) isomerization of the azomethine formed in (*a*), (*c*) interaction of the resulting Schiff base with alloxan.

[Contribution from the Chemical Laboratory of Iowa State College]

RELATIVE REACTIVITIES OF ORGANOMETALLIC COMPOUNDS. XV. ORGANOALKALI COMPOUNDS

HENRY GILMAN and RICHARD V. YOUNG

Received July 24, 1936

INTRODUCTION

Historical.—No systematic study of the relative reactivities of organoalkali compounds has been reported. One of a series of broad generalizations concerning the relative reactivities of all organometallic compounds[1] postulates that the organoalkali compounds will be found to fall in the following order of increasing reactivities: RLi, RNa, RK, RRb, RCs. It might be stated forthwith that the results reported at this time give adequate support to the generalization mentioned.

There are scattered references to the relative reactivities of RLi, RNa and RK compounds. Benzyllithium does not decompose diethyl ether, but benzylsodium decomposes ether in a very short time.[2] Ethyllithium may be prepared in a benzene solution[3] in which it is stable for a long time; however, ethylsodium and ethylpotassium metalate benzene to give phenylalkali and *o*- and *p*-phenylenedialkali compounds.[4] In the metalation of dibenzofuran it was observed that RNa and RK compounds reacted more rapidly than RLi compounds[5a]; and that dimetalation proceeds smoothly with RNa and RK compounds, but does not go at all with RLi compounds.[5b]

In a study of very weak acids, α-naphthyldiphenylmethylsodium reacted erratically with triphenylmethane in periods of a few minutes to several months, whereas the corresponding RK compound reacted smoothly and instantaneously.[6] Organopotassium compounds add more readily than organolithium compounds to the olefinic linkage of some ethylenes.[2]

It is pertinent to observe that organolithium compounds are distinctly more reactive than the corresponding organomagnesium compounds.[7]

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[1] Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

[2] Ziegler and co-workers, (*a*) *Ann.*, **473**, 1 (1929); (*b*) *Ber.*, **64**, 448 (1931).

[3] Schlenk and Holtz, *Ber.*, **50**, 269 (1917).

[4] (*a*) Schorigin, *ibid.*, **41**, 2711 (1908); (*b*) Morton and Hechenbleikner, *J. Am. Chem. Soc.*, **58**, 1024 (1936); (*c*) Gilman and Kirby, *ibid.*, **58**, (October, 1936).

[5] (*a*) Gilman and Young, *ibid.*, **56**, 1415, (1934); (*b*) *ibid*, **57**, 1121 (1935).

[6] Conant and Wheland, *ibid.*, **54**, 1212 (1932).

[7] Gilman and Kirby, *ibid.*, **55**, 1265 (1933).

Phenylacetenylalkali compounds and benzonitrile.—One of the compounds used to compare the relative reactivities of organoalkali compounds was benzonitrile. This compound was selected for several reasons: (1) it was used in studies of relative reactivities of other RM compounds previously reported in this series; (2) it reacts slower than most organic compounds having a functional group reactive to RM compounds;[8] and (3) it undergoes reaction with a minimum of secondary transformations.

The phenylacetenyl radical was selected because it was known from earlier observations that $C_6H_5C{\equiv}CM$ types are of a relatively low order of reactivity, particularly in addition reactions to some unsaturated functional groups.[9] Slow-reacting combinations were desirable in order to measure with some accuracy the time required to use up the highly reactive organoalkali compound when a definite excess of benzonitrile was used. The color test[10] was used to determine the disappearance of RM compound.

The use of the color test involves the periodic removal of small samples of the reaction mixture. This made it desirable to avoid special all-glass-sealed containers, like Schlenk tubes, which have been used so effectively in studies of organoalkali compounds. Although the organoalkali compounds are the most reactive organometallic compounds it seemed likely that special apparatus could be dispensed with, and that with reasonable care these RM compounds could be manipulated in the conventional three-necked, round-bottomed flasks provided with a mercury-sealed stirrer. The chief reason for the use of special sealed tubes is to exclude atmospheric oxygen, moisture and carbon dioxide. However, the Grignard reagents as well as other moderately reactive RM compounds are highly sensitive to these deleterious substances, and yet can be prepared and manipulated with only ordinary precautions in the more conventional apparatus. Furthermore, organolithium compounds can be prepared and used in accordance with RMgX technique, and this is also true of some organosodium compounds.[11] The chief prerequisite to such operations is a stream of dry and pure nitrogen or other inert gas. Even the highly inflammable rubidium and cesium can be transferred by means of regular pipettes. All that is necessary is to cover the upper and lower surfaces of these liquid metals in the pipette with a layer of petroleum ether, and this is done simply and easily when the metals are drawn up into the pipettes. Actually these most reactive metals are

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[8] ENTEMANN AND JOHNSON, *ibid.*, **55**, 2900 (1933). RM is used as a general formula for organometallic compounds.

[9] GILMAN AND CO-WORKERS, *Rec. trav. chim.*, **55**, (October, 1936).

[10] GILMAN AND SCHULTZE, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

[11] GILMAN, ZOELLNER AND SELBY, *ibid.*, **54**, 1957 (1932).

in many ways easier to manipulate, from the viewpoint of getting a definite quantity, than are lithium, sodium and potassium, because of the high accuracy of pipettes for measuring desired quantities.

Apparently, phenylacetenylsodium is the only member of this series reported, and it was prepared by the action of sodium on phenylacetylene in ether[12] and by metalation of phenylacetylene by indenylsodium.[6] We prepared all of the phenylacetenylalkali compounds, with the exception of the lithium compound, by the action of alkali metal on phenylacetylene in ether. Phenylacetenyllithium did not form in this way under our conditions, and was prepared from phenylacetylene and *n*-butyllithium. The organoalkali compounds could be prepared in consistently good yields as evidenced by the yields of phenylpropiolic acid obtained by carbonation.

TABLE I

TIME (IN HOURS) REQUIRED FOR REACTION OF $C_6H_5C{\equiv}CM$ WITH BENZONITRILE

$C_6H_5C{\equiv}CMgBr$	87, 85
$C_6H_5C{\equiv}CLi$	57, 63
$C_6H_5C{\equiv}CNa$	6.5, 7.0
$C_6H_5C{\equiv}CK$	4.3, 4.5
....	....
$C_6H_5C{\equiv}CK$	5.3, 5.1
$C_6H_5C{\equiv}CRb$	4.8, 4.9
$C_6H_5C{\equiv}CCs$	3.8, 3.9

$$C_6H_5C{\equiv}CM + CO_2 \xrightarrow{HOH} C_6H_5C{\equiv}CCO_2H$$

It is interesting that there was no significant reaction of these organoalkali compounds with the ether in the time required to complete addition to benzonitrile.

Table I records the relative times required for reaction with benzonitrile. Phenylacetenylmagnesium bromide is included for purposes of comparison. The experiments with the first four compounds were carried out on a comparatively larger scale and with slightly greater concentrations than those involving the more expensive rubidium and cesium compounds. To make the relative rates of reaction of these last two members of the series comparable with those of the first four, phenylacetenylpotassium was run under conditions and with concentrations like those of phenylacetenylrubidium and -cesium.

Metalation by ethylalkali compounds.—A series of experiments was carried out on the metalation of dibenzofuran by several ethylalkali compounds.

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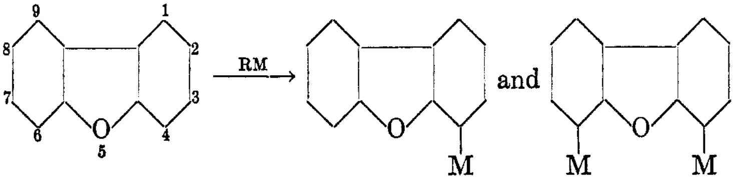
[12] GLASER, *Ann.*, **154**, 161 (1870).

Ethylalkali compounds of lithium, sodium and potassium are known; however, ethylrubidium and ethylcesium have only been prepared as complexes with diethylzinc.[13] We prepared the ethyllithium, -sodium, and -potassium compounds by interaction of a definite excess of alkali metal with diethylmercury in petroleum ether. This reaction is reversible,[14]

$$(C_2H_5)_2\,Hg + M \rightleftarrows 2C_2H_5M + Hg\ (\text{or } Hg\cdot M)$$

but the use of an excess of metal drives the reaction to essential completion. The need of an excess of metal discouraged, at this time, the preparation of ethylrubidium and -cesium.

Dibenzofuran was selected, and it is known that this compound metalates in the 4- and 4,6- positions.



It was first shown that at the end of 15 days, when reaction had reached completion, the quantities of acids resulting subsequent to carbonation (and composed of the 4-acid or the 4-acid and 4,6-diacid) were essentially alike, as determined by the quantity of standard alkali required for neutralization of the acid product. Then the reaction with each of the three ethylalkali compounds was interrupted at the end of two and one-half hours, the mixture carbonated, and the resulting dibenzofuran acids titrated with alkali. The quantity of acids determined in this manner is a measure of the extent of metalation, and the values given in Table II were obtained in this way.

Although the mechanism of such metalations has not been established, and may involve preliminary addition to an olefinic linkage, it is clear that the relative reactivities fall in the same increasing order established in the $C_6H_5C \equiv CM + C_6H_5CN$ reactions: RLi, RNa, RK. Supporting evidence for this order of reactivity in the metalation studies are the facts that (1) ethyllithium gives only monometalation under the experimental conditions; (2) ethylsodium and -potassium give both mono- and dimetalation; and (3) ethylpotassium gives more dimetalation than does ethylsodium. Similar observations were reported recently in the metalation of benzene, where ethyllithium gave no metalation and the sodium and

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[13] von Grosse, *Ber.*, **59**, 2646 (1926).

[14] Ziegler, *ibid.*, **64**, 445 (1931).

potassium analogs gave coincident mono- and dimetalation, ethylpotassium giving the greater quantity of dimetalation products.[4b, c]

The case for polymetalation as a criterion of the relative reactivities of RM compounds is not decisive. If metalation proceeds stepwise, which is a reasonable assumption, then the rate of polymetalation may be determined not only by the inherent reactivity of the metalating agent, but also by the labilizing effect on the nucleus of the initially introduced metal. In short, the monopotassium-dibenzofuran may undergo nuclear substitutions more rapidly than the monosodium-dibenzofuran.

In the ethylalkali experiments it was assumed that the extent of decomposition of the several compounds was essentially alike. It is known that methyl- and ethylsodium and methylpotassium are thermally labile, and that some decomposition occurs at room temperature.[15] In some random observations it was noticed that ethylsodium and -potassium underwent some decomposition (as evidenced by gas evolution) during their preparation; but they appeared to be essentially stable, or to undergo only slight change at room temperature, subsequent to the initial decomposition. No exact measurements were made. To reduce such decomposition, the ethylalkali compounds were prepared without the application of heat, and any rise in temperature during preparation was checked by rapid cooling with a water bath.

TABLE II

RELATIVE QUANTITIES OF DIBENZOFURANCARBOXYLIC ACIDS RESULTING AFTER METALATION BY C_2H_5M COMPOUNDS

C_2H_5Li	0.1, 0.05
C_2H_5Na	4.5, 4.7, 4.5
C_2H_5K	14.1, 12.6, 15.0

The Experimental Part describes some orienting observations on the relative reactivities of 4-dibenzofurylalkali and triphenylmethylalkali compounds.

Formation of organopotassium compounds from sodium-potassium alloy.— Sodium-potassium alloy has been used extensively in reactions culminating in the formation of organoalkali compounds. Inasmuch as there exists some uncertainty concerning the nature of the product or products, we thought it advisable to examine typical reactions to learn whether the product was an RNa or RK compound or a mixture of these two. The first use of the alloy for the preparation of RM compounds involved the

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[15] CAROTHERS AND COFFMAN, *J. Am. Chem. Soc.*, **51**, 588 (1929); *ibid.*, **52**, 1254 (1930).

cleavage of some mixed ethers and some ethanes.[16] Other reactions and references to sodium-potassium alloy may be found in the excellent review by Wooster[17] on organoalkali compounds and in the recent monograph by Schmidt[18] on organometallic compounds. The compounds examined were such that they could yield either sodium or potassium compounds soluble and stable in anhydrous ether. In each case we found that an RK and not an RNa compound was formed. The illustrative reactions follow:

$$C_6H_5C(CH_3)_2OCH_3 + Na\cdot K \rightarrow C_6H_5C(CH_3)_2K$$
$$(C_6H_5)_3COC_2H_5 + Na\cdot K \rightarrow (C_6H_5)_3CK$$
$$(C_6H_5)_2CHOCH_3 + Na\cdot K \rightarrow (C_6H_5)_2CHK$$
$$(C_6H_5)_2CHCH(C_6H_5)_2 + Na\cdot K \rightarrow (C_6H_5)_2CHK$$
$$(C_6H_5)_2C{=}C(C_6H_5)_2 + Na\cdot K \rightarrow (C_6H_5)_2C(K)C(K)(C_6H_5)_2$$
$$(C_6H_5)_3CH + Na\cdot K \rightarrow (C_6H_5)_3CK$$

The ultimate formation of RK rather than RNa compounds is in accordance with a generalization concerning the preparation and relative reactivities of organometallic compounds.[19] For example, all organometallic compounds can be prepared from any selected organometallic compound by one or both of two general reactions. If we select the Grignard reagent as the starting RM compound, *more* reactive RM compounds can be prepared from it by means of the metal of the more reactive compound:

$$RMgX + Li \rightarrow RLi$$

And *less* reactive RM compounds can be prepared from it by means of salts, particularly the halides, of the less reactive metal:

$$RMgX + CdCl_2 \rightarrow R_2Cd \text{ or } RCdX$$

On such a basis, if an RNa compound be formed initially in preparations involving sodium-potassium alloy, the metallic potassium would be expected to react with the RNa compound to give an RK compound:

$$RNa + K \rightarrow RK + Na$$

Actually, triphenylmethyllithium and sodium-potassium alloy gave triphenylmethylpotassium:

$$(C_6H_5)_3CLi + Na\cdot K \rightarrow (C_6H_5)_3CK$$

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[16] ZIEGLER AND THIELMAN, *Ber.*, **56**, 1740 (1923).

[17] WOOSTER, *Chem. Rev.* **11**, 1 (1932).

[18] SCHMIDT, "Organometallverbindungen," Wissentschaftliche Verlagsgesellschaft, Stuttgart, **1934**, Vol. II.

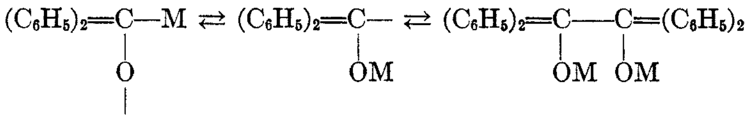
[19] GILMAN AND STRALEY, *Rec. trav. chim.*, **55**, 821, 1936.

Addition of alkali metals to tetraphenylethylene.—The addition of sodium to tetraphenylethylene is a well-known reaction:[20]

$$(C_6H_5)_2C{=}C(C_6H_5)_2 + 2Na \rightarrow (C_6H_5)_2C(Na)C(Na)(C_6H_5)_2$$

It appears that this reaction is essentially peculiar to sodium. Under corresponding conditions, lithium does not add. This is not altogether surprising in view of the lesser general reactivity of lithium. However, potassium alone likewise appeared not to add, and the reaction previously given with sodium-potassium alloy may have been due to initial addition of sodium followed by replacement of the two sodium atoms by potassium. It was quite surprising to note that neither rubidium nor cesium appears to add. The apparent lesser reactivity of these otherwise extremely reactive metals may be due to steric factors; in the case of tetraphenylethylene we are dealing with a highly sterically hindered olefinic linkage, and this together with the relatively huge atomic volumes of rubidium and cesium may combine to frustrate addition. Special conditions permit reaction of rubidium and cesium, but the course of reaction has not yet been established. Significantly, although rubidium alone does not add, a sodium-rubidium alloy adds to give the RRb compound. Here, again, it is probable that sodium first adds and is then replaced by the more reactive rubidium. This is in accordance with the generalization that steric factors have a much greater retarding effect on addition than on substitution reactions. Addition, in general, is not excluded, for 1,1-diphenylethylene dimerizes and adds rubidium.

Metal ketyls and n-butyl chloride.—The relative reactivities of *n*-butyl chloride with the benzophenone alkali compounds of potassium, rubidium and cesium showed the order of increasing reactivity to be: K, Rb, Cs. This is the order one would expect, on the basis of the other results presented at this time, if the metal were attached to carbon. The carbon-alkylation may proceed through the -OM type. What the order would be if the metal were definitely attached to oxygen in a compound like R_2CHOM or R_3COM remains to be established. The following equilibria or their electronic modifications appear valid, depending somewhat on the solvent:[21]



$$(C_6H_5)_2{=}\underset{\substack{|\\ O\\ |}}{C}{-}M \rightleftarrows (C_6H_5)_2{=}\underset{\substack{|\\ OM}}{C}{-} \rightleftarrows (C_6H_5)_2{=}\underset{\substack{|\\ OM}}{C}{-\!-}\underset{\substack{|\\ OM}}{C}{=}(C_6H_5)_2$$

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[20] SCHLENK, APPENRODT, MICHAEL, AND THAL, *Ber.*, **47**, 473 (1914); SCHLENK AND BERGMANN, *Ann.*, **463**, 1 (1928); BLUM-BERGMANN, *ibid.*, **484**, 26 (1930).

[21] SCHLENK AND WEICKEL, *Ber.*, **44**, 1182 (1911); BACHMANN, *J. Am. Chem. Soc.*, **55**, 1179 (1933); WOOSTER AND DEAN, *ibid.*, **57**, 112 (1935). See, however, BENT AND KEEVIL, *ibid.*, **58**, 1367 (1936).

Like the triphenylmethylalkali studies described in the Experimental Part, the relative reactivities may be influenced by the varying positions of equilibria dependent on the nature of the metal.

Should the reaction involve predominatingly the -OM form, it suggests the use of RRb or RCs compounds for establishing the mechanisms of some reactions, particularly that of RM compounds with esters which probably involves preliminary addition to the carbonyl* to give an -OM linkage.

Carbonation of organoalkali compounds.—The carbonation of RM compounds does not always lead to the facile formation of carboxylic acids. For example, Grignard reagents give not only the acid, but also varying quantities of ketone and tertiary alcohol. These chief by-products arise largely from secondary reactions between the Grignard reagent and the RCOOMgX salt which is first formed. The secondary reactions can be effectively depressed by carbonating in the cold or by the use of solid carbon dioxide. Under usual conditions of carbonation the otherwise secondary reactions may become chief reactions with a compound like phenyllithium which gave but a trace of benzoic acid[22] and an excellent yield (upward of 70 per cent.) of benzophenone. With solid carbon dioxide, the yield of benzoic acid from phenyllithium is 60 per cent., and only 15 per cent. of benzophenone is formed.[23] It has been suggested that the relatively low yields of acid and high yields of ketone by carbonation of an aryllithium compound are due, in part, to the greater reactivity of RLi compounds over the corresponding RMgX compounds.[23]

We have found that not only RNa compounds, but also the RK, RRb and RCs compounds give highly satisfactory yields of acids when carbonated in boiling ether. In contrast, the carbonation of phenyllithium in boiling ether gave but 1.6 per cent. of benzoic acid and 76 per cent. of benzophenone. The explanation for these significant differences may reside in the varying solubilities of the salts.

Some methods for the determination and postulation of the relative reactivities of organoalkali compounds.—There is no question concerning the pronounced polar characteristics of organoalkali compounds. All RM compounds are to be considered as salts derived from the weakly acidic RH compounds. As such, the organoalkali compounds should be the most polar RM types inasmuch as they are prepared, directly or indirectly, from the strongest bases. If relative reactivities are to be correlated with

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* This finds support by analogy with the mechanism of reaction of Grignard reagents and thio-esters. In such cases the -SM linkage is more readily converted to an -SEthyl linkage than is the case of the -OM→ -OEthyl conversion.

[22] Ziegler and Colonius, *Ann.*, **479**, 135 (1930).

[23] Gilman and Van Ess, *J. Am. Chem. Soc.*, **55**, 1258 (1933).

the salt-like or polar characteristics of the RM compounds, it should be possible to use conductivity measurements to establish relative reactivities. Unfortunately the less reactive RM types have not lent themselves to such measurements. The more reactive types, of which the organoalkali compounds are distinguished examples, have been examined rather closely. Some of the findings are very pertinent and a particularly happy illustration is contained in Table III, which is taken from some of the studies by Hein and co-workers.[24] For comparative purposes the molar conductance values of 0.1 *N* solution of the corresponding alkali metal hydroxide at 18° are also given.[25]

The splendid correlation between conductivities of the RM compounds and relative reactivities promises a high utility for this method of comparing relative reactivities. However, there are two general reasons for a restricted applicability of the method. First, even though the organoalkali compounds are the best conductors and, with the exception of RM types of the alkaline-earth metals, the only types that conduct adequately for the purposes in hand, they cannot generally be examined in this way. Their thermal instability precludes measurements in the fused state, and their insolubility, together with high reactivity, markedly restricts appropriate solvents. Second, the promise held out by the ethylalkali compounds is not sustained generally because of disturbing anomalous results. For example, phenylsodium in diethylzinc does not conduct at all, whereas phenyllithium which is distinctly less reactive chemically does conduct. Also, the order of conductivity of a given series with a selected metal (like the RLi types) but with different R groups, does not always follow either the order of chemical reactivity or the order established by conductometric methods for corresponding radicals attached to another metal

TABLE III

MOLAR CONDUCTANCES OF C_2H_5M AND MOH

MOLAR CONDUCTANCES OF C_2H_5M SOLVATES OF $(C_2H_5)_2Zn$		MOLAR CONDUCTANCES OF MOH	
C_2H_5Li	0.13	LiOH	74.5
C_2H_5Na	4.01	NaOH	195.3
C_2H_5K	6.49	KOH	213
C_2H_5Rb	9.39	RbOH	213.3

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[24] (*a*) HEIN, *Z. Elektrochem.*, **28**, 269 (1922); (*b*) HEIN, PETZCHNER, WAGLER AND SEGITZ, *Z. anorg. allgem. Chem.*, **141**, 161 (1924); (*c*) HEIN AND SEGITZ, *ibid.*, **158**, 153 (1926).

[25] *International Critical Tables*, McGraw-Hill Book Co., New York, **1929**, Vol. VI, pp. 246–253.

(like the RMgX types). It should be stated that equivalent conductance measurements of triphenylmethylsodium and -potassium in pyridine show the RK compound to be more polar.[26]

A method for arriving at relative reactivities of RM compounds is to postulate a correlation with the electromotive series of the metals, the more electropositive metals forming the more polar and more reactive RM compounds. In a general way there is a correlation, but some of the exceptions are notorious. Table IV lists the alkali metals and calcium in an order of decreasing voltage.[27]

It is at once evident that lithium is entirely out of line in the sense that the above series might lead one to expect that RLi compounds would be the most reactive of the organoalkali compounds whereas they actually are the least reactive. Also, the organocalcium compounds should be more reactive than the organosodium compounds, but they are less reactive than either the organosodium or organolithium compounds;[28] and diethylcalcium has been reported as completely non-conducting in diethylzinc,[24b] whereas ethylsodium is a good conductor.

TABLE IV

E.M.F. SERIES OF SOME METALS

Li	2.959
Cs	
Rb	2.925
K	2.924
Ca	2.76
Na	2.714

All that can be said at this time is that the broad rule formulated on the simple basis of groups and families of the periodic table[1] is most useful because it has fewest exceptions. Undoubtedly more exceptions (see Experimental Part) will be found with further studies, for in the field of organometallics exceptions can be the rule as much as in other fields of organic chemistry.

It should be emphasized, also, that the order of increasing activities of organoalkali compounds (RLi, RNa, RK, RRb, RCs) is dependent both on the metal and the R group. The series can be transposed with different R groups. For example, phenyllithium is decidedly more reactive than phenylacetenylcesium. Also, there is no regular decrease in activity[1]

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[26] ZIEGLER AND WOLLSCHITT, *Ann.*, **479**, 123 (1930).

[27] *International Critical Tables*, McGraw-Hill Book Co., New York, 1929, Vol. VI, p. 332.

[28] GILMAN, KIRBY, LICHTENWALTER AND YOUNG, *Rec. trav. chim.*, **55**, 79 (1936).

(using like R groups), for the difference between RLi and RNa is decidedly greater than that between RNa and RK compounds. Finally, it now appears that when RM compounds shall have been prepared from Element 87 these will prove to be the most reactive types. In contrast, it also appears that organoplatinum compounds may prove to be the least reactive RM types.

EXPERIMENTAL PART

General.—The several reactants were purified prior to use by crystallization, distillation, or combinations of these procedures. Ziegler's[2a] method was used for the purification of ether, and this consists essentially in a preliminary drying over sodium wire, followed by distillation under nitrogen from a mixture of sodium-potassium alloy and benzophenone. The nitrogen was purified by bubbling through two Milligan wash bottles containing strongly alkaline pyrogallol solutions; then through two gas towers containing concentrated sulfuric acid; and, finally, by passage over phosphorus pentoxide. It is quite important to have effective scrubbing towers like Milligan bottles for removal of traces of oxygen.

The solid alkali metals were cut into small pieces under anhydrous petroleum ether and transferred rapidly to the reaction flask. The liquid metals were transferred by means of graduated pipettes which provided a convenient and rapid method to measure them. Because of the spontaneous inflammability of rubidium and cesium they were covered during transfer by a small layer of high-boiling petroleum ether, and sucked into the pipette in such a manner as to provide a thin layer of petroleum ether at the bottom of the metal contained in the pipette. The petroleum ether (b.p. 115–150°) used to protect the metals from the atmosphere was dried for several days over sodium-potassium alloy.

Most of the rate reactions were carried out in a 150-cc. three-necked balloon flask provided with a mercury-sealed stirrer, reflux condenser, and ground-glass stopper. All joints to the flask were ground-glass. Flexibility of the three ground-glass joints was increased by lubricating the upper part of the joints with vaseline. Check runs, to be described later, were carried out in similar conventional flasks having rubber stoppers and no ground joints. After flushing the apparatus with nitrogen, the flask and contents were always protected by admitting nitrogen under a small, positive pressure.

Phenylacetenylalkali reactions.—The phenylacetenyl compounds of magnesium and lithium were prepared in ether from phenylacetylene and phenylmagnesium bromide and phenyllithium, respectively. The acid obtained by carbonation was phenylpropiolic acid free of benzoic acid.

Phenylacetenylsodium and -potassium were prepared from 3.06 g. (0.03 mole) of phenylacetylene in 30 cc. ether and 0.02 g. atom of the alkali metal cut into small pieces. Reaction was allowed to proceed at room temperature with constant stirring until all the metal was used up, as evidenced by absence of hydrogen evolution when a few drops of the suspension was added to an equal volume of water. Reaction with sodium is complete in 8 hours, but potassium requires about 48 hours. The times were checked in five preparations. Under similar conditions lithium and magnesium do not react to give any significant quantity of RM compound (negative color test), although the metals are slightly coated.

In the second series (see Table I) of preparations, 2.04 g. (0.02 mole) of phenylacetylene in 25 cc. of ether was added to 0.01 g. atom of metal. Reaction was completed with potassium in about 40 hours, with rubidium in about 12 hours and with cesium in about 25 hours. The suspended phenylacetenylalkali compounds varied progressively in color from a dark tan for cesium and rubidium, to a light tan for potassium, and to colorless for the sodium and lithium compounds. Each compound was carbonated, the lithium compound by means of solid carbon dioxide and the others with carbon dioxide gas at room temperature, which was frequently at the boiling point of ether. The yields of phenylpropiolic acid were: RLi, 68%; RNa, 74%; RK, 71%; RRb, 74%; RCs, 78%.

Reactions with benzonitrile were carried out at room temperature and with vigorous stirring. In the first series of experiments (Table I), 4.12 g. (0.04 mole) of benzonitrile in 10 cc. of ether was added to the 0.02 mole of RM compound. In the second series (RK, RRb and RCs compounds), 2.06 g. (0.02 mole) of benzonitrile was added to 0.01 mole of RM compound in 25 cc. of an ether suspension. The general procedure for making color tests to determine the reaction rates has been described adequately in earlier papers of this series.

The following times in hours were noted when rate studies were carried out in the flasks provided exclusively with rubber stoppers: RK, 5.1; RRb, 5.2; RCs, 3.7. These experiments were not checked.

When the reaction between phenyllithium and benzonitrile was run under conditions like those used in the corresponding experiments with phenylacetenylpotassium, -rubidium, and -cesium, the time required for completion of reaction was less than 0.05 hour.

Ethylalkali compounds and dibenzofuran.—The ethylalkali compounds were prepared in a 250-cc. flask by adding 0.04 g. atom of the metal cut into small pieces to a solution of 2.59 g. (0.01 mole) of diethylmercury in 25 cc. of petroleum ether (b.p., 68–77°). The mixture was stirred rapidly for 4 days with lithium, 1.5 days with sodium and 2 days with potassium. The times mentioned in the preparation of the ethylalkali compounds are the approximate times required for completion of reaction, as evidenced by a cessation of gas evolution during the preparation of ethylsodium and potassium. No attempt was made to determine the amount or rate of gas evolution from the preparation of ethyllithium, and 4 days was arbitrarily selected as adequate for the completion of this preparation.

To a petroleum ether suspension of the ethylalkali compound prepared in the manner described above, was added 4.20 g. (0.025 mole) of dibenzofuran dissolved in 25 cc. of petroleum ether. The reaction was allowed to proceed for 15 days at room temperature, with constant stirring. At the end of this time, the reaction mixture was poured upon 20 to 30 g. of solid carbon dioxide. When this mixture had warmed to room temperature, it was filtered with suction, and the solid residue was slowly added to 75 cc. of cold water, and the solution subsequently heated to boiling. The hot solution was filtered, and the residue was extracted with 50 cc. of hot water, filtered, and this filtered extract was added to the original solution. The combined filtrates were then cooled to room temperature, and acidified with 10% hydrochloric acid. The insoluble dibenzofuran acids were immediately precipitated, filtered with suction, and washed thoroughly with cold water. The acids that were obtained from this procedure by the reaction of ethyllithium, -sodium and -potassium with dibenzofuran were then compared by titrating them with 0.1380 N sodium hydroxide. The titrations were carried out by dissolving the acids in 50 cc. of a 50% water-acetone solution that had been previously neutralized with the base. Phenolphthalein was used as an indicator. The titration values, in cc. of standard sodium hydroxide, are: C_2H_5Li, 25.6; C_2H_5Na, 29.7; C_2H_5K, 30.9.

In the rate studies the ethylalkali compounds were prepared in the same manner, and after allowing reaction with dibenzofuran to proceed for 2.5 hours, the mixture was carbonated by pouring upon solid carbon dioxide. The results are given in Table II, and the values given there are in terms of cc. of standard sodium hydroxide.

During the preparation of ethylsodium or -potassium, by the method described above, gas is liberated. The evolution of gas starts almost immediately after the addition of the alkali metal to the petroleum ether solution of diethylmercury, and proceeds for a period of 30 to 36 hours for ethylsodium, and from 36 to 48 hours for ethylpotassium. In two experiments in the preparation of ethylsodium, 65 cc. and 90 cc. of gas were evolved. Similar experiments with ethylpotassium yielded 84 cc. and 280 cc. of gas. These volumes of gas were obtained from 0.10 mole of diethylmercury reacting with 0.04 g. atom of the alkali metal, and the volumes are given at standard temperature and pressure. No correction was made for the vapor pressure of the petroleum ether, and the gas was collected over mercury. After the initial period of gas evolution, the ethylalkali compounds appeared to be stable and no gas was evolved. They reacted with the further liberation of gas when a compound, such as benzene, was added to the mixture. The rates of gas evolution of ethylsodium or potassium during reaction were not constant.

An attempted metalation of benzene by ethyllithium was carried out in a Schlenk tube, in which the air was displaced by nitrogen. To 50 cc. of benzene, contained in this tube, was added 3.45 g. (0.5 g. atom) of lithium and 10 g. (0.038 mole) of diethylmercury. The tube was sealed, and the mixture was allowed to react, with constant shaking, over a period of eight weeks. At the end of this time, the tube was cooled in a freezing mixture, opened, and poured upon solid carbon dioxide. Examination of the reaction products revealed large quantities of propionic acid, but no trace of benzoic acid could be found.

Formation of organopotassium compounds from sodium-potassium alloy.—The sodium-potassium alloy was prepared from a mixture of 1 part of sodium and 5 parts of potassium by weight.[2a] The mixture may be heated in anhydrous xylene, or in high-boiling (b.p. 115–150°) petroleum ether, until the sodium and potassium have melted. The molten metals should then be carefully mixed together with a glass rod, and care should be taken to keep the metal in one large globule to facilitate handling. When cooled to room temperature, the alloy will remain liquid, and may be easily transferred by means of clean, dry pipettes. To 150 cc. of absolute diethyl ether was added 2 g. (0.013 mole) of 2-phenylisopropyl methyl ether,[2a] and 2 cc. of liquid sodium-potassium alloy. The reaction started immediately, and the solution became intensely red. After 30 hours of stirring, the reaction was allowed to settle, and a clear red solution of the organoalkali compound was obtained. Fifty cc. of this clear red solution was hydrolyzed by pipetting it into about 25 cc. of distilled water. The ether was evaporated, and the solution was neutralized with 10% hydrochloric acid. Ordinary tests employed in qualitative analysis were then made on the resulting aqueous solution. The test for the sodium ion was made with a concentrated aqueous solution of uranylzinc acetate, and the test for potassium was made with an aqueous solution of sodium cobaltinitrite. The solution gave a positive test for the potassium ion, and a negative test for the sodium ion. Also the flame test indicated a negative test for sodium and a positive test for potassium. Carbonation of a portion of the clear red ether solution with solid carbon dioxide yielded dimethylphenylacetic acid. The reaction was checked with similar results.

In like manner, reactions were carried out with the alloy and triphenylmethyl ethyl ether, diphenylmethyl methyl ether, tetraphenylethane (over a 36 hour period), tetraphenylethylene, and triphenylmethane. In the tetraphenylethylene experiments the reaction with sodium-potassium alloy (1.0 cc.) proceeded slowly, and yielded, instead of a deep red ether solution, a red precipitate. No direct analysis of the precipitate could be made for sodium and potassium because it was contaminated with the alloy. Carbonation of the red precipitate at room temperature yielded 50% of the theoretical amount of tetraphenylsuccinic acid. The tetraphenylethylenedisodium has been found to be soluble in ether, and the red precipitate, which yields the same product upon carbonation, is insoluble, so it is reasonable to assume that the red solid obtained from the action of sodium-potassium alloy on tetraphenylethylene, is tetraphenylethylenedipotassium. Tetraphenylethylene (1.66 g. or 0.005 mole) in 75 cc. of ethyl ether and a sodium-rubidium alloy prepared from 0.1 g. sodium and 0.8 g. rubidium were stirred at room temperature for 43 hours. Within one hour the mixture assumed a dark brown color. Carbonation by carbon dioxide gas at room temperature gave tetraphenylsuccinic acid. The insolubility of the RM compound in ether, prior to carbonation, indicates that the organometallic compound contained rubidium and not sodium inasmuch as the sodium compound is soluble in ether.

When lithium or potassium was substituted for sodium the reaction would not proceed, and the metals remained unchanged after a period of 48 hours of constant stirring.

The reaction with sodium started promptly, and gave a very deep red solution of the disodium addition product. Hydrolysis of this product yielded tetraphenylethane, (mixture m.p.), and carbonation at room temperature yielded 58% of the theoretical amount of tetraphenylsuccinic acid.

In the triphenylmethane experiment, chlorobenzene was found very useful, functioning perhaps in accordance with the very suggestive metal-halyl concept of Morton.[29] To a solution of 2.44 g. (0.01 mole) of triphenylmethane dissolved in 125 cc. of absolute ether was added 1 cc. of sodium-potassium alloy. No reaction could be observed in 30 hours. When one cc. of chlorobenzene was added to the solution, a red coloration appeared immediately, and a red precipitate formed in about three hours. After 24 hours of stirring, the solution was allowed to settle, and analysis of the clear red ether solution showed only the presence of the potassium ion. Carbonation of a portion of the clear red solution with solid carbon dioxide yielded triphenylacetic acid.

To 200 cc. of a red ether solution containing about 0.02 mole of triphenylmethyllithium, was added 2 cc. of liquid sodium-potassium alloy, and the mixture was allowed to stir for 40 hours. At the end of this time the solution was a deeper shade of red, and a red precipitate had formed. The solution was allowed to settle for 6 hours, and was then tested by the methods previously described for sodium and potassium, and an additional test was made for lithium. The aqueous solution was evaporated on the water bath and in a platinum crucible with a small amount of hydrofluoric acid. The residue was treated with a little dilute ammonium hydroxide and completely dissolved. Under these conditions, if lithium is present, it will precipitate as a white gelatinous mass of lithium fluoride. Potassium is the only ion that could be found in the solutions. Carbonation of an aliquot portion of the clear ether solution with solid carbon dioxide yielded a small amount of triphenylacetic acid.

On the basis of observations in this study, the RK compounds are generally distinctly less soluble than the corresponding RNa compounds in diethyl ether. This

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[29] MORTON AND STEVENS, *J. Am. Chem. Soc.*, **54**, 1919 (1932).

is, of course, as one would expect because of the more polar characteristics of RK compounds.

Alkali ketyls and n-*butyl chloride.*—The ketyls were prepared by adding 0.005 g. atom of the metal to 0.92 g. (0.005 mole) of benzophenone in ethyl ether. The mixture was stirred at room temperature for 18 hours, and at the end of this time no metal was observed to be suspended in the mixture. Then 2.8 g. (0.03 mole) of *n*-butyl chloride was added and stirring was continued at room temperature to the disappearance of the blue color of the several ketyls. The average times in hours were:

Benzophenonepotassium	16.5
Benzophenonerubidium	7.5
Benzophenonecesium	4.6

Carbonation of organoalkali compounds.—The results of some carbonations have already been given. Carbonation of phenylacetenyl-sodium and -potassium by means of solid carbon dioxide gave phenylpropiolic acid in 60% and 57% yields, respectively. These single experiments may be anomalous, for not only is there no present reason for expecting a *lower* yield in these cases when solid carbon dioxide is used, but 4-dibenzofurylsodium gave almost the same yield (65%) of 4-dibenzofurancarboxylic acid when carbonated either with gaseous carbon dioxide at room temperature or with solid carbon dioxide.

Some reactions of 4-dibenzofurylalkalis.—In orienting experiments made at the beginning of this study, the 4-sodium and 4-potassiumdibenzofuran compounds were prepared in ether from dibenzofuran and a selected excess of di-*n*-butylmercury and alkali metal. These preparations were not suitable for reasonably accurate rate studies for two reasons: (1) the RM compounds were only slightly soluble in ether and difficult to separate from the excess of metal; and (2) the RM compounds apparently cleaved ethyl ether to an appreciable extent. This latter difficulty was indicated when the ether solutions were titrated by the acid method[30] and by Ziegler's[2a] *n*-butyl bromide titration procedure. For example, some ether solutions of the RNa compound were shown to be 0.041 normal by the acid analysis and 0.001 normal by the *n*-butyl bromide titration.

The low concentrations together with admixed compounds may account for some of the apparently anomalous results. The clear ether solutions were transferred by pipettes, the rubber tubing used for sucking up the solutions being filled as usual with dry nitrogen. The color test technique was used in experiments with 50 cc. of a 0.001 normal ether solution of RM compound together with a definite excess of phenyl halide or *o*-tolunitrile. The average time in minutes for using up the RM compounds follows:

	RNa	*RK*
C_6H_5F	22	19
C_6H_5Cl	29	35
o-$CH_3C_6H_4CN$	0	0

That is, reactions with the nitrile were immediate; the RK compound was more reactive than the RNa compound with fluorobenzene; and the reverse was true with chlorobenzene. Most surprising is the apparent greater reactivity of fluorobenzene over chlorobenzene.

Recent studies by Bergstrom and co-workers [J. ORG. CHEM; 170 (1936)] indicate that catalysts may be responsible for some of the anomalous results.

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[30] GILMAN, WILKINSON, FISHEL AND MEYERS, *J. Am. Chem. Soc.*, **45**, 150 (1923).

Some reactions of triphenylmethylalkali compounds.—The triphenylmethylalkali compounds formed, hitherto, the only representative series of the organoalkalis comprising all five of the metals.[13] The attractiveness of a complete series was diminished somewhat by three facts. (1) The RNa and RK compounds, unlike the RLi compound, give no color test with Michler's ketone because of ketyl formation:

$$(C_6H_5)_3CNa \rightleftarrows (C_6H_5)_3C + Na$$
$$R_2C{=}O + Na \rightleftarrows R_2C{-}ONa$$

No tests were carried out with R_3Rb and R_3CCs compounds, but undoubtedly they would behave like the R_3CNa and R_3CK compounds. (2) All of these triphenylmethylalkali compounds dissociate and to degrees not yet established so that there would be no exact measure of the concentration of RM compound available. (3) The more polar RM compounds are only sparingly soluble in ether.

To make their preparation comparable with the metalation reaction used with dibenzofuran, they were made (in good yields) as follows:—

$$(C_6H_5)_3CH + M \xrightarrow{(n-C_4H_9)_2Hg} (C_6H_5)_3CM + Hg{\cdot}M$$

The R_3CLi compound was also prepared by metalation with *n*-butyllithium.

The clear ether solutions were standardized by the acid titration method, for these RM compounds are essentially stable in ether. Also, carbonation by solid carbon dioxide of the RNa and RLi compounds gave triphenylacetic acid in 90% and 82% yields, respectively. Triphenylmethylpotassium yielded an ether solution of such low concentration that it could not be used in these experiments.

The end-point of the several reactions was the disappearance of the characteristic red color of the organoalkali compound. The average times in hours when 0.008 mole of halide or nitrile was added to 100 cc. of a 0.04 molar ether solution follow.

	$(C_6H_5)_3CLi$	$(C_6H_5)_3CNa$*
C_6H_5Cl	16	40+
C_6H_5Br	10	40+
o-$CH_3C_6H_4CN$	0.04	0.02

It will be noted that here also the halides give anomalous results, the RLi compound being more reactive than the RNa compound. However, the relative reactivities towards the nitrile are about as one might have expected, although much greater differences in time would have been predicted. The aryl halides may possibly react differently in different media, for triphenylmethylsodium with phenyl halides in liquid ammonia gives good yields of tetraphenylmethane.[31]

Dibenzyl and potassium-rubidium alloy.—In connection with studies now in progress on cleavage reactions by the more reactive alkali-alloys, 1.8 g. or 0.01 mole of dibenzyl in 25 cc. petroleum ether and the alloy from 0.2 g. potassium and 0.8 g. of rubidium reacted and gave after carbonation *sym.*-diphenylsuccinic acid. The reaction was allowed to proceed for six days in a Schlenk tube. In general, such tubes are most convenient for extended slow reactions.

Dibenzyl is not cleaved by sodium-potassium alloy or the amalgams of sodium and potassium.[32]

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* In the reactions of triphenylmethylsodium with the phenyl halides no observations were made after 40 hours.

[31] Kraus and Kawamura, *J. Am. Chem. Soc.*, **45**, 2756 (1923).

[32] Conant and Garvey, *ibid.*, **49**, 2599 (1927).

Incidental to cleavage reactions it is interesting to note that phenyllithium is readily cleaved by hydrogen. This may provide a means for comparing the carbon-metal bonds in organoalkali compounds.[33]

Phenylisopropylsodium in quite satisfactory yields from cumene by metalation with ethylsodium.

SUMMARY

1. The order of increasing activity of organoalkali compounds is: RLi, RNa, RK, RRb, RCs.

These results were obtained by an examination of (a) the reaction rates of $C_6H_5C{\equiv}CM$ with benzonitrile; (b) metalation of dibenzofuran by C_2H_5M compounds; and (c) reaction of ketyls with *n*-butyl chloride.

2. In reactions of sodium-potassium alloy, RK and not RNa compounds result.

3. Only sodium adds to tetraphenylethylene to give $(C_6H_5)_2C(Na)C(Na)(C_6H_5)_2$. Potassium will add when sodium-potassium alloy is used, and this is probably due to the prior addition of sodium followed by replacement by potassium. It is suggested that the non-addition of rubidium and cesium may be due to steric factors associated with the large atomic volumes of these metals.

4. The organoalkali compounds other than these of lithium are satisfactorily and preferably carbonated at room temperature. The RLi like the RMgX compounds are better carbonated at low temperatures or with solid carbon dioxide.

5. Attention is directed to some limitations of conductometric methods and the electromotive series for predicting relative reactivities of RM compounds.

6. The organoalkali compounds were prepared, and reacted, in conventional apparatus and not in sealed all-glass containers.

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[33] ZARTMAN AND ADKINS, *ibid.*, **54**, 3398 (1932).

[Contribution from the Frick Chemical Laboratory of Princeton University]

THE PREPARATION AND OPTICAL ROTATION OF DEUTEROMETHYLMETHYLPHENYLMETHANE

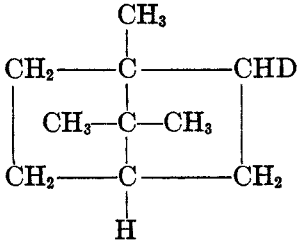
ROBERT L. BURWELL, JR., FRITZ HUMMEL, and EVERETT S. WALLIS

Received August 10, 1936; revised October 2, 1936

The preparation of deuterium oxide has made it possible to investigate experimentally the problem of producing optically active organic compounds, the asymmetry of which is due to certain inherent differences which exist between hydrogen and deuterium. Porter[1] hoped to prepare compounds of the type, RR'CHD, in optically active modifications by means of the Grignard reaction, but this method was doomed to failure since Pickard and Kenyon[2] had previously shown that racemization accompanied the preparation of the Grignard reagent from optically active halides of the type, RR'CHX.

A different approach to the problem has been made by H. Erlenmeyer and H. Gartner.[3] Their experiments, however, failed to produce positive evidence.

Recently Biilman, Jensen and Knuth[4] have published experimental work in which they claim that they have been successful in preparing an optically active 2-deuterocamphane.*



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[1] Porter, *J. Am. Chem. Soc.*, **57**, 1436 (1935).

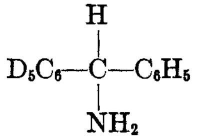
[2] Pickard and Kenyon, *J. Chem. Soc.*, **99**, 65 (1911); see also Wallis and Adams, *J. Am. Chem. Soc.*, **55**, 3838 (1933).

[3] Erlenmeyer and Gärtner, *Helv. Chim. Acta*, **19**, 331 (1936).

[4] Biilman, Jensen, and Knuth, *Ber.*, **69**, 32 (1936).

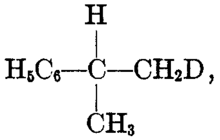
* Since this manuscript was sent to the Editor there has appeared an article by Biilman, Jensen, and Bak, *Ber.*, **69**, 1947 (1936), which shows that the conclusions in the paper cited above are untenable. A paper by Leffler and Adams, *J. Am. Chem. Soc.*, **58**, 1555 (1936), also discusses these results.

Clemo and McQuillen[5] have described experiments which seem to prove that optically active compounds of the type, CR(R′D)XY, can be prepared. Their results justify their claim that they "have proved the resolvability of the base,"



$$D_5C_6\text{—}\overset{\displaystyle H}{\underset{\displaystyle NH_2}{C}}\text{—}C_6H_5$$

During the last two years we have also been engaged on this problem, and we now wish to report the results of certain experiments carried out on a compound different in type, from those studied by other investigators. This paper reports the upper limit of the optical rotation of a deuteromethylmethylphenylmethane,



$$H_5C_6\text{—}\overset{\displaystyle H}{\underset{\displaystyle CH_3}{C}}\text{—}CH_2D,$$

prepared from the Grignard reagent of *d*-2-bromo-1-methyl-1-phenylethane, $[\alpha]_D^{25}$ + 13.75,* and deuterium oxide.

A sixty per cent. ether solution of the deuterocumene thus prepared showed no observable rotation. A determination, however, of the rotatory power of a sample of the pure hydrocarbon gave a value of $[\alpha]_D^{25}$ + 0.019, pure liquid, 1-dm. tube (average of eleven readings; maximum deviation from the mean, 0.011). Samples of this cumene prepared by the action of water, and of deuterium oxide on the Grignard reagent of a bromide† of rotation $[\alpha]_D$ − 1.9 showed no observable rotation.

In submitting these results for publication we do not claim to have proved beyond question that *d*-deuteromethylmethylphenylmethane has an observable rotation, inasmuch as the value obtained, $[\alpha]_D^{25}$ + 0.019, is nearly within the experimental error. We do state, however, that our experiments clearly show that the maximum rotation of compounds of this type is very small. In this respect the results are in agreement with the theoretical considerations of Boys,[6] which predict a small rotation for a

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[5] CLEMO AND MCQUILLEN, *J. Chem. Soc.*, **1936,** 808.

* COHEN, MARSHALL AND WOODMAN, *J. Chem. Soc.*, **107,** 899 (1915), have reported the value of the rotation of a more completely resolved bromide as $[\alpha]_D^{20}$ +15.6.

† This material was kindly furnished to us by Dr. P. A. Levene, Rockefeller Institute, New York City.

[6] BOYS, *Proc. Roy. Soc.*, **A144,** 655 (1934).

compound of the type we have prepared. If one agrees with him that the essential factors determining the value of the rotatory power of a molecule are the effective atomic or group radii of the groups attached to the asymmetric carbon atom, then it is evident that the difference between the effective radii of methyl and deuteromethyl groups is much smaller than between groups commonly causing optical rotation, and hence only a small rotation is to be expected.

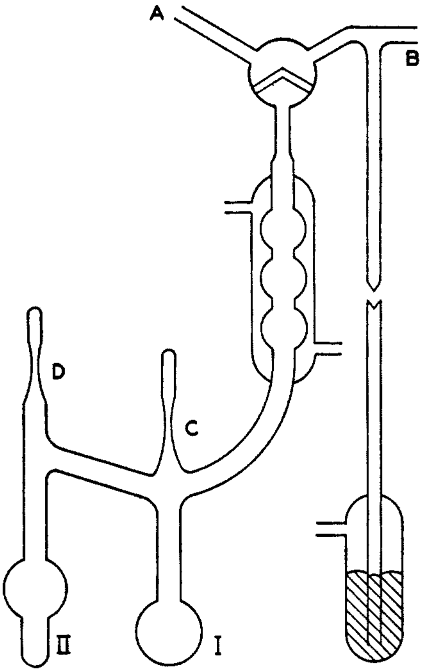

FIG. 1

EXPERIMENTAL

d-*2-Bromo-1-methyl-1-phenylethane* was prepared according to the method of Cohen, Marshall and Woodman (*loc. cit.*) from the corresponding alcohol ($[\alpha]_D^{25}$ + 10.42, pure liquid, 1-dm. tube) by the action of hydrogen bromide. It had a rotation of $[\alpha]_D^{25}$ + 13.74 (pure liquid, 1-dm. tube). The preparation of the Grignard reagent, and its subsequent reaction with deuterium oxide was carried out in the apparatus illustrated in Fig. 1. The apparatus was constructed of Pyrex glass and satisfactorily held a vacuum of 10^{-4} mm. of mercury. Bulbs I and II each had a capacity of about 20 cc. The tube at the bottom of bulb II was marked to indicate a volume of 2 cc. Outlet *A* from the three-way stopcock led to a McLeod gauge, and a mercury vapor diffusion pump backed by an oil pump. Outlet *B* led to a source of nitrogen. Tank nitrogen was passed through a tube containing copper wool maintained at a temperature of 470°, thence through soda lime, calcium chloride, a trap cooled with solid carbon dioxide-toluene mixture, and a trap cooled with liquid air. This purification train was constructed of fused Pyrex tubing. Thus nitrogen admitted to the reaction apparatus was free from oxygen, carbon dioxide, and water vapor.

Four-tenths gram of especially prepared magnesium was washed twice with ether and placed in bulb I, which was then sealed to the apparatus. The apparatus was evacuated through outlet *A* and heated with a free flame to eliminate adsorbed gases. The pumping was continued overnight. Bulb I was cooled with liquid air. Nitrogen was then admitted to the apparatus under a pressure exceeding that of the atmosphere by 2 cm. of mercury. The seal over bulb I was heated and blown out by the nitrogen pressure.

A very small crystal of iodine was added to bulb I; 1.75 cc. of *d*-2-bromo-1-methyl-1-phenylethane and 10 cc. of ether dried over sodium were added by means of especially constructed pipettes, which avoided introduction of light water vapor; the apparatus was then sealed off at *C*.

Water cooled to 0° was run through the condenser. Reaction began when the temperature of bulb I was allowed to rise to room temperature. Auto-refluxing continued for ten minutes. The refluxing was maintained for an hour by the application of heat.

Bulbs I and II were then cooled with liquid air and the seal over bulb II was blown out; 1.00 cc. of 99.5 per cent. deuterium oxide was inserted into bulb II; the apparatus was sealed off at *D*. The apparatus was evacuated through outlet *A*, and then the three-way stopcock was closed. The liquid air was removed from bulb II, and the deuterium oxide distilled into bulb I. Nitrogen was admitted to the apparatus. Reaction took place when bulb I was warmed to room temperature. The contents of bulb I were refluxed for two hours. The volatile contents of bulb I were then distilled into bulb II in the same fashion as described above. Nitrogen was admitted to the apparatus and bulb I was cut off and cleaned. Phosphorus pentoxide was inserted in bulb I and it was resealed to the apparatus. The contents of bulb II were then distilled into bulb I. The excess of deuterium oxide combined with the P_2O_5. Bulbs I and II were cooled with liquid air and then the apparatus was evacuated. Bulb I was allowed to warm to room temperature, and the volatile contents of bulb I were distilled into bulb II. The contents of bulb II were distilled back into bulb I until about 1.75 cc. remained in bulb II. The distillation was then stopped and nitrogen was admitted. Seal *D* was opened and the rotation of the contents of bulb II was determined at 25° in a 1-dm. polarimeter tube. There was no observable rotation. One and eight-hundredths grams of this ether solution was distilled in a micro distillation apparatus; 0.64 g. of deuterocumene, b.p. 151–152°, was obtained. The rotation of this pure deuterocumene was then determined: $[\alpha]_D^{25} + 0.019$ (pure liquid, length of tube 1 dm., average of 11 readings, maximum deviation from the mean 0.011).

Similar experiments carried out on a bromide, $[\alpha]_D - 1.9$,* with deuterium oxide and with water gave a cumene which showed no observable rotation.

SUMMARY

The preparation of *d*-deuteromethylmethylphenylmethane has been described. The upper limit of its optical rotation is reported. The experimental results are briefly discussed in connection with certain theoretical considerations of Boys.

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* Kindly furnished by Dr. P. A. Levene, Rockefeller Institute, New York City.

[Contribution from the Chemistry Department, Purdue University]

THE PREPARATION AND PROPERTIES OF 2,3,4,6-TETRAETHYL-α-METHYL-*d*-GLUCOSIDE AND OF 2,3,4,6-TETRAETHYL-*d*-GLUCOSE*

ALGIE R. PADGETT with ED. F. DEGERING

Received August 12, 1936

Methylated derivatives of *d*-glucose have been known for many years but very few references to ethylated derivatives occur in the literature. In his bibliography on the alkylation of *d*-glucose,[1] Coles states that the 2,3,6-triethylethylglucoside[2] has been prepared from triethylcellulose. This glucose derivative is a colorless, mobile oil (b.p. 120–5°/0.2 mm.), strongly refractive and soluble in water and most organic solvents. Triethylglucose has been studied by means of X-ray diagrams,[3] and other references to it occur in the literature.[4] Reference is made to 2,3,5,6-tetraethylglucose, but it has not been obtained in a pure form.[2] No other ethylated products of *d*-glucose are mentioned in this bibliography,[1] but Muskat reports the preparation and identification of 3-ethyldiacetoneglucose.[5]

With a view to a forward step in the study of such higher alkyl derivatives as well as to establish an additional reference compound for work upon more complicated carbohydrate materials, the preparation of 2,3,4,6-tetraethyl-*d*-glucose was undertaken. Of particular importance in the successful termination of the research was the application to carbohydrate chemistry of low-pressure fractionation of the intermediate glucosides by means of a modified Podbielniak column.

There are, in general, three procedures that have been used for the methylation of the carbohydrates. Purdie and Irvine[6] introduced the use of methyl iodide in the presence of silver oxide as a methylating agent for the glucosides. Somewhat later this procedure was largely re-

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* Abstract of a Master's Thesis presented to the Faculty of the Graduate School of Purdue University by Algie R. Padgett. This paper was presented before the Organic Division at the ninety-first meeting of the American Chemical Society, Kansas City, April 14, 1936.

[1] Coles, *Iowa State Coll. J. Science*, **6**, 33–42, 43–64 (1932).

[2] Hess and Trogens, *Ber.*, **61**, 1982–96 (1928); Hess and Muller, *Ann.* **466**, 94-9 (1928).

[3] Hess and Salzmann, *Ann.*, **445**, 111–22 (1925).

[4] Hess and Muller, *ibid.*, **455**, 205–14 (1927); Hess, Wittlesbach and Messmer, *Z. angew. Chem.*, **34**, 448–54 (1921).

[5] Muskat, *J. Am. Chem. Soc.*, **56**, 693–5, 2449–54 (1934).

[6] Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903); **85**, 1049 (1904).

placed by the use of methyl sulfate in the presence of sodium hydroxide.[7] The methyl sulfate procedure has recently been modified so that it is now possible to methylate sugars directly by using carbon tetrachloride as a solvent.[8] A more recent method consists in the use of methyl iodide or methyl sulfate in the presence of liquid ammonia as the solvent.[5] By this means the direct methylation of *d*-glucose has been effected and the possibility of the preparation of higher alkyl derivatives is indicated. A suitable modification of certain of these methylation procedures made possible the preparation of the desired compounds.

EXPERIMENTAL

*Preparation of 2,3,4,6-Tetraethyl-α-methyl-*d*-glucoside.*—The 2,3,4,6-tetraethyl-α-methyl-*d*-glucoside was prepared from α-methyl-*d*-glucoside by the procedure of Haworth,[7] with certain modifications by Greene and others,[8,9] followed by a final ethylation by the procedure of Purdie and Irvine.[6] The α-methyl-*d*-glucoside was prepared according to *Organic Syntheses*.[10]

The first four ethylations were carried out in a five-liter three-necked flask fitted with a mechanical stirrer, thermometer, reflux condenser, and two burets: one for the introduction of the ethyl sulfate and the other for aqueous sodium hydroxide. The flask was heated by means of a water bath. A 240-g. portion of α-methyl-*d*-glucoside, dissolved in 500 cc. of water, was placed in the ethylation flask. The temperature was raised to 80°, and 2100 cc. of ethyl sulfate and 1350 cc. of 50% sodium hydroxide (50 g. NaOH in 100 cc. of solution) were added dropwise over a period of six hours, the addition being so adjusted that the solution was at all times slightly alkaline to phenolphthalein (a drop of which was added every few minutes). The bath was then raised to boiling, maintained at that temperature for about thirty minutes, and allowed to cool. A yellowish-red oil separated.

The solution was then extracted with four 300-cc. portions of chloroform; the chloroform extract was dried and filtered, and the solvent was removed by distillation up to 60° on a water bath under a pressure of 25 mm. About 200 cc. of a yellow sirup was obtained.

An analogous procedure was followed in the second and third ethylations except that 200 cc. and 50 cc., respectively, of carbon tetrachloride were used to dissolve the partially ethylated glucoside. In the fourth ethylation no solvent was used, the concentration of the alkali was increased to 60%, and one-half amounts of ethyl sulfate and alkali were used.† The chloroform extract from the final ethylation was treated with Norite, filtered, and dried over sodium sulfate, and the solvent was removed by evaporation to give a residue of 150 cc. of crude ethylated glucoside.

This product was then subjected to a fifth ethylation by permitting it to reflux for six days with 150 g. of ethyl iodide and 90 g. of silver oxide. The mixture was extracted with chloroform, and the extract was dried and fractionated through a distilling flask to give a colorless, thin sirup (b.p. 95–100°/0.1 mm.). Then, 108 cc.

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[7] HAWORTH, *ibid.*, **107**, 8 (1915); HAWORTH AND LEITCH, *ibid.*, **113**, 188 (1918).

[8] WEST AND HOLDEN, *J. Am. Chem. Soc.*, **56**, 930–2 (1934).

[9] GREENE AND LEWIS, *ibid.*, **50**, 2813–25 (1928).

[10] HELFERICH AND SCHÄFER, *Organic Syntheses*, **6**, 64 (1926); Collective Volume I, pp. 356–7.

† Subsequent work in this laboratory raises some doubt as to the advisability of re-ethylation.

of sirup was fractionated and refractionated through a modified Podbielniak column of 10-mm. glass tubing containing a twenty-inch spiral of tantalum wire. The distillate was tested hourly with an Abbé refractometer, and a fraction of 79 cc. which showed no variation in refractive index was obtained.

Four carbon determinations on this product by the wet method[11] gave 58.7 ± 0.1% as compared with a theoretical value of 58.78%. Molecular weight determinations in nitrobenzene showed an average of 299 g. per mole as compared with the theoretical value of 306.24 g. per mole.

The glucoside is a colorless, rather sirupy liquid [b.p. 94–6°/0.15 mm., 97–100°/0.2 mm.; $[\alpha]_D^{20}$ +76.5° ($c = 5$ in ethyl alcohol)], which is quite soluble in chloroform, alcohol, ether, petroleum ether, ethylene bromide, and nitrobenzene but only slightly soluble in water. Maintenance of the glucoside in a solid carbon dioxide-alcohol mixture for 24 hours with frequent scratching failed to produce crystallization.

*Preparation of 2,3,4,6-Tetraethyl-*d*-glucose.*—2,3,4,6-Tetraethyl-*d*-glucose was prepared by the hydrolysis of the corresponding methylglucoside (40 g.) by digesting it in an aqueous solution (8% HCl, 9.9% glucoside), under vigorous stirring, on a water bath for a period of four hours.[9,12] The solution was then allowed to cool, and was extracted with four 50-cc. portions of chloroform. The chloroform extract was decolorized with two grams of Norite, filtered, and dried with calcium chloride, and the solvent was removed by evaporation. The light yellow residue, amounting to about 35 cc., was dissolved in an equal volume of low-boiling petroleum ether and allowed to stand in the ice-box with frequent scratching for two days to give about 2 g. of small, very slender needles. Continued crystallization for ten days, yielded about 10 g. of crude tetraethyl-*d*-glucose (m.p. 70–7°) and about 20 cc. of viscous sirup which continued to yield crystals. The 10 g. of crude product, upon two recrystallizations from petroleum ether, yielded 8 g. of slender, white, lustrous, fluffy needles of 2,3,4,6-tetraethyl-*d*-glucose (m.p. 80–2°).

Carbon determination by the wet method[11] gave 57.6 ± 0.1%, as compared with a theoretical value of 57.49%. Molecular weight determinations in nitrobenzene gave 289 g. per mole, as compared with a theoretical value of 292.224 g. per mole. Measurement of the rotation in ethyl alcohol gave $[\alpha]_D^{26}$ +95.9° ($c = 2$). The 2,3,4,6-tetraethyl-*d*-glucose is soluble in water, chloroform, alcohol, ether, ethylene bromide, and nitrobenzene. It is soluble in warm low-boiling petroleum ether but only slightly soluble at 0°.

In assigning the structures to the derivatives obtained in this work it was assumed, in accordance with the work of previous investigators, that the pyranoid ring structure of α-methyl-*d*-glucoside is stable to subsequent alkylation. If this assumption is correct, the delta hydroxyl group would be linked up in the pyranoid ring structure and would not be subject to ethylation. The product obtained, in which four ethyl groups had been introduced, therefore, must be the 2,3,4,6-tetraethyl-α-methyl-*d*-glucoside, and the hydrolytic product must be 2,3,4,6-tetraethyl-*d*-glucose.

SUMMARY

2,3,4,6-Tetraethyl-α-methyl-*d*-glucoside and 2,3,4,6-tetraethyl-*d*-glucose have been prepared, and some of their properties are described. The use of a modified Podbielniak column made possible the successful fractionation of the ethylated methylglucosides.

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[11] Pollard and Forsee, *Ind. Eng. Chem., Anal. Ed.*, **7**, 77 (1935).

[12] Irvine and Moodie, *J. Chem. Soc.*, **87**, 1465 (1905).

[Contribution from the Department of Chemistry, Columbia University]

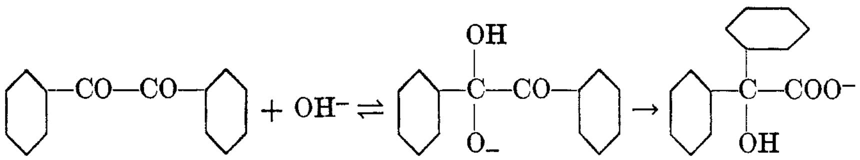
THE SALT EFFECT IN THE REARRANGEMENT OF BENZIL *o*-CARBOXYLIC ACID

F. H. WESTHEIMER*

Received August 13, 1936

INTRODUCTION

In a paper which will be presented elsewhere, the author determined the mechanism of the rearrangement of benzil. He showed that the first intermediate is the negative ion derived from the hydrate:



The present paper deals with the rearrangement of a substituted benzil, namely, benzil *o*-carboxylic acid. The salt effect in this reaction was found to be quite large. Further, on the very probable assumption that the mechanism of the rearrangement of benzil *o*-carboxylic acid is the same as the mechanism of the rearrangement of benzil, the medium effect shows an interesting peculiarity.

METHOD

The method was essentially that used in the case of benzil. The reaction mixture was sealed in ampoules which were placed in a 100° thermostat. The ampoules were removed at known times, and the reaction stopped by cooling, then acidifying. Immediate extraction of the organic matter, and subsequent titration, the method employed in the rearrangement of benzil, could not be applied here, for Graebe and Juillard[1] have shown that the acid, produced by the rearrangement of benzil *o*-carboxylic acid, easily lactonizes.

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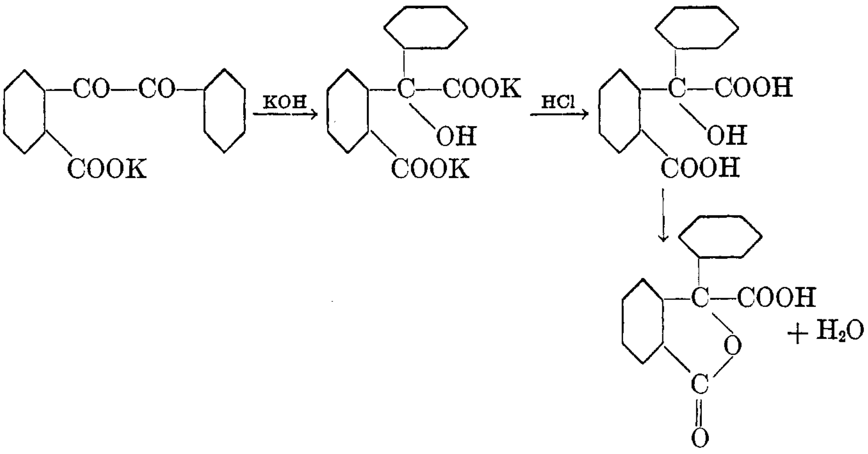
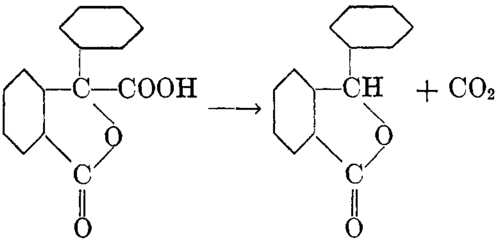
* National Research Fellow in Chemistry.

[1] Graebe and Juillard, *Ber.*, **21**, 2003 (1888).



Then, since both starting product and final product each have one carboxyl group, no separation could be made acidimetrically in the cold; heating to open the lactone is obviously out of the question as it would further the rearrangement. Graebe and Juillard noted, however, that the rearrangement product, the acid lactone, is easily decarboxylated. Blanks showed that this reaction is quantitatively complete on heating one half hour in the presence of 0.005 *M* hydrochloric acid.



Subsequent to the decarboxylation, extraction with ether and titration in the cold with standard alkali would show how much of the starting product is still present; the lactone opens but slowly in the cold.

EXPERIMENTAL

The thermostat was the same employed in the rearrangement of benzil, and described in detail elsewhere. Essentially, it consisted of a water-boiler, in which the pressure was kept constant by the method of Coffin.[2] The thermostat maintained a temperature of 100.04 ±0.03°.

The continuous extractors were the same as those employed in the study of benzil. The analytical method was as follows. The solution in the ampoule was chilled to stop the reaction, and an aliquot was taken. This was neutralized, and sufficient

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[2] Coffin, *J. Am. Chem. Soc.*, **55**, 3646 (1933).

excess hydrochloric acid was added to make the solution 0.005 *M*. It was then refluxed for half an hour in an all glass apparatus, quantitatively transferred to an extractor, and extracted two hours with ether. After distilling off the ether, and adding water and alcohol as solvent, the cold solution of benzil *o*-carboxylic acid and lactone was titrated with standard alkali using thymol blue as indicator. Blanks showed that the results were accurate to 1 per cent.

The benzil *o*-carboxylic acid was made according to the directions of Graebe and Juillard, and was recrystallized four times from benzene, melting at 141.5°. Carbonate free alkali was employed throughout, and all salts were recrystallized from water.

RESULTS

The bimolecular constants for the reaction between salts of benzil *o*-carboxylic acid and hydroxyl ion have an average deviation of about 6 per cent., although there is often a slight downward drift as the reaction proceeds. A typical example is given in Table I. In this tabulation, cc. stands for the number of cubic centimeters of approximately 0.01 *M* potassium hydroxide used in the analysis, *c* for the concentration of potassium benzil *o*-carboxylate, $c + a$ for the concentration of potassium hydroxide present at any time; *t* is quoted in minutes; *k* is calculated according to the standard bimolecular equation using natural logarithms. In this particular case, potassium chloride was added to raise the ionic strength to 3.50.

TABLE I

Typical Velocity Determination

cc.	c	$c + a$	$\log \frac{c+a}{c}$	t	$k \times 10$	DEVIATION
21.58	0.00946	0.1859	1.293			
19.61	0.00860	0.1850	1.333	5.00	1.04	.03
17.60	0.00771	0.1841	1.378	10.17	1.09	.02
15.69	0.00688	0.1833	1.426	15.58	1.11	.04
14.68	0.00643	0.1826	1.453	21.08	1.00	.07
12.59	0.00552	0.1819	1.518	26.08	1.12	.05
Average					1.07	.04 or 4%

At a constant ionic strength of 0.50, when the concentration of alkali was held constant and the concentration of benzil *o*-carboxylic acid varied, the bimolecular constant remained the same. When, however, the concentration of benzil *o*-carboxylic acid was maintained while the concentration of potassium hydroxide was varied, the "constant," calculated according to a bimolecular equation, was found to increase with increasing molality of alkali. The data are recorded in Table II.

Since the reaction is between a salt of benzil *o*-carboxylic acid and hydroxyl ion, that is to say, between two negatively charged particles, the Brønsted theory[3] would predict a large positive salt effect. Such was, indeed, found. Using 0.01 *M* benzil *o*-carboxylic acid and 0.09 *M* potassium hydroxide, the change of rate with change in ionic strength is recorded in Table III and in Fig. 1.

TABLE II

RATE OF REARRANGEMENT OF POTASSIUM BENZIL *o*-CARBOXYLATE

IONIC STRENGTH 0.5

CONCENTRATION OF POTASSIUM BENZIL *o*-CARBOXYLATE	CONCENTRATION OF KOH	CONCENTRATION OF KCl	μ	"k" × 10^2
0.0045	0.095	0.40	0.50	1.25
0.014	0.086	0.40	0.50	1.23
0.05	0.100	0.35	0.50	1.29
0.012	0.028	0.46	0.50	0.86
0.011	0.039	0.45	0.50	1.01
0.014	0.086	0.40	0.50	1.23
0.011	0.19	0.30	0.50	1.48
0.012	0.38	0.11	0.50	2.08

TABLE III

SALT EFFECT IN THE REARRANGEMENT OF POTASSIUM BENZIL *o*-CARBOXYLATE

μ	CONCENTRATION OF KCl	"k" × 10^2
0.1	....	0.75
0.5	0.40	1.23
1.5	1.40	3.43
3.5	3.40	8.3

TABLE IV

RATE OF REARRANGEMENT OF POTASSIUM BENZIL *o*-CARBOXYLATE

IONIC STRENGTH 3.5

CONCENTRATION OF POTASSIUM BENZIL *o*-CARBOXYLATE	CONCENTRATION OF KOH	CONCENTRATION OF KCl	μ	"k" × 10^2
0.011	0.025	3.46	3.50	6.71
0.011	0.089	3.40	3.50	8.3
0.012	0.18	3.31	3.50	10.7

Thus, since there was such a large medium effect, it was thought that the reaction might approach the bimolecular formula more closely in solu-

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[3] BRØNSTED, *Chem. Rev.*, **5**, 231 (1928).

tions of higher ionic strength. That this was not the case can be seen from Table IV.

Since medium effects in concentrated solution are often quite specific, measurements were made on the rate of rearrangement of the sodium salt of benzil *o*-carboxylic acid in solutions of sodium hydroxide and sodium sulfate. The results are recorded in Table V.

TABLE V

RATE OF REARRANGEMENT OF SODIUM BENZIL *o*-CARBOXYLATE

CONCENTRATION OF SODIUM BENZIL *o*-CARBOXYLATE	CONCENTRATION OF NaOH	CONCENTRATION OF Na_2SO_4	μ	"k" × 10^2
0.013	0.087	....	0.1	0.77
0.011	0.038	0.85	2.5	2.67
0.012	0.089	0.81	2.5	3.20
0.011	0.39	0.70	2.5	6.89

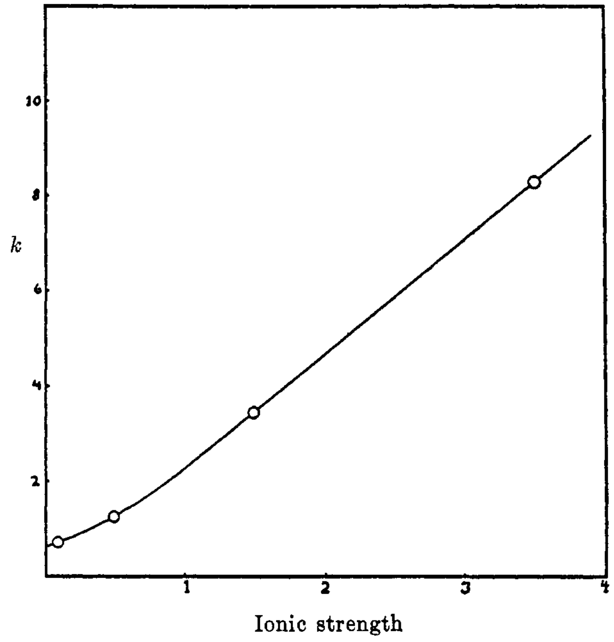


FIG. 1

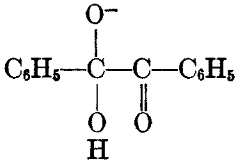
Comparing Table V with Table III, it is worthy of note that, at an ionic strength of 0.1, the rate with sodium hydroxide is the same as the rate with potassium hydroxide.

The rate constant, for 0.09 *M* potassium hydroxide and an ionic strength of 2.5, interpolated from Figure 1, is 5.55, while the constant for the sodium hydroxide-sodium sulfate system, from Table V, is 3.20. Furthermore, while, as is shown in Table IV, the increase in the bimolecular rate constant with a tenfold increase in alkali molality is 1.8-fold in the case of the potassium hydroxide-potassium chloride system at an ionic strength of 3.5, Table V shows that the increase for a tenfold change in alkali molality for the sodium hydroxide-sodium sulfate system, at an ionic strength of 2.5, is 2.6-fold.

THEORETICAL

No consideration of these data is adequate without a review of the facts concerning the rearrangement of benzil itself. In that case, the reaction between benzil and hydroxyl ion is strictly bimolecular. The concentration of benzil was varied tenfold, the concentration of hydroxyl ion more than four-hundredfold without producing changes in the bimolecular rate constant which were outside the experimental error. In buffered solution, the rate varied with the buffer ratio, but not with its concentration. The salt effect, on addition of potassium chloride, was quite small.

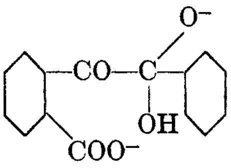
The only valid conclusion to be drawn from these facts is that the ion



$$C_6H_5{-}\overset{\displaystyle O^-}{\underset{\displaystyle OH}{C}}{-}\underset{\displaystyle \| \atop O}{C}{-}C_6H_5$$

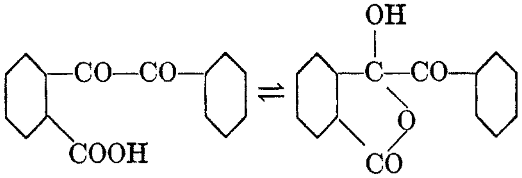
is in equilibrium with benzil and hydroxyl ion, and that the slow step is the further reaction of this ion. Furthermore, the reaction is not a case of general base catalysis; the equilibrium is a true one.

There is no valid reason to suppose that the rearrangement of benzil *o*-carboxylic acid follows any mechanism other than that followed by benzil. The only reasonable assumption is that the reaction, here, too, is one between the substituted benzil and hydroxyl ion, forming the doubly charged ion



as intermediate. Since the salt effect is absent in the rearrangement of benzil, the large medium effect is not inherent in the reaction, but is the result of the substitution, and presumably is caused by the negative charge of the carboxylate ion in the close neighborhood of the seat of the reaction.

Benzil *o*-carboxylic acid can exist, it is true, in two forms. One of these is open-chain, the other cyclic; they exist in equilibrium in solution. The salts, however, are chiefly those of the open-chain variety.[4]



If the ion of the cyclic form rearranged, the rate would vary with less than the first power of the hydroxyl-ion concentration. This equilibrium cannot, therefore, explain the deviation from the bimolecular constant with change of alkali concentration. On the basis of the reasonable assumption, already stated, that benzil and benzil *o*-carboxylic acid rearrange by the same mechanism, the large salt effect must be the cause of the irregularities.

The salt effect is peculiar in two ways: first because of its magnitude, second because the deviation with changing hydroxyl-ion concentration persists even in solutions of high ionic strength.

Considering first the magnitude of the salt effect, one notes that the Brønsted equation holds in dilute solution only. The general equation is:

$$\ln \frac{f_{A^-} f_{B^-}}{f_{X^-}} = \alpha 2 z_A z_B \sqrt{\mu} - (\beta_{A^-} + \beta_{B^-} + \beta_{X^-})c$$

where the rate is proportional to the concentration of a complex, X. While in dilute solution, $\sqrt{\mu}$ is large when compared to c, and, in general, the first term of the equation is large as compared with the second; this situation does not obtain in concentrated solutions. Here the salt effect is, in general, linear with the concentration of the added salt. The Brønsted equation would demand that, in a reaction between two negatively charged ions, the rate increase with increasing salt concentration in dilute solution, and further, that the increase between μ equal to 0.02 and μ equal to 0.1 be in the ratio 1.22.[5] An inspection of Figure 1 shows that this requirement is met qualitatively, although no measurements in the extremely dilute range are available for quantitative comparisons. In the more concentrated range, most authors have found a linear salt effect such as that found in this reaction.

However, in reactions between two negatively charged particles, the ratio of increase in rate was generally much smaller than is found here.

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[4] HANTZSCH, *Ber.*, **49**, 213 (1916).

[5] BRØNSTED, *Z. physik. Chem.*, **102**, 169 (1922).

In the reaction between chloracetate ion and ethyl xanthate ion, for example, Kiss[6] found the ratio of increase, with added sodium chloride to be 2.5 when the salt was increased from 0.5 *M* to 4.0 *M*. Even the large salt effect caused by the addition of 6 *M* potassium thiocyanate in the dealdolization of diacetone alcohol[7] is smaller than the one here recorded, for 6 *M* potassium thiocyanate depressed the rate less than sixfold.

The fact that the rate varied more than linearly with hydroxyl-ion concentration, and that this effect could not be "swamped" out by the addition of large amounts of salt, is the more important consideration. Among the few good studies of a similar nature in which such an effect was found is the work of La Mer and Sandved[8] on the equilibrium between potassium ferricyanide and potassium iodide to produce potassium ferrocyanide and iodine, in the presence of salts. In solutions having an ionic strength of 0.5, a twofold change in the concentration of iodide ion, keeping the concentration of the ferricyanide constant, caused a variation of about 20 per cent. in the equilibrium constant. Increasing the ionic strength to more than two did not eliminate the variation in constant with change in iodide concentration, but the variation was sharply diminished. This is shown by the fact that a twofold change in iodide concentration caused a variation of 6 per cent. in the constant.

In the present case, however, a change in the hydroxyl-ion concentration of tenfold changes the rate constant by a factor of about 2.1, while in solutions with an ionic strength of 3.5, this factor is still 1.8. That is, the deviations are ironed out too slowly by increasing ionic strength, and in no solution available will the rate constant be even fairly regular. The fact that the deviation from a bimolecular constant differs markedly with sodium hydroxide and sodium sulfate from the effect with potassium hydroxide and potassium chloride is sufficient evidence that the deviations are, after all, due to medium effect.

ACKNOWLEDGMENT

The author would like to thank Professor L. P. Hammett for the help and advice he gave in this research.

SUMMARY

1. The rate of rearrangement of the salts of benzil *o*-carboxylic acid have been measured in aqueous alkali solutions at 100°. The reaction is subject to a marked positive salt effect.

2. The rate varies with more than the first power of the hydroxyl-ion concentration, and this effect cannot be swamped out by increased ionic strength.

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[6] Kiss, *Rec. trav. chim.*, **53**, 903 (1934).

[7] Akerlof, *J. Am. Chem. Soc.*, **48**, 3046 (1926).

[8] La Mer and Sandved, *ibid.*, **50**, 2656 (1928).

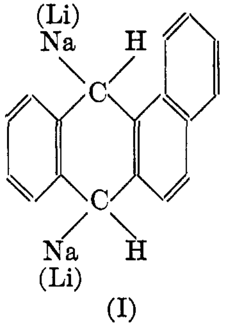
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE REACTION OF ALKALI METALS WITH POLYCYCLIC HYDROCARBONS: 1,2-BENZANTHRENE, 1,2,5,6-DIBENZANTHRACENE AND METHYLCHOLANTHRENE

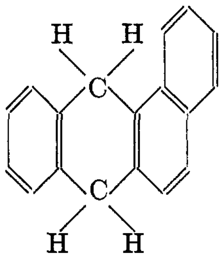
W. E. BACHMANN

Received September 18, 1936

In order to obtain derivatives of polycyclic hydrocarbons we have begun an investigation of the action of alkali metals on the hydrocarbons in organic solvents. Schlenk and Bergmann[1] found that sodium and lithium add to the 9,10 positions of anthracene and give the 9,10-disodium and 9,10-dilithium derivatives of 9,10-dihydroanthracene respectively. We have found that sodium and lithium add to 1,2-benzanthrene in a similar manner. If a solution of 1,2-benzanthrene in ether-benzene is shaken with powdered sodium or with liquid 45 per cent. sodium amalgam a deep blue color develops immediately; this color is gradually replaced by the deep rose-red color of the 7,12-disodium-7,12-dihydro-1,2-benzanthrene (I). The 7,12-dilithium-7,12-dihydro-1,2-benzanthrene, which is formed by interaction of 1,2-benzanthrene and lithium, possesses an intensely blue color. Whether the difference in color of the disodium and the dilithium derivatives is due to *cis-trans* isomerism, as Schlenk and Bergmann suggested for the corresponding alkali derivatives of anthracene, is left undecided at this time. By reaction with methanol the disodium and the dilithium derivatives yield the same colorless 7,12-dihydro-1,2-benzanthrene (II). The structure assigned to the dihydro compound is based on its analysis and on its oxidation to 1,2-benzanthrene-7,12-dione by chromic acid. When heated with sulfur the 7,12-dihydro-1,2-benzanthrene is readily dehydrogenated to 1,2-benzanthrene.



(I)



(II)

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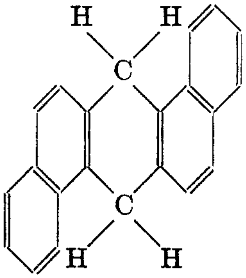
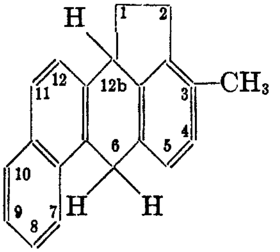
[1] SCHLENK AND BERGMANN, *Ber.*, **47**, 473 (1914); *Ann.*, **463**, 134 (1928).

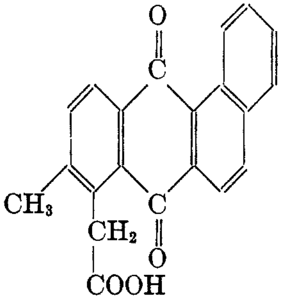
We were particularly interested in the reactions of the carcinogenic hydrocarbons, α,γ'-dibenzanthracene (1,2,5,6-dibenzanthracene) and 3-methylcholanthrene. A solution of α,γ'-dibenzanthracene immediately becomes deep green in color when shaken with powdered sodium in ether-benzene; when addition of the sodium is complete, the solution is intensely blue in color. The dilithium derivative is also intensely blue. From the disodium and the dilithium derivative the same colorless 7,14-dihydro-α,γ'-dibenzanthracene (III) is obtained on alcoholysis. The dihydro compound is readily oxidized by chromic acid to α,γ'-dibenzanthracene-7,14-dione and is rapidly dehydrogenated by sulfur to α,γ'-dibenzanthracene.



(III)



(IV)



(V)

The yellow hydrocarbon, 3-methylcholanthrene, reacts with powdered sodium and with 45 per cent. sodium amalgam in ether-benzene and gives the intensely purple 6,12b-disodium-6,12b-hydro-3-methylcholanthrene and with two atoms of lithium to give the intensely blue 6,12b-dilithium-6,12b-hydro-3-methylcholanthrene. It is apparent that in all three hydrocarbons the alkali metals add to the *meso* positions of the anthracene portion of the molecule. On alcoholysis of the alkali derivatives the same colorless 6,12b-dihydro-3-methylcholanthrene (IV) is formed. Like 3-methylcholanthrene the dihydro compound is readily oxidized by chromic acid to 5-(6-methyl-1,2-benzanthraquinonyl) acetic acid (V); this reaction is the basis of the structure assigned to the dihydro compound and to the alkali derivatives. 6,12b-dihydro-3-methylcholanthrene is easily dehydrogenated by sulfur at 170° to 3-methylcholanthrene.

The dihydro derivatives are being tested for carcinogenic properties. Of especial interest is the dihydro derivative of 3-methylcholanthrene, since 3-methylcholanthrene is the most potent carcinogenic compound discovered so far. The investigation of the alkali derivatives of these and other polycyclic hydrocarbons is being continued. Preliminary experiments on the action of carbon dioxide on the alkali derivatives have yielded acids whose sodium salts are soluble in water; it will be of interest to determine whether these water-soluble derivatives of the carcinogenic hydrocarbons likewise possess cancer-producing properties.

EXPERIMENTAL

1,2-Benzanthrene.—This hydrocarbon was made by pyrolysis of 1-naphthyl *o*-tolyl ketone, which was prepared by means of the Grignard reaction. To the Grignard reagent, which had been prepared from 50 g. of 1-bromonaphthalene in 75 cc. of ether and 75 cc. of benzene, was added 23.4 g. of *o*-tolunitrile. After being refluxed for eight hours the mixture was cooled and hydrolyzed with ice and 100 cc. of concentrated hydrochloric acid. The sparingly soluble ketimine hydrochloride which had crystallized was filtered off from the aqueous and organic solutions and was hydrolyzed by boiling it with water for an hour; when the mixture was cooled the ketone crystallized. Further purification was effected by distillation; b.p. 174°/0.4 mm.; yield, 37.8 g. (76%). After recrystallization from methanol the 1-naphthyl *o*-tolyl ketone melted at 59–61°.

A mixture of 34 g. of the ketone and 10 g. of zinc dust was heated for three hours in a metal bath kept at 410°; the hydrocarbon was distilled from the flask under a pressure of 0.4 mm. and recrystallized several times from benzene-alcohol; weight, 17.2 g. (54%). The yellow color was completely removed from the hydrocarbon by refluxing a solution of the 17.2 g. of hydrocarbon with 1 g. of maleic anhydride in 50 cc. of benzene for three hours.[2] The hot benzene solution was shaken with an aqueous solution of sodium hydroxide, and the benzene solution was filtered, concentrated to a small volume and treated with alcohol; m.p. 155.5–157°. Fieser and Dietz[3] obtained a 10% yield of 1,2-benzanthrene by heating the isomeric ketone, 2-methyl-1-benzoylnaphthalene, at its boiling point for twenty-six hours.

7,12-Dihydro-1,2-benzanthrene (II).—A mixture of 0.5 g. of 1,2-benzanthrene, 1 g. of powdered sodium, 30 cc. of anhydrous ether, 30 cc. of dry benzene (both solvents dried by liquid 40% sodium amalgam) and a few glass beads was shaken in a cylinder (which was nearly completely filled by the mixture). Almost immediately the solution became intensely blue in color; after sixteen hours the solution, which was now intensely rose-red in color, was decolorized by addition of methanol. The solution was quickly filtered through a plug of cotton, shaken with dilute hydrochloric acid, separated, dried and concentrated to a small volume. On addition of alcohol to the hot benzene solution the 7,12-dihydro-1,2-benzanthrene crystallized out; weight, 0.4 g. (80%); m.p. 111–112°. Further recrystallization or purification through the picrate raised the melting point to 112–112.5°. 7,12-Dihydro-1,2-benzanthrene crystallizes from benzene-alcohol and from acetic acid in glistening colorless leaflets; it is little soluble in cold alcohol but is readily soluble in benzene and in acetone.

Anal. Calc'd for $C_{18}H_{14}$: C, 93.89; H, 6.11.
Found: C, 93.88; H, 6.00.

In another experiment a mixture of 1.0 g. of 1,2-benzanthrene, 6 g. of 45% sodium amalgam, 30 cc. of ether and 30 cc. of benzene was shaken for fourteen hours. Alcoholysis of the intensely rose-red solution yielded 0.75 g. (75%) of pure 7,12-dihydro-1,2-benzanthrene.

For the reaction with lithium a mixture of 0.5 g. of 1,2-benzanthrene, 0.8 g. of shining lithium wire (0.5 mm. diameter) in 30 cc. of ether and 30 cc. of benzene was shaken for one week. At the beginning of the experiment the lithium wire was

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[2] COOK, HIEGER, KENNAWAY AND MAYNEORD, *Proc. Roy. Soc.*, **B111**, 469 (1932).

[3] FIESER AND DIETZ, *Ber.*, **62**, 1827 (1929).

pressed with a glass rod in several places in order to start the reaction. Treatment of the intensely blue colored solution with methanol yielded 0.48 g. (96%) of 7,12-dihydro-1,2-benzanthrene melting at 110–112°.

7,12-Dihydro-1,2-benzanthrene Picrate.—The dihydro compound combines with two molecules of picric acid in benzene solution. The dipicrate, which is very soluble in hot benzene, somewhat soluble in cold benzene but sparingly soluble in ligroïn, crystallizes from benzene-ligroïn in fine yellow needles; m.p. 139–139.5°.

Anal. Calc'd for $C_{18}H_{14}\cdot 2C_6H_3N_3O_7$: N, 12.2. Found: 12.3.

Dehydrogenation of 7,12-Dihydro-1,2-benzanthrene.—A mixture of 0.1 g. of 7,12-dihydro-1,2-benzanthrene and 0.02 g. of sulfur was heated in a metal bath; hydrogen sulfide was evolved as soon as the temperature reached 130°. After being kept at 170° for three hours the product was dissolved in benzene and the solution was shaken with mercury for several hours in order to remove excess of sulfur. The filtered solution was evaporated to dryness and the residue was recrystallized from benzene-alcohol, yielding 0.9 g. (90%) of pure 1,2-benzanthrene of melting point 158–158.5°.

Oxidation of 7,12-Dihydro-1,2-benzanthrene.—A mixture of 0.12 g. of 7,12-dihydro-1,2-benzanthrene and 0.1 g. of chromic acid anhydride in 5 cc. of acetic acid containing two drops of water was heated at the boiling point for a few minutes. The product obtained by addition of water was recrystallized from toluene, and proved to be 1,2-benzanthrene-7,12-dione (0.8 g.); m.p. 166–167°. Mixed with authentic 1,2-benzanthrene-7,12-dione (m.p. 167–168°) the melting point was 166.5–167.5°.

α,γ′-Dibenzanthracene.—1-(2-methylnaphthyl) 2-naphthyl ketone, obtained by Clar[4] through the Friedel and Crafts reaction, was prepared by means of the Grignard reaction. A mixture of 54 g. of 1-bromo-2-methylnaphthalene, 6 g. of magnesium and a crystal of iodine was refluxed in 75 cc. of ether and 125 cc. of benzene for two days, the mixture being protected from air by a mercury trap. To the Grignard reagent was added 33 g. of 2-naphthonitrile and the mixture was kept warm for twenty-four hours. Hydrolysis with ice and 100 cc. of concentrated hydrochloric acid gave the ketimine hydrochloride as an insoluble crystalline precipitate (78 g.), which was filtered off from the aqueous and organic solutions. The ketimine is not hydrolyzed appreciably by boiling water. Complete hydrolysis was effected by heating five sealed tubes, each containing 15.6 g. of ketimine hydrochloride, 4 cc. of concentrated hydrochloric acid and 100 cc. of water, at 180° for six hours. The contents of the tubes were combined, the ketone was extracted by benzene, the benzene solution was heated with charcoal, filtered and evaporated. The ketone was then recrystallized from acetone-alcohol, yielding 40 g. (63%) of product melting at 139.5–141°, which was sufficiently pure for the next step.

By heating a mixture of 30 g. of the ketone and 10 g. of zinc dust for one and three-quarters hours in a metal bath kept at 420°, 14 g. (50%) of purified α,γ′-dibenzanthracene was obtained, a yield higher than that previously reported.[3] The compound was obtained completely colorless by the maleic anhydride treatment.[2]

7,14-Dihydro-α,γ′-dibenzanthracene (III).—A mixture of 0.5 g. of α,γ′-dibenzanthracene and 1 g. of powdered sodium was shaken in 40 cc. of ether and 40 cc. of benzene for three days. The initial deep green color gave way to an intensely blue color. Treatment with methanol followed by purification described for the dihydro derivative of 1,2-benzanthrene gave 7,14-dihydro-α,γ′-dibenzanthracene, which was obtained as colorless, glistening leaflets by recrystallization from benzene-alcohol; weight, 0.42 g. (84%); m.p. 218–219°. Further recrystallization or purification through the picrate raised the melting point to 218.5–219.5°. The compound is

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[4] Clar, *ibid.*, **62**, 350 (1929).

nearly insoluble in cold alcohol, sparingly soluble in hot alcohol and very little soluble in cold benzene.

Anal. Calc'd for $C_{22}H_{16}$: C, 94.25; H, 5.75.
Found: C, 94.10; H, 5.72.

In another experiment 0.5 g. of α,γ'-dibenzanthracene was shaken with 0.8 g. of lithium wire in ether-benzene for nine days, after first starting the reaction by pressing the metal with a glass rod. On treatment with methanol the intensely blue colored solution yielded 0.4 g. (80%) of pure 7,14-dihydro-α,γ'-dibenzanthracene identical with the product obtained through the sodium reaction. Cook[5] obtained 7,14-dihydro-α,γ'-dibenzanthracene of m.p. 196–198° in 18% yield by catalytic hydrogenation of α,γ'-dibenzanthracene.

7,14-Dihydro-α,γ'-dibenzanthracene Picrate.—Mixing of hot saturated benzene solutions of picric acid (0.7 g.) and of the dihydrocompound (0.4 g.) precipitated the sparingly soluble dipicrate of 7,14-dihydro-α,γ'-dibenzanthracene in nearly quantitative yield. The dipicrate crystallizes from toluene in long, fine, yellow needles. The melting point depends on the rate of heating, for it decomposes near the melting point. When put in a bath at 210° and heated rapidly, the dipicrate melted with decomposition at 221–222°; when put in at 150° the compound melted at 216–217°.

Anal. Calc'd for $C_{22}H_{16} \cdot 2C_6H_3N_3O_7$: N, 11.4. Found: 11.4.

Dehydrogenation of 7,14-Dihydro-α,γ'-dibenzanthracene.—A mixture of 0.2 g. of 7,14-dihydro-α,γ'-dibenzanthracene and 0.04 g. of sulfur was heated for a few minutes at 220–230°. After removal of the excess of sulfur by mercury, followed by recrystallization from benzene-alcohol, 0.15 g. of α,γ'-dibenzanthracene of m.p. 258–260° was obtained.

Oxidation of 7,14-Dihydro-α,γ'-dibenzanthracene.—A mixture of 0.1 g. of the dihydro compound and 0.5 g. of sodium dichromate in 10 cc. of acetic acid was refluxed for one-half hour. After addition of 50 cc. of water containing a little sulfuric acid the crude quinone was filtered off, washed with water and dried; it was then sublimed at 230°/0.2 mm. The sublimate was recrystallized twice by dissolving it in a small amount of hot xylene and adding alcohol to the solution; in this manner 0.09 g. of α,γ'-dibenzanthracene-7,14-dione of m.p. 244–244.5° was obtained. There was no change in melting point when the substance was mixed with a sample of the quinone (m.p. 244–244.5°) prepared from α,γ'-dibenzanthracene.

3-Methylcholanthrene.—This hydrocarbon was prepared according to the method of Fieser and Seligman[6] with one modification. Fieser and Seligman obtained the intermediate ketone, 4-(1-naphthoyl)-7-methylindan, as an uncrystallizable oil by coupling the Grignard reagent of 4-bromo-7-methylindan with 1-naphthoyl chloride. By substituting 1-naphthonitrile for the latter compound we have obtained the ketone in crystalline form. No difficulty was encountered in preparing the Grignard reagent. A solution of 22 g. of 4-bromo-7-methylindan, 2.6 g. of magnesium ribbon, and a few drops of methyl iodide in 75 cc. of ether and 20 cc. of benzene was refluxed for two days, a mercury trap protecting the solution from air. Practically the theoretical amount of magnesium was used up. After addition of 17 g. of 1-naphthonitrile the mixture was refluxed for six hours, after which it was cooled and hydrolyzed with ice-cold ammonium chloride solution. Addition of 100 cc. of concentrated hydrochloric acid to the ether-benzene solution precipitated the ketimine hydrochloride as an oil which soon crystallized. The precipitate was filtered off and heated with

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[5] COOK, *J. Chem. Soc.*, **1933**, 1596.

[6] FIESER AND SELIGMAN, *J. Amer. Chem. Soc.*, **57**, 942 (1935).

water at 100° for two hours in order to hydrolyze the ketimine to the ketone. The ketone was taken up in benzene, the solution was dried over sodium sulfate and filtered, and after removal of the benzene the ketone was distilled; b.p. 225–228°/0.8 mm.; weight, 14.6 g. (49%). By recrystallization from acetone-alcohol and then from petroleum ether (60–75°) 11.3 g. of 4-(1-naphthoyl)-7-methylindan was obtained in the form of fine, colorless needles; m.p. 82.7–83.5°. The ketone gives a deep yellow color with concentrated sulfuric acid.

Anal. Calc'd for $C_{21}H_{18}O$: C, 88.07; H, 6.34.
Found: C, 88.15; H, 6.38.

Pyrolysis of 11 g. of the pure crystalline ketone followed by purification according to the directions of Fieser and Seligman yielded 4.5 g. (43%) of 3-methylcholanthrene melting at 180.3–180.6° (corr.). Fieser and Seligman reported a value of 178.5–179° (corr.). From propanol the methylcholanthrene was sometimes obtained in the form of large, transparent, yellow plates instead of the usual broad, yellow needles.

Dihydro-3-methylcholanthrene (IV).—A mixture of 0.5 g. of 3-methylcholanthrene and 1 g. of powdered sodium was shaken in 40 cc. of ether and 40 cc. of benzene with several glass beads for forty hours. The solution immediately became intensely purple in color. The solution was decolorized with methanol, filtered from the sodium, shaken with dilute hydrochloric acid, dried, filtered and evaporated; recrystallization of the residue from propanol gave 0.45 g. of cream-colored needles melting at 122–130°. These were found to contain about 0.03 g. of 3-methylcholanthrene. The latter was removed by dissolving the product along with 0.7 g. of picric acid in a small amount of hot benzene; on cooling the solution the picrate of 3-methylcholanthrene precipitated. The solution after being filtered was shaken with dilute sodium hydroxide solution in order to remove the picric acid, and washed thoroughly with water; the product obtained by evaporation of the colorless benzene solution was then recrystallized from propanol, yielding 0.4 g. (80%) of the dihydro compound. Dihydro-3-methylcholanthrene crystallizes from propanol and from benzene-alcohol in long, fine, colorless needles; m.p. 136–137°. The compound is readily soluble in benzene and in acetone but is little soluble in the lower aliphatic alcohols.

Anal. Calc'd for $C_{21}H_{18}$: C, 93.29; H, 6.71.
Found: C, 93.25; H, 6.70.

For addition of lithium a mixture of 0.5 g. of 3-methylcholanthrene and 0.8 g. of lithium wire was shaken in ether-benzene for one week, after first starting the reaction by pressing the lithium with a glass rod. In a few minutes the solution was intensely blue in color. Treatment of the blue solution with methanol yielded the dihydro compound, which after two recrystallizations from propanol was obtained as colorless needles melting at 136–137°; weight, 0.4 g. (80%).

Dehydrogenation of Dihydro-3-methylcholanthrene.—A mixture of 50 mg. of the dihydro compound and 10 mg. of sulfur was heated at 170° for one hour. After shaking a benzene solution of the product with mercury for several hours, the solution was filtered and evaporated to dryness; the residue of 3-methylcholanthrene was obtained pure by recrystallization from propanol; weight, 30 mg. (60%).

Oxidation of Dihydro-3-methylcholanthrene.—A mixture of 0.1 g. of the dihydro compound and 0.5 g. of sodium dichromate in 10 cc. of acetic acid was refluxed for one-half hour; 50 cc. of water containing a little sulfuric acid was added and the 5-(6-methyl-1,2-benzanthraquinonyl) acetic acid (V) which precipitated was filtered off. The product dissolved completely in dilute potassium carbonate solution; addition of hydrochloric acid to this solution reprecipitated the quinone-acid in gelatinous form. This was filtered off and dried (0.1 g.) and recrystallized from xylene, from which it was obtained in the form of microscopic yellow needles. The properties of the compound were identical with those of a sample of 5-(6-methyl-1,2-benzanthraquinonyl) acetic acid prepared by oxidation of 3-methylcholanthrene in exactly the same manner.[7] Further confirmation of the identity of the two acids was obtained by making the methyl ester of each sample in xylene solution by means of diazomethane. In both cases a methyl ester crystallizing from acetone-methanol in broad, thin, lemon-yellow needles was obtained; m.p. 213–214° alone and when mixed with each other.

SUMMARY

Sodium and lithium add to the 7,12 positions of 1,2-benzanthrene and to the 7,14 positions of α,γ'-dibenzanthracene and to the *meso* positions of 3-methyl-cholanthrene, yielding intensely colored organoalkali compounds. On treatment with methanol the corresponding 7,12-dihydro-1,2-benzanthrene, 7,14-dihydro-α,γ'-dibenzanthracene and dihydro-3-methylcholanthrene are formed.

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[7] COOK AND HASLEWOOD, *J. Chem. Soc.*, **1934**, 432.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE RELATIVE STABILITY OF PENTAARYLETHANES. III.[1] THE REVERSIBLE DISSOCIATION OF PENTAARYLETHANES*

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It is well known that hexaarylethanes in solution undergo spontaneous, reversible dissociation into triarylmethyl radicals. Tetraarylethanes, on the other hand, are remarkably inert substances which show no indication of dissociation even at high temperatures. Pentaarylethanes occupy a somewhat intermediate position with regard to stability. At room temperature a solution of pentaphenylethane is colorless and does not absorb oxygen or decolorize iodine to any appreciable extent as triarylmethyl radicals do. If the solution is warmed to about 105°, however, the yellow color of triphenylmethyl develops, and may be removed completely by shaking the cooled solution with air or by adding a small amount of iodine. If the solution is heated to 180–200° the pentaphenylethane is rapidly decomposed and *s*-tetraphenylethane may be isolated among the decomposition products.[2] Solid pentaphenylethane decomposes at its melting point, which is lower in air than in nitrogen.[3] At 100–120° pentaphenylethane is rapidly cleaved by bromine to give triphenylmethyl bromide and diphenylmethyl bromide and by hydrogen iodide to give triphenylmethane and diphenylmethane.[1] Even at room temperature the carbon-carbon ethane linkage is broken by potassium.[4] These reactions indicate a weak carbon-carbon bond in pentaphenylethane with dissociation taking place at slightly elevated temperatures.

Three years ago we began a study of the influence of "dissociating" groups on the properties of pentaarylethanes, and found that the groups can be arranged in the following order of decreasing ability to weaken the ethane linkage:[1] 1-naphthyl, *p*-biphenyl, *p*-anisyl, *p*-tolyl, phenyl, bi-

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[1] II, BACHMANN, *J. Am. Chem. Soc.*, **55**, 3005–3010 (1933).

* From the Sc.D. dissertation of F. Y. Wiselogle.

[2] SCHLENK AND HERZENSTEIN, *Ber.*, **43**, 3542 (1910).

[3] BACHMANN, *J. Am. Chem. Soc.*, **55**, 2135–2139 (1933).

[4] SCHLENK AND MARCUS, *Ber.*, **47**, 1670 (1914).

phenylene/2. We have now undertaken the synthesis of the complete homologous series of pentaarylethanes containing phenyl and *p*-biphenyl groups in order to study the effect of introducing a large number of "dissociating" groups in the pentaarylethane molecule.[*]

SYNTHESIS OF THE PENTAARYLETHANES

There are, in all, eleven pentaarylethanes theoretically derivable from pentaphenylethane through successive replacement of the five phenyl groups by *p*-biphenyl groups (Table I). We have prepared a number of these by coupling the Grignard reagent of a triarylbromomethane with a diarylbromomethane[3] (Equation 1).

TABLE I

PENTAARYLETHANES CONTAINING PHENYL AND *p*-BIPHENYL GROUPS

SYMBOL[*]	$R_3C\overset{1\ 2}{—}CHR_2$
0-	$(C_6H_5)_3C\text{-}CH(C_6H_5)_2$
2-	$(C_6H_5)_3C\text{-}CH(C_6H_5)(C_6H_4\text{-}C_6H_5\text{-}p)$
2,2-	$(C_6H_5)_3C\text{-}CH(C_6H_4\text{-}C_6H_5\text{-}p)_2$
1-	$(p\text{-}C_6H_5\text{-}C_6H_4)(C_6H_5)_2C\text{-}CH(C_6H_5)_2$
1,2-	$(p\text{-}C_6H_5\text{-}C_6H_4)(C_6H_5)_2C\text{-}CH(C_6H_5)(C_6H_4\text{-}C_6H_5\text{-}p)$
1,2,2-	$(p\text{-}C_6H_5\text{-}C_6H_4)(C_6H_5)_2C\text{-}CH(C_6H_4\text{-}C_6H_5\text{-}p)_2$
1,1-	$(p\text{-}C_6H_5\text{-}C_6H_4)_2(C_6H_5)C\text{-}CH(C_6H_5)_2$
1,1,2-	$(p\text{-}C_6H_5\text{-}C_6H_4)_2(C_6H_5)C\text{-}CH(C_6H_5)(C_6H_4\text{-}C_6H_5\text{-}p)$
1,1,2,2-	$(p\text{-}C_6H_5\text{-}C_6H_4)_2(C_6H_5)C\text{-}CH(C_6H_4\text{-}C_6H_5\text{-}p)_2$
1,1,1-	$(p\text{-}C_6H_5\text{-}C_6H_4)_3C\text{-}CH(C_6H_5)_2$
1,1,1,2-	$(p\text{-}C_6H_5\text{-}C_6H_4)_3C\text{-}CH(C_6H_5)(C_6H_4\text{-}C_6H_5\text{-}p)$
1,1,1,2,2-	$(p\text{-}C_6H_5\text{-}C_6H_4)_3C\text{-}CH(C_6H_4\text{-}C_6H_5\text{-}p)_2$

[*] The symbols (0-, 1-, etc.) throughout the paper refer to the positions of the biphenyl groups on the "1" carbon atom (with three aryl groups) and the "2" carbon atom (with two aryl groups) of the pentaarylethane; thus pentaphenylethane is called 0-, penta-*p*-biphenylethane is 1,1,1,2,2-, etc.

$$(C_6H_5)_3CMgBr + (C_6H_5)_2CHBr \rightarrow (C_6H_5)_3C—CH(C_6H_5)_2 + MgBr_2 \quad (1)$$

Triphenylbromomethane and diphenyl-*p*-biphenylbromomethane give highly satisfactory yields of the Grignard reagents, from which the desired pentaarylethanes may be prepared without difficulty. Phenyldi-*p*-biphenylmethylmagnesium bromide was obtained in quantitative yield, but the coupling reaction with diphenylbromomethane was unsatisfactory. Tri-*p*-biphenylbromomethane forms an insoluble double salt with mag-

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[*] It will be recalled that hexa-*p*-biphenylethane is completely dissociated in solution as well as in the solid state; SCHLENK, WEICKEL AND HERZENSTEIN, *Ann.*, **372**, 1-7 (1910); MÜLLER, MÜLLER-RODLOFF AND BUNGE, *Ann.*, **520**, 235 (1935).

nesium bromide which coats the remaining magnesium and prevents further reaction; moreover, prolonged refluxing results in reduction of the double salt to tri-*p*-biphenylmethane through the action of the ether.

Since the Grignard reaction was not generally applicable, the more reactive triarylmethylsodium compounds, which react instantly with diarylbromomethanes were employed (Equation 2). This method has the further advantage over the Grignard reaction that the entire process is carried out at room temperature. By this method all the remaining pentaarylethanes were synthesized in 50–90 per cent. yields.

$$(p\text{-}C_6H_5\text{—}C_6H_4)_3CNa + BrCH(C_6H_5)_2 \rightarrow (p\text{-}C_6H_5\text{—}C_6H_4)_3C\text{—}CH(C_6H_5)_2 + NaBr \qquad (2)$$

TABLE II

Temperature at Which Color Develops
(Solvent: Ethyl Benzoate)

PENTAARYLETHANE	TEMP., °C.	COLOR	COLOR OF R_3C—
0-	105	yellow	yellow
2-	92	yellow	yellow
2,2-	90	yellow	yellow
1-	88	orange-red	orange-red
1,2-	88	orange-red	orange-red
1,2,2-	80	orange-red	orange-red
1,1-	83	light red	light red
1,1,2-	83	light red	light red
1,1,2,2-	82	light red	light red
1,1,1-	81	dark red	dark red
1,1,1,2-	78	dark red	dark red
1,1,1,2,2-	71	dark red	dark red

PROPERTIES OF THE PENTAARYLETHANES

All our pentaarylethanes proved to be relatively stable, colorless, crystalline compounds. They are quite soluble in chloroform and in benzene at room temperature, giving colorless solutions from which the compounds may be precipitated by addition of alcohol. They exhibit a pronounced tendency to crystallize with solvent of crystallization, which is held tenaciously, and in a few cases exhibit polymorphism, existing in two crystalline forms possessing different melting points. The melting points of the compounds are lower in air than in nitrogen, as was found to be the case with the pentaarylethanes previously prepared.[3] Even in an inert atmosphere the compounds melt over a temperature range and the solids generally acquire a color several degrees below the melting point.

The dissociation of pentaphenylethane giving triphenylmethyl radicals has been indicated in the formation of a yellow color on heating a solution to 105°. The effect of the *p*-biphenyl group in promoting dissociation of pentaarylethanes was established in a semi-quantitative way by determining the temperature at which a solution of the pentaarylethane first developed a visible color. In Table II are shown the lowest temperatures at which color could be detected by looking through 10 cm. of a 0.02 molar solution of the pentaarylethanes in ethyl benzoate when the solutions were heated at the rate of 2° per minute. If dissociation occurs on warming then, *a priori*, the colors of the solutions should correspond to the colors of the free triarylmethyl radicals. It is seen that such is the case. Moreover, increasing the number of *p*-biphenyl groups in the molecule, in general, lowers the temperature at which color becomes visible. In every case the color could be discharged completely by quickly cooling the solution and shaking it with air. The appearance of color was often observed during recrystallization of the pentaarylethanes from hot solutions, and for final purification the compounds were dissolved in chloroform or benzene at room temperature and precipitated by alcohol.

CLEAVAGE OF THE PENTAARYLETHANES BY HYDROGEN IODIDE

All the pentaarylethanes are converted quantitatively to a mixture of triarylmethane and diarylmethane by hydrogen iodide in acetic acid at 120° (Equation 3). By this reaction the structures of our pentaarylethanes were confirmed.

$$R_3C\text{—}CHR_2 + 2HI \rightarrow R_3CH + H_2CR_2 + I_2 \qquad (3)$$

CLEAVAGE BY SODIUM AMALGAM

Although pentaphenylethane is not cleaved by liquid 40 per cent. sodium amalgam within twenty-four hours, all the pentaarylethanes containing two or more *p*-biphenyl groups, regardless of their positions, are quantitatively cleaved into triarylmethylsodium and diarylmethylsodium

$$(C_6H_5)_3C\text{—}CH(C_6H_4\text{—}C_6H_5\text{—}p)_2 \xrightarrow{40\%\ NaHg_x} (C_6H_5)_3CNa + NaCH(C_6H_4\text{—}C_6H_5\text{—}p)_2 \qquad (4)$$

(Equation 4). Cleavage of the two pentaarylethanes containing but one *p*-biphenyl group is about one-half complete in this length of time. From these results it is evident that an increase in the number of *p*-biphenyl groups reduces the resistance of the carbon-carbon bond to scission. There was no cleavage of any of the pentaarylethanes by one per cent. sodium amalgam, a reagent known to react with triarylmethyl radicals, which proves that the reaction with the more concentrated amalgam is a direct cleavage of the weak carbon-carbon bond and not a reaction involving radicals.

REVERSIBLE DISSOCIATION OF PENTAARYLETHANES

The dissociation of pentaarylethanes into triarylmethyl and diarylmethyl radicals is evidenced by the formation of triarylmethyl radicals in warm solutions of the hydrocarbons and by the formation of *s*-tetraarylethanes when the pentaarylethanes are decomposed by heating them in ethyl benzoate solution (Equations 5–7). Since the triarylmethyl radicals

$$R_3C—CHR_2 \rightarrow R_3C— + R_2CH— \quad (5)$$

$$R_3C— \rightarrow \text{decomposition products*} \quad (6)$$

$$2R_2CH— \rightarrow R_2CH—CHR_2 \quad (7)$$

undergo complete decomposition at the boiling point of ethyl benzoate (213°) and the *s*-tetraarylethanes do not dissociate at this temperature thermal decomposition of the pentaarylethanes goes rapidly to completion under these conditions.

Since the appearance of color on heating is an indication of dissociation, then it should be possible to obtain *s*-tetraarylethanes by heating solutions of pentaarylethanes to temperatures just above those at which color appears, for the formation of the *s*-tetraarylethanes is an irreversible process. In agreement with this view, *s*-tetraphenylethane was obtained in 30 per cent. yield when a solution of pentaphenylethane in toluene was refluxed (110°) for seventeen hours. Some unchanged pentaphenylethane was recovered, however, an indication that decomposition was incomplete even after this length of time. Similarly, penta-*p*-biphenylethane gave only two per cent. of *s*-tetra-*p*-biphenylethane after being heated for two hours in *o*-dichlorobenzene at 100°, the original compound being recovered in 87 per cent. yield. This relative stability of pentaarylethanes, in marked contrast to their reactivity at these temperatures, made it seem very probable that *the dissociation of pentaarylethanes is a reversible reaction for which the position of equilibrium is practically entirely in favor of the pentaarylethane.* Moreover the immediate appearance of color on heating a solution of pentaarylethane above 100° precludes an explanation of the stability in terms of a slow irreversible dissociation process. The reversible dissociation was definitely proved from a study of the kinetics of oxidation, for it was shown that in a *colorless* solution of pentaphenylethane at 95° a rapid dissociation into triphenylmethyl and diphenylmethyl

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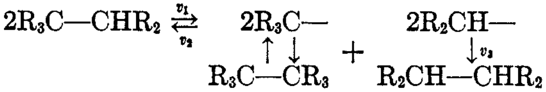
* For the thermal decomposition of triphenylmethyl see SCHMIDLIN, "Das Triphenylmethyl," Ferdinand Enke, Stuttgart, **1913**, p. 85.

radicals is taking place; this means, of course, that the radicals are recombining to form pentaphenylethane as fast as they are formed.

With the dissociation reaction already established we have obtained proof that the reverse reaction, the union of triarylmethyl and diarylmethyl radicals, can take place. Interaction of mercury and triphenylchloromethane or triphenylbromomethane gives triphenylmethyl, which associates nearly completely to hexaphenylethane. Similarly, mercury and diphenylbromomethane give *s*-tetraphenylethane. If now mercury and diphenylbromomethane are shaken together in presence of triphenylmethyl radicals, the principal product is the unsymmetrical compound, pentaphenylethane, which we have isolated in 88 per cent. yield (Equation 8). Similarly, if an equimolecular mixture of triphenylchloromethane and diphenylbromomethane is shaken with mercury, the sole product is pentaphenylethane, which can be isolated in nearly quantitative yield. It is apparent that the triphenylmethyl and diphenylmethyl radicals combine in preference to association of like radicals. This reaction suggests that a similar "capture" of the diphenylmethyl radical by the triphenylmethyl radical to form pentaphenylethane may take place in the original Gomberg and Cone[5] synthesis of the hydrocarbon in which a mixture of triphenylchloromethane and diphenylbromomethane is treated with activated magnesium.

$$(C_6H_5)_3C\text{—} + Hg + BrCH(C_6H_5)_2 \rightarrow (C_6H_5)_3C\text{—}CH(C_6H_5)_2 + HgBr \qquad (8)$$

We may now formulate the equilibria existing in a pentaarylethane solution at slightly elevated temperatures (50–100°) (Equation 9). From the results of kinetic studies to be described later it will be shown that a rapid dissociation into radicals is taking place in solutions of pentaarylethanes which do not show a visible color. This means that the primary dissociation equilibrium ($v_1 = v_2$) must be reached instantly at all temperatures and the position of equilibrium must be nearly entirely in favor of the pentaarylethane. Moreover, we know that diarylmethyl radicals cannot exist in any appreciable concentration. Now, the irreversible formation of an extremely small amount of *s*-tetraarylethane results in a corresponding increase in the concentration of triarylmethyl radicals (under these conditions hexaarylethanes are completely dissociated); as a result the *equilibrium* concentration of diarylmethyl radicals is reduced to such an extent that their association is practically stopped. The



$$2R_3C\text{—}CHR_2 \underset{v_2}{\overset{v_1}{\rightleftarrows}} \begin{array}{c} 2R_3C\text{—} \\ \uparrow\downarrow \\ R_3C\text{—}CR_3 \end{array} + \begin{array}{c} 2R_2CH\text{—} \\ \downarrow{\scriptstyle v_3} \\ R_2CH\text{—}CHR_2 \end{array} \qquad (9)$$

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[5] Gomberg and Cone, *ibid.*, **39,** 1466 (1906).

velocity of formation of pentaarylethane from the radicals, v_2, is a constant, independent of the concentration of diarylmethyl radicals under these conditions; the rate of formation of *s*-tetraarylethane, v_3, however, diminishes as the square of the concentration of diarylmethyl radicals. The formation of every molecule of *s*-tetraarylethane decreases the rate of formation of the next molecule. The concentration of triarylmethyl radicals is always much greater than the concentration of diarylmethyl radicals. Visual proof is found in the fact that the color, arising from the presence of triarylmethyl radicals, in a warm pentaarylethane solution does not disappear on cooling the solution in absence of oxygen. This precludes measurement of the extent of equilibrium from the intensity of the color as is done in the case of dissociation of symmetrical compounds. Even in "colorless" solutions of pentaarylethanes the concentration of diarylmethyl radicals must be much less than that of the triarylmethyl radicals.

The rate of thermal decomposition of pentaarylethanes, at 100° or at 200°, is dependent, then, on the rate of decomposition of the excess of triarylmethyl radicals (Equation 6) and not on the rate of formation of the *s*-tetraarylethane (Equation 7); in support of this statement is the failure to accumulate any appreciable amount of triarylmethyl radicals in the thermal decomposition experiments. It should be borne in mind, however, that from a thermodynamic standpoint a pentaarylethane solution is an unstable system which in infinite time would disproportionate completely into hexaarylethane and *s*-tetraarylethane.

OXIDATION OF PENTAARYLETHANES

Having established the existence of a reversible dissociation process we set out to determine the rate at which this dissociation proceeds. One of the most characteristic reactions of triarylmethyl radicals is a rapid absorption of oxygen to form triarylmethyl peroxides. Because the rate of absorption of oxygen by hexaphenylethane increases somewhat, but not proportionately, with an increase in the partial pressure of oxygen Mithoff and Branch[6] concluded that two competing reactions were involved, the one a rapid coupling of oxygen with the free triphenylmethyl radicals resulting from a relatively slow dissociation, the other a direct and also relatively slow reaction between hexaphenylethane and oxygen. By decreasing the concentration of hexaphenylethane and lowering the partial pressure of oxygen Ziegler[7] found that the rate of absorption of oxygen followed a first-order reaction and was independent of the oxygen pressure.

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[6] MITHOFF AND BRANCH, *J. Am. Chem. Soc.*, **52**, 255–268 (1930).

[7] ZIEGLER, EWALD, AND ORTH, *Ann.*, **479**, 277–303 (1930).

The rate of oxidation, under these conditions, was identical with the rate of reaction between hexaphenylethane and iodine[7] or nitric oxide,[8] and was in no case dependent on the concentration of the added reagent. Since the same rate was obtained in these three different reactions the rate-controlling step in each is undoubtedly the velocity of dissociation of hexaphenylethane into triphenylmethyl radicals. That the oxygen absorption by triphenylmethyl solutions involves only a reaction between radicals and oxygen and no direct reaction of the oxygen with hexaphenylethane was shown from a study of the effect of oxygen inhibitors and acceptors.[9,10]

The mechanism of oxidation is formulated as follows (Equations 10–13):

$$(C_6H_5)_3C—C(C_6H_5)_3 \xrightarrow{\text{slow}} 2(C_6H_5)_3C— \qquad (10)$$

$$(C_6H_5)_3C— + O_2 \xrightarrow{\text{fast}} (C_6H_5)_3CO_2— \qquad (11)$$

$$(C_6H_5)_3C— + (C_6H_5)_3CO_2— \xrightarrow{\text{fast}} (C_6H_5)_3C—O—O—C(C_6H_5)_3 \qquad (12)$$

$$\text{or} \quad 2(C_6H_5)_3CO_2— \xrightarrow{\text{fast}} (C_6H_5)_3C—O—O—C(C_6H_5)_3 + O_2. \qquad (13)$$

The normal triphenylmethyl peroxide, a secondary product, results from the interaction of the primary unstable addition compound of triphenylmethyl and oxygen, $(C_6H_5)_3CO_2$—, with another triphenylmethyl radical (Equation 12), or with another peroxide radical (Equation 13), or through cleavage of hexaphenylethane (Equation 14). The regenerated triphenylmethyl may then pick up another molecule of oxygen and repeat the process; these chain reactions account for the increase in rate of absorption of oxygen with an increase in the oxygen pressure. Under the experimental conditions the chains are very short; therefore the addition of traces of oxidation inhibitors produces no apparent change in the rate of oxidation.

$$(C_6H_5)_3C—C(C_6H_5)_3 + (C_6H_5)_3CO_2— \xrightarrow{\text{fast}} (C_6H_5)_3C—O—O—C(C_6H_5)_3 + (C_6H_5)_3C— \qquad (14)$$

In the presence of one equivalent or more of an oxidation inhibitor, suitably pyrogallol, the total absorption of oxygen by hexaphenylethane is doubled; *i.e.*, two moles of oxygen are absorbed by one mole of hexaphenylethane; furthermore, the rate of absorption of oxygen, a first-order reaction independent of the oxygen pressure or pyrogallol concentration, is identical with the rate of dissociation as determined by the

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[8] ZIEGLER, ORTH, AND WEBER, *ibid.*, **504**, 131–161 (1933).

[9] ZIEGLER AND EWALD, *ibid.*, **504**, 162–181 (1933).

[10] ZIEGLER, EWALD, AND SEIB, *ibid.*, **504**, 182–189 (1933).

three methods just described. The loosely bound hydrogen atoms in the pyrogallol stabilize the active peroxide radicals (Equation 15) before they

$$(C_6H_5)_3CO_2— + (H) \xrightarrow{fast} (C_6H_5)_3CO_2H^* \rightarrow \text{decomposition products} \quad (15)$$

can undergo any of the reactions leading to the formation of triphenylmethyl peroxide (Equations 12–14). Under these conditions each triphenylmethyl radical captures and holds one molecule of oxygen and all chain reactions are eliminated. Since the rate of reaction is identical with the rate of dissociation, a direct reaction between hexaphenylethane and oxygen is eliminated from consideration, for the rate of this second-order reaction should not be affected by the presence of the pyrogallol but would be proportional to the oxygen pressure.

The close relationship between pentaarylethanes and hexaarylethanes is clearly brought out from oxidation studies. Although solutions of our pentaarylethanes are relatively inert at room temperature we found that they rapidly absorb oxygen when warmed.† Semi-quantitative measurements of the rate and extent of absorption were made in a steam cone at 100°. In all cases the rate of absorption of oxygen was a maximum at the beginning of the run, rapidly falling off until a more or less constant value was reached after 1.1 to 1.2 mole of oxygen per mole of pentaarylethane had been absorbed; the absorption did not completely cease even after one hour. The times required for the pentaarylethanes to absorb 0.5 mole of oxygen have been estimated from the data and are presented in Table III. In every case it will be noticed that successive replacement of phenyl groups by *p*-biphenyl groups accelerates the rate of absorption of

TABLE III

TIMES REQUIRED FOR 0.00125 MOLAR SOLUTIONS OF PENTAARYLETHANES IN *o*-DICHLOROBENZENE TO ABSORB 0.5 MOLE OF OXYGEN AT 100°*

COMPD.	MIN.	COMPD.	MIN.	COMPD.	MIN.	COMPD.	MIN.
0-	4.5	1-	3.5	1,1-	2.5	1,1,1-	2.0
2-	3.5	1,2-	2.5	1,1,2-	1.5	1,1,1,2-	1.0
2,2-	2.5	1,2,2-	1.5	1,1,2,2-	1.0	1,1,1,2,2-	0.8

* The effect of replacing phenyl groups on the "1" carbon by biphenyl groups is apparent from reading horizontally; the effect of introducing biphenyl groups on the "2" carbon is shown in the vertical columns.

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* WIELAND AND MAIER, *Ber.*, **64**, 1205–1210 (1931), have prepared triphenylmethyl-hydrogen peroxide, $(C_6H_5)_3C—O—O—H$, and found it to be unstable even at room temperature unless very pure.

† TSCHITSCHIBABIN, *Ber.*, **40**, 368 (1907), observed that pentaphenylethane solutions in hot nitrobenzene absorb oxygen but gave no experimental details.

oxygen; this result is in striking agreement with the reaction between these pentaarylethanes and 40 per cent. sodium amalgam.

NATURE OF THE OXIDATION PRODUCTS

The chief product of the oxidation of a pentaarylethane at 100° was found to be the unsymmetrical triarylmethyl-(diarylmethyl)-peroxide, $R_3C—O—O—CHR_2$;* in addition a small amount (5–10 per cent.) of the symmetrical bis-triarylmethyl peroxide, $R_3C—O—O—CR_3$, was usually found. For the isolation of the unsymmetrical peroxide it was found more practical to work up the reaction mixture as soon as one mole of oxygen had been absorbed; by following this procedure it was possible to isolate six crystalline peroxides in yields of 50–80 per cent. of the calculated amount. In contrast to the symmetrical triarylmethyl peroxides, these unsymmetrical peroxides are all readily soluble in the common organic solvents and crystallize from them with considerable difficulty.

The structures of the unsymmetrical peroxides were established through cleavage by 2 per cent. sodium amalgam (Equation 16); hydrolysis of the

$$R_3C—O—O—CHR_2 + 2Na \rightarrow R_3CONa + R_2CHONa \qquad (16)$$

cleavage products gave the triarylcarbinol and diarylcarbinol corresponding to the triarylmethyl and diarylmethyl radicals originally present in the pentaarylethane. In agreement with this result is the appearance of the color characteristic of the sulfates of the triaryl- and diarylcarbinols when the peroxides are dissolved in sulfuric acid.

MECHANISM OF THE OXIDATION REACTION

The formation of unsymmetrical triarylmethyl-(diarylmethyl)-peroxides as the chief product of the oxidation reaction suggested that the oxygen cleaves the carbon-carbon bond of the pentaarylethanes directly. A study of the kinetics of the reaction has shown, however, that this mechanism cannot be correct; instead the reaction proceeds only through the intermediate formation of triarylmethyl and diarylmethyl radicals. Indeed, the measurement of the rate of oxidation has yielded the rate of dissociation of the pentaarylethane.

If the oxidation reaction involves the direct oxidation of the pentaarylethane, a bimolecular reaction, then the rate, dx/dt, should be dependent not only on the concentration of the ethane, $a - x$ (a being the

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* SCHMIDLIN, "Das Triphenylmethyl," Ferdinand Enke, Stuttgart, **1913**, p. 145, allowed a solution of pentaphenylethane to stand four weeks at room temperature in an oxygen atmosphere, removed the benzene and dissolved the oil in sulfuric acid; hydrolysis gave a trace of triphenylcarbinol and he concluded that the intermediate product was the unsymmetrical peroxide.

initial concentration of pentaarylethane, and x the amount reacted in time t), but also on the oxygen pressure, p_{O_2}:

$$dx/dt = k(a - x)p_{O_2}.$$

If, on the other hand, the reaction proceeds only through radicals, which are so rapidly oxidized that the rate of oxidation depends on the velocity of dissociation, then the speed of the reaction would be independent of the oxygen concentration, for the dissociation process is a unimolecular reaction,

$$dx/dt = k(a - x).$$

Under the conditions of the absorption experiments the reaction, whether unimolecular or bimolecular, would be of the first order since the partial pressure of oxygen (1 atmos.) and therefore the concentration of dissolved oxygen remained constant throughout a run. A definite decision between the two mechanisms was obtained for pentaphenylethane by comparing the rates of reaction when pure oxygen and air (0.2 oxygen) were employed. The rate according to the first mechanism (bimolecular) should be decreased to one-fifth of its value by changing from oxygen to air, while the rate according to the second mechanism (unimolecular), involving radicals, should remain unchanged.

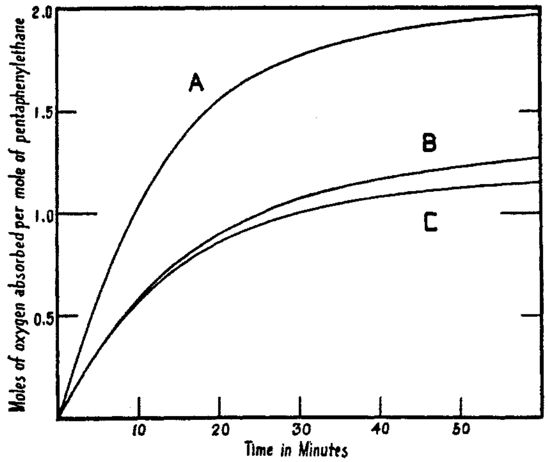


FIG. 1.—Rate of oxygen absorption by 0.025 molar solution of pentaphenylethane in *o*-dichlorobenzene at 94.40°. Curve A, in presence of 3 moles of pyrogallol; Curve B, oxygen pressure: 1 atmos.; Curve C, oxygen pressure: 0.2 atmos. (All experimental points fall on the curves.)

In Fig. 1, Curves B and C, are plotted the time rates of oxygen absorption by a 0.025 molar solution of pentaphenylethane in *o*-dichlorobenzene at 94.40° for oxygen pressures of 1 and 0.2 atmos., respectively. A comparison of the rates of oxygen absorption with different partial pressures by a solution of pentaphenylethane is complicated by side reactions, leading to the absorption of more than one mole of oxygen, for which the extent and perhaps the rate increases with the oxygen pressure. From an inspection of the curves, however, it is evident that initially the rate of absorption of oxygen is independent of the pressure; *i.e.*, the principal reaction is of the first order; the rate-controlling step is therefore a unimolecular process, and the direct reaction between oxygen and pentaphenylethane is eliminated from consideration.

For a unimolecular reaction the rate of absorption of oxygen throughout the reaction would be proportional to the concentration of pentaphenylethane:

$$dx/dt = k(a - x),$$

(k being the usual first-order velocity constant). The integrated equation, which is commonly used, is:

$$k = \frac{2.3}{t} \log \frac{a}{(a - x)}.$$

By considering the fraction, $Z = x/a$, of pentaphenylethane reacted the equation simplifies to:

$$k = \frac{-2.3}{t} \log (1 - Z).$$

If we assume any side reactions (which account for the absorption of more than one mole of oxygen) are negligible during the early course of the reaction we may calculate Z as the ratio of the actual absorption of oxygen in time, t, to the theoretical absorption assuming 100 per cent. unsymmetrical peroxide formation (see Fig. 2). The slopes of the lines, which, multiplied by 2.3, give the velocity constant, k, passing through the first four or five points differ by only 10 per cent., a difference which may be attributed entirely to the difference in total absorption of oxygen and not to any fundamental difference in the reaction rate. We have verified this independence of the rate on the oxygen pressure at temperatures from 85° to 100°. The values of the rate constants, as determined from the minimum slopes through the first reliable points, are recorded in Table IV. The most obvious mechanism for the oxidation of pentaphenylethane, then, is a relatively slow dissociation of the compound into two free radicals followed by a rapid reaction of oxygen with the radicals. The rate of oxidation is a measure of the rate of dissociation, there being no chain reactions under these conditions.

In the presence of pyrogallol in any ratio greater than two moles per mole of pentaphenylethane exactly two moles of oxygen per mole of pentaphenylethane was absorbed (Fig. 1, Curve A); the rate of absorption was correspondingly doubled. The reaction was strictly of the first order throughout 75–90 per cent. of the reaction (Fig. 3), and the rate was totally independent of the volume of solvent, the amount of pyrogallol (in excess of two moles), or the oxygen pressure. A temperature of 95° was adopted

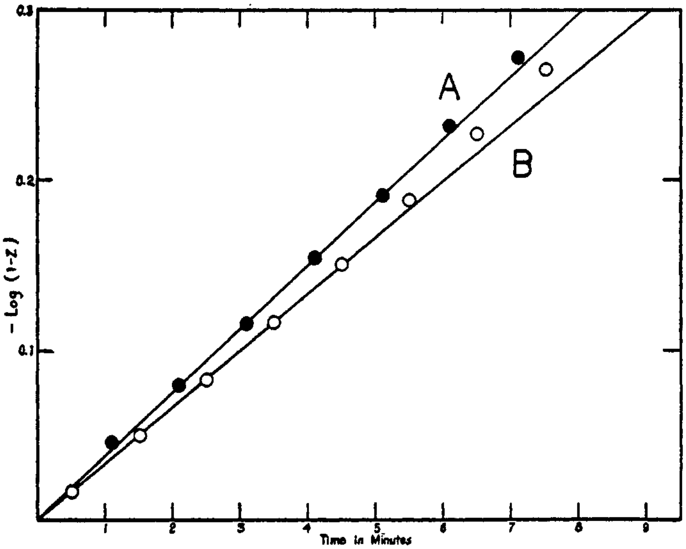


Fig. 2.—Rate of oxygen absorption by 0.025 molar solution of pentaphenylethane in *o*-dichlorobenzene at 94.40°. Curve A, filled circles, oxygen; Curve B, open circles, air. (Note that $-\log(1 - Z) = 0.3$ corresponds to 50 per cent. reaction). k from Curve A = 0.0855, from Curve B = 0.0756.

TABLE IV

Velocity Constants for Absorption of Oxygen by Pentaphenylethane in *o*-Dichlorobenzene

p_{O_2}	conc. (moles per liter)	84.70°	89.55°	94.40°	99.30°
1.0	0.1				0.148
1.0	0.05	0.0306			
1.0	0.025	0.0287		0.0855	
0.2	0.05	0.0309	0.0483	0.0889	0.134
0.2	0.025	0.0260	0.0490	0.0761	0.148
0.2	0.025	0.0276			
Average..................		0.0287	0.0486	0.0835	0.143

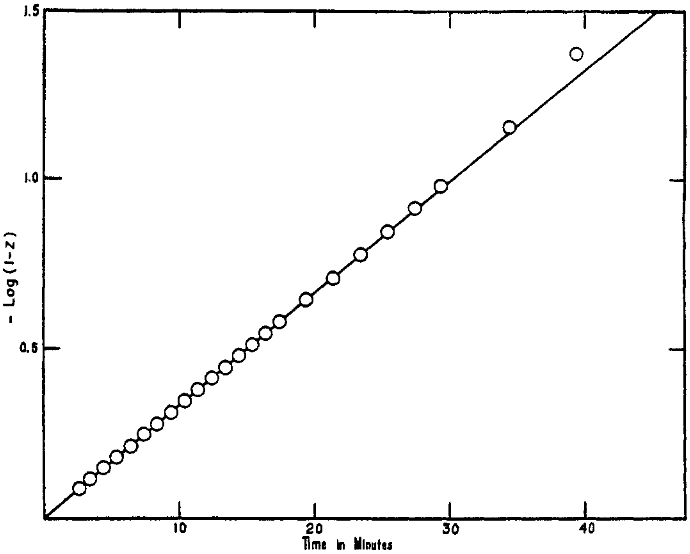


FIG. 3.—Rate of oxygen absorption by 0.025 molar solution of pentaphenylethane in *o*-dichlorobenzene at 94.40° in presence of 3 moles of pyrogallol; oxygen pressure = 0.2 atmos. A typical run. ($-\log(1 - Z) = 1.0$ corresponds to 90 per cent. reaction).

TABLE V

VELOCITY OF ABSORPTION OF OXYGEN BY PENTAPHENYLETHANE IN *o*-DICHLOROBENZENE AT 94.40° UNDER VARIOUS CONDITIONS

CONCENTRATION OF PENTAPHENYLETHANE (MOLES PER LITER)	MOLES PYROGALLOL PER MOLE PENTAPHENYLETHANE	p_{O_2}	k
0.025	1.0	0.2	0.0671*
0.025	2.0	0.2	0.0771
0.025	3.0	0.2	0.0795
0.025	3.0	0.2	0.0766
0.025	3.0	0.2	0.0754
0.025	3.9	1.0	0.0755
0.017	10.0	0.2	0.0762
0.05	1.4	0.2	0.0775
0.05	1.9	0.2	0.0745
0.05	2.0	1.0	0.0804
0.05	3.0	0.2	0.0770
Average of all reliable runs made			0.0765 ±0.004

* Did not absorb the theoretical quantity of oxygen; insufficient pyrogallol to prevent formation of unsymmetrical peroxide.

as the most convenient for the study of the effect of varying the conditions. The results are collected in Table V. We have repeated the oxidations at five-degree intervals from 80° to 105°. The values of the rate constants and half-lives are given in Table VI. The agreement of the constants as determined in the presence and absence of pyrogallol is within 5 per cent. at 84.70° and 13 per cent. at 99.40°. Since the runs made in the presence of pyrogallol are capable of much greater precision we consider these values as the more reliable.

TABLE VI

VELOCITY OF OXYGEN ABSORPTION BY PENTAPHENYLETHANE IN PRESENCE OF PYROGALLOL AT 80° TO 105°

Temperature	79.85°	84.70°	89.55°	94.40°	99.30°	104.15°
Velocity constant (k)	0.0163	0.0274	0.0462	0.0765	0.126	0.201
Half-life (min.)	42.5	25.3	15.0	9.06	5.50	3.44
Number of runs	3	3	5	10	6	7
Mean error of mean (in per cent.)	3.3	0.7	0.8	0.6	1.4	1.2

The mechanism of the oxidation of pentaphenylethane, therefore, is similar to that proposed for the oxidation of hexaphenylethane (Equations 17–19). The symmetrical and unsymmetrical peroxides may be formed

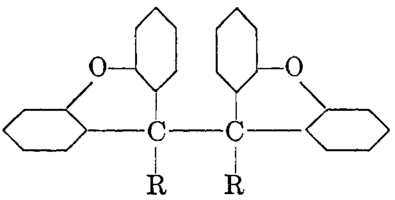
$$(C_6H_5)_3C\text{—}CH(C_6H_5)_2 \xrightarrow{\text{slow}} (C_6H_5)_3C\text{—} + (C_6H_5)_2CH\text{—} \qquad (17)$$

$$(C_6H_5)_3C\text{—} + O_2 \xrightarrow{\text{fast}} (C_6H_5)_3CO_2\text{—} \qquad (18)$$

$$(C_6H_5)_2CH\text{—} + O_2 \xrightarrow{\text{fast}} (C_6H_5)_2CHO_2\text{—} \qquad (19)$$

by combination of the appropriate radicals, but there is no direct reaction between a peroxide radical and pentaphenylethane. The pyrogallol stabilizes both peroxide radicals in the same manner as was observed for hexaphenylethane.

Conant and Evans concluded that they were measuring the rate of dissociation of a series of *s*-dialkyldixanthyls (Formula I) in their measurements of the rate of oxidation of these compounds.[11] Scherp, on the



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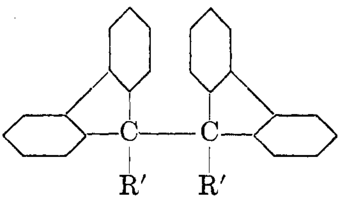

(II)

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[11] CONANT AND EVANS, *J. Am. Chem. Soc.* **51**, 1925–1935 (1929).

other hand, has recently reported that a direct reaction between oxygen and diaryldifluoryls (Formula II) takes place.[12]

HEAT OF ACTIVATION OF THE DISSOCIATION PROCESS

The energy of activation for the dissociation of pentaphenylethane may be calculated from the velocity constants at different temperatures by the Arrhenius equation,

$$E_d = \frac{2.3\,RT_1T_2}{(T_2 - T_1)} \log \frac{k_2}{k_1}.$$

The values calculated from the experimental constants are: $E_{79.85\text{-}84.70°} = 26.8$; $E_{84.70\text{-}89.55°} = 27.8$; $E_{89.55\text{-}94.40°} = 27.6$; $E_{94.40\text{-}99.30°} = 27.7$; $E_{99.30\text{-}104.15°} = 27.0$ kcal. The average was determined graphically, as is customary, from the equation written in the form,

$$\log k = \frac{E_d}{2.3R}\,(1/T) + C.$$

If $\log k$ is plotted against $(1/T)$ (Fig. 4), the slope of the line multiplied by 2.3 gives 27.6 kcal. as the heat of activation. We consider that this value is accurate to within $\pm$ 0.5 kcal.

The heat of activation of the dissociation of polyarylethanes is of considerable significance, since it represents a maximum value for the strength of the ethane linkage in the hydrocarbons. In Table VII are compared the half-lives and heats of activation of ethane and a number of substituted ethanes. It is seen that the half-life of pentaphenylethane in *o*-dichlorobenzene at 100° is approximately the same as the half-life of hexaphenylethane in toluene at 0°.

The heat of dissociation of pentaphenylethane could be calculated from measurements of the equilibrium constants at different temperatures, but we see no way of determining the position of equilibrium experimentally. The heat of dissociation is closely related to the heat of activation for the dissociation reaction, E_d, and the heat of activation for the reverse reaction, E_c, by the equation, $\Delta H = E_d - E_c$. It follows that the heat of dissociation cannot exceed the value 27.6 kcal. Of interest in this connection are some calculations made by Conant[13] on the effects of different groups on the strength of the carbon-carbon bond. From a comparison of the heat of dissociation of dixanthyl and diphenyldixanthyl Conant has estimated the effect of replacing a hydrogen by a single phenyl group on the strength of the ethane linkage to be −11 kcal. The heat of dissociation

[12] SCHERP, *ibid.*, **58**, 576–580 (1936).

[13] CONANT, *J. Chem. Phys.*, **1**, 427–431 (1933).

of pentaphenylethane would then be 11 kcal. greater than the heat of dissociation of hexaphenylethane[14] (11.5 kcal.), or 22 kcal., a value which seems to us very reasonable.

We are now in a position to reinterpret several of the reactions of penta-arylethanes as most likely taking place through radicals. Although cleavage by alkali metals is not a reaction of radicals, cleavage by bromine and hydrogen iodide,[1] by sulfuryl chloride[15] and by phosphorus pentachloride[16] probably involve only reaction of the reagents with the radicals. The products, tricyclohexyl- and dicyclohexylmethanes which Zartman and Adkins obtained by hydrogenation of pentaphenylethane at 125° are undoubtedly the result of hydrogenation of the intermediate radicals.[17]

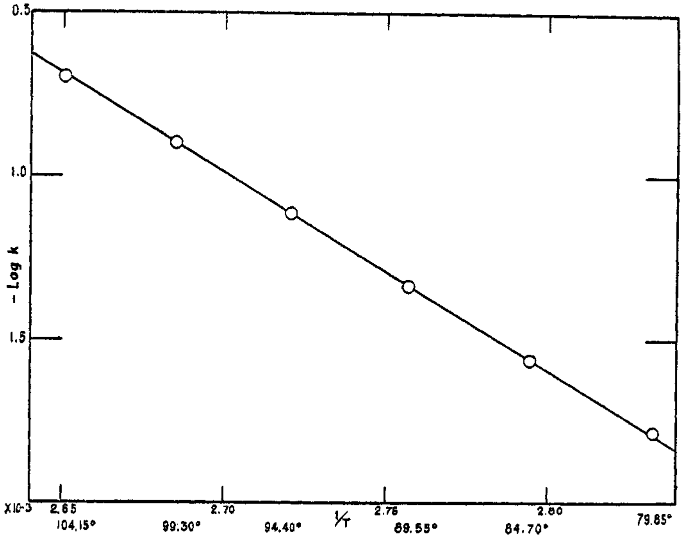

FIG. 4.—The rate of dissociation of pentaphenylethane at various temperatures

TABLE VII

HALF-LIFE AND HEAT OF ACTIVATION OF ETHANE AND SUBSTITUTED ETHANE DERIVATIVES

COMPOUND	HALF-LIFE (MIN.)	TEMP. (°C.)	SOLVENT	HEAT OF ACTIVATION (KCAL.)
Hexaphenylethane[9]	4.7	0	Toluene	19.5
Pentaphenylethane	5.2	100	o-Dichlorobenzene	27.6
Dimethyldixanthyl[11]	55	35	Bromobenzene	34
Ethane				84

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[14] ZIEGLER AND EWALD, *Ann.*, **473**, 180 (1929).

[15] NORRIS, THOMAS AND BROWN, *Ber.*, **43**, 2945 (1910).

[16] CONE AND ROBINSON, *ibid.*, **40**, 2166 (1907).

[17] ZARTMAN AND ADKINS, *J. Am. Chem. Soc.*, **54**, 1668–1674 (1932).

EXPERIMENTAL

Because we had originally intended to use the Grignard reaction to prepare all the pentaarylethanes, we synthesized the triaryl- and diarylbromomethanes; the chlorides could undoubtedly be used with equal success for the sodium reactions. The preparation of triphenylbromomethane, the diarylbromomethanes, pentaphenylethane, 1,1,1,2-tetraphenyl-2-*p*-biphenylethane and 1,1,1-triphenyl-2,2-di-*p*-biphenylethane has been described previously.[3]

*Diphenyl-*p*-biphenylbromomethane.*—To prepare diphenyl-*p*-biphenylcarbinol 51.8 g. of phenyl *p*-biphenyl ketone was added to the Grignard reagent which had been prepared from 47.1 g. of bromobenzene in 90 cc. of anhydrous ether. After being refluxed for forty-five minutes, the clear solution was hydrolyzed with ice and dilute hydrochloric acid. The ether solution was concentrated and treated with petroleum ether (60–70°), whereupon 61.5 g. (92 per cent.) of the nearly pure carbinol, m. p. 132.5–134.5°, crystallized. A mixture of 33.6 g. of diphenyl-*p*-biphenylcarbinol, 15 cc. of benzene and 20 g. of acetyl bromide was heated on a steam bath for one hour. After addition of 100 cc. of petroleum ether (60–70°), 36.8 g. (92 per cent.) of the triarylmethyl bromide precipitated. Diphenyl-*p*-biphenylbromomethane crystallizes from benzene-petroleum ether in the form of colorless hexagonal plates; m. p. 127.5–128°.

Anal. Calc'd for $C_{25}H_{19}Br$: Br, 20.0. Found: Br, 20.0.

*Phenyl-di-*p*-biphenylbromomethane.*—The corresponding carbinol was prepared in 83 per cent. yield from di-*p*-biphenyl ketone and a slight excess of phenylmagnesium bromide in ether solution; it is entirely unnecessary to replace the ether by xylene as recommended by Schlenk[18] in order to achieve addition. Forty-eight grams of phenyl-di-*p*-biphenylcarbinol was heated for two hours on a steam bath with 20 g. of acetyl bromide and 25 cc. of 30 per cent. hydrogen bromide in glacial acetic acid. After addition of 50 cc. of petroleum ether (60–70°) the mixture was cooled; the phenyl-di-*p*-biphenylbromomethane was filtered off (48.5 g.) and recrystallized from petroleum ether containing a small amount of benzene, from which it was obtained in small colorless crystals; yield, 77 per cent.; m. p. 145–146.5°. A low-melting form, m. p. 70–72°, which contained solvent of crystallization, was often obtained when a larger proportion of benzene was used for recrystallization.

Anal. Calc'd for $C_{31}H_{23}Br$: Br, 16.8. Found: Br, 17.0.

*Tri-*p*-biphenylcarbinol.*—Morton and Stevens[19] have described a method for the preparation of this compound in small amounts from sodium, *p*-chlorobiphenyl and diethyl carbonate. By the simple expedient of adding the *p*-chlorobiphenyl and diethyl carbonate slowly to the sodium in hot benzene we found that the reaction began at once and all hazards involving the induction period were avoided so that much larger quantities could be run at one time. Thirty-three grams of sodium wire was suspended in 200 cc. of benzene in a two-liter round-bottomed flask provided with a return condenser, and the liquid was brought to gentle reflux. A solution of 120 g. of *p*-chlorobiphenyl and 23.6 g. (0.2 mole) of diethyl carbonate in 200 cc. of benzene was slowly added through the top of the condenser. A brown color on the sodium appeared immediately and the reaction was at no time violent. The mixture was heated for one hour after all the solution had been added; the excess sodium was then dissolved through addition of alcohol. Hydrolysis of the resulting mixture gave 60 g. of crude material which was contaminated, however, by considerable amounts of a very insoluble product. Recrystallization from benzene gave 42.5 g.

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[18] SCHLENK, *Ann.*, **368**, 298–300 (1909).

[19] MORTON AND STEVENS, *J. Am. Chem. Soc.*, **53**, 4028 (1931).

(42 per cent.) of tri-*p*-biphenylcarbinol melting at 208–210°. Morton and Stevens reported a 23 per cent. yield of pure product in a smaller run.

*Tri-*p*-biphenylbromomethane.*—Fifteen grams of acetyl bromide was added to a suspension of 40 g. of tri-*p*-biphenylcarbinol in 50 cc. of benzene and the reaction mixture was heated for three hours on a steam bath. The bromide, which separated out on cooling, was recrystallized from benzene and dried in a vacuum desiccator over soda-lime and paraffin; yield, 43 g. (95 per cent.) of colorless needles melting at 207.5–208° to a brown liquid.

Anal. Calc'd for $C_{37}H_{27}Br$: Br, 14.5. Found: Br, 14.2.

*Diphenyl-*p*-biphenylmethylmagnesium Bromide.*—In a 500 cc. round-bottomed flask provided with a condenser and mercury trap were placed 19.95 g. of diphenyl-*p*-biphenylbromomethane, 1.232 g. of magnesium ribbon, 25 cc. of anhydrous ether and 50 cc. of dry benzene; the air was then removed and replaced by nitrogen. The solution, protected from light by a black cloth, was refluxed for ten hours. The characteristic red color of the free radical, diphenyl-*p*-biphenylmethyl, developed immediately and gradually gave way to the lighter brown color of the Grignard reagent. Since 0.100 g. of magnesium was recovered, the yield of Grignard reagent was calculated to be 85 per cent.

*Phenyl-di-*p*-biphenylmethylmagnesium Bromide.*—The Grignard reagent was prepared from 2.375 g. of pure phenyl-di-*p*-biphenylbromomethane and 0.285 g. of magnesium, activated by iodine, in 6 cc. of ether and 11 cc. of benzene. After one hour of refluxing in a nitrogen atmosphere the filtered solution was hydrolyzed with excess of standard acid which was titrated with standard alkali. The yield of Grignard reagent as determined from the loss in weight of the magnesium and from titration was quantitative. The successful preparation of the Grignard reagent is contingent on the purity of the bromide.

*Attempts to Prepare Tri-*p*-biphenylmethylmagnesium Bromide.*—In the attempts to prepare the Grignard reagent from 2.735 g. of tri-*p*-biphenylbromomethane and 0.24 g. of magnesium in 15 cc. of ether and 30 cc. of benzene iridescent green needles formed on the magnesium and sides of the flask immediately. Continued refluxing over a period of several hours gave a colorless precipitate which proved to be tri-*p*-biphenylmethane (yield 62 per cent.). No appreciable loss in the weight of the magnesium could be detected.

In order to prepare the double salt a solution of anhydrous magnesium bromide, prepared from 3.6 g. of mercuric bromide and excess of magnesium in 20 cc. of ether and 40 cc. of benzene, was filtered into a benzene solution of 1.1 g. of tri-*p*-biphenylbromomethane. The double salt, which precipitated immediately, was filtered off and washed by digestion with hot benzene. The crystals were immediately decomposed by a solution of potassium hydroxide in methanol. Quantitative estimation of bromine, magnesium and the organic product, the methyl ether of tri-*p*-biphenylcarbinol, (m. p. 162–163°), indicated the composition: $2(C_6H_5—C_6H_4)_3CBr \cdot 3MgBr_2$. In another experiment the double salt prepared from 2.75 g. of tri-*p*-biphenylbromomethane was refluxed in ether-benzene for a day; from the mixture 1.72 g. (73 per cent.) of tri-*p*-biphenylmethane was isolated.

Synthesis of Pentaarylethanes through the Sodium Reaction.—Unless otherwise stated the pentaarylethanes were prepared by this reaction. To 45 g. of molten sodium under xylene in a 250-cc. Erlenmeyer flask 55 g. of mercury was added slowly from a medicine dropper. After the flask had cooled to room temperature the amalgam was carefully pipetted into a clean flask and stored under benzene. The density of the amalgam is approximately 2 g. per cubic centimeter.

To 10 g. of 45 per cent. sodium amalgam in a 70 cc. glass-stoppered bottle (the glass-stoppered graduated cylinders are most suitable) containing 20 cc. of ether and 30 cc. of benzene was added 0.01 mole of the triarylbromomethane. The bottle was repeatedly evacuated and filled with nitrogen and then sealed with special stop-cock grease.[20] The bottle was shaken by hand, cooling when necessary, until the characteristic color of the radical had changed to the intense color of the triarylmethylsodium compound; the bottle was then mechanically shaken for several hours. The sodium amalgam was now frozen by immersing the bottle in an ice-salt mixture, and 0.01 mole of the diarylbromomethane was added. In every case the intense color of the triarylmethylsodium disappeared completely on shaking the mixture, showing that the reaction was at an end almost immediately. The solution, containing a suspension of sodium bromide, was decanted from the solid amalgam into a separatory funnel. The amalgam was washed with benzene containing a small amount of alcohol and the washings were added to the main solution. When all the particles of amalgam in the separatory funnel had reacted with the alcohol, the ether-benzene solution was washed with dilute hydrochloric acid, and with water, dried, filtered, and evaporated at room temperature. Crystallization of the residual oil was accomplished by stirring with acetone or alcohol; the crude product was filtered, dried, and recrystallized.

1-p-Biphenyl-1,1,2,2-tetraphenylethane (1-).—To the Grignard reagent, prepared in 86 per cent. yield from 19.95 g. of diphenyl-*p*-biphenylbromomethane as already described, was added 12.35 g. of diphenylbromomethane. After being refluxed for two hours the reaction mixture was hydrolyzed with dilute acetic acid. The dark-red oil, which was obtained from the ether-benzene solution, crystallized when stirred with a mixture of acetone and methanol. Two recrystallizations from chloroform-alcohol yielded 16.8 g. (80 per cent., based on the Grignard reagent) of 1-*p*-biphenyl-1,1,2,2-tetraphenylethane in the form of colorless, refracting prisms, melting at 190–192° to a light red liquid.*

Anal.† Calc'd for $C_{38}H_{30}$: C, 93.8; H, 6.2.
Found: C, 93.6; H, 6.4.

1,2-Di-p-biphenyl-1,1,2-triphenylethane (1,2-).—To the Grignard reagent from 13.3 g. of diphenyl-*p*-biphenylbromomethane was added 10.77 g. of phenyl-*p*-biphenylbromomethane. After standing at room temperature for twelve hours the mixture was hydrolyzed. The residue obtained by evaporation of the organic solvents crystallized when stirred with acetone. Recrystallization of the pentaarylethane from chloroform-alcohol gave 7.76 g. (46 per cent.) of diamond-shaped plates, melting at 180–185° to an orange-red liquid, the solid acquiring a color at about 170°. A 77 per cent. yield of the same compound of m.p. 172–178° was obtained through the sodium reaction; recrystallization raised the melting point to 180–185°.

Anal. Calc'd for $C_{44}H_{34}$: C, 93.9; H, 6.1.
Found: C, 93.6; H, 6.3.

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[20] MELOCHE AND FREDERICK, *ibid.*, **54**, 3264 (1932).

* For determining the melting points of all the pentaarylethanes the melting-point tube containing the material was placed in a test-tube which was repeatedly evacuated and filled with nitrogen; just before inserting the tube in the bath, which was preheated to within 20–30° of the melting point, the open end was sealed.

† In order to drive off the solvent of crystallization it was necessary to fuse the pentaarylethane under reduced pressure; all the pentaarylethanes, except the 1,1,1,2- and the 1,1,1,2,2- were brought to incipient fusion.

*1,2,2-Tri-*p*-biphenyl-1,1-diphenylethane* (1,2,2-).—A 75 per cent. yield of crude pentaarylethane was obtained by coupling diphenyl-*p*-biphenylmethylsodium with di-*p*-biphenylbromomethane. Recrystallization from chloroform, acetone, carbon tetrachloride, ether, petroleum ether or from benzene invariably gave a product which melted between 100° and 150° with effervescence, indicating the presence of solvent of crystallization. A sample which had been allowed to stand for several months melted at 227–230°, with previous softening at 223°.

Anal. Calc'd for $C_{50}H_{38}$: C, 94.0; H, 6.0.
Found: C, 93.7; H, 6.2.

*1,1-Di-*p*-biphenyl-1,2,2-triphenylethane* (1,1-).—The yield of crude pentaarylethane prepared from phenyl-di-*p*-biphenylmethysodium and diphenylbromomethane was 89 per cent. The hydrocarbon crystallizes from chloroform-alcohol as colorless, diamond shaped plates, melting at 198–199° to a dark-red liquid, with decomposition beginning at 193°. Interaction of the Grignard reagent from phenyl-di-*p*-biphenylbromomethane and diphenylbromomethane gave a deeply colored oil from which no pentaarylethane crystallized.

Anal. Calc'd for $C_{44}H_{34}$: C, 93.9; H, 6.1.
Found: C, 93.9; H, 6.3.

*1,1,2-Tri-*p*-biphenyl-1,2-diphenylethane* (1,1,2-).—The crude pentaarylethane was isolated in 72 per cent. yield. By recrystallization from chloroform-alcohol the hydrocarbon was obtained in the form of colorless prisms (64 per cent. yield), melting at 206–209° to an intensely dark-brown liquid, the solid turning orange at 190°.

Anal. Calc'd for $C_{50}H_{38}$: C, 94.0; H, 6.0.
Found: C, 94.2; H, 6.2.

*1,1,2,2-Tetra-*p*-biphenyl-1-phenylethane* (1,1,2,2-).—A 66 per cent. yield of product melting above 214° was obtained. By recrystallization from chloroform-alcohol the 1,1,1,2- compound was obtained in clusters of blunt, colorless needles; m. p. 222–228°, the solid darkening at 210°.

Anal. Calc'd for $C_{56}H_{42}$: C, 94.1; H, 5.9.
Found: C, 93.9; H, 6.1.

*1,1,1-Tri-*p*-biphenyl-2,2-diphenylethane* (1,1,1-).—This compound was obtained in 79 per cent. yield; recrystallization from chloroform-alcohol gave four-sided prisms, melting at 164–167° to a greenish-yellow fluorescent liquid; the melt turns red on heating to a higher temperature.

Anal. Calc'd for $C_{50}H_{38}$: C, 94.0; H, 6.0.
Found: C, 93.9; H, 6.3.

*1,1,1,2-Tetra-*p*-biphenyl-2-phenylethane* (1,1,1,2-).—A 51 per cent. yield of colorless needles was obtained when the crude product was recrystallized from chloroform-alcohol. If heated very slowly from room temperature the product melted at 215–220° to a dark-red liquid, the solid turning dark at 195°. If inserted in the melting point bath above 177°, however, the solid instantly melted and almost instantly resolidified to melt again at 223–226°.

Anal. Calc'd for $C_{56}H_{42}$: C, 94.1; H, 5.9.
Found: C, 93.7; H, 6.0.

*1,1,1,2,2-Penta-*p*-biphenylethane* (1,1,1,2,2-).—This pentaarylethane was obtained in two forms. The low-melting form crystallized in fine interlocking needles from a chloroform-alcohol solution, melting at 172–185° to a red liquid. If the pentaarylethane was allowed to stand in contact with the solvent or was recrystallized from benzene colorless rhombic plates of the high-melting form were obtained;

melting point 226–234° (black opaque liquid), the solid turning dark and sintering at 210°. The yield of pure material was 63 per cent.

Anal. Calc'd for $C_{62}H_{46}$: C, 94.1; H, 5.9.
Found: C, 94.5; H, 5.9.

Cleavage by Hydrogen Iodide.—A mixture of 0.2 g. of iodine and 0.6 g. of red phosphorus was allowed to react in 20 cc. of acetic acid until the iodine color disappeared; 0.3 cc. of water and 0.0025 mole of pentaarylethane were added and the mixture was refluxed in a nitrogen atmosphere for one hour.[1] In no case was any unreacted pentaarylethane recovered. The separation of the triarylmethane and diarylmethane depended upon the relative solubilities of the cleavage products. In the cleavage of the 1-, 1,1- and 1,1,1-, all of which gave diphenylmethane, the reaction mixture following removal of the solvent was extracted with 30–40° petroleum ether leaving the triarylmethane as a residue. Recrystallization gave yields of triarylmethane of 90 per cent., 98 per cent. and 94 per cent. respectively; in each case a 61 per cent. yield of diphenylmethane was isolated.

Since tri-*p*-biphenylmethane is insoluble in cold chloroform, in which the diarylmethanes are soluble, the products from the cleavage of the 1,1,1,2- and 1,1,1,2,2- were extracted with chloroform. The yields of tri-*p*-biphenylmethane were 90 per cent. and 82 per cent.; those of the diarylmethanes were 78 per cent. and 99 per cent. respectively.

In the cleavage of the 1,1,2- compound the products were separated by dissolving the phenyl-*p*-biphenylmethane in 60–70° petroleum ether; the yields of triarylmethane and diarylmethane were 76 per cent. and 69 per cent. respectively.

Phenyl-di-*p*-biphenylmethane and di-*p*-biphenylmethane, obtained from the cleavage of the 1,1,2,2- were isolated by cooling a benzene solution of the mixture, whereupon the latter compound crystallized. By removing the benzene and taking up the oil in acetone and cooling, the phenyl-di-*p*-biphenylmethane was deposited; yields of 26 per cent. and 30 per cent. respectively were isolated.

Cleavage products from the 1,2- and 1,2,2- were identified by allowing the solutions to evaporate slowly to dryness and mechanically separating the different crystals.

Cleavage by Sodium Amalgam.—The procedure was the same as that previously described[1] except that more solvent was used. A solution of 0.0015 mole of the pentaarylethane in 20 cc. of ether and 10 cc. of benzene in a 70-cc. glass-stoppered bottle was shaken for twenty-four hours with (a) 30 g. of 1 per cent. sodium amalgam, and (b) 7 g. of 45 per cent. sodium amalgam. The extent of the reaction was determined by freezing out the sodium amalgam and titrating the colored organometallic compounds with a 0.6 normal solution of alcohol in benzene, the end point being the complete disappearance of the color. For the titration the glass stopper of the reaction bottle was quickly replaced by a rubber stopper containing the burette tip. The flask was evacuated through the burette, which was then filled with the standard solution. As soon as the bottle had been chilled a small cork was inserted in the top of the burette and the alcohol solution was quickly added, with shaking, until the color disappeared. A correction was applied for the volume of solution used to fill the tip of the burette. The accuracy of the method, although limited by the trapping of some of the colored sodium compounds by the solid amalgam and also by the reaction of the sodium in the amalgam with alcohol, is considerably greater than any results based upon the separation and isolation of the reaction products from the unreacted pentaarylethane.

The only pentaarylethane to give a color with 1 per cent. sodium amalgam in twenty-four hours was the 1,2,2- which gave a very faint purple color; titration indicated less than 0.1 per cent. cleavage and the original pentaarylethane was recovered. With 45 per cent. sodium amalgam the highly colored triarylmethyl- and diarylmethylsodium compounds formed fairly rapidly. The titrations of all the pentaarylethanes containing two or more biphenyl groups, with one exception, indicated between 94 per cent. and 105 per cent. cleavage; the 1,1,1- was apparently only 2 per cent. cleaved and we attribute this result to the probable presence of chloroform of crystallization which reacted with the cleavage products. Titration of the cleavage products from the 1,1- was inadvertently spoiled but an 88 per cent. yield of the triarylmethane was isolated. In two experiments the cleavage of the 1- was 49 per cent. and 38 per cent.; the 2- was cleaved to the extent of 32 per cent. and 64 per cent. The differences between the two values are attributed chiefly to the physical condition of the amalgam during the reaction. The amalgam when shaken exhibits a tendency to disperse into a finely divided form; whenever this happened there was an induction period of two to four hours before the appearance of any color, which otherwise became noticeable within a relatively few minutes.

When a solution of 0.615 g. of pentaphenylethane in 20 cc. each of ether and benzene was shaken with 45 per cent. sodium amalgam for thirty days the color was brown rather than red, as it should have been for cleavage to $(C_6H_5)_3CNa$, and hydrolysis gave no triphenylmethane, the original pentaarylethane being recovered in 85 per cent. yield. It is quite probable that the sodium displaced the hydrogen to give pentaphenylethylsodium, $(C_6H_5)_3C—CNa(C_6H_5)_2$, a reaction similar to that reported by Dorfman, who found that pentaphenylethylpotassium is formed by the interaction of pentaphenylethane and phenylisopropylpotassium.[21]

Thermal Decomposition.—(213°) A solution of 0.972 g. of 1-*p*-biphenyl-1,1,2,2-tetraphenylethane in 10 cc. of ethyl benzoate was refluxed for one hour in a nitrogen atmosphere. The characteristic orange-red color of the diphenyl-*p*-biphenylmethyl radical soon gave way to a darker brown. The solvent was removed by distillation under reduced pressure at 100°; the dark-red oil was taken up in benzene and decolorized with norit; on cooling 0.155 g. (46 per cent.) of *s*-tetraphenylethane crystallized.

A solution of 1.580 g. of penta-*p*-biphenylethane in 20 cc. of ethyl benzoate was refluxed for one hour in a nitrogen atmosphere; the residue, after removal of the solvent at 100°, in chloroform gave 0.335 g. (52 per cent.) of *s*-tetra-*p*-biphenylethane.

(100–110°) A solution of 1.025 g. of pentaphenylethane in 15 cc. of toluene was refluxed in a nitrogen atmosphere for seventeen hours. The toluene was allowed to evaporate at room temperature; the light-yellow oil partially crystallized when stirred with benzene and petroleum ether; 0.125 g. (30 per cent.) of pure *s*-tetraphenylethane was isolated. From the filtrate 0.030 g. of pentaphenylethane was recovered. In a similar experiment with 2.05 g. of pentaphenylethane in 25 cc. of toluene after eight hours of refluxing the pentaphenylethane was recovered in 20 per cent. yield; a 10 per cent. yield of *s*-tetraphenylethane was isolated.

A solution of 0.790 g. of penta-*p*-biphenylethane in 11 cc. of *o*-dichlorobenzene was heated at 100° for two hours in a nitrogen atmosphere. A total of 0.685 g. (87 per cent.) of penta-*p*-biphenylethane was recovered; fractional crystallization established the absence of any *s*-tetra-*p*-biphenylethane in the recovered product; from the filtrate 0.005 g. of *s*-tetra-*p*-biphenylethane was isolated.

Formation of Pentaphenylethane from Radicals.—To a mixture of 0.01 mole each of

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[21] DORFMANN, *ibid.*, **57**, 1457 (1935).

triphenylchloromethane and diphenylbromomethane in a 70-cc. glass-stoppered bottle containing 40 cc. of benzene was added 2 cc. of mercury. The air was displaced by nitrogen and the bottle was shaken for one day. The nearly colorless solution was filtered from the mercury and mercurous salts, and the solvent was allowed to evaporate at room temperature. The oil was crystallized by stirring with alcohol and again allowed to evaporate in order to crystallize any triphenylmethyl peroxide which might have been formed. Since the crystalline product was completely soluble in 10 cc. of warm chloroform, the presence of more than traces of the peroxide was excluded; by addition of alcohol a 95 per cent. yield of pentaphenylethane melting at 176–180° was isolated. In another experiment the triphenylchloromethane was first shaken with the mercury for eight hours in order to convert it to triphenylmethyl. Then the diphenylbromomethane was added and the mixture was shaken for thirty-six hours. At the end of the time no radical remained; on working up the mixture an 88 per cent. yield of pure pentaphenylethane (melting point 182–183°) was isolated.

Oxygen Absorption by Pentaarylethanes at 100°.—The apparatus consisted of a 200-cc. round-bottomed flask provided with an interchangeable ground-glass stopper carrying an entrance tube which was connected to a 100-cc. gas burette by heavy rubber tubing. A three-way stopcock in the line provided for evacuating and filling the system with oxygen. The burette was provided with a water jacket and leveling tube by which the system could be maintained at atmospheric pressure throughout the run. The procedure for a typical run was as follows: 25 cc. of redistilled *o*-dichlorobenzene was placed in the absorption flask which was connected to the gas burette, filled with oxygen, and mechanically shaken while completely immersed in a steam cone for twenty minutes; during this period the level of the *o*-dichlorobenzene used as retaining liquid in the gas burette was brought to the 100 cc. mark. The flask was then cooled to room temperature, finally being placed in a large beaker of water until the burette reading (about 45 cc.) became constant; the difference in readings represented the expansion of gas due to the rise in temperature. The flask was now opened; 0.00125 mole of pentaarylethane was introduced and the system was refilled with oxygen. After shaking by hand for a few minutes to saturate the solvent the flask was again placed in the beaker of water and the burette reading was adjusted to the same value as before. Since the increase in volume due to the expansion had just been measured under identical conditions, the initial reading when the flask containing the pentaarylethane solution was at 100° was now known (100 cc.). The flask was now placed in the steam bath and connected to a mechanical shaker operated by a water motor; the steam was turned on, and readings were taken periodically until the rate of absorption became constant, when the flask was removed from the steam bath and cooled as before described. The total absorption was determined from the difference in volume at room temperature and from the difference in volume of the system containing the solvent at 100°; as evidence for the reliability of the method the two usually gave results agreeing to with 0.3 cc. The moles of oxygen absorbed per mole of pentaarylethane were calculated from the measured absorption, the burette temperature and the atmospheric pressure.

Triphenylmethyl-(diphenylmethyl)-peroxide $(C_6H_5)_3C—O—O—CH(C_6H_5)_2$.—A solution of 0.1230 g. (0.03 mole) of pentaphenylethane in 25 cc. of *o*-dichlorobenzene was shaken at 100° in an oxygen atmosphere for twenty minutes. In this time 110 per cent. of the theoretical amount of oxygen was absorbed and the solution acquired a yellow color. The solvent was removed by distillation under reduced pressure at 100°, and the residual oil was taken up in acetone; from the solution 0.060 g. (12 per cent.) of bis-triphenylmethyl peroxide was filtered off. The acetone was allowed to evaporate and the residue was taken up in alcohol; on standing the solution deposited 0.630 g. (48 per cent.) of the unsymmetrical peroxide. Triphenylmethyl-(diphenylmethyl)-peroxide crystallizes from petroleum ether in the form of colorless prisms; melting point 93–94° without decomposition. This unsymmetrical peroxide, in contast to bis-triphenylmethyl peroxide, is very soluble in the usual organic solvents; it gives a yellow color with concentrated sulfuric acid. By carrying out the oxidation with air instead of oxygen a 69 per cent. yield of peroxide was isolated.

Anal. Calc'd for $C_{32}H_{26}O_2$: C, 86.8; H, 5.9.
Found: C, 86.7; H, 6.2.

Cleavage of Peroxide.—A mixture of 0.2210 g. of the aforementioned peroxide, 10 g. of 2 per cent. sodium amalgam, 20 cc. of ether, 30 cc. of benzene and a few drops of absolute alcohol was shaken for twenty-four hours. The reaction mixture was hydrolyzed and the benzene-ether solution was dried, filtered and concentrated. By crystallization of the mixture from carbon tetrachloride a 72 per cent. yield of triphenylcarbinol was obtained; the filtrate gave a 54 per cent. yield of benzohydrol. In a parallel experiment 0.518 g. of bis-triphenylmethylperoxide was shaken with 5 g. of 2 per cent. sodium amalgam in 20 cc. of ether and 30 cc. of benzene. Even after five days 74 per cent. of the peroxide was recovered unchanged; only 19 per cent. of triphenylcarbinol was isolated. It was found that 45 per cent. sodium amalgam cleaves the symmetrical peroxide readily.* When 1.03 g. of triphenylmethyl peroxide was shaken with 45 per cent. sodium amalgam for twenty-four hours and the product was hydrolyzed, 0.975 g. (94 per cent.) of triphenylcarbinol was obtained.

Reaction with Methylmagnesium Iodide.—No gas was evolved when 5 cc. of 0.75 normal methylmagnesium iodide in *n*-butyl ether was added to 0.4262 g. of the unsymmetrical peroxide. Upon heating for forty-five minutes at 100° 88 per cent. of the calculated amount of gas was evolved, assuming the reaction:

$$(C_6H_5)_3C—O—O—CH(C_6H_5)_2+2CH_3MgI\rightarrow(C_6H_5)_3COMgI+(C_6H_5)_2CHOMgI+C_2H_6.$$

The solution, after hydrolysis and removal of the *n*-butyl ether gave 64 per cent. of the theoretical amount of triphenylcarbinol and 59 per cent. of benzohydrol. Bis-triphenylmethylperoxide is not cleaved by the Grignard reagent under these conditions.

Triphenylmethyl-(phenyl-p-biphenylmethyl)-peroxide $(C_6H_5)_3C\text{-}O\text{-}O\text{-}CH(C_6H_5)\text{-}(C_6H_4\text{-}C_6H_5\text{-}p)$.—In twenty minutes at 100° 0.972 g. of the pentaarylethane in 25 cc. of *o*-dichlorobenzene absorbed 130 per cent. of the calculated amount of oxygen. The solvent was removed and the oil was taken up in acetone. Bis-triphenylmethyl peroxide in 9 per cent. yield (0.045 g.) crystallized out. The acetone was removed from the filtrate, and the residue was recrystallized from chloroform-alcohol, from which 0.600 g. (58 per cent.) of the unsymmetrical peroxide was obtained as colorless, rectangular prisms; melting point 129.5–130°. The peroxide gives a brownish-yellow color with concentrated sulfuric acid.

Anal. Calc'd for $C_{38}H_{30}O_2$: C, 88.0; H, 5.8.
Found: C, 88.0; H, 6.0.

Cleavage of Peroxide.—By shaking 0.2590 g. of the aforementioned unsymmetrical peroxide with 2 per cent. sodium amalgam for two days an 84 per cent. yield of triphenylcarbinol and a 41 per cent. yield of 4-phenylbenzohydrol were obtained. The two products were separated by recrystallization from carbon tetrachloride, from which the triphenylcarbinol separated; the *p*-phenylbenzohydrol in the filtrate was recrystallized from benzene and petroleum ether.

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* ZIEGLER AND THIELMANN, *Ber.*, **56B**, 1742 (1923), observed the cleavage of bis-triphenylmethyl peroxide by potassium, giving triphenylcarbinol.

*Triphenylmethyl-(di-*p*-biphenylmethyl)-peroxide* $(C_6H_5)_3C\text{-}O\text{-}O\text{-}CH(C_6H_4\text{-}C_6H_5\text{-p})_2$.—For the preparation of this peroxide fifteen minutes was allowed for the oxidation of 1.404 g. of the pentaarylethane; 116 per cent. of the theoretical amount of oxygen was absorbed. After removal of the solvent and digestion of the product with acetone 0.130 g. of an insoluble material, probably a mixture of the symmetrical peroxide and di-*p*-biphenyl ketone, and 0.815 g. (55 per cent.) of the unsymmetrical peroxide were isolated. Recrystallization from chloroform-alcohol gave colorless crystals of triphenylmethyl-(di-*p*-biphenylmethyl)-peroxide; melting point 148–149°.

Anal. Calc'd for $C_{44}H_{34}O_2$: C, 88.8; H, 5.8.
Found: C, 88.3; H, 6.0.

Cleavage of Peroxide.—A mixture of 0.1919 g. of the aforementioned peroxide, 10 g. of 2 per cent. sodium amalgam, 0.5 cc. of absolute alcohol, 20 cc. of ether and 30 cc. of benzene was shaken for seven days. The reaction mixture was hydrolyzed, the ether-benzene solution was filtered, dried and concentrated. Since the mixture of carbinols could not be separated the solvent was removed and the oil was treated with a solution of 0.09 g. of chromic anhydride in 9 cc. of acetic acid. After standing at room temperature for fifty minutes the mixture was poured into water; the precipitate was extracted with benzene and the solution was concentrated. From the solution 0.0828 g. (76 per cent.) of di-*p*-biphenyl ketone precipitated; from the filtrate 0.0456 g. (54 per cent.) of triphenylcarbinol was isolated.

The peroxide was also cleaved by sulfuric acid. A solution of 0.594 g. in 10 cc. of concentrated sulfuric acid gave a dark-green color which soon changed to orange. The solution was poured into water and extracted with chloroform, using in all 300 cc. The chloroform was removed and the residue dissolved in hot carbon tetrachloride; on cooling 0.225 g. (86 per cent.) of triphenylcarbinol crystallized.

Thermal Decomposition of Peroxide.—The triphenylmethyl-(di-*p*-biphenylmethyl) peroxide (0.3253 g.) was heated in an oil bath at 180° in a nitrogen atmosphere for one hour; from the resulting oil there was isolated 0.0759 g. (41 per cent.) of di-*p*-biphenyl ketone and a trace (0.004 g.) of triphenylcarbinol.

*Diphenyl-*p*-biphenylmethyl-(di-*p*-biphenylmethyl)-peroxide* $(\text{p-}C_6H_5\text{-}C_6H_4)(C_6H_5)_2C\text{-}O\text{-}O\text{-}CH(C_6H_4\text{-}C_6H_5\text{-p})_2$.—From the reaction products obtained by one-hour oxidation of 0.797 g. of the (1,2,2-) ethane there was isolated a trace of di-*p*-biphenyl ketone and 0.400 g. (48 per cent.) of the unsymmetrical peroxide. This peroxide crystallizes from benzene and petroleum ether in colorless prisms; it melts at 161° with decomposition, the melt solidifies and remelts again by 194–197°; the result is probably due to the di-*p*-biphenyl ketone (melting point 236°) formed in the pyrolysis.

Anal. Calc'd for $C_{50}H_{38}O_2$: C, 89.5; H, 5.7.
Found: C, 89.8; H, 5.9.

*Phenyl-di-*p*-biphenylmethyl-(diphenylmethyl)-peroxide* $(C_6H_5)(\text{p-}C_6H_5\text{-}C_6H_4)_2C\text{-}O\text{-}O\text{-}CH(C_6H_5)_2$.—This peroxide was obtained when 1.124 g. (0.002 mole) of the pentaarylethane (1,1-) was heated on a steam bath for thirty minutes, 103 per cent. of the calculated amount of oxygen having been absorbed in this time. From acetone-alcohol 0.77 g. (65 per cent.) of the peroxide crystallized in the form of colorless tetragonal prisms; the pure product melts at 151–152° and gives a wine-red color with sulfuric acid.

Anal. Calc'd for $C_{44}H_{34}O_2$: C, 88.8; H, 5.8.
Found: C, 88.8; H, 6.1.

Cleavage of Peroxide.—For the cleavage 0.2970 g. of the peroxide was shaken with 10 g. of 2 per cent. sodium amalgam, 0.5 cc. of absolute alcohol, 25 cc. each of ether and benzene for five days. The colorless solution was hydrolyzed, filtered and concentrated. The secondary alcohol was dissolved in petroleum ether, leaving the tertiary alcohol as an insoluble residue. Phenyl-di-*p*-biphenylcarbinol was isolated in 89 per cent yield, benzohydrol in 55 per cent yield.

*Tri-*p*-biphenylmethyl-(phenyl-*p*-biphenylmethyl)-peroxide* $(p\text{-}C_6H_5\text{-}C_6H_4)_3\text{-}C\text{-}O\text{-}O\text{-}CH(C_6H_5)(C_6H_4\text{-}C_6H_5\text{-}p)$.—When 1.071 g. of the (1,1,1,2-) pentaarylethane was shaken with oxygen for ten minutes the absorption was 103 per cent.; 0.960 g. (86 per cent.) of the unsymmetrical peroxide was isolated. Recrystallization from chloroform-alcohol gave 0.900 g. (80 per cent.) of colorless needles; melting point 168°. The peroxide gave a purple-red color with concentrated sulfuric acid.

Anal. Calc'd for $C_{56}H_{42}O_2$: C, 90.0; H, 5.7.
Found: C, 90.0; H, 5.9.

Cleavage of Peroxide.—A solution of 0.3730 g. of the peroxide was shaken for fourteen days with 10 g. of 2 per cent. sodium amalgam in 25 cc. each of ether and benzene and 0.5 cc. of alcohol. From a benzene solution 0.1788 g. (73 per cent.) of tri-*p*-biphenylcarbinol was isolated; the filtrate in petroleum ether (60–70°) gave 0.402 g. (31 per cent.) of 4-phenylbenzohydrol.

Oxygen Absorption by Pentaphenylethane at 80° to 105°.—The oxygen absorptions were carried out in a large air thermostat the temperature of which could be maintained constant to within ±0.05°. To obtain consistent rate measurements it was found necessary to allow the thermostat to attain thermal equilibrium before making any runs; at the higher temperatures this required from three to four hours. The absorption vessel and gas burette were the same as previously described for the oxidation of pentaarylethanes at 100°. The flask was held in a metal cup by spring clamps and was shaken at a speed of 700 r. p. m. A short 40–110° thermometer, graduated in fifths of a degree and calibrated against a Bureau of Standards thermometer, was mounted in the box with the bulb about 2 cm. from the absorption flask. The pentaphenylethane was purified by dissolving it in hot benzene (2 cc. per g.) and precipitating it by adding warm alcohol (5 cc. per g.) followed by cooling. The filtered product was dried at room temperature and then for six hours at 100° under reduced pressure. When the pentaphenylethane was recrystallized from chloroform-alcohol, ether or petroleum ether it was impossible to remove the solvent without decomposing the product. *o*-Dichlorobenzene was used as the solvent and as retaining liquid in the burette; the vapor pressure was neglected in the calculations.

Preliminary experiments showed that neither solid pentaphenylethane nor a pyrogallol solution alone absorbs any oxygen at 100°. The procedure for a typical run was as follows, 50 cc. of redistilled *o*-dichlorobenzene was saturated with oxygen (or air) by shaking in the absorption flask at the desired temperature for from ten to fifteen minutes at 100°; then approximately 0.00125 mole of pentaphenylethane, which had been weighed to 0.1 mg. in a small thin-walled glass bulb, was carefully introduced along with several glass chips in the flask and reinserted in the thermostat. After the temperature had again been brought to 100° the flask was gently rocked by rotating the shaker shaft, which extended through the box, and then the system was allowed to stand until the burette reading became constant. In this manner the entire system was at the thermostat temperature and the solvent was saturated with oxygen from the start of the run. When the shaker was started the bulb broke and absorption of oxygen began. The pentaphenylethane dissolved rapidly and the time of solution probably affected only the first few readings. Burette readings were taken at periodic intervals such that there would be from six to ten during the first half of the reaction period. In all runs the burette was filled with oxygen; in this way the partial pressure of oxygen in the absorption flask when air was used remained constant at 0.2 atmos. The only variation for the pyrogallol experiments was the addition of the vacuum-distilled pyrogallol to the solvent at the beginning of the run. The solution of the pyrogallol often required fifteen to thirty minutes. The theoretical oxygen absorption was calculated from the equation,

$$V = (2)\ 152.0\ \frac{w(t + 273)}{b}$$

where w is the weight of pentaphenylethane, t the average temperature of the burette during the run and b is the barometric reading in mm. The factor 2 is used only in those runs with pyrogallol. The factor 152.0 is the value of $760R/M$, where R is the gas constant, 82.07, and M is the molecular weight of pentaphenylethane, 410.4. By subtracting the oxygen absorption from the theoretical absorption the volume yet to be absorbed was obtained; the logarithm of this volume was then subtracted from the logarithm of the theoretical oxygen absorption giving directly $-\log (1 - Z)$. Zero time was determined by extrapolation of the log.-time curve to $-\log (1 - Z) = 0.0$. The results and calculations of a typical run are recorded in Table VIII.

TABLE VIII

TYPICAL DATA OBTAINED IN REPRESENTATIVE EXPERIMENT

Wt. pentaphenylethane, 0.5096 g.; 0.470 g. pyrogallol (3/1); 50 cc. *o*-dichlorobenzene; oxygen pressure, 0.2 atmos.; temp. 99.30°; burette temp., 31.1°; barometer, 735 mm.; theoretical absorption, 64.1 cc.; time correction, for start of run, 0.0 min.

TIME MIN.	BURETTE READING	ABSORPTION (CC.)	YET TO BE ABSORBED	$-\log (1 - Z)$	Z FOUND	Z* CALC'D	DIFF.
0.00	98.4	0.00	64.1	0.0000	0.0000	0.0000	0.000
0.50	93.6	4.8	59.3	0.0338	0.075	0.061	+0.014
1.00	90.3	8.1	56.0	0.0587	0.126	0.119	+0.007
1.50	87.1	11.3	52.8	0.0843	0.176	0.173	+0.003
2.00	84.0	14.4	49.7	0.1105	0.225	0.223	+0.002
2.50	81.1	17.3	46.8	0.1367	0.270	0.271	−0.001
3.00	78.4	20.0	44.1	0.1625	0.312	0.316	−0.004
3.50	75.7	22.7	41.4	0.1899	0.354	0.357	−0.003
4.00	73.2	25.2	38.9	0.2170	0.393	0.397	−0.004
4.50	70.8	27.6	36.5	0.2446	0.431	0.434	−0.003
5.00	68.6	29.8	34.3	0.2716	0.465	0.468	−0.003
6.00	64.5	33.9	30.2	0.3269	0.529	0.531	−0.002
7.00	60.9	37.5	26.6	0.3820	0.585	0.587	−0.002
8.00	57.7	40.7	23.4	0.4377	0.635	0.636	−0.001
9.00	55.0	43.4	20.7	0.4909	0.677	0.679	−0.002
10.00	52.6	45.8	18.3	0.5444	0.714	0.717	−0.003
12.00	48.6	49.8	14.3	0.6516	0.777	0.780	−0.003
14.00	45.6	52.8	11.3	0.7538	0.824	0.830	−0.006
16.00	43.3	55.1	9.0	0.8527	0.860	0.868	−0.008
18.00	41.5	56.9	7.2	0.9496	0.888	0.897	−0.009
20.00	40.1	58.3	5.8	1.0435	0.910	0.920	−0.010

* Z calc'd is from the average rate constant at 99.30°, 0.126; the slope in the above run gave a value of 0.125 for the rate constant.

In the presence of pyrogallol the solution first turned pink and then became a dark brown; at the end of the oxidation considerable amounts of a dark-brown water-soluble precipitate was present. From the combined products of several runs we were able to isolate benzophenone, as the oxime, but we found no triphenylcarbinol. Experiment showed that $(C_6H_5)_3COOH$, the primary oxidation product, undergoes extensive decomposition under the same conditions, yielding a dark-brown precipitate. That the unsymmetrical peroxide is not an intermediate product of the oxidation of pentaphenylethane in the presence of pyrogallol was proved by adding pyrogallol to a solution of pentaphenylethane that had already been oxidized in an oxygen atmosphere at 100°; no absorption of oxygen took place.

SUMMARY

(1) A complete homologous series of pentaarylethanes containing phenyl and *p*-biphenyl groups has been synthesized. These compounds, although possessing a weakened carbon-carbon bond, do not dissociate at an appreciable rate at room temperature.

(2) The successive introduction of biphenyl groups progressively weakens the carbon-carbon bond.

(3) Solutions of pentaarylethanes rapidly absorb oxygen at 80–105°; the principal products are the unsymmetrical peroxides, $R_3C—O—O—CHR_2$, although the oxidation proceeds only through the intermediate formation of triarylmethyl and diarylmethyl radicals.

(4) Pentaarylethanes in solution undergo *reversible* dissociation into free radicals in which the position of equilibrium is practically entirely in favor of the undissociated pentaarylethane.

(5) The rate of dissociation of pentaphenylethane is approximately the same at 100° as that of hexaphenylethane at 0°.

(6) The heat of activation for the dissociation of pentaphenylethane is 27.6 kcal., a value 50 per cent. greater than the corresponding value for hexaphenylethane.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

MOLECULAR REARRANGEMENTS INVOLVING OPTICALLY ACTIVE RADICALS. VI. THE DISPLACEMENT OF HYDROXYL BY CHLORINE IN OPTICALLY ACTIVE 2-METHYL-2-PHENYLBUTANOL-1*

EVERETT S. WALLIS AND PHILIP I. BOWMAN†

Received October 5, 1936

From earlier work carried out in this laboratory[1] the fact has emerged that in certain molecular rearrangements involving optically active radicals, notably of the Curtius, Lossen, and Hofmann types, the optically active group maintains an asymmetric configuration during rearrangement, and undergoes no appreciable racemization during the process. The mechanism of these rearrangements has been the subject of much discussion, and the electronic nature of the migrating group has been variously interpreted.[2] But in certain previous discussions[3] of the views which have been expressed it has been pointed out that the optical stability of such molecules during rearrangement is most easily explained by an electronic mechanism involving the shift of a group with its pair of electrons, and that at no time is the asymmetric carbon atom without its complete octet of electrons. That this electronic viewpoint has certain distinct advantages over the older ionic mechanisms has been shown by certain in-

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[*] Some of the experimental results herein described were discussed in a paper read at the Fifth Organic Chemistry Symposium at Ithaca, New York, December 28–30, 1933. See also Communication to the Editor, *J. Am. Chem. Soc.*, **56**, 491 (1934).

[†] This paper is based upon a thesis submitted by Philip I. Bowman, Harvard Fellow in Chemistry, to the faculty of Princeton University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[1] JONES AND WALLIS, *J. Am. Chem. Soc.*, **48**, 169 (1926); WALLIS AND NAGEL, *ibid.*, **53**, 2787 (1931); WALLIS AND DRIPPS, *ibid.*, **55**, 1701 (1933); WALLIS AND ADAMS, *ibid.*, **55**, 3838 (1933).

[2] STIEGLITZ, *Am. Chem. J.*, **29**, 57 (1903); *J. Am. Chem. Soc.*, **36**, 288 (1914); HESSE, STIEGLITZ, *Am. Chem. J.*, **29**, 56 (1903); JONES, *ibid.*, **50**, 441 (1913); JONES AND WALLIS, ref. 1; WHITMORE, *J. Am. Chem. Soc.*, **54**, 3274 (1932).

[3] WALLIS AND MOYER, *J. Am. Chem. Soc.*, **54**, 3426 (1932); WALLIS AND BOWMAN, *ibid.*, **56**, 491 (1934); WALLIS AND WHITMORE, *ibid.*, **56**, 1427 (1934); SPRUNG AND WALLIS, *ibid.*, **56**, 1715 (1934).

vestigations carried out in this laboratory[4] on an optically active amide (*d*-3,5-dinitro-6-α-naphthylbenzamide), of a sterically hindered biphenyl derivative.

The results of these experiments raised the question as to whether in any rearrangements involving optically active molecules the optical stability of the tercovalent group during the rearrangement is dependent upon its electronic nature. If the migrating group is never completely free, either as a negative, positive or neutral fragment but in some way is always within the influence of the forces within the molecule during the rearrangement process, then it might happen that regardless of the type of rearrangement studied the reaction would take place with no racemization, and the products formed would be always optically active. Facts previously recorded[5] indicate that this is not the case.

In an attempt to obtain further evidence which would throw light on this question Sprung and Wallis[6] made a detailed study of the rearrangements of certain optically active alkyl phenyl ethers. The results of their investigations strongly indicated that a particular electronic arrangement of the migrating group was of fundamental importance in maintaining asymmetry. However, in the discussion of their results they pointed out that a second explanation involving a bimolecular process had to be considered, and that it was possible that the alkyl phenols were not produced from the alkyl phenyl ethers by rearrangement, but by a metathetical reaction involving two molecules of the ether. Evidence that such bimolecular processes have to be considered had already been reported.[7] It seemed necessary, therefore, to continue further our studies in this series in order to obtain added evidence that the electronic arrangement about a group plays a vital rôle in producing optical stability sufficient to maintain an asymmetric configuration during rearrangement processes.

In this paper we wish to describe certain experiments which we have made in a study of a reaction process which, essentially, is closely allied to a Wagner rearrangement, and to discuss the results so obtained in the light of certain views which have been expressed with regard to the mechanism of this rearrangement. It is well known that tertiary butyl compounds are often produced in metathetical reactions involving isobutyl alcohol, and that nitrous acid reacts with tertiary-butyl-methylamine to produce

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[4] WALLIS AND MOYER, ref. 5. See also FRANK BELL, *J. Chem. Soc.*, **1934,** 835.

[5] MCKENZIE, ROGERS AND WILLS, *J. Chem. Soc.*, **129,** 779 (1926); MCKENZIE AND DENNLER, *Ber.*, **60,** 220 (1927); ROGER AND MCKENZIE, *ibid.*, **62,** 272 (1929); KENYON AND PHILIPS, *J. Chem. Soc.*, **133,** 1677 (1930); WALLIS AND ADAMS, ref. 3.

[6] SPRUNG AND WALLIS, ref. 5.

[7] SHORT AND STEWART, *J. Chem. Soc.*, **1929,** 553; SOWA, HINTON, AND NIEUWLAND, *J. Am. Chem. Soc.*, **54,** 2019, 3694 (1932); **55,** 3402, (1933); LAUER AND SPIELMAN, *ibid.*, **55,** 4923 (1933).

dimethylethylcarbinol. Many other reactions of this type are known. The dehydration of isobutyl alcohol to give normal butylene may serve as another example. Applying an electronic mechanism for intramolecular rearrangements first enunciated by Jones[8] and by Stieglitz[8] for rearrangements of organic nitrogen compounds, Whitmore[8] has successfully put many types of rearrangements on a common basis, and has shown how in reactions involving molecules of the type, $:\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}:$, the products formed may be (1) normal, (2) abnormal, (3) olefinic. In the light of what has been written above it is of interest to know the nature of the products formed when a substitution reaction is carried out on this type of molecule in which atom "A" is asymmetric. Such knowledge would give us a more definite answer to the question of the optical stability of tercovalent groups during rearrangement processes; for in this type of compound the migration of a group attached to "A" with its electron pair leaves the asymmetric carbon atom, "A", with only a sextet of electrons, as contrasted with other rearrangements of the Hofmann type, studied in this laboratory, in which the asymmetric carbon atom appears to be at no time during the rearrangement process without its octet of electrons.

Accordingly we prepared *l*-2-methyl-2-phenylbutanol-1, $CH_3CH_2C(CH_3)(C_6H_5)CH_2OH$, ($[\alpha]^{19}_{5893} = -4.90$, without solvent). A study was made of the products formed when this compound was allowed to react with thionyl chloride. It was expected on the basis of the conceptions of molecular rearrangements outlined above that the replacement of the hydroxyl group by chlorine would lead to both (a) "abnormal" products resulting from rearrangement and (b) to olefine compounds, inasmuch as it is well known that the tendency to rearrange increases with the number of carbon atoms directly attached to "A". This was found to be the case. No detectable amount of the primary chloride, *l*-1-chloro-2-methyl-2-phenylbutane, $C_2H_5C(CH_3)(C_6H_5)CH_2Cl$, was found in the reaction products. The unsaturated hydrocarbon which was produced was identified as 1-phenyl-2-methylbutene-1, $C_2H_5C(CH_3){=}CHC_6H_5$, showing that rearrangement took place with migration of the phenyl group. The halide formed was a tertiary chloride, $C_2H_5C(CH_3)(CH_2C_6H_5)Cl$. The corresponding tertiary carbinol, 1-phenyl-2-methylbutanol-2, was produced in small amounts as a result of partial hydrolysis which occurred in working up the products of the reaction. A quantitative analysis of the products showed no primary chloride, 31.3 per cent. tertiary chloride, 59.1 per cent. unsaturated hydrocarbon, and 9.6 per cent. tertiary carbinol (by difference). Both the tertiary chloride, and the corresponding carbinol pos-

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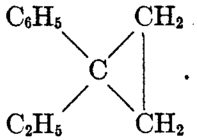
[8] JONES, ref. 4; STIEGLITZ, ref. 4; WHITMORE, ref. 4.

sessed optical activity, although partial racemization occurred during the reaction. It was also observed that an inversion in sign of the rotatory power took place during the rearrangement since the lævorotatory alcohol, α_{5893}^{19} -4.90 (without solvent, 1-dm. tube), yielded a dextrorotatory rearrangement product, α_{5893}^{18} $+0.63$ (without solvent, 1-dm. tube). Conversion of a portion of the chloride obtained in the reaction to the carbinol by hydrolysis with aqueous silver nitrate increased the positive rotatory power of the material, α_{5893}^{19} $+0.88$ (without solvent, 1-dm. tube); the presence of any primary chloride would have decreased this value by yielding lævorotatory primary alcohol.

These facts are pertinent when viewed in the light of certain theories which have been proposed to explain the mechanism of this type of rearrangement. They are not in agreement with the hypothesis upheld by Ruzicka[9] to explain the mechanism of the rearrangement which takes place in the dehydration of tertiary alkyl carbinols. This hypothesis postulates the intermediate closure of a cyclopropane ring, and then its rupture in a different position so that the radical which supplies the hydrogen for elimination as water, or in this case as hydrogen chloride, is the radical which migrates to the adjoining carbon atom. In the reaction under discussion it is the phenyl group which migrates, and not one of the alkyl groups. The fact that the products of the rearrangement possess optical activity also precludes the intermediate formation of cyclopropane rings of the type,



Ionic hypotheses[10] are not excluded by the above facts if we assume that carbonium ions can have an independent existence without loss of optical activity. This assumption has been made by McKenzie, Roger and Wills[11] to explain the retention of optical activity during the "semipinacolenic deamination of certain amino alcohols." It was also discussed as a possible explanation of the results obtained in the early work in this laboratory[12] on molecular rearrangements involving optically active radicals. However, in the light of more recent experimental studies on the

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[9] RUZICKA, *Helv. Chim. Acta*, **6**, 267 (1923).

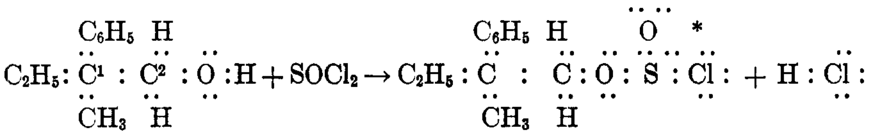
[10] MEERWEIN AND WORTMEN, *Ann.*, **435**, 190 (1924).

[11] McKENZIE, ROGER, AND WILLS, ref. 7.

[12] JONES AND WALLIS, ref. 3.

spatial configuration of the valences in tercovalent compounds[13] it seems very doubtful that one is dealing with true carbonium ions. Application of the newer theoretical methods[14] of considering such systems also leads to the conclusion that such ions are not likely to be formed. It is imperative that one take into account the energy required to break the bonds in these molecules. In molecular rearrangements which proceed at room temperature it is improbable that the molecules are sufficiently "energy-rich" to allow dissociation into either ions or radicals. Therefore it seems reasonable to regard them as intramolecular processes.

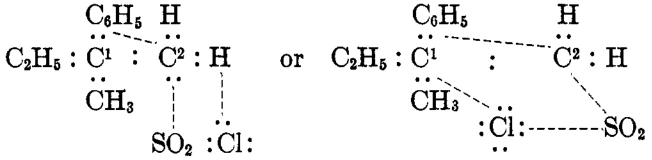
It seems to us that in the particular reaction under discussion the facts may be easily explained on the basis of an electronic mechanism of intramolecular rearrangements involving the essential ideas put forward by Whitmore[15] for reactions involving molecules of the type $:\underset{..}{\overset{..}{A}}:\underset{..}{\overset{..}{B}}:\underset{..}{\overset{..}{X}}:$. With the aid of this concept the reaction may be formulated as follows:



$$C_2H_5:\underset{CH_3}{\overset{C_6H_5}{C^1}}:\underset{H}{\overset{H}{C^2}}:\underset{..}{\overset{..}{O}}:H + SOCl_2 \rightarrow C_2H_5:\underset{CH_3}{\overset{C_6H_5}{C}}:\underset{H}{\overset{H}{C}}:\underset{..}{\overset{..}{O}}:\overset{O^{*}}{S}:\underset{..}{\overset{..}{Cl}}: + H:\underset{..}{\overset{..}{Cl}}:$$

II

Compound II undergoes decomposition and rearrangement. At the moment when sulfur dioxide begins to be removed from the molecule the approximate picture of the system must be much like that indicated in one of the following diagrams, depending on the position of the chlorine atom.



Dotted lines indicate the more important partial valences which influence the rearrangement. Electronically this corresponds to the system $:\underset{..}{\overset{..}{A}}:\underset{..}{\overset{..}{B}}:$ discussed by Whitmore. With the removal of sulfur dioxide there is a simultaneous migration of an electron pair with its attached phenyl group

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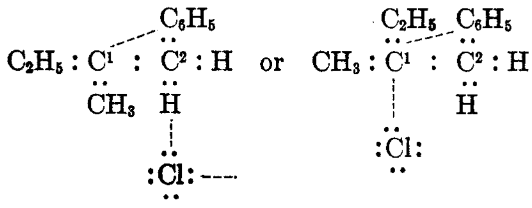
[13] WALLIS AND ADAMS, ref. 3.

[14] EYRING, *J. Chem. Phys.*, **3**, 107 (1934); WALLIS AND MOYER, ref. 5.

[15] WHITMORE, ref. 4.

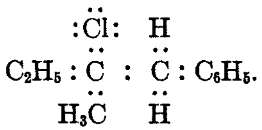
* In some reactions of thionyl chloride on alcohols, compounds of this type have actually been isolated.

from carbon atom (1) to carbon atom (2). In this process the phenyl group does not leave the molecule's sphere of influence. No ions are formed. The system may now be illustrated as:



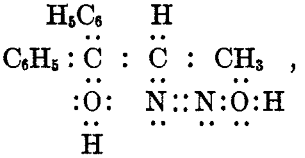
$$\begin{array}{ccccc} & & & C_6H_5 & \\ & & & \cdot\cdot & \\ C_2H_5: & C^1 & : & C^2 & :H \\ & \cdot\cdot & & \cdot\cdot & \\ & CH_3 & & H & \\ & & & \vdots & \\ & & & :\ddot{\underset{\cdot\cdot}{Cl}}:--- & \end{array} \quad \text{or} \quad \begin{array}{ccccc} & C_2H_5 & & C_6H_5 & \\ & \cdot\cdot & & \cdot\cdot & \\ CH_3: & C^1 & : & C^2 & :H \\ & \vdots & & \cdot\cdot & \\ & \vdots & & H & \\ & :\ddot{\underset{\cdot\cdot}{Cl}}: & & & \end{array}$$

with the remaining partial valence of the chlorine taken up by the departing molecule of sulfur dioxide. Electronically this is essentially $:\ddot{A}:\underset{\cdot\cdot}{\ddot{B}}:$, and can stabilize itself, with loss of a proton, to yield 1-phenyl-2-methylbutene-1, $C_2H_5{:}\underset{H_3C}{\underset{\cdot\cdot}{C}}{::}\underset{H}{\underset{\cdot\cdot}{C}}{:}C_6H_5$, or by addition of an electron pair from the adjacent chlorine to give, 1-phenyl-2-chloro-2-methylbutane,



$$\begin{array}{ccccc} & :\ddot{Cl}: & & H & \\ & \cdot\cdot & & \cdot\cdot & \\ C_2H_5: & C & : & C & :C_6H_5. \\ & \cdot\cdot & & \cdot\cdot & \\ & H_3C & & H & \end{array}$$

Such a concept can be applied equally well to the deamination of amino alcohols. In this it is the compound,



$$\begin{array}{ccccc} & H_5C_6 & & H & \\ & \cdot\cdot & & \cdot\cdot & \\ C_6H_5: & C & : & C & :\ CH_3\ , \\ & \cdot\cdot & & \cdot\cdot & \\ & :\underset{\cdot\cdot}{O}: & & \underset{\cdot\cdot}{N}{::}\underset{\cdot\cdot}{N}{:}\underset{\cdot\cdot}{\dot{\dot{O}}}{:}H & \\ & H & & & \end{array}$$

which undergoes decomposition and intramolecular rearrangement. It is of special interest to note that in both instances the process is accompanied by partial racemization, and by an inversion in the sign of the rotatory power. It can be stated, therefore, that regardless of the mechanism by means of which the rearrangement takes place the action of thionyl chloride on *l*-2-methyl-2-phenylbutanol-1 constitutes added evidence that in rearrangements involving optically active molecules the stability of the asymmetric tercovalent group during the process is dependent on its electronic nature, and that in rearrangements of the above type the asymmetric group possesses a stability far less rigid than in rearrangements of the Hofmann, Curtius, Lossen type, in which the process takes place with no detectable racemization and with no inversion in sign.

In conclusion we wish to state that the facts obtained in the study of this reaction also have an important bearing in all investigations on the study of configurational relationships of organic compounds. It can no longer be taken for granted that in substitution reactions of the above type the products formed are configurationally related to the original material. The asymmetric carbon atom may very well become involved in such reactions, and although the products are optically active this in itself is no criterion that the molecule has not undergone a complete structural change.

EXPERIMENTAL PART

Preparation of the Methyl Ether of 2-Phenylbutanol-2, $C_2H_5\text{-}C(CH_3)(C_6H_5)(OCH_3)$.—Methylethylphenylcarbinol was prepared by the action of ethylmagnesium bromide on acetophenone; yield of carbinol, 88.06 per cent. theoretical; b. p., 85–88° at 2–3 mm.[*] A solution of 61.20 g. of the carbinol in 100 ml. of ethyl alcohol, and 3.6 ml. of concentrated sulfuric acid was allowed to stand overnight. It separated into two layers upon addition of water. The product of the reaction was dissolved in ether, and the ether extract was washed with sodium carbonate solution. The dried solution was evaporated, and the residue was distilled under diminished pressure; yield, 53 g. (79.21 per cent. theoretical yield); b. p. 63–65° at 2–3 mm.

Preparation of 2-Methyl-2-phenylbutanoic Acid, $C_2H_5\text{-}C(CH_3)(C_6H_5)COOH$.—This acid was prepared from the above ether according to a method described by Conant and Carlson[16] for the preparation of 2-methyl-2-phenyl-*n*-caproic acid. Fifty grams of the ether gave 23.4 g. of an acid (43.12 per cent. theoretical) of b. p. 136–137° at 2–3 mm.; m.p. 57–58°.[†] A study of the nature of the by-products was made in another experiment on the preparation of this acid. 2-Phenylbutane was isolated, b.p. 173–174° at 760 mm.[‡] This compound is formed whenever any moisture is present to react with the red potassium alkyl.

Resolution of 2-Methyl-2-phenylbutanoic Acid.—The acid was resolved by fractional crystallization of its quinine salt. One hundred ten grams of the acid and 203.5 g. of quinine were dissolved in 700 ml. of hot alcohol and filtered. Sufficient water was added to the filtrate to cause a turbidity, which was dispelled by the addition of alcohol. Three crystallizations gave a salt which, upon decomposition with 10 per cent hydrochloric acid at 0° yielded an acid of the following specific rotation in benzene: $[\alpha]^{20}_{D}$ $-$ 23.28. Neutralization equivalent calculated for $C_{11}H_{14}O_2$, 178.11; found, 178.39.

Preparation of l-*2-Methyl-2-phenylbutyramide,* $C_2H_5C(CH_3)(C_6H_5)CONH_2$.—Twenty-one grams of the above acid dissolved in 40 ml. of benzene was treated with 55.6 g. of thionyl chloride. The mixture was refluxed on the water bath for one hour. Excess thionyl chloride was removed at reduced pressure. The acid chloride

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[*] TIFFENEAU, *Ann. chim. phys.*, [8], **10**, 362, gives b. p. 103–104° at 16 mm.; INGLIS, *J. Chem. Soc.*, **99**, 540, (1911), reports b. p. 106.5° at 15 mm.

[16] CONANT AND CARLSON, *J. Am. Chem. Soc.*, **54**, 4054 (1932).

[†] BLONDEAU, *Compt. rend.*, **174**, 1424–26 (1922), reports m.p. 60° for this acid prepared by a different method.

[‡] KLAGES, *Ber.*, **35**, 3509 (1902), reports b.p. 173–174° at 760 mm.

so formed was added slowly to 200 ml. of concentrated ammonium hydroxide solution at 0°. The precipitated amide was purified in the usual manner. Two recrystallizations from petroleum ether (60–65°) gave a product which melted at 64.0–64.6°,* and had the following specific rotation in benzene solution: $[\alpha]^{20}_{5893}$ − 14.90.

Preparation of l-2-Methyl-2-phenylbutanol-1, $C_2H_5C(CH_3)(C_6H_5)CH_2OH$.—Six grams of *l*-methylphenylbutyramide was thoroughly desiccated in a vacuum over phosphorous pentoxide for 24 hours. Absolute ethyl alcohol (58.9 g.), prepared from ordinary absolute alcohol (99.5–99.8 per cent.) by refluxing with one-twentieth of its weight of sodium metal for one hour, was distilled directly from the sodium ethylate into a 500-ml. Pyrex three-necked flask containing the dry amide. The flask was fitted with a large water-cooled condenser (106 cm. long, with 16 mm. internal diameter condenser tube) and a thermometer. With the temperature of the reaction mixture at 80° (oil bath), 9.3 g. (three times theoretical equivalent) of carefully cleaned sodium metal was added all at once through the top of the condenser. During the violent reaction the temperature rose to 95°. Throughout the following half-hour period it was maintained at 100–103°. Excess sodium was decomposed at 95° by addition of alcohol. To the cooled reaction mixture was added sufficient water to dissolve the sodium ethylate. The ethyl alcohol was removed by distillation. The product was extracted from the remaining alkaline water solution with ether, and was freed from amines by washing, first with dilute hydrochloric acid, and then with sodium carbonate solution. The ether extract was dried over sodium sulfate, and the ether was removed at reduced pressure. Distillation of the residue gave 3.80 g. (68.4 per cent. theoretical yield) of product of the following physical properties: b.p. 123–125° at 12–13 mm.; m.p. of benzoyl derivative, 46–46.2°; observed rotation in 1 dm. tube at 19°, without solvent:† α_{6563} − 4.20°; α_{5893} − 4.90°; α_{5463} − 5.78; α_{4861} − 7.35; α_{4358} − 9.6.

Experiments on the Action of Thionyl Chloride on l-2-Methyl-2-phenylbutanol-1.—(*A*) Formation of 2-methyl-1-phenylbutene-1, $C_2H_5C(CH_3){=}CHC_6H_5$: A qualitative study of this reaction indicated that an unsaturated hydrocarbon was produced as one of the products. The following experiment was made to determine its structure. Ten grams of thionyl chloride was added at 0° over a period of twenty minutes to 5.4 g. of *l*-2-methyl-2-phenylbutanol-1. The mixture was allowed to stand overnight, and then refluxed for thirty minutes. On cooling, it was poured on ice. The product was extracted with ether and washed. The dried ether solution was evaporated. Qualitative experiments showed that the residue contained halides and unsaturated compounds. It was also found that the halide gave an immediate precipitate with either aqueous or alcoholic silver nitrate solution, that it was hydrolyzed by dilute sodium carbonate solution, and that it lost hydrogen chloride either on heating at atmospheric pressure or on refluxing with pyridine.

Distillation of the residue at reduced pressure gave (*a*) 2.7 g. of material, b.p. 87–89° at 13 mm., and (*b*) 1.1 g., b.p. 90–95° at 13 mm. Fraction (*a*) was refluxed with five times its weight of pyridine for one hour. The product was poured on ice, and after acidifying with hydrochloric acid was extracted with ether. The hydro-

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* Ramart and Amagat, *Ann. chim.*, [10], **8**, 276 (1927), report m.p. 85–86° for the racemic amide.

† Blondeau, *Compt. rend.*, **174**, 1424 (1922), reports b.p. 138° at 23 mm; m.p. of benzoyl derivative 46° for the racemic modification.

carbon obtained from the ether extracts boiled at 205° (corr.).* Its nitrosyl chloride derivative was prepared by dissolving the unsaturated hydrocarbon in ethyl nitrite and adding an equivalent amount of acetyl chloride at $-10°$. The mixture was allowed to stand for thirty minutes. On addition of alcohol a crystalline powder separated; this was filtered and washed with absolute ether. Recrystallization gave a product which melted at 105.7–106°.†

Anal. Calc'd for $C_{11}H_{14}ClNO$: C, 62.43; H, 6.62.
Found: C, 62.42; H, 6.81.

(*B*) Quantitative determination of the course of the rearrangement: Three and a half grams of *l*-2-methyl-2-phenylbutanol-1 was treated at 0° over a period of one-half hour with 7.0 g. of thionyl chloride. The mixture was held at room temperature for thirty minutes, then warmed to 80–85° for an equal period, and finally held at room temperature for another half-hour period. The reaction product was poured on ice, extracted with ether, washed with 10-ml. portions of 5 per cent. sodium bicarbonate solution and of water. It was dried over sodium sulfate, filtered through animal charcoal, and the ether was removed at reduced pressure. The residue gave the following rotation at 18° without solvent in a 1-dm. tube: α_{6563} + 0.49; α_{5893} + 0.63; α_{5463} + 0.75. A quantitative analysis was made of this material.

(*1*) Analysis for tertiary chlorides: Two methods of analysis were used for the determination of the total amount of chlorine present. The results obtained were as follows: Carius method, 6.16 per cent.; Schultz method, 6.15 per cent.[17] The amount of chlorine present as tertiary halide was determined by precipitation with aqueous silver nitrate at room temperature; 0.3006 g. of sample gave 0.0724 g. of AgCl, or 5.96 per cent. chlorine as tertiary halide. Therefore, within the experimental error all the chlorine was present as tertiary halide. This corresponds to 31.3 per cent. 1-phenyl-2-chloro-2-methylbutane.

(*2*) Determination of the percentage of unsaturated hydrocarbons: A method of analysis previously described by McIlhiney[18] was used in these analyses. The analytical results were as follows: titration with bromine in carbon tetrachloride (0.3 *N*), addition of potassium bromate, then potassium iodide, and back-titration with sodium thiosulfate (0.08820 *N*) gave, as an average of three determinations, 59.10 per cent. unsaturated hydrocarbon.

In our qualitative experiments described in (*A*), it was found that the halide present was hydrolyzed by sodium bicarbonate solution. In working up the products of the reaction in (*B*), it was necessary to wash the material thoroughly with 5 per cent. bicarbonate solution and water. Partial hydrolysis of the halide took place at this point. The analytical data described above indicate that the percentage of carbinol so formed (obtained by difference) was approximately 10 per cent.

(*C*) Change in value of the optical rotatory power with hydrolysis of 1-phenyl-2-chloro-2-methylbutane to the corresponding carbinol: A sample of material obtained in (*B*), α^{18}_{5893} + 0.63, was dissolved in acetone and hydrolyzed with aqueous silver nitrate. On working up the material a product was obtained which gave the following rotation at 19° in a 1-dm. tube without solvent: α_{5893} + 0.88.

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* Franke and Stern, *Monatsh.*, **49**, 21–6 (1928), report b.p. 205–206° for 2-methyl-1-phenylbutene-1 (prepared by another method).

† This shows that the hydrocarbon was not 3-phenylpentene-2. Klages, *Ber.*, **36**, 3692 (1903), reports that this hydrocarbon boils at 197–8° at 753 mm., but that it gives a nitrosyl chloride derivative which melts at 117°.

[17] Schultz, *Ber.* **17**, 1695 (1884); see also Cohen *et al.*, *J. Chem. Soc.*, **97**, 1625 (1910).

[18] McIlhiney, *J. Am. Chem. Soc.*, **21**, 1084 (1899).

CONCLUSIONS

The reaction of thionyl chloride with *l*-2-methyl-2-phenylbutanol-1 has been studied quantitatively.

Unsaturated and rearrangement products have been identified.

Optical activity is maintained during rearrangement, but with partial racemization and inversion in sign.

An interpretation of the experimental results based on modern electronic theories of intramolecular rearrangements is advanced.

The bearing of these results on studies of configurational relationships is indicated.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

THE PEROXIDE EFFECT IN THE ADDITION OF REAGENTS TO UNSATURATED COMPOUNDS. XIII. THE ADDITION OF HYDROGEN BROMIDE TO BUTADIENE*

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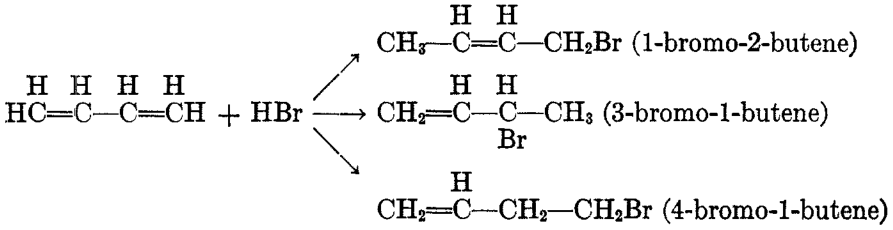
INTRODUCTION

It has been proved that the presence or absence of peroxides in the reaction mixture exercises an important effect on the direction of addition of hydrogen bromide to certain ethylene derivatives.[1] Further study[2] has shown that this effect appears only when the double bond in question is terminal. These observations have naturally made it necessary to reinvestigate, under rigidly controlled conditions, the addition of hydrogen bromide to conjugated systems. 1,3-Butadiene was selected for study because it is the simplest symmetrical diene, and because *a priori* the difficulties involved in the analysis of the reaction product seemed less formidable for this than for any other conjugated system.

From structural considerations, it is obvious that the addition of one molecule of hydrogen bromide to butadiene may result in any or all of three bromobutenes:



$$\overset{H}{H C}=\overset{H}{C}-\overset{H}{C}=\overset{H}{C H} + HBr \longrightarrow$$

$$CH_3-\overset{H}{C}=\overset{H}{C}-CH_2Br \text{ (1-bromo-2-butene)} \qquad I$$

$$CH_2=\overset{H}{C}-\overset{H}{\underset{Br}{C}}-CH_3 \text{ (3-bromo-1-butene)} \qquad II$$

$$CH_2=\overset{H}{C}-CH_2-CH_2Br \text{ (4-bromo-1-butene)} \qquad III$$

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* This work is an abstract, in part, of a dissertation submitted by Elly T. Margolis to the Faculty of the Graduate School of The University of Chicago in partial fulfilment of the requirements for the degree of Doctor of Philosophy. A preliminary note appeared in the *J. Soc. Chem. Ind.*, **55**, 663 (1936).

[1] KHARASCH AND CO-WORKERS, *J. Am. Chem. Soc.*, **55**, 2468, 2521, 2531 (1933); **56**, 244, 712, 1212, 1243, 1642, 1782 (1934); **57**, 2463 (1935); **58**, 57 (1936).

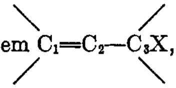
[2] KHARASCH AND M. C. MCNAB, *J. Soc. Chem. Ind.*, **54**, 989–990 (1935); KHARASCH AND KLAAS, unpublished work; KHARASCH AND WALKER, unpublished work.

Of these, I (crotyl bromide) should occur in two dimeric, and II in two enantiomorphic forms.

We have found that in the absence of oxygen and peroxides, and in the presence of an antioxidant, butadiene adds hydrogen bromide at low temperatures to give, principally, II by 1,2 addition. At higher temperatures under the influence of hydrogen bromide, and particularly under the combined influence of hydrogen bromide and peroxides, this product rearranges to I. The addition product obtained in the presence of air or added peroxides is principally I (crotyl bromide). Evidence to show whether peroxides cause direct formation of crotyl bromide by 1,4 addition of hydrogen bromide to butadiene, or merely rearrange the 1,2 addition product is lacking. All that can be said with assurance is that in the absence of peroxides 1,4 addition does not occur. A careful but unsuccessful search was made for the third possible addition product, III. Two independent analytical methods indicate that not more than 5 per cent. of this substance could have been present in our reaction products.

PREVIOUS WORK

There is a widespread impression that butadiene adds reagents in the 1,4 positions.[3] The addition of bromine to this substance has been studied extensively, and, in view of the fact that our results bear also upon this reaction, it will be discussed in some detail. As early as 1894, Griner[4] reported that when bromine is added to a chloroform solution of butadiene at −21°, the addition product is 3,4-dibromo-1-butene. He noted also that this compound when heated to 100° rearranges to 1,4-dibromo-2-butene. Farmer, Lawrence, and Thorpe[5] confirmed Griner's observations. They obtained a mixture of these two dibromobutenes by addition of bromine to butadiene, and they further state that either of the two dibromides rearranges to an equilibrium mixture containing 20 per cent. of 3,4-dibromo-1-butene and 80 per cent. of 1,4-dibromo-2-butene. Equilibrium is attained slowly at room temperature but rapidly at higher temperatures. These findings, they point out, are in accord with the generalization of Gillet,[6] whom they quote and interpret as follows:



"'If in the system $C_1{=}C_2{-}C_3X$, the total effect of the radicals saturating C_3 is strongly negative in comparison with that of the groups saturating C_1, the most negative radical attached to C_3 tends to migrate to C_1 . . . . If one compares the compound $CH_2{=}CH{-}CHBrCH_2Br$ with the examples cited, (examples which follow

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[3] *Cf.* Thiele, *Ann.*, **306**, 87 (1899).

[4] Griner, *Compt. rend.*, **117**, 553 (1893).

[5] Farmer, Lawrence and Thorpe, *J. Chem. Soc.*, **1928**, 729.

[6] Gillet, *Bull. soc. chim. Belg.*, **31**, 365 (1922).

the rule) it is found to be in the same category and should very easily undergo, under the influence of traces of acid, the transformation $CH_2{=}CH{-}CHBr{-}CH_2Br \rightarrow CH_2BrCH{=}CH{-}CH_2Br$. Thus in effect two forms are obtained by combining one molecule of bromine with one molecule of butadiene, the second form predominating.' Addition is therefore regarded as taking place at one double bond, the apparent 1:4 addition being sufficiently explained by including the 1:2 dibromide in the category of substances subject to 'negative' migration."

Farmer, Lawrence, and Thorpe point out that the problem is not as simple as Gillet supposed, for the rearrangement is reversible, and the amount of dibromide obtained in some solvents is far more than can be accounted for by rearrangement at the reaction temperature. They also state that the hydrogen bromide which inevitably appears during the bromination of butadiene catalyzes the rearrangement. Careful scrutiny of their paper fails to reveal any unequivocal evidence in support of this statement. By analogy between this addition and that of hydrogen bromide to butadiene, it now seems highly probable that at low temperatures the important catalyst in the rearrangement is not hydrogen bromide alone but hydrogen bromide plus peroxides (oxygen).

The above remarks are equally pertinent to the observations of Prévost[7] on the addition of bromine to 1,1,4,4-tetramethylbutadiene. He obtained a mixture of liquid and solid dibromides which solidified rapidly; the 1,2 dibromide is a liquid, the 1,4 dibromide a solid.

Several workers have reported on the addition of hydrogen bromide to butadiene[8], but they were unaware of the easy isomerization of the addition products; hence their work need not be discussed here. Similar objections may be raised to the methods used in the preparation of the bromobutenes from the corresponding alcohols.[9]

Our investigation was greatly facilitated by the work of Young and Winstein.[10] These investigators showed that 3-bromo-1-butene (II) and 1-bromo-2-butene (I) are partially interconvertible. Each yields an equilibrium mixture containing 15 per cent. of II and 85 per cent. of I. The data of Young and Winstein, besides furnishing important physical constants of the two bromides, show the necessity for the low-temperature technique which we had already adopted in the distillation of the mixture formed by the addition of hydrogen bromide to butadiene.

ADDITION OF HYDROGEN BROMIDE TO BUTADIENE

The technique and precautions necessary to obtain the results here recorded and the constants needed for the analysis of the reaction products

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[7] Prévost, *Compt. rend.*, **184**, 1460 (1927).

[8] Ipatiew, *J. prakt. Chem.*, [2], **67**, 420 (1903); *D. R. P.*, 522, 650.

[9] Charon, *Ann. chim. phys.*, 7, 17, 232 (1899); Baudrenghien, *Bull. soc. chim. Belg.*, **31**, 160 (1922); Gredy and Piaux, *Bull. soc. chim.*, [5], **1**, 1481 (1934).

[10] Young and Winstein, *J. Am. Chem. Soc.*, **57**, 2013 (1935); **58**, 104 (1936).

are described in the experimental part. Data supporting the claim that no appreciable quantities of 4-bromo-1-butene (III) appear in the reaction products are also given there.

Table I shows the results obtained when hydrogen bromide is added to butadiene *in vacuo* and in the presence of antioxidants. At −78° about 80 per cent. of the product is *3-bromo-1-butene* (II). Around 0°, the yield of this product decreases to 60–70 per cent.; at room temperature still less is obtained. These results indicate that the primary product of the uncatalyzed reaction is 3-bromo-1-butene (II, formed by 1,2 addition), and that under the experimental conditions, the amount of rearrangement of this bromide to 1-bromo-2-butene (I) depends either upon the temperature, or, more probably, upon the increased activity at higher temperatures of minute amounts of peroxides present in butadiene.

TABLE I

ADDITION OF HYDROGEN BROMIDE TO BUTADIENE IN VACUO AND IN THE PRESENCE OF ANTIOXIDANTS

ANTIOXIDANT[a]	REACTION		YIELD[b] BROMOBUTENES (%)	COMPOSITION OF BROMOBUTENE MIXTURE			
	Temp. (°C.)	Time (hours)		(By n_D^{23})		(By d_4^{25})	
				1-Br-2-butene (%)	*3-Br-1-butene* (%)	*1-Br-2-butene* (%)	*3-Br-1-butene* (%)
Diphenylamine[c]	−78	1	65	10	90		
Diphenylamine[c]	−78	2	76	10	90		
Diphenylamine	−78	3	82	19	81	10	90
Hydroquinone	−78	18	89	18	82	14	86
Diphenylamine	−12 −78	1.5 15	78	28	72	18	82
Diphenylamine	−12	2	85	25	75	18	82
Thiophenol[d]	−12	4	92	31	69	26	74
Thiophenol	−12	4	90	21	79	20	80
Diphenylamine[e]	−12	4	>70	35	65	35	65
Diphenylamine[e]	−12	4	>80	31	69		
Diphenylamine	0	1.5	90	38	62	36	64
Diphenylamine	0	1.5	93	29	71	29	71
Diphenylamine	room	1.5	92	56	44	54	46

[a] Quantities given in experimental part.

[b] On initial butadiene, after first distillation to remove free hydrogen bromide and part of unchanged butadiene.

[c] Distilled only once before analysis by index of refraction.

[d] Distilled three times before analysis by index of refraction.

[e] Hydrogen bromide added very slowly in special apparatus described in experimental part.

Table II shows that more 1-bromo-2-butene (I) is obtained under corresponding conditions (*cf.* Table I) in the presence of air or when the antioxidant is replaced by an "added" peroxide. At −78°, about 40 per cent., at −15°, about 70–80 per cent., of I is obtained. As in the case of the antioxidant experiments *in vacuo*, the proportion of 1-bromo-2-butene increases with temperature, but we are unable to state the precise cause of this change. It may be due either to a direct or an indirect effect. That is, the peroxide may produce a 1,4 instead of a 1,2 addition, or it may catalyze the isomerization of the 1,2-addition product first formed. More crotyl bromide than corresponds to the equilibrium mixture (85 ± 5 per cent.) was not found in any experiment.

TABLE II

ADDITION OF HYDROGEN BROMIDE TO BUTADIENE IN THE PRESENCE OF AIR AND PEROXIDES

PEROXIDE[a]	REACTION		YIELD[b] BROMOBUTENES (%)	COMPOSITION OF BROMOBUTENE MIXTURE			
	Temp. (°C.)	Time (hours)		(By n_D^{23})		(By d_4^{25})	
				1-Br-2-butene (%)	*3-Br-1-butene* (%)	*1-Br-2-butene* (%)	*3-Br-1-butene* (%)
Ascaridole[c]	−78	1	71	41	59		
Ascaridole[c]	−78	2	96	44	56		
Ascaridole	−12	2	93	78	22	74	26
Benzoyl peroxide	−12	3.5	85	77	23	71	29
Ascaridole	−12	3		81	19		
None	−12	3.5	82	73	27	56	44

[a, b, c] Have the same significance as in Table I.

TABLE III

EFFECT OF HYDROGEN BROMIDE AND PEROXIDES ON MIXTURES OF 1-BROMO-2-BUTENE AND 3-BROMO-1-BUTENE.

ADDENDA	TEMP.	TIME	n_D^{23} INITIAL	n_D^{23} FINAL	CONCLUSIONS
Ascaridole	−12°	4 hr.	1.4666	1.4666	No effect
Ascaridole and HBr	−12°	4 hr.	1.4666	1.4778	Converted to equilibrium mixture
HBr alone	−12°	4 hr.	1.4644	1.4666	Slight effect
HBr alone	30–45°	5 min.	1.4671	1.4771	Converted to equilibrium mixture

Table III shows the remarkable effect of hydrogen bromide and peroxides in rearranging 3-bromo-1-butene (more correctly a mixture of 70 per cent. of II and 30 per cent. of I) to the equilibrium mixture (15 per cent. II and 85 per cent. I).

Thus, at −12° ascaridole alone has no effect on the rearrangement; hydrogen bromide alone has a slight effect; but the two reagents together cause rapid isomerization. No undue importance should be attached to the time interval of four hours, for equilibrium by isomerization may have been attained in less time. The action of hydrogen bromide at 30–45° may be an effect *per se*; more probably what is observed is the combined isomerizing effect of hydrogen bromide plus minute, yet significant, quantities of peroxides. This latter suggestion is in harmony with all our knowledge of the relationship between temperature and peroxide (oxygen) effect.

The rate of introduction of hydrogen bromide into butadiene is of minor importance. Table I shows that when hydrogen bromide was added to butadiene very slowly (3–4 hours) so as to retard the addition reaction the results were the same as when theoretical quantities of butadiene and hydrogen bromide were brought to the reaction temperature in a few minutes. The addition of hydrogen bromide to butadiene, in contrast to some other unsaturated compounds, is very rapid (almost instantaneous) even at low temperatures.

ADDITION OF HYDROGEN BROMIDE TO 1-BROMO-2-BUTENE AND 3-BROMO-1-BUTENE

The two products of the addition of one mole of hydrogen bromide to butadiene may add a second mole of hydrogen bromide as follows:

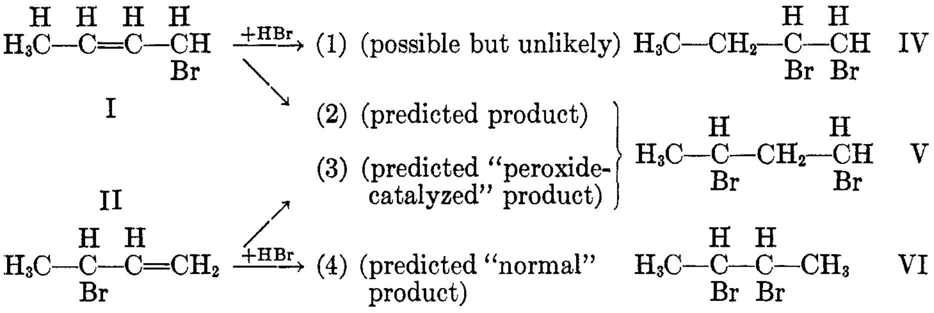

Table IV shows the results of the addition of hydrogen bromide to both 1-bromo-2-butene and 3-bromo-1-butene in the presence of peroxides or antioxidants. The mixtures were analyzed by index of refraction and also by distillation through a modified Podbielniak column[11] at 50 mm. pressure. Good separations were obtained, and the two methods of analysis

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[11] Podbielniak, *Ind. Eng. Chem.*, *Anal. Ed.*, **5**, 119 (1933).

checked satisfactorily. The products from either bromobutene, under both sets of conditions, were mixtures of 1,3- and 2,3-dibromobutanes (V and VI). There was no indication of the presence of any 1,2-dibromobutane (IV).

The experimental results of Table IV confirm previous observations that substances which contain nonterminal double bonds give the same addition product either in the presence or the absence of peroxides. Thus, 1-bromo-2-butene (I) gives about 80 per cent. of the predicted product, 1,3-dibromobutane (V), irrespective of the experimental conditions. But hydrogen bromide accelerates the attainment of equilibrium between I and II; hence the 20 per cent. of VI found in the reaction mixture probably comes from the normal addition of HBr to II. The addition of hydrogen bromide to 3-bromo-1-butene in the presence of added peroxide gives the same mixture (80 per cent. V and 20 per cent. VI). The fact that, upon addition of hydrogen bromide, 3-bromo-1-butene, in the presence of peroxides, and 1-bromo-2-butene, under all conditions, give the same reaction mixture, is to be expected in view of the rapidity with which equilibrium is established between the two bromobutenes under "peroxide" conditions. In the absence of air and peroxides, however, 3-bromo-1-butene (II) gives mostly (60 per cent.) 2,3-dibromobutane (VI). The formation of such a large quantity of 2,3-dibromobutane is most striking because the addition was carried out at room temperature, *i.e.* under conditions which cause exceedingly rapid rearrangement of the 3-bromo-1-butene to

TABLE IV

ADDITION OF HYDROGEN BROMIDE TO 1-BROMO-2-BUTENE AND 3-BROMO-1-BUTENE

BROMIDE	PEROXIDE OR ANTIOXIDANT	MOLES[a]	BY n_D^{20}		BY FRACTIONAL DISTILLATION		REACTION		YIELD (%)
			% 2,3	% 1,3	% 2,3	% 1,3	Time	Temp.	
1-Br-2-butene	Ascaridole	.077	20–0	80–100	22[b]	78	2 days	0°	60
1-Br-2-butene	Diphenylamine	.076	13	87			2 days 1½ days	0° Room	 88
1-Br-2-butene	Ascaridole	.075	17	83			4 days	Room	94
1-Br-2-butene	Diphenylamine	.077	13	87			4 days	Room	56[c]
3-Br-1-butene	Diphenylamine	.062	53	47	62	38	3½ days	Room	82
3-Br-1-butene	Ascaridole	.070	17	83	25	75	3½ days	Room	95

[a] Moles peroxide or antioxidant per mole of bromobutene.

[b] Since these addition products had the same boiling ranges on preliminary distillation and approximately the same indices of refraction, they were distilled together.

[c] Yield actually obtained, not allowing for loss in accident. Estimated yield 80–95 per cent.

1-bromo-2-butene in the presence of minute amounts of peroxides. Our samples of 3-bromo-1-butene were, therefore, quite free of peroxides and, furthermore, considerable addition must have taken place before the equilibrium between the two bromobutenes was established.

These results on the addition of hydrogen bromide to the two bromobutenes, under peroxide and antioxidant conditions, are in complete agreement with our thesis, developed on the basis of the addition of hydrogen bromide to butadiene, that the rearrangement of 3-bromo-1-butene (II) to 1-bromo-2-butene (I) (crotyl bromide) is due to a combined effect of hydrogen bromide and peroxide (and/or oxygen). For emphasis it is repeated that the observed effect of temperature on this rearrangement is due to increased activity with increasing temperature of minute quantities of peroxides (and/or oxygen) in the reaction mixture. Furthermore, because of the rearrangement of 3-bromo-1-butene to 1-bromo-2-butene under the influence of peroxides, it is impossible to conclude from our data whether in the presence of peroxides V is formed from II by reaction (3) or from I by reaction (2). Whatever the mechanism, however, peroxides play an important part in the addition.

EXPERIMENTAL

Preparation of Butadiene.[12]—Cyclohexene was placed in a 500-cc. round-bottomed flask on a hot-plate. From the flask, cyclohexene vapor passed up into a tube containing a spiral made of four feet of #24 platinum wire, maintained at a bright red heat. Atop this tube was a condenser to reflux back unchanged cyclohexene. The effluent vapors were passed through a trap in an ice bath to remove any cyclohexene passing through the condenser, and condensed in a second trap at −78°. From this trap the crude butadiene was distilled into a solution of bromine in carbon tetrachloride until the solution was colorless. This mixture, on standing several hours in the refrigerator, yielded crystalline material. The crystals were collected on a filter, washed with small portions of carbon tetrachloride and crystallized three times from alcohol; m.p. 117°. Medium-boiling ligroïn (60°) can also be used as a solvent.

To regenerate the butadiene, the purified tetrabromide was put in the thimble of a large Soxhlet extractor fitted to a one-liter round-bottomed flask containing zinc and alcohol. To the Soxhlet was fitted a large double-jacketed condenser to which was sealed a Kjeldahl bulb to protect the scrubbing train in case the condenser flooded. From the condenser the butadiene passed down through a long tower of calcium chloride, and final traces of alcohol were removed by passing the gas through a U-tube of calcium chloride maintained at 0°. It was then trapped at −78°. Butadiene was drawn from the trap as required.

The addition of hydrogen bromide to butadiene under antioxidant conditions: Method 1.—The technique was essentially that described by Kharasch and Mayo,[1] modified because of the very rapid reaction of hydrogen bromide and butadiene even at low temperature. A tube of convenient length was fitted with a two-hole stopper

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[12] Kistiakowsky *et. al.*, *J. Am. Chem. Soc.*, **58**, 146 (1936).

carrying a delivery tube and a calcium chloride tube. The tube was then immersed in an acetone-carbon dioxide bath, and the requisite amount of butadiene, 6–10 g., was distilled in. Phosphorus pentoxide was added and a glass-wool plug was inserted. One equivalent of hydrogen bromide per mol of butadiene was condensed, using the same procedure (save that liquid nitrogen was necessary as the refrigerant). Phosphorus pentoxide was added and a glass-wool plug was inserted. The two tubes were strongly cooled and sealed to the yoke. In the third tube was placed 0.3 g. of antioxidant. After reducing the pressure to the limit of a three-stage mercury-vapor pump, the system was sealed off from the vacuum line, the tube containing the antioxidant was cooled in liquid nitrogen and the contents of the other two were allowed to thaw. After distillation was complete the reaction tube was sealed off and plunged into a bath at the desired temperature.

Method 2.—Runs wherein the hydrogen bromide was to be added slowly were carried out in the apparatus illustrated in Fig. 1. The antioxidant was inserted through opening *C*. A plug was then put in opening *A*, a calcium chloride tube was attached at *C*, and the desired amount of butadiene was distilled in through *B*. *C* was then sealed off, the vessel was sealed to the vacuum line at *A*, and the side-arm was sealed on at *B*. The requisite amount of hydrogen bromide was condensed in a long, narrow (16 mm.) tube, and phosphorus pentoxide and a glass-wool plug were put in. The tube was sealed to the reaction vessel as indicated in the diagram. The system was then evacuated and sealed off at *A* and *D*. It was found that when the reaction vessel was kept at −12° in an ice-salt bath, hydrogen bromide would bubble in at a suitable rate from an acetone-carbon dioxide bath. By raising and lowering the Dewar about the hydrogen bromide tube the rate of passage of the hydrogen bromide could be regulated so as to take 3 to 4 hours for completion; the rate could be followed by means of a marker on the hydrogen bromide tube.

When the hydrogen bromide had all passed over, the reaction vessel was cooled and sealed off at *B*.

The addition of hydrogen bromide to butadiene under peroxide conditions.—The butadiene was drawn as described under method 1 in the previous section, and 0.5 g. of a peroxide was then weighed into the tube. Because of the fairly high vapor pressure of butadiene at ice-salt bath temperatures, the tube was immersed in the bath for a period before weighing. Hydrogen bromide was then passed in until the calculated gain in weight had taken place and the tube was then sealed.

The treatment of the reaction products.—At the desired time the end of the reaction tube was cooled to −78° and the tip was broken off; a delivery tube into which a Kjeldahl bulb was incorporated was then sealed on. The delivery tube led into a receiver into which had been weighed one gram of anhydrous potassium carbonate for the purpose of removing unreacted hydrogen bromide and traces of water. The receiver used was a test-tube which had a side-arm sealed on near the top. The receiver was immersed in an acetone-carbon dioxide bath and attached in some instances to a water pump, in others to an oil pump. In the former cases the tube containing the reaction product was warmed to 50–60°; in the latter, distillation was carried out at room temperature. When, however, the low pressure distillation was eliminated, the product, regardless of experimental conditions, assayed 82 per cent of crotyl bromide by refractive index, 84 per cent of this substance calculated from the density. The logical explanation for this, confirmed by Table IV, is that at the higher temperature of the distillation the combined effects of small amounts of peroxides and free hydrogen bromide cause rearrangement. The product was therefore shaken with potassium carbonate until no fumes could be detected, and filtered into a distilling apparatus consisting of a modified Claisen flask of about

15 cc. capacity, with a relatively long side-neck indented in the manner of a Vigreux column; to this was sealed a small water condenser terminating in a delivery tube which reached well down into the receiver. The receiver was immersed in an ice bath, and distillation was interrupted while the receivers were changed. The pressure was maintained at 93 mm. by means of a constant pressure regulator. Experiments showed that in the absence of hydrogen bromide, rearrangement did not take place during this distillation.

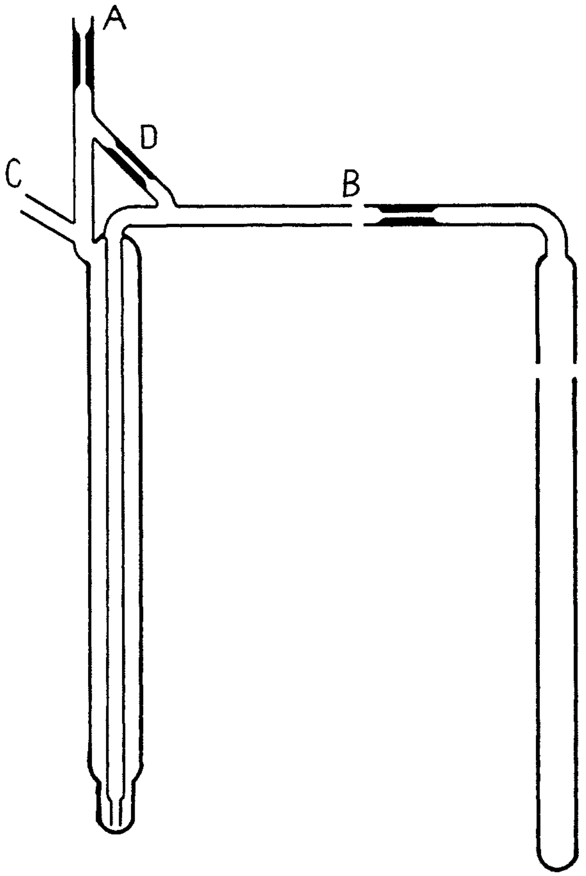

FIG. 1

The addition of hydrogen bromide to bromobutene.—Ten grams of the bromobutene was weighed into a tube, the tube was cooled to −78°, and 1.5 to 2 moles of hydrogen bromide was passed in in the manner described by Kharasch and Mayo.[1] For a peroxide run ascaridole was added, and the tube was sealed; in the case of an antioxidant run phosphorus pentoxide was added, and the tube was sealed to a yoke in the manner described by Kharasch and Mayo. The bombs were allowed to stand four days at room temperature, cooled, opened, and after the major portion of the excess hydrogen bromide had escaped, distilled at 50 mm. The distillate in the case of the peroxide runs was shaken with concentrated sulfuric acid to remove possible ascaridole decomposition products, washed with water, dried with calcium chloride and distilled at 50 mm.; the sulfuric acid wash was omitted in working up the antioxidant runs. The yield was about 90 per cent. In each case the first 3–5 per cent of the final distillate was rejected. This may make our estimate of composition as much as 5 per cent low in 2,3-dibromobutane.

Physical constants and methods of analysis of the bromobutenes.—The papers of Young and Winstein[10] provided the constants shown in Table V, and showed that the indices of refraction of mixtures vary linearly with composition. At the conclusion of our work on the addition of hydrogen bromide to butadiene, the addition products were combined and fractionally distilled at 10 mm. pressure through a modified Podbielniak column.[11] Pure samples of 3-bromo-1-butene and 1-bromo-2-butene were thus obtained and the supply of the former was amplified by distillation of the latter at atmospheric pressure and redistillation at 10 mm. No indication of any other bromobutene was found. We redetermined the constants of Young and Winstein with our pure samples, using a Bausch and Lomb Abbé refractometer and a 3-cc. Ostwald pycnometer. Our density determinations were made with smaller samples than they used, and are not corrected to vacuum, but we have checked all our values and we find that the composition of a mixture obtained from a density measurement agrees better with that obtained from index of refraction when our constants are used. Our constants appear in Table V together with those of Young and

TABLE V

PHYSICAL CONSTANTS OF BROMOBUTENES

	B.P./10 MM.	n_D^{20}	n_D^{23}	n_D^{25}	d_4^{25}
1-Bromo-2-butene (K., M., M.)	13°	1.4822	1.4805	1.4794	1.3371
Young and Winstein			1.4805	1.4795	1.3335
3-Bromo-1-butene (K., M., M.)	7°	1.4618	1.4608	1.4599	1.2998
Young and Winstein			1.4612	1.4602	1.2998

TABLE VI

PHYSICAL CONSTANTS OF SOME DIBROMOBUTANES

DIBROMOBUTANES	B.P./50 MM.		n_D^{20}	
	Expt.	Recorded	Expt.	Recorded
2,3-Dibromobutanes[13]	meso 71–4°	72.7–72.9°	1.5123	1.5116
	rac.	75.6–75.8°		1.5147
1,2-Dibromobutane[13]		80.5–80.7°		1.5150
1,3-Dibromobutane	88°	89.5°[14]	1.5093	1.507[15]

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[13] DILLON, YOUNG, AND LUCAS, *J. Am. Chem. Soc.*, **52,** 1953 (1930).

[14] FARGHER AND PERKIN, *J. Chem. Soc.*, **105,** 1356 (1914).

[15] PARISELLE, *Ann. chim. phys.*, [8], **24,** 332 (1911).

Winstein. The density of 3-bromo-1-butene is estimated (but with considerable precision) because it isomerized so rapidly. Thus the index of refraction of a sample was found to increase by .0003 during a density determination.

According to Newman and Rydon[16] either 1-bromo-2-butene or 3-bromo-1-butene hydrolyzes to the extent of 70 per cent in 24 hours at room temperature in 50 per cent. acetone while 4-bromo-1-butene is not attacked. Our addition products showed a uniform hydrolysis of 96 per cent. under the same conditions. We take this to indicate the absence of appreciable quantities of 4-bromo-1-butene in our addition products, in confirmation of the fractional distillation already referred to. We are unable to account at this time for the discrepancy in the rates of hydrolysis reported by Newman and Rydon and those observed by us.

Physical constants and methods of analysis of the dibromobutanes.—Fractional distillation of the dibromobutanes obtained from the addition of hydrogen bromide to the bromobutenes gave good separations of the 2,3- and 1,3-dibromobutanes, with no indication of the presence of 1,2-dibromobutane. Our determinations of the physical constants are compared with the recorded values in Table VI.

The data indicate that our 2,3-dibromobutane was a mixture of the meso and racemic forms. Compositions of addition products based on indices of refraction in Table IV assume that the index of refraction is a linear function of composition.

SUMMARY

1. In the presence of antioxidants and in the absence of air, hydrogen bromide adds to butadiene to give mostly the 1,2-addition product, namely, 3-bromo-1-butene. In the presence of air (or peroxides) the major product is 1-bromo-2-butene, corresponding to 1,4 addition.
2. Hydrogen bromide in the presence of oxygen or peroxides, has a pronounced catalytic effect on the isomerization of 3-bromo-1-butene to an equilibrium mixture containing 80–85 per cent. 1-bromo-2-butene.
3. The addition of hydrogen bromide to 1-bromo-2-butene (a substance which does not contain a terminal double bond) in the presence of either antioxidants or peroxides, yields the same mixture of 1,3- and 2,3-dibromobutanes.
4. The addition of hydrogen bromide to 3-bromo-1-butene in the presence of air and peroxides gives 80 per cent. of 1,3-dibromobutane and 20 per cent. of 2,3-dibromobutane, while under antioxidant conditions 60 per cent. of the 2,3-dibromobutane is formed.
5. A consistent adequate explanation, based upon the effect of oxygen (or peroxides) in the isomerization of the bromobutenes, is developed to account for the observed results.
6. It has been definitely shown that the apparent 1,4 addition of hydrogen bromide to butadiene at low temperatures is due to an oxygen (or peroxide) effect.
7. It is suggested that the 1,4 addition of bromine to butadiene proceeds through the formation of the 1,2 addition product (as assumed by many) and that the rearrangement is catalyzed by hydrogen bromide and peroxides.

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[16] Newman and Rydon, *J. Chem. Soc.*, **1936**, 261.

RECENT BOOKS

PERFUMES, COSMETICS AND SOAPS, VOLS. I AND II. *William A. Poucher*, Ph.C. D. Van Nostrand Company, Inc., New York City, 1936. x + 439 pp., xiii + 426 pp. 14 x 21 cm. $8.00 per volume.

These volumes are intended as "a dictionary of the raw materials of perfumery, together with formulae for synthetics and their physical constants." In this objective the author has succeeded admirably. The treatment of the origin of the perfumes is most thorough and indicates an extensive knowledge of the field and a devotion to the task. The chemical description of the "synthetics" is quite adequate for the purpose, and an excellent appendix on the nomenclature of the synthetic materials should be of great help to those not thoroughly versed in organic chemistry. The description of the odors of the synthetics is excellent, and new uses of some materials are indicated.

The second volume is devoted to the production, manufacture and application of flower perfumes of all types. Here, again, the information is covered in a most thorough manner. Each chapter on the flower perfumes has an excellent historical sketch. Numerous formulas for the compounding of various perfumes are given. The scheme adopted by the author for the description of the synthetic compounding of each flower perfume is somewhat as follows. A short note on the chemistry of the flower perfume is given. Then follows a paragraph or two of "Compounding Notes," and a list of synthetic compounds. These are divided into (a) Bases, (b) Blends, (c) Modifiers, (d) Fixers, (e) Florales, (f) Aldehydes. A number of actual formulas, as used in the art, are then given. The large number of compounds given under the different headings suggests, however, many other possibilities, and the number of the possible combinations is very large. A list of formulas for miscellaneous fancy perfumes is given, as well as formulas for toilet waters, perfumed soaps, sachets and solid perfumes, perfumed cards, perfumed programs, etc. Verily, the author can say, "If anything has an odor, we have the formula for it."

The books should be of interest to chemists in general, and we trust that some of the information will gradually find its way into texts on organic chemistry. Thus, a recent textbook on organic chemistry gives coumarin as an adulterant of vanilla, and a flavoring for tobacco. To the reviewer, however, it is much more gratifying to know that coumarin is responsible for the odor of new-mown hay.

Avoiding the cliché that the book should be on the shelf of everyone interested in the field, the reviewer would prefer to conclude with a challenge—if you have the curiosity to know what are the odors you enjoy so immensely, read the books. The books are a veritable treasure-house of information on cultural, historical, chemical and practical aspects of perfumes, cosmetics and soaps.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

HYDROGEN BRIDGES IN ORGANIC COMPOUNDS*

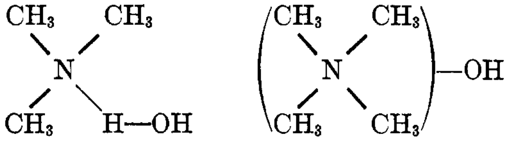
MAURICE L. HUGGINS†

Received October 26, 1936

HISTORICAL INTRODUCTION

Werner,[1] as early as 1903, assumed that when hydrochloric acid forms a salt with ammonia or a primary, secondary or tertiary amine, the hydrogen of the acid, while maintaining its relationship to the chlorine essentially the same as in the free acid, at the same time occupies one of the four coördination positions around the nitrogen: $(NH_3 \cdots H)Cl$. The addition of water to ammonia or an amine was similarly considered to yield compounds represented by the formulas $(NH_3 \cdots H)OH$ and $(NR_3 \cdots H)OH$. He assumed, furthermore, that in a quaternary ammonium salt or hydroxide a methyl or other radical plays a rôle similar to that of the bridging hydrogen in the above examples: $(N(CH_3)_3 \cdots CH_3)Cl$.

Moore and Winmill,[2] in 1912, concluded from a consideration of the relative strengths of substituted ammonium bases that Werner's picture of these was essentially correct except for the quaternary compounds, but that a methyl or other radical cannot play the same dual rôle as hydrogen:



Pfeiffer and co-workers,[3] in 1913, assumed "dass das H atom des o-Hydroxyls koordinativ an ein Carbonylsauerstoffatom gebunded ist (inner Komplexsalzbindung) und dadurch in seiner Additionskraft für Amine und Metallhydroxyde geschwächt wird." A similar state of affairs was

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* Expanded from a paper presented at the Kansas City Meeting of the American Chemical Society, April, 1936.

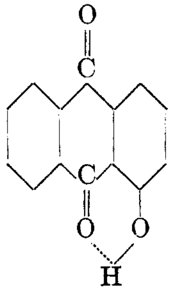
† Present address: Research Laboratory, Eastman Kodak Company, Rochester, N. Y.

[1] WERNER, *Ber.*, **36**, 147 (1903).

[2] MOORE AND WINMILL, *J. Chem. Soc.*, **101**, 1635 (1912).

[3] PFEIFFER, FISCHER, KUNTNER, MONTI, AND PROS, *Ann.*, **398**, 137 (1913).

assumed to exist in corresponding *peri* compounds such as hydroxyanthraquinone:



The writer,[4] in 1919, showed that Werner's "secondary valence" compounds are simply accounted for on the basis of the Lewis theory of atomic structure by assuming their formation to involve the production of electron-pair bonds by the addition of atoms (or ions) containing "lone pairs" in their valence shells to other atoms (or ions) having an attraction for such lone pairs:

$$A + :B \rightarrow A:B$$

According to this theory there is no difference between a secondary valence *bond* and a primary valence *bond*, although a distinction can be made between a secondary valence *reaction*, of the type just described, and a primary valence *reaction*, in which the bond is formed by the interaction of one electron from each of the two bonded atoms.

It was assumed, with Lewis, that electronegative atoms in stable ions and molecules customarily have four pairs of electrons in their valence shells; to account for the coördination numbers of many positive atoms in known secondary valence compounds, however, it was necessary to postulate larger or smaller numbers, *e. g.*, six in the cobaltammines and two in the complex $Ag(NH_3)_2^+$. It seemed reasonable that a hydrogen kernel, like the silver kernel in this example, should be able to hold to two sufficiently electronegative atoms in this way: X : H : X. Such "hydrogen bridges"* were postulated, for instance, between oxygen atoms of oxyacids and between fluorine atoms in polymerized hydrogen fluoride.

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[4] HUGGINS, Undergraduate Thesis, University of California (1919).

* The writer prefers the term "hydrogen bridge" to the expression "hydrogen bond" introduced by Latimer and Rodebush, believing it best to use the word "bond" (in chemistry) only for a system consisting of one or more (nearly always two) electrons holding together two atoms. "Hydrogen bond" is also confusing, since it suggests the electron-pair bond between two hydrogen atoms in the H_2 molecule or between a hydrogen atom and another atom in any hydrogen compound.

The term "hydroxyl bond," introduced by Bernal and Megaw[4a] to designate a

Latimer and Rodebush,[5] in 1920, used the same concept in discussing molecular association in water and other associated liquids and the weak basicity of ammonium hydroxide.

Shortly thereafter, the writer,[6] applying the hydrogen bridge theory to crystals, pointed out that the distribution of nitrogen and chlorine atom centers in solid ammonium chloride[7] is such as to place the hydrogens of a tetrahedral ammonium group on the N ··· Cl center lines and made the assumption that the chlorine valence pairs are "located" on the same center lines, thus giving four unsymmetrical hydrogen bridges connecting each nitrogen with neighboring chlorine atoms.† It was also shown that the distribution[9] of sodium and fluorine atoms in $NaHF_2$ crystals makes it probable that they contain F:H:F bridges and a prediction, soon verified,[10] was made that ice would be found to have a structure in which each oxygen is surrounded tetrahedrally by four others, these being connected (according to the theory) by hydrogen bridges.

Since that time an abundance of evidence from crystal structure studies has accumulated, showing the common existence of hydrogen bridges between two electronegative atoms, of N, O or F. In the inorganic field we may mention OHO bridges in $AlHO_2$ (= $Al_2O_3 \cdot H_2O$),[11] KH_2PO_4,[12]

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hydrogen bridge connecting two hydroxyl oxygens, is, in the writer's opinion, both confusing and unnecessary, implying a (non-existent) difference in type between such bridges and other OHO bridges.

[4a] Bernal and Megaw, *Proc. Roy. Soc.*, **A151**, 384 (1935).

[5] Latimer and Rodebush, *J. Am. Chem. Soc.*, **42**, 1419 (1920).

[6] Huggins, *Phys. Rev.*, **18**, 333 (1921); **19**, 346 (1922).

[7] W. H. Bragg and W. L. Bragg, "X-rays and Crystal Structure," G. Bell & Sons, London, 1st Edition, **1918**, p. 158; Bartlett and Langmuir, *J. Am. Chem. Soc.*, **43**, 84 (1921).

† What were previously considered as "locations" of electron-pairs, of course, merely indicate the directions of maximum density of the electron-pair orbitals. Pauling has proposed that the ammonium groups in ammonium chloride are rotating at temperatures above −30°C. The question as to whether or not this is the case is at present still unsettled.[8] (See the later discussion, in the section on "NHX Bridges.")

[8] Pauling, *Phys. Rev.*, **36**, 430 (1930); Bridgman, *ibid.*, **38**, 182 (1931); Pohlman, *Z. Physik*, **79**, 394 (1932); Laschkarew and Usyski, *ibid.*, **85**, 618 (1933); Ketelaar, *Nature*, **134**, 250 (1934); Hettich, *Z. physik. Chem.*, **A168**, 353 (1934); Menzies and Mills, *Proc. Roy. Soc.*, **A148**, 407 (1935); Holmes, *J. Chem. Phys.*, **4**, 88 (1936); J. Sherman, *Chem. Rev.*, **11**, 93 (1932) (*cf.* p. 152).

[9] Rinne, Hentschel, and Leonhardt, *Z. physik. Chem.*, **100**, 408 (1922); *Z. Krist.*, **58**, 629 (1923); Andersen and Hassel, *Z. physik. Chem.*, **123**, 151 (1926).

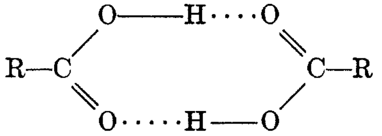
[10] W. H. Bragg, *Proc. Phys. Soc.* (London), **34**, 98 (1922); Barnes, *Proc. Roy. Soc.*, **A125**, 670 (1929).

[11] Ewing, *J. Chem. Phys.*, **3**, 203 (1935).

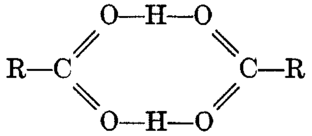
[12] West, *Z. Krist.*, **74**, 306 (1930).

$NaHCO_3$,[13] and certain silicates;[14] NHO bridges in $(NH_4)H_2PO_4$;[15] NHF bridges in NH_4F,[16] and NH_4HF_2,[17] and NHN bridges in NH_4N_3.[18] For discussion of a number of other inorganic examples see reference 4*a*. Various organic examples will be mentioned later.

It has long been known, as a result of cryoscopic,[19] partition coefficient[20] and vapor density[21] measurements, that fatty acid molecules are largely polymerized to dimers in solution in non-polar solvents and in the vapor state. It was predicted by the writer that these dimers would be found to contain two hydrogen bridges each, connecting the two carboxyl groups:*



or



In agreement with this prediction are the conclusions of Smyth and Rogers,[22] from dielectric constant studies of acetic and butyric acid solutions in benzene and in ether, that the double molecule has zero or negligible dipole moment and the electron diffraction work of Pauling and Brockway[23] on formic acid vapor, which may be considered as definitely proving the correctness of the proposed model.

Sidgwick[24] has extended Latimer and Rodebush's treatment of associated liquids in terms of the hydrogen bridge concept and shown that an *intra*-molecular hydrogen bridge, in a substance such as

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[13] Zachariasen, *J. Chem. Phys.*, **1**, 634 (1933).

[14] Naray-Szabo, *Z. Krist.*, **71**, 103 (1929); Warren and W. L. Bragg, *ibid.*, **76**, 201 (1930).

[15] Zachariasen and Mooney, *J. Chem. Phys.*, **2**, 34 (1934).

[16] Zachariasen, *Z. physik. Chem.*, **127**, 218 (1927).

[17] Hassel and Luzanski, *Z. Krist.*, **83**, 448 (1932); Pauling, *ibid.*, **85**, 380 (1933).

[18] Frevel, *Z. Krist.*, **94**, 197 (1936).

[19] Beckman, *Z. physik. Chem.*, **6**, 440 (1890); **22**, 609 (1897); Auwers, *ibid.*, **12**, 689 (1893); Trautz and Moschel, *Z. anorg. Chem.*, **155**, 13 (1926); Turner, "Molecular Association," Longmans, Green & Co., New York, **1915**, p. 33.

[20] Herz and Fischer, *Ber.*, **38**, 1138 (1905).

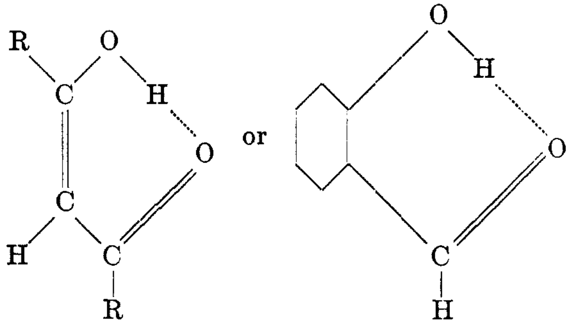
[21] Trautz and Moschel, ref. 19.

* Regarding the representation of five bonds attached to each carbon atom in the second of these formulas, see the footnote at the end of the next section.

[22] Smyth and Rogers, *J. Am. Chem. Soc.*, **52**, 1824 (1930).

[23] Pauling and Brockway, *Proc. Nat. Acad. Sci.*, **20**, 336 (1934).

[24] Sidgwick, "The Electronic Theory of Valency," Oxford Univ. Press, **1929**; *Annual Reports of the Chemical Society*, **30**, 110 (1933); "Some Physical Properties of the Covalent Link in Chemistry," Cornell Univ. Press, **1933**.



decreases or eliminates entirely the association. He has also discussed the effect of intermolecular and intramolecular hydrogen bridge formation on solubilities of organic substances, pointing out for instance that ether is an abnormally good solvent for many compounds containing hydroxyl groups, presumably due to the possibility of bridge formation between solvent and solute molecules.

Hildebrand[25] has carried the relationship between bridge formation and solubility farther, showing with striking examples that bridge formation is often much more important than dipole moment in determining solubilities, deviations from Raoult's law, etc.

Aniline and phenol, which form strong hydrogen bridges with water molecules, are much more soluble in water than in nitrobenzene, which does not, even though nitrobenzene has a much larger dipole moment (Table I). Alcohols are likewise much more soluble than corresponding chlorine, bromine or iodine derivatives having nearly the same dipole moment, these halogen compounds forming only weak bridges, if any.

Figure 1, taken from Hildebrand's article on this subject, shows the variation with temperature of the logarithm of the solubility of naphthalene, expressed as mole fraction, in certain solvents. It may be regarded as showing the freezing-point lowering of naphthalene. Note the marked difference in behavior between nitrobenzene and acetone (which form no hydrogen bridges), acetic and benzoic acids (which form dimers, by hydrogen bridge formation, in non-polar solvents), and alcohols such as butanol (the simple molecules of which interact by bridge formation to form chains of greater average length the greater the concentration of the alcohol).

Kumler[26] has shown that the square root of the dielectric constant (cor-

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[25] HILDEBRAND, *Science*, **83**, 21 (1936) "Solubility of Non-Electrolytes," Reinhold Publ. Corp., New York, **1936**.

[26] KUMLER, *J. Am. Chem. Soc.*, **57**, 600 (1935).

TABLE I*

	SOLUBILITY IN H_2O AT 20°C. %	DIPOLE MOMENT $\mu \times 10^{18}$
Benzene	0.06	0
$C_6H_5NO_2$	.19	4.19
$C_6H_5NH_2$	3.49	1.51
C_6H_5OH	8.2	1.70
C_2H_5I	0.40	1.66
C_2H_5OH	∞	1.70
C_3H_7Cl	.27	2.0
C_3H_7I	.11	1.6
C_3H_7OH	∞	1.7
H_2O		1.85

* Reproduced from HILDEBRAND, ref. 25, by permission of the author.

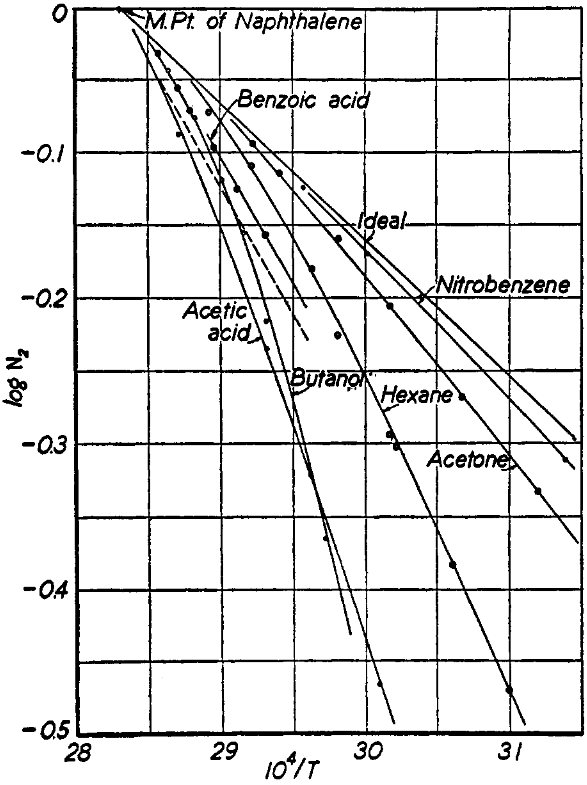

FIG. 1.†—FREEZING-POINT LOWERING OF NAPHTHALENE CAUSED BY VARIOUS LIQUIDS

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† Reproduced from Hildebrand, Reference 25, by permission of the author. The broken curve is for an ideal solution of a completely dimerized solute.

rected for electronic polarization and for differences in density) is quite closely proportional to the molecular dipole moment for various organic liquids which certainly do not contain hydrogen bridges, wide deviations being encountered for those in which such bridges would be expected. Similar abnormalities appear when boiling points and dipole moments of compounds having practically equal molecular weights are compared and when the boiling points and molecular weights of substances having nearly the same values of dipole moment are compared.

Studying the infra-red absorption spectra of solutions of substances supposedly containing OH groups, Hilbert, Wulf, Hendricks and Liddel[27] have noted the absence of characteristic OH absorption from many compounds in which one might reasonably expect hydrogen bridges and have used this absence as a criterion for determining the existence or non-existence of bridges in doubtful cases.*

In this brief introduction many papers dealing with hydrogen bridges or with phenomena which can be satisfactorily interpreted by means of the hydrogen bridge theory, have necessarily been omitted. Some of them, however, will be mentioned in the pages which follow.

OBJECTIONS TO THE HYDROGEN BRIDGE THEORY

From the foregoing outline it is evident that there is ample evidence for the existence of hydrogen bridges. Two objections to the theory have been raised, however, which warrant a brief discussion.

One objection is that the theory gives hydrogen a valence of two. It is true that, according to the theory, each hydrogen atom is bonded to two other atoms; yet, as the writer has repeatedly pointed out,[28] the number of bonds connecting an atom to others is very frequently not the same as the usual valence number (*e. g.*, in "pentavalent" nitrogen compounds, in the Werner complex compounds, and in most inorganic compounds in the solid state). This is due, as inferred above, to the fact that a normal electron-pair bond can be formed by the addition of a lone pair to the incomplete valence shell of another atom.

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[27] HILBERT, WULF, HENDRICKS, AND LIDDEL, *Nature*, **135**, 147 (1935); *J. Am. Chem. Soc.*, **58**, 548 (1936); HENDRICKS, WULF, HILBERT, AND LIDDEL, *ibid.*, **58**, 1991 (1936); WULF, LIDDEL, AND HENDRICKS, *ibid.*, **58**, 2287 (1936); ERRERA AND MOLLET, *Compt. rend.*, **200**, 814 (1935); *J. Phys. Radium*, **6**, 281 (1935).

* The writer gratefully acknowledges the kindness of these authors in making available to him before publication the results of their more recent studies in this field.

[28] HUGGINS, ref. 4; *Science*, **55**, 459 (1922); *J. Phys. Chem.*, **26**, 601 (1922), and more recent papers.

It has further been objected[29] that, according to the Pauli exclusion principle, the *K* shell of a hydrogen atom cannot contain more than two electrons. This objection cannot have much weight, since hydrogen bridges are always between very electronegative atoms, hence the shared electron-pairs are much more tightly held by these other atoms than by the hydrogen. The ends of the "molecular orbitals" nearer the hydrogen nucleus probably more closely approximate "*L* atomic orbitals" than "*K* atomic orbitals." The limitation on the number of *K* atomic orbitals, of course, does not apply to such molecular orbitals. Resonance between an electron-pair-bonded state (*K* with respect to the hydrogen) and an "ionic" state is frequently postulated. If such resonance exists, however, there should be still more resonance between one bonded state which is *K* with respect to the hydrogen and another bonded state which is *L* with respect to the hydrogen. In other words the actual orbital, as regards its relation to the hydrogen, is intermediate in character between a *K* atomic orbital and an *L* atomic orbital.*

TABLE II

Heats and Energies of Dissociation of Hydrogen Bridges (18°C.)

		$\frac{\Delta H}{\text{kcal.}}$	$\frac{\Delta E}{\text{kcal.}}$	REF.
$1/6\ H_6F_6 \rightarrow HF$	FHF	6.67	6.18	(31)
$1/2\ (HCO_2H)_2 \rightarrow HCO_2H$	OHO	7.05	6.76	(32)
$1/2\ (CH_3CO_2H)_2 \rightarrow CH_3CO_2H$	OHO	6.89	6.60	(33)
$1/2\ H_2O(s) \rightarrow 1/2\ H_2O(g)$	OHO	6.2	5.9	(34)*
$ROH(l) \rightarrow ROH(g)$	OHO	7.2	6.6	(34)
$1/2\ C_2O_4H_2(s) \rightarrow 1/2\ C_2O_4H_2(g)$	OHO	10.8	10.5	(34)*
$HCN(l) \rightarrow HCN(g)$	CHN	6.7	6.1	(34)*
$HCN(s) \rightarrow HCN(g)$	CHN	8.4	7.8	(34)*
$1/4\ NH_4F(s) \rightarrow 1/4\ NH_4^+(g) + 1/4\ F^-(g)$	NHF	6.3	6.0	(34)*
$(C_2H_5)_2O \cdot HCCl_3 \rightarrow (C_2H_5)_2O + HCCl_3$	CHO	6.0	6.0	(35)*
$(CH_3)_2CO \cdot HCCl_3 \rightarrow (CH_3)_2CO + HCCl_3$	CHO	4.1	4.1	(36)*
$C_5H_5N \cdot HOC_6H_4Cl\text{-}o \rightarrow C_5H_5NH^+ + o\text{-}OC_6H_4Cl^-$	NHO	6.8	6.8	(37)*
$C_{11}H_7N \cdot HOC_6H_4Cl\text{-}o \rightarrow C_{11}H_7NH^+ + o\text{-}OC_6H_4Cl^-$	NHO	6.8	6.8	(38)*
$p\text{-}C_6H_4(CH_3)NH_2 \cdot HOC_6H_4CH_3\text{-}o \rightarrow p\text{-}C_6H_4(CH_3)NH_3^+ + o\text{-}OC_6H_4(CH_3)^-$	NHO	6.0	6.0	(39)*

* No corrections made for non-bridge attractions, which in some instances are considerable.

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[29] Pauling, *Proc. Nat. Acad. Sci.*, **14**, 359 (1928); *J. Am. Chem. Soc.*, **53**, 1367 (1931).

* The corresponding argument against the writer's proposal that there are more than four electron-pairs shared between a single carbon and other atoms in carbonate and carboxylate ions is equally invalid, as a similar line of reasoning shows.[30]

[30] Huggins, Paper presented at the Kansas City Meeting of the American Chemical Society, April, 1936.

THE STRENGTH OF HYDROGEN BRIDGES

From the heat of dissociation[31] of H_6F_6 into 6 HF one can readily calculate the average dissociation energy per FHF bridge as 6.2 kcal. per mole (*i. e.*, for Avogadro's number of bridges). Since the bond strength of the H—F bond in the HF molecule is about 148 kcal. per mole, the average bond strength of the H—F bonds in H_6F_6 is about 77 kcal. per mole. It is interesting that the energy required to break a bridge is such a small fraction of the bond energy (or "strength") of each of the two bonds constituting the bridge. As one of these bonds is broken, the other increases greatly in strength, the energy changes nearly balancing each other. Even so, the dissociation energy per bridge is many times the average kinetic energy per molecule, $\frac{3}{2}\,kT$ being about 0.06×10^{-12} ergs (corresponding to 0.58 kcal. per mole) at room temperature, hence collisions will only rarely have sufficient energy to break one of these bridges.

The heats of dissociation of gaseous formic[33] and acetic[34] acid dimers are known. Since dissociation of such a dimer breaks two hydrogen bridges, we can use these data to calculate the average dissociation energy of these OHO bridges. The resulting values are slightly larger (Table II) than for the FHF bridges. Since, however, the bond energy of a normal O—H bond is[40] about 109 kcal. per mole, the bond strength of each O—H bond in an OHO bridge of this sort averages about 58 kcal. per mole, somewhat less than in the FHF case. Whether the two bonds of each bridge are equivalent in these acid dimers is doubtful (see the next section).*

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[31] Simons and Hildebrand, *J. Am. Chem. Soc.*, **46**, 2183 (1924); Thorpe and Hamby, *J. Chem. Soc.*, **55**, 163 (1889).

[32] Coolidge, *J. Am. Chem. Soc.*, **50**, 2166 (1928).

[33] Fenton and Garner, *J. Chem. Soc.*, **1930**, 694.

[34] Bichowsky and Rossini, "The Thermochemistry of the Chemical Substances," Reinhold Publ. Corp., New York, 1936.

[35] MacLeod and Wilson, *Trans. Faraday Soc.*, **31**, 596 (1935); Glasstone, Faraday Society Discussion, Sept., 1936.

[36] Schulze, *Z. physik. Chem.*, **93**, 370 (1919); Moelwyn-Hughes and Sherman, *J. Chem. Soc.*, **1936**, 101.

[37] Glass and Madgin, *J. Chem. Soc.*, **193**, 1431 (1933).

[38] Glass, Madgin, and Hunter, *ibid.*, **1934**, 260.

[39] Glass and Madgin, *ibid.*, **1934**, 1292.

[39a] Burnham and Madgin, *ibid.*, **1936**, 1303.

[40] Pauling, *J. Am. Chem. Soc.*, **54**, 3570 (1932).

* Gillette and Albert Sherman[40a] have attempted a quantum mechanical calculation of the dissociation energy and length of each hydrogen bridge in $(HCO_2H)_2$. Making arbitrary assumptions which are certainly incorrect, they arrive at a bridge length about 0.73 Å too short and a dissociation energy about 70 per cent. too large. In view of these discrepancies, little faith can be put in their conclusion that the hydrogen atoms of the bridges are, in the normal state of the molecule, midway between the bridged oxygens.

[40a] Gillette and A. Sherman, *ibid.*, **58**, 1135 (1936).

From the heat of sublimation[34] of ice one can calculate a value for the dissociation energy of an OHO bridge (Table II) which is somewhat less than for these bridges in the acids, as would be expected from the larger O ··· O distance (Table III) and the less polar character of the O—H bond in H_2O. The calculated value is to be considered a maximum value, as van der Waals attractions between atoms other than those directly connected by bridges are neglected. In this instance the OHO bridges are undoubtedly unsymmetrical, one of the bonds of the bridge being much stronger than the other.

Another rough value for the energy of dissociation of an OHO bridge can be obtained from the heats of vaporization[39] of liquid alcohols using the assumption (shown by X-ray work to be approximately correct, as discussed below) that each oxygen is connected by two bridges to oxygens of neighboring molecules, and using the heats of vaporization of ethyl, *n*-propyl and *n*-butyl alcohols to estimate a correction for the contribution of van der Waals attractions between hydrogen atoms. The calculated dissociation energy per bridge is practically the same as in the acid dimers.

The effect of the methyl and methylene groups can also be allowed for by comparing the heat of vaporization of an alcohol with that of the appropriate paraffin, with the same result.[41] From measurements of the heat of mixing of alcohols in hydrocarbons, von Elbe[42] has calculated 5.8 kcal. for the heat of association per mole, while Wolf, Pahlke, and Wehage,[43] have obtained about 8 kcal. per mole.

It is likely that in both liquid and solid HCN the molecules are held together largely through CHN bridges, forming linear molecular strings. From the heat of vaporization[34] of the liquid, the average vaporization energy per mole can be calculated to be 6.1 kcal. Assuming each molecule to be held by bridges to two others, this is greater than the true bridge strength, since intermolecular attractions are certainly not negligible. If there should be many molecules not held by bridges in this way, the strength of each bridge might be greater. In the solid the forces between atoms in different chains are surely more important than in the liquid. This fact is chiefly responsible for the heat of fusion.

The results of calculations for OHO bridges in oxalic acid and for NHF bridges in ammonium fluoride crystals are also included in Table II. These must be considered merely as maximum values, since other attractive forces than those due to the bridges are neglected.

MacLeod and Wilson,[35] studying the heats of mixing of ether-chloroform

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[41] DUNKEL, *Z. physik. Chem.*, **138**, 42 (1928).

[42] VON ELBE, *J. Chem. Phys.*, **2**, 73 (1934).

[43] WOLF, PAHLKE, AND WEHAGE, *Z. physik. Chem.*, **B28**, 1 (1935); WOLF, Faraday Society Discussion, Sept., 1936.

solutions, conclude that a compound consisting of one molecule of ether and one of chloroform is formed, from 15 to 20 per cent of the molecules being combined at 15°C. They compute the heat of reaction to be about 6.0 kcal. It seems likely that a C—H ··· O bridge is responsible for the major part of this. For the addition compound of acetone and chloroform the heat of formation from the two components is −4.1 kcal., calculated from the vapor pressure data of Schulze.[36]

Glass and Madgin[39] obtain a value of 6.0 kcal. per mole also for the heat of dissociation of the additive compound formed when *p*-toluidine and *o*-cresol are mixed in an inert solvent. Somewhat higher values are obtained[37,38] for the corresponding compounds formed by pyridine and quinoline with *o*-chlorophenol.

It is interesting that all of the foregoing calculations (except those for oxalic acid) give dissociation energies of nearly the same magnitude. We have no reason to believe, however, that other bridges with smaller dissociation energies do not exist. Such weak bridges may, in fact, be very important in water solutions, in surface adsorption, in intermediate complexes formed during reactions, etc.

The ease of dissociation of hydrogen bridges is due primarily to the large interpenetration repulsions between the electronegative atoms, as shown by the writer's calculations[44] of potential energy curves for various bridges. Comparing different bridges between the same two elements, *e. g.*, different OHO bridges, these calculations suggest that, in general, the shorter the bridge the stronger it is. It will be interesting to see if this prediction is borne out by future experimental results.

One would expect "deuterium bridges" to be less easily broken than ordinary hydrogen bridges The zero-point energy for the oscillation of a bridging atom is smaller the heavier that atom, hence more additional energy must be supplied to produce dissociation in the deuterium case. The difference in zero-point energies being an appreciable fraction of the bridge dissociation energy, equilibria involving the making and breaking of these bridges are measurably shifted, on substitution of deuterium compounds for corresponding hydrogen compounds. One, therefore, expects and finds[45] considerable differences in the vapor pressure (and other properties) between liquid H_2O and liquid D_2O, for which the vaporization process involves the breaking of bridges, and between HAc and DAc, the vapors of which consist of monomers and dimers in equilibrium with each other.

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[44] HUGGINS, *J. Am. Chem. Soc.*, **58**, 694 (1936); *J. Phys. Chem.*, **40**, 723 (1936).

[45] LEWIS AND MACDONALD, *J. Am. Chem. Soc.*, **55**, 3057 (1933); LEWIS AND SCHUTZ, *ibid.*, **56**, 493 (1934).

THE POLARITY OF HYDROGEN BRIDGES

In assuming that in a hydrogen bridge the hydrogen atom is bonded to two other atoms, one need not assume the two bonds to be equal in strength or in other respects, even when the two electronegative atoms are alike. Several years ago the writer concluded that in ice and liquid water the bridges are probably unsymmetrical, each hydrogen being more tightly held to one of its oxygen neighbors than to the other. The line of reasoning was as follows. From comparisons of the densities and dielectric constants[46, 47] of ice and liquid water and from information gleaned from an X-ray study[48] of the liquid in this laboratory, it seems necessary to conclude that the distribution of other atoms immediately around each atom in the liquid differs but little from that in the solid. If one assumes symmetrical bridges throughout the liquid, however, it is difficult to account for the great difference in electrical conductivity between pure water and a dilute solution of a strong acid. On the other hand, by assuming unsymmetrical bridges so distributed as to give each oxygen two close hydrogen neighbors and two others somewhat more distant, a thoroughly satisfactory explanation[44] is possible. The variation of the dielectric constant with temperature in the solid is also readily explicable in terms of the unsymmetrical bridge concept, but difficultly so, if at all, if symmetrical bridges only are postulated. Somewhat similar conclusions regarding the atomic arrangement in water were arrived at independently by Bernal and Fowler[39] at about the same time.

More recently, Pauling[49] has shown that entropy calculations for ice are in agreement with the assumption of unsymmetrical bridges, the tighter O—H bonds being randomly oriented except for two requirements—that they all point toward neighboring oxygen atoms and that each oxygen have just two close hydrogen neighbors.

Hydrogen bridges can, of course, be unsymmetrical in solid and liquid H_2O and yet symmetrical in some other cases. In this connection it is pertinent to call attention to such figures as are available for the distance between the two negative atom centers in various hydrogen bridges (Table III). The distance between two bridged oxygen atoms varies from about 2.55 Å to approximately 2.8 Å. As will be shown presently, the longer hydrogen bridges are probably unsymmetrical, the shorter ones symmetrical.

Energy-distance curves for hydrogen bridges of various types have been computed[30, 44] on the assumption that the O—H and F—H interactions are

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[46] Smyth and Hitchcock, *J. Am. Chem. Soc.*, **54**, 4631 (1932).

[47] Bernal and Fowler, *J. Chem. Phys.*, **1**, 515 (1933).

[48] Katzoff, *ibid.*, **2**, 841 (1934).

[49] Pauling, *J. Am. Chem. Soc.*, **57**, 2680 (1935).

TABLE III

Lengths of Hydrogen Bridges

BRIDGE	COMPOUND	DISTANCE (Å)	REFERENCE
FHF	$NaHF_2$	2.51 ± 0.20	(9)
FHF	KHF_2	2.25 ± 0.20	(50)
FHF	NH_4HF_2	2.37 ± 0.10	(17)
OHO	H_2O	2.78	(10)
OHO	H_3BO_3	2.71	(51)
OHO	$AlHO_2$	2.71	(11)
OHO	$FeHO_2$	2.70	(52)
OHO	$NaHCO_3$	2.55	(13)
OHO	KH_2PO_4	2.54	(12)
OHO	$CaHPO_4 \cdot 2H_2O$	2.55	(53)
OHO	$(HCO_2H)_2$	2.67	(23)
OHO	$\alpha(CO_2H)_2$	2.55 ± 0.15	(53)
OHO	$\beta(CO_2H)_2$	2.71 ± 0.15	(53)
OHO	$(CO_2H)_2 \cdot 2H_2O$	2.60 – 2.87	(54)
OHO	KHC_2O_4	2.60	(53)
OHO	$K_2C_2O_4 \cdot H_2O$	3.30(?)	(53)
OHO	$(NH_4)_2C_2O_4 \cdot H_2O$	2.80	(55)
OHO	Naphthazarine	2.5	(56)
OHO	$CaSO_4 \cdot 2H_2O$	2.70	(57)
NHN	NH_4N_3	(2.94 ± 0.03) (2.99 ± 0.03)	(18)
NHN	Phthalocyanines	2.65	(58)
NHF	NH_4F	2.63	(16)
NHF	NH_4HF_2	(2.75 ± 0.06) (2.77 ± 0.06)	(17)
NHO	$(NH_4)H_2PO_4$	2.81	(15)
NHO	$(NH_4)_2C_2O_4 \cdot H_2O$	2.76 – 2.88	(55)

sufficiently accurately represented by the appropriate curves for diatomic molecules, these being obtained[59] from the band spectrum constants. Although undoubtedly inaccurate for large interatomic separations, these energy curves should be reasonably close to the true ones for distances not far from the experimental equilibrium values and should illustrate satis-

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[50] Bozorth, *ibid.*, **45**, 2128 (1923).

[51] Zachariasen, *Z. Krist.*, **88**, 150 (1934).

[52] Ewing, *J. Chem. Phys.*, **3**, 420 (1935).

[53] Hendricks, *Z. Krist.*, **91**, 48 (1935).

[54] Zachariasen, *ibid.*, **89**, 442 (1934).

[55] Hendricks and Jefferson, *J. Chem. Phys.*, **4**, 102 (1936).

[56] Palacios and Salvia, *Anales soc. española fís. quím.*, **32**, 49 (1934).

[57] Wooster, *Z. Krist.*, **A94**, 375 (1936).

[58] Robertson, *J. Chem. Soc.*, **1935**, 615; **1936**, 1195.

[59] Huggins, *J. Chem. Phys.*, **4**, 308 (1936).

factorily the effect on the shape of the curve of changing various factors. Several interesting conclusions can be drawn from these energy studies.

(1) For O—O distances in the neighborhood of 2.55 Å and F—F distances of about 2.35 Å, the hydrogen oscillates (slowly, with large amplitude) about the midpoint; *i. e.*, the bridge is symmetrical. For somewhat larger distances, *e. g.*, $d_{O-O} = 2.70$ Å, the hydrogen oscillates about a position somewhat closer to one negative atom than to the other; the bridge is unsymmetrical.

(2) In both symmetrical and unsymmetrical bridges, the hydrogen is considerably farther away from each negative atom center than in the diatomic molecules. Each half of the bridge is correspondingly much weaker (also more polar) than the bond in the corresponding diatomic molecule or a normal bond to a non-bridging hydrogen in an ordinary organic molecule. As a rule, the greater the distance between negative atom centers, the weaker the bridge. For the same distance, an unsymmetrical bridge is weaker (on one side) than a symmetrical one.

(3) The distance between the centers of the electronegative atoms is decreased and the strength of the bridge increased by increasing the strength of the X—H attractions (especially of the weaker X—H bond, if the bridge is unsymmetrical) and by polarization of the X atoms due to strong attractions for their electron clouds by atoms (such as the carbon atoms in CO_3 groups or the phosphorus atoms in PO_4 groups) other than the bridging hydrogen.

(4) A bridge which would otherwise be symmetrical is made quite unsymmetrical and considerably weaker (on one side) by slight differences in the attractions of the two X atoms for the hydrogen. (It seems probable that symmetrical OHO′ bridges occur only in cases of O—H and O′—H attractions which are moderately strong and nearly the same, with the oxygen atoms strongly polarized by the attractions of other atomic kernels.)

(5) The O · · · O center line (for example) may make angles with the center lines connecting each oxygen to the other atom or atoms to which it is bonded which are quite far from the preferred angle (which we may assume to be about 105° as in the H_2O molecule) without much weakening of the bridge. This is partly because the O · · · H interactions are so largely polar (Coulombic) and partly because the orbitals of the bonding electrons are intermediate in character, with respect to the oxygen, between *p* orbitals and tetrahedral orbitals. Pure *p* orbitals would give the greatest bond strengths for 90° angles (neglecting interactions between atoms not directly bonded together); pure tetrahedral orbitals would give the greatest bond strengths for angles of about 110° between the bonds; the hybrid orbitals give nearly equal strengths for all angles between 90° and 110°.

If the O · · · O center line, because of other constraints in the molecule, makes angles with the other bonds to these oxygens which are less than the angles for strongest bonds, the hydrogen nucleus would be expected to be slightly off this O · · · O center line. The bond angle forces tend to "bend" the bridge; Coulomb attractions between the hydrogen and the oxygens tend to keep it straight.

In discussing the energy, symmetry and other properties of hydrogen bridges, a table giving the relative attractive force of electronegative atoms (N, O, F) for a bridging hydrogen, always at the same distance (say 1.3 Å), would be useful. Although the order of these hydrogen attractions should be approximately the reverse of the order of the corresponding "electronegativities" obtained from bond energies,[40] ionization energies and electron affinities,[60] dipole moments,[61] acidic and basic ionization constants,[62] etc.,[63] this relationship is not exact (nor do the electronegativities obtained by these different methods agree with each other). The hydrogen-attracting power in which we are interested is essentially an "effective charge," since the larger part of the interatomic attraction in a bridge is due to the average positive charge on the hydrogen and the average negative charges on the atoms it bridges between.

We may, therefore, start our table (Table IV) by assigning to F^-, O^{--} and N^{---} the values -1, -2 and -3, respectively. Next we add a fixed amount (say 2/3) for each hydrogen bonded by an ordinary bond to the F, O or N atom and a smaller amount for each bridging hydrogen (say 1/3 for a hydrogen on the near side of an unsymmetrical bridge, 1/6 for one on the far side of an unsymmetrical bridge, and 1/4 for a symmetrically-bridging hydrogen). This procedure is admittedly quite arbitrary and cannot be expected to give more than very rough values for the effective charges; still the relative order of different simple atomic groups should be nearly right.

Columns 2 and 3 of Table IV give the effective charges arrived at in this manner for N, O and F attached to various numbers of bridging and non-bridging hydrogen atoms. Partly to avoid further complication and partly because most of the bridges in organic compounds are probably of the unsymmetrical type, no symmetrical bridges are represented.

The table may be extended by making use of the idea that an atom to which a group R is bonded has a less negative effective charge (*i.e.*, has a smaller attraction for H^+) the more electronegative R is. In this connec-

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[60] Mulliken, *ibid.*, **2**, 782 (1934); **3**, 573 (1935).

[61] J. G. Malone, *ibid.*, **1**, 197 (1933); M. G. Malone and A. L. Ferguson, *ibid.*, **2**, 99 (1934).

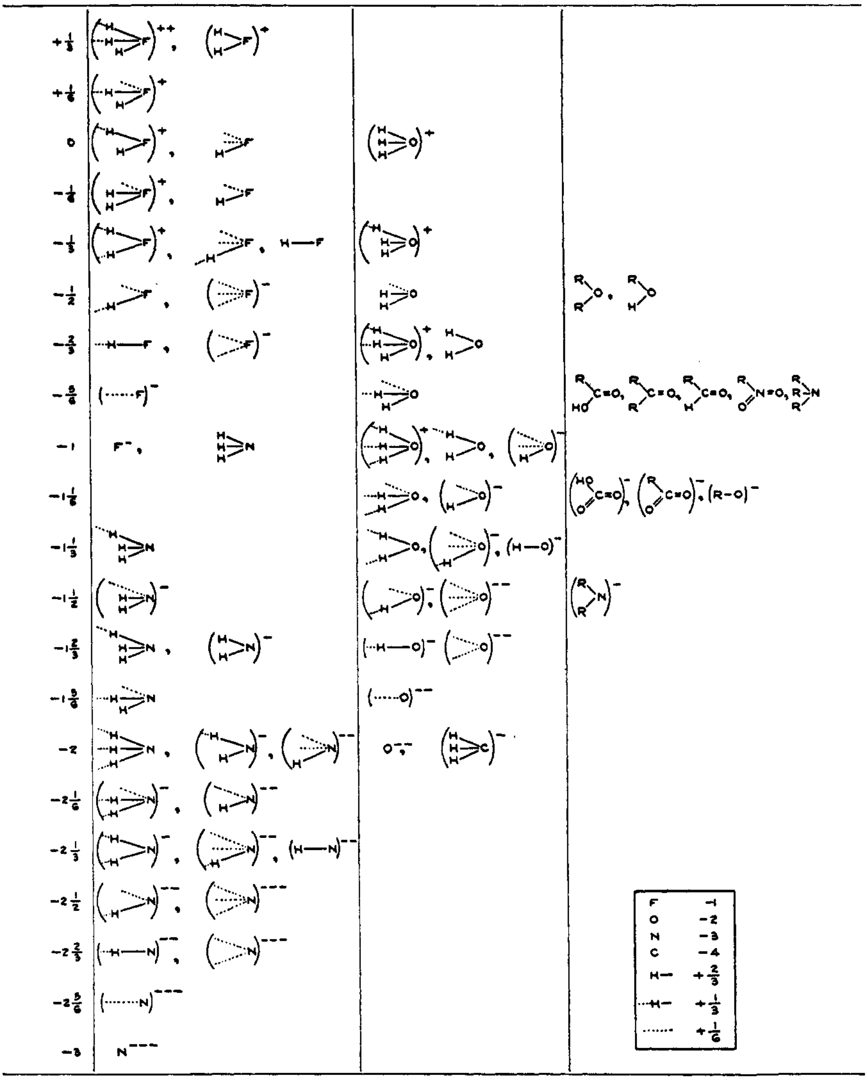
[62] Hixon and Johns, *J. Am. Chem. Soc.*, **49**, 1786 (1927); Goodhue and Hixon, *ibid.*, **56**, 1329 (1934); **57**, 1688 (1935).

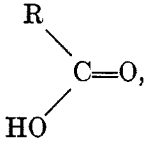
[63] Kharasch and Marker, *ibid.*, **48**, 3130 (1926); Kharasch and Flenner, *ibid.*, **54**, 674 (1932); Kharasch and Reinmuth, *J. Chem. Educ.*, **5**, 408 (1928).

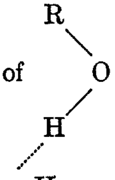
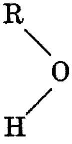
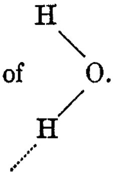
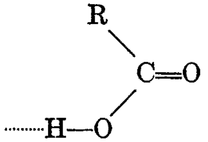
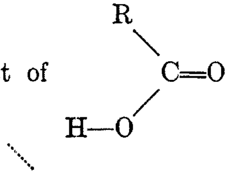
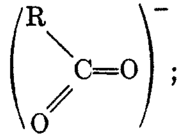
tion calculations of electronegativity or "electron sharing ability" made by Hixon and others[62,63] from ionization constant data for organic acids

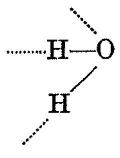
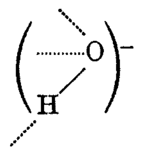
TABLE IV

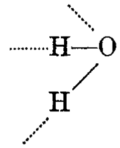
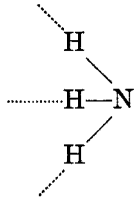
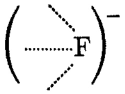
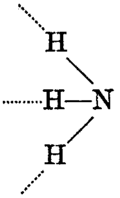
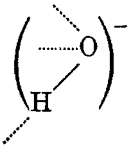
Approximate "Effective Charges" of C, N, O, and F Atoms Bonded in Various Ways to Other Atoms



and bases and from other sources are of considerable value, if used with due care. (The value given by Hixon for hydrogen, based primarily on a comparison of the dissociation constants of HNH_3OH and RNH_3OH in water solution, is for a hydrogen bridging to a water oxygen, and quite different from that for a non-bridging hydrogen.) Since the purpose of the present article is not to give a critique of electronegativity values for organic radicals, only a few are included in the table. The order in each row of Column 4 is the order of increasingly negative effective charges. For instance, of the molecules listed in the row labelled −5/6, the effective charge of the first, , is slightly more negative than that of H_2O, the effective charge of the last, R_3N, is slightly less negative than H_3N, and the others have intermediate values of effective charge.

The table of effective charges can be readily extended further by simple qualitative considerations. For example, the effective charge of  is more negative than that of  but less negative than that of . Likewise, the effective charge of  is more negative than that of  but less negative than that of ; R_2C=O has a less negative effective charge than R_2C=O, etc.

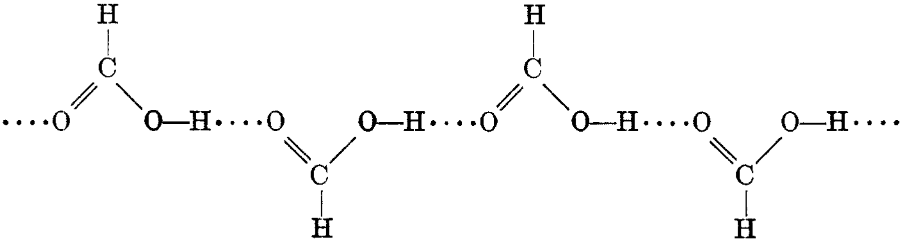
In most of the known examples of hydrogen bridges, the bridged atoms have effective charges between −1/2 and −1 1/2. In ice each hydrogen bridges between  (e. c. = −1 1/6) and  (e. c. =

−1 1/3). The polarity or dissymmetry of the bridge is not very great. A hydrogen ion in water solution is probably $H_5O_2^+$, consisting of a symmetrical bridge between two  groups (e. c. = −1 1/6). In solid NH_4F the bridges are quite unsymmetrical, being between  and  systems (e. c. = −2 and −1/2 respectively). (The difference in effective charges is partly compensated for by the smaller size of the fluorine atom as compared to the nitrogen. The interatomic distance in the normal HF molecule is considerably less than that in NH or NH_3). The hydrogen joining nitrogen and oxygen atoms in an ammonium hydroxide molecule bridges between  and  (e. c. = −2 and −1 1/3 respectively). The central hydrogen is more tightly held by the nitrogen than by the oxygen.

For an unsymmetrical bridge the degree of dissymmetry, as regards the strengths of the two bonds of the bridge, must approximately parallel the difference in the effective charges. If both X atoms have small values of effective negative charge, the bridge is unsymmetrical and weak, readily broken by molecular collision and intramolecular vibrations. If one of the X atoms has a very large (negative) value of effective charge, the bridge is very strong on one side and weak on the other. (The weak side is stronger the more negative the effective charge at the second X atom; both sides cannot be strong at the same time, however.) The strongest bridges are those in which both X atoms have intermediate effective charges of practically the same magnitude. Suitable polarization of the X atoms also helps, especially if sufficient to make the potential curve for the oscillating hydrogen one with a single minimum.

OHO BRIDGES INVOLVING CARBOXYL GROUPS

Carboxyl groups seem to be especially well adapted to bridge formation. The carboxyl hydrogen is held loosely enough so that it can be shared readily with a suitable electronegative atom elsewhere. The carboxyl oxygen atoms likewise act as receivers for hydrogen atoms held loosely enough elsewhere. One result of this dual rôle played by carboxyl groups is the tendency shown by carboxylic acids to polymerize, in the vapor and liquid states and in solution in non-polar solvents such as benzene. As already noted, this polymerization usually stops at the double molecule,* in which both of the acidic hydrogen atoms are utilized in bridge formation. With formic acid in the liquid state, however, Kumler's dielectric constant evidence[26] indicates some string polymerization, perhaps in this manner:



(Although here and elsewhere we are tentatively assuming the hydrogen bridges to be unsymmetrical, as represented by O—H ··· O, the possibility that in some cases they may be of the symmetrical type, O—H—O, must be borne in mind.) Perhaps the closing of the ring, to form a dimer containing two bridges, involves more strain—more deviation from the preferred angles between bonds—in this case than in the cases of the higher fatty acids. The strain cannot be great, however, judging from the existence and stability of the formic acid dimers in the vapor state. Alternatively, one can explain Kumler's results by postulating intermolecular C—H ··· O bridges, as discussed in a later section.

X-ray studies[64] of fatty acids in the solid state show that the molecules are arranged in parallel layers "head to head" (Fig. 2). One may feel sure that the heads are joined through hydrogen bridges, either (*a*) to form

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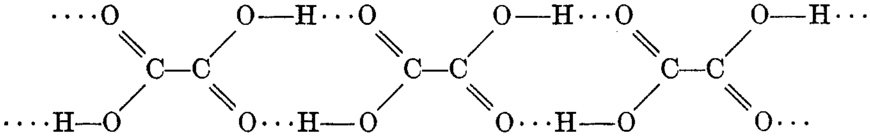
* For spectrum evidence for association involving hydrogen bridge formation in liquid acetic acid, see reference 64*a*.

[64] For references see Ewald and Hermann, "Strukturbericht, 1913–1928," Akademische Verlagsgesellschaft, Leipzig, **1931**, or Wyckoff, "The Structure of Crystals," Chemical Catalog Co., New York, 2nd Edition, **1931**.

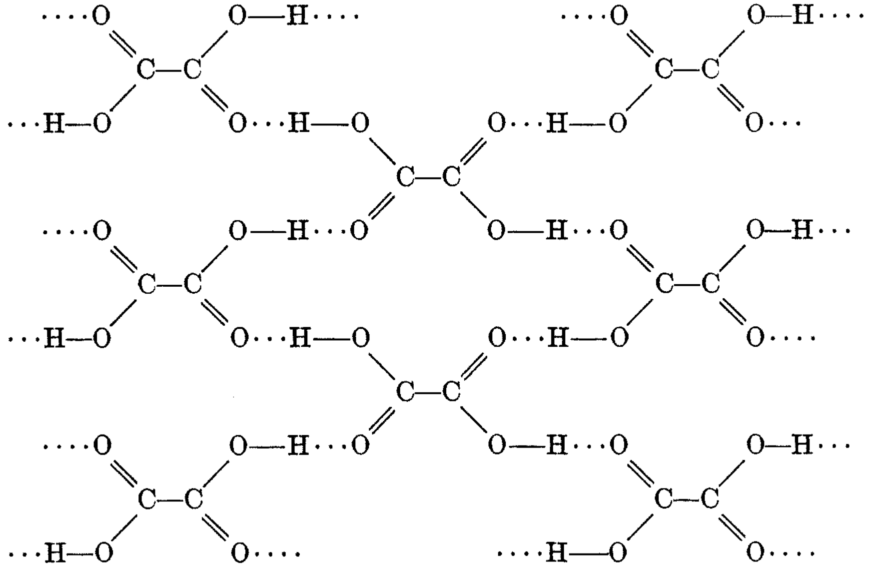
[64a] Gillette and Daniels, *J. Am. Chem. Soc.*, **58**, 1139 (1936); Wilson, *J. Chem. Soc.*, **1936**, 492.

dimers, or (*b*) to form strings of molecules somewhat like the ionic strings in the $NaHCO_3$ crystal.

X-ray studies of oxalic acid and some of its derivatives have led to very interesting results. In the β form of oxalic acid[53] two-bridge rings like those in formic and acetic acid dimers exist, joining the oxalate groups together into long strings extending completely through the crystal:



In the α form of oxalic acid the four oxygen atoms of each oxalate group are connected by hydrogen bridges with oxygen atoms of *four* other oxalate groups, somewhat as represented below:



The α and β forms of the acid are related to each other as are the two possibilities mentioned above for the solid fatty acids.

In crystals of oxalic acid dihydrate,[54] $H_2C_2O_4 \cdot 2H_2O$, there are no bridges directly joining carboxyl oxygens. The water oxygen atoms are so placed, however, as to make it very probable that each is connected by (unsymmetrical) hydrogen bridges to three oxygens of different oxalate groups. If, as seems likely, the stronger end of each OHO bridge is that at the water oxygen, the structure can be described as an assemblage of $C_2O_4^{--}$ and H_3O^+ ions, joined by hydrogen bridges. As would be expected from the electronic structure of the H_3O^+ ion, $\mathrm{H}:\underset{\mathrm{H}}{\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{O}}}}:\mathrm{H}$, the three bridges radiating from its oxygen are not coplanar. One of the two oxygen atoms of each carboxyl group is connected by two bridges to water oxygens; the other is the terminus for only one bridge.

In[53] $K_2C_2O_4 \cdot H_2O$ and $Rb_2C_2O_4 \cdot H_2O$ each water oxygen is tetrahedrally surrounded by two potassium ions and two oxalate oxygens, the water hydrogen atoms undoubtedly bridging to the latter. The water molecules and oxalate ions are in strings, somewhat as represented below:

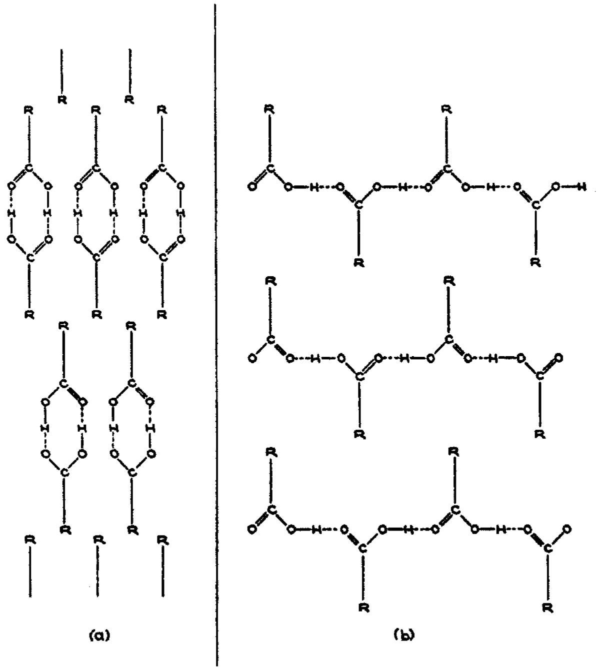
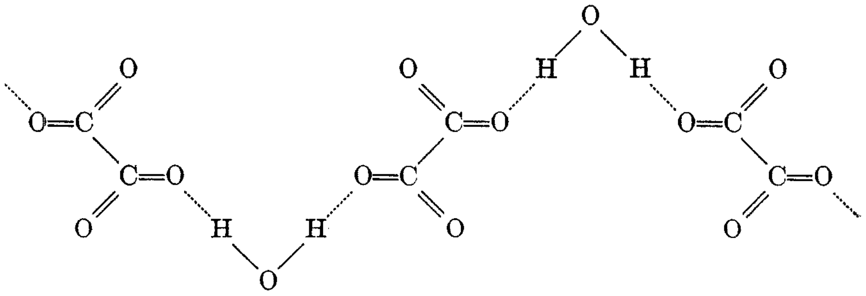


FIG. 2.—DIAGRAMMATIC REPRESENTATION OF ALTERNATIVE ATOMIC DISTRIBUTIONS IN FATTY ACID CRYSTALS

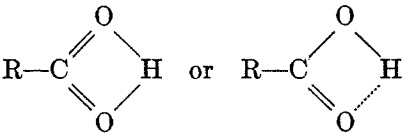


The bridges are here probably more unsymmetrical and weaker than in $H_2C_2O_4 \cdot 2H_2O$, principally on account of the greater electronegativity of the H_2O oxygen as compared with the H_3O^+ oxygen. The reported value for the OHO bridge distance of about 3.3 Å is somewhat larger than would be expected; it is very likely in error, owing to the probably incorrect assumption of coplanar oxalate groups (see reference 55).

In crystals[53] of KHC_2O_4 and $RbHC_2O_4$, as in solid oxalic acid itself, the hydrogen atoms bridge between oxygen atoms of different oxalate groups. A distribution of hydrogen atoms such that each is surrounded at practically equal distances by three oxalate oxygen atoms is not definitely ruled out by the X-ray data but would seem to be quite improbable.

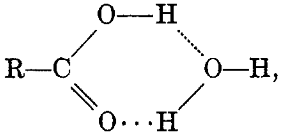
The monohydrate of ammonium oxalate, $(NH_4)_2C_2O_4 \cdot H_2O$, has been especially carefully studied.[55] Each ammonium nitrogen atom is tetrahedrally surrounded by three oxalate oxygens (2.76–2.85 Å) and one water oxygen (2.88 Å). Each water oxygen is tetrahedrally surrounded by two ammonium nitrogens (2.88 Å) and by two oxalate oxygens (2.80 Å). In the writer's opinion, these adjacent electronegative atoms are connected by hydrogen bridges. This makes each oxalate oxygen the weaker terminal for *two* bridges, instead of one, as in the two forms of anhydrous oxalic acid, or two for two of the oxygens and one for each of the other two, as in oxalic acid dihydrate. This fact and the larger number of bridges ending at each water oxygen probably are responsible for the larger OHO distances observed. The large NHO distances agree with the large values found for corresponding bridges in $NH_4H_2PO_4$ and are probably due in part to the large dissymmetry of such bridges. The N—H end is much stronger than the O—H end, as shown by a comparison of the effective charges.

In a single unpolymerized carboxylic acid molecule (not in water or alcohol solution) it seems reasonable to suppose that the acidic hydrogen bridges between the two oxygen atoms of the same carboxyl group (one of two alternatives suggested by the writer in 1920), either symmetrically or unsymmetrically:

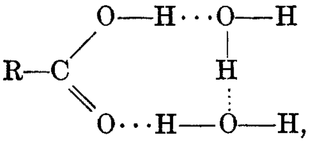


In either case there must be considerable strain. Bridges between different carboxyl groups would be expected to be much more stable, in agreement with experiment.

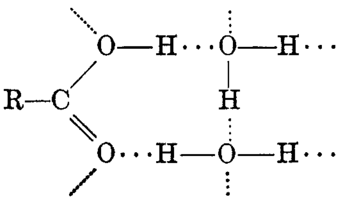
In dilute water solution the carboxylic acids are apparently monomeric, although undoubtedly hydrated. Small rings, involving only one carboxyl and one water molecule would seem to be possible, with some strain:



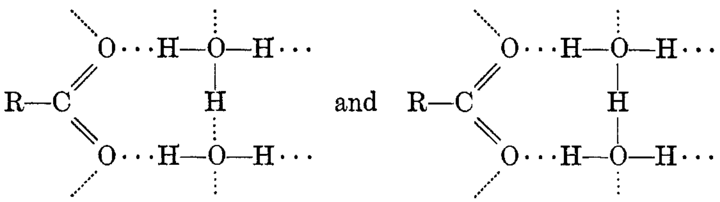
but larger rings, *e.g.*,



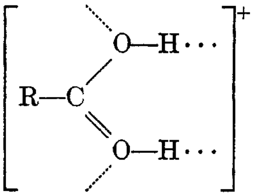
are more probable, especially reasoning by analogy with the structure of crystalline oxalic acid dihydrate. Besides the bridges represented in this formula, each carboxyl oxygen can, of course, be a terminal for another bridge to a water oxygen. The average RCO_2H molecule, like the average H_2O molecule, is thus connected by bridges to several (probably usually four) neighboring water molecules. Assuming these bridges to be all unsymmetrical, one can properly speak of a "molecule" of the acid if one (only) of the bridging hydrogens is tightly held to its carboxyl oxygen:



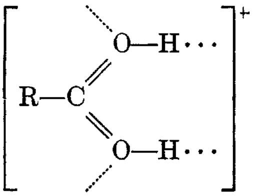
If the carboxyl end is the weaker end of *all* these bridges, the stronger ends all being oxygens of water molecules, one can properly speak of a carboxyl "ion." Bridge systems such as represented by the formulas



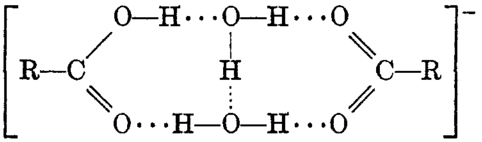
may also exist. If so, should we refer to the assemblage as a molecule or as an aggregate of ions? Furthermore, other systems such as



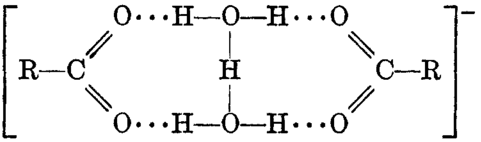
or



which we might call an H_2A^+ ion, and



and



which are perhaps best considered as HA_2^- ions, would also seem reasonable. Considerations such as these show how over-simplified is the usual treatment of water solutions of ionizable substances as containing (besides water) only three substances—AB, A^+ and B^-—in equilibrium with each other.

Greenspan[65] has shown that the ratios of the first and second dissociation constants of the "straight-chain" dicarboxylic acids (with the possible exception of malonic acid), in water solution, can be very nicely accounted for on the assumption of zigzag chains of the dimensions found for long chains in the solid state. It seems certain, therefore, that these acids (excepting malonic) contain intramolecular hydrogen bridges, joining the end carboxyl groups, only infrequently, if at all.* This may be explained either as a result of saturation of the "affinities" of the carboxyl oxygens and hydrogens by bridge formation to water molecules, or as due to the

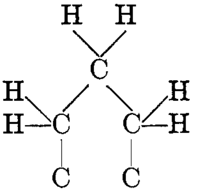
[65] GREENSPAN, *Chem. Rev.*, **12**, 339 (1933).

* The assumption of extended zigzag chains also seems necessary to account for the relationships found by MacInnes[66] and by Greenstein[67] between the dissociation constants of substituted acids and the distance between the carboxyl and the substituent group.

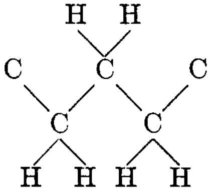
[66] MACINNES, *J. Am. Chem. Soc.*, **50**, 2587 (1928); SCHMIDT, APPLEMAN, AND KIRK, *J. Biol. Chem.*, **81**, 723 (1929); EDSALL AND BLANCHARD, *J. Am. Chem. Soc.*, **55**, 2337 (1933); GREENSTEIN, *J. Biol. Chem.*, **96**, 499 (1932).

[67] GREENSTEIN, *J. Am. Chem. Soc.*, **58**, 1314 (1936).

repulsions between hydrogen atoms on adjacent carbon atoms, making the zigzag arrangement for the hydrocarbon part of the chain more stable than the type of arrangement which would be necessary in a ring.†

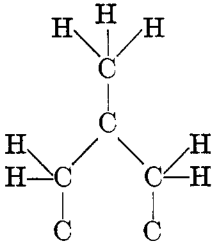


Considerable repulsion between hydrogen atoms attached to adjacent carbon atoms



Little or no repulsion between hydrogen atoms attached to adjacent carbon atoms

If the first of these explanations is correct and the second relatively unimportant, the "straight-chain" dicarboxylic acids (except oxalic acid and possible malonic acid) might well prefer a ring structure in dilute solutions in non-polar solvents. It is interesting that in *substituted* glutaric acids the carboxyl groups are apparently quite close to each other, undoubtedly held together by hydrogen bridges, either directly or through water molecules. An R group would be expected to have little or no repulsion for hydrogen atoms attached to the adjacent carbon atoms, whether a coiled or zigzag arrangement existed. Substitution, therefore, permits a bend in the chain and so aids hydrogen bridge formation between the end groups



Little or no repulsion between the atoms of an R group and the H atoms attached to the adjacent C atoms

Cis $C_2H_2(CO_2H)_2$ and cyclo acids such as cyclopentane-1,1-diacetic acid also have small apparent distances between carboxyl groups. We would certainly expect hydrogen bridges joining the carboxyl groups in these compounds.

As will be mentioned in the next section, hydroxyl hydrogen atoms

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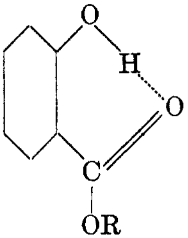
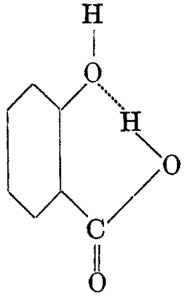
† This line of argument is essentially the same as that used (independently) by Pauly[68] and the writer[69] to account for the zigzag structure which we postulated as the preferred orientation for long-chain compounds (thereby accounting for the well-known alternation in their melting points and other properties).

[68] PAULY, *Z. anorg. Chem.*, **119**, 271 (1922).

[69] HUGGINS, Boston Meeting of the American Association for the Advancement of Science, 1922.

frequently form intramolecular bridges to suitably place ketonic oxygens of carboxylic esters. One may predict with reasonable assurance also that the acidic hydrogens of carboxyl groups can bridge to properly placed oxygens of such groups as —OH, —NO_2, —CO_2R, etc., or to nitrogens in —NH_2 etc., just as they do to the oxygens of H_2O molecules or other —CO_2H groups. The bridges in salicylic acid and in salicylic esters probably have different polarity, as indicated by the following formulas:





OHO BRIDGES INVOLVING HYDROXYL GROUPS

Long-chain alcohols in the solid state exist,[70] like the acids, in pairs of layers, with the heads (hydroxyl groups) of one layer adjacent to the heads of each pair of the other layer. The results of an X-ray investigation made by Wilson and Ott[71] of a number of these alcohol crystals are in agreement[72] with a structure such as indicated in Figure 3. Assuming as an approximation that all adjacent bonds make tetrahedral angles with each other and that the C—C and C—O distances are equal to the sums of the single bond radii, it can be readily calculated from the X-ray intensity data that the OHO bridge length is 2.68 Å. Although no accuracy can be claimed for this result, it is approximately what would be expected.

In crystalline hydroquinone,[73] centrosymmetric molecules are grouped around threefold symmetry axes, with hydrogen bridges connecting adjacent molecules.

Alcohols have long been considered as associated liquids. Cryscopic measurements[74] on their solutions in non-polar solvents show that, unlike the carboxylic acids, the association does not stop at the dimer stage. The association was explained by Latimer and Rodebush[5] as due to hydro-

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[70] Malkin, *J. Am. Chem. Soc.*, **52**, 3739 (1930).

[71] Wilson and Ott, *J. Chem. Phys.*, **2**, 231, 239 (1934).

[72] Huggins, Unpublished calculations.

[73] Huggins, Unpublished results reported at the Kansas City Meeting of the American Chemical Society, 1936.

[74] Auwers, ref. 19; *Z. physik. Chem.*, **15**, 33 (1894).

gen bridge (or "bond") formation. Kumler's dipole moment studies[26] furnish definite evidence for the existence of such bridges in the liquid. Most conclusive, however, is the analysis by Zachariasen[75] of the X-ray data obtained by Stewart and Morrow[76] from liquid methyl alcohol. He concludes that nearly every molecule is connected to two others by unsymmetrical hydrogen bridges roughly 2.6 Å long and making approximately tetrahedral angles with each other. This is the same type of arrangement as that deduced by the writer for the solid alcohols, differing in that it is less regular and is constantly changing.

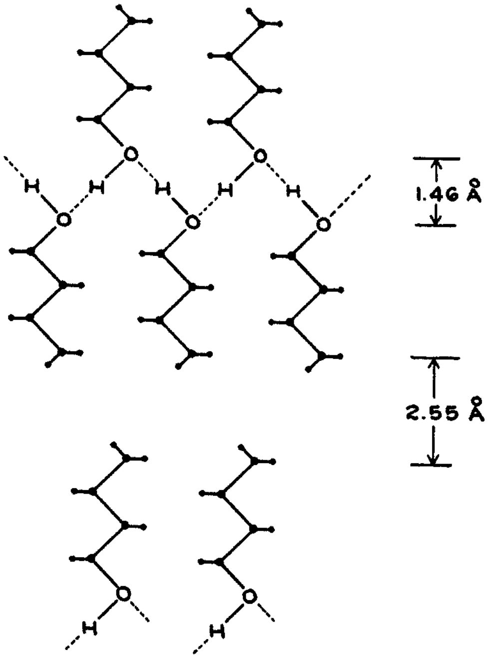

Fig. 3.—Diagrammatic Representation of the Atomic Distribution in a Crystal of a Solid Alcohol

The tendency of a compound composed of molecules to form a glass rather than a crystal on cooling can be related to the possibility of satisfying to practically the same degree the intermolecular forces by various different relative orientations of neighboring molecules. With the alcohols the chief intermolecular forces are those involved in hydrogen-bridge formation. With a simple alcohol we may reasonably assume two hydrogen bridges terminating at each oxygen atom, but these may be oriented in various ways with respect to the rest of the molecule and, within rather wide limits

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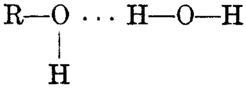
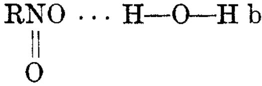
[75] Zachariasen, *J. Chem. Phys.*, **3**, 158 (1935).

[76] Stewart and Morrow, *Phys. Rev.*, **30**, 232 (1927).

with respect to each other. This permits many different configurations, all having nearly the same energy, for groups of neighboring molecules, thus accounting for the well known tendency shown by many alcohols to form glasses, instead of crystals, on supercooling. As would be expected, this is especially marked for poly-alcohols in which the relative positions and orientations of the different C—O bonds are not fixed by intramolecular forces.

As pointed out by Hildebrand,[25] the high solubility of alcohols in water, as compared with organic chlorides and iodides (having roughly equal dipole moments) for instance, is attributable to the possibility of bridge formation between the alcohols and water molecules (See Table I). The fact that both $R—O—H \cdots OH_2$ and  $R—\underset{\underset{H}{|}}{O} \cdots H—O—H$ bridges are possible, with strengths comparable with the strengths of the bridges between different water molecules in liquid water and between different alcohol molecules in the liquid and solid alcohols, is an important factor. Although a nitrobenzene molecule may form  $R\underset{\underset{O}{\|}}{N}O \cdots H—O—H$ bridges, these are more polar and considerably weaker.

Plotting the heat of hydration against the entropy of hydration for various organic compounds, Butler[77] finds the values for non-polar molecules lying on or near one straight line, while those for alcohols and amines (which can hold, by bridge formation, to both oxygens and hydrogens of water molecules) lie on or near another straight line. The values for acetone, ethyl acetate and ethyl ether (which can form bridges to water only through the water hydrogens) are near a third straight line intermediate in position between the other two.

The ability of molecules of water, hydrogen fluoride, carboxylic acids and alcohols to form bridges both by giving hydrogens and by adding hydrogens is undoubtedly largely responsible for their solvent power for polar compounds.

There is considerable evidence for the existence of weak additive compounds between phenols and ketones[78] and between phenols and cyclic ethers.[79] These in all probability contain OHO bridges.*

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[77] BUTLER, Faraday Society Discussion, Sept., 1936.

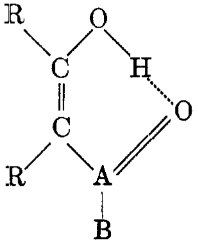
[78] BRAMLEY, *J. Chem. Soc.*, **109**, 496 (1916).

[79] BELLUCCI AND GRASSI, *Gazz. chim. ital.*, **43**, 712 (1913); MORGAN AND PETTETT, *J. Soc. Chem. Ind.*, **54**, 22 (1935).

* Gordy,[79a] studying the infra-red spectra of various liquid mixtures, has recently reported evidence for the existence of hydrogen bridges in mixtures of an alcohol (or water) with various other organic liquids (*e.g.*, ethyl acetate).

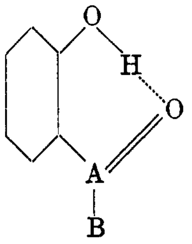
[79a] GORDY, *J. Chem. Phys.*, **4**, 749 (1936).

The careful and extensive studies by Hilbert, Wulf, Hendricks and Liddel[27] of intramolecular hydrogen bridges between hydroxyl groups and electronegative atoms in other groups furnishes us with considerable evidence regarding the limitations of such bridges. All but one of the compounds that these authors report as containing OHO hydrogen bridges, on the basis of the absence of the characteristic OH absorption band in the near infra-red, belong to the following three similar classes:*

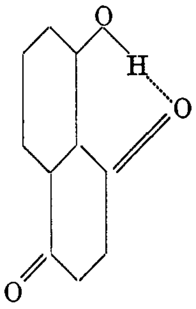


I

A = C, N or S; B = H, R, OR, O, NH$_2$ or nothing

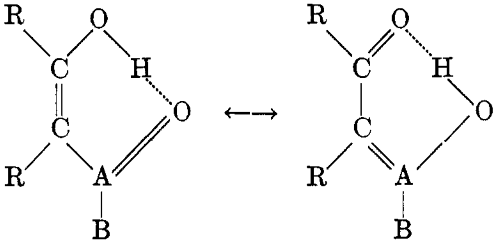


II



III

The ring produced by the bridge is in all three types six-membered; also it contains either two conjugated double bonds or one bond conjugated with a benzene ring. Such a distribution of bonds weakens the attraction of the hydroxyl oxygen for its hydrogen, at the same time strengthening the attraction of the oxygen on the other side for this same hydrogen. Using the resonance terminology, one can say that the ring containing the bridge is stabilized because of resonance between two forms. We may represent this (for Type I) as follows:



Another contributing factor is the increased rigidity imparted to a ring by a double bond or a benzene ring, making the single bonds on each side

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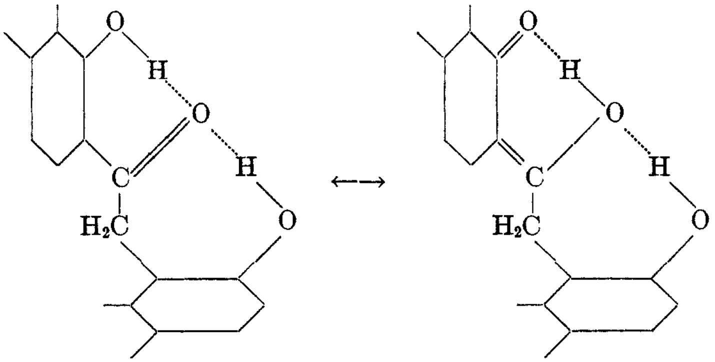
* It should be noted that compounds of these types had previously been considered, on the basis of evidence of other kinds, to have bridge structures. A number of such cases have been discussed by Sidgwick,[24] for instance.

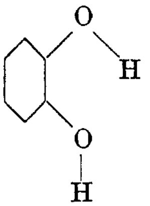
necessarily coplanar, or very nearly so. The resonance just mentioned undoubtedly increases this rigidity. Since one of the bonds of a hydrogen bridge is relatively easily broken, compared with most ordinary bonds, this rigidity may be necessary in many cases in order that the bridge withstand the forces due to intramolecular vibrations and collisions.

The only case reported[27] of an intramolecular OHO bridge system not conforming to one of the three types mentioned is that of derritol. The part of the molecule of interest may be represented as follows:

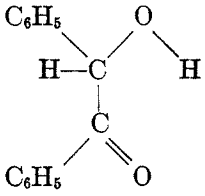


Besides a normal six-membered hydrogen-bridge ring, there is a seven-membered ring containing a bridge. The distance and angle requirements for hydrogen-bridge stability are satisfactorily met, since the atoms need not all be in the same plane, and a double bond and a benzene ring contribute to the rigidity, but resonance such as is assumed for the six-membered ring is impossible. It would be interesting to see whether the hydrogen bridge would be stable in a similar compound without the adjacent six-membered resonating ring.

Of the compounds studied by Hilbert, Wulf, Hendricks, and Liddel which might possibly have been expected to contain OHO bridges, but which, from their experiments, do not (in a large proportion of the molecules at least), some such as

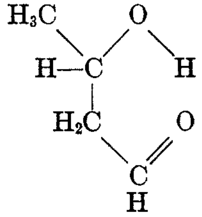


and



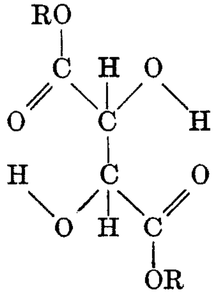
have unfavorably large distances between the oxygen atoms which would be bridged together and would also require a very much bent bridge or one in which the O—H bonds make angles with the other bonds which are far from the preferred angles.

In several compounds, such as aldol (β-hydroxybutyraldehyde)



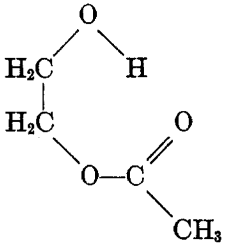
in which hydrogen bridges would produce six-membered rings, it has been suggested that the failure to find these is due to "low electron affinity" (*i. e.*, too large an attraction for the hydrogen) of the hydroxylic oxygen. It would be better to say that the non-existence of a stable bridge is due to the combination of too large an effective (negative) charge on one oxygen with too small an effective (negative) charge on the other oxygen concerned. If the non-hydroxylic oxygen had a sufficiently great hydrogen-ion attraction, a stable bridge should result, in spite of the "low electron affinity" of the hydroxylic oxygen. (See the discusson of diethylaminopropanol in the next section.)

Other factors which, as pointed out by Hilbert, Wulf, Hendricks, and Liddel, also tend to decrease the stability of the hypothetical hydrogen bridges in these cases are the lack of rigidity and the impossibility of resonance (of the kind discussed above for Types I, II and III), when only one double bond is present. An additional important factor is that the so-called "free" rotation around single bonds is hindered by the attractions and repulsions of neighboring non-bonded atoms. It may well be that repulsions between neighboring hydrogen atoms or between hydrogen atoms and larger groups are sufficient to prevent a plane or nearly plane bridge ring and make the distance between the oxygens concerned too large for a strong bridge. In the tartaric esters (which also apparently do not contain hydrogen bridges)

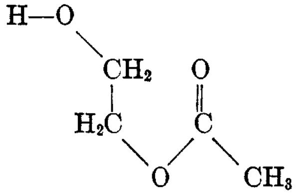


the repulsions between non-bonded oxygen atoms (other than those which might be joined by bridges) are probably important, forcing orientations around the various single bonds which result in too large an O—O distance for each of the hypothetical bridges.

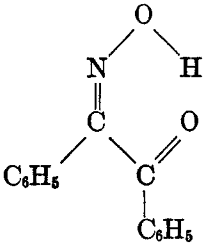
Similar reasoning can be used to explain the apparent non-existence of a seven-membered ring bridge in ethylene glycol monoacetate,



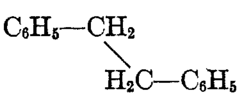
or



and of a six-membered ring bridge in either α or β benzil monoxime, one or the other of which might be expected to have the orientation,



In this last compound a planar ring containing a bridge would make the two phenyl groups so close together that rotation around the $C-C_6H_5$ bonds would not be possible, unless suitably synchronized. The "collisions" which would be expected between these rings, as a result of their normal thermal motions, would be expected to be powerful enough to break any but a very strong bridge. It may be noted in this connection that in crystalline bibenzyl[80] each molecule has a center of symmetry, the orientation of the single C—C bonds being as indicated by the formula



$$\begin{array}{l} C_6H_5\text{—}CH_2 \\ \qquad\quad \diagdown \\ \qquad\quad H_2C\text{—}C_6H_5 \end{array}$$

The enolic forms of acetylacetone and similar β diketones are typical examples of substances of Type I. For these and also for various com-

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[80] DHAR, *Current Sci.*, **2**, 480 (1934); *Indian J. Physics*, **9**, 1 (1934); ROBERTSON, *Proc. Roy. Soc.* (London), **A146**, 473 (1934); *ibid.*, **A150**, 348 (1935); *Nature*, **134**, 381 (1934).

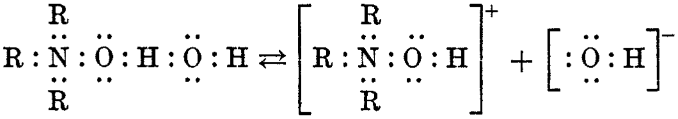
pounds of Types II and III the reactivity of the bridge hydrogen, for certain kinds of reactions such as replacement by a suitable metal, has long been realized. The negative ion resulting from the removal of the (bridging) hydrogen as hydrogen ion normally occupies *two* coördination positions around the metal ion, as would be expected. The metal serves to bridge between two oxygens just as did the hydrogen.

It has also been recognized for many years that hydroxyl groups which are *ortho* to certain other groups such as —CO_2R and —N═N—R do not behave like other hydroxyl groups.[3] In solution in benzene for instance, they do not show the association characteristic of the corresponding *meta* and *para* compounds.[81] As a rule these *ortho* compounds have lower boiling points and are less soluble in hydroxylic solvents. The optical rotations,[82] parachors, surface tensions, and densities[83] of *o*-substituted phenols are also anomalous. The hydrogen-bridge theory readily explains these and other similar facts.

The amine oxides, R_3NO are very soluble in water. Without hydrogen bridges, one would expect these compounds either to show no basicity or to be strong bases, like the quaternary ammonium hydroxides, due to the reaction:

$$R_3NO + H_2O \rightarrow R_3NOH^+ + OH^-.$$

Actually the solutions are weakly basic,[84] a fact which must be attributed to hydrogen bridge formation:



$$R:\overset{\displaystyle R}{\underset{\displaystyle R}{\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:H \rightleftarrows \left[R:\overset{\displaystyle R}{\underset{\displaystyle R}{\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:H\right]^+ + \left[:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:H\right]^-$$

OHO hydrogen bridges have been postulated by Brady and Muers[84a] in certain metal dioximes, thus accounting for the lack of reactivity of the hydroxyl groups.

Hydrogen bridges are undoubtedly of great importance in the sugars and in such substances as starch and cellulose. It has been known for some years that cellulose consists of long strings of glucose rings, connected

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[81] AUWERS AND ORTON, *Z. physik. Chem.*, **21**, 337 (1896).

[82] RULE AND MACGILLIVRAY, *J. Chem. Soc.*, **1929**, 401; RULE, SPENCE AND BRETSCHER, *ibid.*, **1929**, 2516.

[83] BURAWAY AND MARKOWITSCH-BURAWAY, *ibid.*, **1936**, 36.

[84] STEWART AND MAESER, *J. Am. Chem. Soc.*, **46**, 2583 (1924); LEWIS, "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., New York, **1923**, p. 111.

[84a] BRADY AND MUERS, *J. Chem. Soc.*, **1930**, 1599; CAVELL AND SUGDEN, *ibid.*, **1935**, 621.

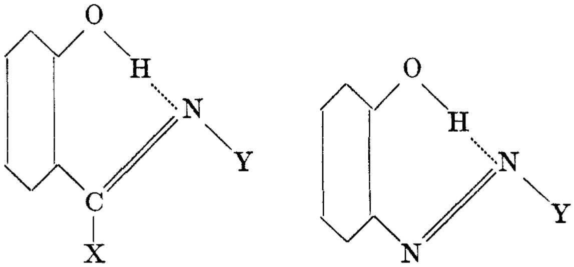
through oxygen atoms, yet the exact distribution of atomic centers is still unknown. It seems safe to predict, however, that the interchain forces will be found to be largely of the hydrogen-bridge type. The ability of cellulose to absorb water is attributable (in part at least) to the possibility of obtaining more nearly the preferred valence angles and interatomic distances by "double bridges"—chain oxygen to water oxygen to chain oxygen—than by single chain-to-chain bridges. (A similar explanation can be given for the absorption of water by various other carbohydrates and proteins.) Hydrated and anhydrous cellulose are related to each other in much the same way as are oxalic acid dihydrate and anhydrous oxalic acid, discussed above.

NHO BRIDGES

Bridges between nitrogen and oxygen atoms in $(NH_4)H_2PO_4$, $(NH_4)_2C_2O_4 \cdot H_2O$ and substituted and unsubstituted ammonium hydroxides have already been mentioned. In general, one would expect ammon*ium* hydrogens to be capable of forming stronger bridges than amino hydrogens, reasoning either from qualitative considerations of negativity or from the results of potential energy calculations made by the writer using band spectrum data. This seems to be in accord with all the observations so far published regarding the existence of hydrogen bridges. For instance, Kumler found no evidence of bridging between molecules in liquid amines.

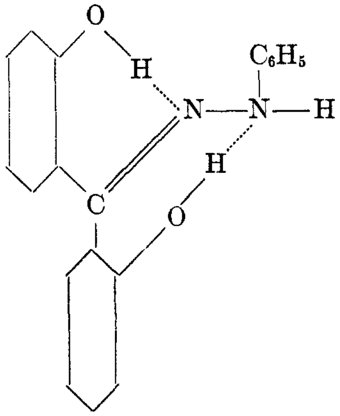
In $(NH_4)_2C_2O_4 \cdot H_2O$ and in $(NH_4)H_2PO_4$ the NHO bridge length is about 2.8 Å, somewhat greater than the usual OHO distance. In general, bridges connecting nitrogen to oxygen are probably quite polar (the N—H bond being stronger than the H $\cdots$ O bond) and weak.

Hendricks, Wulf, Hilbert, and Liddel have recently[27] made a systematic study of intramolecular bridges in which a hydroxyl hydrogen atom bridges to a neighboring nitrogen atom, using, as in their study of OHO bridges, the absence of characteristic OH absorption in the infra-red as their criterion for the presence of a bridge. Their results are quite similar to those obtained in their previous study. Nearly all examples of NHO (or, better, O—H $\cdots$ N) bridges which they report may be represented by the following general formulas:

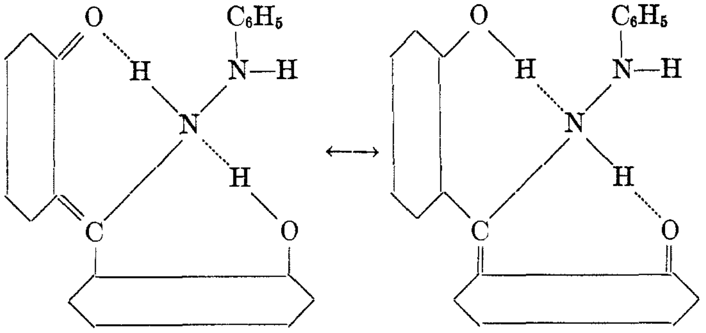


X = H or R
Y = R or OH or OAc or NR_2 or NH_2 or NHR

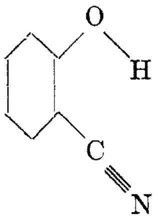
2, 2′-Dihydroxybenzophenone-α-methyl-α-phenylhydrazone, which shows extremely low OH absorption, constitutes a probable exception. Besides the normal six-membered ring containing a hydrogen bridge, most of the molecules (at a given instant) apparently contain a seven-membered ring including a bridge to the α nitrogen atom:

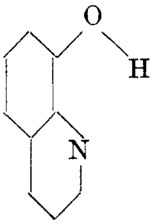


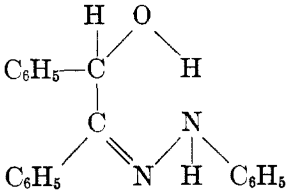
Another possibility is a resonating structure such as represented by the following formulas:

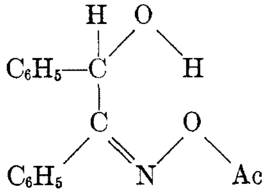


No bridge apparently exists in the following compounds:









In 2-hydroxybenzonitrile, as pointed out by the authors, the distance between the N and O atoms is too large to permit a stable bridge. In addition, it may be noted that the lone pair on the nitrogen is on the side away from the oxygen. The distance argument can also be used to account for the non-existence of five-membered rings in the other three compounds. The absence of six-membered rings containing O—H ··· N and O—H ··· O bridges in the last two substances may be attributed (as in the cases discussed in the preceding section) to insufficient rigidity in the rings, insufficient resonance, insufficient electron affinity of the hydroxyl oxygen, insufficient negativity of the O or N atom on the weak side of the hypothetical bridge, or to repulsion between the phenyl groups, forcing the C—O and C=N out of the same plane and so making the O ··· O or O ··· H distance too large.

This work on O—H ··· N bridges definitely determines the orientation (*cis* or *trans*, *syn* or *anti*) of a number of oximes and related compounds,[84b] thus settling questions which have been debated by organic chemists for many years. Another point to be noted is that, in general, the isomer containing a bridge is more stable than that which has no bridge; in many cases of aldoximes the only form known is the *trans* form, the one in which a bridge occurs. The isomers which cannot form intramolecular bridges can, of course, associate to form intermolecular bridges. Association of oximes is well known. One may make the prediction that a *syn* oxime (for instance) will show more association than its *anti* isomer.

Attempts to find a compound in which there are two O—H ··· N bridges to the same nitrogen, like the two bridges to the same oxygen in 2,2′-dihydroxybenzophenone, were not successful. This is probably due to the existence of only one lone pair of electrons in the valence shell of the nitrogen in all the compounds studied. An appropriately chosen hydroxyazide might conceivably contain two bridges to the same nitrogen, but one would certainly not expect them to any nitrogen atom bonded to two or more other atoms. Two (or more) N—H ··· O bridges or one (or more) N—H ··· O and one O—H ··· N bridge to a single nitrogen are, of course, possible. In $(NH_4)_2C_2O_4 \cdot H_2O$ and in $NH_4H_2PO_4$ a single nitrogen is connected by four N—H ··· O bridges to neighboring atoms. (See also the following discussion of ammonium ion and ammonium hydroxide in solution.)

Just as the hydrogen atoms of each ammonium ion in ammonium oxalate monohydrate and in ammonium dihydrogen orthophosphate bridge to neighboring oxygen atoms, so one would expect such bridges in a water solution containing substituted or unsubstituted ammonium ions. How strong they are and how well they resist thermal agitation and collision, we do not know. The larger the number of such bridges connecting a given nitrogen to neighboring oxygens, the weaker each bridge is, hence

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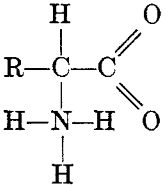
[84b] Blatt and Russell, *J. Am. Chem. Soc.*, **58**, 1903 (1936).

it may be that an ammonium ion in water solution is a terminal for only one, two or three bridges, on the average, at ordinary temperatures, instead of four, as in the crystals mentioned. Increasing the temperature of course tends to break the bridges, decreasing the average number per nitrogen. Since the oxygen of a hydroxyl ion has a much greater attraction for hydrogen ion (*i.e.*, has a larger effective charge) than a water oxygen, a bridge between an ammonium nitrogen and a hydroxyl oxygen is considerably stronger and less easily broken than one between an ammonium nitrogen and a water oxygen. This is undoubtedly the reason for the weak basicity of ammonium hydroxide, a solution of ammonia in water. The nitrogen atom in ammonia or a primary, secondary, or tertiary amine has a negative enough effective charge to have a strong attraction for a water hydrogen atom; this attraction resulting in an NHO bridge (*i.e.*, in NH_4OH or R_3NHOH) as soon as the ammonia or amine is dissolved in water. Whether the hydrogen in this bridge is more tightly held by the nitrogen or by the oxygen is not known. Since the oxygen of an OH^- ion has a more negative effective charge than the nitrogen of an NH_3 or NR_3 molecule, one might jump to the conclusion that a hydrogen bridging between them is more strongly bound by the oxygen. However, the presence of other water molecules around the oxygen in question decreases its effective negative charge (by forming bridges to the lone pairs of that oxygen) and water molecules around the ammonia nitrogen increase its effective charge (by bridge formation through its hydrogen atoms), and the magnitude of these effects can hardly be predicted at present.

The following argument is of interest in this connection. The replacement of one of the hydrogen atoms of ammonia by a more "electronegative" group decreases the attraction of the nitrogen for a hydrogen ion or for a bridging hydrogen of an attached water molecule. The bridge is thus weakened, in such a way as to favor dissociation into RNH_2 and H_2O, with less dissociation into RNH_3^+ and OH^-. Several lines of evidence[40,60] lead to the conclusion that carbon in an aliphatic radical is more electronegative than hydrogen, hence one would expect, from this argument, that the series HNH_2, CH_3NH_2, $(CH_3)_2NH$, $(CH_3)_3N$ would show decreasing basicities, in the order named. Actually, the reverse is the case, a fact which has led chemists[62] to consider the methyl group less electronegative than hydrogen. A simple explanation is possible: the hydrogen atoms of NH_3, RNH_2 and RNH can all form bridges to oxygen atoms of adjacent water molecules. The attractions of these water oxygens, pulling the hydrogen nuclei further from the nitrogen, make them each considerably *more* electronegative than a methyl group. Thus the more hydrogens replaced by methyl groups, the greater the attraction of the nitrogen for the hydrogen bridging it to OH and the greater the basicity. Similar reasoning accounts for the fact that aliphatic alcohols are weaker acids in water solution than is water itself.

Bramley,[78] studying the heat of mixing of pyridine and *o*-chlorophenol, and Glass and Madgin,[33] studying the freezing points of mutual solutions of these substances in benzene and in *p*-dichlorobenzene, have concluded that an additive compound, pyridine *o*-chlorophenoxide, is formed. Glass and Madgin deduce from their data a heat of dissociation of this compound of 6800 cals. per mole. This is presumably the energy of dissociation of the NHO bridges we can assume to be involved. The bridges in the corresponding quinoline compound[38] have, within the error of measurement, the same strength, but those in the compound of *p*-toluidine with *o*-cresol[39] are somewhat weaker (Table II).*

The importance of amino acids justifies a somewhat speculative discussion of their structure, in so far as related to the hydrogen bridge theory, in this paper. An amino nitrogen atom and an oxygen of a carboxyl ion have nearly the same attraction for hydrogen ion, hence, without hydrogen bridges, one would expect nearly equal stability of the two forms



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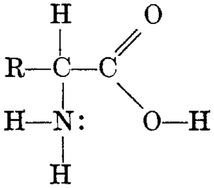


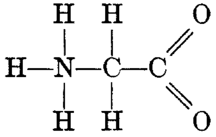
probably with tautomeric equilibrium between them. In water solution, the presence of bridges to the water molecules would be expected to shift the equilibrium in favor of the first ("zwitterion") form. Intramolecular hydrogen-bridge formation in alpha amino acids would require five-membered bridge rings, which, as noted above, apparently are not stable. The fact that ethylene glycol monoacetate and aldol apparently do not form stable bridge rings, (for reasons discussed above) makes their existence in *beta* amino acids somewhat doubtful. However, because the oxygen of a carboxyl ion undoubtedly has a greater attraction for hydrogen ion than has either the ketonic oxygen in an aliphatic acetate or the aldehydic oxygen in aldol, a hydrogen bridge in a *beta* amino acid would certainly be stronger than one in either of these other compounds. Such

* Burnham and Madgin[39a] have recently reported values of 3.5 and 4.2 kcal. per mole for the dissociation energies of compounds of *p*-toluidine with *o*-chlorophenol and *p*-chlorophenol, respectively. Gordy[79a] reports infra-red evidence for hydrogen bridges in mixtures of aniline with several other organic liquids. Changes in the water spectrum on dissolving methyl cyanide he also attributes to association, presumably NHO bridge formation.

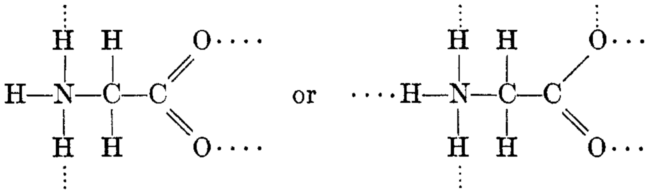
bridges may exist in *beta* amino acid molecules when in the liquid state or in solution in organic solvents, but probably not in water solution.

Gamma and other amino acids which could only form intramolecular bridges by closing seven-membered or larger rings, probably do not do so, except in occasional molecules for limited periods of time, for reasons similar to those mentioned in the discussion of the dicarboxylic acids.

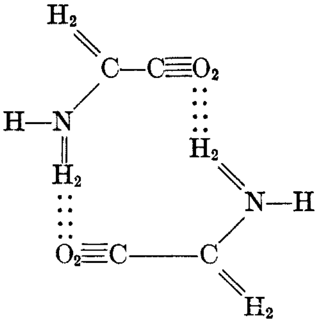
Returning to the consideration of *alpha* amino acids, a few remarks will be made concerning the crystal structure of glycine, the molecular formula of which we may write as



Although we do not expect intramolecular hydrogen bridges, such bridges between different molecules in the crystal (and in the liquid state) would seem to be probable. One would predict that each molecule would be joined to others by at least four, and very likely six, hydrogen bridges, as diagrammatically indicated below:



It will be recalled that in $(NH_4)_2C_2O_4 \cdot H_2O$ each carboxyl oxygen is a terminus for *two* bridges (either both from ammonium nitrogen atoms or one from an ammonium nitrogen and one from a water oxygen) and in $H_2C_2O_4 \cdot 2H_2O$ or $(H_3O)_2C_2O_4$ half of the carboxyl-oxygens are bridged to two water oxygens, the other half to only one. The molecules might conceivably be in pairs, with four hydrogen bridges connecting the two halves of each pair:

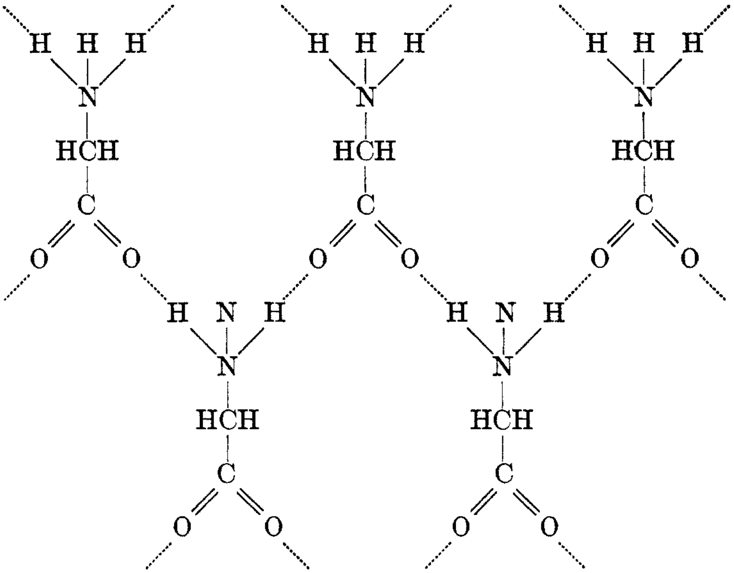


In such a structure though, there would necessarily be strain, due to the considerable bending of the bridges which would be necessary and to the forced close approach of the two hydrogen atoms of adjacent bridges.

One would expect a more stable structure (if geometrically possible with suitable bridge lengths and angles between adjacent bridges) to be one in which the two (or three) bridges leading from each end of a given molecule connect it to two (or three) *different* molecules.

X-ray studies of glycine crystals have been made by Hengstenberg and Lenal[85] and by Bernal.[86] The first study led to the assignment of atomic positions which are certainly incorrect, the methylene carbon being placed quite far out of the plane containing the carbon and oxygens of the carboxyl group. Bernal did not arrive at atomic positions, but came to some conclusions regarding the symmetry and relative orientations of the molecules (in both α and β crystal forms) from considerations of symmetry, cleavage and the assumption that the strongest intermolecular forces are between positive ammonium groups and negative carboxyl groups.

Structures are possible for these crystals which agree both with Bernal's deductions and with the predictions regarding intermolecular bridges made above. In both forms one can assume layers of molecules joined by hydrogen bridges in the manner schematically represented here:



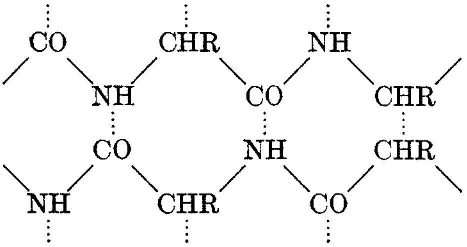
The third hydrogen attached to each nitrogen is not far from a carboxyl oxygen of a molecule in an adjacent layer, probably forming a bridge to it.

[85] Hengstenberg and Lenal, *Z. Krist.*, **77**, 424 (1931).

[86] Bernal, *ibid.*, **78**, 363 (1931).

The distribution within each layer is practically the same in the two crystal forms. They differ chiefly in having different ways of placing the layers relative to each other, both ways satisfying the N—H ··· O attractions just mentioned.

The deductions of Astbury and coworkers[87] regarding protein structure, and, in particular, the structure of *alpha* (unstretched) and *beta* (stretched) keratin (hair), fit in very well with the hydrogen-bridge theory. The *alpha* form is depicted as consisting of extended chains held together by van der Waals attractions between the R radicals and between CO groups of each chain and NH groups of adjacent chains, thus:



Except where there are cross-linkages, as by cystine radicals, or "interchain salt linkages" (probably involving hydrogen bridges similar to those we have assumed in glycine crystals), the dots between CHR groups in this diagram probably represent only very weak attractions compared to those between CO and NH and would perhaps be better omitted. The CO ··· NH dots undoubtedly represent hydrogen bridges. If so, Astbury's picture must be modified slightly, for several reasons. (1) The NH bonds would not be expected to be coplanar with the two adjacent C—N bonds, since three bonds attached to a nitrogen atom are usually tetrahedrally directed. This N—H bond will, therefore, not point toward the nearby oxygen (in another chain), unless the planes of the two chains are not the same. (2) The NHO distance given (∼ 2.50 Å) is too small as compared with other NHO bridges. (3) The orbitals of the two lone pairs on each oxygen both have their maxima in the plane of the chain to which the oxygen is attached, hence with the orientation shown, the direction of neither of these maxima coincides even approximately with the direction of the hydrogen of the adjacent NH. How important this factor is we do not know; if the O ··· H attractions are largely of an ion-dipole nature, without much direct electron-pair sharing, it may have little influence. (4) The measured "unit distance" along the chain (6.76 Å) is somewhat

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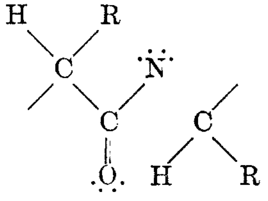
[87] Astbury, "Fundamentals of Fibre Structure," Oxford Univ. Press, **1933**; see also Wrinch, *Nature*, **137**, 411 (1936); **138**, 241 (1936); Frank, *ibid.*, **138**, 242 (1936); Wrinch and Lloyd, *ibid.*, **138**, 758 (1936).

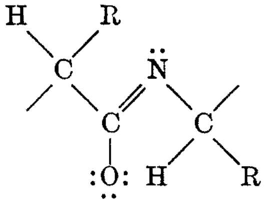
smaller than would be expected (7.32 Å calculated from the atomic radii, assuming tetrahedral angles) on the basis of a plane chain.

The foregoing objections to the details of Astbury's picture can readily be taken care of by shifting somewhat the relative positions and orientations of the two chains, with some twisting and folding and considerable bending of the bridges. There is, however, another way out of the difficulty. Since with hydrogen bridges both the NH and the OH bonds are quite polar, the structure of the rest of the assemblage would be expected to approximate what it would be with complete removal of the hydrogens (as ions). Without introducing resonance there are three reasonable possibilities for the structure of each resulting negative ion:

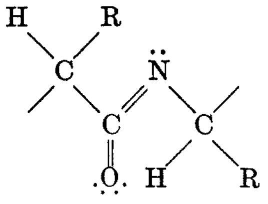
(*a*)



(*b*)



(*c*)



Of these, the first would have a higher energy (be less stable) than either of the others, hence the actual electron distribution would be expected to correspond to a state of affairs intermediate between (*b*) and (*c*) (*i. e.*, to "resonate between these states"). Both (*b*) and (*c*) place the direction of the maximum of the orbital of the lone pair on the nitrogen in the plane of the chain. This removes one of the difficulties mentioned above. The distortions in the chains resulting from the substitution of a double bond between carbon and nitrogen for the single bond takes care of the other two. A portion of the structure so arrived at is represented in Figure 4 (assuming tentatively that all the atoms, other than the H and R atoms of the CHR groups, are in the same plane).

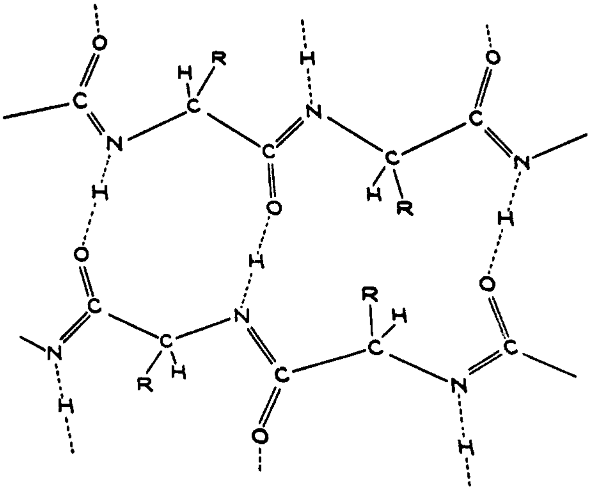


FIG. 4.—REPRESENTING THE STRUCTURE OF *beta* KERATIN

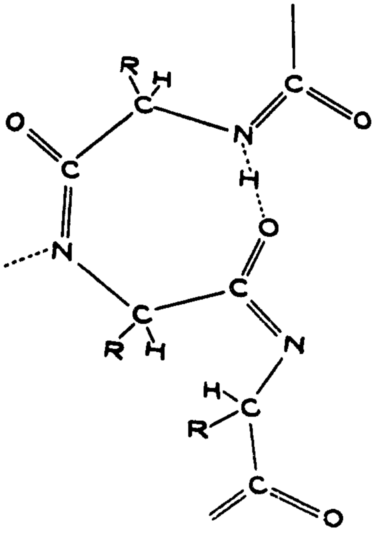


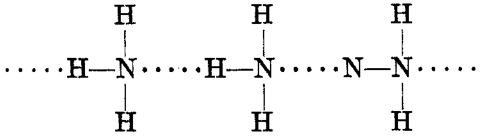
FIG. 5.—REPRESENTING THE STRUCTURE OF *alpha* KERATIN

Corresponding objections to the details of Astbury's picture of *alpha* keratin are similarly eliminated. A portion of a single chain may be represented as in Figure 5. The bonds are undoubtedly not all coplanar, but are so oriented as to give the most favorable angles and distances at the hydrogen bridges and elsewhere.

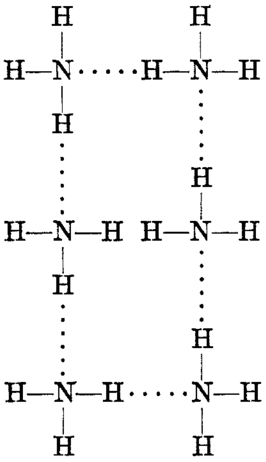
Mirsky and Pauling,[88] assuming the protein chains in native proteins to be held together in a "uniquely defined configuration" by means of interchain hydrogen bridges, have recently advanced the hypothesis that denaturation consists of the breaking of many or all of these bridges, leaving each molecule free to assume any one of a very large number of configurations. "It is evident that with loss of the uniquely defined configuration there would be loss of the specific properties of the nature protein; it would not be possible to grow crystals from molecules of varying shapes, for example, nor to distinguish between closely related proteins when the molecules of each protein show a variability in configuration large compared with the differences in configuration of the different proteins."

NHN BRIDGES

It has been suggested[89] that in liquid ammonia, as in liquid water, the molecules are held together by a network of hydrogen bridges. One can postulate long strings or rings of molecules



$$\cdots\cdots \mathrm{H-\overset{H}{\underset{H}{N}}\cdots\cdots H-\overset{H}{\underset{H}{N}}\cdots\cdots N-\overset{H}{\underset{H}{N}}}\cdots\cdots$$



with or without side chains, but the apparent instability of such NHN bridges in amines makes their existence in liquid ammonia quite doubtful. Solid ammonia, unlike ice, is a close-packed assemblage of molecules, without hydrogen bridges, and the melting process would be expected to break such bridges, rather than to form them. The small increase in

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[88] Mirsky and Pauling, *Proc. Nat. Acad. Sci.*, **22**, 439 (1936).

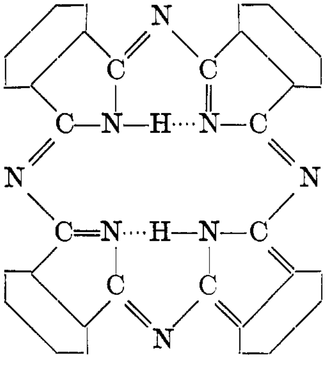
[89] Rodebush, *Chem. Rev.*, **19**, 59 (1936).

specific volume on melting is evidence against the existence of bridges between any large proportion of molecules in the liquid.

It is much more probable that one (or more) of the hydrogen atoms of a NH_4^+ ion may bridge to a nitrogen atom of a neighboring NH_3 molecule. There is less chance that a bridge of this sort would be symmetrical than in the case of a hydrogen ion in water solution, ($H_2OHOH_2^+$), however, and if an unsymmetrical bridge of this sort exists, the energy hump tending to prevent the shift $H_3N — H \cdots NH_3 \rightarrow H_3N \cdots H — NH_3$ must be quite large, otherwise the ammonium ion in liquid ammonia would show the abnormally high mobility characteristic of the hydrogen ion in water.

These conclusions about liquid ammonia apply with equal validity to the amines. The hydrogen atoms of one RNH_2 molecule undoubtedly attract the electronegative side of a nitrogen in another molecule, but this attraction is considerably weaker than for corresponding hydroxyl compounds. In agreement with this conclusion, Kumler[26] found no evidence of hydrogen bridge formation in liquid amines, from his comparison of dielectric constants with dipole moments.

The hydrogen attached to nitrogen in pyrrol is, as is well known, much more "acidic"—*i.e.*, more easily removed as hydrogen ion—than an ordinary amino hydrogen. It should, therefore, serve better to bridge to another nitrogen (oxygen or fluorine). The recent crystal structure study of the phthalocyanines by Robertson[58] has led to the conclusion that the four pyrrol nitrogens are connected together in pairs by means of two hydrogen bridges. The formula of phthalocyanine according to the usual conventions, is



but the distinctions therein indicated between the "single" and "double" bonds do not exist, on account of resonance. It may be also that the forces represented by N — H and by N · · · H are also identical, the NHN bridges being symmetrical. (In the cupric and nickelous derivatives the metal atom is attached to all four of the inner nitrogen atoms.)

CHN AND CHO BRIDGES

A hydrogen attached to carbon is ordinarily too firmly held to serve as a bridge to another atom. If, however, the carbon atom is sufficiently polarized by attachment to one or more electronegative atoms the hydrogen in question may become loosely enough bound to serve as a bridge. This seems to be the case in the HCN molecule, especially if the nitrogen is connected by a hydrogen bridge to an electronegative atom in another molecule. Liquid and solid hydrogen cyanide are probably composed largely of linear aggregates such as represented by the formula

$$\cdots\cdot H-C\equiv N\cdots\cdot H-C\equiv N\cdots\cdot H-C\equiv N\cdots\cdot H-C\equiv N\cdots\cdot$$

The hydrogen plays a rôle similar to that of silver in crystals of silver cyanide, which contain linear macro-molecules:

$$\cdots\cdot\cdot Ag\cdots\cdot C\equiv N\cdots\cdot Ag\cdots\cdot C\equiv N\cdots\cdot Ag\cdots\cdot C\equiv N\cdots\cdot$$

Like molecules of water, hydrogen fluoride, alcohols, and carboxylic acids, a molecule of HCN can both supply a hydrogen for a bridge to another molecule and add (by bridge formation) a hydrogen supplied by another molecule. The solvent power of liquid HCN for polar substances may be attributed to this fact.

Chloroform forms complexes,[35,36] $R_2O\cdot HCCl_3$, $R_2CO\cdot HC\ Cl_3$ $C_9H_7N\cdot HC\ Cl_3$, with ethers, ketones, quinoline, etc., which may be assumed to contain CHO or CHN bridges. MacLeod and Wilson[35] conclude from data on heats of mixing that in an equimolar mixture of ethyl ether and chloroform, for instance, between 15 per cent. and 20 per cent. of the (simple) molecules are combined.

It is apparent that the presence of three electronegative atoms of chlorine attached to a carbon atom so decreases its attraction for hydrogen (*i. e.*, its "effective charge") as to make the hydrogen capable of bridging to a nitrogen or oxygen. A similar line of reasoning leads one to expect the CH hydrogen atom in formic acid to be capable of bridging to an oxygen of another molecule. CHO bridges formed in this way may be responsible for the difference[26] between the dielectric constant behavior of formic acid and acetic acid, for certain peculiarities observed[90] in the Raman spectra obtained from formic acid and formate solutions, and for various other phenomena.

NHX BRIDGES

As noted in the introduction, NHF bridges apparently exist in crystalline NH_4F, and NHCl bridges were postulated by the writer to exist in the

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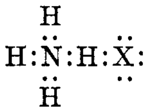
[90] RÂY, *Nature*, **133**, 646 (1934); SARKAR AND RÂY, *ibid.*, **137**, 495 (1936); GUPTA, *Ind. J. Physics*, **10**, 117 (1936).

form of NH_4Cl which is stable at room temperature. The existence of hydrogen bridges in the latter case is doubtful, however. Specific heat curves obtained by Simon and coworkers[91] for ammonium halide crystals show humps, indicating some sort of structural change, in the neighborhood of −30°C. X-ray photographs show no apparent difference in structure, other than a slight volume change, above and below the transition temperature. Pauling[8] has advanced the hypothesis that the ammonium ions are constantly rotating, above the transition, in the chloride, bromide and iodide crystals, leaving the small energy hump observed for the fluoride unexplained. This hypothesis gives no explanation also for the electron diffraction results obtained by Natta[92] and attributed by him to diffraction by the hydrogen atoms and for various other experimental observations.

If one assumes NHX bridges throughout, the energy-distance curves for the motion of a hydrogen along the N ··· X centerline having two minima with a small hump between (as in ice), the observed transition may be between a state in which one hydrogen out of every four is on the halogen side of the hump and a state in which all four are on the nitrogen side. More likely, perhaps, the transition temperature is that at which the average vibrational energy of the hydrogen is just sufficient to carry it over the hump. Still another alternative is to assume



$$\begin{array}{ccccccc} & & \text{H} & & & & \\ \text{H} & : & \ddot{\underset{\cdot\cdot}{\text{N}}} & : & \text{H} & : & \ddot{\underset{\cdot\cdot}{\text{X}}}: \\ & & \text{H} & & & & \end{array}$$

"molecules," each continuously rotating about its threefold symmetry axis, above the transition temperature. A detailed discussion of the experimental evidence concerning the disposition of the hydrogen atoms in ammonium chloride, bromide and iodide crystals would be out of place here. For those who wish to go into the matter further, however, various pertinent papers are listed as reference 8.

There is some evidence for the existence of weak hydrogen bridges connecting nitrogen with chlorine in other compounds. In solid tribenzylammonium chloride, for example, the nitrogens, the ammonium hydrogen atoms, and the chlorine atoms lie on threefold symmetry axes, suggesting —N—H ··· Cl bridges.[93] Likewise, in hydrazinium dichloride[94]

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[91] Simon, *Ann. Physik.*, **68**, 263 (1922); Simon and v. Simson, *Naturwissenschaften*, **38**, 880 (1926); Simon, v. Simson, and Ruhemann, *Z. physik. Chem.*, **129**, 339 (1927).

[92] Natta, *IX. Congr. intern. quim. pura aplicada*, **2**, 177 (1934); *Giorn. chim. ind. appl.*, **16**, 285 (1934).

[93] Huggins, Unpublished results.

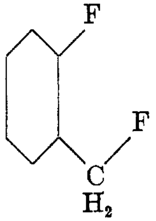
[94] Wyckoff, *Am. J. Sci.*, **5**, 15 (1923).

(H_3NNH_3)Cl_2 (*i. e.*, hydrazine dihydrochloride) the nitrogen atoms are in pairs on threefold symmetry axes, each pair surrounded by six chlorine atoms in such a way that the N—H bonds, assuming tetrahedral angles, may be pointing approximately toward them. The N—H bonds are not necessarily oriented in this manner, as the $N_2H_6^{++}$ ions may be in rotation around their symmetry axes.

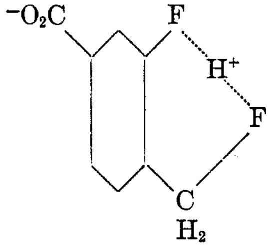
Although the author is aware of no definite evidence for the existence of NHF or OHF bridges in organic substances, there is every reason to expect them in suitable compounds.

OTHER TYPES OF BRIDGES

It is interesting to speculate regarding the possibility of the existence of FHF bridges in organic molecules. Organic fluorides, crystallized from solution containing hydrogen fluoride, might well form additive compounds: RF—H—F. From solutions of other acids one might obtain salts of the composition $(RF—H—FR)^+ X^-$. In general, organic fluorides would be expected to show slightly basic properties, because of this tendency to add hydrogen ion. With two fluorine atoms in suitable relative positions for bridge formation in the same molecule, in a compound such as



for instance, the basicity should be considerably enhanced. With a carbonyl elsewhere in the same molecule, intramolecular salt formation would be expected:



The writer knows of no examples of hydrogen bridges joining a sulfur atom with another electronegative atom. Such bridges, if they exist at all, are undoubtedly very weak. Mercaptans behave cryoscopically as non-associating substances,[95] differing markedly from alcohols in this respect.

It is quite possible that the hydration of ions such as Cl^-, S^{--} and HS^- in water solution is due in part to the formation of weak hydrogen bridges, rather than entirely to ion-dipole attractions.

The weakness of X—H ··· Y bridges, where Y is an atom such as chlorine, not in the first row of the periodic table, may be attributed to the greater interpenetration repulsion between X and Y atoms (than when both X and Y are first row elements), making the X ··· Y distance and, therefore, the H ··· Y distance so large that the attraction between H and Y is relatively weak.

There seems to be little or no evidence for the existence at ordinary temperatures of YHY bridges, both bridged atoms being elements other than first-row elements. The Y ··· Y distance is so large that at least one of the H ··· Y distances must be much larger than that in the HY molecule. The attraction energy associated with this H ··· Y bond is, therefore, very small and the bond is easily broken by collisions and in other ways. These energy relationships can be treated semi-quantitatively by the methods used by the author for OHO and FHF bridges, but the calculations have not yet been made.

SUMMARY AND CONCLUSION

Evidence from many sources has been presented for the frequent occurrence of hydrogen bridges connecting N, O, F and occasionally C atoms in organic molecules. Weak bridges involving heavier electronegative atoms may also exist.

Bridge lengths, bridge strengths, and bridge polarities have been discussed and related to the "effective charges" on the bridged atoms.

No claim is made that all the evidence regarding the existence and nature of the hydrogen bridges in organic compounds has been collected or even mentioned in this paper. Enough has been included, however, to show that these bridges are real and important, being related to a wide variety of experimental phenomena. Many properties of organic substances which have been vaguely attributed to "van der Waals forces," "polarity," "steric hindrance," "catalysis," etc., are definitely due to the formation and existence of hydrogen bridges. Not only can one now picture better the structure and behavior of many substances, but one can treat them in more nearly quantitative fashion. Although most of the work on hydrogen bridges to date has been of a qualitative nature, the

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[95] AUWERS, Ref. 19.

methods of attack along semi-quantitative lines are being worked out and should soon be available.

The writer ventures to predict that the most fruitful applications of hydrogen-bridge theory will be to a better understanding of the nature and behavior of complicated organic substances such as gels, proteins, starch, cellulose, sugars and other carbohydrates, chlorophyl, haemoglobin and related substances, etc.

[Contribution from the Converse Memorial Laboratory of Harvard University]

ORGANOMETALLIC COMPOUNDS OF STYRENE

GEORGE F. WRIGHT*

Received October 22, 1936

This investigation has developed from numerous attempts to obtain the stereoisomers of 1-phenylbutadiene-1,3. The methods employed in this study, as well as those of Muskat and co-workers[1] have failed to differentiate either the *cis* and *trans* phenylbutadienes or the isomeric carbinols from which they are formed. It is probable that Muskat and Herrman had neither isomer of styrylmethylcarbinol in the pure state, because this compound, prepared from methylmagnesium chloride and fractionated cinnamaldehyde by varying the method of Klages,[2] is not a liquid, as they thought, but a solid melting at 31°.[3] Upon dehydration of this purer carbinol, the ordinary phenylbutadiene was obtained and characterized by mercuration;[4] it is possible that the differences in physical constants reported by Muskat and Herrman were caused by varying amounts of the ever-present dimeric analogs.

Since the reported methods of obtaining these isomers proved abortive, the approach *via cis-* and *trans*-styrylmagnesium bromide and acetaldehyde was investigated. This likewise failed; the styrylmethylcarbinol so obtained was a mixture of the geometric isomers. The failure to obtain the pure compound did, however, suggest a study of the cause of such isomerization and of the reaction step wherein it occurred.

Because of the possible catalytic effect, such substances as iodine, iodine-activated magnesium, or Grignard reagents prepared by such catalysts were avoided in starting the reaction between β-bromostyrene and magnesium although this halide is notorious[5] for its sluggishness toward Grignard formation. Nevertheless, by scrupulous attention to purity of reagents[6] it has been found possible to start the reaction spontaneously. A reproducible induction period before reaction set in was characteristic of either the solvent or the halide, but not of the magnesium or the reaction vessel. This was proved by carrying out a second reaction on the excess

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* National Research Fellow in Chemistry.

[1] Muskat and Herrman, *J. Am. Chem. Soc.*, **53**, 252 (1931).

[2] Klages, *Ber.*, **39**, 2591 (1906).

[3] Kenyon, Partridge, and Phillips, *J. Chem. Soc.*, **1936**, 86.

[4] Wright, *J. Am. Chem. Soc.*, **57**, 1993 (1935).

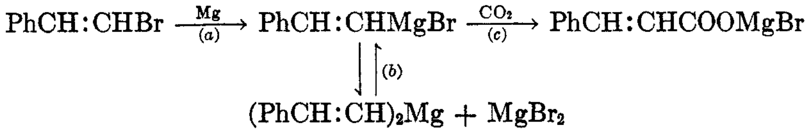
[5] Gilman and Kirby, *Rec. trav. chim.*, **54**, 577 (1935).

[6] Gilman, Zoellner, Selby, and Boatner, *ibid.*, **54**, 589 (1935).

of magnesium remaining after a previous preparation; the identical induction period was observed. Incidence of reaction was characterized by the red coloration of the solution in the case of the *trans* isomer, or by the Gilman test with the pale yellow solution obtained from *cis*-bromostyrene.

On the basis of comparative yields, as well as amount of bromostyrene recovered after reaction, the *trans* halide was converted to the magnesium derivative more rapidly than the *cis* modification (Table I). Since a mixture of cinnamic acids resulted upon carbonation of the Grignard reagents from both forms, the apparent difference in reaction rate suggests that such isomerization does not occur in the halide itself. This evidence, in itself insecure, is supported by the fact that the equilibrium mixture (m.p. +2°), which Dufraisse[7] found to consist largely of the *trans* β-bromostyrene, yielded more *cis*- than *trans*- cinnamic acid. In other words the isomerization is away from, rather than toward, the composition of the mixture resulting from either thermal or photochemical equilibration of the geometric isomers. For these reasons it is probable that isomerization does not occur until the Grignard reagent is formed. Another possibility was eliminated by ascertaining that the chloromagnesium cinnamates did not isomerize in aqueous solution.

The isomerization must, then, take place: (*a*) when the Grignard reagent is formed; or (*b*) when it undergoes reaction with itself; or (*c*) when it reacts with another substance. If the distinctive red color of the Grignard solution prepared from *trans*-β-bromostyrene is truly characteristic of *trans*-styrylmagnesium bromide, then the isomerizing step must be (*c*), since the Grignard reagent prepared from *cis*-bromostyrene shows no red color.



$$\begin{tikzcd} PhCH{:}CHBr \arrow[r, "Mg", "(a)"'] & PhCH{:}CHMgBr \arrow[r, "CO_2", "(c)"'] \arrow[d, shift right] & PhCH{:}CHCOOMgBr \\ & (PhCH{:}CH)_2Mg + MgBr_2 \arrow[u, shift right, "(b)"'] & \end{tikzcd}$$

If this be true, then it is probable that the extent of isomerization will differ with various reactants. Admittedly poor evidence for this reasoning is offered in the fact that only one styrylmercuric bromide can be detected when styrylmagnesium bromide from the equilibrium mixture of β-bromostyrene is treated with mercuric bromide. This compound, which was prepared in order to ascertain the stability of the hitherto unknown type of vinylmercurial, was found to be much less susceptible to decomposition than certain presumably aromatic types,[8] and it suffered no change over a period of eighteen months.

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[7] Dufraisse, *Compt. rend.*, **172**, 67 (1921).

[8] Gilman and co-workers, *J. Am. Chem. Soc.*, **55**, 3302, 4197 (1933).

Although previous reports[9] have indicated that styryllithium could not be prepared, it was found in the present investigation that either *cis*- or *trans*-bromostyrene reacted immediately with lithium to give a reagent in 50 to 70 per cent. yield which, when carbonated, yielded a 4:1 mixture of *trans*-cinnamic and phenylpropiolic acids. No *cis*-cinnamic acid could be detected from either isomer. The formation of the acetylenic acid is remindful of the conversion of β-bromostyrene to phenylpropiolic acid with sodium and carbon dioxide,[10] but the mechanism of dehydrogenation is not apparent, since no gas is evolved during the reaction. Furthermore the volume increase on adding the solution of styryllithium to cracked ice is insufficient to account for the phenylacetylene formed. A possible oxidation-reduction involving formation of phenylpropionic acid is likewise eliminated by the absence of this saturated acid among the carbonation products.

I wish to thank Professor E. P. Kohler for his advice and perspective, which were so helpful in this research.

EXPERIMENTAL

Cis- *and* trans-*β-bromostyrene.*—When the powdered equilibrium mixture* was allowed to melt partially on a suction filter at +6° the *trans* isomer was retained. Repetition of this process gave a *trans*-β-bromostyrene (m.p. 6.5°, b.p. 88°/4 mm., n_D^{20} 1.6093), which was considered pure because it showed only a 0.2° drift on a twenty-five minute cooling curve. The melt from the equilibrium mixture was repeatedly fractionated at 4 mm. in a smoked Claisen flask until about one-third of this melt boiled at 63.7–64.5° and melted at −8° to −7.5°, n_D^{22} 1.5990. These are capillary melting points determined in the apparatus of Stolzenberg[11] which was constructed with a vacuum jacket around the bath, thus obviating difficulties due to fogging. This *cis* compound compares closely with that prepared by Dufraisse[12] except in odor, but probably neither is pure. The *cis* halide is odorless, in contrast to the *trans* isomer with its characteristic hyacinth odor. About ten per cent. of the equilibrium mixture was obtained as *cis*-bromostyrene.

Optimum conditions for reaction.—The flask illustrated in Fig. 1 has been chosen from a number of designs as satisfactory for preparation of organomagnesium compounds. It is conveniently made from an Erlenmeyer flask; a siphon tube filled with glass wool serves to filter the prepared reagent. The following characteristics recommend this flask. The reaction is started in the constricted base where the volume is small, and hence maximum contact between solution and magnesium is obtained. The narrow base likewise facilitates removal of the prepared reagent by means of the siphon tube. The conical shape obviates "bumping" and, with a properly designed stirrer, no magnesium is thrown out of the zone of reaction. The latter is a troublesome disadvantage of the spherical flask. In the 10-, 25-

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[9] Gilman, Zoellner and Selby, *ibid.*, **55**, 1252 (1933).

[10] Glaser, *Ann.*, **154**, 140 (1870); Nef, *ibid.*, **308**, 268 (1899).

* Kindly furnished by Mr. A. L. van Amerigen of van Ameringen Haebler, Inc.

[11] Stolzenberg, *Ber.*, **42**, 4323 (1909).

[12] Dufraisse, *Compt. rend.*, **171**, 960 (1920).

and 50-cc. sizes a condenser finger is connected, as illustrated, to the jacket *A* which also is used for introduction of the siphon tube, the while nitrogen is passed into *C*. An auxiliary gas inlet is placed at *B*. For reaction, the magnesium is placed in the flask, which is then swept out with nitrogen, and finally heated gently to remove residual moisture from the metal. Premature heating while oxygen yet remains in the flask may deposit an oxide coating on the magnesium; this should be avoided, since certain halides will not react spontaneously unless unusually pure magnesium is employed. All of the commercially available grades are ineffective for spontaneous reaction[6] unless they be activated. However, the magnesium generously supplied by Professor Gilman and Dr. Zoellner reacted without catalyst after a reproducible induction period of fifteen to twenty minutes when the following conditions were maintained.

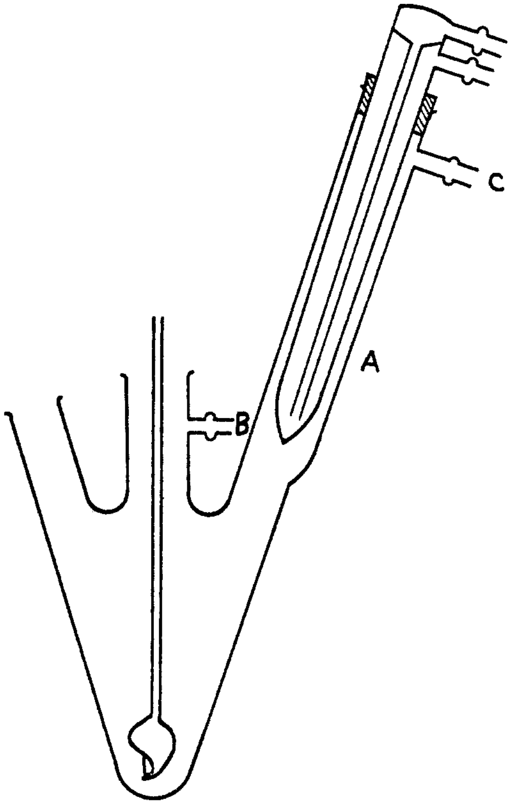

FIG. 1

Styrylmagnesium bromide.—The reaction flask was coated with soot to exclude light since the isomeric β-bromostyrenes are photosensitive. To 2.4 g. (0.1 mole) of 30–80 mesh magnesium was added *ca.* 0.5 cc. of a solution of 5.49 g. (0.03 mole) of freshly distilled β-bromostyrene in 30 cc. of ether distilled from methylmagnesium iodide. When the reaction started, the remainder of the halide was added over a ninety-minute period. After one-half hour of subsequent stirring, the reaction mixture was siphoned into a flask containing powdered dry ice which had been freed of water ice by violently shaking while evacuating the flask at the water pump. The solution was hydrolyzed with iced, dilute acid and the mixture of *cis*- and *trans*-cinnamic acids removed with dilute alkali and separated by the difference in solubility of their calcium salts.[13] The non-acidic products of the reaction were evidently a complicated mixture; the only constituents thus far identified are *trans*,*trans*-1,4-diphenylbutadiene-1,3 and unchanged β-bromostyrene (in the case of the *cis* halide which reacts more slowly than the *trans* compound).

Attempted isomerization of cinnamic acids.—When an ether solution of either *cis*- or *trans*-cinnamic acid was treated dropwise with exactly one equivalent of methylmagnesium bromide and the magnesium salts allowed to stand overnight, the acids were recovered, upon acidification, without isomerization. Likewise, the calcium salt of *trans*-cinnamic acid was converted, after two days, to *trans*-cinnamic acid containing no trace of *cis*-cinnamic acid.

TABLE I

PRODUCTS FROM CARBONATION OF STYRYLMAGNESIUM BROMIDE

RUN NO.	HALIDE	CRUDE ACIDS		PURIFIED ACIDS				*trans*, *trans*-DIPHENYLBUTADIENE, YIELD	REMARKS
				trans-Cinnamic		*cis*-Cinnamic			
		Yield	M.p.	Yield	M.p.	Yield	M.p.		
		per cent.	°*C.*	*per cent.*	°*C.*	*per cent.*	°*C.*	*per cent.*	
1	*cis*-Bromostyrene, m.p. −7.5°	35	52	9	130	19	48	3.0	Reaction mixture, pale yellow
2	Equilibrium mixture bromostyrene, m.p. +2°	48	85	12	130	19	48	4.4	By acid titration, RMgX, 56%†
3	*trans*-Bromostyrene, m.p. +6.5°	62	75–80	30	132	20.5	53*	11.0	Reaction mixture, deep red

* The yields of *cis*-cinnamic acid are all of equal purity, the 53° sample being a mixture of the polymorphs.

† When the quantities used in Run 2, Table I, were increased tenfold, using a threefold period of addition, the yield was not decreased.

Styrylmethylcarbinol.—To the organomagnesium compound prepared from 0.025 moles of β-bromostyrene (m.p. 6.5°) was added 0.025 moles of gaseous acetaldehyde. Hydrolysis with ammonium chloride solution yielded 1.13 g. (30%) of styrylmethyl carbinol; b.p. 94–106°/4 mm. That this was a mixture of stereoisomers, was shown by the fact that the crude phenylurethane melted at 79° whereas the crude phenylurethane from the solid styrylmethylcarbinol melts at 87°. Furthermore, the reaction product would not crystallize at 0° even after seeding with the solid carbinol (m.p. 31°, b.p. 109°/3.5 mm.), n^{31} 1.5700), prepared in 77% yield by adding one mole of cinnamaldehyde (b.p. 137°/20 mm.) to two moles of methylmagnesium chloride. The same styrylmethylcarbinol, identified by mixture melting point, was obtained

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[13] LIEBERMANN, *Ber.*, **23**, 141 (1890).

by repeating Burton's saponification of the acetate prepared from his α-phenylcrotyl alcohol.[14] The latter compound can be prepared in 87% yield by filtering off the magnesium alcoholate prior to hydrolysis.

Styrylmercuric bromide.—To the stirred solution prepared from 0.33 moles of β-bromostyrene (equilibrium mixture, m.p. +2°) and one mole of magnesium was added slowly 100 g. (0.28 mole) of mercuric bromide. After eight hours' stirring the reaction was filtered to remove 61 g. (m.p. 198°) of mercurial which was purified by Soxhlet extraction with ethanol to yield 39 g. (36%) of styrylmercuric bromide; m.p. 202–203°. The ethereal filtrate was evaporated and the residue washed with benzene to yield 16.5 g. of impure product melting at 190°. Upon solution in hot acetone and precipitation of this solution into water the melting point was raised to 201°. The mercurial is insoluble in cold ethanol and hot or cold benzene, slightly soluble in chloroform but readily soluble in acetone.

Anal. Calc'd for C_8H_7BrHg: C, 25.10. Found: 25.31.

The mercurial was characterized by treating a suspension of 3.89 g. (0.01 mole) in 20 cc. of chloroform with a solution of 1.6 g. (0.01 mole) bromine in 5 cc. of chloroform. The 74% yield of β-bromostyrene boiling at 79–81°/4 mm. melted at 2.5°; a mixture melting point with the equilibrium mixture was not lowered.

β-Iodostyrene.—When 2.56 g. (0.01 mole) of iodine was added to the shaken suspension of 3.89 g. (0.01 mole) of styrylmercuric bromide in 25 cc. of chloroform the solution became colorless in ten minutes with precipitation of mercuric salt. The latter was filtered off, and the filtrate was distilled under reduced pressure to yield 1.81 g. (79% theoretical) of β-iodostyrene; b.p. 101°/4 mm., n^{20} 1.6621, n^{25} 1.6583.

Anal. (by Mr. F. B. Pickett). Calc'd for C_8H_7I: I, 55.20. Found: 55.24.

Styryllithium.—Following the suggestion of Dr. E. B. Herschberg, 0.7 g. (0.1 mole) of 18-gauge lithium wire (prepared in a sodium press and the required 100 inches folded into a ten-strand bundle) was cut into 1–2 mm. lengths over the mouth of the flask jacket *A* from which nitrogen was streaming. To this metal was added a solution of 5.49 g. (0.03 mole) of β-bromostyrene (m.p. 6.5°) in 30 cc. of Grignard-dried ether. The reaction started immediately and continued over an addition period of seventy-five minutes. By means of a gas burette filled with sulfuric acid and attached to the outlet of the condenser, it was found that no gas was evolved during the reaction. The blood-red solution was added dropwise to a 200-cc. flask containing 100 g. of cracked ice and connected to the gas burette. A volume increase of 25 cc. was detected during the hydrolysis. The vapor pressure of ether at 0° accounts for this augmentation. The hydrolysate was separated and the aqueous layer titrated, being equivalent to 0.021 moles of hydrochloric acid, or 68% of the theoretical yield of R–Li. The ether layer was distilled at 50–60° under 2 mm. pressure into a dry-ice trap, to yield 1.32 g. of product. Upon treatment with ammoniacal cuprous chloride solution this precipitated 0.40 g. of cuprous phenylacetylide, a yield of 8% of the bromostyrene used in the reaction. The styrene remaining after removing the phenylacetylene was identified as the dibromide; m.p. 71–72°. It represented 34% of the theoretical yield.

When the styryllithium from an identical preparation was carbonated with dry ice, a mixture of crude acids melting at 104° was obtained; 1.1–1.3 g. or 25–30% of theoretical. Separation by means of the calcium salts[13] revealed that this was a mixture of *trans*-cinnamic and phenylpropiolic acids in the ratio of 4:1. The purity (m.p. 132–134°) of the phenylpropiolic acid regenerated from its calcium salt

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[14] BURTON, *J. Chem. Soc.*, **1929**, 455.

confirms the absence of more than a trace of *cis*-cinnamic acid. Upon brominating the mixture of acids in aqueous suspension, excess of bromine being removed with formic acid, and centrifuging the cold suspension to remove the brominated acids no phenylpropionic acid was found in the remaining aqueous solution.

The non-acidic products from the carbonation reaction were exceedingly complex. The residue from evaporation of the ether solution, weighing 0.95 g., was crystallized from ethanol. It weighed 0.28 g., melted at 144°, and was identified by mixture melting point as *trans,trans*-1,4-diphenylbutadiene-1,3.

In a larger preparation (0.25 mole β-bromostyrene added over a 400-minute period) the yield by acid titration was 61%; the yield of crude acid mixture was 33%. The non-acidic reaction products were fractionated at 2 mm. pressure, yielding a small fraction boiling up to 163°, a second boiling at 167–200° and a resinous third fraction, b.p. 200–230°.

SUMMARY

The reactions for preparation of *cis*- and *trans*-styrylmagnesium bromide, styrylmercuric bromide and styryllithium have been studied.

[Contribution from the Research Laboratories of the Universal Oil Products Company, Riverside, Illinois]

CONJUNCT POLYMERIZATION—THE INFLUENCE OF TEMPERATURE, CONCENTRATION, AND QUANTITY OF SULFURIC ACID ON POLYMERIZATION OF OLEFINS

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The chemical literature contains a number of papers dealing with the polymerization of olefins containing four or more carbon atoms, using sulfuric acid as a catalyst. It is surprising to notice that although many investigators studied the different factors influencing this reaction, none of them has given a clear picture of the influence of the concentration and of the ratio of the sulfuric acid used, or of the effect of the temperature of reaction upon the composition of the products formed.

Norris and Joubert[1] studied the action of sulfuric acid on pentenes, using different concentrations of the acid. They did not, however, submit the products obtained to a complete analysis.

Ormandy and Craven[2] noticed that pentenes when reacted with large excess of acid (600 cc. of 96 per cent. sulfuric acid to 200 cc. of pentenes), yielded a product containing paraffinic hydrocarbons. On the basis of only one experiment they stated that only paraffins were present in the high-boiling fraction of the upper layer, while the lower-boiling fractions contained also olefins. No mention was made by the authors of the presence of cycloparaffins. Our investigations* have not confirmed Ormandy and Craven's conclusions.

In order to elucidate this very interesting reaction, many experiments were made with gaseous and liquid olefins; from the large number of experiments carried out it was possible to explain some details of the reaction.

A study was made of the effect of sulfuric acid on polymerization of isopropylethylene, trimethylethylene, butenes, mono-, di-, and trimers of isobutene, and trimers and tetramers of propene, using different temperatures, concentrations of acid, and ratios of sulfuric acid to olefins treated. The investigation of the products obtained from the polymerization of

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[1] Norris and Joubert, *J. Am. Chem. Soc.*, **49**, 873 (1927).

[2] Ormandy and Craven, *J. Inst. Petroleum Tech.*, **13**, 311 (1927).

* Preliminary work was published in the book "Catalytic Reactions at High Pressures and Temperature" by V. N. Ipatieff on page 593.

olefins indicated that the reaction is a very complicated one; besides olefins, paraffinic and cyclic hydrocarbons are formed; the predominance of the one or other type of hydrocarbons formed depends greatly upon the concentration and amount of sulfuric acid used. It was found that regardless of whether we treat isobutene, its dimer, or its trimer, with concentrated sulfuric acid, the character of the final product obtained is the same. With dilute sulfuric (87 per cent. or less) the products obtained from the reaction consist only of open-chain olefins; cyclic and paraffinic hydrocarbons are absent.

In the case of sulfuric acid we can distinguish (1) true polymerization, and (2) conjunct polymerization. The same types of polymerization were observed in the treatment of olefins with phosphoric acid.

CONCENTRATION OF ACID

The concentration and the amount of acid have a great effect on the type of hydrocarbons formed.

1. Large Ratios of Acid to Olefins Treated; Temperature of Reaction 0° (1.5 to 7 parts by weight of acid to 1 part of olefins)

(*a*) *96 per cent. sulfuric acid.*—When olefinic hydrocarbons like *n*-butene, mono-, di-, and triïsobutene, isopropylethylene, nonene, and dodecene are treated with sulfuric acid, the hydrocarbons are first dissolved in the acid. On standing at 0° two layers are formed: the upper, hydrocarbon layer, and the lower, sulfuric acid layer. The yield of hydrocarbon layer amounts to about 70 per cent. by weight of the olefins treated. It was found that in all the cases, without exception, the hydrocarbon layer boiling up to 225–250° *does not contain any olefinic hydrocarbons,* as shown by the stability of the fractions to the action of a nitrating mixture (2 vol. 96 per cent. sulfuric acid and 1 vol. of nitric acid, density 1.5). The higher-boiling fractions, however, contain olefinic, cycloölefinic and saturated hydrocarbons. The percentage of unsaturated hydrocarbons found in the fractions distilling above 250° amounted to 30 per cent. of the total upper layer.

For the first time it was shown that *cyclic* compounds are formed by treating olefins with concentrated sulfuric acid. (The presence of cyclic hydrocarbons was demonstrated by the destructive hydrogenation method described under Methods of Analysis.) The hydrogen necessary to form paraffinic hydrocarbons is derived from the dehydrogenation of the cyclic compounds to form cycloölefins. In all the cases it was found that the sulfuric acid layer, on decomposition with water and steam distillation of the separated oily product, yields a *cycloölefin* hydrocarbon corresponding to the formula C_nH_{2n-4}. This product on hydrogenation is converted into a cycloparaffin C_nH_{2n}. We deal here then, with intermolecular hydrogenation-dehydrogenation.

Diïsobutene and triïsobutene, when treated with the same ratio of sulfuric acid, yield products having practically the same boiling range and properties (see Fig. 4). We observe here a new reaction, namely, depolymerization under the influence of strong sulfuric acid, since the products resulting from the reaction contain octane and dodecane, which indicates that cleavage of longer chains into shorter has taken place, otherwise diïsobutene could not form a product containing twelve carbon atoms.

From the results obtained from our experiments, we could hardly agree with the conclusions drawn by Ormandy and Craven: these authors claimed that the hydrocarbon layer formed from the action of large quantities of 96 per cent. sulfuric acid upon pentenes contained 6 per cent. of olefins, the remainder being paraffins.

The work of Ormandy and Craven was repeated and the product investigated. The material boiling below 250° did not contain any olefinic hydrocarbons; a large amount of decane was formed during the reaction. The higher-boiling fractions contained unsaturated hydrocarbons, the amount of which, based on the total upper layer, was equal to 30 per cent.

The sulfuric acid layer contained cycloölefins of the formula C_nH_{2n-4}, and not open-chain diölefins as stated by Ormandy and Craven.

Cycloölefins were also found in the sulfuric acid layer obtained from the treatment of mono-, di-, and triïsobutene.

The amounts of reagents used, and the results obtained are summarized in Table I.

(*b*) *91, 87, 77 and 67 per cent. sulfuric acid; temperature 0°.*—The yield of paraffinic hydrocarbons formed decreases considerably with decrease in concentration of sulfuric acid. The treatment of olefins with 91 per cent. sulfuric acid yields a product which contains 63 per cent. of paraffins in the fraction boiling up to 200°, but with 87 per cent. sulfuric acid only traces of paraffins are found in a similar fraction; while with the 77 per cent. acid no paraffins are formed.

Isobutene, on treatment with 87 per cent. sulfuric acid, yields mostly triïsobutene and very little diïsobutene. When diïsobutene is reacted with 87 per cent. sulfuric acid, the main product found is tetraïsobutene. By comparing the action of 96 per cent. and 87 per cent. sulfuric acid (Expts. 2 and 9), we notice that the concentrated acid yields lower-boiling hydrocarbons than the more dilute acid. This is due to the fact that with 87 per cent. acid true polymerization, and with 96 per cent. acid conjunct polymerization takes place.

Sulfuric acid of 77 per cent. concentration polymerizes isobutene to di-, tri-, and tetraïsobutene; diïsobutene, when treated with the same concentration of acid, yields 45 per cent. of unchanged diïsobutene and 50 per cent. of tetraïsobutene. The sulfuric acid layer increases considerably when isobutene is treated with 77 per cent. of acid as compared with 87 per cent. acid.

TABLE I

EXPT. NO.	REAGENTS USED				RESULTS OBTAINED			DISTILLATION	
	Hydrocarbons			H_2SO_4 (96%)	Hydrocarbon layer		H_2SO_4 layer	% by wt. of product boiling below 220°	
	Kind	Vol., cc.	Wt., g.	Vol., cc.	% yield by vol.	% yield by wt.	Increase in vol. of acid layer (%)	Based on the hydroc. layer	Based on orig. prod.
1	Isobutene	450	245	200	49	71	20	30	22
2	Diïsobutene	250	182	250	65	71	21	47	33
3	Triïsobutene	250	190	250	56	67	20	47	32
3*a*	*n*-Butene	400	242	175	58	64	29	31	20
4	Isopropylethylene	200	134	200	57	68	18	42	29
5	Pentenes*	200	135	600	64	74	6	47	35
6	Nonene	100	73	150	73	—	—	32	23
7	Dodecene	100	77	150	77	—	—	32	25

* Temperature of reaction 30°; in the remaining experiments, 0°.

TABLE II

EXPT. NO.	REAGENTS USED					RESULTS OBTAINED			DISTILLATION	
	Hydrocarbons			H_2SO_4		Hydrocarbon layer		H_2SO_4 layer	% by wt. of product boiling below 220°	
	KIND	Vol., cc.	Wt., g.	Vol., cc.	Conc. (%)	% yield by vol.	% yield by wt.	Increase in vol. of acid layer (%)	Based on the hydroc. layer	Based on orig. prod.
8*a*	Isobutene	450	245	214	91	67	96	12	18	18
8	Isobutene	450	245	200	87	64	97	7	78	76
9	Diïsobutene	250	182	275*	87	88	95	27	20	19
10	Isobutene	345	190	276*	77	39	53	35	84	29
11	†Diïsobutene	250	182	335*	77	93	96	0	47	45

* The volume of concentrated sulfuric acid diluted with water to produce the different concentrations of acid was the same as in corresponding experiments in Table I.

† The composition of the hydrocarbon layer was as follows: non-reacted diïsobutene, 45 per cent.; triïsobutene, 0 per cent.; tetraïsobutene, 50 per cent.

No polymerization was noticed with 67 per cent. acid at 0°.
The results of the experiments are indicated in Table II.

2. Small Ratios of Acid to Olefins Treated (0.35 to 0.6 parts by weight of acid to 1 part of olefin treated)

(*a*) *96 per cent. sulfuric acid; temperature 0°.*—The ratio of acid to olefins tested has an effect on the type of products formed. When the ratio of acid to olefins is large (compare Tables I and III), the compounds boiling below 225–250° are, without exception, paraffinic in nature; when the same olefins are treated with smaller amounts of acid, unsaturated hydrocarbons are formed; fractions boiling below 225° contain 50 to 60 per cent. of olefins. The boiling range of the products changes with the quantity of acid used; the larger the amount of acid, the greater is the yield of lower-boiling products. (See Figs. 2 and 3.)

TABLE III

EXPT. No.	REAGENTS USED					PRODUCTS OBTAINED			DISTILLATION	
	Hydrocarbons			H_2SO_4		Hydrocarbon layer		H_2SO_4 layer	% by wt. of product boiling below 220°	
	Kind	Vol., cc.	Wt., g.	Vol., cc.	Conc. (%)	% yield by vol.	% yield by wt.	Increase in vol. of acid layer (%)	Based on hydroc. layer	Based on orig. prod.
12	Isobutene	450	245	50	96	57	82	44	27	22
13	Diïsobutene	250	182	50	96	80	87	46	16	14
14	Triïsobutene	225	171	50	96	80	84	48	17	14
15	Isopropylethylene	200	134	50	96	68	82	—	17	14
16	Isobutene	455	248	50	87	67	97	12	85*	82
17	Diïsobutene	250	182	50	87	90	96	14	35*	32
18	Diïsobutene	250	182	67	77	96	98	2	76*	74

* The following is the composition of the hydrocarbon layer:

	EXPERIMENT 16 (%)	EXPERIMENT 17 (%)	EXPERIMENT 18 (%)
Diïsobutene	2	0	75
Triïsobutene	75	2	—
Tetraïsobutene	18	87	22

(*b*) *87, 77, and 67 per cent. sulfuric acid.*—There is, essentially, not much difference in the character of the products formed when we treat isobutene or diïsobutene with large or small ratios of 87 per cent. sulfuric acid.

Large proportions of 87 per cent. sulfuric acid polymerize isobutene mostly to triïsobutene, while small ratios of acid yield, besides triïsobutene, 35 per cent. of diïsobutene.

The polymerization of diïsobutene with small amounts of acid yields the same results as the polymerization of diïsobutene with large proportions of acid.

Diïsobutene, when treated with 77 per cent. acid, yields only 22 per cent. of tetraïsobutene, the remainder being unchanged diïsobutene (Expt. 18); with larger amounts of acid, 45 per cent. of diïsobutene remains unchanged (Expt. 11).

Sulfuric acid of 67 per cent. concentration does not cause any polymerization.

EFFECT OF TEMPERATURES ON POLYMERIZATION

The product obtained from the treatment of isobutene or diïsobutene with sulfuric acid changes with the temperature of reaction. When the reaction is carried out at a temperature of −35° with 96 per cent. sulfuric acid, the product obtained has a higher boiling range than that of the similar reaction carried out at 0°.

The treatment of olefins at −35° with large ratios of sulfuric acid yields only paraffins in the fractions distilling up to 250° (similar results were obtained at 0°).

In two experiments (Expts. 21 and 23), immediately after all the olefins were added to sulfuric acid, at −35° (time required for addition, 1.5 hours), the product was poured slowly into a 20 per cent. solution of sodium hydroxide held at −30°. This was done in order to determine whether a short period of time is sufficient for the reaction to be completed. In other cases, the product was kept at −35° over night. It was found that there was little or no difference between the products obtained from the two procedures.

When isobutene is treated with small ratios of sulfuric acid olefinic hydrocarbons are present even in the lowest-boiling fractions.

With more dilute acids (87 per cent. or less) the reaction could not be carried out at −35°, since at that temperature the acid crystallizes. Some experiments were made at +35° and +65° with 77 and 67 per cent. sulfuric acid. Isobutene when reacted with 77 per cent. acid at +35° yields mainly dimer and trimer, and small amounts of tetramer. These results are the same as were obtained from similar experiments at a temperature of 0° (Expts. 10, 25, and 26). With 67 per cent. acid, no polymerization occurs at 0°, it takes place, however, at +35°; the products formed are composed mainly of diïsobutene, triïsobutene and some tetraïsobutene.

It was shown in Table III that diïsobutene treated with 77 per cent.

acid at 0° yields 22 per cent. of tetraïsobutene, the rest being unreacted diïsobutene (Expt. 18). Similar reactions carried out at +55° (Expt. 27) yielded about 47 per cent. of triïsobutene. This result indicates that at higher temperatures depolymerization occurs.

More dilute sulfuric acid (67 per cent.) does not cause polymerization of diïsobutene even at +65°.

The conditions of reactions carried out below and above 0° are given in Table IV.

TABLE IV

EXPT. NO.	REAGENTS USED					TEMP. OF REACTION, °C.	RESULTS OBTAINED			DISTILLATION	
	Hydrocarbons			H_2SO_4			Hydrocarbon layer		H_2SO_4 layer	% by wt. of product boiling below 220°	
	Kind	Vol., cc.	Wt., g.	Vol., cc.	Conc. (%)		% yield by vol.	% yield by wt.	Increase in vol. of acid layer (%)	Based on hydroc. layer	Based on orig. prod.
19	Isobutene	450	245	200	96	−35	58	82	32	30	25
20	Isobutene	425	233	50	96	−35	66	94	40	13	12
21	Isobutene*	425	233	50	96	−35	—	97	—	20	19
22	Diïsobutene	250	182	250	96	−35	—	87	8	10	9
23	Diïsobutene*	250	182	50	96	−35	—	94	—	3	3
25	Isobutene	420	231	276	77	+35	37	54	56	89	48
26	Isobutene	450	245	330	67	+35	76	98	76	95	93
27	Diïsobutene	250	182	68	77	+55	93	96	0	86†	83
28	Diïsobutene	250	182	453	67	+65	99	95	0	97‡	92

* Immediately after the isobutene was added the product was decomposed with a 20 per cent. solution of sodium hydroxide kept at −30°.

† The hydrocarbon layer contains 45 per cent. of triïsobutene.

‡ Unchanged diïsobutene.

DISCUSSION OF RESULTS

The results obtained from the treatment of olefins with concentrated sulfuric acid show that the following reactions occur: (1) polymerization, (2) depolymerization, (3) cyclization, (4) dehydrogenation ,(5) hydrogenation, (6) isomerization.

With more dilute acids, polymerization and, in some cases, depolymerization were noticed. For the complex reaction taking place during the treatment of olefins with concentrated sulfuric acid, the term *"conjunct polymerization"* is used to differentiate it from *"true polymerization"* as in the case of the action of dilute sulfuric acid on olefins.

"Conjunct polymerization" of olefins yielding, besides paraffins and polymers, also cyclic compounds, was noticed by the authors[3] in the case of polymerization of ethylene and propylene under high pressure and temperature with phosphoric acid as a catalyst.

The formation of the paraffinic hydrocarbons was shown by us to be due to intermolecular dehydrogenation-hydrogenation. The cyclic hydrocarbons which are formed lose hydrogen to give cycloölefins or aromatic hydrocarbons; the hydrogen liberated hydrogenates the olefins to paraffins.

The term "intermolecular hydrogenation" is used for a double reaction; that is, one molecule of a hydrocarbon loses hydrogen atoms and the liberated hydrogen atoms combine with a molecule of another hydrocarbon which can be hydrogenated under the given conditions. Thus, intermolecular hydrogenation can take place without the introduction of molecular hydrogen. This type of hydrogenation was first observed by us during the study of the polymerization of ethylene under pressure in the presence of phosphoric acid. Experimental work made it possible to clear up the mechanism of the latter reaction and to check quantitatively all products derived in its course.

The accomplishment of hydrogenation without participation of molecular hydrogen requires conditions favorable to the dehydrogenation of an organic compound formed during the reaction; on the other hand, an acceptor which can combine with the liberated hydrogen must be found.

In the case of the treatment of olefins with phosphoric acid, sulfuric acid, or aluminum chloride the open-chain olefins are the acceptors of hydrogen formed from the dehydrogenation of cycloparaffins. Similar reactions of dehydrogenation and hydrogenation were observed during the action of aluminum chloride on various aromatic compounds.[4]

The polymerization of ethylene and propylene in the presence of phosphoric acid, studied by us, has shown that intermolecular hydrogenation actually takes place, and the amount of paraffins that could be formed by hydrogen liberated on dehydrogenation of naphthenes was determined. Analysis and calculations have fully confirmed the suggested mechanism of this reaction, and it was shown that the products of the polymerization of ethylene contain 46 per cent. of paraffins, 7 per cent. of olefins, 21 per cent. of naphthenes, and 26 per cent. of aromatic hydrocarbons. The isobutane amounts to 18 per cent. of the total hydrocarbons, or 39 per cent. of the paraffins. Thus, during the polymerization of ethylene in the presence of phosphoric acid intermolecular hydrogenation takes place to such an extent that almost one-half of the product is the result of

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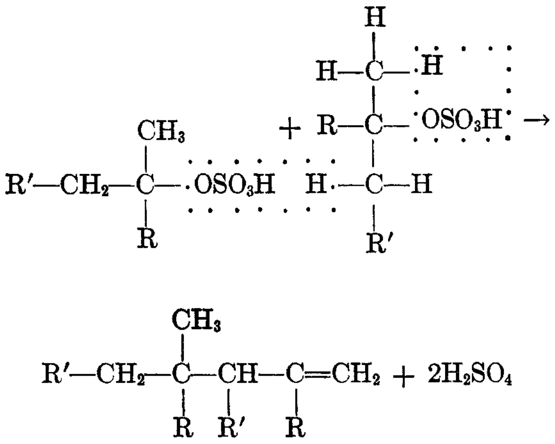
[3] Ipatieff and Pines, *Ind. Eng. Chem.* **27**, 1364 (1935); *ibid.*, **28**, 684 (1936); *J. Gen. Chem.* (U. S. S. R.), **5**, 1407 (1935).

[4] Ipatieff and Pines, *J. Am. Chem. Soc.*, (In publication).

hydrogenation. Ipatieff and Grosse[5] have also shown that in the case of polymerization of ethylene by means of aluminum chloride, the paraffins are formed at the expense of cycloparaffins which were converted into cycloölefins of the formulae C_nH_{2n-2}, C_nH_{2n-4}, etc. and found in the catalyst layer.

Scheme of Reaction

A—True polymerization.—Experiments have shown that when we "dissolve" an olefinic hydrocarbon in the *proper concentration* of sulfuric acid and allow the solution to stand for some time, a hydrocarbon layer consisting of polymers of the original olefinic hydrocarbon separates. In this case a true *polymerization* takes place because only olefins are formed. The polymerization takes place through the formation of alkyl esters of sulfuric acid, therefore it is necessary for the olefins to go into solution in sulfuric acid. The reaction can be presented schematically in the following manner.



$$R'-CH_2-\underset{R}{\overset{CH_3}{C}}-OSO_3H + R-\underset{H-\underset{R'}{C}-H}{\overset{H-\overset{H}{C}-H}{C}}-OSO_3H \rightarrow R'-CH_2-\underset{R}{\overset{CH_3}{C}}-\underset{R'}{CH}-\underset{R}{C}=CH_2 + 2H_2SO_4$$

B—Conjunct polymerization.—A different picture is obtained when concentrated sulfuric acid is used for polymerization. Upon treatment of olefinic hydrocarbons with 96 per cent. sulfuric acid at 0° the olefins without exceptions go into solution, forming esters of sulfuric acid. These esters on standing react, yielding hydrocarbons, insoluble in the sulfuric acid. The chemical analysis of the formed hydrocarbons has shown that the reaction that took place was a very complicated one, similar to the one described by us in the case of polymerization of ethylene and propylene by means of phosphoric acid.

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[5] IPATIEFF AND GROSSE, *ibid.*, **58**, 915 (1936).

So far none of the mechanisms mentioned in the literature account for the formation of the different types of hydrocarbons.

The main reaction proceeds according to the following scheme: (1) formation of alkyl esters; (2) reaction of the esters to yield open-chain olefins or cyclic hydrocarbons; (3) dehydrogenation of cycloparaffins to yield cycloölefins and hydrogen atoms; (4) hydrogenation of olefins to paraffins by means of the liberated hydrogen atoms.

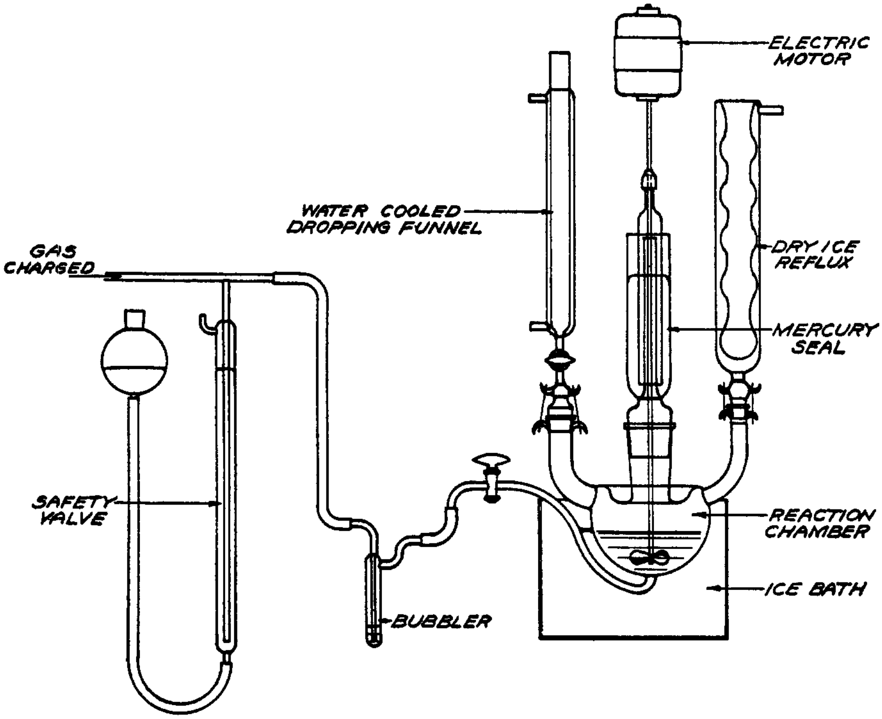

FIG. 1

EXPERIMENTAL

Apparatus and Procedure

The apparatus used is represented in Fig. 1. It consisted of a three-necked, 1-liter flask provided with a dropping funnel which was surrounded with a water jacket, a dry-ice reflux condenser, and a mercury-sealed stirrer. The reaction flask was surrounded by an ice bath.

Sulfuric acid was placed in the reaction flask, and the olefins added from the dropping funnel. Whenever butenes were used they were passed in the form of a gas through the inlet tube (Fig. 1). The time taken to add the hydrocarbons to the sulfuric acid varied from 1.5 to 3 hours. After the addition was completed the product was stirred for an additional 15 minutes. In the experiments where the volume ratio of sulfuric acid to olefins was 1:1, the product of the reaction was homogenous and only on standing did a hydrocarbon layer separate. Usually it requires three to four hours for complete separation of the hydrocarbons from the sulfuric acid layer. The hydrocarbon layer was washed with 15% solution of sodium hydroxide, followed by a water wash, dried and distilled. The sulfuric acid layer was decomposed with water. An oily layer separated. This was neutralized with sodium hydroxide and subjected to steam distillation. The distillate after being dried was fractionally distilled over metallic sodium. Some of the fractions were analyzed.

Preparation of Hydrocarbons

Isopropylethylene.—To prepare isopropylethylene, isoamyl alcohol was dehydrated by passing it through activated alumina at 400°. A mixture of isopropylethylene and trimethylethylene was formed. The product was treated at 0° with 75% sulfuric acid, which "dissolves" trimethylethylene and leaves isopropylethylene unchanged. The latter was distilled in a precision still; b. p. 20.8 – 21.7°.

Isobutene.—Isobutene was obtained by dehydration of isobutyl alcohol over precipitated alumina.[6]

Diïsobutene and Triïsobutene.—Diïsobutene and triïsobutene were prepared by polymerizing isobutene by passing it over "solid" phosphoric acid catalyst at a temperature of 110–120°.[7] The mixture of di-, and triïsobutene obtained was separated by fractional distillation. For the diïsobutene the fraction boiling at 100–106° was taken, which consisted of two isomers, 2,4,4-trimethylpentene-1 and 2,4,4-trimethylpentene-2. On hydrogenation the mixture yields 2,2,4-trimethylpentane. For triïsobutene the fraction boiling at 176–178° was used.

Nonene and dodecene.—The olefins were prepared by passing propene over "solid" phosphoric acid catalyst at 205° and 11 atmospheres of pressure.[7]

For nonene the fraction boiling at 130–135°, and for dodecene the fraction boiling at 190–200° was taken.

Methods of Analysis

At the time we were mainly interested in the identification of the types of hydrocarbons present rather than in separating individual hydrocarbons. The analytical methods available in the literature were not in all cases of sufficiently general nature to adopt them without reservation for our study. In many cases it was necessary to develop our own methods of analysis.

1. Determination of Paraffins.—The existence of paraffinic hydrocarbons was demonstrated by the following criteria: *A*, index of refraction; *B*, stability towards a nitrating mixture, which consisted of 1 volume of concentrated nitric acid and 2 volumes of 96% sulfuric acid; *C*, carbon-hydrogen analysis and molecular-weight determination.

2. Determination of Olefins.—The usual methods proposed in the literature to determine the quantity of olefins present consist in (*a*) the determination of bromine numbers, and (*b*) the treatment of the product with sulfuric acid. The data given in this paper show conclusively that the sulfuric acid method could not be used for this purpose. The bromine number method,[8] in most cases, gives reliable results as to the percentage of olefins present in a given product; this method could not be used,

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[6] IPATIEFF, *Ber.*, **36**, 2011 (1903); PINES, *J. Am. Chem. Soc.*, **55**, 3892 (1933).

[7] IPATIEFF AND SCHAAD, Unpublished results.

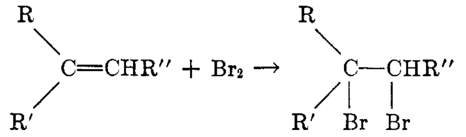
[8] FRANCIS, *Ind. Eng. Chem.*, **18**, 821 (1926).

however, without reservation. It was found that the percentage of triïsobutene present in a mixture could not be determined by it.

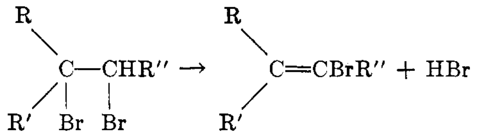
In general, branched-chain hydrocarbons may give side reactions with bromine. One of such possibilities might be:

Theoretical bromine number for triïsobutene = 95
Found = 72

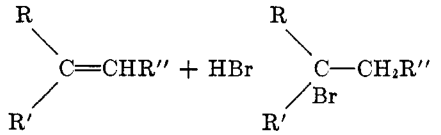
(1)



(2)



(3)



The product formed from reaction 2 is relatively stable towards bromine.

Branched-chain olefins of lower molecular weight like 2,4,4-trimethylpentene-1 could be determined by the bromine number method.

(*a*) *Hydrogenation.*—The percentage of olefins was determined by the hydrogenation method. For instance, in experiment 26 the fraction distilling at 170–185° has a bromine number of 73 and a molecular weight of 160, and organic analysis shows C, 85.71%; H, 14.38%. This indicates that the product contains 75% of olefins, the rest being cycloparaffins. By hydrogenation, however, a saturated product was obtained having approximately the same boiling point as the original product and the organic analysis showed that it contained C, 84.45 and H, 15.45; mol. wt. 162. Calculated for $C_{12}H_{24}$: C, 85.63; H, 14.37; mol. wt. 168. Calculated for $C_{12}H_{26}$: C, 84.70; H, 15.30; mol. wt. 170. This indicates that the product corresponds to a dodecane, which could have been formed only from dodecene. Triïsobutene by the same method gave similar results.

Procedure.—Fifteen grams of the product to be analyzed was dissolved in 10 cc. of cyclohexane and hydrogenated with Raney nickel at 160° under 100 atm. pressure. The apparatus used for the hydrogenation was a 150-cc stainless-steel Ipatieff-type autoclave. The product after hydrogenation was fractionally distilled to separate the cyclohexane from the rest of the product.

(*b*) *Alkylation Method.*—We found alkylation to be one of the best methods for the determination of the amount of olefins in the absence of aromatic hydrocarbons. From the study of alkylation of aromatic hydrocarbons with olefins in the presence of sulfuric acid,[9] it was observed that with 96% sulfuric acid at 0° polymerization of olefins does not take place.

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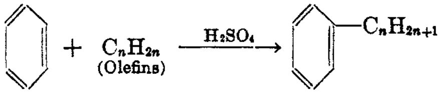
[9] Ipatieff, Corson, and Pines, *J. Am. Chem. Soc.*, **58**, 919 (1936).



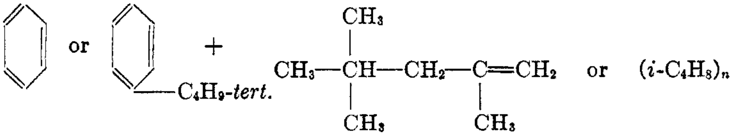
In order to separate olefins from paraffins and naphthenes 1 volume of the product to be tested was mixed with 1 volume of benzene and treated with 1.5 volumes of 96% sulfuric acid at 0°. The upper layer was then shaken with 1.5 volumes of 15% fuming sulfuric acid at 0°; this had to be done two or three times in all in order to dissolve all the benzene and alkylated benzene formed. The hydrocarbons undissolved in 15% fuming sulfuric acid consisted of saturated hydrocarbons originally present in the product. This method was studied with many synthetic mixtures and seems to give satisfactory results.

The upper layer remaining from the treatment was submitted to carbon-hydrogen analysis. From the organic analysis and molecular weight, it was possible to calculate the percentage of cycloparaffins present.

3. Determination of Naphthenes.—Naphthenes of high molecular weight could hardly be differentiated from paraffins of high molecular weight by organic analysis, since the difference in the hydrogen content between C_nH_{2n+2} and C_nH_{2n} is very small. We used the destructive hydrogenation method to differentiate the two hydrocarbons. The method consists in partial decomposition of the hydrocarbons by means of hydrogen at elevated pressure and temperatures in the presence of a catalyst. The cycloparaffinic side chains are split off as paraffins. The liquid product obtained from the destructive hydrogenation is fractionally distilled; a fraction boiling lower than the original product is analyzed for carbon-hydrogen. From the hydrogen content and molecular weight of this fraction it is possible to determine the percentage of cycloparaffins.

Procedure.—Twenty grams of the sample to be analyzed (b.p. 290–325°) and 5 grams of catalyst (60 parts NiO + 40 parts Al_2O_3) were placed in a stainless-steel autoclave of 450 cc. capacity. The autoclave was charged with 100 kg./cm.^{2} of hydrogen and heated at 275° for 3 hours. The pressure dropped from 100 kg./cm.^{2} at 25° to 85 kg./cm.^{2} at 25°. The yield of liquid product obtained was 60%; the fraction boiling at 200–225° was analyzed for carbon-hydrogen, and its molecular weight was determined.

4. The Study of the Structure of Polymers. (*Depolyalkylation*).—The structures of the high-boiling polymers were determined by the "depolyalkylation method".[10] The principle of the method is as follows: polymers of isobutene when treated with *tert.*-butylbenzene or benzene depolymerize and the products of the depolymerization react with benzene to yield among other compounds *p*-di-*tert.*-butylbenzene which is easily identified by its melting point. This method permits us to demonstrate the presence of the tertiary butyl group in the high-boiling polymers obtained from the treatment of isobutene with sulfuric acid. Polymers of *n*-butene do not yield solid products when they are caused to react with *tert.*-butylbenzene in the presence of sulfuric acid.



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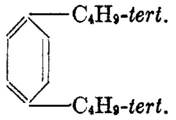
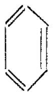
[10] Ipatieff and Pines, *ibid.*, **58**, 1056 (1936).

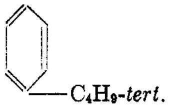
yields polyalkyl aromatic compounds and

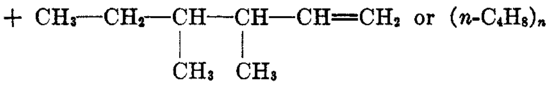


(Crystals; m.p. 78°)



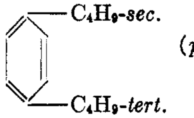
or





$$+\ CH_3—CH_2—\underset{CH_3}{\underset{|}{CH}}—\underset{CH_3}{\underset{|}{CH}}—CH{=}CH_2 \text{ or } (n\text{-}C_4H_8)_n$$

yields polyalkyl aromatic compounds and



(*p*-*sec.*-Butyl-*tert.*-butylbenzene is a liquid at room temperature.)

Procedure.—One volume of polymers was dissolved in 1 volume of *tert.*-butylbenzene or benzene and the mixture was shaken with 1 volume of sulfuric acid at 0°. The hydrocarbon layer was then separated from sulfuric acid, washed with 15% sodium hydroxide solution, followed by water, and distilled. In case the polymer contained a tertiary butyl group a solid product separated from the fraction boiling at 225–250°; the solid after recrystallization from hot alcohol melted at 78°, and consisted of *p*-di-*tert.*-butylbenzene.

EXPERIMENTAL RESULTS

I. Large Ratios of Acid at 0°

96% Sulfuric Acid

The conditions of the experiments are given in Table I.

Experiment 1: Isobutene.—The distillation is presented in Fig. 2, and the index of refraction in Fig. 6.

Fractions boiling up to 218° are composed of paraffinic hydrocarbons. The fraction boiling between 218 and 235° contains 5% of olefins, the rest being paraffins.

A fraction boiling at 160–180° was isolated, and on analysis gave the following results.

Found: C, 84.24; H, 15.45; mol. wt. 140; n_D^{20} 1.4149.

Calc'd for $C_{10}H_{22}$: C, 84.40; H, 15.60; mol. wt. 142.

Experiment 2: Diïsobutene.—The distillation is represented in Fig. 3 and the index of refraction in Fig. 7.

The product distilling up to 250° did not contain any olefins. Higher-boiling fractions (295–340°) consist almost entirely of unsaturated hydrocarbons since they are completely soluble in fuming sulfuric acid; the bromine number of these fractions is also high. The product boiling at 295–315° has a bromine number of 47 and a molecular weight of 316.

The fraction distilling at 195–210° was analyzed.

Found: C, 84.56; H, 15.39; mol. wt. 181; bromine number 0.

Calc'd for $C_{13}H_{26}$: C, 84.68; H, 15.32; mol. wt. 184.

Experiment 3: Triïsobutene.—The distillation curve is given in Fig. 4.

Fractions boiling up to 225° consist entirely of paraffinic hydrocarbons. Higher-boiling fractions contain olefins. According to the bromine-number determination,

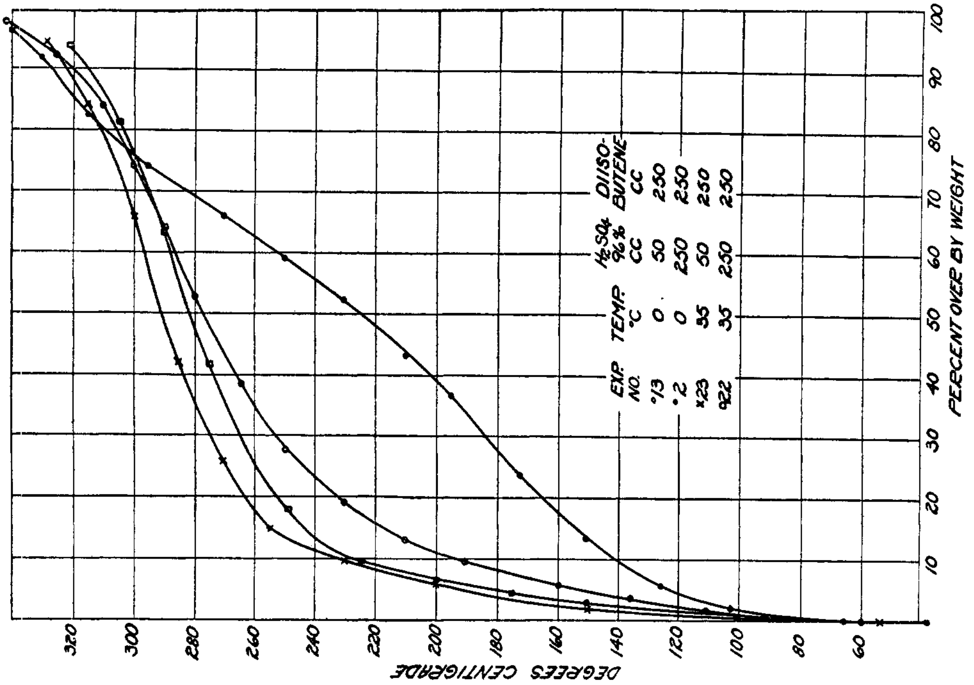

DEGREES CENTIGRADE
320
300
280
260
240
220
200
180
160
140
120
100
80
60
PERCENT OVER BY WEIGHT
10
20
30
40
50
60
70
80
90
100
EXP. NO. | TEMP. °C | H_2SO_4 96% CC | DIISO-BUTENE CC
○13 | 0 | 50 | 250
•2 | 0 | 250 | 250
×23 | 35 | 50 | 250
□22 | 35 | 250 | 250

Fig. 3

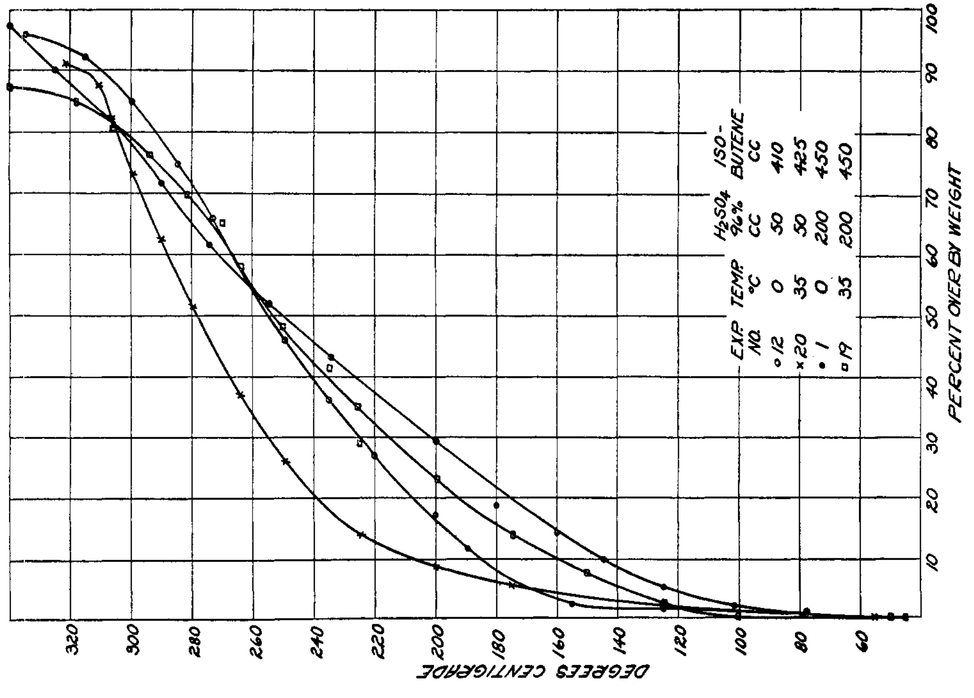

DEGREES CENTIGRADE
320
300
280
260
240
220
200
180
160
140
120
100
80
60
PERCENT OVER BY WEIGHT
10
20
30
40
50
60
70
80
90
100
EXP. NO. | TEMP. °C | H_2SO_4 96% CC | ISO-BUTENE CC
○12 | 0 | 50 | 410
×20 | 35 | 50 | 425
•1 | 0 | 200 | 450
□19 | 35 | 200 | 450

Fig. 2

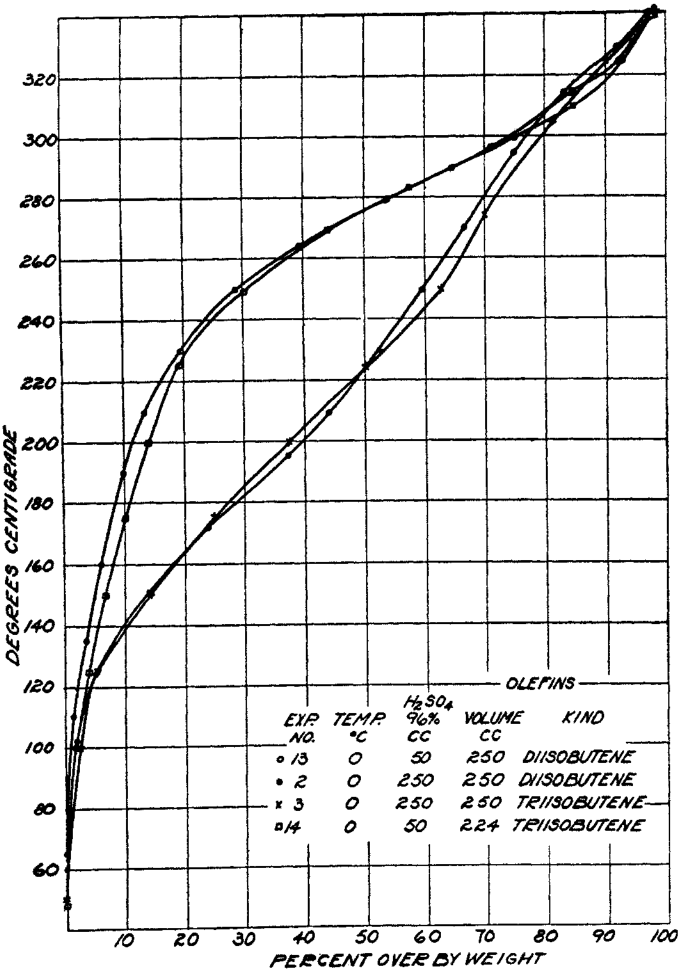


FIG. 4

the percentage of unsaturated hydrocarbons increases with the increase in boiling point. The following fractions were separated and analyzed.

BOILING RANGE, °C.	BROMINE NO.	MOL. WT.	UNSATURATED HYDROCARBONS CALCULATED FROM BROMINE NUMBER, %
225–250	13	231	18
275–305	38	284	62
325–340	48	361	108

The product boiling between 225 and 250° corresponds to a mixture consisting of 80% of hexadecane and 20% of olefins.

Found: C, 85.12; H, 14.90; mol. wt. 231; bromine number 13; n_D^{19} 1.4556.

Calc'd for 80% $C_{16}H_{34}$ + 20% $C_{16}H_{32}$: C, 85.0; H, 15.0; mol. wt. 226; bromine number 14.

Fraction boiling 325–340° contains tertiary butyl groups as shown by the depolyalkylation method.

Experiment 4: Isopropylethylene.—The boiling range of the hydrocarbon layer is as follows.

BOILING RANGE, °C.	WT., %	n_D^{20}
67–150	11.1	1.3770 to 1.4057
150–195	20.7	1.4193
195–265	18.2	1.4369
265–325	33.1	1.4571

The products distilling up to 265° do not contain any olefins. The following fractions were isolated.

Fraction 90–125°.

Found: C, 83.86; H, 16.05; mol. wt. 105; n_D^{20} 1.3770.

Calc'd for C_7H_{16}: C, 83.89; H, 16.11; mol. wt. 100.

Fraction 165–182°

Found: C, 84.24; H, 15.47; mol. wt. 148.

Calc'd for $C_{10}H_{22}$: C, 84.40; H, 15.60; mol. wt. 142.

Experiment 5: Pentenes.—Hydrocarbon Layer.—The following is the boiling range of the hydrocarbon layer.

BOILING RANGE, °C.	WT., %	n_D^{20}
55–150	11.3	1.3768 to 1.4015
150–200	25.2	1.4176
200–275	33.5	1.4420
275–350	22.9	1.4560

The products distilling up to 250° do not contain any olefins. The higher boiling fractions contain 30% of unsaturated hydrocarbons (Tested by Alkylation Method).

A fraction of boiling range 175–200° was analyzed.

Found: C, 84.64; H, 15.39; n_D^{20} 1.4176; d_4^{20} 0.7460; mol. wt. 149.

Calc'd for $C_{10}H_{22}$: C, 84.51; H, 15.49; mol. wt. 142.

Sulfuric Acid Layer.—The lower layer was decomposed with water; the oily layer which separated was neutralized with caustic and steam-distilled. The distillate was dried and fractionally redistilled.

BOILING RANGE, °C.	WT., %	n_D^{20}
160–200	4.8	1.4500
200–250	40.8	to 1.4777
250–293	50.1	to 1.4940

The fraction distilling at 225–250° was analyzed.

Found: C, 87.12; H, 12.52; mol. wt. 184; n_D^{20} 1.4831.

Calc'd for $C_{14}H_{24}$: C, 87.50; H, 12.50; mol. wt. 192.

After hydrogenation: C, 85.59; H, 14.17; mol. wt. 184. The values for the hydrogenated product correspond to the cycloparaffin $C_{14}H_{28}$.

Experiment 6: Nonene.—The following is the result of the fractional distillation of the hydrocarbon layer.

BOILING RANGE, °C.	WT., %	n_D^{20}
60–145	16.7	1.3990 to 1.4039
145–200	8.8	to 1.4155
200–280	21.2	to 1.4405
280–350	50.9	to 1.4535

The product boiling up to 240° was stable towards nitrating mixture, which indicates the absence of olefins.

The fraction of boiling range 175–200° was separated and analyzed.

Found: C, 84.71; H, 15.57; mol. wt. 148.

Calc'd for $C_{10}H_{22}$: C, 84.40; H, 15.60; mol. wt. 142.

The fraction of boiling range 280–350° was destructively hydrogenated to show the presence of cyclic hydrocarbons. A colorless product was obtained after hydrogenation, having the boiling range 130 to 270°. Two fractions were separated and analyzed.

Fraction A, b.p. 210–230°.

Found: C, 85.19; H, 14.72; mol. wt. 177.

This fraction consists of 30% of paraffins ($C_{12}H_{26}$) and 70% of cycloparaffins. (The H_2 content of dodecane is 15.40%.)

Fraction B, b.p. 245–255°.

Found: C, 85.20; H, 14.70; mol. wt. 217.

The analysis shows that this fraction consists of a mixture of paraffins (pentadecane) and cycloparaffins.

Experiment 7: Dodecene.—The following is the result of the fractional distillation of the product.

BOILING RANGE, °C.	WT., %	n_D^{20}
100–180	5.9	1.4101
180–230	25.5	to 1.4235
230–270	8.9	to 1.4341
270–340	44.2	to 1.4450
340–350	17.0	to 1.4580

The first two fractions were stable towards nitrating mixtures, indicating the absence of olefins.

The fraction of boiling range 340–350° was analyzed.

Found: C, 85.77; H, 14.20; mol. wt. 269.

The presence of cyclic hydrocarbons in the last two fractions was shown by the destructive hydrogenation method. A liquid product distilling between 90 and 330° was obtained.

A fraction boiling at 200–240° was separated.

Found: C, 84.94; H, 15.07; n_D^{20} 1.4291; mol. wt. 168.

Calc'd for a mixture consisting of $C_{12}H_{24}$ (70%) and $C_{12}H_{26}$ (30%): C, 84.90; H, 15.10; mol. wt. 168.

91, 87, 77 and 67% Sulfuric Acid at 0°.

The conditions under which the experiments were made are given in Table II.

Experiment 8a: Isobutene: 91% Sulfuric Acid.—The boiling range of the hydrocarbon layer is as follows.

BOILING RANGE, °C.	WT., %	n_D^{20}
46–100	1.2	1.3979
100–175	8.1	to 1.4110
175–225	8.5	to 1.4338
225–265	31.3	to 1.4450
265–290	27.2	to 1.4578
290–320	18.7	to 1.4571

The fraction boiling from 46 to 200° contains 37% of olefins as shown by the alkylation method.

Experiment 8: Isobutene: 87% Sulfuric Acid.—The boiling range of the hydrocarbon layer is as follows.

BOILING RANGE, °C.	WT., %	n_D^{20}
110–170	4.5	1.4329
170–200	63.8	to 1.4387
200–225	12.6	to 1.4439
225–250	12.2	to 1.4504
250–280	5.4	to 1.4550

The fraction boiling at 170–180° was studied: it had a bromine number of 73; mol. wt. 163. By the alkylation it was shown that it consisted of olefinic hydrocarbons only. The formation of *p*-di-*tert.*-butylbenzene indicates that tertiary butyl groups were present in the original product, which probably consists of triïsobutene isomers. The low bromine number found is characteristic of branched-chain dodecene.

Experiment 9: Diïsobutene: 87% Sulfuric Acid.—The following is the result of the distillation of the hydrocarbon layer.

BOILING RANGE, °C.	WT., %	n_D^{20}
60–200	5.1	1.3983 to 1.4250
200–250	66.7	to 1.4463
250–305	23.6	to 1.4538

All the fractions consist of olefinic hydrocarbons.

Experiment 10: Isobutene: 77% Sulfuric Acid.—The hydrocarbon layer consisted of olefinic hydrocarbons. The boiling range of the product corresponds to: diïsobutene, 45%; triïsobutene, 35%; tetraïsobutene, 15%.

Experiment 11: Diïsobutene: 77% Sulfuric Acid.—The results of the distillation of the hydrocarbon layer are given in Fig. 5. The product consists of diïsobutene (45%) and tetraïsobutene (50%). Practically no triïsobutene was formed.

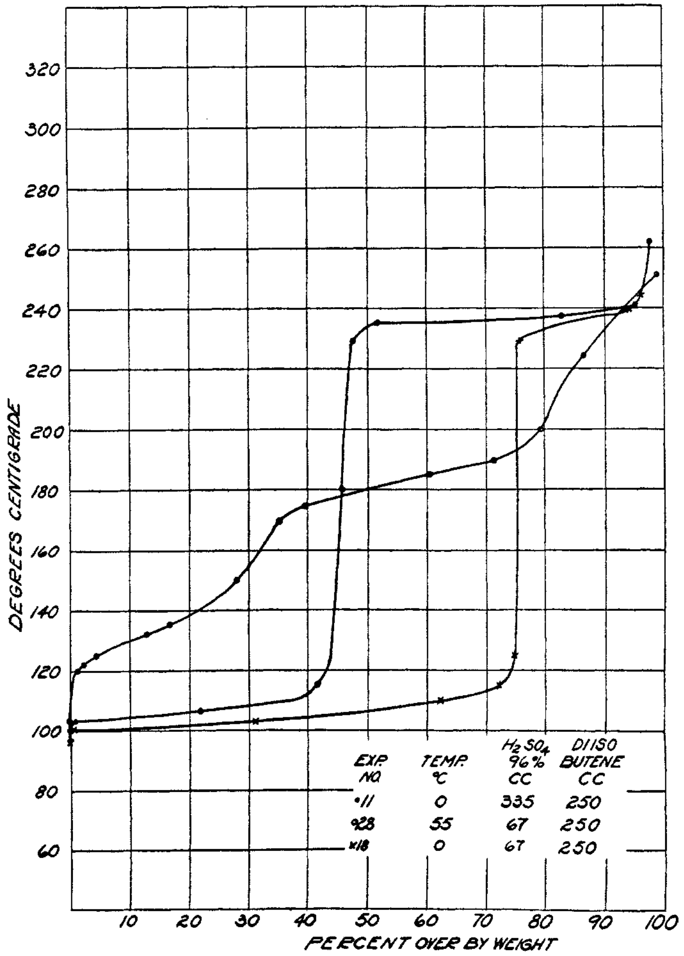


FIG. 5

II. Small Ratios of Acid at 0°

96% Sulfuric Acid

The conditions under which the experiments were made are given in Table III.

Experiment 12: Isobutene.—The results of the distillation of the hydrocarbon layer are given in Fig. 2, and the index of refraction in Fig. 6.

Olefinic hydrocarbons are present in all the fractions, including the lowest-boiling. The product boiling up to 220° contains 60% of olefins. Some fractions were submitted to analysis.

Fraction of boiling range 155–175°

Found: C, 84.85; H, 15.09; mol. wt. 148; bromine number 60; n_D^{20} 1.4220.

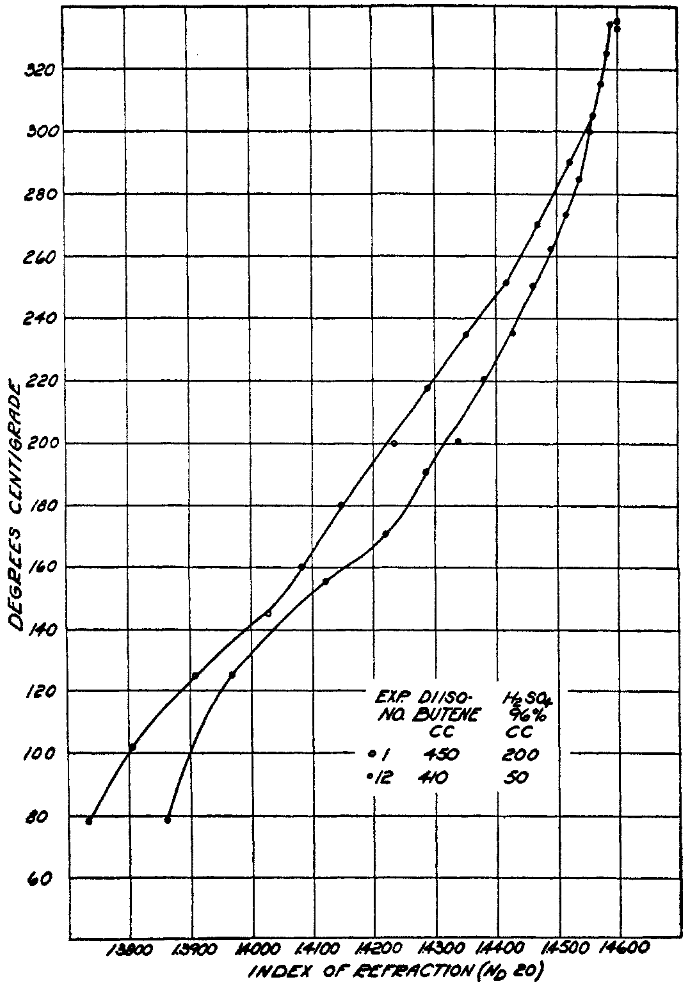


FIG. 6

This fraction corresponds to a mixture consisting of 50 parts of decane and 50 parts of decene.

Fraction of boiling range 300–315°

Found: C, 85.38; H, 14.28; mol. wt. 291.

Submitted to destructive hydrogenation, this fraction yielded a saturated product from which a fraction boiling at 225–250° was separated.

The analysis showed: C, 85.17; H, 14.55; mol. wt. 179.
From the carbon-hydrogen analysis and molecular-weight determination, it was calculated that this fraction contained about 60% of cycloparaffinic hydrocarbons.

Experiment 13: Diïsobutene.—The distillation curve of the hydrocarbon layer is given in Fig. 3, and the index of refraction Fig. 7.

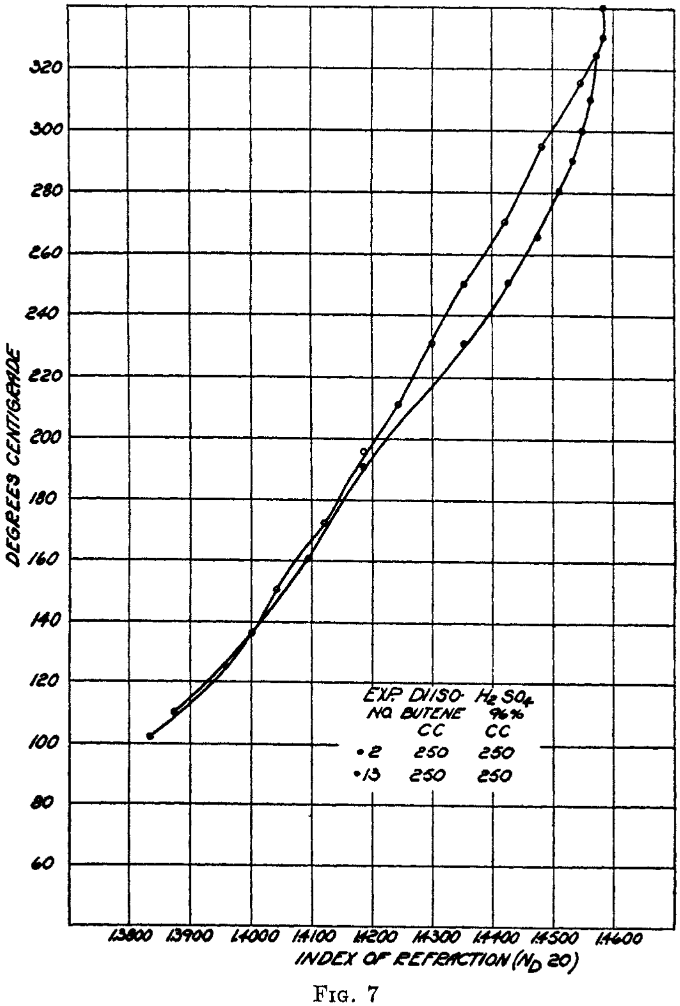


Fig. 7

Unsaturated hydrocarbons were found in all the fractions, including the lowest-boiling.

Fraction of boiling range 190–210°
Found: C, 84.67; H, 15.05; mol. wt. 181; bromine number 35; n_D^{20} 1.4270.
On the basis of bromine number, carbon-hydrogen, and molecular-weight determination, it was calculated that this fraction consists of 70% of paraffins and 30% of olefins.

The fraction of boiling range 290–325° was destructively hydrogenated. The hydrogenated product was distilled; a fraction boiling at 225–250°, stable towards nitrating mixture, was separated and analyzed.
Found: C, 85.28; H, 14.66; mol. wt. 187; n_D^{20} 1.4356. On the basis of analysis, it was calculated that about 65% of cycloparaffins was present in this fraction.

Experiment 14: Triïsobutylene.—Hydrocarbon Layer.—The distillation curve is given in Fig. 4. All the fractions, including the lowest-boiling ones, contain unsaturated hydrocarbons.

The fraction of boiling range 100–125° consists of octane with some admixture of octene.
Found: C, 83.94; H, 15.59; mol. wt. 108; n_D^{20} 1.3980
Calc'd for C_8H_{18}: C, 84.10; H, 15.90; mol. wt. 114.

Fraction of boiling range 200–225°
Found: C, 85.51; H, 14.57; mol. wt. 184; bromine number 40; n_D^{20} 1.4351
On the basis of the organic analysis, molecular-weight determinations, and the percentage of olefins present, it was calculated that this fraction consisted of: olefins, 45%; cycloparaffins, 25%; paraffins, 30%.

Sulfuric Acid Layer.—The layer was decomposed with water. An oily layer separated and was neutralized with caustic and steam-distilled. The distillate was fractionally redistilled and a product boiling at 220–235° was separated and investigated.
Found: C, 87.10; H, 12.81; mol. wt. 198; bromine number 235; n_D^{20} 1.4730.

The product was submitted to hydrogenation, and the hydrogenated material was distilled. A fraction boiling at 210–225° and stable to a nitrating mixture was analyzed.
Found: C, 85.46; H, 14.50; n_D^{20} 1.4445.
The results show that the original product before hydrogenating consisted of an unsaturated cyclic compound $C_{14}H_{24}$.

Experiment 15: Isopropylethylene.—The boiling range of the hydrocarbon layer is as follows.

BOILING RANGE, °C.	WT., %	n_D^{20}
62–170	8.2	1.3755 to 1.4112
170–225	9.4	to 1.4287
225–265	12.5	to 1.4452
265–305	35.3	to 1.4550
305–345	33.0	to 1.4570

The product boiling up to 170° was fairly stable towards nitrating mixture; 5% of olefins was present in this fraction. The content of unsaturated hydrocarbons formed in the different fractions is as follows: 225–250°, 50%; 265–280°, 81%; 295–305°, 87%; 315–335°, 94%.

87% Sulfuric Acid

Experiment 16: Isobutene.—The hydrocarbon layer consisted of olefinic hydrocarbons only. The boiling range of the product indicates the following composition: diïsobutene, 2%; triïsobutene, 75%; tetraïsobutene 18%.

The fraction of boiling range 170–180°, corresponding to triïsobutene, was analyzed.
Found: C, 85.45; H, 14.43; n_D^{20} 1.4313; mol. wt. 155; bromine number 69.

On hydrogenation, a product corresponding to triïsobutane was obtained:
Found: C, 84.49; H, 15.35; mol. wt. 155; d^{20}_4 0.7499.
Calc'd for $C_{12}H_{26}$: C, 84.70; H, 15.30.

The existence of the tertiary butyl group was shown by the depolyalkylation method.

Experiment 17: Diïsobutene.—The hydrocarbon layer consisted of the following products: diïsobutene, none; triïsobutene, 2%; tetraïsobutene, 87%; penta- and hexaïsobutenes, 10%.

77% Sulfuric Acid

Experiment 18: Diïsobutene.—The following is the composition of the hydrocarbon layer: diïsobutene, 75%; tetraïsobutene, 22%.

Effect of Temperature on Polymerization

The experimental conditions are given in Table IV.

Temperature −35°.

Experiment 19: Isobutene: Large ratio of 96% sulfuric acid.—The distillation curve is given in Fig. 2. The hydrocarbon layer distilling up to 250° consists of saturated hydrocarbons only. Higher-boiling fractions contain olefinic hydrocarbons the percentage of which increases with the rise in boiling point. The fraction boiling at 280–300° was analyzed; it contained 90% unsaturated hydrocarbons. The tertiary butyl group was found in this fraction, as shown by the formation of *p*-di-*tert.*-butylbenzene by the depolyalkylation method.

Experiment 20: Isobutene: Small ratio 96% sulfuric acid.—The distillation curve of the hydrocarbon layer is given in Fig. 2. All the fractions, including the lowest-boiling, react violently with nitrating mixtures, which indicates the presence of olefinic hydrocarbons.

The content of unsaturated hydrocarbons in the different fractions, found by the alkylation method, is as follows.

BOILING RANGE, °C.	% UNSATURATED HYDROCARBONS
55–250	75
250–290	85
290–322	100

Experiment 21: Isobutene: Small ratio of 96% sulfuric acid.—The product obtained is almost identical with the one obtained in Experiment 20.

Experiment 22, Diïsobutene: Large ratio of 96% sulfuric acid.—The distillation curve is given in Fig. 3. The hydrocarbon layer boiling up to 250° is stable towards nitrating mixture. The higher-boiling fractions contain olefinic hydrocarbons. The fraction distilling at 205–320° contains tertiary butyl groups as shown by the depolyalkylation method.

Experiment 23: Diïsobutene: Small ratios of sulfuric acid.—The distillation curve of the hydrocarbon layer is given in Fig. 3. The hydrocarbon layer, including even the fractions boiling to 150°, contains unsaturated hydrocarbons.

Temperature Above 0°.

Experiment 25: Isobutene: 77% Sulfuric acid at +35°.—The following is the record of distillation of the hydrocarbon layer.

BOILING RANGE, °C.	WT., %	n_D^{20}
100–122	30	1.4218
122–175	27	to 1.4275
175–190	20	to 1.4383
190–250	20	to 1.4525

Experiment 26: Isobutene: 67% Sulfuric acid at +35°.—The boiling range of the hydrocarbon layer is as follows.

BOILING RANGE, °C.	WT., %	n_D^{20}
100–122	45	1.4098 to 1.4168
122–175	17	to 1.4289
175–184	31	to 1.4315

The fraction of boiling range 175–184° was analyzed.

Found: C, 85.71; H, 14.38; mol. wt. 161.

After hydrogenation, Found: C, 84.45; H, 15.45; mol. wt. 162.

Calc'd for $C_{12}H_{26}$: C, 85.70; H, 15.30.

The original product corresponds to $C_{12}H_{24}$.

Experiment 27: Diïsobutene: 77% Sulfuric acid at +55°.—The following are the boiling points of the hydrocarbons formed.

BOILING RANGE, °C.	WT., %	n_D^{20}
120–150	28	1.4173 to 1.4276
150–175	12	to 1.4273
175–200	45	to 1.4352
200–250	14	to 1.4521

Experiment 28: Diïsobutene: 67% Sulfuric acid at +65°.—Unreacted diïsobutene forms 95% of the hydrocarbon layer, the rest being triïsobutene.

SUMMARY

1. Olefinic hydrocarbons treated with large amounts of 96 per cent. sulfuric acid at 0° yield a mixture of paraffins, olefins, and cycloölefins. The latter two are present in the fractions boiling above 250°. The fraction boiling below 250° consists entirely of saturated hydrocarbons.
2. The treatment of olefinic hydrocarbons with small ratios of 96 per cent. sulfuric acid at 0° yields a product having a higher boiling range than those treated with large quantities of acid. The product obtained consists of a mixture of hydrocarbons; olefins are present in the fractions boiling below 250°.
3. The yield of paraffinic hydrocarbons increases with the increase in the ratio of concentrated sulfuric acid to olefins treated.

4. The treatment of olefins at −35° with large or small amounts of 96 per cent. sulfuric acid yields liquid hydrocarbons having a higher boiling range than the product resulting from similar treatment at 0°.

5. Di- and triïsobutene when reacted with concentrated sulfuric acid yield liquid hydrocarbons with identical boiling ranges.

6. The treatment of olefinic hydrocarbons like diïsobutene and triïsobutene with concentrated sulfuric acid causes the cleavage of the chains, followed by hydrogenation. Triïsobutene yields a fraction corresponding to octane, diïsobutene yields a compound corresponding to dodecane.

7. Cycloölefins of the formula C_nH_{2n-4} were found in the decomposition product of the sulfuric acid layer.

8. Sulfuric acid of concentrations of 87, 77, and 67 per cent. does not cause the formation of paraffinic or cyclic hydrocarbons.

9. Dilute sulfuric acid at higher temperatures causes depolymerization. Diïsobutene, when treated with 77 per cent. sulfuric acid at 55° yielded triïsobutene.

10. New methods of analysis of different types of hydrocarbons are given.

Acknowledgment.—The authors wish to express their appreciation to Mr. Bruno Kvetinskas for the valuable assistance rendered.

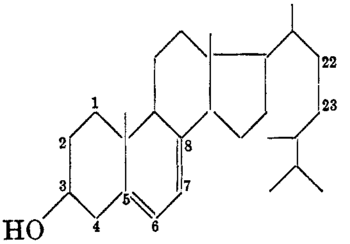
[Contribution from the George Herbert Jones Chemical Laboratory of The University of Chicago]

PROVITAMIN D ACTIVITY AND STRUCTURE—ADDITION OF GRIGNARD REAGENTS TO 7-KETOCHOLESTERYL ACETATE*

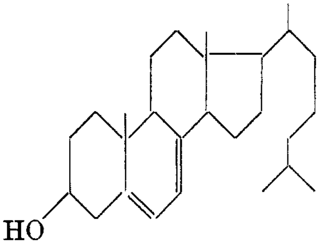
S. WEINHOUSE and M. S. KHARASCH

Received November 23, 1936

In recent years considerable chemical and biological evidence has been accumulated to show that antirachitic provitamin activity is not restricted to ergosterol, but is exhibited by several structurally related compounds, notably 22-dihydroergosterol (I)[1] and 7-dehydrocholesterol (II).[2]



I



II

The high activatability of these substances indicates that provitamin activity is associated with the pair of conjugated double bonds at C_{5-6} and C_{7-8}, and is probably independent of minor changes in the structure of the side-chain.

During the past thirteen months we have investigated the preparation of 7-dehydrocholesterol and its substitution products from cholesterol. As the first step in the preparation of derivatives of this type we have studied the products of the addition of various Grignard reagents to 7-ketocholesteryl acetate. Although the work is still incomplete, the recent publication of Bann, Heilbron, and Spring on 7-methylenecholesterol[3] suggests that duplication of effort may be avoided by disclosure of our observations to date.

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* The authors are indebted to Eli Lilly and Co. for a generous grant which made this work possible, and to Mr. C. R. Eckler of the Lilly Research Laboratory for the biological assays reported in this paper.

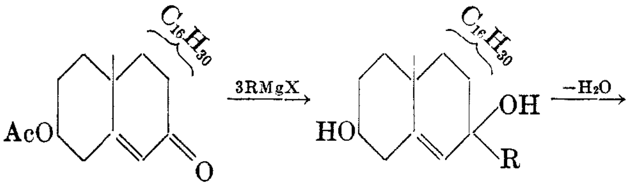
[1] Windaus and Langer, *Ann.*, **508**, 105 (1933).

[2] Windaus, Lettré, and Schenck, *ibid.*, **520**, 98 (1935).

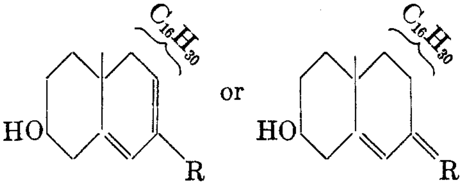
[3] Bann, Heilbron, and Spring, *J. Chem. Soc.*, **1936**, 1274.

THE ACTION OF GRIGNARD REAGENTS ON 7-KETOCHOLESTERYL ACETATE

The addition of three moles of a Grignard reagent to 7-ketocholesteryl acetate (III) may give rise to the following products.



III IV



V VI

The tertiary alcohol (IV) should, on partial dehydration, give rise to one or both of two isomeric dienols (V, VI). The product of annular dehydration (V) should exhibit intense absorption of light between 2600 and 3000 Å, and should be susceptible to isomerization by ultra-violet light.

Our study included the reaction of 7-ketocholesteryl acetate with the following Grignard reagents: methylmagnesium iodide, and ethyl-, isobutyl-, phenyl-, allyl-, cyclopentyl-, cyclohexyl-, and *tert.*-butylmagnesium bromides. Only the first four of these reactions have been studied exhaustively; the study of the others is still in progress. The interaction of 7-ketocholesteryl acetate and methylmagnesium iodide yielded both 7-hydroxy-7-methylcholesterol and 7-methylenecholesterol, but the latter was the sole product if the Grignard addition compound was refluxed for a long time or if it was hydrolyzed with dilute hydrocholoric acid. The only isolable product of the reaction between the ketone and ethylmagnesium bromide was 7-ethylidenecholesterol. Reaction of the ketone with isobutylmagnesium bromide yielded an uncrystallizable oil, from which 7-isobutylidenecholesteryl benzoate was isolated on esterification. Saponification of the benzoate yielded 7-isobutylidenecholesterol. The sole product obtainable from the reaction of the ketone with phenylmagnesium bromide was 7-hydroxy-7-phenylcholesterol. Attempts to dehydrate the latter have been unsuccessful up to the present time.

ABSORPTION SPECTRA

The absorption spectra (Fig. 1) of 7-alkylidene derivatives of cholesterol show a single intense band at 2400 Å, as a consequence of the conjugation at C_5 and C_7. The striking difference from the spectra of ergosterol derivatives, and the similarity to the typical absorption curves of α, β unsaturated ketones is worthy of note. The lack of absorption exhibited by 7-hydroxy-7-phenyl-, and 7-hydroxy-7-methylcholesterol is not unexpected. The absorption curves of some of the benzoates are shown in Fig. 2.

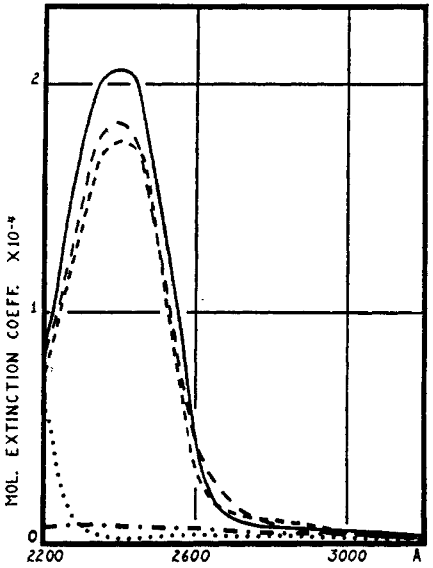


FIG. 1

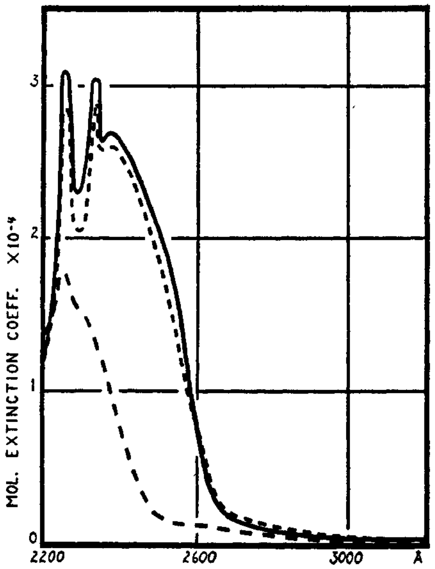


FIG. 2

FIG. 1.—ABSORPTION SPECTRA

———————— 7-methylenecholesterol

— — — — 7-isobutylidenecholesterol

------------- 7-ethylidenecholesterol

—·—·—·— 7-hydroxy-7-methylcholesterol

.... 7-hydroxy-7-phenylcholesterol

FIG. 2.—ABSORPTION SPECTRA

———————— 7-ethylidenecholesteryl benzoate

------------- 7-isobutylidenecholesteryl benzoate

— — — — 7-hydroxy-7-phenylcholesteryl benzoate

POSITION OF THE SECOND DOUBLE BOND

The position of the double bond in the side-chain of the 7-alkylidene derivatives was determined as follows: 7-ethylidenecholesteryl acetate was oxidized by means of chromic acid in glacial acetic acid. The product was identified as 7-ketocholesteryl acetate by its melting-point and by the melting-point of a mixture with an authenticated specimen. The similarity in the absorption spectra of the three alkylidene derivatives was interpreted as sufficient evidence for their identity with respect to the position of the second double bond.

ANTIRACHITIC ACTIVATABILITY

The 7-alkylidene derivatives, irradiated with ultra-violet light, were inactive on rats in daily doses of 0.1 milligram. We have, however, succeeded in obtaining a substance of low, but unquestionable antirachitic provitamin activity from the crude product of the reaction between 7-ketocholesteryl acetate and isobutylmagnesium bromide. Heating to 200°, or slow distillation at low pressure, of the crude reaction product yielded an oil which, when irradiated, was active on rats in daily doses of 0.01 milligram. None of the crude products arising from the other Grignard reactions could be thus activated. One might seek an explanation of the activatability of this crude product in the possibility that in the course of the Grignard reaction some direct reduction of the ketone may have taken place. This side-reaction would lead to the formation of 7-hydroxycholesterol, which on partial dehydration would yield the highly activatable 7-dehydrocholesterol. However, the distillation, at low pressure, of 7-hydroxycholesterol, prepared by the method of Windaus, Lettré, and Schenck,[2] yielded an oil which was completely inactive after irradiation.

Another tentative hypothesis to explain the unusual behavior of the isobutyl derivative is now under experimental investigation in this laboratory, as is the active principle in this preparation. We hope to publish the results of our findings shortly.

EXPERIMENTAL

Grignard reaction.—The following general procedure was adopted. 7-Ketocholesteryl acetate (6.60 g.—0.015 mole), dissolved in 30 cc. of anhydrous benzene, was dropped slowly into the solution of the Grignard reagent prepared in the usual manner from 0.1 mole of the halide. After addition, the solution was refluxed for from four to six hours, and then decomposed by means of iced ammonium sulfate solution. The reaction product was extracted with ether, the ether solution dried with anhydrous sodium sulfate, and the solvent removed.

7-Hydroxy-7-methylcholesterol.—The oily Grignard reaction product was dissolved in 25 cc. of hot methanol, the solution filtered, and allowed to cool slowly. A yield of 2.25 g. of 7-hydroxy-7-methylcholesterol was obtained; prisms from methanol, containing solvent; needles from benzene; m. p. 164–165°.

Anal. Calc'd for $C_{28}H_{48}O_2$: C, 80.8; H, 11.52.
Found: C, 81.0; H, 11.49.

7-Methylenecholesterol.—Concentration and cooling of the filtrate of the above yielded 1.10 g. of 7-methylenecholesterol; further concentration of the mother-liquor yielded an addition quantity of 0.95 g. The product crystallizes from methanol in the form of tufts of needles, containing solvent, which could not be removed by drying at 40° under extremely low pressure; m. p. 81–82°.

7-Hydroxy-7-methylcholesteryl monobenzoate.—The diol (0.5 g.) was dissolved in 2 cc. of pyridine, and 1.0 g. of benzoyl chloride added. The mixture was allowed to stand for 24 hours. The gummy reaction product was washed several times with water, then digested with boiling methanol, and the insoluble residue dissolved in hot acetone. The benzoate was obtained in needles; m. p. 172–173°.

Anal. Calc'd for $C_{35}H_{52}O_3$: C, 80.7; H, 10.00.
Found: C, 80.6; H, 10.11.

7-Methylenecholesteryl benzoate.—Treatment of the alcohol with pyridine and benzoyl chloride yielded the benzoate; slender prisms from acetone; m. p. 139–140°.

Anal. Calc'd for $C_{35}H_{50}O_2$: C, 83.7; H, 9.96.
Found: 83.6; H, 9.79.

7-Ethylidenecholesterol.—The Grignard reaction product was dissolved in hot methanol, filtered, and cooled. No crystalline product could be isolated, but the lack of absorption exhibited by the crude material indicated that it probably consisted almost entirely of the diol. A few drops of hydrochloric acid was added to the methanol solution, and the latter was refluxed for one hour. Upon cooling of the solution, 7-ethylidenecholesterol separated in large, flat, elongated prisms; m. p. 66–68°.

Anal. Calc'd for $C_{29}H_{48}O$: C, 84.5; H, 11.67.
Found: C, 84.3; H, 11.45.

7-Ethylidenecholesteryl benzoate.—Treatment with benzoyl chloride in pyridine in the usual manner yielded the benzoate; needles from acetone; m. p. 109–110°.

Anal. Calc'd for $C_{36}H_{52}O_2$: C, 83.7; H, 9.92.
Found: C, 83.6; H, 9.71.

7-Ethylidenecholesteryl acetate.—7-Ethylidenecholesterol (1 g.) was refluxed for one hour with 5 cc. of acetic anhydride, and the reaction mixture poured into cold water. The solid which precipitated was filtered off and crystallized from hot acetone; glistening plates, m. p. 110–111°.

Anal. Calc'd for $C_{31}H_{50}O_2$: C, 81.9; H, 11.01.
Found: C, 81.7; H, 10.95.

7-Isobutylidenecholesteryl benzoate.—The Grignard reaction yielded a colorless gum which could not be crystallized. It was dissolved in 10 cc. of pyridine, and 5 g. of benzoyl chloride was added in small portions with cooling. After standing at room temperature for 48 hours, the product was washed several times with water, then digested with boiling methanol, and the residue dissolved in hot acetone. On cooling, 7-isobutylidenecholesteryl benzoate was obtained; needles from acetone; m. p. 164–165°.

Anal. Calc'd for $C_{38}H_{56}O_2$: C, 83.8; H, 10.37.
Found: C, 83.8; H, 10.36.

7-Isobutylidenecholesterol.—Three hundred fifty milligrams of the above benzoate was refluxed with 8 cc. of 0.5 *N* alcoholic potassium hydroxide for 15 minutes. The solution was then cooled, water was added, and the precipitated white solid was filtered off and dissolved in a small quantity of methanol. On cooling, 7-isobutylidenecholesterol came down in flat prisms (m. p. 120–121°), containing solvent, which could not be removed by long drying *in vacuo.*

7-Hydroxy-7-phenylcholesterol.—The crude reaction product was dissolved in hot benzene and filtered. The product was then precipitated by means of petroleum ether, filtered off, and recrystallized from a mixture of benzene and petroleum ether. 7-Hydroxy-7-phenylcholesterol came down in the form of extremely fine needles; m. p. 151–152°.

Anal. Calc'd for $C_{33}H_{50}O_2$: C, 82.8; H, 10.46.
Found: C, 82.6; H, 10.48.

7-Hydroxy-7-phenylcholesteryl monobenzoate.—The usual reaction with benzoyl chloride in pyridine yielded the benzoate, needles from acetone; m. p. 201–202°.

Anal. Calc'd for $C_{40}H_{54}O_3$: C, 82.4; H, 9.27.
Found: C, 82.3; H, 9.20.

Oxidation of 7-ethylidenecholesteryl acetate.—The acetate (0.5 g.) was dissolved in 50 cc. of glacial acetic acid; 0.4 g. of chromic acid, dissolved in a mixture of 5 cc. of water and 5 cc. of acetic acid, was added in small portions, while the solution was maintained at a temperature of between 40 and 50°. A few cubic centimeters of alcohol was added after the solution had stood for two hours, and the solvent was evaporated *in vacuo.* The crystalline residue was dissolved in hot dilute acetic acid. The product which came down on cooling melted at 154–156°, and showed no depression of melting point when mixed with an authenticated specimen of 7-ketocholesteryl acetate; m. p. 157°.

SUMMARY

The reaction of 7-ketocholesteryl acetate with various Grignard reagents has been studied.

Of the two isomeric dienols which might result from the dehydration of the tertiary alcohol formed in the Grignard reaction, in each case the only substance obtained was the product of side-chain dehydration. None of the 7-alkyl-7-dehydro derivatives were found.

A substance of antirachitic provitamin activity was obtained by heating the crude product of the reaction between 7-ketocholesteryl acetate and isobutylmagnesium bromide.

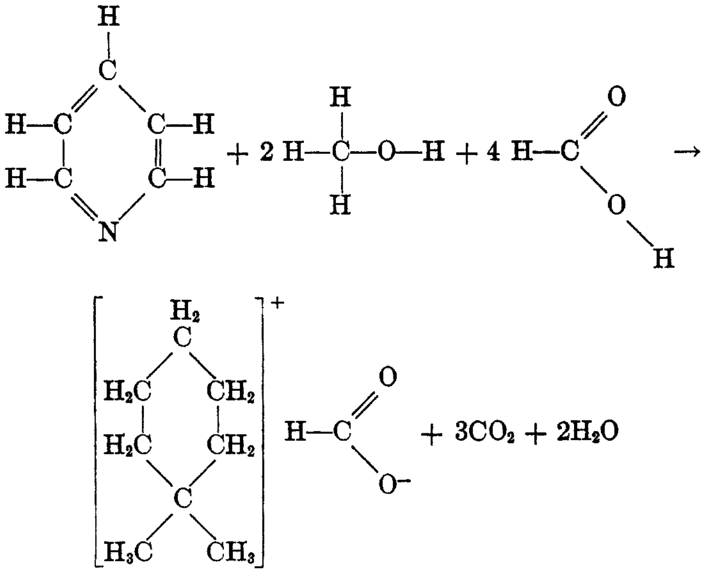
[Contribution from the Jackson Laboratory of E. I. du Pont de Nemours & Co.]

THE REDUCTION OF THE PYRIDINE RING BY FORMIC ACID

FRANK R. MAYO*

Received December 10, 1936

During an investigation of quaternary pyridinium salts, the appearance of a paper by Clarke, Gillespie, and Weisshaus[1] on the methylation of primary and secondary amines with formaldehyde and formic acid led to the application of this process to pyridine. For conversion of a secondary to a tertiary amine, they recommend refluxing the amine for 8 to 12 hours with 1.1 moles of 35 per cent. aqueous formaldehyde and 2.5 moles of 90 per cent. formic acid. When pyridine was thus treated for 64 hours, only a negligible reaction resulted. Heating a similar mixture under pressure for two hours at 175° or 200° yielded a small proportion of quaternary salt. Subsequent work showed that under these conditions, formaldehyde could be replaced by an equivalent quantity of methanol with no decrease in yield. Investigation of the quaternary salt thus formed revealed that it was not the expected *N*-methylpyridinium formate but *N*,*N*-dimethylpiperidinium formate, in which the pyridine ring had been completely reduced. The overall reaction was therefore



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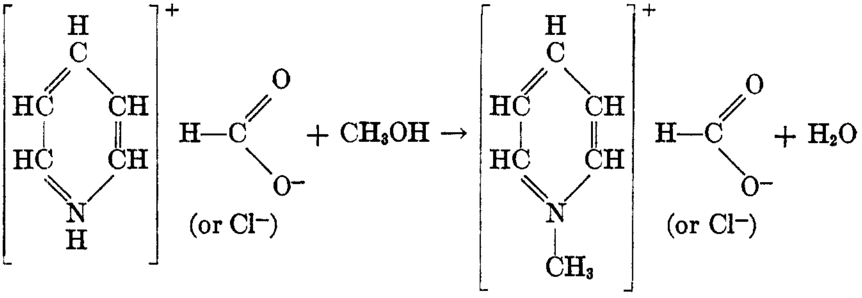
[*] Present address, Department of Chemistry, The University of Chicago.

[1] Clarke, Gillespie, and Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

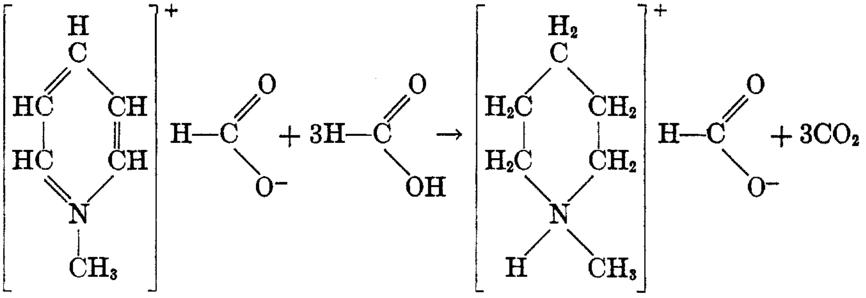
At the time, the large-scale preparation of this salt seemed desirable. Attempts to improve the yields led to the elucidation of the mechanism by which this reaction takes place. The details are given in the experimental part. From them the following conclusions are drawn concerning the mechanism of the high-temperature reaction between pyridine, methanol, and formic acid.

(1) The first step in the reaction is the formation of *N*-methylpyridinium formate, although none of this salt has been sought or found in the final product. Under similar conditions, the analogous reaction with hydrochloric acid takes place to the extent of 80 or 90 per cent.



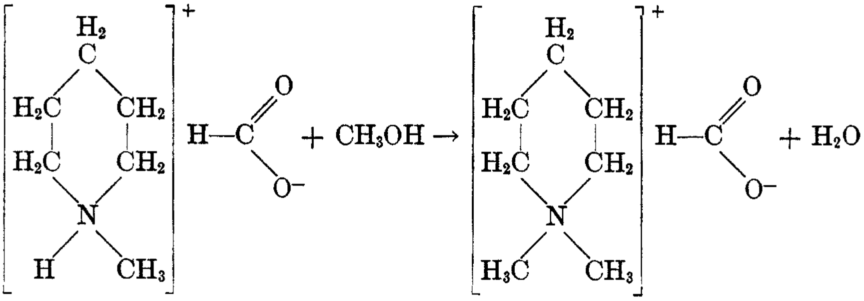
It is concluded that the nitrogen atom is methylated before the ring is reduced because, under the same conditions, pyridine was not reduced by formic acid alone, and because piperidine was not readily alkylated by formic acid and methanol.

(2) The second step in the reaction is the reduction of methylpyridinium formate to *N*-methylpiperidinium formate by formic acid.



Methylpyridinium formate is readily reduced by formic acid, while methylpyridinium chloride is not reduced at all, except in the presence of alkali metal formate which can produce a greater concentration of formate than can formic acid. Since formate ion rather than free formic acid takes part in the reduction, it is concluded that methylpyridinium formate is reduced by rearrangement to *N*-methyldihydropyridine and carbon dioxide. Reduction is completed by repeated salt formation with formic acid and rearrangement. No intermediate unsaturated bases have been isolated, but indications of their presence have been found. Small quantities of high-boiling bases which have been obtained are thought to be dimers of intermediate products. The data show that reduction of the pyridinium salt is practically complete when sufficient formic acid is present. The complete reduction of the formate in the absence of methanol shows that methylation is not a necessary part of the reduction mechanism. Why methylpyridinium chloride with 10 to 20 per cent. of potassium formate is largely reduced by formic acid in the presence of methanol but only slightly in its absence is not clear.

(3) The final step in the reaction is the methylation of *N*-methylpiperidinium formate by methanol to give *N*,*N*-dimethylpiperidinium formate.



Data show that this reaction proceeds easily with a yield of better than 50 per cent. under the usual experimental conditions.

EXPERIMENTAL

Low-temperature reaction.—One-half mole of C.P. pyridine was mixed with 1.25 moles of 88–90% C.P. formic acid and 0.55 mole of C.P. 37% formaldehyde. The mixture was heated on a steam bath under a reflux condenser for 64 hours. Evaporation of the product showed that no more than traces of quaternary salt had been formed.

Conditions of high-temperature reaction.—All subsequent preparations and experiments were carried out in thin-walled, unstoppered, Pyrex bottles of about 130 cc. capacity. The bottles fitted rather snugly in securely sealed steel bombs of about 230 cc. capacity. The bombs were heated in an oil bath. On cooling and opening, large quantities of carbon monoxide (from thermal decomposition of formic acid) and carbon dioxide were evolved. Slow release of this gas was necessary to prevent its violent liberation from the liquid in the bottle. In all normal experiments, the reaction mixtures were liquid, homogenous, and almost colorless, before and after heating. The quantities of reagents used depended on the capacity of the bottle and usually included one-fourth mole of pyridine.

Isolation and identification of reaction products.—The reaction product was transferred from the bottle to a distilling flask and heated to a liquid temperature of approximately 160° at 20 mm. pressure to remove pyridine, formic acid and methanol. (Pyridine formate,[2] $C_5H_5N \cdot 3HCO_2H$, boils at 66° at 20 mm. and 148–50° at atmospheric pressure.) The residue, designated hereafter as crude dimethylpiperidinium formate, contained small proportions of formic acid and reduced and unreduced non-quaternary bases in addition to the dimethylpiperidinium salt. The crude product was usually a colorless, low-melting, deliquescent solid. It was purified, for purposes of identification, by treating it with enough aqueous sodium hydroxide to liberate all the non-quaternary bases. The latter were then distilled out at about 50 mm. pressure until the liquid temperature reached 80–100°. The residue was acidified with formic acid and concentrated nearly to dryness. Sodium formate was separated from the organic formate by means of alcohol in which the sodium salt is only slightly soluble. The alcohol was then removed by distillation. The residue could be heated to 190° at 35 mm. for a short period (2 to 5 minutes) without much decomposition, in order to remove solvents. At room temperature the product was a pale yellow, deliquescent solid, melting at 140–80°. The yield on purification was 70–75% of the weight of the crude salt. Judging from its color and melting range, the *N*,*N*-dimethylpiperidinium formate was still not very pure, but it was too soluble in water and alcohols to be recrystallized conveniently. It was completely soluble in fairly concentrated sodium hydroxide solution, as is characteristic of quaternary salts.

This salt was identified positively by converting it to the chloride by repeated concentration *in vacuo* of concentrated hydrochloric acid solutions of the salt. The *N*,*N*-dimethylpiperidinium chloride thus obtained could be recrystallized from hot methyl or ethyl alcohols or from the cold absolute alcohols by addition of anhydrous ether. The recrystallized, colorless product was dried over phosphorus pentoxide *in vacuo* and analyzed.

Anal. Calc'd for $C_7H_{16}ClN$: C, 56.15; H, 10.78; N, 9.37; Cl, 23.70; mol. wt. in water, 149.59/2.

Found: C, 55.02; H, 10.55; N, 9.64; Cl, 23.6; mol. wt. in water, 71.0.

Because of the hygroscopic nature of the salt, the agreement is considered adequate in the above analyses, for which indebtedness to Mr. G. F. Palfrey is acknowledged.

N,*N*-Dimethylpiperidinium chloride was also prepared directly from piperidine. Technical piperidine, methyl chloride, and methanol in the molar proportions of 1:1.16:1.1 were heated as in previous experiments for 1 hour at 200°. Non-quaternary bases were removed as in the case of the formate, and the chloride was recrystallized and dried. The yield, based on the piperidine, was 60%. This salt and the one prepared from pyridine through the formate decomposed at approximately 340° and 330° respectively. The latter showed more reaction with bromine water and alkaline permanganate than the former, indicating that the salt from pyridine was not entirely free from incompletely reduced salts, which is not surprising in view of its method of preparation.

Reaction of pyridine, formaldehyde, and formic acid.—Table I summarizes bomb experiments with pyridine, formaldehyde, and formic acid. It is evident that the reaction proceeds nearly as well at 175° as at 200° and it is therefore assumed that the reaction goes to completion (or equilibrium) at the higher temperature. Attempts to replace formic acid as reducing agent by formaldehyde failed because of the formation of tars. Such experiments were based on the erroneous assumption that the end product was *N*-methylpyridinium formate.

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[2] GARDNER, *Ber.*, **23**, 1591 (1890).

Reaction of pyridine, methanol, and formic acid.—Table II shows that 11–15% yield of crude *N*,*N*-dimethylpiperidinium formate can be obtained from an equimolecular mixture of pyridine, methanol, and formic acid. Increasing the proportion of either methanol or formic acid improves the yield slightly but increasing the proportions of both to the theoretical increases the yield to nearly 60%. Pyridine does not react with either formic acid or methanol alone. The non-quaternary bases in one experiment were isolated by partial distillation of the reaction mixture after it had been made alkaline with sodium hydroxide. That the base had the odor and approximate boiling point of piperidine and yet was a tertiary amine (gave no reaction with carbon disulfide, while piperidine reacts vigorously) was considered sufficient evidence that it was *N*-methylpiperidine.

TABLE I

REACTION OF PYRIDINE, FORMALDEHYDE, AND FORMIC ACID

MOLES[a] 37% AQ. FORMALDEHYDE	MOLES[a] 88–90% FORMIC ACID	REACTION		YIELD[a] CRUDE *N*, *N*-DIMETHYLPIPERIDINIUM FORMATE (%)	REMARKS
		Time, hours	Temp., °C.		
1.1	2.5	2	175	12	
1.1	2.5	2	200	15–20	3 experiments
2.5	0.1	2	200	0[b]	2 experiments
1.65	1.1	1	200	0[b]	

[a] Based on pyridine used.

[b] Product a black, water-insoluble tar.

TABLE II

REACTION OF PYRIDINE, METHANOL, AND FORMIC ACID

MOLES[a] METHANOL	MOLES[a] 88–90% FORMIC ACID	REACTION TIME AT 200°, HOURS	YIELD[a] CRUDE *N*, *N*-DIMETHYLPIPERIDINIUM FORMATE (%)	REMARKS
1.0	1.0	1	11–15	3 experiments
1.25	1.5	1	17	2 moles[a] H_2O added
1.0	1.5	1	19	
1.0	3.0	1	12	Considerable *N*-methylpiperidine found
2.0	1.0	1	16	
3.0	1.0	1	19	
2.0	4.0	1	59	
0.0	4.0	1	0	
3.0	0.0	1	0	

[a] Based on pyridine used.

Reduction of N-*methylpyridinium salts with formic acid.*—When methylpyridinium chloride and formic acid in the proportion of 1 mole to 4 were heated for 1 hour at 200°, the salt was recovered practically unchanged. A similar result was obtained when 1.33 moles of methanol were added to the same mixture. It was then found that the addition of sodium or potassium formate caused reaction to take place. Since sodium formate was not very soluble in the reaction mixture, potassium formate was used in subsequent experiments.

Two procedures were used in the experiments with potassium formate. In the first, methylpyridinium chloride was dissolved in 88–90% formic acid, with or without methanol, and the required proportion of 50% aqueous potassium formate was then added. In the other, methylpyridinium chloride was dissolved in an equivalent quantity of 50% aqueous potassium formate. Most of the water was then removed at reduced pressure, and potassium chloride crystallized out, leaving a very concentrated solution of methylpyridinium formate. The mixture was extracted with methanol whereby all of the methylpyridinium formate and 7–12% of the potassium chloride were dissolved, leaving 88–93% of the latter to be removed by filtration. The solvents were then largely removed from the filtered solution by heating at reduced pressure. The residue consisted of 0.07 to 0.12 mole of potassium chloride and 15–40 g. of water per mole of methylpyridinium formate. It was then treated as shown in Table III.

TABLE III

REDUCTION OF METHYLPYRIDINIUM SALTS WITH FORMIC ACID

INITIAL REACTION MIXTURE, MOLES[a]				REACTION PRODUCTS, MOLES[a]			
Potassium Formate added	Potassium chloride removed	88–90% Formic acid	Methanol	Pyridine	*N*-Methylpiperidine	Quaternary salts	Unaccounted for
1.0	0.93	3.25	2.00	none	0.18	0.17 piperidinium	0.65
1.0	0.90	3.30	1.20	0.03	0.29	0.37 piperidinium	0.31
1.0	0.88	3.30	none	0.04	0.52	0.04 mixture	0.40
0.055	none	3.36	1.55	0.03	0.28	0.39 mixture	0.30
0.060	none	3.50	none	0.03	0.02	Balance mostly unchanged methylpyridinium chloride	
0.105	none	3.53	none	0.03	0.04		

[a] Based on *N*-methylpyridinium chloride used.

In all cases the reaction mixtures were heated for one hour at 200°. The product was completely converted to chloride by repeated concentration with hydrochloric acid and a final heating *in vacuo*. Aqueous sodium hydroxide was added and the mixture was distilled until the liquid temperature reached about 80° at 120 mm. In the first experiment in Table III, the bases in the distillate were separated from water by the addition of solid sodium hydroxide. They were shown to be substantially free from pyridine (no color on treatment with 1-chloro-2,4-dinitrobenzene and sodium hydroxide) and piperidine (no heat evolved on treatment with carbon disulfide). Since they boiled below 110° and had the odor of piperidine, it was assumed that they consisted almost entirely of *N*-methylpiperidine (b.p. 107°). In the other experiments, the distillate was titrated with standard hydrochloric acid, using phenolphthalein and bromophenol blue as indicators, thus giving the amount of strong base (*N*-methylpiperidine) and weak base (pyridine) in the distillate. The residue from the distillation was acidified, separated from alkali chlorides as previously described, dried, and weighed. The quaternary chlorides were identified qualitatively by their melting points as *N*-methylpyridinium chloride (m.p. 137°), *N*,*N*-dimethylpiperidinium chloride (dec. near 330°), or a mixture of the two.

The recorded yields of the products in Table III correspond to products actually isolated or determined by titration. The part of the original salt which is not accounted for should probably be distributed proportionately among the three types of products listed. In the analysis, some pyridine distilled with the formic acid and excess hydrochloric acid and was thus lost. During the alkaline concentration of the quaternary salt, a small part was decomposed and a small proportion of non-quaternary bases did not distill out completely. In all experiments in Table III in which considerable reduction took place, except the first, one-third to one-half of the total bomb contents were found in the bomb outside of the Pyrex bottle. Presumably they blew out of the bottle when the pressure was released, for they had the same physical characteristics as the bottle contents and did not contain much iron. In these experiments, the bomb contents outside are assumed to be the same as those inside the bottle and are so included in Table III, although they were not included in the analyses. Leakage of gases and vapors from the bomb may also account for some of the deficiency in material. The reversible dissociation of methylpyridinium chloride into pyridine and methyl chloride accounts for the pyridine and dimethylpiperidinium chloride formed in the experiments without added methanol.

Table III shows that methylpyridinium formate is almost completely reduced by formic acid; the presence of methanol has no great influence on the extent of reduction although it does determine whether the reduced salt will be tertiary or quaternary. In the presence of sufficient methanol a large part of the reduction product is further alkylated to quaternary salt. However, the presence of methanol makes a great difference in the extent of reduction by formic acid of a methylpyridinium salt mixture which contains about ten times as much chloride as formate. In the presence of methanol, most of the pyridinium salt is reduced; in its absence, reduction is negligible.

Methylation of piperidine and N-*methylpiperidine with methanol and formic acid.*—Piperidine is not readily alkylated by methanol and formic acid. When these three substances were mixed in the molecular proportion of 1:2.1:1.1 and heated for one hour at 200°, no more than a trace of quaternary salt was formed, demonstrated by the fact that the product was almost completely volatile. However, *N*-methylpiperidine is readily alkylated by methanol and formic acid under the same conditions. When heated for 1 hour at 200° in the proportion of 1:1.25:1.15, the mixture yielded 59% of crude, colorless, crystalline *N*,*N*-dimethylpiperidinium formate, indicating that this step may determine the yield in the reaction starting with pyridine.

Preparation of N-*methylpyridinium chloride.*—*N*-Methylpyridinium chloride was conveniently prepared[3] by passing methyl chloride for a few hours into pure pyridine at 70°. The quaternary salt crystallized out of the pyridine. The salt was a pure-white, crystalline, deliquescent solid, becoming orange on heating, and melting at 137° (uncorrected).

N-Methylpyridinium chloride was also prepared by heating pyridine hydrochloride with 2 moles of absolute methanol,[4] or 2.5 moles of 37% formaldehyde, for 2 hours at 200° in the apparatus described. Yields were 80–90%. Pyridine hydrochloride was separated from the product with sodium hydroxide by methods already indicated.

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[3] Ernst and Berndt, *U. S. Patent* 1,960,334; *Chem. Abstr.*, **28,** 4434 (1934).

[4] Haack, *German Patent* 593,670; *Chem. Abstr.*, **28,** 3421 (1934). Ostermayer, *Ber.* **18,** 591 (1885).

The author wishes to acknowledge his appreciation of the interest taken in this work by Mr. Ira Williams of the Rubber Division and of permission granted by Mr. W. S. Calcott, Director of Jackson Laboratory, to publish this paper.

SUMMARY

Pyridine reacts with formic acid and methanol (or formaldehyde) at 175° to 200° to give up to 60 per cent. yield of *N*,*N*-dimethylpiperidinium formate. *N*-Methylpyridinium formate and *N*-methylpiperidine are shown to be intermediate products.

[Contribution from the Laboratories of the National Bureau of Standards, U. S. Department of Commerce, Washington, D. C.]

A STUDY OF THE α- AND β-ALDOSES AND THEIR SOLUTIONS BY BROMINE OXIDATION AND MUTAROTATION MEASUREMENTS

HORACE S. ISBELL and W. W. PIGMAN

Received November 30, 1936

I. REACTIONS OF THE ALPHA AND BETA SUGARS WITH BROMINE WATER

An examination of the reaction rates of all the members of a stereomeric series brings out important information relative to the mechanism of the reactions and the structures of the reactive substances which cannot be obtained by other methods. The determination of the relative reactivity of the various modifications of the sugars is of value in order to understand their reactions in biological systems and in aqueous solutions in general. Previously Isbell and Hudson[1] found that the aldose sugars on oxidation with bromine water in slightly acid solution are converted into delta lactones, while Isbell[2] showed qualitatively that the beta sugars are oxidized more rapidly than the alpha sugars, and that the pyranose modifications give delta lactones without the intermediate formation of the free acid. Lippich[3] found that the alpha sugars react with hydrogen cyanide in neutral or alkaline solution slightly more rapidly than the beta sugars. Since the relative rates of reaction for the alpha and beta isomers with bromine and with hydrogen cyanide are different, the reactions do not take place in the same manner. Supposedly the aldehyde modification reacts rapidly with hydrogen cyanide, so that the reaction rate is determined by the rate at which the free aldehyde is formed. On the other hand, the cyclic forms of the sugars are oxidized by bromine water without the intermediate formation of the free aldehyde, so that the reaction rate is not dependent on the rate of aldehyde formation. Our studies[4] with *d*-glucose show that the rate of oxidation of the sugar by bromine water in the presence of barium carbonate is determined by the concentration of the oxidant (free bromine) and by the concentrations and proportions of the alpha and beta modifications of the sugar. The bromine oxidation is particularly suitable for investigation because it gives nearly quanti-

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[1] Isbell and Hudson, *B. S. J. Research*, **8**, 327 (1932); RP418.

[2] Isbell, *ibid.*, **8**, 615 (1932); RP441.

[3] Lippich, *Biochem. Z.*, **248**, 280 (1932).

[4] Isbell and Pigman, *B. S. J. Research*, **10**, 337 (1933); RP534.

tative yields of the free aldonic acids or their lactones and takes place under conditions such that the change of one sugar to another is slow.

Although there is considerable variation in the reactivity of the separate sugars, the most striking difference is found for the alpha and beta modifications of the same sugar. The existence of the alpha and beta modifications requires the presence of a ring structure, and the difference in the reactivity indicates an important structural difference in the two modifications. If the sugars had a uniplanar ring, the oxygen of the ring would lie in the plane of the carbon chain and the alpha and beta positions would be symmetrical in respect to the carbon-oxygen skeleton of the sugar. But if the oxygen and the carbon atoms forming the ring did not lie in one plane,[5, 6, 7] the alpha and beta positions would not be symmetrical with respect to the carbon-oxygen skeleton. That is, the alpha and beta positions would be inclined at different angles to the ring and would be influenced to different degrees by the neighboring groups, especially the oxygen. It was pointed out by Isbell[8] that if the sugars are divided into two groups, alpha when the hydroxyl of the first carbon lies in the same direction as the oxygen of the ring (*cis*), and beta when it lies in the opposite direction (*trans*), there is marked similarity in the behavior of all alpha sugars (and derivatives) on the one hand, and in the beta on the other. On account of the fundamental structural similarities of isomers in which the hydroxyl of the reducing carbon and the oxygen of the ring lie in the same or in opposite directions, it was suggested that this structural feature be used for naming the alpha and beta sugars. The nomenclature in use at present[9] depends on the *d* and *l* classification[10]. The *d* and *l* classification does not necessarily have any relation to the structure of the group being named. According to the nomenclature which is advocated *the names of the members of the alpha and beta pair of sugars or sugar derivatives are so selected that when the oxygen ring lies to the right, as in d-glucose, the more dextrorotatory member of the α-β pair shall be designated α, and the less dextrorotatory member β; when the oxygen ring lies to the left, as in l-glucose (or in d-galaheptose), the less levorotatory member is called β.* This results in names for which the subtraction of the rotation of the beta form from that of the alpha gives a positive difference whenever the oxygen ring lies to the right, and a negative difference when the oxygen ring lies to the

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[5] HAWORTH, "The Constitution of Sugars", Edward Arnold & Co., London, **1929**, page 90.

[6] SODA, *Bull. Chem. Soc. Japan*, **8**, 49 (1933).

[7] BRAUNS, *J. Am. Chem. Soc.*, **51**, 1820 (1929).

[8] ISBELL, *J. Chem. Educ.*, **12**, 96 (1935).

[9] HUDSON, *J. Am. Chem. Soc.*, **31**, 66 (1909).

[10] ROSANOFF, *ibid.*, **28**, 114 (1906).

left[11]. If the carbon atom united with the hydroxyl forming the oxygen ring is asymmetric, the oxygen of the resulting ring is considered to lie in the direction of the parent hydroxyl. This direction is ascertained by inspection of the Fischer projectional formulas[12]. In the case of the pentoses the direction of the ring is allocated empirically after comparison of their properties with those of sugars with similar configurations. The studies of Cox,[13] and others[14] show that the oxygen of the ring in the pentose series is not in the plane of the carbon atoms. Therefore the molecule as a whole is dissymmetric, so that it is permissible to postulate structural differences in the alpha and beta pentoses similar to those of the hexoses. In this respect it may be noted that the alpha and beta pentoses reveal differences in the chemical reactions of the first carbon which are analogous to those found for the alpha and beta hexoses.

It may be observed from the formulas in Fig. 1 that crystalline *l*-arabinose could be structurally related to either α-*d*-galactose or to β-*l*-altrose. The marked similarity of crystalline *l*-arabinose (+191) to α-*d*-galactose has been stressed by Hudson,[15] Riiber[16, 17] and others. The rates of oxidation reported in this paper substantiate the correlation of crystalline *l*-arabinose with α-*d*-galactose and indicate that it should be classified with the alpha sugars. Crystalline *d*-xylose (+94) could be related to either α-*d*-glucose or to β-*l*-idose. It resembles α-*d*-glucose in that it is oxidized slowly and hence it is properly classified as α-*d*-xylose. Crystalline α- and β-*d*-lyxose resemble *d*-mannose rather than *l*-gulose. Since α-*d*-lyxose is oxidized more slowly than β-*d*-lyxose they are properly classified. Classification of crystalline *d*- and *l*-ribose, however, is more perplexing. The *d*-sugar could be structurally related to *l*-talose or to *d*-allose. Ribose[18] gives a rapid and complex mutarotation but the total change is small. The compound character of its mutarotation shows that the equilibrium solution contains at least three modifications. The mutarotation of α-*d*-talose is also complex,[19] while the mutarotation of β-*d*-allose[20] appears to follow the first-order equation at least approximately. The oxidation of crystalline ribose takes place at a rate faster than that of any alpha sugar so far investigated but also at a rate slower than that of any beta sugar. The

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[11] Kreider and Evans, *ibid.*, **58**, 799 (1936).

[12] Fischer, *Ber.*, **27**, 3211 (1894).

[13] Cox, *J. Chem. Soc.*, **1931**, 2313.

[14] Sponsler and Dore, *Annual Rev. Biochem.*, **5**, 65 (1936).

[15] Hudson, *B. S. Sci. Papers*, **21**, 342 (1926); S533.

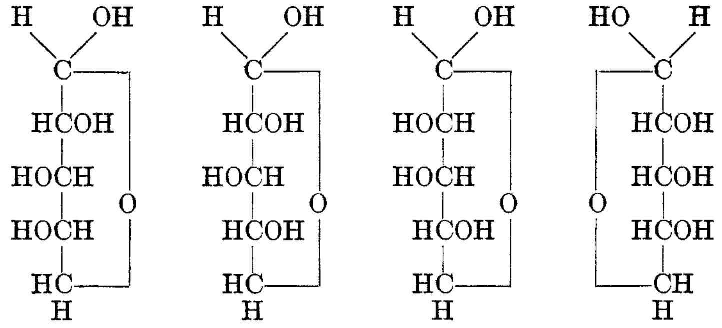
[16] Riiber, *Saertrykk av Tidsskrift for kjemi og bergvesen*, Nr. 10 (1932).

[17] Riiber and Sørensen, *Kgl. Norske Videnskab. Selskabs, Skrifter*, No. 7 (1933).

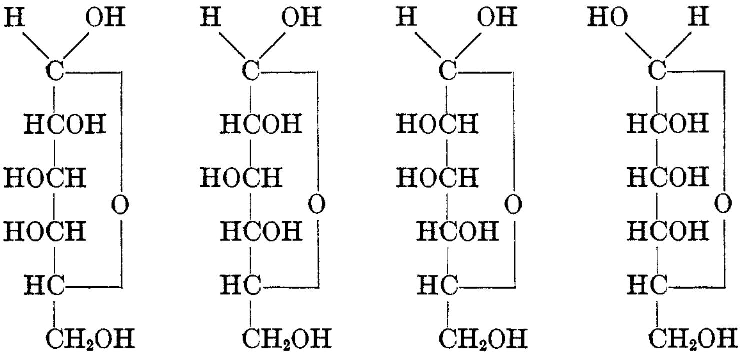
[18] Phelps, Isbell, and Pigman, *J. Am. Chem. Soc.*, **56**, 747 (1934).

[19] Isbell and Pigman, *B. S. J. Research*, **16**, 553 (1936); RP 892.

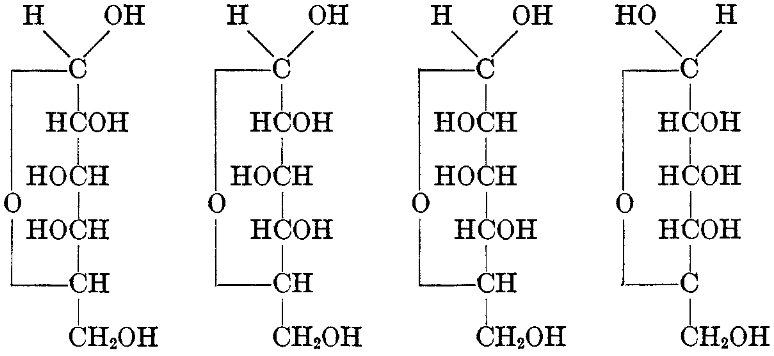
[20] Phelps and Bates, *J. Am. Chem. Soc.*, **56**, 1250 (1934).



α-*l*-Arabinose α-*d*-Xylose α-*d*-Lyxose *d*-Ribose



α-*d*-Galactose α-*d*-Glucose α-*d*-Mannose β-*d*-Allose



β-*l*-Altrose β-*l*-Idose β-*l*-Gulose α-*l*-Talose

FIG. 1.—COMPARISON OF THE FORMULAS OF THE PENTOSES AND HEXOSES

rate of oxidation appears to decrease slightly as the reaction proceeds. This small decrease in rate might be caused by the formation of less easily oxidizable sugar, or it might be explained by the presence of two modifications of the sugar in the original sample. The equilibrium solutions of *d*-

and *l*-ribose appear to contain about 10 per cent. of some modification which is more easily oxidized than the crystalline substance. As shown on page 520, the modification which predominates in the equilibrium solution is the isomer for which the hydroxyls of carbons 1 and 2 are "*trans*." Since the oxidation measurements show the presence of a large proportion of sugar in the equilibrium solution similar to the crystalline modification of ribose, it is probable that the hydroxyl of carbon 1 is "*trans*" to the hydroxyl of carbon 2. Although there is very little known of the properties of talose and allose, the available data appear to support the correlation of crystalline *d*-ribose with α-*l*-talose rather than with β-*d*-allose as originally suggested. When Phelps, Isbell, and Pigman[18] discovered the mutarotation of crystalline *d*- and *l*-ribose they suggested that these sugars be tentatively designated as β-*d*- and β-*l*-ribose. The existence of a small quantity of a more easily oxidizable sugar in the equilibrium solution throws doubt on the correctness of this classification, and until a more thorough study has been made they will be termed merely crystalline *d*- and *l*-ribose.

It may be seen from the results given in Table I that if the sugars are classified as suggested the beta isomers are oxidized by bromine more rapidly than the alpha isomers. This generalization is based on all the sugars so far investigated, which include the alpha and beta modifications of five of the eight pyranose types. Measurements on the idose, allose, and altrose types are necessary, however, before it is certain that the generalization applies to all pyranose sugars.

In conducting the oxidation measurements the crystalline sugar (0.025 mole) or the equilibrium solution (0.025 mole sugar in 100 ml. of water) was added to a cold mixture consisting of 10 ml. of bromine, 30 g. of barium carbonate, and either 500 ml. or 400 ml. of aqueous barium bromide solution containing 30 g. of $BaBr_2 \cdot 2H_2O$, saturated with carbon dioxide. The oxidation mixture was contained in a 1-liter 3-necked flask, which was surrounded with a cooling bath and equipped with a mechanical stirrer and a thermocouple for measuring the temperature. A slow stream of carbon dioxide saturated with bromine vapor was bubbled through the flask during the reaction. The concentration of bromine was determined at various times by sodium thiosulfate titration of the iodine liberated from the potassium iodide by a weighed sample of the mixture. The concentration of the sugar was measured at intervals on samples in which the oxidation had been stopped by the removal of the bromine with linseed oil solution (1 part of raw oil dissolved in 2 parts of benzene). Sugar was determined in the filtered solutions by Scales' method,[21] slightly modified by increasing the time of boiling to six minutes and increasing the time

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[21] Scales, *J. Ind. Eng. Chem.*, **11**, 747 (1919).

TABLE I

The Rates of Oxidation of the Alpha and Beta Sugars in Aqueous Solutions Containing 0.05 Mole Sugar and 0.08 Mole Free Bromine per Liter and Buffered with Barium Carbonate and Carbon Dioxide*

SUGAR	OXIDATION WITH BROMINE WATER			MUTAROTATION CONSTANTS AT 0.2 ± 0.2°C.	
	Average value for velocity constant	Relative reaction rates	Ratio of the rates for the α and β isomers		
	$k \times 10^3$	$\frac{k_{\text{sugar}}}{k_{\alpha\text{-}d\text{-glucose}}}$	k_β/k_α	$m_1 \times 10^3$	$m_2 \times 10^3$
α-*d*-Glucose	32	1	39.2	0.741	
β-*d*-Glucose	1255	39		0.738	
α-*d*-Mannose	51	1.6	15.3	2.16	
β-*d*-Mannose	781	24		2.14	
α-*d*-Galactose	42	1.3	37.9	0.93	11.9
β-*d*-Galactose	1590	50		0.90	16.7
α-*d*-Talose	78	2.4	10.8	3.62	25.5
β-*d*-Talose (from equilibrium solution)	844	26			
α-*d*-Gulose·$CaCl_2$·H_2O	71	2.2	5.9	1.88	
β-*d*-Gulose (from equilibrium solution)	418	13			
α-*l*-Arabinose	95	3.0	17.5	3.62	21.7
β-*l*-Arabinose·$CaCl_2$·$4H_2O$	1658	52		3.84	36.9
α-*d*-Xylose	90	2.8	18.6	2.45	
β-*d*-Xylose (from equilibrium solution)	1673	52			
α-*d*-Lyxose	156	4.9	2.9	8.44	
β-*d*-Lyxose	449	14		8.40	
d-Ribose (crystalline)	196	6.1	5.2		
β-*d*-Ribose (from equilibrium solution)	1010	32			
l-Ribose (crystalline)	195	6.1	7.5	6.87	54.0
β-*l*-Ribose (from equilibrium solution)	1456	45.5			
α-*l*-Rhamnose, hydrate	90	2.8	8.6	5.68	
β-*l*-Rhamnose (from equilibrium solution)	770	24			
α-Lactose, hydrate	29	0.9	32.8	0.54	
β-Lactose	952	30		0.52	
α-Maltose (from equilibrium solution)	24	0.8	64.0		
β-Maltose, hydrate	1528	48		0.58	

* The detailed experimental measurements summarized in this table will be published in the *Journal of Research of the National Bureau of Standards* for February, 1937.

required to produce boiling to four minutes. The procedure was standardized by determinations on known quantities of the sugar in the presence of various concentrations of barium bromide.

The study of the mechanisms of the reactions is complicated by the interconversion of the various modifications which exist in the aqueous solutions. The mutarotation reaction which occurs when the sugar is dissolved in water results in the formation of either more or less easily oxidizable modifications. The production of a less readily oxidizable substance retards the rate of oxidation, while the formation of a more readily oxidizable substance accelerates the rate. Thus the reaction of the alpha sugars with bromine water can be considered to consist in two simultaneous reactions. One of these is the oxidation of the alpha sugar directly, and the other the conversion of the alpha sugar to beta or other easily oxidizable substance and the subsequent oxidation thereof. In the oxidation of α-*d*-glucose it was shown[4] that if the concentration of the oxidant (free bromine) is held constant, and if it is assumed that the beta sugar is oxidized as fast as it is formed, the usual formula for two simultaneous reactions gives the equation

$$k_1 + ak_\alpha = \frac{1}{t} \ln \frac{A}{A - X}.$$

In this equation k_1 is the velocity constant for the conversion of α-glucose to easily oxidizable sugar, a is the concentration of free bromine, k_α the velocity constant for the oxidation of the alpha isomer, and A and $A-X$ are the quantities of sugar present at the beginning and end of the time interval, t. There is no reliable method for determining k_1. In our previous paper on the oxidation of *d*-glucose its value was assumed to be the same as that obtained from the mutarotation coefficient, $k_1 + k_2$ (expressed in natural logarithms). This represents an approximation which permits an evaluation of the relative importance of the mutarotation and direct oxidation reactions. Since the mutarotations of many sugars are complex, the value of k_1 cannot be determined even approximately, and consequently a correction for the mutarotation reaction is not feasible. In certain cases the oxidation of the beta isomers is less rapid than that of glucose, and hence the assumption that the beta isomer is oxidized as rapidly as it is formed is not justified. For these reasons the reaction rates for the alpha and the beta sugars were calculated, using common logarithms, by the simple formula

$$ak = \frac{1}{t} \log \frac{A}{A - X}$$

without attempting to make a correction for the mutarotation reaction.

It can be seen from the data of Table I that the pentoses, with the exception of β-*d*-lyxose, are oxidized more readily than the corresponding hexoses. The more rapid oxidation of the alpha pentoses is probably caused by the more rapid mutarotation reaction with the accompanying production of easily oxidizable modifications; the less rapid oxidation of β-*d*-lyxose may result from a similar cause, the formation of the less readily oxidizable alpha modification. The values for the mutarotation constants, m_1 and m_2, are given in Table I so that the reader can judge for himself the importance of these reactions in the interpretation of the oxidations. The constants, m_1 and m_2, were obtained as described on page 523; m_1 is the same as the mutarotation coefficient, $k_1 + k_2$, calculated for the later part of the mutarotation; m_2 also represents the sum of several constants which individually cannot be satisfactorily evaluated.

It will be noted that the velocity constants given for β-*d*- and *l*-ribose do not agree closely. These constants were obtained from a very rapid reaction involving only 10 per cent. of the sugar in the equilibrium solution and consequently the experimental error is large and the values are only approximate.

It can be seen from the data in Table I that α-*d*-galactose is oxidized slightly more rapidly than α-*d*-glucose but less rapidly than β-*d*-glucose, while β-*d*-galactose is oxidized more rapidly than either α- or β-*d*-glucose. The properties of the alpha and beta modifications of *d*-galactose and *d*-glucose in the equilibrium solutions are such that the oxidation of the equilibrium solution of *d*-galactose is more rapid than that of *d*-glucose. Hence our results confirm and extend the observation[22] that *d*-galactose is oxidized by bromine water more rapidly than *d*-glucose. It may be noted also that α-*d*-talose, α-*d*-mannose, and α-*d*-gulose$\cdot CaCl_2 \cdot H_2O$ are oxidized more rapidly than α-*d*-glucose. On the other hand, the corresponding equilibrium solutions are initially oxidized more slowly than the equilibrium solution of glucose, while in the latter stages they are oxidized more rapidly. Therefore, it is evident that a comparison of the reaction rates should not be made in general terms. Although several relationships between the configurations and the rates of reaction are apparent, such comparisons will be held up until sugars containing the allose, altrose, and idose structures have been investigated.

II. THE COMPOSITION OF EQUILIBRIUM SUGAR SOLUTIONS

In 1846, Dubrunfaut[23] discovered that when glucose is dissolved in water the optical rotatory power of the solution decreases on standing until finally it reaches a constant value. Subsequently Pasteur,[24]

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[22] Votoček and Němeček, *Z. Zuckerind, Böhm.*, **34**, 237 (1910).

[23] Dubrunfaut, *Compt. rend.*, **23**, 38 (1846).

[24] Pasteur, *Ann. chim. phys.*, **31**, 67 (1851); *Compt. rend.*, **42**, 347 (1856).

Erdmann,[25] Urech,[26] and others[27] found that the optical rotations of freshly prepared solutions of the reducing sugars in general change on standing, a phenomenon which came to be known as mutarotation. In the beginning Dubrunfaut suggested that the change in optical rotation is caused by a change in molecular structure, but at that time the structures of even simple organic compounds were not known. The aldehyde structure for glucose was suggested by von Baeyer in 1870,[28] but it did not satisfactorily represent the experimental facts, because the sugar did not give the characteristic aldehyde reactions. In order to explain the absence of these reactions Colley[29] postulated an ethylene oxide structure and Tollens[30] a butylene oxide structure. It was pointed out by von Lippman[31] that the first carbon in the cyclic sugar is asymmetric and that two stereomeric isomers are possible. Erdmann[25] had previously prepared two forms of lactose, one having a higher rotation than the stable solution and the other a lower rotation. Modifications of similar character were found for numerous sugars by Tanret[32] and others. A ring structure is necessary to account for these isomeric forms, and for the two methyl glucosides prepared by Fischer.[33] These glucosides did not give the aldehyde reactions and apparently contained ring structures. Because they resembled the gamma lactones they were assigned a 1,4 ring structure and erroneously considered as such, until later work by Haworth[34] and others established that they contain the 1,5 or pyranose ring. In the meantime other glycosides had been prepared which do contain the 1,4 or furanose ring[35] so that there are two series of glycosides containing different ring structures. Supposedly, the 1,4 ring modifications of the sugars also exist but little is known about the proportions of these in aqueous solutions or of their part in the mutarotation reaction. Because products corresponding to both ring types are obtained by methylation of the sugars,[36] other methods must be used to ascertain their structure.

The methods for determining the ring structure of the sugars are (1) a

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[25] Erdmann, *Ber.*, **13**, 2180 (1880).

[26] Urech, *ibid.*, **16**, 2270 (1883); **17**, 1547 (1884); **18**, 3060 (1885).

[27] Lowry and Smith, *Rapports sur les Hydrates de Carbone*, 10th Conference of the International Union of Applied Chemistry, Liege, (1930), page 79.

[28] von Baeyer, *Ber.*, **3**, 67 (1870).

[29] Colley, *Compt. rend.*, **70**, 403 (1870).

[30] Tollens, *Ber.*, **16**, 922 (1883).

[31] von Lippmann, "Chemie der Zuckerarten", F. Vieweg und Sohn, Braunschweig, **1895**, pp. 130, 990–992.

[32] Tanret, *Bull. soc. chim.*, **15**, 195, 349 (1896).

[33] Fischer, *Ber.*, **28**, 1145 (1895).

[34] Haworth, "The Constitution of Sugars" Edward Arnold & Co., London, **1929**.

[35] Fischer, *Ber.*, **47**, 1980 (1914).

[36] Haworth, Ruell, and Westgarth, *J. Chem. Soc.*, **125**, 2468 (1924).

comparison of the optical rotations of the sugars with the optical rotations of the corresponding methyl glycosides whose structures are known; [37, 38, 39, 40](2) a correlation of the methyl glycosides with the alpha and beta sugars by enzymatic hydrolysis; [41](3) a measurement of the direction of the optical rotation of a solution containing equivalent quantities of the alpha and beta isomers; [42](4) a comparison of the X-ray diffraction patterns of crystalline sugars and crystalline glycosides of known structure; [43](5) a study of various chemical reactions under conditions such that the rate of change from one form of the sugar to another is slow, as in the oxidation of the sugars with bromine water in the presence of a suitable buffer. According to the last method[1, 2] delta lactones are obtained by the oxidation of pyranoses, gamma lactones from furanoses, and supposedly free acids from aldehyde sugars. The structures of these are illustrated in Fig. 2.

The results obtained by one of us[2] with α- and β-*d*-glucose, α- and β-*d*-mannose, α- and β-*l*-rhamnose, α- and β-lactose, β-cellobiose, and β-maltose show that on oxidation with bromine these sugars give delta lactones. Mannose$\cdot CaCl_2 \cdot 4H_2O$, however, gives mannonic gamma lactone and presumably has the furanose structure.[44] The information thus derived shows that the crystalline sugars, which have been investigated with the exception of mannose$\cdot CaCl_2 \cdot 4H_2O$, have the pyranose structure. The results obtained by the other methods also lead to this conclusion, but since *d*-talose, *d*-ribose, and *l*-ribose have not been extensively studied, an allocation of the pyranose structure to these is entirely arbitrary.

The spontaneous crystallization of the alpha and beta pyranoses, the course of the mutarotation reactions, the solubility measurements with the crystalline sugars,[45] and the bromine oxidation method indicate that the pyranose modifications comprise by far the largest part of the sugar in solution. Nevertheless, the complex character of the solutions is plainly apparent from the numerous products which can be derived from reaction with various reagents. As shown by Fischer, and by others,[46] when a reducing sugar is treated with methyl alcohol containing hydrogen chloride, alpha and beta methyl pyranosides, and alpha and beta methyl

[37] SIMON, *Compt. rend.*, **132**, 487 (1901).
[38] HUDSON, *J. Am. Chem. Soc.*, **48**, 1434 (1926).
[39] ISBELL, *B. S. J. Research*, **3**, 1041 (1929); RP128.
[40] ISBELL, *ibid.*, **5**, 1179 (1930); RP253.
[41] ARMSTRONG, *J. Chem. Soc.*, **83**, 1305 (1903).
[42] DREW AND HAWORTH, *ibid.*, **1926**, 2303.
[43] COX, GOODWIN, AND WAGSTAFF, *ibid.*, **1935**, 978, 1495.
[44] ISBELL, *J. Am. Chem. Soc.*, **55**, 2166 (1933).
[45] HUDSON AND YANOVSKY, *ibid.*, **39**, 1013 (1917).
[46] LEVENE, RAYMOND, AND DILLON, *J. Biol. Chem.*, **95**, 699 (1932).

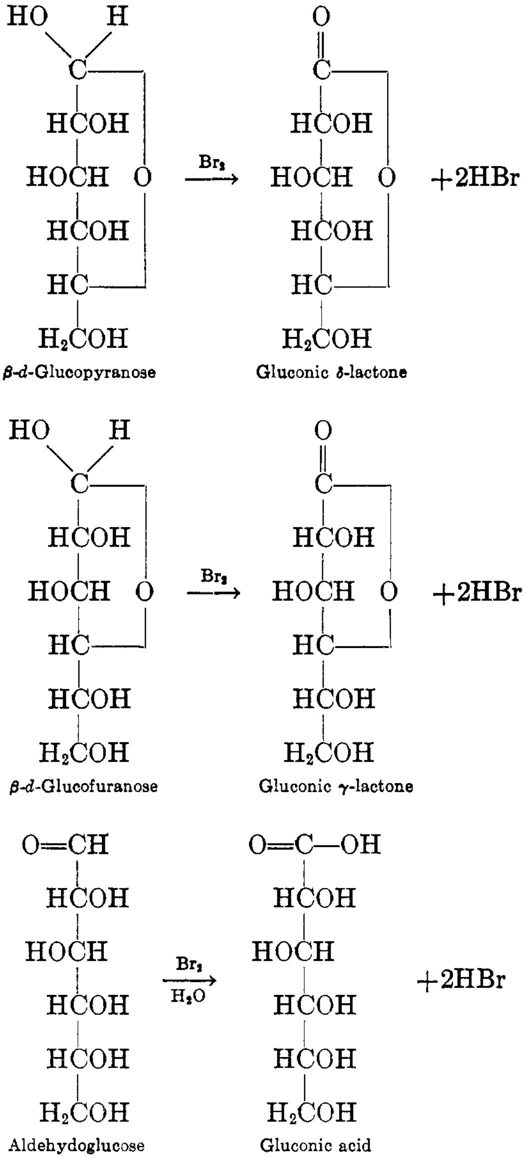

FIG. 2—OXIDATION OF THE PYRANOSE, FURANOSE, AND ALDEHYDO SUGARS WITH BROMINE WATER

furanosides are formed. Derivatives containing the furanose ring are given by other reactions, especially when the hydroxyl on the first or fifth carbon is substituted so that formation of pyranose derivatives is not possible. Seven isomeric pentacetates of galactose are known products. These appear to be derivatives of alpha and beta galactofuranose,[47, 48] alpha and beta galactopyranose,[49, 50] alpha and beta *d*-galactoseptanose,[51] and aldehydogalactose.[52] The fact that these derivatives can be obtained lends credence to the concept that minute quantities of the corresponding modifications of the sugars are present in aqueous solutions. The various ring isomers may also give rise to several modifications[5, 6] containing strainless Sachse rings, and the open-chain isomers may exist partially in hydrated[53, 54] and enolic[55, 56] forms. In addition to these the sugars dissociate slightly, giving ions[57, 58] and free hydrogen.[59] Thus an aqueous sugar solution is indeed a complex dynamic system.

The method for studying the compositions of the solutions in the present investigation is based on the oxidation of the sugars in the equilibrium mixture with bromine water under such conditions that equilibrium between the various isomers is not established prior to oxidation. Inasmuch as the beta sugars are oxidized rapidly and the alpha sugars slowly, the proportion of the beta isomer in the original solution cannot exceed the proportion of the easily oxidizable substance, and the proportion of the alpha cannot exceed the proportion of the slowly oxidizable material. It was shown previously[4] that about 64 per cent. of the sugar present in the equilibrium solution of glucose is oxidized rapidly at a rate comparable to the oxidation of β-*d*-glucose, and 36 per cent. is oxidized slowly at a rate comparable to the oxidation of the alpha isomer. Since these proportions agree with the amounts of α- and β-*d*-glucose estimated from the rotation of the solution, and calculated on the assumption that the solution contains only two isomers, it appears that the equilibrium solution of glucose contains, at least largely, the alpha and beta normal forms.

Application of this method to numerous equilibrium solutions of sugars has shown that a portion of the sugar in each case is oxidized rapidly at a rate comparable to the oxidation of the corresponding beta sugar, while

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[47] Hudson and Johnson, *J. Am. Chem. Soc.*, **37**, 1591 (1915).
[48] Schlubach and Prochownick, *Ber.*, **62**, 1502 (1929).
[49] Erwig and Königs, *ibid.*, **22**, 2207 (1889).
[50] Hudson and Parker, *J. Am. Chem. Soc.*, **37**, 1589 (1915).
[51] Micheel and Suckfüll, *Ann.*, **502**, 85 (1933).
[52] Wolfrom, *J. Am. Chem. Soc.*, **52**, 2464 (1930).
[53] Wolfrom, *ibid.*, **53**, 2275 (1931).
[54] Wolfrom and Morgan, *ibid.*, **54**, 3390 (1932).
[55] Nef, *Ann.*, **403**, 204 (1914).
[56] Wolfrom and Lewis, *J. Am. Chem. Soc.*, **50**, 837 (1928).
[57] von Lippmann, "Chemie der Zuckerarten", 3rd edition, **1904**, p. 268.
[58] Cohen, *Z. phys. Chem.*, **37**, 69 (1901).
[59] Ort and Roepke, *J. Phys. Chem.*, **38**, 1061 (1934).

the remainder is oxidized slowly at a rate corresponding to that of the alpha sugar. This can be seen by the results illustrated for *d*-galactose in Fig. 3. The oxidation of β-*d*-galactose is rapid and virtually complete in 20 minutes, while α-*d*-galactose requires 5 hours for approximately 80 per cent. oxidation. The equilibrium solution supposedly containing these constituents is oxidized rapidly for about 20 minutes, and then more slowly. When the percentage of oxidation is expressed on a logarithmic scale, the oxidation curve should be linear for a first-order reaction, or for a

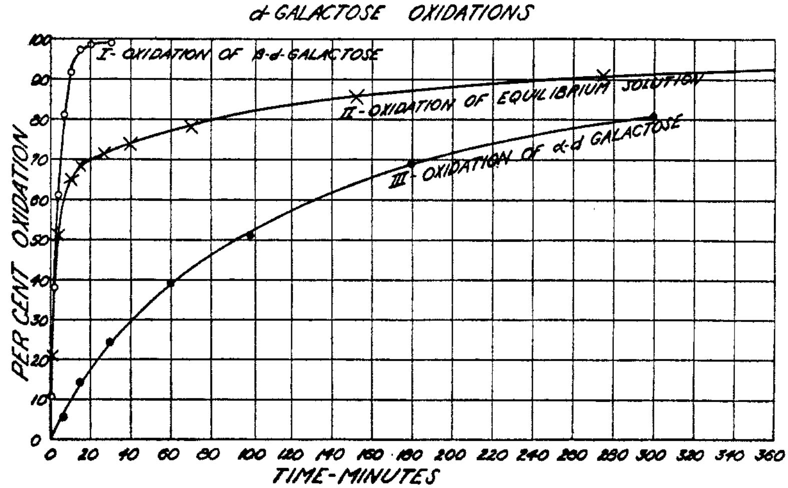

FIG. 3.—*d*-GALACTOSE OXIDATIONS

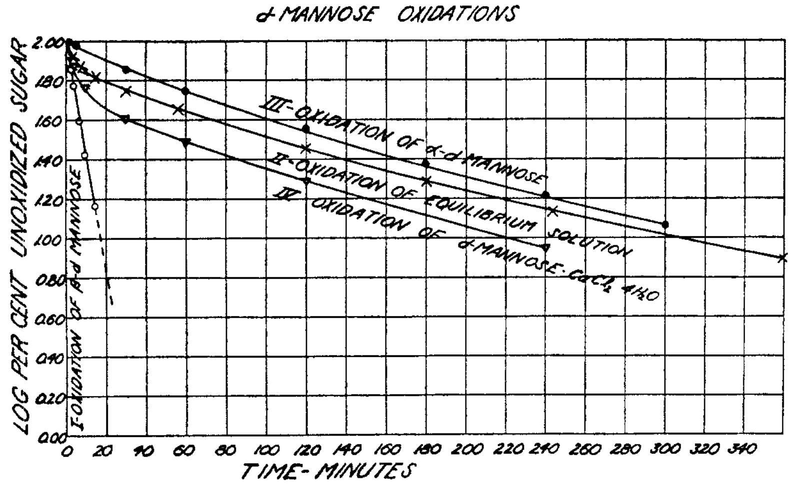

FIG. 4.—*d*-MANNOSE OXIDATIONS

second-order reaction in which the concentration of the oxidant is maintained constant. In Figs. 4 and 5 the oxidations of lactose and *d*-mannose are given on such a scale. It will be noted that the curves representing α- and β-lactose and α- and β-*d*-mannose are approximately linear. The small curvature is largely due to a decrease in the concentration of the oxidant, free bromine, as the reaction progressed. But for α-*d*-gulose, α-*d*-galactose, and α-*d*-xylose the drifts in the velocity constants are slightly larger than the experimental error. This may be due to an accumulation of unknown, less readily oxidizable modifications of the sugars in the solution, or to the production of other products which interfere with the analytical method.

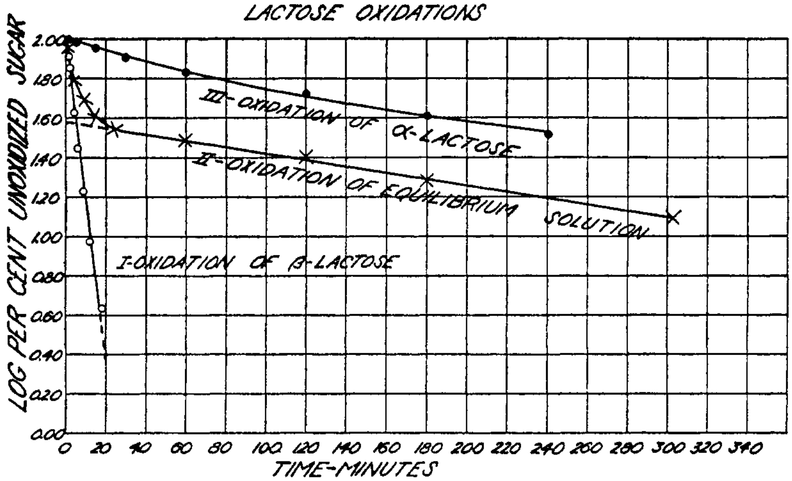

FIG. 5.—LACTOSE OXIDATIONS

The latter portions of the curves for the oxidation of the equilibrium solutions of lactose and *d*-mannose parallel those for the corresponding alpha isomers when the semilog scale is used as in Figs. 4 and 5. The equal slopes indicate that the reactions proceed at equal rates. Extrapolation of the portion of the curve representing the oxidation of the less reactive sugar, as represented by the dotted line, to zero time gives the logarithm of the less reactive sugar at zero time from which the proportions of less reactive and more reactive sugar can be calculated.

It may be observed from the data given in Table II that the proportions of the less reactive and more reactive sugars do not differ widely from the hypothetical proportions of the alpha and beta sugars, which were calculated from the optical rotations by assuming that the equilibrium solutions contain only normal alpha and beta isomers. Inasmuch as all of the less reactive sugar is not necessarily alpha, nor all of the more reactive, beta, the proportions of the less reactive and of the more reactive sugar represent limiting values for the alpha and beta normal sugars rather than absolute values. The striking agreement of the proportions obtained from the oxidation studies with those obtained from the optical measurements, however, makes it seem probable that the equilibrium solution consists, at least largely, of the normal alpha and beta isomers.

TABLE II

The Oxidation of Sugar Solutions at 0°C. with Bromine Water in the Presence of $BaCO_3$*

SUGAR	COMPOSITION OF EQUILIBRIUM SOLUTION				RATES OF OXIDATION WITH BROMINE WATER AT 0°C.			
	Estimated from the oxidation measurements		Calculated from optical rotations, assuming only two constituents		Obtained with equilibrium solutions at 0.3°C.		Obtained with crystalline sugars	
	Less reactive sugar	More reactive sugar	α-sugar	β-sugar	$k_A \times 10^3$	$k_B \times 10^3$	$k_\alpha \times 10^3$	$k_\beta \times 10^3$
	per cent.	*per cent.*	*per cent.*	*per cent.*				
d-Glucose	37.4	62.6	36.2	63.8	27.5	1362	32.4	1255
d-Mannose	68.9	31.1	68.8	31.2	45.2	860	51.1	781
d-Galactose	31.4	68.6	29.6	70.4	37.9	1720	42.3	1590
d-Talose	55.9	44.1			84.8	844	78.5	
$(d\text{-Gulose})_2 \cdot CaCl_2 \cdot H_2O$	18.5	81.5			52.6	418	54.8	328
l-Arabinose	32.4	67.6	26.5	73.5	84.2	1608	95.3	1658
d-Xylose	32.1	67.9	34.8†	65.2†	80.3	1673	89.9	
d-Lyxose	79.7	20.3	76.0	24.0	189	717	156	449
d-Ribose	89.3	10.7			180	1010	196	
l-Ribose	89.0	11.0			170	1456	195	
l-Rhamnose	69.0	31.0	73.1†	26.9†	83.4	770	89.7	
Lactose	37.5	62.5	36.8	63.2	20.9	1475	29.3	952
Maltose	37.7	62.3	36.0†	64.0†	23.7	1388		1528

* The experimental details for the oxidation measurements will be published in the *Journal of Research of the National Bureau of Standards* for February, 1937.

† Percentage calculated from Hudson's optical rotations derived from measurements of the initial and final solubilities at 20°C. [*B.S. Sci. paper*, **21**, 267 (1926); S533].

It may be observed from the data of Table II that the equilibrium solutions of sugars of similar structure frequently have approximately the same proportions of less reactive and more reactive substances. Thus the proportions of the two fractions for glucose, lactose, and maltose are nearly the same. Also the proportions for galactose and arabinose and for mannose and rhamnose are alike, while the proportions for xylose, lyxose, and ribose differ slightly from those for glucose, mannose, and talose, respectively. For every sugar so far investigated, the less reactive modification (the alpha form according to the suggested nomenclature) predominates in the equilibrium solution whenever the hydroxyl of carbon 2 is directed away from the ring. This generalization is in agreement with the statement of Haworth and Hirst[108] "that in the equilibrium mixture of the two isomerides the tendency is for the *trans* form to predominate." The results of our mutarotation and oxidation measurements extend this rule to the talose and gulose structures and probably to that for ribose.

Since the equilibrium solutions of the aldonic acids contain substantial proportions of the open-chain acid and butylene oxide forms (gamma lactone)[60] one would anticipate that the closely related sugars would also give substantial proportions of the open-chain and butylene oxide or furanose modifications. It is noted that the less reactive constituent for *l*-arabinose comprises 32.4 per cent. of the equilibrium mixture, while the proportion of alpha isomer calculated from the optical rotation is only 26.5 per cent. The differences in the rates of oxidation of the various isomers are not sufficient to permit the further classification of the constituents, and it is entirely possible that these solutions contain several per cent. of modifications other than the normal alpha and beta. The presence of such substances is of importance and may determine the course of many chemical reactions and give rise to the derivatives containing the furanose or the free aldehyde structures.

Although there are many qualitative data indicating the presence of furanose modifications, there is no satisfactory method for the identification and estimation of these modifications, but fortunately the presence or absence of even a small quantity of the aldehyde modification can be ascertained with certainty. Thus it has been shown by Gabryelski and Marchlewski[61] and others[62] that glucose, galactose, maltose, arabinose, and rhamnose in alkaline solution give strong absorption bands in the ultraviolet, but after neutralization of the alkali with acid the bands (supposedly due to the free aldehyde modification) disappear or become very faint. This indicates that in alkaline solution the open-chain modification is present in detectable amount, but that in acid solution not more than a minute quantity of this modification is present. This conclusion is also in harmony with the fact that most sugar solutions do not give the characteristic aldehyde reactions, whereas the true aldehyde sugars and their acetates give positive reactions with reagents which react with aldehydes.[63, 64]

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[60] LEVENE AND SIMMS, *J. Biol. Chem.*, **65**, 31 (1925); **68**, 737 (1926).

[61] GABRYELSKI AND MARCHLEWSKI, *Biochem. Z.*, **261**, 393 (1933).

[62] MARCHLEWSKI AND URBANCZYK, *ibid.*, **262**, 248 (1933).

[63] WOLFROM, *J. Am. Chem. Soc.*, **51**, 2188 (1929).

[64] WOHL AND NEUBERG, *Ber.*, **33**, 3095 (1900).

III. THE COURSE OF THE MUTAROTATION REACTIONS

Before much progress can be made in solving the problem of the composition of sugar solutions, new methods must be evolved for determining the minor constituents and the rates at which they are formed. A step in this direction has been made by Riiber[65] and coworkers, as well as by Smith and Lowry[66] and by Worley and Andrews[67] and others, in their investigations on small deviations in the mutarotation reaction.

The mutarotation measurements of Trey,[72] Osaka,[73] and other early investigators appeared to follow the first-order or unimolecular law. According to this law, the optical rotation at any time after dissolving the sugar in water can be expressed by the equation

$$[\alpha]_{\mathrm{D}} = Ae^{-kt} + C \tag{I}$$

in which $[\alpha]_{\mathrm{D}}$ is the specific rotation at the time, t, e the logarithmic base, A the difference between the initial and final specific rotations, C the final or equilibrium specific rotation, and k the velocity constant for the change in rotation. In 1899 Lowry[68,69] suggested that the mutarotation reaction was a reversible one, and in 1903 Hudson[70] showed that the two forms of lactose have equal velocity constants for their mutarotations, and that the maximum rate of solution is in accord with the hypothesis that the changes in rotation are not due to different reactions but to opposite parts of one balanced reaction. By applying the mass action law to the reversible reaction represented as

$$\alpha \underset{k_2}{\overset{k_1}{\rightleftarrows}} \beta$$

Hudson[71] developed the following equation:

$$k_1 + k_2 = \frac{1}{t} \log \frac{r_0 - r_\infty}{r_t - r_\infty} \tag{II}$$

in which t equals the time after dissolution, r_0 the optical rotation at zero time, r_t the rotation at the time, t, and r_∞ the final or equilibrium rotation. The mutarotation coefficient, $k_1 + k_2$, was shown to be the sum of the

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[65] RIIBER AND MINSAAS, *ibid.*, **59,** 2266 (1926).
[66] SMITH AND LOWRY, *J. Chem. Soc.*, **1928,** 666.
[67] WORLEY AND ANDREWS, *J. Phys. Chem.*, **32,** 307 (1928).
[68] HUDSON, *J. Am. Chem. Soc.*, **32,** 892 (1910).
[69] LOWRY, *J. Chem. Soc.*, **83,** 1314 (1903).
[70] HUDSON, *Z. phys. Chem.*, **44,** 487 (1903).
[71] HUDSON, *J. Am. Chem. Soc.*, **26,** 1067 (1904).
[72] TREY, *Z. phys. Chem.*, **18,** 193 (1895).
[73] OSAKA, *ibid.*, **35,** 661 (1900).

constants for the two opposing reactions. The mutarotation coefficient is usually expressed in common logarithms, but if the values of k_1 and k_2 are to be applied in kinetic problems they must be reduced to a natural logarithmic base by multiplication by 2.3026. This equation is merely the logarithmic form of equation I expressed in terms of the observed rotations and the separate velocity constants.

Until relatively recently it was believed that the monomolecular equation adequately represents the mutarotation of the reducing sugars. In 1926 Riiber and Minsaas published a paper[65] on the existence of a third modification of galactose in which they showed that during the mutarotation of alpha and beta galactose the changes in refractive index and molecular volume give evidence for at least three modifications of the sugar. Shortly afterwards Smith and Lowry[66] as well as Worley and Andrews[67] reported deviations in the mutarotation of α- and β-*d*-galactose which had been neglected by earlier workers. By assuming that three substances are involved Riiber and Minsaas developed an equation which satisfactorily expresses their experimental results. By a somewhat similar process Smith and Lowry applied equations previously developed by Lowry and John[74] to their measurements, and calculated the optical rotations and proportions of the constituents in the equilibrium solutions. The calculations were based on different hypothetical three-component systems, on the measurement of different physical properties, and on deviations only slightly larger than the experimental error. Consequently it is not surprising that there was considerable difference in the results from the two laboratories. As pointed out by Riiber, Minsaas, and Lyche[75] the proportions estimated by Riiber and Minsaas, as well as those calculated by Smith and Lowry, are based on the assumption that only three isomers are present; if more substances are present the proportions will be incorrect. The prevalence of equilibrium systems containing three or more constituents is shown by recent work. Thus Dale[76] reported a calcium chloride compound of mannose which exhibits a complex mutarotation, while Phelps, Isbell, and Pigman[18] and Isbell[77] showed that *d*- and *l*-ribose and β-*d*-glucoheptose give similar mutarotations. The compound character of these mutarotations clearly shows that the reactions are more complex than the simple interconversion of two isomers, and that it is necessary to adopt a method for expressing the mutarotation which renders account of these characteristic properties.

Smith and Lowry's fundamental equation for expressing the complex

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[74] LOWRY AND JOHN, *J. Chem. Soc.*, **97**, 2634 (1910).

[75] RIIBER, MINSAAS, AND LYCHE, *J. Chem. Soc.*, **1929**, 2173.

[76] DALE, *B. S. J. Research*, **3**, 459 (1929); RP106.

[77] ISBELL, *J. Am. Chem. Soc.*, **56**, 2789 (1934).

mutarotations is difficult to apply because it involves numerous constants which must be determined by laborious mathematical calculations. The evaluation of these constants requires the postulation of a definite number of reactions taking place in a certain manner, so that values thus obtained are highly speculative. The fundamental equation was simplified by them to the following form:

$$[\alpha]_D = Ae^{-m_1't} + Be^{-m_2't} + C \tag{III}$$

This equation satisfactorily represents two consecutive reactions as $x \rightleftarrows y \rightleftarrows z$. As applied to the sugar series the equation is more or less empirical, but it appears to fit the data for the simple and complex mutarotations as completely as the monomolecular equation fits the simple alpha-beta interconversions. Term C in equation III is the equilibrium rotation, A is the total change in optical rotation due to the slow or principal mutarotation reaction, and B is the deviation between the initial rotation and that obtained by extrapolation of the slow mutarotation to zero time. The exponents m_1' and m_2' are functions of the velocity constants for the separate reactions which occur during the mutarotation and represent the rate at which the optical rotation changes. The equation can be conveniently expressed to the base 10 rather than e, in which case m_1 and m_2 are in common logarithms rather than in natural logarithms.

In order to develop equations of this type from the experimental data by the method of Lowry and Smith[78] the mutarotation is divided into two periods, a short period, beginning at zero time during which a rapid change occurs, and a long period, beginning when the rapid change is substantially complete. By applying the formula

$$m_1 = \frac{1}{t_2 - t_1} \log \frac{r_1 - r_\infty}{r_2 - r_\infty} \tag{IV}$$

to the data representing the long period (that is, the last part of the mutarotation) values of m_1 are obtained. It will be observed that m_1 is the ordinary mutarotation coefficient measured for the latter part of the mutarotation, and that a mutarotation which follows the unimolecular law gives rise to only one exponential term. The constant, m_2, for the initial rapid change is calculated from the following equation:

$$m_2 = \frac{1}{t_2' - t_1'} \log \frac{d_1}{d_2} \tag{V}$$

in which d_1 and d_2 represent the differences between the observed rotations and those obtained by extrapolation of the long period back to the cor-

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[78] Lowry and Smith, *J. Phys. Chem.*, **33**, 9 (1929).

responding times. The extrapolation is accomplished mathematically by substitution of the calculated value of m_1, the observed equilibrium rotation, r_∞, and the observed rotation, r_2, at the time, t_2, selected after the rapid period is over, in equation IV, and solving for the rotation, r_1, at the desired time, t_1.

The mutarotation of each sugar used in this investigation was carefully determined. The results expressed in equations are given in Table III. The mutarotations which follow the monomolecular course are represented by equations which have only one exponential term; the mutarotations which deviate from the monomolecular course are given by equations containing two exponential terms.

By inspection of Table III it may be seen that the values of m_1 (the constant representing the principal mutarotation reaction) obtained from the alpha sugars agree within reasonable experimental error with those obtained from the corresponding beta sugars. The values of m_2 (the constant representing the rapid change) vary over a wider range, but since the experimental error is large the differences are not significant.

The molecular rotations and the differences in the molecular rotations ($2A$) for the alpha and beta isomers are given for convenience in comparing the optical rotations, and to show that the differences in the molecular rotations of the alpha and beta sugars at 0°C. are practically the same as those obtained at 20°C.

The initial specific rotation for *α-d*-talose was calculated by Isbell[39] in 1929 to be +60. This is in approximate agreement with that found (+68). The predicted rotation was based on values for the optical rotations of the various asymmetric carbon atoms, which were calculated by application of the van't Hoff[79,80] theory of optical superposition. According to the accepted formulas, *α-d*-talose differs from *α-d*-galactose in the configuration of the second carbon, and this difference is analogous to the difference in the structures of *α-d*-mannose and *α-d*-glucose. Sugars which differ in the stereomeric configuration of the second carbon have been designated "epimers" and the difference in their optical rotation is called epimeric difference[38]. According to our measurements at 20°C. the difference in the molecular rotations of *α-d*-glucose and *α-d*-mannose is 14,930, and of *α-d*-galactose and *α-d*-talose is 14,900. The approximate agreement might have been anticipated because the two calculations are made on substances which differ only in the configuration of the fourth carbon, and this carbon is removed from the asymmetric center involved in the calculation. The approximate agreement of the optical rotation

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[79] VAN'T HOFF, "La Chimie dans l'Espace," Rotterdam, **1875**.

[80] VAN'T HOFF, "The Arrangement of Atoms in Space" (translated by Eiloart), Longmans, Green and Co., London, **1898**, p. 160.

of talose with the calculated value is probably due in large measure to the similarity of the structures and not to the general validity of the theory of optical superposition. The new measurements extend the field for such comparison and should aid in the correlation of optical rotation and structure.

In contradiction to the deviations in the mutarotations of α- and β-*d*-glucose reported by Worley and Andrews, our mutarotation measurements with α- and β-glucose conducted at 0° and at 20°C. did not reveal deviations from the monomolecular equation larger than the experimental error. Although the equilibrium specific rotation of *d*-glucose is reported to be independent of the temperature[81] our measurements at 20°C. and at 0°C. give values of 52.7 and 52.1, respectively. Even though the difference is not large, it is sufficient to require revision of the concept that the equilibrium rotation of this sugar is independent of temperature.

The equilibrium rotations of *d*-mannose$\cdot CaCl_2 \cdot 4H_2O$ and *l*-arabinose$\cdot CaCl_2 \cdot 4H_2O$ differ slightly from the equilibrium rotations of the sugars in the absence of calcium chloride. This is due, at least in part, to an alteration in the equilibrium between the various modifications of the sugars by the calcium chloride which is similar to that found by Isbell for *d*-gulose[82]. By changing the concentration of calcium chloride in aqueous solutions of galactose, arabinose, and mannose sufficient equilibrium displacements occur to give rise to mutarotation.

The mutarotations of both α-*d*-gulose$\cdot CaCl_2 \cdot H_2O$ and (*d*-gulose)$_2 \cdot CaCl_2 \cdot H_2O$ take place in the same direction and at like rates, but the initial rotations (calculated on the same basis) have widely different values. Although the two compounds are crystalline and apparently homogeneous, since the mutarotations follow the monomolecular equation, it seems probable that the compound with lower optical rotation contains some of the heretofore unknown beta modification. The bromine oxidation of α-*d*-gulose$\cdot CaCl_2 \cdot H_2O$ proceeds at a fairly uniform rate, but that of (*d*-gulose)$_2 \cdot CaCl_2 \cdot H_2O$, proceeds rapidly until a part of the sugar is used up and then more slowly as the remaining sugar continues to be oxidized. The rates of reaction indicate that (*d*-gulose)$_2 \cdot CaCl_2 \cdot H_2O$ contains about 32 per cent of easily oxidizable sugar. When (*d*-gulose)$_2 \cdot CaCl_2 \cdot H_2O$ was first reported it was thought to represent another ring modification[83] because its optical rotation changed in the same direction as the gulose$\cdot CaCl_2 \cdot H_2O$, first obtained, while the rate of mutarotation appeared to increase after the first few minutes. Unfortunately the optical rotation was measured in a nickel-plated brass polariscope tube.

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[81] NELSON AND BEEGLE, *J. Am. Chem. Soc.*, **41**, 570 (1919).

[82] ISBELL, *B. S. J. Research*, **5**, 741 (1930); RP226.

[83] ISBELL, *J. Am. Chem., Soc.*, **55**, 2166 (1933).

TABLE III

SUMMARY OF OPTICAL ROTATION MEASUREMENTS MADE IN THIS INVESTIGATION

SUGAR	CONCENTRATION	TEMPERATURE	INITIAL	EQUILIBRIUM	MOLECULAR ROTATION	HUDSON'S $2A$	$[\alpha]_D$ AT t MINUTES AFTER DISSOLVING CRYSTALS	REFERENCES TO RELATED DATA
	g./100 ml.	°C.	$[\alpha]_D$	$[\alpha]_D$	$[M]$	$[M]_\alpha - [M]_\beta$		
1	2	3	4	5	6	7	8	9
α-*d*-Glucose	3.9	20.0	+112.2	+52.7	+20,210	+16,840	$+59.5 \times 10^{-.00632t} + 52.7$	100, 101, 107
α-*d*-Glucose	3.9	0.2	+111.5	+52.1	+20,080	+16,770	$+59.4 \times 10^{-.000741t} + 52.1$	81, 90
β-*d*-Glucose	3.9	20.0	+18.7	+52.7	+3,370		$-34.0 \times 10^{-.00625t} + 52.7$	102, 103
β-*d*-Glucose	3.9	0.2	+18.4	+52.1	+3,310		$-33.7 \times 10^{-.000738t} + 52.1$	81, 67
α-*d*-Galactose	5.0	20.0	+150.7	+80.2	+27,150	+17,640	$+64.9 \times 10^{-.00803t} + 5.6 \times 10^{-.0790t} + 80.2$	65, 78, 107
α-*d*-Galactose	4.1	0.0	+152.9	+84.0	+27,540	+17,630	$+66.3 \times 10^{-.000930t} + 2.7 \times 10^{-.0119t} + 84.0$	66, 67
β-*d*-Galactose	4.0	20.0	+52.8	+80.2	+9,510		$-32.3 \times 10^{-.00812t} + 4.9 \times 10^{-.0883t} + 80.2$	78, 75
β-*d*-Galactose	4.1	0.0	+55.0	+84.0	+9,910		$-31.5 \times 10^{-.000897t} + 2.5 \times 10^{-.0167t} + 84.0$	66
α-*d*-Mannose	4.0	20.0	+29.3	+14.2	+5,280	+8,340	$+15.1 \times 10^{-.0173t} + 14.2$	104, 105
α-*d*-Mannose	4.0	0.2	+28.8	+14.6	+5,190	+8,200	$+14.2 \times 10^{-.00216t} + 14.6$	104
β-*d*-Mannose	4.0	20.0	−17.0	+14.2	−3,060		$-31.2 \times 10^{-.0178t} + 14.2$	89, 45
β-*d*-Mannose	4.0	0.3	−16.7	+14.6	−3,010		$-31.3 \times 10^{-.00214t} + 14.6$	89, 104
Mannose·$CaCl_2 \cdot 4H_2O$	9.1	20.0	−31.3	+6.0	−11,370		$+4.0 \times 10^{-.0245t} - 41.1 \times 10^{-.311t} + 6.0$	76
Mannose·$CaCl_2 \cdot 4H_2O$	8.4	0.0	−29.7	+6.2	−10,790		$+4.5 \times 10^{-.00267t} - 40.3 \times 10^{-.0608t} + 6.2$	76
α-*d*-Talose	3.8	20.0	+68.0	+20.8	+12,250		$+9.3 \times 10^{-.0263t} + 37.9 \times 10^{-.126t} + 20.8$	106, 19
α-*d*-Talose	4.0	0.1	+62.5	+25.2	+11,260		$+9.8 \times 10^{-.00362t} + 27.5 \times 10^{-.0255t} + 25.2$	19
α-*d*-Gulose·$CaCl_2 \cdot H_2O$	6.807	20.0	+37.1	−10.0	+11,470		$+47.1 \times 10^{-.0191t} - 10.0$	82
α-*d*-Gulose·$CaCl_2 \cdot H_2O$	6.468	0.2	+40.5	−9.4	+12,520		$+49.9 \times 10^{-.00188t} - 9.4$	
(*d*-Gulose)$_2$·$CaCl_2 \cdot H_2O$	4.281	20.1	+29.4	−16.5	+7,190*		$+45.9 \times 10^{-.0197t} - 16.5$	83
(*d*-Gulose)$_2$·$CaCl_2 \cdot H_2O$	4.215	0.2	+34.6	−16.9	+8,460*		$+51.5 \times 10^{-.00202t} - 16.9$	
α-*l*-Arabinose	4.3	20.0	+190.6	+104.5	+28,610	+17,050	$+77.3 \times 10^{-.0300t} + 8.8 \times 10^{-.138t} + 104.5$	17, 93, 107

α-*l*-Arabinose	4.1	0.0	+194.0	+109.2	+29,120	+17,330	$+78.9 \times 10^{-.00362t} + 5.9 \times 10^{-.0217t} + 109.2$	19
β-*l*-Arabinose·$CaCl_2 \cdot 4H_2O$	8.9	20.0	+34.7	+48.0	+11,560		$-16.8 \times 10^{-.0300t} + 3.5 \times 10^{-.169t} + 48.0$	92, 93
β-*l*-Arabinose·$CaCl_2 \cdot 4H_2O$	9.3	0.0	+35.4	+50.1	+11,790		$-16.8 \times 10^{-.00384t} + 2.1 \times 10^{-.0369t} + 50.1$	19
α-*d*-Xylose	4.4	20.0	+93.6	+18.8	+14,050		$+74.8 \times 10^{-.0203t} + 18.8$	45, 107
α-*d*-Xylose	4.2	0.0	+95.2	+17.3	+14,310		$+77.9 \times 10^{-.00245t} + 17.3$	45
α-*d*-Lyxose	4.0	20.0	+5.6	−13.8	+860	+11,790	$+19.4 \times 10^{-.0568t} - 13.8$	45
α-*d*-Lyxose	3.9	0.2	+4.7	−13.4	+710	+11,340	$+18.1 \times 10^{-.00844t} - 13.4$	
β-*d*-Lyxose	4.0	20.0	−72.6	−13.8	−10,930		$-58.8 \times 10^{-.0591t} - 13.8$	108
β-*d*-Lyxose	4.0	0.2	−70.8	−13.4	−10,630		$-57.4 \times 10^{-.00840t} - 13.4$	
l-Ribose	4.0	20.0	+20.3	+20.7	+3,050		$-7.6 \times 10^{-.0492t} + 7.2 \times 10^{-.231t} + 20.7$	109
l-Ribose	4.1	0.2	+23.4	+23.2	+3,510		$-7.9 \times 10^{-.00687t} + 8.1 \times 10^{-.054t} + 23.2$	18
α-*l*-Rhamnose·H_2O	4.0	20.2	−8.6	+8.2	−1,570		$-16.8 \times 10^{-.0430t} + 8.2$	45, 110
α-*l*-Rhamnose·H_2O	4.5	0.0	−7.4	+8.7	−1,370		$-16.1 \times 10^{-.00568t} + 8.7$	
α-Lactose·H_2O	7.6	20.0	+85.0	+52.6	+30,620	+18,680	$+32.4 \times 10^{-.00471t} + 52.6$	45, 105, 111
α-Lactose·H_2O	4.9	0.2	+86.4	+53.6	+31,130	+18,710	$+32.8 \times 10^{-.000544t} + 53.6$	71
β-Lactose	4.0	20.0	+34.9	+55.4	+11,940		$-20.5 \times 10^{-.00466t} + 55.4$	111, 86
β-Lactose	3.9	0.2	+36.3	+56.4	+12,420		$-20.1 \times 10^{-.000524t} + 56.4$	71
β-Maltose·H_2O	4.2	20.0	+111.7	+130.4	+40,240		$-18.7 \times 10^{-.00527t} + 130.4$	45
β-Maltose·H_2O	4.5	0.0	+114.8	+131.5	+41,360		$-16.7 \times 10^{-.000580t} + 131.5$	

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* [*M*] for one molecule of *d*-gulose.

[98] Bates and Jackson, *Bull. B. S.*, **13**, 67 (1916); S268.

[99] *Circ. B. S.*, **44** (ed. 2), "Polarimetry" (1918).

[100] Brønsted and Guggenheim, *J. Am. Chem. Soc.*, **49**, 2554 (1927).

[101] Richards, Faulkner, and Lowry, *J. Chem. Soc.*, **1927**, 1733.

[102] Riiber, *Ber.*, **56**, 2185 (1923).

[103] Euler and Ölander, *Z. anorg. allgem. Chem.*, **152**, 113 (1926).

[104] Levene, *J. Biol. Chem.*, **59**, 129 (1924).

[105] Whittier, *Chem. Rev.*, **2**, 85 (1925).

[106] Bosshard, *Helv. Chem. Acta*, **18**, 482 (1935).

[107] Mackenzie and Ghosh, *Proc. Roy. Soc. Edinburgh*, **35**, 22 (1915).

[108] Haworth and Hirst, *J. Chem. Soc.*, **1928**, 1221.

[109] Austin and Humoller, *J. Am. Chem. Soc.*, **54**, 4749 (1932).

[110] Grossmann and Bloch, *Z. Ver. deut. Zuckerind.*, **62**, 19 (1912).

[111] Gillis, *Rec. trav. chim. Pays-Bas*, **39**, 88 (1920).

Subsequent investigation has revealed that such tubes give erratic mutarotation measurements. The metal or oxide film appears to dissolve and catalyze the mutarotation reaction. Sugar solutions taken from brass tubes give positive tests for heavy metals with hydrogen sulfide. Although it is recorded in the literature[84] that traces of metals accelerate the rate of mutarotation, this has not been emphasized sufficiently and is not generally appreciated. According to our experience contact of the sugar solutions with nickel, Monel metal, brass, and copper causes a drift in the mutarotation constants of the sugars. On the other hand, silver tubes give mutarotation constants which agree with those obtained with glass tubes. The small deviation in the mutarotation of xylose, previously reported by Isbell[85] also appears to be due to experimental error.

The only mutarotations in the group (summarized in Table III) which require two exponential terms for expression are α- and β-*d*-galactose, α- and β-*l*-arabinose, α-*d*-talose, *d*- and *l*-ribose, and mannose·$CaCl_2 \cdot 4H_2O$. It is possible that there are very small deviations in the mutarotations of some of the others, but careful investigation at 0°C. has failed to establish any larger than the experimental error.

In Table IV the values of m_1 and m_2 as determined by the various investigators are compared for α- and β-*d*-galactose and α-*l*-arabinose. Where no references are given the values are those obtained in the present investigation.

The mutarotations of α- and β-*d*-galactose are given in Fig. 6, in which the observed optical rotations are represented by the solid lines; the dotted lines represent the course of a first-order reaction calculated from the constant obtained for the last part of the mutarotation. The distances between the solid and dotted lines represent the deviations. For galactose and arabinose (Figs. 6 and 7) the deviations are small; larger differences are found for α-*d*-talose (Fig. 8) and *l*-ribose (Fig. 9).

The reality of the deviations in the mutarotation of *d*-galactose is demonstrated by measuring the optical rotation of a freshly prepared solution containing α- and β-*d*-galactose in the proportions required to give a solution whose optical rotatory power equals the equilibrium rotation. As may be seen by inspection of curve 3 in Fig. 10 and the data given in Table V, the optical rotation decreases to a minimum at a rate comparable to that of the rapid mutarotation reaction, and thereafter increases at a rate comparable to the slow mutarotation until it reaches the initial value. This complex mutarotation is in marked contrast to the total

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[84] Garner and Jackson, *J. Chem. Soc.*, **119**, 1936 (1921).

[85] Isbell, *B. S. J. Research*, **13**, 515 (1934); RP723.

absence of mutarotation in the case of a similar solution of *d*-glucose[86]. The presence of any mutarotation proves that the equilibrium mixture does not consist solely of the normal alpha and beta isomers.

Another method for the study of the complex mutarotation reactions was outlined in a previous publication[19] in which we called attention to the surprisingly large differences in the equilibrium rotations of galactose, arabinose, and talose at various temperatures and showed that after changing the temperature complex "thermal mutarotations" occur. As may be seen from curve II in Fig. 10, the optical rotation of an aqueous solution of *d*-galactose after lowering the temperature from 25° to 0°C. rises to a maximum and then decreases. Analysis of the data and the

TABLE IV

Comparison of Mutarotation Constants Obtained by Different Investigators

SUGAR	TEMPERATURE	CONCENTRATION	m_1	m_2	REFERENCES
	°C.	*per cent*			
α-*d*-Galactose	20.0	5.0	0.00799	0.079	
	20.0	7	0.00803	0.078	Lowry and Smith*[78]
β-*d*-Galactose	20.0	4.0	0.00812	0.0883	
	20.0	7.7	0.00834	0.113	Lowry and Smith[78]
	20.0		0.0083	0.060	Riiber, Minsaas, and Lyche[75]
α-*d*-Galactose	0.0	4.1	0.00093	0.0119	
	0.8	10	0.00094	0.0161	Lowry and Smith[78]
β-*d*-Galactose	0.0	4.1	0.00090	0.0167	
	0.8	10	0.00094	0.0161	Lowry and Smith[78]
α-*l*-Arabinose	20.0	4.3	0.030	0.138	
	20.0		0.029	0.108	Riiber and Sorenson[17]

* The constants reported by Lowry and Smith were calculated for the natural logarithmic base, but in the above table they have been made comparable to the other values by conversion to the base 10 by use of the factor 0.4343. Since the paper of Lowry and Smith [*J. Phys. Chem.*, **33**, 9 (1929)] is of unusual importance to those applying their method of analysis, it seems desirable to correct a number of obvious typographical errors which might prove confusing. Comparison of the values given in table 4 with those in table 1 (both of their paper) shows that m_1 for the latter table should be 0.00216 instead of 0.000216. In tables 3 and 4 and on page 13, the first terms of the equations representing the mutarotations of the beta forms should be negative. Similarly the values of k_4 at 20° on page 13 should be 0.0788 instead of 0.788; and at 0.8° should be 0.02163 rather than 0.2163.

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[86] Rowx, *Ann. chim. phys.*, **30**, 429 (1903).

development of equations similar to those used for the mutarotations of the crystalline sugars show that the thermal mutarotation consists in two

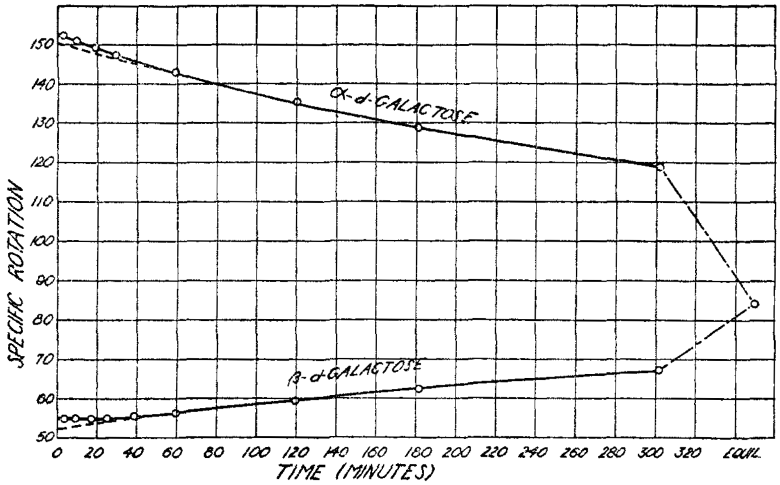

FIG. 6.—MUTAROTATIONS OF α- AND β-*d*-GALACTOSE IN WATER AT 0°C.

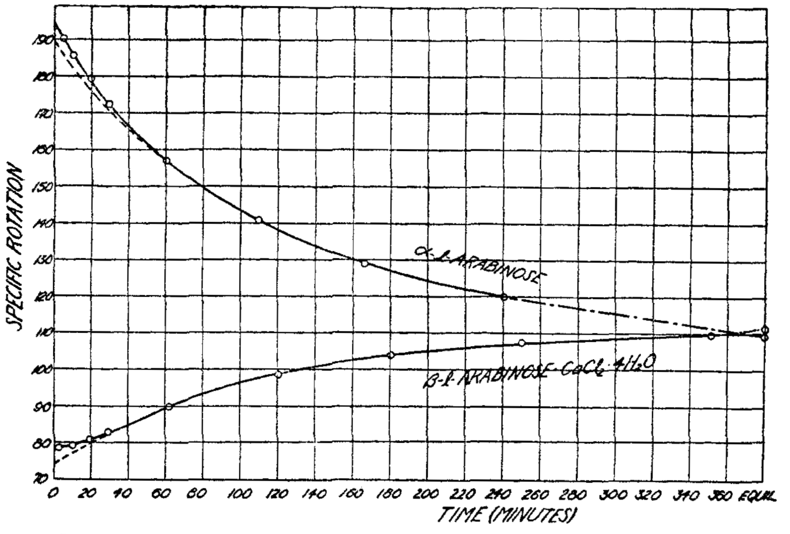

FIG. 7.—MUTAROTATIONS OF α-*l*-ARABINOSE AND β-*l*-ARABINOSE·$CaCl_2 \cdot 4H_2O$ IN WATER AT 0°C.

reactions. The first is rapid and appears to take place at the same rate as the rapid reaction found in the mutarotations of α- and β-*d*-galactose. A large part of the thermal mutarotation is due to this rapid reaction; the subsequent slow reaction, which is probably due to a readjustment in the proportions of the normal alpha and beta isomers, causes only a small change in optical rotation. As might be expected, the

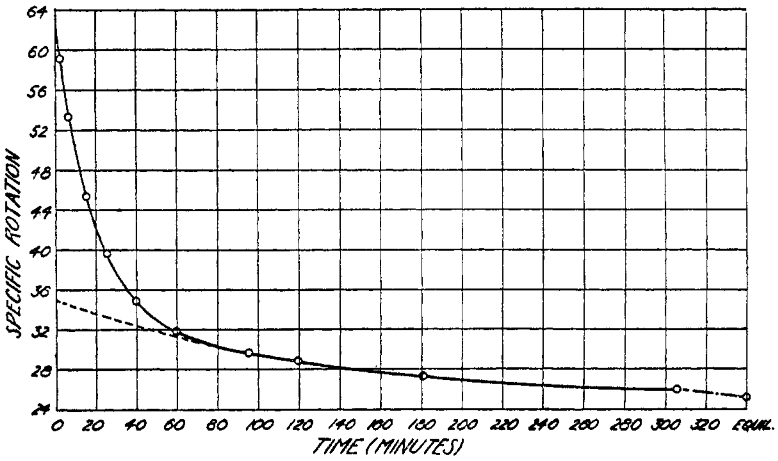

FIG. 8.—MUTAROTATION OF α-*d*-TALOSE IN WATER AT 0°C.

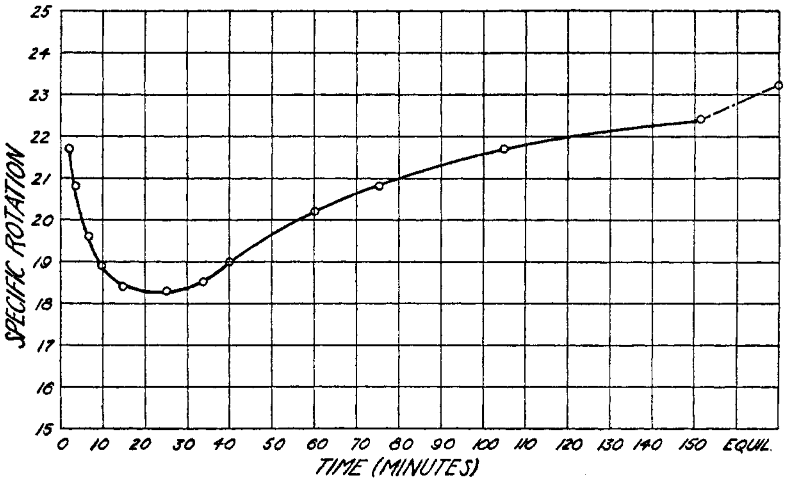

FIG. 9.—MUTAROTATION OF *l*-RIBOSE IN WATER AT 0°C.

thermal mutarotation of arabinose (curve I) is similar to that of galactose. The thermal mutarotation of talose consists in a rapid change which is followed by a small but real slow change.

The thermal mutarotations were conducted in the following manner.

TABLE V

Mutarotation at 0.3°C. of an Aqueous Solution of α- and β-*d*-Galactose in Proportions Corresponding to the Equilibrium Rotation*

$$°S = 37.91 - 1.15 \times 10^{-.00106t} + 1.22 \times 10^{-.0168t}$$

TIME (MINUTES)	OBSERVED READING °S	$m_1 \times 10^3$	DEVIATION	$m_2 \times 10^3$
3.09	37.84		1.08	
4.71	37.78		1.01	18.0
9.19	37.62		0.84	17.9
12.85	37.55		0.76	15.6
15.49	37.51		0.71	14.7
21.02	37.35		0.54	16.8
25.88	37.27		0.44	17.1
31.62	37.20		0.36	16.7
43.38	37.07		0.20	18.2
51.26	37.05		0.16	17.2
61.38	37.05		0.13	15.8
88.4	36.98			
138.8	37.09	1.08		
180.6	37.16	1.01		
244.8	37.27	1.04		
376.2	37.46	1.10		
∞	37.91			
Average......................		1.06		16.8

* The experiment was conducted like the usual mutarotation measurement except that a mixture of β-galactose (2.1334 g.) and α-galactose (0.8975 g.) was used. The solution, made by adding approximately 75 ml. of water to this mixture, was read in a 4-dm. tube.

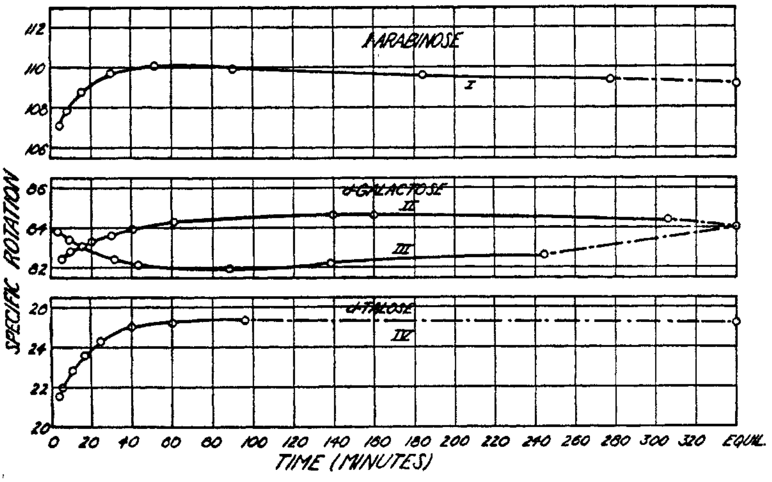

Fig. 10.—New Methods for Demonstrating the Complex Character of the Equilibrium Solutions

Curve I.—Thermomutarotation of *l*-arabinose at 0°C.

Curve II.—Thermomutarotation of *d*-galactose at 0°C.

Curve III.—Mutarotation at 0.3°C of an aqueous solution of α- and β-*d*-galactose in proportions corresponding to the equilibrium rotation.

Curve IV.—Thermomutarotation of *d*-talose at 0°C.

TABLE VI

THERMAL MUTAROTATIONS

TIME,* MINUTES	SACCHARIMETER READING °S	$m_1 \times 10^3$	DEVIATION °S	$m_2 \times 10^3$
Thermal mutarotation of a 10 per cent. aqueous solution of *d*-galactose after cooling from 25°C. to 0.3°C. $°S = 1.10 \times 10^{-.00107t} - 3.49 \times 10^{-.0132t} + 97.87$				
5.74	+96.02		−2.93	
6.95	+96.13		−2.82	13.8
10.00	+96.49		−2.45	18.2
15.13	+96.74		−2.19	13.5
20.09	+97.04		−1.88	13.4
26.15	+97.32		−1.58	13.1
30.20	+97.46		−1.43	12.7
40.27	+97.76		−1.10	12.3
50.11	+98.02		−0.82	12.5
60.96	+98.23		−0.59	12.6
75.23	+98.41		−0.37	12.9
89.97	+98.48		−0.27	12.3
126.54	+98.53		−0.14	10.9
139.88	+98.60		−0.05	13.2
160.18	+98.61			
244.19	+98.45	1.26		
306.1	+98.39	1.05		
365.2	+98.30	1.15		
502.1	+98.24	0.88		
738.7	+98.06	1.02		
∞	+97.87			
Average		1.07		13.2
Thermal mutarotation of an 8 per cent. aqueous solution of *l*-arabinose after cooling from 25.2°C. to 0.2°C. $°S = 1.52 \times 10^{-.00364t} - 4.56 \times 10^{-.0271t} + 101.71$				
4.57	+99.74		−3.43	
5.94	+100.01		−3.15	27.0
8.29	+100.38		−2.75	25.8
10.64	+100.75		−2.35	27.1
15.16	+101.30		−1.75	27.6
20.21	+101.71		−1.28	27.4
25.58	+102.01		−0.93	27.0
30.06	+102.20		−0.69	27.3
40.10	+102.45		−0.35	27.9
51.15	+102.55		−0.12	(31.3)
75.14	+102.52			
90.19	+102.41	4.21		
121.06	+102.26	3.66		
154.66	+102.11	3.85		

TABLE VI—*Continued*

TIME, *MINUTES	SACCHARIMETER READING °S	$m_1 \times 10^3$	DEVIATION °S	$m_2 \times 10^3$
Thermal mutarotation of an 8 per cent aqueous solution of *l*-arabinose after cooling from 25.2°C. to 0.2°C.—*Continued*				
184.1	+102.06	3.34		
214.6	+101.98	3.42		
277.9	+101.87	3.47		
330.6	+101.81	3.56		
389.9	+101.77	3.59		
∞	+101.71			
Average		3.64		27.1
Thermal mutarotation of an 8 per cent. aqueous solution of *d*-talose after cooling from 25.8°C. to 0.1°C. °$S = 0.14 \times 10^{-.0036t} - 4.69 \times 10^{-.0289t} + 23.62$.				
3.94	+20.14		−3.61	
5.41	+20.57		−3.18	(37.5)
7.42	+20.93		−2.82	30.8
10.24	+21.35		−2.39	28.4
13.55	+21.84		−1.90	29.0
16.85	+22.15		−1.59	27.6
19.97	+22.40		−1.33	27.0
24.98	+22.76		−0.97	27.1
29.92	+23.10		−0.63	29.2
39.98	+23.45		−0.27	31.2
50.07	+23.56		−0.15	29.9
60.09	+23.61		−0.09	28.6
96.3	+23.68	(3.8)†		
∞	+23.62			
Average				28.9

* Time is measured from the beginning of the cooling process.

† The mutarotation due to the slow reaction is scarcely more than the experimental error and therefore the value of m_1 (.0036) obtained from the mutarotation of α-*d*-talose was used for extrapolating the slow reaction back to zero time. The existence of the maximum was shown by comparing the average of a large number of readings at about 90 minutes with the average of similar readings after equilibrium was established. Several duplicate experiments revealed a difference of about 0.08°S which corresponds to a total change of 0.14°S.

The sugar solution in a 4-dm. water-jacketed silver tube was allowed to reach equilibrium at 25°C., and its optical rotation was read. The water (at 25°C.) was drained from the water jacket and a stream of aqueous alcohol cooled to 0°C. was pumped through the jacket. Time was measured from the moment when the cold aqueous alcohol was turned on.

The temperature dropped in about 3 minutes to approximately 0°C., at which time saccharimeter readings were made. The results are given in Table VI.

The variation of the equilibrium proportions of the labile constituents with temperature, as revealed by the thermal mutarotations, indicates that the heat of the rapid reaction is considerable and probably larger than the heat of reaction for the slow change. Information in respect to the heat of activation, Q, can be derived from a comparison of the velocity constants at different temperatures. The results of such comparison are given in Table VII.

TABLE VII

EFFECT OF TEMPERATURE ON RATES OF MUTAROTATION

SUGAR	SLOW CHANGE						RAPID CHANGE			
	t_1 °C.	$m_1 \times 10^3$ at t_1 °C.	t_2 °C.	$m_2 \times 10^3$ at t_2 °C.	Q	Temperature coefficient*	$m_2 \times 10^3$ at t_1 °C.	$m_2 \times 10^3$ at t_2 °C.	Q	Temperature coefficient*
α-*d*-Glucose	20.0	6.32	0.2	0.741	17,200	2.6				
β-*d*-Glucose	20.0	6.25	0.2	0.738	17,200	2.6				
α-*d*-Mannose	20.0	17.3	0.2	2.16	16,700	2.5				
β-*d*-Mannose	20.0	17.8	0.3	2.14	17,100	2.5				
Mannose·$CaCl_2$·$4H_2O$	20.0	24.5	0.0	2.67	17,600	2.6	311	60.8	13,000	2.0
α-*d*-Galactose	20.0	8.03	0.0	0.93	17,100	2.5	79.0	11.9	15,000	2.3
β-*d*-Galactose	20.0	8.12	0.0	0.90	17,500	2.6	88.3	16.7	13,200	2.1
α-*d*-Talose	20.0	26.3	0.1	3.62	15,900	2.4	126	25.5	12,800	2.0
α-*d*-Gulose·$CaCl_2$·H_2O	20.0	19.1	0.2	1.88	18,600	2.8				
(*d*-Gulose)$_2$·$CaCl_2$·H_2O	20.1	19.7	0.2	2.02	18,200	2.7				
α-*l*-Arabinose	20.0	30.0	0.0	3.62	16,800	2.5	138	21.7	14,700	2.2
β-*l*-Arabinose·$CaCl_2$·$4H_2O$	20.0	30.0	0.0	3.84	16,300	2.4	169	36.9	12,100	1.9
α-*d*-Lyxose	20.0	56.8	0.2	8.44	15,300	2.3				
β-*d*-Lyxose	20.0	59.1	0.2	8.40	15,700	2.4				
α-*d*-Xylose	20.0	20.3	0.0	2.45	16,800	2.5				
l-Ribose	20.0	49.2	0.2	6.87	15,800	2.4	231	54	11,700	1.9
α-*l*-Rhamnose·H_2O	20.2	43.0	0.0	5.68	15,900	2.4				
α-Lactose·H_2O	20.0	4.71	0.2	0.544	17,300	2.6				
β-Lactose	20.0	4.66	0.2	0.524	17,600	2.6				
β-Maltose·H_2O	20.0	5.27	0.0	0.580	17,500	2.6				
Average					16,900	2.52			13,200	2.06

* $\frac{m \text{ at } 35°\text{C.}}{m \text{ at } 25°\text{C.}}$ as calculated from the value of Q by use of the equation $\log \frac{m \text{ at } 35°}{m \text{ at } 25°} = \frac{Q}{42{,}011}$.

Inasmuch as m_1 and m_2 are not necessarily true velocity constants but probably represent complex changes, Q as obtained by the Arrhenius equation does not correspond to the activation of any one substance but applies to a group of substances and should be considered somewhat empirical. The temperature coefficients reported in Table VII were obtained from measurements at 20° and 0°C. on portions of the same samples under approximately like conditions, so that they are strictly comparable with one another. Temperature coefficients determined by others for the mutarotations of glucose[67, 88] mannose,[89] xylose,[45] galactose,[78, 87] and lactose[27] were not obtained under strictly comparable conditions and are not always expressed in the same manner, so that comparison with our results is not convenient. According to our measurements, Q as obtained from m_1 varies for different sugars from 15,300 to 18,600, with an average of 16,900. On the other hand, the value from m_2 varies from 11,700 to 15,000 with an average of 13,200. The marked difference in the values of Q obtained from the slow and from the fast reactions is evidence that the two are of different types. It is noted that talose and ribose give the lowest values for Q as obtained from both m_1 and m_2. This characteristic as well as the complex mutarotations of the two sugars appears to support a structural similarity. Although data are given for twenty sugars, similar measurements are being conducted on the remaining sugars because a complete study may reveal important differences and correlations which are not apparent from the study of only a few individuals.

IV. PREPARATION AND PURIFICATION OF THE SUGARS

The numerous errors in the optical rotations recorded in the literature attest to the need of great care in the preparation and purification of the sugars used for physical measurements. The tendency of two or more forms of the same sugar to crystallize simultaneously always leaves some uncertainty as to the homogeneity of the product, and it is only after many crystallizations under widely different conditions that it may be assumed that the product is pure. Because pure products are obtained only by slow crystallizations, whenever possible the sugars used in this investigation were crystallized very slowly in the following manner. A slightly supersaturated solution of the sugar was prepared, seeded with the desired modification and placed in a flask which was rotated slowly for at least one week while crystallization took place. The crystals were then separated, washed thoroughly with aqueous alcohol, and dried at 50°C. *in vacuo*. The samples of α-*d*-glucose, mannose·$CaCl_2 \cdot 4H_2O$, α-*d*-galactose, α-*d*-talose, α-*d*-gulose·$CaCl_2 \cdot H_2O$, α-*l*-arabinose, α-*d*-xylose, α-*l*-rhamnose hydrate, lactose hydrate, and maltose hydrate were crystallized in this manner from aqueous solution; α- and β-*d*-lyxose, α-*d*-mannose, and *d*- and *l*-ribose were crystallized slowly from aqueous methyl or ethyl alcohol, while β-*d*-

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[87] Lowry and Smith, *J. Phys. Chem.*, **33**, 13 (1929).

[88] Euler and Hedelius, *Biochem. Z.*, **107**, 1501 (1920).

[89] Hudson and Sawyer, *J. Am. Chem. Soc.*, **39**, 470 (1917).

mannose was crystallized in like manner from acetic acid. The crystallizations of β-*d*-glucose and β-*d*-galactose were carried out rapidly from aqueous acetic acid according to the method of Hudson and Dale[90]. Although two forms of *l*-arabinose are known, only one exists as the free crystalline sugar. The other modification is available as a calcium chloride compound which was prepared by Dale[91] and also, independently at about the same time, by Austin and Walsh[92] who kindly supplied us with some of it for use in the present investigation. As explained on page 507, the crystalline form of *l*-arabinose (+191) is called α-*l*-arabinose, and the calcium chloride modification is designated β-*l*-arabinose·$CaCl_2 \cdot 4H_2O$, in contradiction to the nomenclature of Austin and Walsh as well as of Montgomery and Hudson[93]. Inasmuch as the initial specific rotation of β-*l*-arabinose·$CaCl_2 \cdot 4H_2O$ was reported by Austin and Walsh to correspond to +75 for the arabinose constituent, while Montgomery and Hudson gave +89.4, we prepared a new sample and determined the specific rotation. It gives $[\alpha]_D^{20} = +34.7$, which corresponds to a specific rotation of +77 for the arabinose constituent. In our experience β-*l*-arabinose·$CaCl_2 \cdot 4H_2O$ on recrystallization loses calcium chloride very readily and gives a mixture containing (α-*l*-arabinose)$_2 \cdot CaCl_2 \cdot 2H_2O$. This can be avoided by conducting the crystallization at a low temperature in the presence of an excess of calcium chloride.

The sample of (*d*-gulose)$_2 \cdot CaCl_2 \cdot H_2O$ used in this investigation was obtained by adding hot ethyl alcohol to a concentrated aqueous solution of α-*d*-gulose·$CaCl_2 \cdot H_2O$. By crystallization in this manner the original double compound gives up half of its calcium chloride.* The resulting crude product was recrystallized by dissolving it in a small quantity of water, adding several volumes of ethyl alcohol, and allowing crystallization to proceed slowly over the course of about one week.

The sample of α-*d*-talose was prepared from *d*-galactose by the method of Levene and Tipson[94]. The crude sugar was recrystallized from aqueous alcohol until further recrystallization did not lower the equilibrium rotation. It was then recrystallized very slowly from water.

The samples of α- and β-*d*-lyxose were prepared from calcium galactonate by the method of Ruff and Ollendorf[95] as modified by Hockett and Hudson[96]. The crystalline sugars were separated originally from aqueous alcoholic solutions without the use of seed crystals. Particular care must be used in the crystallization of the alpha form to avoid accidental seeding with the beta form. The recrystallizations were conducted slowly from aqueous methyl alcohol in the usual manner.

V. SUMMARY

Fundamental characteristics of the alpha and beta sugars which furnish the basis for the changes in nomenclature previously suggested by Isbell are discussed, and it is shown that when the sugars are classified according

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[90] Hudson and Dale, *ibid.*, **39**, 320 (1917).

[91] Dale, *ibid.*, **56**, 932 (1934).

[92] Austin and Walsh, *ibid.*, **56**, 934 (1934).

[93] Montgomery and Hudson, *ibid.*, **56**, 2074 (1934).

* According to a private communication from J. K. Dale *d*-glucose·$CaCl_2$ also loses $CaCl_2$ by crystallization from ethyl alcohol and gives a product which appears to be similar to (*d*-gulose)$_2 \cdot CaCl_2 \cdot H_2O$.

[94] Levene and Tipson, *J. Biol. Chem.*, **93**, 631 (1931).

[95] Ruff and Ollendorf, *Ber.*, **33**, 1798 (1900).

[96] Hockett and Hudson, *J. Am. Chem. Soc.*, **56**, 1632 (1934).

to the proposed system the beta modifications are oxidized by bromine more rapidly than the alpha isomers.

The oxidation of the equilibrium solutions of the sugars proceeds rapidly until a part of the sugar is used up, and then more slowly as the remaining sugar continues to be oxidized. The oxidation of the more reactive fractions takes place at rates comparable to those found for the beta sugars, while the rates for the less reactive fractions agree within reasonable experimental error with the rates for the oxidation of the alpha sugars. The proportions of the more rapidly and the less rapidly oxidizable sugars were determined and compared with the proportions of the alpha and beta isomers, calculated from the optical rotations on the assumption that the equilibrium solutions contain only the alpha and beta normal isomers. The results of these comparisons indicate that the equilibrium solutions are principally of the normal alpha and beta sugars, but the presence of small quantities of other modifications is not excluded, especially for the solutions of galactose, arabinose, talose and ribose. The oxidation of equilibrium solutions of *l*-ribose has revealed that they contain a small quantity of some modification which is more easily oxidizable than the crystalline sugar which was previously classified as β-*l*-ribose. The existence of this easily oxidizable modification throws doubt on the correctness of the classification of the known sugar as the beta form. The oxidation of (d-gulose)$_2\cdot CaCl_2\cdot H_2O$ shows that the crystalline sugar contains about 32 per cent of easily oxidizable modification which is presumably the heretofore unknown beta isomer.

Mutarotation measurements at 20°C. and at 0°C. reveal that the mutarotations of α- and β-*d*-glucose, α- and β-*d*-mannose, α-*d*-gulose$\cdot CaCl_2\cdot H_2O$, (d-gulose)$_2\cdot CaCl_2\cdot H_2O$, α- and β-*d*-lyxose, α-*d*-xylose, α-*l*-rhamnose (hydrate), α- and β-lactose, and β-maltose follow the first-order equation, while the mutarotations of α- and β-*d*-galactose, α-*l*-arabinose, β-*l*-arabinose$\cdot CaCl_2\cdot 4H_2O$, *d*-mannose$\cdot CaCl_2\cdot H_2O$, α-*d*-talose, and *l*-ribose are complex. The initial and equilibrium specific rotations of these sugars were determined at 0°C. and 20°C., and values for the rotation of the first carbon (Hudson's A) were calculated at both temperatures. The effect of traces of heavy metals on the rates of mutarotation is pointed out and attention is directed to errors caused by the use of nickel-plated brass tubes in mutarotation measurements. The optical rotations of mannose$\cdot CaCl_2\cdot 4H_2O$ and arabinose$\cdot CaCl_2\cdot 4H_2O$ are reduced to equations containing two exponential terms, and attention is directed to the fact that the addition of calcium chloride produces a change in the equilibrium between the various modifications of these sugars in solution. Detailed data for the optical rotations of α-*d*-talose at 20°C. and at 0°C. are reported for the first time.

Temperature coefficients were determined for the mutarotations of twenty sugars. The principal mutarotation reactions (supposedly the reversible interconversion of the normal alpha and beta isomers) are on the average 8.34 times as fast at 20°C. as at 0°C., while the rapid reaction is on the average only 5.32 times as fast at 20°C. as at 0°C. The higher temperature coefficient for the principal mutarotation reaction shows that the heat of activation is greater for the interconversion of the normal isomers than for the rapid reaction. The mutarotations which occur after a sudden change in temperature prove that the compositions of equilibrium solutions of galactose, arabinose, and talose are altered markedly by a change in temperature. The proportions of the labile constituents vary with temperature more than the proportions of the normal alpha and beta isomers. In this respect it is shown that the bromine oxidation of solutions of *d*-galactose in equilibrium at 20°C. do not differ widely from the oxidation of solutions in equilibrium at 0°C.

The optical rotation of a freshly prepared solution containing α- and β-*d*-galactose in proportions corresponding to the equilibrium rotation decreases to a minimum and then increases to the original value. This is conclusive proof that the deviations in the mutarotations of α- and β-*d*-galactose are real.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE COLLEGE OF WASHINGTON]

THE INTERACTION OF SELENIUM TETRACHLORIDE AND BENZENE IN THE PRESENCE OF ANHYDROUS ALUMINUM CHLORIDE*

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INTRODUCTION

Between 1888 and 1894 M. C. Chabrie[1] presented the results he obtained by the interaction of $SeCl_4$ and benzene in the presence of anhydrous $AlCl_3$. He reported the following four products.

(*a*) Chlorobenzene.

(*b*) A yellow liquid boiling at 227–8°/50–60 mm. which he stated was diphenyl selenide, $(C_6H_5)_2Se$. This substance, Chabrie said, reacted with aqueous bromine to form di-(bromophenyl) selenide, $(C_6H_4Br)_2Se$ which crystallized from alcohol in white hexagonal prisms melting at 112°.

(*c*) A red oil boiling at 245–50°/50–60 mm., to which he assigned the formula $(C_6H_5)_3(C_6H_4Cl)Se_2$.

(*d*) Yellow crystals (m.p. 60°) stated to be phenylselenol, C_6H_5SeH, which were precipitated from alcoholic solutions by salts of mercury and silver.

In 1894 F. Krafft and R. E. Lyons[2] expressed the opinion that Chabrie's phenylselenol was diphenyl diselenide, $(C_6H_5)_2Se_2$. Later F. Krafft and A. Kaschau[3] repeated the interaction of $SeCl_4$ and benzene in the presence of anhydrous aluminum chloride and reported the three products to be (*a*) chlorobenzene, (*b*) diphenyl selenide, and (*c*) diphenyl diselenide. They found that alcoholic solutions of diphenyl diselenide gave precipitates with metallic salts, but that these precipitates differed from those obtained from phenylselenol prepared by a method other than that under discussion.

They established in this way that Chabrie had not prepared phenylselenol. This has been verified by later investigators.[4]

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[1] CHABRIE, *Bull. soc. chim.*, [2], **50**, 133–7 (1888); [3], **2**, 796 (1889); [3], **11**, 1080–3 (1894); *Compt. rend.*, **109**, 182–5 (1889); *Ann. chim. phys.*, [6], **20**, 202–86 (1890).

[2] KRAFFT AND LYONS, *Ber.*, **27**, 1761–8 (1894).

[3] KRAFFT AND KASCHAU, *ibid.*, **29**, 429–35 (1896).

[4] BRADT AND CROWELL, *Proc. Ind. Acad. Sci.*, **41**, 227–33 (1931);
BRADT AND GREEN, *ibid.*, **41**, 215–25 (1931).

EXPERIMENTAL*

Fifty grams of pure $SeCl_4$,† with 136.5 g. of benzene, was placed in a flask, and 30 g. of anhydrous $AlCl_3$,‡ was added in four equal parts during the reaction period. After heating for one hour and allowing to stand at room temperature for 60 hours no further reaction was observed. The products then were carefully hydrolyzed by the addition of 100 cc. of cold water, made strongly acid by the addition of 50 cc. of concentrated hydrochloric acid and separated into a brown benzene and a cloudy aqueous layer.

The benzene layer was washed, dried and distilled under reduced pressure.

The three products identified were: (*a*) *chlorobenzene*, previously reported both by Chabrie and by Krafft with his coworkers (b.p. 130–1°/700 mm.), (*b*) *diphenyl selenide*, $(C_6H_5)_2Se$, reported previously both by Chabrie and by Krafft and coworkers (b.p. 301–03°/700 mm.; product + concentrated HNO_3, followed by HCl → diphenylselenonium dichloride; m.p. 183°), and (*c*) *diphenyl diselenide* $(C_6H_5)_2Se_2$ previously reported by Krafft and co-workers and considered by Chabrie to be phenylselenol. The latter product was obtained in the form of golden-yellow crystals from alcohol, melting at 63°. The melting point was not depressed by the presence of diphenyl diselenide prepared either by the method of Krafft and Lyons[2] or that of Lyons and Bradt.[5] No product corresponding to Chabrie's $(C_6H_5)_3(C_6H_4Cl)Se_2$ was present. No phenylselenol resulted from the reaction.

Diphenylselenonium dibromide.—Diphenyl selenide was treated with cold bromine water for two hours in an effort to duplicate Chabrie's work; the product of this reaction was identified as diphenylselenonium dibromide: m.p. (recrystallized from alcohol) 141°; the melting point of a mixture with diphenylselenonium dibromide prepared according to the method of Krafft and Vorster[6] was not depressed; color, orange-red.

*Di-*p*-bromophenyl selenide.*—The diphenylselenonium dibromide described above was heated over a flame, cooled, and purified, and the resulting products were identified as diphenyl selenide and di-*p*-bromophenyl selenide: m.p. (from 95% alcohol) 115°. The mixture melting point with di-*p*-bromophenyl selenide prepared according to the method of Edwards *et al.*[7] was not depressed. Chabrie had reported the formation of dibromophenyl selenide, melting at 112°, without indicating that the bromine atoms were in the para positions.

Mercuric chloride addition compound.—The addition of aqueous mercuric chloride solution to an alcoholic solution of diphenyl diselenide caused the formation of a white precipitate. This compound, after purification by washing with hot water, then with alcohol, followed by recrystallization from acetone, was identified as the mercuric chloride addition compound of diphenyldiselenide, $(C_6H_5)_2Se_2 \cdot 2HgCl_2$.

Anal. Calc'd for $C_{12}H_{10}Cl_4Hg_2Se_2$: C, 16.83; H, 1.18; Cl, 16.58; Hg, 46.89; Se, 18.51.

Found: C, 17.07; H, 1.13; Cl, 16.46; Hg, 46.74; Se, 18.43.

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* The selenium used in this work was supplied in stick form by the courtesy of the Baltimore Copper Smelting and Rolling Company, Baltimore, Maryland.

† Prepared according to the method of BELL AND GIBSON, *J. Chem. Soc.*, 127, 1880 (1925).

‡ Commercial aluminum chloride purchased from the J. T. Baker Chemical Company.

[5] LYONS AND BRADT, *Ber.*, **60**, 60–63 (1927).

[6] KRAFFT AND VORSTER, *ibid.*, **26**, 2813–22 (1893).

[7] EDWARDS *et al.*, *J. Chem. Soc.*, **1928**, 2293–2303.

The mercuric chloride addition compound of diphenyldiselenide is very slightly soluble in water, alcohol, ether, benzene, and may be crystallized from acetone as a white powder melting at 187–8° (corr.). An analogous compound has been prepared by the action of silver nitrate on diphenyl diselenide. This, however, was not completely analyzed.

Krafft and Kaschau[3] stated that alcoholic solutions of diphenyl diselenide formed precipitates with metallic salts, but did not establish their structure. It is the opinion of the authors that these addition compounds $(C_6H_5)_2Se_2\cdot(MX)_n$ are identical with those reported by Chabrie as selenomercaptides $(C_6H_5Se\cdot M)$.

No trace of the red oil described by Chabrie as corresponding to the formula $(C_6H_5)_3(C_6H_4Cl)Se_2$ (b.p., 245–50°) was detected. It was noted, however, that mixtures of crude diphenyl selenide and diphenyl diselenide exhibited a red oily appearance and that, as Chabrie observed, the latter compound separated upon standing.

Zinc chloride addition compound of triphenylselenonium chloride.—Only one water-soluble organoselenium compound was found as a product of the interaction of selenium tetrachloride and benzene in the presence of anhydrous aluminum chloride. An excess of aqueous 20% zinc chloride was added to the water-soluble reaction products, and a very heavy white precipitate was obtained. After washing and repeated crystallization from hot water this was identified as the zinc chloride addition compound of triphenylselenonium chloride, $[(C_6H_5)_3SeCl]_2\cdot ZnCl_2$; m.p. 274°.

Anal. Calc'd for $C_{36}H_{30}Cl_4Se_2Zn$: C, 52.17; H, 3.66; Se, 19.13; Zn, 7.89; Cl, 17.13.
Found: C, 52.40; H, 3.69; Se, 19.10; Zn, 7.7.

The melting point was not depressed by the presence of the zinc chloride addition compound of triphenylselenonium chloride prepared by the method of Bradt and Crowell.[8] Addition of silver nitrate to the water solution precipitated as silver chloride 74.7% of the chlorine in the addition compound. The $ZnCl_2$ addition compound crystallizes from water in short rhombic crystals. In the presence of hydrochloric acid its solubility in water decreased to a sufficient extent to make possible its easy isolation. It is sparingly soluble in alcohol and less so in chloroform, ether, benzene, carbon disulfide and nitrobenzene. This zinc chloride addition compound is quite stable even at high temperatures. Treatment with concentrated potassium hydroxide solution decomposed it, forming a crystalline product and a dark brown oil.

The approximate yields of the crude products isolated are given by the following data, which represent the average values from two duplicate reactions in which 50 g. of selenium tetrachloride was used as previously described: chlorobenzene, 1 g.; diphenyl selenide, 20 g.; diphenyl diselenide, 5 g.; triphenylselenonium chloride + $ZnCl_2$, 20 g.

SUMMARY

Chabrie reported that the interaction of selenium tetrachloride and benzene in the presence of anhydrous aluminum chloride formed: (*a*) chlorobenzene, (*b*) diphenyl selenide, (*c*) a compound, $(C_6H_5)_3(C_6H_4Cl)Se_2$, and (*d*) phenylselenol. He also reported the preparations of selenomercaptides of the type C_6H_5SeAg and a dibromophenyl selenide in which the position of the bromine on the benzene ring was not specified.

Krafft and his co-workers in criticism of Chabrie's results established the

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[8] Bradt and Crowell, *J. Am. Chem. Soc.*, **55**, 1500–2 (1933).

fact that the phenylselenol reported was diphenyl diselenide and that the supposed selenomercaptides were not derivatives of phenylselenol but of diphenyl diselenide. They, however, did not identify the latter derivatives.

No investigator of this reaction has reported the presence of any water-soluble products.

The products of this reaction have been shown to be: (*a*) chlorobenzene, (*b*) diphenyl selenide, (*c*) diphenyl diselenide, and (*d*) triphenylselenonium chloride. It has also been shown that the compounds reported by Chabrie as selenomercaptides are addition compounds of metallic salts with diphenyl diselenide. The pure mercuric chloride addition compound $(C_6H_5)_2Se_2 \cdot 2HgCl_2$ has been prepared.

The preparation of the dibromophenyl selenide reported by Chabrie has been repeated and the compound identified as di-*p*-bromophenyl selenide.

The following equations are proposed to explain these facts. Identified organic products are underlined.

I. $SeCl_4 + 3C_6H_6 \xrightarrow{(AlCl_3)} \underline{(C_6H_5)_3SeCl} + 3HCl$

II. $(C_6H_5)_3SeCl \xrightarrow{heat} \underline{(C_6H_5)_2Se} + \underline{C_6H_5Cl}$

III. $(C_6H_5)_2Se + Se \xrightarrow{heat} \underline{(C_6H_5)_2Se_2}$

IV. $(C_6H_5)_2Se + Br_2 \rightarrow \underline{(C_6H_5)_2SeBr_2}$

V. $(C_6H_5)_2SeBr_2 \xrightarrow{heat} \underline{(p\text{-}BrC_6H_4)_2Se} + \underline{(C_6H_5)_2Se} + 2HBr$

VI. $(C_6H_5)_2Se_2 + 2HgCl_2 \rightarrow \underline{(C_6H_5)_2Se_2 \cdot 2HgCl_2}$

VII. $2(C_6H_5)_3SeCl + ZnCl_2 \rightarrow \underline{[(C_6H_5)_3SeCl]_2 \cdot ZnCl_2}$

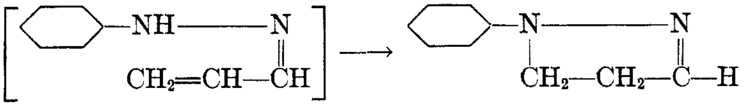
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

IDENTIFICATION OF PHENYLHYDRAZONES AND ISOMERIC PYRAZOLINES OBTAINED FROM CHALCONES

L. CHAS. RAIFORD AND WALTER J. PETERSON

Received November 11, 1936; revised December 4, 1936

In their study of the behavior of aldehydes toward phenylhydrazine Fischer and Knoevenagel[1] found that when acrolein is used the product is 1-phenylpyrazoline instead of the expected hydrazone. Much later



Auwers and Müller[2] studied this reaction further, and reached the conclusion that the pyrazoline in this and other instances is formed through the rearrangement of an unstable hydrazone and noted that in those cases where the latter can be isolated, treatment of it with hot acetic acid causes rearrangement. This view was supported by the work of Auwers and Voss[3] who isolated the hydrazones of cinnamic aldehyde and benzalacetone, and showed that heating them with acetic acid causes their rearrangement to the corresponding pyrazolines. But some hydrazones of this group failed to respond to this test, for the authors just quoted were unable to rearrange the product obtained from cinnamic aldehyde and *p*-nitrophenylhydrazine, although the compound was subsequently shown by reduction to be a hydrazone.

In extension of their study Auwers and co-workers specified the characters of the radicals in an α,β-unsaturated ketone of the type R—CH=CH—CO—R′ which they thought would permit the formation of a stable hydrazone, and Straus[4] studied the behavior of a few such ketones in which R and R′ contained a halogen atom or the nitro radical as substituents. He found that the closing of the pyrazoline ring occurs readily when the substituent is in either ketone or hydrazine residue, and that when both are substituted the hydrazone is quite stable and requires

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[1] FISCHER AND KNOEVENAGEL, *Ann.*, **239**, 194 (1887).

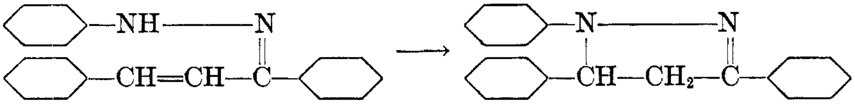
[2] AUWERS AND MÜLLER, *Ber.*, **41**, 4230 (1908).

[3] AUWERS AND VOSS, *ibid.*, **42**, 4412 (1909).

[4] STRAUS, *ibid.*, **51**, 1458 (1918).

energetic treatment for rearrangement. Raiford and Davis[5] studied the behavior of five ketones the structures of which, according to the above view, seemed most favorable to the formation of stable hydrazones. They were unable to confirm Straus' prediction with regard to the stability conferred by substituents. In no case was a hydrazone isolated but in each instance the required pyrazoline was obtained.

With respect to the unsubstituted ketone chalcone, Auwers and Voss reached the conclusion that the "hydrazone of benzalacetophenone is so labile that it cannot be isolated, even at low temperature, but that it rearranges at once to give 1,3,5-triphenylpyrazoline." Although Raiford and Davis succeeded in isolating and characterizing this hydrazone, the need was felt, in this and other work published from this Laboratory,[6] for more satisfactory tests to distinguish between these hydrazones and their rearrangement products.



In previous work it has been found that the Knorr[7] color test for pyrazoline bases, in which a drop of solution of ferric chloride, chromic acid, nitrous acid or similar oxidizing agent is added to a concentrated sulfuric acid solution of the suspected compound, to give a blue-violet color, is so sensitive that a hydrazone containing only a trace of pyrazoline will give a positive reaction.[8] But the fact that acids are the reagents which most readily bring about the rearrangement of these hydrazones raises the question whether some pyrazoline is formed when these reagents are applied. Auwers and co-workers also noted that the Knorr test is often given by the mother liquors from which the hydrazones have been crystallized, and that such solutions frequently show a blue fluorescence if pyrazoline is present.

In the present work an attempt was made to find a qualitative test for distinguishing between these isomers by utilizing an observation made by Knorr and Laubmann.[9] These workers found that, in the bromination of 1,3,5-triphenylpyrazoline, a bluish-green color was developed at the beginning of the reaction. In our experiments it was found that when a very small portion of a hydrazone of this group, spread on a filter paper, is brought in contact with bromine vapor the color changes from yellow

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[5] Raiford and Davis, *J. Am. Chem. Soc.*, **50**, 159 (1928).

[6] Raiford and co-workers, *J. Am. Chem. Soc.*, **55**, 1125 (1933); **56**, 174 (1934).

[7] Knorr, *Ann.*, **238**, 200 (1887).

[8] Auwers and Voss, *Ber.*, **42**, 4417 (1909).

[9] Knorr and Laubmann, *ibid.*, **21**, 1210 (1888).

to orange, and frequently to brick-red. Under the same treatment a pyrazoline turns green almost instantaneously.

Another test which has been used to distinguish between these isomers is their behavior toward reducing agents. Reduction of the hydrazones by sodium amalgam in presence of alcohol and acetic acid, as directed by Tafel,[10] to give aniline and the corresponding aliphatic amine, was found by Auwers and Kreuder[11] to be unsatisfactory because too large an amount of hydrazone is required to give a suitable quantity of aniline, and for the further reason that in some cases the test fails to give any aniline regardless of the amount of hydrazone used.

In the present work when the phenylhydrazone of benzalacetone, m.p., 138–139°,* which may here be called the β form, was reduced by sodium and alcohol at about the boiling point of the latter, and the reaction mixture was worked up in the manner described by Raiford and Davis,[5] 50 per cent. of the aniline required by the expected reaction was obtained, about 30 per cent. of unchanged starting material was recovered, and there remained a small portion of oil which should have been α-phenyl-γ-aminobutane, but which could not be identified.

This hydrazone was also reduced by Schlenk's[12] method modified to the extent that the reaction was carried through at about 55° rather than at the boiling point of the alcohol used as a solvent. In this case there was obtained a 76 per cent. yield of a product that turned out to be the phenylhydrazone of benzylacetone. To identify this compound it was prepared in a different way. First, separate portions of benzalacetone were reduced to benzylacetone. With the method of Harries and Eschenbach[13] the yield was low, while with that described by Adams, Kern and Shriner[14] it was much better. This product was identified by conversion of one portion of it into the semicarbazone, and another into the phenylhydrazone. These changes are indicated below.

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[10] Tafel, *ibid.*, **22**, 1854 (1889).

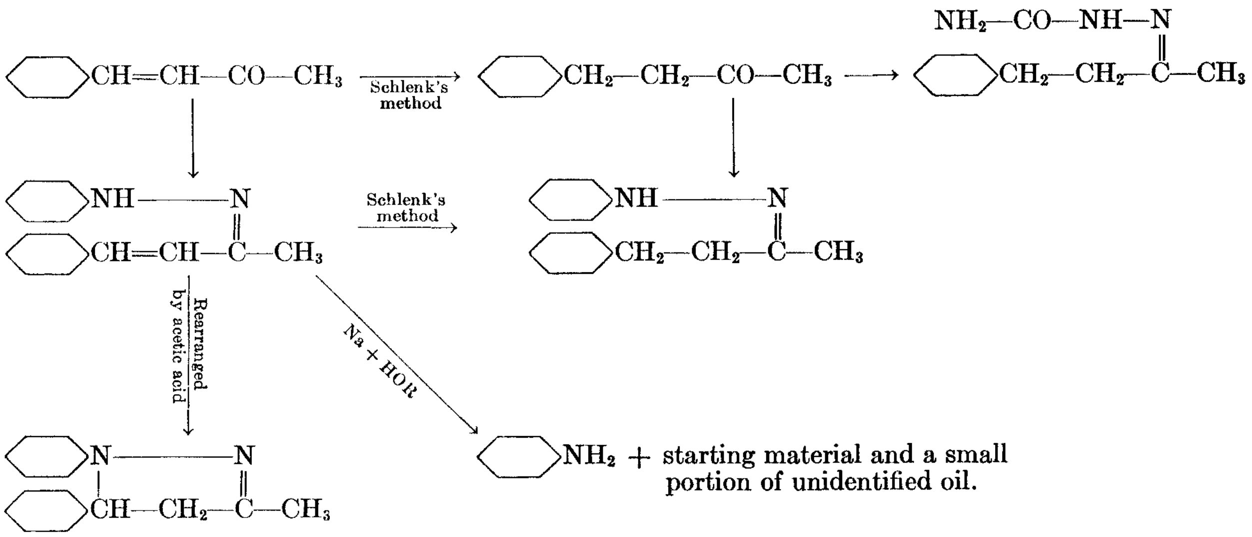
[11] Auwers and Kreuder, *ibid.*, **58**, 1976 (1925).

* The first lot of this material prepared melted at 156–157.5°, which agrees with the observations of Fischer [*Ber.*, **17**, 576 (1884)] who found 157°. When this product was allowed to stand in a glass container for about six months and was then recrystallized from alcohol it melted at 138–139°. All subsequent attempts to prepare this hydrazone by the method which in the first instance gave the higher-melting product, gave material that melted at 138–139°. The yields were comparable. Analysis of the product indicated that it was pure, and rearrangement of it gave the expected pyrazoline.

[12] Schlenk, *J. prakt. Chem.*, [2], **78**, 50 (1908).

[13] Harries and Eschenbach, *Ber.*, **29**, 383 (1896).

[14] Adams, Kern, and Shriner, "Organic Syntheses," Wiley, New York, **1932**, Coll. Vol., p. 95.



REDUCTION OF BENZALACETONE AND THE CORRESPONDING PHENYLHYDRAZONE

Reduction of the phenylhydrazone of chalcone was carried out with sodium amalgam in alkaline solution as directed by Schlenk. In this case 20 per cent. of the required aniline was obtained, 5 per cent. of the hydrazone was rearranged to 1,3,5-triphenylpyrazoline, while 20 per cent. was reduced to give the hydrazone of β-phenylpropiophenone. The identity of this product was established by subjecting chalcone to the series of reactions specified above for benzalacetone. With the phenylhydrazone of 4′-chlorochalcone, reduction gave 12 per cent. of the required aniline, and 21 per cent. of a heavy brown oil that gave a good analysis for the phenylhydrazone of β-phenylethyl 4-chlorophenyl ketone. The same product was obtained by catalytic reduction of 4′-chlorochalcone to the saturated ketone, and treatment of the latter with phenylhydrazine. Although a small amount of aniline was obtained in the reduction of each of these hydrazones, the aliphatic amines which might have been expected, in terms of Tafel's observations, were not obtained.

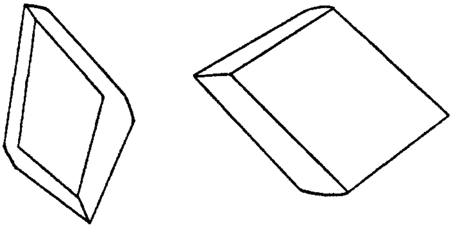


FIG. 1

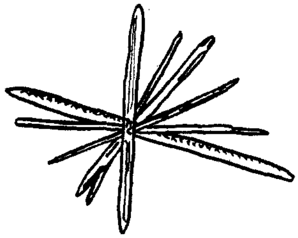


FIG. 2

FIG. 1.—PHENYLHYDRAZONE OF 4′-CHLOROCHALCONE

FIG. 2.—1,5-DIPHENYL-3-(4-CHLOROPHENYL)PYRAZOLINE

An additional aid used to distinguish between these isomers was microscopic examination of the forms in which they separate when they are crystallized from certain solvents. In almost every case when the hydrazones here under consideration separated from the acetic acid solution, in which they were usually prepared, they were deposited as flat plates. From methyl or ethyl alcohol needles were obtained. The crystal shapes of the pyrazolines varied but little when different solvents were used. With acetic acid the needles formed were long and characteristic in appearance. Frequently, in carrying through a preparation of these hydrazones or an attempt to reduce or rearrange them, it was found possible to follow the change by removal of a few drops of the reaction mixture, evaporation to crystallization, and examination of the residue with a microscope. The appearance of these crystals is shown in Figs. 1 and 2 for a typical hydrazone-pyrazoline pair crystallized from acetic acid.

EXPERIMENTAL

Ketones containing saturated hydrocarbon residues.—Benzylacetone was obtained in 34% yield as an oil that boiled at 235–236° under 748 mm. pressure, by reduction of benzalacetone by the method of Harries Eschenbach.[13] When reduction was carried through as directed by Adams, Kern, and Shriner[14] the same oil was obtained, but the yield was 67%. The product was further characterized by conversion into a semicarbazone which crystallized from alcohol in colorless plates that melted at 142°.

Anal. Calc'd for $C_{11}H_{15}N_3O$: N, 20.48. Found: N, 20.51.

β-Phenylpropiophenone was prepared in 87% yield by reduction of chalcone by the method of Adams, Kern and Shriner. The product was identified by conversion into the oxime, which melted at 82° as previously recorded.[15] A portion of the ketone was dissolved in a mixture of alcohol and acetic acid, and was refluxed for an hour with phenylhydrazine. The alcohol was evaporated, the oily residue was extracted with dilute hydrochloric acid, then with ether; the ether solution was dried with anhydrous sodium sulfate, and the solvent was distilled off. The residue was a yellowish-brown oil which did not crystallize. A yield of 56% was obtained. The same product was obtained in part by reduction of the phenylhydrazone of benzalacetophenone by Schlenk's method. Each was analyzed for nitrogen.

TABLE I

PHENYLHYDRAZONES FROM SUBSTITUTED CHALCONES

SUBSTITUENT IN PHENYL'	YIELD, %	M.P., °C.	FORMULA	ANALYSES			
				Halogen, %		Nitrogen, %	
				Calc'd	Found	Calc'd	Found
4'-Bromo-	69	116–118[a]	$C_{21}H_{17}BrN_2$	21.22	21.30		
4'-Methyl-[b]	53	101–102	$C_{22}H_{20}N_2$			8.97	9.04
4'-Methoxy-	37	106–107	$C_{22}H_{20}N_2O$			8.53	8.60

[a] Though this compound gave a satisfactory analysis for halogen there is some uncertainty concerning its purity. In repeated preparations of the compound crystallization from acetic acid gave material that showed a melting range of 110–120°. After one recrystallization from alcohol the product melted at 100–101°, but repeated crystallizations from the same solvent raised this to 116–118°. The pyrazoline obtained from it by rearrangement was readily purified and melted satisfactorily.

[b] According to Weygand and Matthes [*Ann.*, **449**, 31, 59 (1926)], 4'-methylchalcone used in the preparation of this hydrazone can exist in alpha and beta forms that melt at 74.8–75.4° and 55–56°, respectively. When either of these is heated to about 220° and quickly cooled the gamma form melting at 44° is obtained. The product used here melted at 77° and was regarded as the alpha form.

Anal. Calc'd for $C_{21}H_{20}N_2$: N, 9.33. Found: N, 9.24 and 9.26.

β-Phenylethyl 4-chlorophenyl ketone was prepared by reduction of 4'-chlorochalcone as described above. The yield was 93%. Crystallization from alcohol gave color-

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[15] PERKIN AND STENHOUSE, *J. Chem. Soc.*, **59**, 1008 (1891).

less needles that melted at 73°. The product was further identified by conversion into an oxime, which separated from dilute alcohol in colorless needles that melted at 91–92°.

Anal. Calc'd for $C_{15}H_{14}ClNO$: Cl, 13.67. Found: Cl, 13.40.

The phenylhydrazone, obtained as explained above for the non-halogenated compound, was a reddish-brown oil that could not be crystallized. Analysis indicated that it was nearly pure.

Anal. Calc'd for $C_{21}H_{19}ClN_2$: Cl, 10.61. Found: Cl, 10.70.

Phenylhydrazones of α,β-unsaturated ketones.—The ketones used here are on record, and were prepared by standard methods. To obtain the hydrazones the calculated quantity of phenylhydrazine was added with efficient stirring to a saturated acetic acid solution of the ketone at room temperature, and stirring was continued until the product crystallized out. The solid was immediately collected on a gravity filter, and washed with several portions of warm methyl alcohol in order to remove adhering acetic acid which would slowly bring about rearrangement of a portion of the hydrazone during the drying of the material. In this way the hydrazones listed in Table I were obtained. When 4′-hydroxy-, 4′-acetoxy-, and 3′-nitrochalcone, respectively, were used no hydrazones could be isolated. In each case the required pyrazoline was obtained, which indicated that the hydrazones were too unstable to exist under the conditions of the experiment.

TABLE II

SUBSTITUTED 1,5-DIPHENYLPYRAZOLINES FROM α,β-UNSATURATED KETONES

SUBSTITUENT IN POSITION 3	FORMULA	M.P., °C.	ANALYSES			
			Halogen, %		Nitrogen, %	
			Calc'd	Found	Calc'd	Found
4-Chlorophenyl-	$C_{21}H_{17}ClN_2$	150–0.5	10.67	10.68		
4-Bromophenyl-	$C_{21}H_{17}BrN_2$	156–7	21.22	21.43		
4-Tolyl-	$C_{22}H_{20}N_2$	152–3			8.97	8.94
3-Nitrophenyl-	$C_{21}H_{17}N_3O_2$	131			12.24	12.38
4-Hydroxyphenyl-	$C_{21}H_{18}N_2O$	116–8			8.91	8.87
4-Acetoxyphenyl-	$C_{23}H_{20}N_2O_2$	165–6			7.86	7.75[a]
4-Methoxyphenyl-[b]	$C_{22}H_{20}N_2O$	141–1.5			8.54	8.71

[a] This compound was further identified by preparing it directly by acetylation of 1,5-diphenyl-3-(4-hydroxyphenyl)pyrazoline. A mixture of these products melted without depression.

[b] This product crystallized in fine colorless needles from alcohol. All others were crystallized from alcohol or acetic acid in yellow needles.

Preparation of pyrazolines.—When the hydrazones indicated above were mixed with acetic acid and heated under reflux for one hour they were rearranged to the isomeric pyrazolines. Also, the latter were obtained directly by boiling a mixture of the required ketone, phenylhydrazine, and acetic acid. Analytical data and other properties for products obtained by both methods are given in Table II.

SUMMARY

1. It has been found that several substituted chalcones can be reduced in the presence of platinum oxide as catalyst to give the corresponding β-phenylpropiophenones.

2. Phenylhydrazones were obtained from 4′-chloro-, 4′-bromo-, 4′-methyl-, and 4′-methoxychalcone, while 3′-nitro-, 4′-hydroxy- and 4′-acetoxy- derivatives gave pyrazolines directly.

3. Reduction of the phenylhydrazones of α,β-unsaturated ketones with sodium amalgam, with the continual passage of carbon dioxide into the reaction mixture gave the hydrazones of the corresponding saturated ketones. This indicated that only the ethylenic linkages had been affected. When attempts were made to reduce the isomeric pyrazolines the starting material was recovered quantitatively.

4. From acetic acid these hydrazones crystallize in flat plates, while the pyrazolines separate in needles. The colors developed by these compounds in the presence of bromine vapor are different, and may assist in distinguishing the isomers.

CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

A STUDY OF SOME UREA DERIVATIVES IN THE ALKANOLAMINE SERIES

RALPH W. CHARLTON AND ALLAN R. DAY

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The monoalkyl derivatives of urea have long been known to possess hypnotic properties. While the relative effects of alkyl groups on hypnotic activity have been studied,[1] few attempts have been made to study the effects produced by the presence of substituted alkyl groups.

With this fact in mind it was decided to prepare and study some hydroxyalkyl-substituted ureas. It was to be expected that the presence of the hydroxyl group would produce a decrease in hypnotic activity as well as lower the toxicity. One of the necessary qualifications a hypnotic must have is a safe margin between the effective dose and the toxic dose, and since the presence of the hydroxyl group affects both, it was hoped that such a combination might be obtained in this way.

The starting materials for these compounds were the alkanolamines except in one case where 6-aminothymol was used. These amino compounds when treated with nitrourea yielded the corresponding hydroxyalkyl ureas.

In addition to the simple substituted ureas certain of their derivatives appeared to be of interest. The *p*-aminobenzoyl and cinnamoyl derivatives were prepared. Since many of the esters of *p*-aminobenzoic acid and cinnamic acid have local anesthetic properties, it was thought that the corresponding carbamidoalkyl esters of these two acids might have similar properties.

Two of the hydroxyalkylureas, β-hydroxyethylurea[2] and *unsym.*-di-β-hydroxyethylurea[3] had been previously prepared. The remaining hydroxyalkylureas as well as the derivatives of all of the hydroxyalkylureas represent new compounds.

EXPERIMENTAL

Preparation of the hydroxyalkylureas.—A slight excess of nitrourea[4] was added in small portions to a concentrated aqueous solution of the alkanolamine, and the

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[1] DE BEER, BUCK, AND HJORT, *J. Pharmacol.*, **52**, 216, (1934).

[2] FRANCHIMONT, *Rec. trav. chim.*, **13**, 488, (1894).

[3] PRELOG, DRIZA, AND HANOUSEK, *Collection Czechoslov. Chem. Communications*, **3**, 578, (1931).

[4] DAVIS AND BLANCHARD, *J. Am. Chem. Soc.*, **51**, 1790, (1929).

solution was allowed to stand for several hours. When the reaction was completed, as evidenced by the cessation of gas evolution, the water was removed by slow evaporation on the steam bath. The crude products were purified by recrystallization from water, alcohol or dioxane. The yields obtained by this method were uniformly good, ranging from 85 to 95 per cent. Equally good yields were obtained by carrying out the reaction in 50 to 95 per cent. alcohol solution. During the course of this work Buck and Ferry[5] reported the use of alcohol as a solvent in the nitrourea method for the preparation of substituted ureas from amines.

Preparation of α-naphthylhydroxyalkylureas.—Slightly less than the theoretical amount of α-naphthyl isocyanate was added in small portions to a cold ether or dioxane suspension of alkanolamine, and the mixture was allowed to stand with occasional stirring until the odor of isocyanate was no longer noticeable. The product was filtered, washed with ether, and recrystallized from dioxane or alcohol. The yields were practically quantitative.

That the isocyanate reacted with the amino group rather than the hydroxyl group was readily established. These reactions were quite vigorous, and considerable heat was evolved. When α-naphthyl isocyanate was added to a primary alcohol, such as ethyl alcohol or ethylene chlorohydrin, a vigorous reaction did not take place. With a primary amine such as ethylamine, however, a rapid and fairly vigorous reaction resulted. From the qualitative standpoint it was not difficult to show that urethane formation was slow compared to urea formation. Finally, if the isocyanate had reacted with the hydroxyl group, the resulting product would form a hydrochloride, as it would contain a free primary amino group. This was not the case. When the isocyanate was added slowly and with stirring to the alkanolamine the resulting product was entirely the urea derivative, and no hydrochloride was obtained.

Acylation.—The hydroxyalkylurea (0.1 mole) was suspended in 200–300 cc. of dry benzene, and slightly less than the theoretical quantity (0.1 mole) of acyl chloride was added. The mixture was refluxed on the steam bath until hydrogen chloride evolution ceased. The product was separated from the benzene by decantation, and washed several times with dry benzene to remove traces of unreacted acyl chloride. Purification was accomplished by recrystallization from alcohol or dioxane. The yields of acylated product varied from 50 to 65 per cent.

The acylation of the hydroxyalkylureas proceeded smoothly in most cases, but difficulties were encountered in determining the position of acylation. These compounds contain two groups, amide and alcohol, either or both of which might be acylated. The acylated compounds were studied qualitatively for evidence which might indicate the direction of acylation. β-Hydroxyethylurea, β-hydroxy-*n*-propylurea and di-(β-hydroxyethyl)urea after being dried over phosphorus pentoxide gave marked tests with sodium in dry benzene or toluene. The dried *p*-nitrobenzoyl and *p*-aminobenzoyl derivatives, however, did not give tests under the same conditions, which would indicate that the free hydroxyl group was no longer present. Another reaction which gave confirmatory evidence for the above statement was that of ammonolysis. When the *p*-nitrobenzoyl derivatives of β-hydroxyethylurea and β-hydroxy-*n*-propylurea were treated with a solution of ammonia in dry alcohol at 100° in a pressure flask, *p*-nitrobenzamide was readily obtained. This reaction indicated the presence of an ester linkage.

Reduction of nitro compounds.—Reduction was carried out at room temperature

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[5] Buck and Ferry, *ibid.*, **58**, 854, (1936).

with the nitro compound in alcoholic solution or suspension, and freshly prepared palladium black as the catalyst. The apparatus and procedure, otherwise, were essentially those of Shaefer.[6] When the reaction was complete, as indicated by the fact that the volume of hydrogen in the buret became constant, the catalyst was filtered from the alcoholic solution containing the amino compound. In some cases, heating was necessary to effect complete solution of the reduction product before filtration. The product was recovered from the filtrate by evaporation of the alcoholic solution and dilution with water. In some cases treatment with animal charcoal was necessary to obtain a colorless product. The yields, as shown by comparison of the theoretical and experimental volumes of hydrogen absorbed, were quantitative.

The preparation of hydrochlorides of these amino compounds was attempted, but the results were not uniformly successful. Dry hydrogen chloride was passed over a cold saturated alcoholic solution of the amine until no more hydrogen chloride was absorbed. The hydrochlorides were less soluble than the parent compounds, and precipitated as colorless crystals under these conditions. In general the products so obtained were not stable, could not be purified by recrystallization, and were highly hygroscopic.

Analysis.—The macro Kjeldahl method was used for the analytical determination of nitrogen in the compounds not previously prepared. Ten cc. of 10 per cent. copper sulfate solution was used as the digestion catalyst. The distillate was absorbed in 4 per cent. boric acid solution and titrated to a methyl red endpoint.[7] The analytical results reported under the individual compounds are average results based on determinations which checked within the accepted limit of error.

Molecular weights.—The Rast method of molecular weight estimation was used. With a few of the compounds, decomposition or chemical reaction occurred, rendering the method impractical.

β-Hydroxyethylurea.—This urea was previously prepared by the action of potassium cyanate on ethanolamine hydrochloride.[2] It was obtained by the nitrourea method in yields of 85 to 90 per cent. The crystalline mass was purified by recrystallization from alcohol, and finally from a large volume of dioxane. The crystals so obtained were needles which melted at 94–5° (corr.)

*β-*p*-Nitrobenzoxyethylurea.*—The yields of this compound varied from 50 to 55 per cent. It was purified by recrystallization from alcohol and obtained in the form of colorless needles which melted at 183–183.4° (corr.). Mol. wt.: calc'd, 253; found, 249.

That a *p*-nitrobenzoate and not a *p*-nitrobenzoylurea was formed in this reaction was further indicated in the following reactions. β-Hydroxyethylurea was suspended in dry xylene, and heated with the theoretical amount of sodium. When this reaction was complete, slightly less than the theoretical amount of *p*-nitrobenzoyl chloride was added, and refluxing was continued for several hours. The sodium chloride formed during the reaction was filtered out, and the xylene was evaporated. The resulting product after recrystallization from alcohol had the same melting point as the product prepared without the use of sodium. A mixture melting point completed the proof of the identity of the two products. While this did not give absolute proof of structure, it confirmed the qualitative evidence given earlier that benzoylation occurred on the hydroxyl group.

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[6] SHAEFER, *Ind. Eng. Chem.*, *Anal. Ed.*, **2**, 115, (1930).

[7] MEEKER AND WAGNER, *ibid.*, **5**, 396, (1933).

β-p-*Aminobenzoxyethylurea.*—This compound was prepared in almost quantitative yields by the method outlined. The crude product was purified by recrystallization from hot dilute alcohol solution from which it crystallized in colorless needles; m.p. 203° (corr.).

Anal. Calc'd for $C_{10}H_{13}N_3O_3$: N, 18.83. Found: N, 18.63.

sym.-*α-Naphthyl-β-hydroxyethylurea.*—The yield of the symmetrical urea was practically quantitative. It was recrystallized from dioxane; colorless needles, m.p. 186° (corr.).

Anal. Calc'd for $C_{13}H_{14}N_2O_2$: N, 12.17. Found: 11.98.

Mol. wt.: calc'd, 230; found, 224.

sym.-*α-Naphthyl-β*-p-*nitrobenzoxyethylurea.*—The yields varied between 55 and 65 per cent. The crude product was recrystallized from alcohol and obtained in the form of colorless needles; m.p. 191° (corr.), with decomposition.

sym.-*α-Naphthyl-β*-p-*aminobenzoxyethylurea.*—After the catalytic hydrogenation, the alcohol solution was partly evaporated, and the product was precipitated by dilution with water. On recrystallization from alcohol the urea was obtained in almost quantitative yield in the form of fine colorless needles; m.p. 193–193.5° (corr.), with decomposition.

Anal. Calc'd for $C_{20}H_{19}N_3O_3$: N, 12.03. Found: 11.85.

Mol. wt.: calc'd, 349; found, 357.

sym.-*Cinnamoyl-β-cinnamoxyethylurea.*—This product was obtained in yields of only 50 per cent. It was purified by recrystallization from alcohol, from which it precipitated in the form of colorless needles; m.p. 173.5–174° (corr.). The monocinnamoyl derivative was expected, but a dicinnamoyl compound was always obtained even when the conditions of acylation were varied. This was shown by nitrogen analysis, molecular weight determination and quantitative hydrogenation of the double bonds in which the sample absorbed a volume of hydrogen corresponding to two double bonds, within the experimental error introduced in reading the buret.

Anal. Calc'd for $C_{21}H_{20}N_2O_4$: N, 7.69. Found: 7.64.

Mol. wt.: calc'd, 364; found, 368.

β-Hydroxy-n-*propylurea.*—This urea was obtained in yields of 85 to 88 per cent. Recrystallization from alcohol and then from dioxane yielded colorless prisms; m.p. 119° (corr.).

Anal. Calc'd for $C_4H_{10}N_2O_2$: N, 23.73. Found: 23.84.

β-p-*Nitrobenzoxypropylurea and* sym.-p-*Nitrobenzoyl-β*-p-*nitrobenzoxypropylurea.*—The yields in this case varied from 60 to 65 per cent. On recrystallization from alcohol, colorless needles of uniform appearance formed. The melting points of several preparations varied from 182 to 186° (corr.). The variation in melting point indicated a mixture, but the product could not be further purified by fractional crystallization from alcohol or dioxane. That it was a mixture was established by the fact that reduction yielded two amino compounds.

β-p-*Aminobenzoxypropylurea and* sym.-p-*Aminobenzoyl-β*-p-*aminobenzoxypropylurea.*—The alcoholic solution containing the reduction product was diluted with one-fourth its volume of water and slowly evaporated on a steam bath until crystals separated on cooling to room temperature. After several recrystallizations from alcohol this product was obtained in colorless plates; m.p. 210–211° (corr.). The analysis and molecular weight of this compound corresponded to *sym.*-*p*-aminobenzoyl-*β*-*p*-aminobenzoxypropylurea.

Anal. Calc'd for $C_{19}H_{20}N_4O_4$: N, 15.73. Found: 15.57.

Mol. wt.: calc'd, 356; found, 376.

The filtrate from the less soluble compound was further diluted with water, heated with charcoal and filtered. It was then evaporated until on cooling colorless prisms separated; m.p. 149–150° (corr.). The analysis of this compound corresponded to β-*p*-aminobenzoxypropylurea.

Anal. Calc'd for $C_{11}H_{15}N_3O_3$: N, 17.72. Found: 17.64.

Mol. wt.: calc'd, 237; found, 249.

sym.-*α-Naphthyl-β-hydroxypropylurea.*—The yields of this urea were practically quantitative. Purification was accomplished by dissolving it in hot dioxane followed by dilution with one and one-half volumes of water. The product separated in colorless needles; m.p. 162° (corr.).

Anal. Calc'd for $C_{14}H_{16}N_2O_2$: N, 11.48. Found: 11.47.

Mol. wt.: calc'd, 244; found, 245.

sym.-*α-Naphthyl-β-*p-*nitrobenzoxypropylurea.*—The yields varied from 50 to 60 per cent. The product was obtained in colorless needles by recrystallization from a large volume of dioxane; m.p. 218–221° (corr.), with decomposition. Mol. wt.: calc'd, 393; found, 370.

sym.-*α-Naphthyl-β-*p-*aminobenzoxypropylurea.*—The catalytic hydrogenation of the corresponding nitro compound did not proceed smoothly. When approximately half of the theoretical volume of hydrogen had been absorbed, the mixture set to a gel. The apparatus was disconnected, and more alcohol was added, but the hydrogenation of the remainder of the material was extremely slow. The mixture was then heated to dissolve the reduction product, and was filtered while hot. The product separated as a gel from the filtrate. After filtration it dried slowly to a hard amorphous mass. The dried material was dissolved in a hot mixture of dry benzene and dry alcohol, from which it separated, on cooling, in the form of fine needles; m.p. 171° (corr.).

Anal. Calc'd for $C_{21}H_{21}N_3O_3$: N, 11.57. Found: 11.50.

sym.-*Cinnamoyl-β-cinnamoxypropylurea.*—Cinnamoylation of β-hydroxypropylurea yielded a diacyl derivative as in the case of hydroxyethylurea. The product was obtained in yields of 50 to 55 per cent. It was recrystallized from dioxane, from which it separated in the form of colorless prisms; m.p. 179–179.5° (corr.).

Anal. Calc'd for $C_{22}H_{22}N_2O_4$: N, 7.41. Found: 7.39.

Mol. wt.: calc'd, 378; found, 380.

unsym.-*Di-(β-hydroxyethyl)urea.*—This compound had been previously prepared by Prelog, Driza and Hanousek[3] by the potassium cyanate method. Their product was a heavy, viscous liquid which they identified by means of its dibenzoate; m.p. 108°.

By the action of nitrourea on a concentrated aqueous solution of diethanolamine, this same urea was prepared in quantitative yields.

unsym.-*Di-(β-*p-*nitrobenzoxyethyl)urea.*—Nitrobenzoylation of the above urea produced two products of different melting points, crystal structures and solubilities in dioxane. The yields varied from 55 to 65 per cent. The two products were separated by means of their different solubilities in dioxane and further purified by recrystallization from alcohol, in which the solubilities were not noticeably different. The least soluble form crystallized in needles, m.p. 140–140.5° (corr.), while the more soluble form was obtained in plates, m.p. 152–153° (corr.). These two forms were hydrogenated separately and yielded the same amino compound, as shown by the melting point, mixture melting point, and analysis.

unsym.-*Di-(β-*p-*aminobenzoxyethyl)urea.*—When either form of the corresponding nitrobenzoate or a mixture of the two forms was catalytically hydrogenated, the theoretical quantity of hydrogen was absorbed. After the removal of the catalyst, the alcohol solution was diluted with three times its volume of water, boiled with charcoal, filtered hot and cooled. The amino compound separated in colorless prisms; m.p. 172.5–172.8° (corr.).

Anal. Calc'd for $C_{19}H_{23}N_4O_5$: N, 14.51. Found: 14.54.

Mol. wt.: calc'd, 386; found, 392.

α,α-Di-(β-hydroxyethyl)-α'-(α-naphthyl)urea.—This derivative, which was obtained in practically quantitative yields, was purified by adding water to its hot alcohol solution until precipitation started. On cooling colorless prisms were formed; m.p. 126–127° (corr.).

Anal. Calc'd for $C_{15}H_{19}N_2O_3$: N, 10.22. Found: 10.06.

Mol. wt.: calc'd, 274; found, 275.

Nitrobenzoylation of the above compound was attempted, but it did not proceed smoothly, yielding a mixture of at least three products which could not be separated satisfactorily.

1,3-Dicarbamidopropanol-2.—This diurea was prepared in 85 to 90 per cent. yields by the nitrourea method. It was very soluble in water, and crystallized only after most of the water had been removed on the steam bath. Recrystallized from a little water it was obtained in colorless prisms; m.p. 86–87° (corr.).

The crystals could not be dried satisfactorily. The compound fused in the oven (with some decomposition) even at low temperatures and failed to give up its water completely over phosphorus pentoxide. Attempted molecular weight determinations were unsuccessful. The analysis indicated the probable presence of one molecule of water.

Anal. Calc'd for $C_5H_{12}N_4O_3$: N, 31.82.
$C_5H_{12}N_4O_3 \cdot H_2O$: N, 28.87. Found: 28.52.

1,3-Di-(α-naphthylureido)propanol-2.—Purification of this compound was difficult because of its relative insolubility in organic solvents. From a large volume of alcohol it separated as a gel which dried to a fine powder, definitely crystalline but of indeterminate structure; m.p. 171.5–172° (corr.).

Anal. Calc'd for $C_{25}H_{24}N_4O_3$: N, 13.08. Found: 13.12.

Mol. wt.: calc'd, 418; found, 388.

Acylation of this and the preceding urea was attempted without success. In each case a product of indefinite composition was produced.

6-Carbamidothymol.—This compound was prepared from 6-aminothymol hydrochloride,[8] by dissolving the latter in water, adding the theoretical amount of nitrourea and then slowly neutralizing with the calculated amount of sodium bicarbonate. The reaction product was washed with ether, dissolved in hot dilute alcohol, heated with animal charcoal and filtered. On cooling, the derivative crystallized in colorless silky needles; m.p. 179° (corr.).

Anal. Calc'd for $C_{11}H_{16}N_2O_2$: N, 13.46. Found: 13.55.

Mol. wt.: calc'd, 208; found, 187.

Pharmacological Results

A complete report cannot be made at this time, for the compounds have not been fully investigated. Four of the compounds of the ethanolamine series have

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[8] KREMERS AND WAKEMAN, "Organic Syntheses," John Wiley and Sons, New York, **1932**, Coll. Vol., p. 498.

been studied for hypnotic action by the Merck Institute of Therapeutic Research. The hypnotic effects in the four cases examined were weak, and two of the compounds appeared to be rather toxic to white rats. The results are indicated below.

β-Hydroxyethylurea.—No effects were produced by doses of 0.1 to 4.0 grams per kilogram, given both subcutaneously and orally in water solution. This would indicate that the compound was not only much less efficient than ethylurea, but apparently weaker than urea itself.

*β-*p*-Aminobenzoxyethylurea.*—The only effect noticed upon subcutaneous injection of 1 gram per kilogram, in alcohol solution, was quietness; 0.5 gram per kilogram of the same solution administered orally caused a slight loss in the sense of balance of the rat. One gram per kilogram finally resulted in the death of the rat due to respiratory failure.

sym.*-α-Naphthyl-β-hydroxyethylurea.*—No symptomatic effect was produced by oral doses of 0.5 g./kg. or 2.0 g./kg. However, the rat receiving the latter dose died several hours later.

sym. *-α-Naphthyl-β-*p*-aminobenzoxyethylurea.*—No effects were produced by oral doses in glycerol of 0.2 g./kg. A dose of 2.0 g./kg., however, induced the appearance of drowsiness which lasted for some time.

SUMMARY

1. β-Hydroxyethylurea, β-hydroxy-*n*-propylurea, *unsym.*-di-(β-hydroxyethyl)urea, 1,3-dicarbamidopropanol-2 and 6-carbamidothymol were prepared by the action of nitrourea on the corresponding aminoalcohols.

2. *sym.*-α-Naphthyl-β-hydroxyethylurea, *sym.*-α-naphthyl-β-hydroxy-*n*-propylurea, α,α-di(β-hydroxyethyl)-α′-(α-naphthyl)urea, and 1,3-di-(α-naphthylureido)propanol-2 were prepared by the action of α-naphthyl isocyanate on the corresponding aminoalcohols.

3. The *p*-nitrobenzoyl and the *p*-aminobenzoyl derivatives of the following compounds were prepared: β-hydroxyethylurea, β-hydroxy-*n*-propylurea, *unsym.*-di-(β-hydroxyethyl)urea, *sym.*-α-naphthyl-β-hydroxyethylurea, and *sym.*-α-naphthyl-β-hydroxy-*n*-propylurea.

4. The cinnamoyl derivatives of the following compounds were prepared: β-hydroxyethylurea, and β-hydroxy-*n*-propylurea.

5. A preliminary pharmacological report has been included for four of the above compounds.

[Contribution from the Research Laboratories of the Universal Oil Products Company, Riverside, Illinois]

NEW METAL HALIDE CATALYSTS FOR HYDROCARBON REACTIONS

ARISTID V. GROSSE and VLADIMIR N. IPATIEFF

We have recently described[1,2,3,4,5,6,7] how different classes of hydrocarbons, such as paraffins, naphthenes, aromatics, etc., originally considered very unreactive, react among themselves in the presence of catalysts. Previously the only known reaction of this kind was the alkylation of aromatics with olefins in the presence of aluminum chloride, discovered by Balsohn[8] nearly sixty years ago.

We have found that, besides aluminum chloride, the halides of a large number of metals standing near aluminum and forming a diagonal band in the periodic table (see Table I), that is, beryllium, boron, titanium, zirconium, hafnium, thorium, columbium, and tantalum, proved effective in these reactions (and also generally in reactions of the Friedel-Crafts type). These halides all have a similar chemical nature and show similar behavior towards water and in the formation of double salts or addition compounds; they form the transition between the purely heteropolar salt-type halides and the typically homopolar covalent halides.

As a means of comparing the halides, we have chosen Balsohn's classical example, namely, the reaction between benzene and ethylene.[8] The reaction proceeds smoothly according to the equations:

$$C_6H_6 + C_2H_4 \xrightarrow{\text{Catalyst}} C_6H_5 \cdot C_2H_5,$$

$$C_6H_5 \cdot C_2H_5 + C_2H_4 \xrightarrow{\text{Catalyst}} C_6H_4(C_2H_5)_2, \text{ etc.},$$

$$C_6H_1(C_2H_5)_5 + C_2H_4 \xrightarrow{\text{Catalyst}} C_6(C_2H_5)_6,$$

yielding a product consisting of a mixture of mono- and poly-, up to hexaethylbenzenes. All our new catalysts, like $AlCl_3$,[8] produce all ethyl-

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[1] Ipatieff and Grosse, *J. Am. Chem. Soc.*, **57**, 1616, (1935).

[2] Ipatieff, Komarewsky, and Grosse, *ibid.*, **57**, 1722 (1935).

[3] Grosse and Ipatieff, *ibid.*, **57**, 2415, (1935).

[4] Ipatieff and Grosse, *Ind. Eng. Chem.*, **28**, 461 (1936).

[5] Ipatieff and Grosse, *J. Amer. Chem. Soc.*, **58**, 915 (1936).

[6] Ipatieff, Grosse, Pines, and Komarewsky, *ibid.*, **58**, 913 (1936).

[7] Grosse and Ipatieff, Reaction of Cycloparaffins with Aromatics and Paraffins, *Libr. Bull. of the Universal Oil Products Co.*, **11**, 161 (1936).

[8] Balsohn, *Bull. soc. chim.*, [2] **31**, 539 (1879).

benzenes from mono- to hexa-. The hexaethylbenzene has been identified in all cases by determinations of the melting point of a mixture with an authentic sample. Ethylbenzene was identified by its constants and especially through oxidation to benzoic acid. The proportions of the ethylbenzenes vary to a great extent depending on the catalyst, ratio of available ethylene to benzene, time, temperature and pressure conditions. However, with most catalysts, even under conditions favoring formations of monoethylbenzene, the higher alkylated products, up to hexaethylbenzene, are formed simultaneously.[9] The details of our procedure, nature and compositions of our products, etc., are given in the experimental part.

TABLE I

DISTRIBUTION OF CATALYTICALLY EFFECTIVE HALIDES IN THE PERIODIC SYSTEM

GROUP I	GROUP II	GROUP III	GROUP IV	GROUP V	GROUP VI
Li	**$BeCl_2$**	**BF_3**	C	N	O
Na	Mg	**$AlCl_3$**	Si	P	S
K	Ca	Sc	**$TiCl_4$**	V	Cr
Rb	Sr	Y	**$ZrCl_4$**	**$CbCl_5$**	Mo
Cs	Ba	La	**$HfCl_4$**	**$TaCl_5$**	W
—	Ra	Ac	**$ThCl_4$**	**$EtCl_5$**	U

TABLE II

CATALYST EFFICIENCY

METAL HALIDE	TEMPERATURE, °C.	MOLES OF ETHYLENE CONVERTED PER MOLE OF CATALYST
$BeCl_2$	200	50
BF_3	25	35
$AlCl_3$	75	75
$TiCl_4$	170	5
$ZrCl_4$	100	90
$CbCl_5$	75	25
$TaCl_5$	75	60

The metal halides investigated by us behave as real catalysts, as does aluminum chloride in the Balsohn reaction, though not in many other organic reactions in which it takes part. This can be seen from the fact that, even disregarding the preliminary character of our experiments, one mole of almost any of our halides can convert over fifty moles of ethylene into ethylbenzenes. In Table II the efficiencies of these catalysts are roughly compared (based on data from Table III).

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[9] See MILLIGAN AND REID, *J. Am. Chem. Soc.*, **44**, 206–10 (1922).

TABLE III

	CATALYST:				
	$BeCl_2$	$TiCl_4$	$ZrCl_4$	$CbCl_5$	$TaCl_5$
Grams of catalyst	6.62	17.1	12.37	18.2	19.71
Grams of benzene	125; 145*	148.8	126.4; 136.8	170	152.7
Grams of hydrogen chloride	≃6; 6	≃6	≃6; ≃6	≃6	≃7
Grams of ethylene absorbed	14.6; 93.1 Σ = 107.7	12.5	58.0; 72.3 Σ = 130.3	47	37.7; 55.1 Σ = 92.8
Temperature	50–125°; 200°	120°; 170°	25–50°; 100°	25°; 75°	25–50°; 25–75°
Max. pressure, kg./cm.^{2}	10; 35	25; 40	15; 15	10; 10	10; 10
Reaction time, hours	12; 60	6; 28	29; 48	5; 45	6; 28
Grams of total reaction product (hydrocarbon part)	142.2; 235.7	161.3	184.3; 220.9	221.4	252.5
Grams of upper layer	142.2; 224.1*	161.3	169.5; 211.3	216.5	237.5
Grams of lower layer or solid (hydrocarbon part)	142.2; 11.6	161.3	14.8; 9.6	4.9	15.0
Unreacted gas, composition	C_2H_4 (96%); (97%)	C_2H_4 (98%)	C_2H_4 (92%); (98%)	C_2H_4 (93%)	
Unreacted gas, liters (N.T.P.)	5.35; 9.20	14.5	0.30; 5.00	1.50	None
Grams C_2H_4 absorbed per 100 g. catalyst	Σ1630	73	468; 583 Σ1051	260	Σ475
Moles C_2H_4 absorbed per mole of catalyst	47	5	40; 50 Σ90	25	61

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* Fifty grams from one period.

Tantalum pentachloride seems nearly as efficient as aluminum chloride, whereas zirconium tetrachloride appears equal or superior to the latter. Beryllium chloride has the disadvantage that it becomes active only at higher temperatures. Titanium tetra chloride is the poorest catalyst of those investigated.

The appearance of the reaction product is similar for the chlorides of the uppermost metals in each group; that is, columbium, titanium, and probably boron, chlorides form homogenous mixtures with the hydrocarbon product, whereas the other catalysts—like aluminum chloride—give rise to two liquid layers, the dark-brown viscous lower layer containing most of the chloride.

For the catalytic action of the halides the presence of hydrogen halide (in most cases hydrogen chloride) seems to be necessary, as in the conjunct polymerization of ethylene with aluminum chloride,[5] which does not take place at all in the absence of hydrogen chloride.

The action of the hydrogen halide seems to consist in its addition to the olefin to form an alkyl halide, which then reacts with the aromatic hydrocarbon whose C-H bond is activated by the metal halide with the elimination of hydrogen halide. The hydrogen halide can then repeat the same cycle indefinitely. With benzene, ethylene, and hydrogen chloride, for example, the following cycle would take place:

$$CH_2{:}CH_2 + HCl \longrightarrow CH_3{\cdot}CH_2{\cdot}Cl$$

$$H_5C_6{\cdot}\boxed{H + Cl}{\cdot}CH_2{\cdot}CH_3 \xrightarrow[\text{Chloride}]{\text{Metal}} C_6H_5{\cdot}CH_2{\cdot}CH_3 + HCl.$$

This viewpoint is supported by the fact that if larger quantities of hydrogen chloride are used ethyl chloride can be readily detected in the reaction product.

EXPERIMENTAL

Reagents.—The chlorides used were prepared either from the C.P. metals (Cb and Ta) and redistilled chlorine, or from C.P. oxides (BeO, ZrO_2, ThO_2, etc.) and C.P. phosgene, and purified by sublimation, except titanium tetrachloride which was fractionated. Ethylene was obtained from a cylinder of the gas, and was over 99% pure. Eastman's benzene "for molecular-weight determinations" was used. The hydrogen chloride was pure compressed gas stored in cylinders.

Apparatus and procedure.—All experiments were carried out in rotating Ipatieff autoclaves.[1] The benzene and the halides were placed in glass liners fitted with capillary tubes* (to avoid the catalytic effects of autoclave walls), inserted into the bombs; the latter evacuated to 2 to 5 mm. (correction being made for the evaporated benzene); the desired amounts of hydrogen chloride were passed in, and then ethylene was added up to the desired pressure. As the pressure fell, fresh ethylene was added,

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* To be described separately.

the refillings being repeated a number of times. In some cases the alkylation was allowed to take place first at one temperature range and then at a higher temperature level; in the cases of beryllium chloride and zirconium tetrachloride most of the product was decanted from the catalyst, and fresh benzene was added before going to the second temperature level.

The amounts of reagents used and the experimental conditions are recorded in Table III.

Nature of Products

Without catalysts.—Benzene and ethylene with small quantities of hydrogen chloride were heated to 25°, 125°, and 225°, respectively, for 30 hours in a glass liner. No alkylation took place, and the benzene was recovered pure, containing less than 0.5% of higher-boiling material, if any.

TABLE IV A

PRODUCTS	% BY VOLUME	n_D^{20}	REMARKS
Benzene	12.5		Contains trace of C_2H_5Cl.
Ethylbenzene	21	1.4945	All fractions olefin-free (stable to $KMnO_4$ test).
Diethylbenzenes	40	1.4999	
Triethylbenzenes and higher	16.5	1.5136	
Hexaethylbenzene	10		M.p. 128.5°; mixture (1:1) with pure sample, m.p. 128.0°.

TABLE IV B

PRODUCTS	% BY WEIGHT	n_D^{20}	REMARKS
Benzene (and possibly toluene, 80–111°)	30		
Ethylbenzene (111–160°)	23	1.4938	Olefin-free.
Di- and higher alkylbenzenes (160–265°)	24	1.5022	Olefin-free.
Fraction > 265°	20		Partly crystallized from CH_3OH; hexaethylbenzene (m.p. 128°).

From beryllium chloride.—After the first part of the experiment (50–125° during 12 hrs.) the product had the appearance of a water-white liquid with suspended white powder. A Podbielniak distillation showed it to consist of 82% benzene (containing a trace of ethyl chloride in the head fraction), 14% ethylbenzene (n_D^{20} = 1.4958; b.p. 139°/760 mm.). and 4.7% higher boiling benzenes. After the second part of the experiment (200° for 60 hrs.) the appearance of the product changed to that of a yellow liquid with blue fluorescence, containing a brownish suspended precipitate. The filtered liquid was absolutely clear, nearly water-white, and contained no beryllium. The results of a Podbielniak distillation of the filtrate are recorded in Table IV A. The precipitate (18.21 g.) was decomposed with ice in the presence of ether; the results of Podbielniak distillation of the ether extract are recorded in Table IV B.

These results show that in the presence of beryllium chloride aromatic hydrocarbons form addition compounds similar to those formed in the presence of aluminum chloride.

From boron trifluoride.—The ethylation of benzene with boron fluoride has already been described elsewhere.[10]

From titanium tetrachloride.—The product is a homogenous clear yellow-orange liquid, with a trace of black suspended powder. Water and ice decomposed the dissolved titanium tetrachloride immediately, and the liquid became water-white and clear. A Podbielniak distillation of this liquid, after washing and drying, yielded the products recorded in Table V.

From these results it can be concluded that titanium tetrachloride starts to alkylate at about 170°. On the basis of the beryllium chloride experiments it can be foreseen that at higher temperatures (*ca.* 250°) the alkylation will proceed with fair rapidity.

From zirconium tetrachloride.—After the first half of the experiment (25–50° during 29 hrs.), the product consisted of two layers, an upper, light, perfectly clear, orange-colored layer, and a deep-orange-red, pasty lower layer. The upper layer (169.5 g.) was separated, washed (washings contained only 75 mg. ZrO_2), dried, and fractioned with a Podbielniak column, with the results recorded in Table VI A. The ethylbenzene was further identified through oxidation with potassium permanganate to benzoic acid (m.p. 122°).

TABLE V

PRODUCTS	% BY VOLUME	n^{20}_{D}	REMARKS
Benzene (80°)	≃96	1.4964	Solidifies in ice.
Ethylbenzene (137°)	2.8	1.4960	Olefin-free.
Higher alkylbenzenes (150–250°)	1.0		Olefin-free.
Higher alkylbenzenes (>250°)	0.3		

The lower layer (27.12 g.) was used again for ethylation, after adding a fresh quantity of benzene (136.8 g.), at 100° for 48 hours. After the experiment a brown liquid product, containing a yellow-brown pasty precipitate (21.92 g.), but no lower layer was obtained. Upon filtration from the precipitate, a clear, water-white liquid (211.3 g.) was obtained (containing only 5–10 mg. ZrO_2).

The Podbielniak distillation of this product is reported in Table VI B.

The yellow-brown precipitate was readily decomposed by water. The hydrocarbons liberated (9.6 g.) consisted of small quantities of benzene and ethylbenzene and larger amounts of higher ethylbenzenes up to hexaethylbenzene; the latter was isolated in the form of crystals melting at 128°.

From columbium pentachloride.—The reaction product is a dark-brown liquid, with a dark red-brown-grayish solid suspended in it. The filtered liquid is also dark brown, similar in appearance to the titanium tetrachloride product and in contrast to those of all our other halides. Water decomposes the halide readily, forming a water-white hydrocarbon layer. From the watery layer 2.94 g. columbium pentoxide, corresponding to 5.88 g. columbium pentachloride, or about 30% of the charge, was recovered.

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[10] Ipatieff and Grosse, *ibid.*, **58**, 2339 (1936).

TABLE VI A

PRODUCTS	% BY WEIGHT	n_D^{20}	REMARKS
Benzene (80°)	12.7	1.4904	Contains trace of C_2H_5Cl in head fraction; melts partly above 0°.
Ethylbenzene (138°)	41.0	1.4950	Olefin-free.
Diethylbenzenes (185°)	34.9	1.4962	Olefin-free
Tri- and higher ethylbenzenes (210–220°)	4.9	1.4979	Olefin-free
Higher ethylbenzenes (>220°)	6.6	1.5129	No hexaethylbenzene present.

TABLE VI B

PRODUCTS	% BY VOLUME	n_D^{20}	REMARKS
Benzene (80°)	37.5	1.4925	Freezes in ice.
Ethylbenzene (136°)	23.5	1.4951	Olefin-free.
Diethylbenzenes (185°)	17.0	1.4970	Olefin-free.
Higher ethylbenzenes (200–225°)	6.5	1.5005	Olefin-free.
Higher ethylbenzenes (225–245°)	8.0	1.5111	Contains also C_6Et_6.
Hexaethylbenzene (>245°)	7.5		Crystals of some C_6Et_6 (m.p. 128.5°) were separated besides a yellow oil; C, 89.38%; H, 10.58%.

TABLE VII

PRODUCTS	% BY VOLUME	n_D^{20}	REMARKS
Benzene (80°)	53.5	1.4968	Crystallizes in ice; head fraction contains trace C_2H_5Cl.
Ethylbenzene (136°)	23.5	1.4957	Olefin-free.
Diethylbenzene (183–185°)	10.0	1.4964	Olefin-free.
Higher ethylbenzenes (200–245°)	5.5	1.4996	Contains crystals of C_6Et_6; m.p. (from CH_3OH) 128.5°; mixture m.p. (1:1) 128°.
Hexaethylbenzene (>245°)	7.5	1.5040	

TABLE VIII

PRODUCTS	% BY VOLUME	n_D^{20}	d_4^{20}	REMARKS
Benzene (80°)	22.5	1.4921	0.8755	Solidifies in ice.
Ethylbenzene (138°)	25.0	1.4963	0.8671	Olefin-free.
Diethylbenzenes (183–185°)	20.5	1.4978	0.8668	Olefin-free.
Higher ethylbenzenes (200–225°)	12.0	1.5046	0.8779	Olefin-free.
Higher ethylbenzenes (225–245°)	6.5	1.5130	—	Contains some C_6Et_6.
Hexaethylbenzene (>245°)	13.5	—	—	Crystals from C_2H_5OH; m.p. 128.5°.

The water-white product (217 g.) gave, on Podbielniak distillation, the results recorded in Table VII.

The red-brown solid gave, after decomposition with water, a small quantity of higher alkylbenzenes.

From tantalum pentachloride.—After the first half of the elapsed time of treatment the product consisted of a clear yellow upper layer and a liquid red-brown lower layer; at the end of the treatment, only one layer and a sticky red-brown solid were present. The liquid product (237.5 g.) contained only very small quantities of tantalum pentachloride (150 mg. Ta_2O_5). After washing and drying a Podbielniak distillation was carried out (Table VIII).

The red-brown solid, on decomposition with water, gave hydrocarbons (15.0 g.) containing: benzene (*ca.* 17%), ethylbenzene (*ca.* 17%), higher ethylbenzenes; 165–245° (34%), and hexaethylbenzene; m.p. 128° (32%), together with small quantities of unsaturated (easily oxidizable by $KMnO_4$) hydrocarbons.

Other metal halides.—Results with other halides (thorium tetrachloride, hafnium tetrachloride) will be described later.

SUMMARY

New metal halide catalysts, including beryllium chloride, titanium tetrachloride, zirconium tetrachloride, hafnium tetrachloride, thorium tetrachloride, columbium pentachloride, and tantalum pentachloride, have been found for hydrocarbon reactions. The ethylation of benzene with these catalysts and the nature of products obtained have been described.

CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

THE CHEMISTRY OF UNSATURATED STEROIDS. I. THE CONSTITUTION OF CHOLESTERILENE*

HOMER E. STAVELY AND WERNER BERGMANN

Received December 31, 1936

In recent years it has been shown that certain dehydrogenated steroids possess carcinogenic properties. For example, oestrone, a steroid containing one aromatic ring, has been found by Lacassagne[1] to be definitely carcinogenic. In order to discover whether the presence of any particular number and arrangement of double bonds will produce carcinogenicity in steroids an investigation of their stepwise dehydrogenation has been initiated.

The simplest unsaturated hydrocarbons of the C_{27} series are cholestene and coprostene, which contain one double bond each in the $\Delta 5$ and $\Delta 4$ position respectively. At least one of them, cholestene,[2] is not carcinogenic. Of the cholestadienes, several representatives have been described. The structure of all but one of these, 7-dehydrocholestene,[3] is unknown. We have therefore begun our investigation with a study of the structure of the cholestadienes.

In 1849 Zwenger[4] found that the treatment of cholesterol with phosphoric acid yields a hydrocarbon, which however was not sufficiently characterized. In later publications by various authors it has been shown that the elimination of water from cholesterol, either by direct or indirect methods, leads to a hydrocarbon containing two double bonds, which is generally known as cholesterilene. A summary of these methods is contained in Table I. With one exception (method 2) the melting point of cholesterilene has been found to be between 75° and 80°. There is, however, no agreement as to the specific rotation. Values ranging from $+1.45°$ to $-116.2°$ have been recorded.

The elimination of one molecule of water from cholesterol might rea-

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* Aided by a grant from the International Cancer Research Foundation.

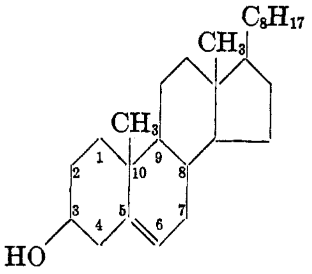
[1] LACASSAGNE, *Compt. rend.*, **195**, 630–2 (1932); LACASSAGNE AND NYKA, *Compt. rend. soc. biol.*, **116**, 844–5 (1934).

[2] BARRY, COOK *et al.*, *Proc. Roy. Soc.* (London), **117B**, 345 (1935).

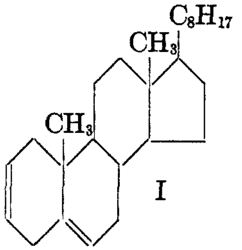
[3] DIMROTH AND TRAUTMANN, *Ber.*, **69**, 673 (1936).

[4] ZWENGER, *Ann.*, **69**, 347 (1849).

sonably lead to the formation of one or more of the three cholestadienes diagrammed below.

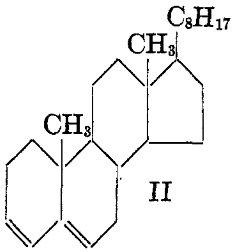


cholesterol



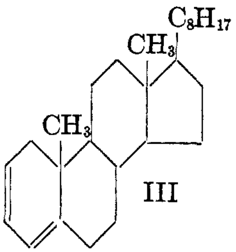
I

2,5-cholestadiene



II

3,5-cholestadiene



III

2,4-cholestadiene

The formation of III would involve a shift of the double bond of cholesterol from the Δ5 to the Δ4 position. Such rearrangement, which involves the formation of a conjugated system of double bonds, occurs during the oxidation of cholesterol to cholestenone.

The best known cholesterilene is that obtained through dehydrogenation of cholesterol with anhydrous copper sulfate. In accord with previous investigators we have found that cholesterilene prepared by method 1 reacts with but one molecule of bromine,[5] that it contains two double bonds,

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[5] Mauthner and Suida, *Monatsh.*, **17**, 34 (1896).

TABLE I

SUMMARY OF THE PREPARATION AND PROPERTIES OF CHOLESTERILENE

NO.	METHOD	M.P. IN °C.	$[\alpha]_D$	REFERENCE
1	Cholesterol + copper sulfate	80	−104	5, 6
2	Cholesterol + zinc dust (distilled)	68, 75	+1.45—−53	7
3	Cholesterol + kieselguhr	79	−47	8
4	Cholesteryl chloride + $NaOC_2H_5$	79–80	−65.9	9, 5
5	Cholesteryl chloride + calciumoxide	79	−61.55	10
6	Cholesteryl chloride + quinoline	77	−86.09	11
7	Cholesteryl chloride + zinc oxide	79–80	−116.2	11
8	Cholesteryl chloride + potassium cholesterolate	79–80		11
9	Cholesteryl bromide + NaI in acetone	77–78	−65.4	12
10	Cholseteryl bromide + NaI + piperidine acetate in acetone	78–79	−103	12
11	Cholesteryl phenylurethane (distilled)	75		13
12	Methylcholesterylxanthate (distilled)	79–80		14, 15, 16
13	Cholesterol + phosphoric acid	79–80.5		4, 5
14	Monocholesteryl phosphate (heated)	76–78	−68.99	17
15	Dicholesteryl phosphate (heated)	78.2	−77.53	17
16	Allo- or epiallocholesterol + HCl	80	−112	18
17	Epicholesterol + HCl	76–77	−78.3	19
18	Reduction of 7-ketocholesterilene semicarbazone	78–79	−63.75	

that it can be hydrogenated catalytically to produce cholestane as the principal product, together with a small amount of coprostane[7, 16, 21], and that it is not reduced by the action of sodium in amyl alcohol.[22] The latter observation eliminates formula III from consideration, as it contains

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[6] HEILBRON, MORTON AND SEXTON, *J. Chem. Soc.*, **1928,** 50.

[7] FANTL, *Monatsh.*, **47,** 256–7 (1926).

[8] STEINKOPF, *J. prakt. Chem.*, **100,** 70 (1920).

[9] WALITSKY, *J. russ. chem. Ges.*, **8,** 237.

[10] MAUTHNER AND SUIDA, *Monatsh.*, **24,** 666 (1903).

[11] STEINKOPF AND BLUMNER, *J. prakt. Chem.*, **84,** 466–7 (1911).

[12] WAGNER-JAURREG AND WERNER, *Z. physiol. Chem.*, **213,** 119 (1932).

[13] BLOCH, *Bull. soc. chim.*, **31,** 73 (1904).

[14] TSCHUGAEV AND GASTEFF, *Ber.*, **42,** 4633 (1902).

[15] TSCHUGAEV AND FOMIN, *Ann.*, **375,** 293 (1910).

[16] BOSE AND DORAN, *J. Chem. Soc.*, **1929,** 2246.

[17] MULLER AND PAGE, *J. Biol. Chem.*, **101,** 128 (1933).

[18] SCHOENHEIMER AND EVANS, *ibid.*, **114,** 568 (1936).

[19] MARKER, KAMM, OAKWOOD AND LAUCIUS, *J. Am. Chem. Soc.*, **58,** 1950 (1936).

[20] HEILBRON, "Dictionary of Organic Compounds," Oxford University Press, New York City, **1934,** Vol. I, p. 337.

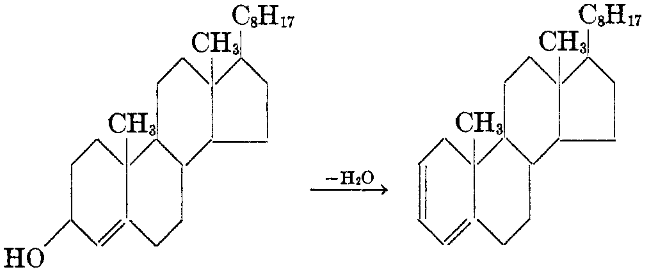
[21] WINDAUS AND SENG, *Z. physiol. Chem.*, **117,** 158 (1921).

[22] HEILBRON, MORTON AND SEXTON, *J. Chem. Soc.*, **1928,** 48.

a conjugated system of double bonds which should be easily reduced by this method. It does not, however, eliminate formula II, whose conjugated double bonds are located in two different rings.

Wagner-Jauregg[12] has found that maleic anhydride does not add to cholesterilene in boiling toluene. We have found that under more drastic conditions, namely the heating of cholesterilene, maleic anhydride, and and xylene in a sealed tube for 12 hours at 135°, addition takes place. As yet we have been able to obtain the acid only as an amorphous white powder which decomposes from 240–245°. Analyses indicate that this material has been formed from one molecule each of cholesterilene and maleic acid. The alkali salts of this substance are extremely insoluble, and in this respect differ from other known maleic acid addition products of steroids. For stereochemical reasons, normal 1,4-addition of maleic anhydride to a substance of formula II is inconceivable. If II is the correct structure for cholesterilene addition would have to take place in some unusual manner.

Schoenheimer and Evans[18] found that allo- and epiallocholesterol, when refluxed with dilute alcoholic hydrochloric acid, lose water rapidly to form a cholestadiene. This substance possessed a melting point and specific rotation similar to those of cholesterilene prepared by method 1. Since, however, the absorption spectrum was different from that given by Heilbron[6] for cholesterilene, the authors felt justified in denying the identity of these two dienes and in assigning structure III to their compound. This substance seemed to be the logical dehydration product of allo- or epiallocholesterol.



allocholesterol 2,4-cholestadiene

However, when we studied the absorption spectrum* of cholesterilene prepared by method 1, we found it to have the same typical absorption maxima at 229, 235 and 244 mμ as Schoenheimer and Evans' hydrocarbon, indicating the identity of these two cholestadienes. That this conclusion

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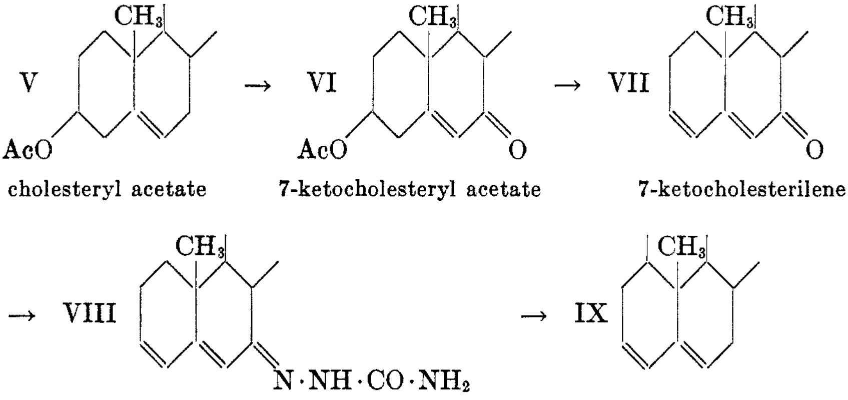
* The authors are greatly indebted to Drs. Schoenheimer and Evans for measuring this and subsequent absorption spectra.

was correct we could further demonstrate by chemical evidence. Like cholesterilene, Schoenheimer and Evans' diene could not be reduced by sodium in amyl alcohol; cholestane and coprostane were the products of catalytic hydrogenation; and maleic anhydride was added in the same unusual manner. Schoenheimer and Evans' hydrocarbon therefore does not possess formula III, but is identical with cholesterilene prepared by method 1.

Of the remaining two possible formulas for cholesterilene, namely I and II, I has been assigned to it by Heilbron,[20] although there is very little evidence to support this view. Because of its high absorption in the ultraviolet, which is indicative of a system of conjugated double bonds, we believe cholesterilene, prepared by method 1 or 16, to possess formula II.

In order to obtain further evidence in support of formula II for cholesterilene we have prepared a cholestadiene by the Wolf-Kishner reduction of 7-ketocholesterilene, which was prepared by the oxidation of cholesteryl acetate with chromium trioxide, and subsequent loss of acetic acid.[23]



cholesteryl acetate

7-ketocholesteryl acetate

7-ketocholesterilene

7-ketocholesterilene semicarbazone

3,5-cholestadiene

The cholestadiene obtained by this method melted at 78–79° and showed $[\alpha]_D = -64°$. Although the specific rotation of this substance is about 50° lower than that of cholesterilene prepared by method 1 or 16, its absorption spectrum is quite similar. On comparing the specific rotations given in Table I, one may separate the cholesterilenes into two groups. Substances prepared by the methods 4, 5, 9, 14, and 18 have rotations between −60 and −70°, while those obtained by methods 1, 7, 10, and 16 have a specific rotation greater than −100°. Since a representative of one group possessed an absorption spectrum similar to that shown by a representative of the other, we are inclined to believe that members of

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[23] Mauthner and Suida, *Monatsh.*, **17**, 496 (1896).

both groups contain the same 3,5-conjugated system. An investigation as to the cause of the differences in rotation is now under way.

EXPERIMENTAL

Preparation of cholesterilene.—Cholesterol was dehydrated according to the method of Mauthner and Suida.[5] After several recrystallizations from ether and ethanol the resulting hydrocarbon melted at 78–79°, and $[\alpha]_D^{20} = -97.5°$ (27.2 mg. in 3.04 cc. $CHCl_3$, 1 dm. tube, $\alpha = -0.88°$).

Properties of Cholesterilene

Reaction with bromine.—When a solution of bromine in glacial acetic acid was added to a solution of cholesterilene in ether, decolorization took place until exactly one mole of bromine had been absorbed. The addition product could not be isolated in crystalline form. When two moles of bromine were added to a solution of cholesterilene a brown liquid was obtained from which even on long standing at low temperature no crystalline bromides separated. Attempts to recover cholesterilene from the bromides according to the method described by Schoenheimer[24] gave only a black, tarry material. This observation is in disagreement with the statement of Marker[19] *et al.* that a tetrabromide of cholesterilene had been prepared. They gave no details concerning the preparation, properties, and composition of this tetrabromide.

Titration with perbenzoic acid.—When treated with perbenzoic acid in the usual manner 0.192 gm. of cholesterilene absorbed 16.5 mg. of oxygen during 48 hours, an amount corresponding to 1.97 double bonds.

Catalytic hydrogenation.—Cholesterilene was hydrogenated in ethyl acetate with platinum oxide as catalyst. The hydrogenated substance was then treated with acetic anhydride and sulfuric acid according to Anderson's[25] method to remove any unsaturated material that might have escaped hydrogenation. The purified saturated material, on recrystallization from ethanol, crystallized in plates. It was identified as cholestane, m.p. 78–79°, $[\alpha]_D^{28} = +22.5°$. From the mother liquors the characteristic needles of coprostane could be isolated, m.p. 58–60° and $[\alpha]_D^{28} = +25.9°$. The yields were 80 per cent. cholestane and 20 per cent. coprostane.

Reaction with maleic anhydride.—When cholesterilene and maleic anhydride were refluxed in benzene for several hours no reaction occurred. Four grams of cholesterilene and 2 g. of maleic anhydride were then dissolved in 15 cc. of xylene, and the mixture was heated in a sealed tube at a temperature of 135° for 12 hours. After cooling, the contents of the tube were evaporated to dryness *in vacuo* and the residue was refluxed with a solution of 3 g. of potassium hydroxide in 40 cc. of methanol for 3 hours. During the saponification a considerable amount of insoluble material was observed. A large volume of water failed to dissolve it. The suspension was extracted thrice with low-boiling petroleum ether to remove any uncondensed material. From the petroleum-ether extract 600 mg. of cholesterilene was recovered.

The insoluble material was filtered, washed with water, and dried. It was a slightly yellow amorphous powder, insoluble in ether, alcohol, benzene, and water. On combustion an ash was obtained, indicating that the substance was a salt. The free acid was prepared by heating the salt with glacial acetic acid at a moderate temperature for a few minutes. Water was then added, and the precipitated acid

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[24] Schoenheimer, *J. Biol. Chem.*, **110**, 461–462 (1935).

[25] Anderson and Nahenhauer, *J. Am. Chem. Soc.*, **46**, 1959 (1924).

was extracted with ether. After washing with water the ether extract was shaken vigorously with a concentrated aqueous solution of sodium bicarbonate, whereby the sodium salt of the acid was precipitated. The entire mixture was centrifuged, and the sodium salt, which formed a solid layer between the ether and water, was filtered, washed with water, ethanol, and ether, dried and extracted with ether in a Soxhlet apparatus. The salt was shaken vigorously with dilute hydrochloric acid and ether, until all liberated acid had been dissolved in the ether. After the ether layer had been removed, washed with water, dried and evaporated, a white amorphous material was obtained. This was redissolved in ether and was precipitated as a snow-white amorphous material by the addition of methanol. Further attempts to crystallize it were unsuccessful. The material decomposed at 240–245°.

Anal. Calc'd for $C_{31}H_{48}O_4$: C, 76.80, H, 9.99. Found: C, 75.90; H, 10.11.

Properties of Schoenheimer and Evans' Hydrocarbon

Treatment with sodium in amyl alcohol.—To 1 g. of hydrocarbon dissolved in boiling amyl alcohol 15 g. of sodium was added over a period of four hours. The product had a m.p. of 80° and $[\alpha]_D = -111°$ (42.2 mg. in 3.04 cc. $CHCl_3$, 1 dm. tube, $\alpha = -1.54°$). No reduction had taken place.

Catalytic reduction.—On hydrogenation with platinum the hydrocarbon gave approximately 85 per cent. cholestane (m.p. 76–78°, and $[\alpha]_D^{20} = +25.5°$) and 15 per cent. coprostane (m.p. 64–66° and $[\alpha]_D^{21} = +24.6°$).

Reaction with maleic anhydride.—The hydrocarbon (4.4 g.) and maleic anhydride (2.4 g.) were treated in the manner described above. In addition to 1.9 g. of uncondensed material, 2.4 g. of an acid was obtained, which in every respect behaved like the acid obtained by the condensation of cholesterilene and maleic anhydride. It decomposed at 240–245°.

Anal. Calc'd for $C_{31}H_{48}O_4$: C, 76.80; H, 9.99. Found: C, 75.79; H, 10.14.

Preparation of 3,5-Cholestadiene

7-Keto-3,5-cholestadiene.—Cholesteryl acetate was oxidized with chromium trioxide according to the directions given by Windaus.[26] Five grams of 7-ketocholesteryl acetate was refluxed for one hour with 100 cc. of absolute ethanol containing 5 cc. of dilute hydrochloric acid. After cooling, the 7-ketocholesterilene was filtered, washed, and recrystallized twice from 95% ethanol.

7-Ketocholesterilene semicarbazone.—7-Ketocholesterilene was refluxed with twice the theoretical amount of semicarbazide in alcohol for 24 hours. After cooling, the semicarbazone was filtered and recrystallized from chloroform and ethanol. It formed long soft yellow needles and melted at 198–200°.

Anal. Calc'd for $C_{28}H_{45}N_3O$: C, 76.40; H, 10.56. Found: C, 76.47; H, 10.52.

Reduction of the semicarbazone.—The semicarbazone was heated in a sealed tube with a solution of an equal weight of sodium in ten times the amount of absolute ethanol for 8 hours at 200°. After cooling, the contents of the tube was dissolved in ether and water, the ether solution was washed with water, dried and evaporated to dryness. The oily residue was twice extracted with boiling absolute ethanol. A resinous substance which could not be obtained in a crystalline form remained. After addition of water to the alcoholic extracts crystals separated; these were recrystallized several times from ether and ethanol or ether and acetone; m.p. 78–79°,

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[26] WINDAUS, LETTRÉ AND SCHENCK, *Ann.*, **520**, 102 (1935).

and $[\alpha]_D^{21} = -63.75°$ (0.0312 g. in 3.04 cc. $CHCl_3$, 1 dm. tube, $\alpha = 65.03°$). The yield of the hydrocarbon was rather small.

SUMMARY

1. A discussion of the literature on the dehydration products of cholesterol has been presented.

2. The cholestadiene of Schoenheimer and Evans has been shown to be identical with the cholesterilene of Mauthner and Suida.

3. 3,5-Cholestadiene has been prepared by the reduction of 7-keto-cholesterilene.

4. Because of its great absorption in the ultraviolet, characteristic of conjugated systems, cholesterilene has been assigned the structure of 3,5-cholestadiene.

[Contribution from the Sterling Chemistry Laboratory of Yale University]

THE CHEMISTRY OF UNSATURATED STEROIDS. II. THE PREPARATION AND PROPERTIES OF 2,4-CHOLESTADIENE*

HOMER E. STAVELY and WERNER BERGMANN

Received December 31, 1936

While looking for an efficient method for the dehydration of cholesterol we found that the distillation of cholesterol over aluminum oxide in vacuo led to a hydrocarbon which differed radically from other cholestadienes. It melted at 63° and showed a specific rotation of +114°. Of all the various methods for the dehydration of cholesterol which have been described by previous investigators, only one,[1] namely the distillation of cholesterol over zinc dust, has led to a crystalline hydrocarbon of positive specific rotation. Since it was, however, only +1.45° we believe that this substance was a mixture of cholesterilene, which has a high negative specific rotation and the new hydrocarbon of $[\alpha]_D = +114°$.

In steroid chemistry, a change of the specific rotation from a negative to a positive value or an increase in dextrorotatory power in general, is indicative of a shift of a double bond from the Δ5 to the Δ4 position. Simple steroids containing a Δ4 bond always have positive rotations, while their isomers, containing Δ5 bonds have negative rotations. No exceptions to this rule have yet been found. The following pairs of isomers illustrate this point (Table I).

TABLE I

Comparison of the Specific Rotations of Steroids Containing a Δ4 or Δ5 Bond

Δ 4	$[\alpha]_D$	Δ 5	$[\alpha]_D$
Pseudocholestene	+62.8°	Cholestene	−54.9°
Allocholesterol	+43.7°	Cholesterol	−37.5°
Epiallocholesterol	+120.8°	Epicholesterol	−35.0°
Cholestenone	+87.6°	Cholesten-5-one-3	−4.2°

In accordance with this rule we have postulated that the new dextrorotatory hydrocarbon contains a Δ4 bond and consequently possesses structure I. That this is the case could be shown by chemical evidence

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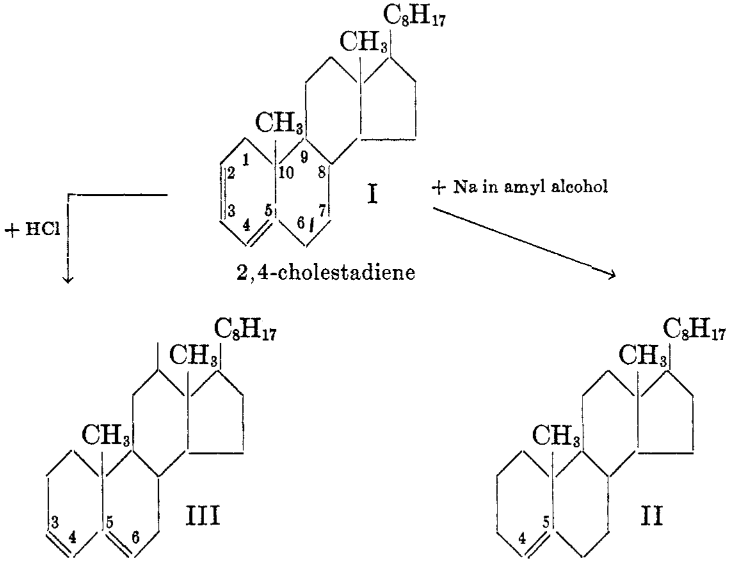
* Aided by a grant from the International Cancer Research Foundation.

[1] Fantl, *Monatsh.*, **47**, 251 (1926).

and by the measurement of the absorption spectrum. Catalytic hydrogenation of the diene in a neutral medium yielded coprostane. This is another indication of the presence of Δ4 bond, since under the conditions chosen derivatives of coprostane are the principal hydrogenation products of Δ4-unsaturated steroids. Under the same conditions derivatives of cholestane are the principal products of Δ5-unsaturated steroids.



2,4-cholestadiene

3,5-cholestadiene (cholesterilene)

cholestene-4 (coprostene or pseudocholestene)

The presence of two double bonds was demonstrated by titration with perbenzoic acid. That the double bonds are conjugated is indicated by the absorption spectrum, which has a maximum at 260 $m\mu$*, and that they are contained in the same ring could be shown by the ease with which maleic anhydride was added. The acid obtained from the addition product is a well-defined crystalline material, which forms easily soluble alkali salts. Further evidence in support of formula I is our observation that the diene can be reduced by sodium in amyl alcohol to yield a monounsaturated hydrocarbon identified as cholestene-4 (pseudocholestene) (II).

In the presence of acids 2,4-cholestadiene rearranged into a laevorotatory cholestadiene, which by its melting point, specific rotation and absorption spectrum was identified as cholesterilene or 3,5-cholestadiene (III). The relative ease with which this rearrangement took place explains why the treatment of allo- or epiallocholesterol[2] with alcoholic hydrochloric acid

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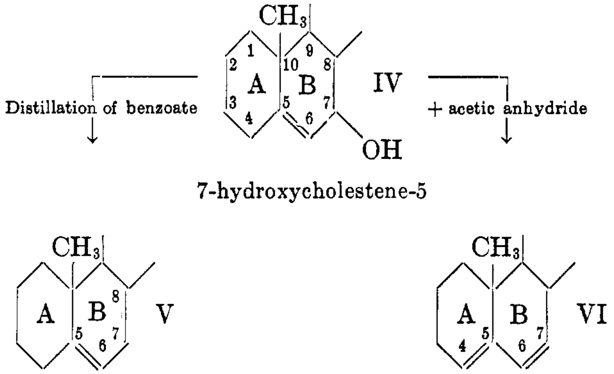
* The authors are greatly indebted to Drs. Schoenheimer and Evans for measuring this and subsequent absorption spectra.

[2] Stavely and Bergmann, J. Org. Chem., **1**, 567 (1936).

does not yield the expected 2,4-diene but its rearrangement product, the 3,5-cholestadiene.

A conjugated system of double bonds located in one ring is apparently less stable in the presence of acids than a system of conjugation extending over two rings. The former has the tendency to rearrange into the latter. This behavior offers an explanation for an observation made by Dimroth and Trautmann[3] in Windaus' laboratory. These authors prepared 7-dehydrocholestene (V) by the vacuum distillation of the benzoate of 7-hydroxycholestene (IV). They found that under certain conditions this reaction leads to the formation of an isomeric hydrocarbon, which could also be prepared by treating 7-hydroxycholestene with acetic anhydride.

That formula V represents the true structure of 7-dehydrocholestene has been shown beyond doubt. No structure has yet been proposed for the isomeric hydrocarbon. Dimroth and Trautmann found that this hydrocarbon possesses a slight positive rotation, as against a strong negative rotation of the 7-dehydrocholestene. For reasons explained above this indicates that a shift of a double bond from the Δ5 to the Δ4 position has taken place. The hydrocarbon shows a maximum absorption at 238mμ quite similar to that of 3,5-cholestadiene. We therefore believe that it has structure VI.



7-hydroxycholestene-5

7-dehydrocholestene-5

4,6-cholestadiene

The formation of this diene is an interesting parallel to the dehydration of allo- or epiallocholesterol with dilute acids.[3] The same conditions which induce a substance containing a conjugated system of double bonds in ring A, such as 2,4-cholestadiene, to undergo rearrangement into its isomer with a conjugation extending over two rings, are effective also in ring B, where in perfect analogy a rearrangement of 5,7 into a 4,6 conjugation takes place.

[3] DIMROTH AND TRAUTMANN, *Ber.*, **69**, 675 (1936).

EXPERIMENTAL

Preparation of 2, 4-cholestadiene.—This hydrocarbon was first obtained by heating 2 g. of cholesterol and 3 g. of aluminum oxide *in vacuo* at 200° for one hour, and distilling the reaction product at 240°. When the distillate was recrystallized from ether and ethanol, a substance was obtained which crystallized in needles and had a m.p. of 59–60° and $[\alpha]_D^{23} = +89.2°$. Subsequent experiments showed that the best yield can be obtained by the following procedure. Three parts of aluminum oxide and two parts of cholesterol are thoroughly mixed and heated in a retort on a metal bath at a temperature of 200–220° for two hours at 1 mm. pressure. The temperature is then raised to 240–270°, whereupon distillation takes place. It is necessary to distill rather slowly. The average yield of hydrocarbon obtained by this method is 30 per cent. If the heating at 200° was carried out for seven hours, on subsequent distillation a laevorotatory hydrocarbon resulted, m.p. 72–74°, $[\alpha]_D^{23} = -56.5°$. In some experiments apparently carried out under identical conditions, cholesterol was recovered unchanged.

After repeated recrystallizations from ether and acetone the 2,4-diene melted at 63°, $[\alpha]_D^{27} = +114.0°$ (46.3 mg. in 3.04 cc. $CHCl_3$, 1 dm. tube, $\alpha = +1.57°$).

Anal. Calc'd $C_{27}H_{44}$: C, 87.96; H, 12.04.
Found: C, 88.01; H, 12.06.

Catalytic hydrogenation.—Nine hundred milligrams of the diene was hydrogenated in ethylacetate, with 250 mg. of platinum oxide as catalyst. The hydrogenated product was freed from traces of unsaturated material with acetic anhydride and sulfuric acid. The purified product crystallized in needles. It was identified as coprostane; m.p. 58–60° and $[\alpha]_D^{29} = +27.2°$. No cholestane was found.

Titration with perbenzoic acid.—By titration with perbenzoic acid in the usual manner, 178 mg. of diene took up 15.1 mg. of oxygen in 48 hours, an amount corresponding to 1.94 double bonds.

Reaction with maleic anhydride.—Three hundred twenty milligrams of diene and 142 mg. of maleic anhydride were refluxed with dry benzene for eight hours. The solvent was removed *in vacuo*, and the residue was hydrolyzed with 20 cc. of a 5% solution of potassium hydroxide in methanol for 3 hours. After the addition of a large volume of water the mixture was extracted with petroleum ether, from which 132 mg. of a crystalline substance was isolated; m.p. 70–72°, $[\alpha]_D^{21} = -77.8°$ (14.4 mg. in 3.04 cc. $CHCl_3$, 1 dm. tube $\alpha = -0.37°$). Hence the uncondensed portion of the dextrorotatory diene had been rearranged into a laevorotatory substance. The aqueous solution was acidified and extracted with ether. A crystalline acid was obtained from the ether extract, which after several recrystallizations from ether and petroleum ether, melted at 268–270° with decomposition. The yield was 15 per cent.

Anal. Calc'd for $C_{31}H_{48}O_4$: C, 76.80; H, 9.99.
Found: C, 76.51; H, 10.03.

A much better yield was obtained when the condensation was carried out in xylene in a sealed tube for 18 hours at 135°. From 5.8 g. of diene and 2.6 g. of maleic anhydride treated in this manner 1.05 g. of rearranged hydrocarbon of m.p. 77–78° and $[\alpha]_D^{20} = -96.6°$ were isolated. The condensation product weighed 3.3 g. (43% yield). It was recrystallized from ether and chloroform, m.p. 268–270°.

Attempts to recover the diene from the addition product by distillation under low pressure failed because the addition product distilled before decomposition took place.

Reduction with sodium in amyl alcohol.—To a solution of 1.2 g. of diene in 100 cc.

of boiling amyl alcohol 18 g. of sodium were added during 4 hours. After cooling, the mixture was diluted with a large volume of water and extracted with ether. The ether was washed, dried, and evaporated to dryness at reduced pressure. The slightly brown residue was purified with Norite, and recrystallized several times from ether and ethanol. The reduction product had a m.p. of 68–70° and $[\alpha]_D^{21} = +61.6°$ (40 mg. in 3.04 cc. $CHCl_3$, 1 dm. tube, $\alpha = +0.94°$).

The material was subjected to a second hydrogenation. It was dissolved in amyl alcohol, and the solution was introduced dropwise during 4 hours into a flask containing 10 g. of sodium in 70 cc. of boiling amyl alcohol. After three recrystallizations from ether and ethanol the reduced material melted at 77–78°, $[\alpha]_D^{20} = +66.9°$ (37.2 mg. in 3.04 cc. $CHCl_3$, 1 dm. tube, $\alpha = +0.82°$). It was identical with cholestene-4 (pseudocholestene or coprostene).

For further identification the dibromide was prepared by adding 1 mole-equivalent of bromine in glacial acetic acid to a weighed amount of the reduction product in ether. After a few seconds the crystalline dibromide separated. It melted at 115–116°. The m.p. of the dibromocholestene-4 is 116–117°.[4]

Anal. Calc'd for $C_{27}H_{44}Br_2$: C, 61.11; H, 8.75.
Found: C, 60.92; H, 8.70.

Rearrangement under the influence of hydrochloric acid.—Three hundred milligrams of diene was refluxed with 20 cc. of 95% ethanol and 0.3 cc. of concentrated hydrochloric acid for six hours. A large volume of water was added, and the mixture was extracted with ether. The ether extract was washed with sodium carbonate solution, then with water, dried, and evaporated to dryness. The residue was recrystallized from ether and ethanol; m.p. 70–72°, $[\alpha]_D^{24} = -52.7°$.

To insure complete rearrangement the substance was subjected to a second treatment with boiling alcoholic hydrochloric acid. After refluxing for 20 hours a substance was isolated which showed a m.p. of 78° and $[\alpha]_D^{23} = -103.8°$ (29.6 mg. in 3.04 cc. $CHCl_3$, 1 dm. tube, $\alpha = -1.01°$). This substance was identical in every respect with 3,5-cholestadiene (cholesterilene).

SUMMARY

1. A dextrorotatory cholestadiene has been prepared by the action of aluminum oxide on cholesterol.
2. It has been demonstrated that this substance is 2,4-cholestadiene.
3. The rearrangement of conjugated double bonds in steroids has been discussed.

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[4] MAUTHNER, *Monatsh.*, **28**, 1124 (1907).

[Contribution from the Sterling Chemistry Laboratory of Yale University]

THE CHEMISTRY OF UNSATURATED STEROIDS. III. THE TITRATION OF UNSATURATED STEROIDS WITH THIOCYANOGEN*

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Aside from catalytic hydrogenation the only satisfactory method for the determination of double bonds in steroids is titration with perbenzoic acid. Since this method requires a considerable amount of time as well as a large sample it seemed desirable to look for another method. As has been shown repeatedly, titration of double bonds with halogen is not suitable in the case of unsaturated steroids because of secondary reactions. Thiocyanogen, however, which has been used successfully in fat chemistry, only adds to certain types of double bonds and never substitutes. For this reason thiocyanogen appeared to be an ideal reagent for the determination of double bonds in steroids and we have therefore carried out several titrations to determine its usefulness.

TABLE I

SUBSTANCE	NUMBER OF DOUBLE BONDS	
	Present	Found
Cholestanone	0	0.1
Cholesteryl chloride	1	0.02
Cholesteryl benzoate	1	0.05
Cholestene-5	1	0.1
Cholestenone	1	0.11
Sitosteryl acetate	1	0.04
Stigmasteryl acetate	2	0.03
Cholesterilene	2	0.99
2,4-Cholestadiene	2	0.95
Ergosteryl acetate	3	2.03

0.1N solution of thiocyanogen in carbon tetrachloride and glacial acetic acid can easily be prepared by the method which has been described by Jamieson.[1] For the determination of double bonds 0.1 to 0.2 gram samples

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[1] Jamieson, "Vegetable Fats and Oils," Chemical Catalog Co., New York City, **1932**, p. 345.

of the steroids were placed in a 250-cc. glass-stoppered Erlenmeyer flask and dissolved in 10 cc. of dry carbon tetrachloride. Twenty-five cubic centimeters of an approximately tenth-normal thiocyanogen solution was added, and the mixture allowed to stand for 24 hours in the dark. Then 10 cc. of a 10 per cent potassium iodide solution was added quickly with shaking. After the mixture had been diluted with 100 cc. of water titration of the liberated iodine was carried out in the usual manner. Two blanks were titrated for comparison.

By this method the results tabulated have been obtained.

The following results were obtained with four aromatic substances which had been titrated for comparison. Phenanthrene and stilbene showed no double bonds, anthracene 0.914, and 1,4-diphenylbutadiene 0.95 double bonds.

These results demonstrate that the usefulness of thiocyanogen for titrations in the field of steroids is rather limited. Double bonds such as Δ4, Δ5, and Δ22, which are frequently present in steroids, do not react with thiocyanogen. On the other hand, if titration with this reagent shows the presence of one or more double bonds, the presence of double bonds other than those mentioned is indicated. In the case of cholesterilene it is probably the Δ3 double bond which reacts. In a system of conjugated double bonds such as is present in ergosterol two double bonds are titrateable. 2,4-Cholestadiene, which is easily rearranged in acid medium to cholesterilene, shows the same number of double bonds as the latter.

SUMMARY

The application of thiocyanogen to the titration of double bonds in steroids has been investigated.

RECENT BOOKS

ORGANIC CHEMISTRY. *Lucius Junius Desha,* Professor of Chemistry in Washington and Lee University. McGraw-Hill Book Co., 330 West 42nd Street, New York City, 1936. xv + 750 pages. 13.5 x 20.5 cm. $3.75.

The author in his introduction states that "This textbook has been written for college students, and primarily for those whose formal instruction ends with a one-year course. . . . The guiding policy has been to consider compounds if, where and as they serve usefully to illustrate and explain the general principles of organic chemistry."

The arrangement of material is, to the best of the reviewer's knowledge, different from that in any elementary organic textbook now on the American market, because of the parallel treatment of aliphatic and aromatic compounds. Thus, we find Part I (one hundred twenty-eight pages) devoted exclusively to hydrocarbons and some of their simpler derivatives, the chapter headings being: saturation and unsaturation (methane, ethane, ethylene, acetylene) isomerism, homology, natural gas and petroleum, ring formation (alicyclic hydrocarbons), the aromatic nucleus (benzene and its homologues), polynuclear hydrocarbons, by-products of coking (diphenyl, naphthalene, anthracene, etc.). Part II (two hundred fifteen pages) is divided into the following chapters: halogen derivatives of the hydrocarbons, hydroxyl derivatives of the hydrocarbons (alcohols and phenols), ethers, carbonyl derivatives of the hydrocarbons (aldehydes and ketones), carboxylic acids, derivatives of the carboxylic acids, amines (aryl amines are discussed before aliphatic amines), organic compounds of sulfur, organometallic and related compounds. Part III (one hundred sixty pages) deals with derivatives of unsaturated hydrocarbons, aliphatic polyhalides, polyhydric alcohols, polybasic acids, substituted acids, derivatives of benzene, toluene and naphthalene, and the more common heterocyclic compounds. Part IV (one hundred six pages), entitled "Special Results of Certain Structures," contains chapters on tautomerism, molecular rearrangements, color and constitution (dyes and dyeing) and stereoisomerism. Natural products, such as the carbohydrates, fats, fatty oils and lipides, proteins and terpenes are taken up in Part V. There is appended a short chapter (twenty-two pages) on the identification of organic compounds.

A summarizing paragraph or two at the end of each chapter, followed by an unusually large number of problems is a noteworthy feature of this well-written book. The subject matter is satisfactorily up to date, and there are very few factual errors. Among these may be noted the following:

p. 92 "Iodine, also, can be introduced by direct substitution (into benzene) . . . ." (an oxidizing agent is required).

p. 236 The statement "In general, when the salt of any acid is strongly heated with soda lime, the product is the hydrocarbon containing one less carbon atom" is not true, at least under the conditions in which these reactions are usually carried out.

p. 345 "This (the double bond) causes it (oleic acid) to add bromine and iodine readily." Iodine does not add to oleic acid. The statements, "Aminoethyl alcohol occurs in cephalin" (*p. 369*) and "piperidine occurs in piperine and in the alkaloid coniine," (*p. 487*) do not convey the intended meaning.

p. 485 ". . . pyridine acts as a tertiary aryl amine" is misleading, since pyridine is much more basic than triphenylamine.

p. 350 The statement that " . . . phenyl radicals retard the rate at which halogen is added at the ethylenic double bond . . . " is not altogether correct, since styrene brominates more rapidly than ethylene (C. K. INGOLD AND E. H. INGOLD, *J. Chem. Soc.*, **1931,** 2354–68.)

p. 488 Isoquinoline cannot be regarded as the parent substance of all of the opium alkaloids (*e.g.*, not of morphine).

p. 522 Absorption spectra measurements alone do not permit one to distinguish with certainty between the lactim and lactam forms of isatin, since a portion of the classical work of Hartley and Dobbie has been shown to be in error (R. G. AULT, E. L. HIRST AND R. A. MORTON, *J. Chem. Soc.*, **1935,** 1653–7.)

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