[Contribution from the Department of Chemistry, University of Notre Dame]

THE PREPARATION AND ALKYLATION OF METAL ACETYLIDES IN LIQUID AMMONIA[*]

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INTRODUCTION

In 1913 Lebeau and Picon[1] reported that 1-alkynes were produced in good yield by the action of certain alkyl iodides on sodium acetylide in liquid ammonia. The synthesis assumed importance when Picon[2] claimed that alkynes prepared by this method were extremely pure and free from products of rearrangement, and that the reaction was general for alkyl iodides as high as $C_{16}H_{33}I$.[3] The ease of manipulation and the ready availability of the necessary materials make this synthesis attractive, and it has accordingly been used by various investigators[4] for the preparation of the lower members of the acetylene series. Hurd and Meinert[5] have shown that the alkyl sulfates may be substituted for the alkyl iodides in the preparation of propyne and 1-butyne.

Lespieau and Journaud[6] have studied the action of allyl halides on sodium acetylide. The principal product is not pentenyne but a complex compound obtained by the action of two or more moles of allyl halide on each mole of sodium acetylide.

Recently Vaughn and Danehy[7] have shown that calcium acetylide may be used in this synthesis in place of sodium acetylide with comparable results.

The principal reaction occurring in this synthesis of alkynes and the only

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[*] Paper XIX on the chemistry of alkyl acetylenes and their addition compounds; previous paper, *J. Am. Chem. Soc.*, **59,** 213 (1937).

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[1] Lebeau and Picon, *Compt. rend.*, **156,** 1077 (1913).

[2] Picon, *ibid.*, **158,** 1184, 1346 (1914).

[3] Picon, *ibid.*, **169,** 32 (1919).

[4] (*a*) Maas and Russell, *J. Am. Chem. Soc.*, **43,** 1227 (1921); (*b*) Hurd, Meinert, and Spence, *ibid.*, **52,** 1138 (1930); (*c*) Heisig, *ibid.*, **53,** 3245 (1931); (*d*) Tchao, *Bull. soc. chim.*, [4], **53,** 687 (1933).

[5] Hurd and Meinert, *J. Am. Chem. Soc.*, **52,** 4540 (1930); **53,** 289 (1931).

[6] Lespieau and Journaud, *Bull. soc. chim.*, [4], **49,** 423 (1931).

[7] Vaughn and Danehy, *Proc. Ind. Acad. Sci.*, **44,** 144 (1935).

one to which much attention has previously been directed is the simple action of the straight-chain alkyl compounds on sodium acetylide to yield the monoalkyl derivative,

$$RX + NaC{\equiv}CH \rightarrow RC{\equiv}CH + NaX$$

As we needed rather large quantities of alkynes for use in research projects, we have made over five hundred separate runs of this general type, and have prepared about 200 liters of alkynes, including 1-propyne, 1-butyne, 1-pentyne, 1-hexyne, 1-heptyne, 1-octyne, 1-nonyne, 1-decyne, and 1-hendecyne. In the course of this work we have applied the reaction to sodium, potassium, barium, and calcium acetylides and to alkyl chlorides, bromides, iodides, and sulfates. Certain improvements in technique have been devised, and a number of by-products, including acetylene, alkenes, alcohols, mono-, di-, and trialkylamines, dialkyl ethers, and dialkylethynes have been identified and their formation explained. Due to lack of space only a few selections from this mass of experimental data can be presented in this article.

PREPARATION AND PROPERTIES OF THE METAL ACETYLIDES

The synthesis of alkali and alkaline earth acetylides in liquid ammonia has usually been conducted by passing acetylene into a previously prepared solution of the metal or metal amide, reaction occurring according to the equations,

$$M + HC{\equiv}CH \rightarrow MC{\equiv}CH + \tfrac{1}{2}\,H_2$$
$$MNH_2 + HC{\equiv}CH \rightarrow MC{\equiv}CH + NH_3.$$

At ordinary pressure the first of these methods is much too slow for the preparation of large quantities of acetylides, while with the second difficulty is encountered in determining the end of the reaction. The preparation of sodium acetylide in an autoclave from sodium in liquid ammonia at room temperature and under acetylene pressures of 100 to 250 p.s.i. has been found to be more rapid. This method, however, has a number of disadvantages, the most important being the great danger of violent explosions, particularly unless air is completely displaced from all parts of the apparatus.

It was found that a far more rapid and satisfactory method for making the metal acetylides consisted in adding the blue solution of the metal in liquid ammonia to a solution of acetylene in liquid ammonia, with stirring and without allowing the entire body of the reacting solution to become blue at any time. Acetylene is apparently not very soluble in boiling liquid ammonia, but is markedly soluble at temperatures below the boiling point at atmospheric pressure, so that concentrated solutions may be obtained either by precooling or by sweeping an excess of acetylene through the ammonia, thus cooling it by evaporation. We have observed that the presence of dissolved metal greatly decreases the rate and extent of solution of acetylene in liquid ammonia and thus retards the reaction. This effect of dissolved metal seems to be general for solutions of many gases in ammonia.

This manner of preparing metal acetylides results in the saving of considerable time. The conversion of 5 moles of sodium (dissolved in 2.5 liters of ammonia) by treatment with acetylene requires 5 to 7 hours for completion. The same amount of sodium may be converted to acetylide in 40 minutes by the new procedure.

The method works equally well with the metals sodium, potassium, calcium, and barium, and acetylides of all these metals[8] have been so prepared for use in this work. Samples of these acetylides were freed from ammonia by evacuation at room temperature and analyzed for metal content. An examination of Table I shows that with the exception of barium acetylide the compounds were very pure.

TABLE I

ANALYSES OF METAL 1-ACETYLIDES

ACETYLIDE	% OF METAL FOUND		% OF METAL CALCULATED
Sodium	47.55	47.65	47.92
Potassium	60.72	60.52	60.74
Calcium	44.80	44.20	44.44
Barium	82.38	84.12	73.40

As expected, these metal acetylides were very unstable in air. The degree of their stability, however, varied considerably. Sodium and potassium acetylides, being the most stable, remain in white crystalline form for approximately 10 hours when exposed to dry air. Under similar conditions calcium acetylide is noticeably decomposed (brown color) after 5 hours. Our samples of barium acetylide were so unstable that they decomposed on standing for a few minutes, even in an atmosphere of ammonia.

Since, as will be shown later, no very significant differences in the reactivities of these acetylides were noted, the cheaper and more soluble sodium acetylide was used in most cases.

Since the total exclusion of air in the preparation of large quantities of sodium acetylide was not attempted, the material always contained some sodium hydroxide due to moisture occurring both in the air and in some

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[8] MOISSAN, *Compt. rend.*, **127**, 911 (1898).

samples of commercial liquid ammonia, and it also undoubtedly contained small amounts of sodium oxide due to atmospheric oxygen. Traces of sodamide may also have been present in some cases since in the absence of excess acetylene, the reaction

$$NaNH_2 + HC{\equiv}CH \rightarrow NaC{\equiv}CH + NH_3$$

may be somewhat reversible. Some few preparations were carried out in iron vessels and in these there was no doubt but that a larger amount of sodamide, which was obtained by the action of ammonia on the metallic sodium in the presence of sodium oxide and iron salts,[9] was present. The acetylene used was from commercial cylinders and was usually passed through a porous alundum cup into concentrated sulfuric acid and then through a sodalime tower, thus removing practically all of the acetone, and obviating the presence of sodium acetone in the acetylide.

EXPERIMENTAL

Preparation of sodium acetylide.—Three (3) liters of liquid ammonia was placed in a 10-liter steel container and saturated with acetylene by bubbling the gas through the ammonia at a very rapid rate for 2 minutes. In a separate container a solution of 300 g. of sodium in 3 liters of liquid ammonia was prepared. This solution was added to the acetylene solution with stirring at such a rate that the entire mixture never became entirely blue at any time. If a slight excess of sodium was inadvertently added the solution was allowed to clear up completely, and was then treated with acetylene for 1 minute before continuation of the additions of metal solution. Ammonia was added as necessary to maintain the volume of the mixture.

Analysis of metal acetylides.—The metal acetylides were analyzed by determining the amount of base liberated upon hydrolysis with water. A small portion of the acetylide solution was taken, and the ammonia was removed from the sample by evaporation through a mercury trap at room temperature. After the sample had evaporated to dryness it was evacuated at room temperature until no more ammonia was evolved. In the case of some of the acetylides, such as barium and calcium, small amounts of impurities such as oxide, chloride, etc. were permitted to settle out of the reaction mixture before a sample was taken.

The dried samples of acetylide were ground by adding glass balls to the flask and rotating by hand for some time. In an atmosphere of nitrogen a sample of 0.1–0.2 g. of the acetylide was placed in a small sample bottle and weighed. The sample bottle was allowed to drop in an upright position into a 500-ml. Erlenmeyer flask containing about 150 ml. of previously boiled, distilled water. A rubber stopper was placed in the mouth of the Erlenmeyer flask, and the sample bottle was opened by shaking. After hydrolysis of the sample the shaking was continued for a few moments until the gas, smoky in appearance, had completely cleared. The basic solution was then titrated with decinormal acid, with phenolphthalein as an indicator. To insure against the presence of ammonia the titrated solutions were treated with an excess of standard base, boiled for ½ hour, and then back-titrated. No ammonia was found in any case.

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[9] VAUGHN, VOGT, AND NIEUWLAND, *J. Am. Chem. Soc.*, **56**, 2120 (1934).

In the analysis of calcium and barium acetylides, 25 ml. of decinormal acid was added to the water used in hydrolysis and the analysis then completed by back-titrating with decinormal sodium hydroxide.

REACTION OF SODIUM ACETYLIDE WITH ALKYL HALIDES AND ALKYL SULFATES IN LIQUID AMMONIA

The reaction of sodium acetylide with a number of alkyl halides has been carried out under a great variety of conditions, and the effect of some of these variables may be stated as follows.

The reactivity of the alkyl halides increases with the atomic weight of the halogen and decreases with the increasing size of the alkyl group, possibly due to the decreasing solubility in liquid ammonia. The reaction with alkyl sulfates is much more rapid than with any of the alkyl halides. Alkyl bromides are in general the most satisfactory for this reaction because they react more rapidly than alkyl chlorides and give smaller quantities of amine by-products than either the iodides or sulfates, and for other reasons which will be given below.

Some of the runs were made in an autoclave at room temperature and above and at pressures of 100 to 250 p.s.i.; some were made at atmospheric pressure and temperatures slightly above −34°C., while still others were made at 25 p.s.i. pressure in an aluminum pressure cooker. Higher temperatures increased the rate of the principal reaction and also that of some of the side reactions such as the formation of alkylamines from ammonia and the alkyl halides. Use of the autoclave obviated a part of the loss of liquid ammonia and of volatile products and by-products by evaporation, although some loss did occur when the pressure in the autoclave was released. A somewhat better recovery of products could be obtained by venting the autoclave through a condenser cooled by liquid ammonia.[10] The final yield of 1-alkynes in a number of cases appeared to be somewhat higher‡ at −34°C. than at higher temperatures.

EXPERIMENTAL

The two experiments that follow may be considered typical of those run at atmospheric and super-atmospheric pressures, respectively.

Preparation of 1-hexyne at atmospheric pressure.‡—Ninety (90) grams of sodium was converted to acetylide in a 5-liter 3-necked flask equipped with a high-speed, mercury-sealed stirrer and a gas-inlet tube, by the procedure previously described.

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‡ Mr. Stefan J. Slanina, who devised this modified procedure, has recently demonstrated that this procedure is capable of producing 80 per cent. yields of hexyne and heptyne in an over-all time of four hours. The essential modifications comprise very effective stirring and recovery of volatile and entrained material. Entrainment may be markedly minimized by mounting a second liquid ammonia-cooled condenser of the coil type above the bulbed condenser.

The gas-inlet tube was then replaced with a dropping funnel, and a liquid-ammonia-cooled reflux condenser[10] was put into place. Then 413 g. of butyl bromide was slowly added during a period of 2.25 hours. During the addition of the bromide it was necessary to add an additional liter of ammonia to maintain the volume of the solution. After stirring for 2.5 hours after the final addition of butyl bromide, during which time it was necessary to add 2 liters of liquid ammonia, the reaction mixture was hydrolyzed by the dropwise addition of 750 ml. of water, the hydrolysis requiring 1.5 hours. The reaction mixture separated into 2 layers, the upper of which was removed, washed with 10% hydrochloric acid until acid to litmus, then with 2% sodium carbonate, and, finally, twice with water. The product, weighing 200 g., was dried over calcium chloride and carefully fractionated through an efficient total condensation column (packed with glass spirals), 1 m. long and 1 cm. in diameter, using a reflux ratio of 10:1. After three fractionations the following fractions were collected:

(1)	70–72°	137 g.
(2)	72–98°	12 g.
(3)	98–102°	15 g.
(4)	residue	25 g.

A bromide analysis of fraction 1 by the sodium-liquid-ammonia method[11] showed that 0.88% of butyl bromide was present. The hexyne is equivalent to a 55.7% yield while the recovery of butyl bromide is 3.7%. By careful fractionation of the residue, 10 g. of dibutyl ether and 10 g. of 5-decyne boiling at 172–5°, were obtained.

Preparation of 1-heptyne in autoclave.—Twelve moles of sodium acetylide suspended in 3 liters of ammonia in a 10-liter steel autoclave, was treated with 12 moles of normal amyl chloride previously cooled by mixing with a small quantity of liquid ammonia. The head of the autoclave was made up as rapidly as possible and stirring started. During 4 hours the pressure gradually rose to 160 p.s.i., this being equivalent to a temperature of about 30°. The pressure was then slowly released, and the reaction mixture was hydrolyzed by addition of water until vigorous bubbling no longer occurred. The top layer which separated was removed, washed with water, dilute hydrochloric acid, and again with water. After drying over calcium chloride the crude product was combined with the product from another run of 11.5 moles and fractionally distilled through a column (packed with glass spirals) 1 m. long and 4 cm. in diameter, using a reflux ratio of 10:1. The following fractions were obtained:

(1)	41–50°	4.5 g.
(2)	50–97°	86 g.
(3)	97–98°	74 g.
(4)	98–99°	1150 g.
(5)	99–100°	187 g.
(6)	100–103°	142 g.
(7)	103–106°	72 g.
(8)	106–115°	84 g.
(9)	residue	104 g.

An analysis of fraction 4 indicated that 5.92% amyl chloride was present. This fraction therefore contained 1082 g. of heptyne, equivalent to a yield of 52.5%. By taking into account the heptyne contained in the other fractions boiling between 50 and 98°, and 99 and 103° the total yield is raised to the order of 60%.

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[10] Vaughn and Pozzi, *J. Chem. Educ.*, **8**, 2433 (1931).

[11] Vaughn and Nieuwland, *Anal. Ed., Ind. Eng. Chem.*, **3**, 274 (1931).

In the preparation of propyne and butyne all runs were made at atmospheric pressure. Various procedures were used for the collection of the alkyne, depending on whether or not it was desired as a gas, in solution, or as a liquid. A typical large-scale procedure will be described.

Preparation of propyne—Apparatus.—A cylindrical steel reaction chamber measuring 15 x 30 in. with a capacity of 23 gal. was used for this preparation. The bottom of this vessel was fitted with a 1.5-in. gate valve to facilitate cleaning, and a 0.5-in. line for the admission of acetylene. A spare 0.5-in. line was also run into the lower side of the vessel so that acetylene might be introduced should the bottom line become clogged. The upper side of the vessel was fitted with a 0.5-in. line for the exit of gases and a 1-in. gate valve for safety release. The removable head of the vessel was fitted with a stirrer driven by a 0.25-H.P. motor. The head also bore a pressure gage and was fitted with a sight glass and a 2-liter dropping funnel that protruded 6 in. into the reaction chamber. This funnel, which was used for the introduction of liquids into the closed reactor, was kept under constant pressure by means of compressed air acting against a column of mercury, in order that materials might be forced into the vessel against slight pressure. The head assembly was fastened to a block and tackle in order that it might be readily lifted and handled.

Although the reaction was run at −34°C. the vessel was not insulated. It was found that the frost formed from the moisture in the air made a rather efficient insulator and that after the vessel had once been cooled, ammonia losses were rather small. The reaction vessel was mounted in a shallow pan which served to collect the melted frost at the end of a run.

The exit gas line of the reactor was connected with a washer which was made from a 22-liter Pyrex flask. The inlet tube of this washer terminated in a perforated bulb which served to break up the gas stream and facilitate washing. In addition to the exit tube for gases, this washer was fitted with an inlet and outlet tube for the wash water which was constantly changed during the run. The gas from this aqueous wash was passed through a vapor trap held at 20° and then into a 2.5-liter wash bottle containing 25% sulfuric acid and an indicator. The exit from the sulfuric acid bottle was connected to an ice-cooled trap and then to three 36 x 2 in. towers connected in series and containing, in order, sodalime, calcium chloride and potassium hydroxide. A mercury manometer, arranged so as to ring an alarm bell in case of a sudden pressure rise, was inserted in the gas line just ahead of the three towers. The outlet from the potassium hydroxide tower was connected to a condenser made up of fifteen 6-in. turns of 0.5-in. black iron pipe. The bottom of this spiral was connected to a 3-liter flask carrying a vent tube, and the entire assembly suspended in a 12 x 22-in. insulated tin container, which was filled with dry ice and acetone.

Process.—After the head of the reactor had been raised out of the way, liquid ammonia was run directly into the reaction vessel from a cylinder mounted on a dolly. Acetylene from a low-pressure generator was passed through a calcium chloride dryer and then admitted through the acetylene inlet, and the ammonia was saturated. During the saturation of the ammonia a solution of sodium metal in ammonia was made up in a separate container. While the passage of acetylene was continued this solution of sodium metal was added to the reaction vessel at such a rate that the entire solution never became blue due to the presence of excess sodium. During the metal addition the mixture was stirred by hand, and when foaming occurred a portable motor-driven stirrer was employed. Attempts were made to add the sodium metal in chunks but it was found that the conversion to acetylide was much slower than was the case with solutions, and considerable trouble due to foaming was encountered. The solution process was highly satisfactory when properly conducted. In converting the sodium to sodium acetylide the end-point was readily determined by noting the disappearance of the blue color of sodium. In every case this end-point was rather carefully observed in order to avoid an excess of acetylene in the solution.

The head was then lowered into place and bolted down. The stirrer was started, and the mixture was allowed to stand from 1 to 2 hours in order to eliminate ethylene and any slight excess of acetylene that might be present. This ethylene, formed from the hydrogen liberated during the preparation of the acetylide, was not present to any large extent but it was necessary to allow time for its removal.

After the elimination of ethylene, the gas exit of the reactor was connected with the washing, drying, and condensing system, and methyl sulfate was added through the separatory funnel at a rate as rapid as the washing system would permit. Propyne was produced and came off with ammonia. Most of this ammonia was removed by the aqueous wash and the remainder by the sulfuric acid washes. A certain loss of propyne occurred during the washing with water, but this was unavoidable. After leaving the sulfuric acid washers, the propyne, which now contained as impurities water vapor and sulfuric acid spray, was passed through the cooled trap to remove the bulk of the entrained acid solution. The gas was then passed through sodalime to complete this removal. Water was then removed by the calcium chloride and potassium hydroxide towers and the propyne was condensed in the carbon dioxide-acetone cooled condenser.

In a typical run of this sort 1200 g. of sodium was converted to acetylide with the use of 18 kg. of liquid ammonia. The solution was then diluted with 30 kg. of ammonia, and 8.5 kg. of dimethyl sulfate was added during 6.5 hours. A yield of 1596 g. of crude propyne, equivalent to 83% of the theoretical yield, was obtained. The purification of this propyne by low-temperature rectification indicated that the principal impurity was acetylene which was present to the extent of about 17%. This gives a corrected yield of 69% of the theoretical.

DISCUSSION

In Table II the yields of alkynes, from what may be regarded as typical experiments, are tabulated. Data on various combinations of acetylides and halides are given. Yields are not strictly reproducible, even within the limits given, but major deviations are not often met with in any given series of runs. The variations indicated in the table are largely due to the various methods of isolation and in part to the formation of by-products.

The yields of alkynes as indicated in Table II are so low that even by taking into account the formation of by-products (to be discussed later) it is evident that losses are encountered at some stage in the procedure. Since loss is most likely to occur during the hydrolysis and separation of the reaction mixture, experiments were conducted in which known amounts of alkynes were dissolved in liquid ammonia and immediately treated with sufficient water to stop boiling at room temperature. The alkyne was then recovered and the loss determined.

The solubility of 1-hexyne in concentrated aqueous ammonia was deter-

TABLE II

YIELDS OF 1-ALKYNES

METAL ACETYLIDE	ALKYL COMPOUND	YIELD ± 5%
Sodium	$(CH_3)_2SO_4$	100[a, e, i]
Sodium	$(CH_3)_2SO_4$	40[b, e]
Sodium	$(CH_3)_2SO_4$	69[g, e]
Sodium	$(C_2H_5)_2SO_4$	100[a, e, i]
Calcium	$(C_2H_5)_2SO_4$	100[a, e, i]
Potassium	$(C_2H_5)_2SO_4$	100[a, e, i]
Sodium	$(C_2H_5)_2SO_4$	52[c, e]
Calcium	$(C_2H_5)_2SO_4$	75[c, e]
Sodium	*n*-C_3H_7Br	44[c, e]
Sodium	*i*-C_3H_7Cl	0[f]
Sodium	*i*-C_3H_7Br	0[e]
Sodium	*n*-C_4H_9Br	47[f]
Sodium	*n*-C_4H_9Br	53[d]
Sodium	*n*-C_4H_9Br	56[e]
Sodium	*n*-C_4H_9Br	80[e, h]
Calcium	*n*-C_4H_9Br	45[f]
Sodium	*n*-$C_5H_{11}Cl$	53[f]
Calcium	*n*-$C_5H_{11}Cl$	56[f]
Sodium	*n*-$C_5H_{11}Br$	56[f]
Potassium	*n*-$C_5H_{11}Br$	54[f]
Calcium	*n*-$C_5H_{11}Br$	31[f]
Barium	*n*-$C_5H_{11}Br$	41[f]
Sodium	*n*-$C_5H_{11}Br$	50[d]
Sodium	*n*-$C_5H_{11}Br$	50[e]
Sodium	*n*-$C_5H_{11}Br$	80[e, h]
Sodium	*n*-$C_6H_{13}Br$	40[f]
Sodium	*cyc.*-$C_6H_{11}Br$	0[f]
Sodium	*n*-$C_7H_{15}Br$	46[f]
Sodium	*n*-$C_8H_{17}Br$	53[f]
Sodium	*n*-$C_9H_{19}Br$	51[f]
Sodium	C_3H_5Cl,Br,I	0[d, e, f]
Sodium	$CH_2{:}CHCl$	0[e, f]
Sodium	$C_6H_5CH_2Cl$	0[f, j]

[a] Collected as gas.

[b] Absorbed in ether at −34°.

[c] Passed through ammonia condenser and liquefied.

[d] Reaction conducted at 25 lb. pressure.

[e] Reaction conducted at atmospheric pressure.

[f] Reaction conducted in autoclave and allowed to come to room temperature.

[g] Liquefied by condenser cooled with solid CO_2-acetone.

[h] See footnote ‡.

[i] Yield based on volume of gaseous product soluble in alkaline mercuric cyanide solution.

[j] Product was a greenish waxy solid,—evidently a mixture of polymers of 3-phenyl-1-propyne.

mined by adding 20 ml. of the compound to a solution made by adding 100 ml. of water to 100 ml. of ammonia and vigorously agitating the mixture. On standing, 19.5 ml. of the alkyne separated, indicating that the solubility of the compound was less than 2.5 per cent. of the amount taken. This experiment was repeated several times with similar results.

That the solubility of alkynes in concentrated aqueous ammonia is low is further demonstrated by the fact that ether extraction of the aqueous layer resulting from the hydrolysis of reaction mixtures does not result in the recovery of substantial amounts of alkynes.

From these data it is evident that the large losses shown in Table III are due to vaporization and entrainment during the addition of the water. Losses are also sustained during release of the pressure on the autoclave after a run at superatmospheric pressures. By passage of the gases (ammonia, acetylene, and alkyne) from the autoclave through water and then through an ammonia-cooled condenser[10] a sufficient amount of alkyne could be recovered to increase the yields by 2 to 7 per cent., depending on the particular alkyne.

TABLE III

RECOVERY OF ALKYNES FROM LIQUID AMMONIA SOLUTIONS

ALKYNE	AMMONIA (ML.)	ALKYNE RECOVERED (ML.)	LOSS, %
20 ml., 1-Hexyne	150	12.75	37
50 ml., 1-Hexyne	250	32.5	35
50 ml., 1-Hexyne	250	39.0	32
50 ml., 1-Heptyne	250	44	12
50 ml., 1-Heptyne	250	44[a]	12
50 ml., 1-Heptyne	250	43.5[b]	13

[a] Water (250 ml.) added dropwise.

[b] Water (250 ml.) added as rapidly as possible.

In attempts to improve yields many variations in conditions attending the preparation of hexyne and heptyne from sodium acetylide and the appropriate bromide were made, and their effect on the reaction determined. A discussion of some of this work will be given.

Volume of solution.—Best results were obtained when 0.5 to 1.0 liter of ammonia was present for every mole of sodium acetylide. The use of smaller amounts of ammonia lowered the yield by reducing the extent of reaction. This is shown by the recovery of large amounts of alkyl bromide from these runs. Larger amounts of ammonia lowered the yield by increasing the amount of loss due to vaporization and entrainment.

The presence of adequate amounts of ammonia during hydrolysis was necessary to prevent rearrangement of the alkyne by the concentrated (and in extreme cases, hot) sodium hydroxide[12] produced. While preparing 1-hexyne, Hurd[13] observed that addition of water to the crude reaction product *after* removal of ammonia gives a product boiling at 71–72°, but containing only 79 per cent. of hexyne. It is likely that the impurities are rearranged products.

Time of reaction.—Several experiments were run at atmospheric pressure with moderate agitation to determine the optimum time of reaction. Data from these experiments are given in Table IV. All variables other than time of reaction were, of course, stabilized during these experiments.

These data indicate that 2 hours is sufficient time for reaction to occur to its maximum extent at atmospheric pressure, and that longer standing results in loss of alkyne by evaporation and entrainment.

In experiments run in the autoclave maximum reaction seemed to take place within the time the reaction mixture required to rise to room temperature. In preparative work, however, we have customarily allowed such mixtures to stand for at least 30 minutes before reducing the pressure. Allowing such runs to stand for longer times (overnight) did not affect the yield.

TABLE IV

EFFECT OF TIME OF REACTION ON YIELD OF 1-HEXYNE

TIME (IN MINUTES)	% YIELD
10	6.7
20	14.3
30	24.1
60	32.8
120	37.8
180	37.0
1440	15.7

Stirring.—At atmospheric pressure vigorous stirring was essential to good results. The more nearly homogeneous the reaction mixture the higher the yield of alkyne obtained.

In runs in the autoclave stirring greatly reduced the time of reaction. A well-stirred mixture proceeded to maximum reaction in about one-tenth the time required for an unstirred mixture. Stirring did not seem to produce any effect on the yields obtained from autoclave runs.

Use of solvents.—Several attempts were made to replace a part of the liquid ammonia with an organic solvent. In experiments at atmospheric

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[12] FAVORSKII, *J. Prakt. Chem.*, [2], **37**, 531 (1888); *ibid.*, [2], **44**, 208 (1891).

[13] HURD, Private communication, Dec. 13, 1934.

pressure the use of small amounts of ether produced no effect on the yield but gave some apparent increase in the rate of reaction by causing the two phases of the reaction mixture to disperse more readily. Increasing amounts of ether decreased the yield. In a solution containing 50 per cent. of ether and 50 per cent. of ammonia reaction proceeded too slowly to be practical.

The addition of 15 per cent. of dichlorodiethyl ether to the ammonia lowered the yield of alkyne by one-third. This substance also caused the formation during hydrolysis of emulsions which were difficult to break.

Addition of anhydrous ethylenediamine destroyed the sodium acetylide, presumably by the formation of sodium ethylenediamine with evolution of acetylene.

Addition of various materials.—In the synthesis of 1-heptyne the addition of water to the extent of 10 g. per mole of acetylide decreased the yield of alkyne by 50 per cent., while the same amount of *n*-pentanol reduced the yield by one-third.

Excess alkyl bromide did not increase the yield of alkyne, and there is some evidence that large excesses decrease the yield slightly. Large excesses of sodium acetylide lowered the yield slightly. The addition of sodium bromide in amounts above 1 mole per mole of sodium acetylide decreased the yield of alkyne somewhat, probably due to its effect in decreasing the solubility of sodium acetylide in ammonia and its salting-out action on the alkyl halide. Initial concentrations of sodium bromide similar to those resulting from the reaction of the alkyl bromide and the acetylide had no effect on the yield of alkyne.

The addition of calcium chloride to the extent of 0.5 mole per mole of acetylide did not affect the yield of alkyne. It was, however, necessary to increase the amount of ammonia when the salt was used, because of its ammonation.

With a given acetylide and halide various metals appear to have no influence on the reaction, for it has been carried out in vessels of glass, cadmium, aluminum, and iron, both rusty and bright, without any apparent difference. Likewise, stirrers of Monel metal, nickel, brass, and glass produced no discernible effects.

Alkyl halides as impurities in 1-alkynes.—The higher alkynes prepared by this reaction from alkyl bromides and chlorides were always contaminated with unreacted halide which we have been unable to remove completely by distillation, even through highly efficient fractionating columns. This contamination is most serious with chlorides because of the closeness of their boiling points to those of the corresponding 1-alkynes and because of their lower reactivity with ammonia and sodium acetylide. The amount of alkyl halide in the 1-alkyne is usually between 0.5 and 1 per cent. with bromides, and 5 and 20 per cent. for chlorides. The use of a large excess of sodium acetylide did not have much effect in reducing the unreacted halide but some improvement resulted from thorough stirring of the reaction mixture.

A number of attempts were made to remove this alkyl halide by chemical means. Refluxing with pyridine or with magnesium for from 2 to 5 hours failed to eliminate the halides. Refluxing for 6 hours with aniline in the presence of *p*-toluenesulfonic acid and anthranilic acid had no effect on the chlorides but caused a material decrease in bromides. Refluxing for 5 hours with an excess of 50 per cent. alcoholic potassium hydroxide was effective, giving an 85 to 90 per cent. reduction in bromide content. Alcoholic sodium hydroxide is not as good as the potassium compound but does give some reduction of both bromides and chlorides. This method, however, is open to some objection, as rearrangement may take place during the treatment.[12] Treatment with sufficient sodamide in liquid ammonia to convert the alkyne to alkynylsodium and the alkyl halide to alkene and alkylamines gave a product containing only a trace of halide. Sodium metal in ammonia destroyed all of the alkyl halide but the alkynes recovered from this treatment were contaminated with alkenes.[24]

This presence of unreacted alkyl halide was found to be the most objectionable feature of the method as a source of *pure* alkynes because halide impurities were found to be the most difficult of any to remove from the finished product. For most purposes, fortunately, the presence of small amounts of alkyl halide in the alkyne is of no consequence. Because of this no persistent effort was made to overcome this difficulty.

SIDE REACTIONS

As has been previously stated, in the course of this work, several commonly occurring by-products, which appear to have been overlooked by other workers, were separated and identified. A number of attempts were also made to prevent or control the formation of these by-products which consist principally of alkenes, alkylamines, acetylene, dialkyl ethers, and dialkylethynes.

Alkenes.—It has been known since 1919 that secondary and tertiary alkyl halides,[14] as well as primary alkyl halides having a side chain on either of the two adjacent carbon atoms,[15] give only traces of 1-alkynes with sodium acetylide, but are dehydrohalogenated, giving alkenes:

$$H_3C-CHXR + NaC\equiv CH \rightarrow CH_2=CHR + NaX + C_2H_2$$
$$RR'HC-CH_2X + NaC\equiv CH \rightarrow RR'C=CH_2 + NaX + C_2H_2.$$

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[14] PICON, *Compt. rend.*, **168**, 825 (1919).

[15] PICON, *ibid.*, **168**, 894 (1919).

It has not been previously pointed out, and has in fact been denied,[16] that straight-chain primary alkyl halides may react in this way. It has been our experience that the halides higher than ethyl gave a considerable proportion of 1-alkene by this method:

$$RCH_2-CH_2X + NaC\equiv CH \rightarrow RCH=CH_2 + NaX + C_2H_2.$$

Amyl bromide, for example, often gave yields of as much as 8 per cent., and occasionally 20 per cent., of an amylene which was shown by reactions as well as physical properties to be 1-pentene. Similar yields of other alkenes were also sometimes obtained. Cyclohexyl bromide reacted as a secondary halide, giving no alkyne and moderate yields of cyclohexene. Dimethyl and diethyl sulfates gave only very small amounts of ethylene, less than 0.5 per cent. being found.

It should be noted that saturated solutions containing undissolved sodium acetylide were used in most of this work. In a few cases where calcium acetylide was employed the production of alkene appeared to be diminished. From this point of view the reactions of more dilute solutions of sodium acetylide and of other less soluble acetylides should be investigated in the future.

The proportion of alkene appeared to be somewhat characteristic for each alkyl halide, but no exact correlation has been found as yet between the physical conditions of experiment and the varying yields of alkenes. The alkenes may also have resulted in part from the reaction of alkyl halides with sodamide, sodium hydroxide, or sodium alcoholates which were sometimes present.

Amines.—It has been reported[17] that the lower alkyl halides react with liquid ammonia, yielding mixtures of primary, secondary and tertiary alkylamines, and tetraalkylammonium halides. We have found that the higher alkyl halides react in similar fashion, and that in the presence of sodium acetylide this reaction is competitive with the reaction yielding the alkynes. The alkyl iodides reacted most rapidly with ammonia, with the bromides and chlorides following in decreasing order. Temperature appeared to be an important factor in controlling the rapidity of amine formation. At −34° and atmospheric pressure, the reaction between ammonia and butyl bromide, for example, was rather slow, but at −18° and two atmospheres pressure it was 91 per cent. complete in 3 hours, while at ten atmospheres, due to conservation of the heat of reaction in the autoclave, it was practically complete in 1 hour. Accordingly in the preparation of alkynes from alkyl chlorides or bromides at temperatures slightly above −34° this side reaction causes little loss, but at 25° it may account

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[16] PICON, *ibid.*, **169**, 32 (1919).

[17] PICON, *Bull. soc. chim.*, [4], **35**, 979 (1924).

for 10 to 15 per cent. of the alkyl bromide used. If it was desired to conserve the alkyl halide the use of the autoclave was, therefore, less advantageous than reaction at lower temperatures and pressures. On the other hand, if it was desired to eliminate as amine practically all of the alkyl halide not consumed in the principal reaction, the use of the autoclave with stirring gave the most satisfactory results.

Some amines may possibly have resulted from the reaction of alkyl halides with sodamide[17] which, as previously mentioned, may have existed in a small proportion in equilibrium with sodium acetylide in liquid ammonia solution,

$$NaC{\equiv}CH + NH_3 \rightleftharpoons NaNH_2 + C_2H_2$$

or which may have been formed from sodium and ammonia as previously mentioned.

In order to remove the amines from the alkynes and other products, the crude upper layer obtained from the reaction mixture was washed with dilute hydrochloric acid until acid, and then with water to remove the amine hydrochlorides which are somewhat soluble in the crude product. The omission of the washing with water led to the contamination of the distilled product with amine hydrochlorides, which dissociate during distillation and are re-formed on condensation.

Isolation of alkylamines.—The acid and water washes obtained in the treatment of crude alkynes were combined and treated with an excess of solid sodium hydroxide. The upper layer which separated was removed, dried over solid potassium hydroxide and distilled, cuts being made at points appropriate for the amines being collected. In this manner yields of butyl- and amylamines varying from 2 to 15 per cent. were obtained from various alkyne runs.

The amines obtained as by-products usually consisted of about equal proportions of the mono- and dialkylamines with variable quantities of the trialkyl compounds.

Acetylene.—The ammonium halide or sulfate formed in the ammonolysis of the alkyl esters to amines would be expected to react as an acid in liquid ammonia, and attack the sodium acetylide, with the liberation of acetylene.

$$NaC{\equiv}CH + NH_4X \rightarrow C_2H_2 + NH_3 + NaX$$

Maas and Russell[4] have claimed that propyne prepared from sodium acetylide and methyl iodide in liquid ammonia does not give a positive test for acetylene by the procedure developed by Berthelot,[18] while Tchao,[4d] states that 1-butyne prepared by this method contains small amounts of acetylene.

[18] BERTHELOT, *Ann. chim. phys.*, [4], **9**, 423 (1866).

It has been our experience that acetylene is practically always one of the products obtained in this reaction. While we have made no effort to measure the extent of acetylene formation with any accuracy, considerable quantities are formed. It will be recalled that in the experiment detailing the preparation of propyne 17 per cent. of the crude reaction product was acetylene.

In one preparation of 1-hexyne in the autoclave at room temperature, employing 5 moles of butyl bromide and other reactants, 2.5 liters of acetylene was contained in the gas evolved on releasing the pressure. This corresponds to a yield of 2 per cent. of the theoretical, assuming that all the alkyl halide reacts to form ammonium halide which in turn reacts completely with sodium acetylide. Since acetylene is very soluble in liquid ammonia, it is obvious that a still larger amount of this substance remained in solution and that the yield was actually much higher.

The removal of acetylene from alkynes causes no difficulty, as mere fractionation suffices in every instance to give good separation.

Ethers.—Unless extraordinary precautions are taken to exclude water, alcohols, and sodium hydroxide from the starting materials in this synthesis, ethers are always among the products of the reaction of alkyl halides and sodium acetylide in liquid ammonia. We have recently shown[19] that alcoholates and alkyl halides interact in liquid ammonia to give ethers by the well-known Williamson reaction. These ethers result from a series of reactions that may be represented by the scheme,

$$H_2O \xrightarrow{HC_2Na} NaOH \xrightarrow{RX} ROH \xrightarrow{HC_2Na} RONa \xrightarrow{RX} ROR.$$

The quantities of ether obtained are obviously dependent upon the amounts of water and other hydroxylic impurities present in the starting materials. With the usual precautions to exclude these compounds, yields of dialkyl ether of the order of 1 to 5 per cent. are ordinarily obtained. The ethers may be readily isolated in a pure condition by the fractionation of the residues from the distillation of the crude alkynes.

Alcohols.—As would be expected, ether formation is not always entirely complete, and an excess of alcoholate generally remains at the end of the reaction. This alcoholate upon hydrolysis, of course, gives the corresponding alcohol. We have in several instances actually isolated small amounts of amyl alcohol from residues from the distillation of 1-heptyne. The amount of this material usually represents less than 1 per cent. of the alkyl halide taken, although at times it reached 10 per cent. Because of the depressing action of alcohols on the yields of alkynes even these small amounts of alcohols may be of importance.

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[19] VAUGHN, VOGT, AND NIEUWLAND, *J. Am. Chem. Soc.*, 57, 510 (1935).

Dialkylethynes.—Some dialkylethyne nearly always resulted from the action of sodium acetylide with an alkyl halide in liquid ammonia. Butyl and amyl bromides for example, usually yielded 2.4 to 2.7 per cent of dialkylethyne, although on one occasion 30 per cent. was obtained.

Dialkylethynes have been reported[20] previously among the products of the action of alkyl halides on the Grignard reagent derived from acetylene. This reagent has been considered to be a mixture of the compounds $HC{\equiv}CMgX$ and $XMgC{\equiv}CMgX$, in a proportion dependent on the conditions of experiment, and the percentage of dialkylethyne produced from from it has been looked upon as being a measure of the quantity of $XMgC{\equiv}CMgX$ present.[21]

Previous work[8] as well as our own results indicate that the sodium acetylide prepared in liquid ammonia was substantially free from sodium carbide, $Na{-}C{\equiv}C{-}Na$. Enough could scarcely have been present to account for the yields of dialkylethynes obtained. It was concluded that the following series of reactions was largely responsible for the production of dialkylethynes:

$$(1)\ RX + MC{\equiv}CH \rightarrow RC{\equiv}CH + MX;$$
$$(2)\ RC{\equiv}CH + MC{\equiv}CH \rightleftharpoons RC{\equiv}CM + C_2H_2;$$
$$(3)\ RC{\equiv}CM + RX \rightarrow RC{\equiv}CR + MX.$$

Reactions of type (3) have been reported by others,[4c, 4d, 27, 28] and confirmed by us in the course of the present work. The existence of reactions of type (2) was proved by treating a solution of potassium acetylide in liquid ammonia with a number of monosubstituted ethynes and noting the instantaneous precipitation of the corresponding potassium salt. Thus, with 1-heptyne a precipitate of heptynylpotassium was obtained, which, after filtration and washing with liquid ammonia, was hydrolyzed. The recovered 1-heptyne was identified from the melting point of its mercury derivative.[22] Only scanty precipitates of the apparently more soluble sodium compounds were observed, but in this case equilibrium between the ions $(C{\equiv}CH)^-$ and $(C{\equiv}CR)^-$ and the corresponding 1-alkynes probably existed in solution.

The dialkylethynes obtained from the acetylenic Grignard reagent possibly may be accounted for by a similar set of reactions (particularly in view of the fact that pure $XMgC{\equiv}CMgX$ has been shown not to react with alkyl halides[23]). It follows also that the proportion of mono- and dimetallic acetylides in any mixture such as the acetylenic Grignard

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[20] GRIGNARD, LAPAYRE, AND FAKI, *Compt. rend.*, **187**, 517 (1928).

[21] FAKI, *Contrib. Inst. Chem. Natl. Peiping*, **1**, 127 (1934).

[22] JOHNSON AND MCEWEN, *J. Am. Chem. Soc.*, **48**, 469 (1926).

[23] VAUGHN AND NIEUWLAND, to be published.

reagent cannot be safely estimated from the proportion of the derived mono- and disubstituted ethynes.

Among the factors that should influence the yield of dialkylethynes from the proposed mechanism, there was considered the proportions of acetylene and alkyne in solution, the comparative solubility and ionization of their metal salts, and the quantity of solvent ammonia. The most obvious method of decreasing the by-production of dialkylethynes is the use of excess acetylene in solution, and conversely, continuous removal of acetylene during reaction should give increased yields of dialkylethynes. Further experiments along these lines will be attempted.

The properties of the disubstituted ethynes that we have isolated from the residues from the distillation of crude 1-alkynes are listed in Table V.

Other impurities.—Besides the by-products discussed above, small quantities of other substances were sometimes present. Among these were probably dimethylethynylcarbinol and other condensation products arising from the acetone present in Prest-O-Lite acetylene. In view of the isomerization of alkynes with both sodamide and sodium hydroxide, it seems quite possible that the shift of hydrogen atoms along the carbon chain under the influence of sodium acetylide or other alkalies may have been responsible for small quantities of by-products. Traces of sodium peroxide resulting from the action of the air on sodium solutions may have produced by-products by the oxidation or polymerization of the alkynes. The distillation of the higher-boiling alkynes usually caused polymerization of a small fraction of the material.

TABLE V

PROPERTIES OF DIALKYLETHYNES

ALKYNE	B.P., °C.	d_{25}	n^{25}_{D}	MR_D	
				Found	Calc'd
4-Octyne	130.4–130.6/745 mm.	0.7484	1.4226	37.4	37.2
5-Decyne	105.2–105.8/ 79 mm. 172/745 mm.	0.7692	1.4311	46.5	46.4
6-Dodecyne	97.0–98.0/16 mm. 209/745 mm.	0.7753[a]	1.4351[a]	55.9	55.6

[a] At 30°.

RELATIVE REACTIVITY OF VARIOUS ACETYLIDES

The relative order of activity of potassium, sodium, calcium and barium acetylides with respect to alkyl halides in liquid ammonia was determined.[29] Separate runs with each acetylide were made in the same autoclave, all variables being held constant so far as possible. The rate of pressure increase in each of these experiments was measured and plotted. It was found that the slopes of the various curves were, within the limits of error, equal. There was, however, some difference in the time required for initiation of reaction. This indicates that different temperatures are necessary to initiate the reaction with various acetylides. The order of reactivity as indicated by this lag in reaction is, in decreasing order, potassium, sodium, calcium, and barium acetylide. The data on barium acetylide are not as accurate as might be desired in view of the difficulty of obtaining pure barium acetylide. The yields of alkynes obtained in these experiments are shown in Table VI.

With all these acetylides, the side reactions previously mentioned take place. No accurate data as to the extent of these side reactions and their dependence on the character of the acetylide used, were collected.

TABLE VI

YIELDS WITH METAL ACETYLIDES

ACETYLIDE	% OF 1-HEPTYNE	% OF 6-DODECYNE
Potassium	54	—
Sodium	50	—
Barium	41	—
Calcium	31	7

PREPARATION OF SODIUM ALKYNYLIDES IN LIQUID AMMONIA

Several workers[24] have reported that 1-alkynes are hydrogenated by sodium in ammonia, simultaneously with the formation of the sodium derivative. Picon[25] has advocated the use of sodamide in the preparation of alkynylides to avoid these hydrogenation losses. Work in these laboratories has shown that sodium in ammonia does hydrogenate 1-alkynes, but not to the extent previously reported. The losses, however, are serious enough to justify the use of sodamide, which in ammonia solution has lately been made available.[9] The conversion of amide to alkynylide is rapid and complete at atmospheric pressure.

PREPARATION OF DIALKYLETHYNES

Although it has been known for a number of years that sodium alkynylides can be alkylated by methyl sulfate in ether with the production of

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[24] MOISSAN, *Compt. rend.*, **127**, 911 (1898); LEBEAU AND PICON, *ibid.*, **157**, 137, 223 (1913).

[25] PICON, *ibid.*, **173**, 155 (1921); *Bull. soc. chim.*, **29**, 709 (1921).

very good yields of dialkylethynes,[26] it is only recently[4c, 27, 4d] that attempts have been made to carry out this reaction in liquid ammonia. Heisig,[4c] and Heisig and Davis[28] have reported that propynylsodium can be alkylated by either methyl iodide or dimethyl sulfate, a yield of 36 per cent of 2-butyne being obtained from the iodide. We have prepared a unmber of dialkylethynes by this reaction, the sodium alkynylides being prepared from the alkynes and sodamide in liquid ammonia. Various halides and sulfates have been used. Data on yields are included in Table VII.

TABLE VII

YIELDS OF DIALKYLETHYNES

METALLIC COMPOUND	ALKYL COMPOUND	YIELD ± 5%
$PrC\equiv CNa$	PrBr	45[a]
$BuC\equiv CNa$	MeI	38[b]
$BuC\equiv CNa$	EtCl	17[b]
$BuC\equiv CNa$	Et_2SO_4	29[b]
$BuC\equiv CNa$	PrBr	45[b]
$BuC\equiv CNa$	BuBr	54[a]
$AmC\equiv CNa$	MeI	36[b]
$AmC\equiv CNa$	Me_2SO_4	17[b]
$AmC\equiv CNa$	Et_2SO_4	23[b]
$AmC\equiv CNa$	EtCl	24[b]
$AmC\equiv CNa$	EtBr	54[b]
$AmC\equiv CNa$	PrBr	42[a]
$AmC\equiv CNa$	AmCl	56[a]
$AmC\equiv CNa$	AmBr	58[a]
$PhC\equiv CNa$	MeI	43[b]

[a] Reaction conducted in autoclave and allowed to come to room temperature.

[b] Reaction conducted at atmospheric pressure.

TABLE VIII

PHYSICAL PROPERTIES OF DIALKYLETHYNES

ALKYNE	B.P. AT 750 MM.	n_D^{25}	d_{25}
$BuC\equiv CMe$	107–111°	1.4220	0.745
$BuC\equiv CEt$	127–130	1.4273	0.763
$BuC\equiv CPr$	150–154	1.4296	0.757
$AmC\equiv CMe$	131–135	1.4285	0.761
$AmC\equiv CEt$	150–154	1.4300	0.762

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[26] BOURGUEL, *Ann. chim.*, [10], **3**, 191 (1925); *Compt. rend.*, **179**, 686 (1934).

[27] JACOBSON AND CAROTHERS, *J. Am. Chem. Soc.*, **55**, 1622 (1933).

[28] HEISIG AND DAVIS, *ibid.*, **57**, 339 (1935).

It will be seen that with the lower alkyl esters good yields were not generally obtained at atmospheric pressure. With the higher alkyl esters, however, and the use of an autoclave, moderate yields were produced. These yields, however, are not so good as those claimed by Bourguel for the reaction when conducted in ether.

The nature of the alkyl group in the alkyne did not seem to influence the yield of the product to any great extent. The negative group of the alkylating agent did seem to influence the yield of the product. Alkyl bromides were the most effective reagents for this reaction, the iodides, sulfates and chlorides following in the order named.

The physical properties of the dialkylethynes not listed in Table V have been collected in Table VIII.

EXPERIMENTAL

Since the preparation of dialkylethynes at atmospheric pressure has been described elsewhere,[4c, 27, 28, 9] only the procedure used in preparing these compounds in the autoclave will be described.

Preparation of 6-dodecyne.—A solution of 125 g. of sodium in 2 liters of liquid ammonia contained in a 10-liter steel autoclave was treated with 2 g. of ferric nitrate and 1 g. of sodium peroxide. A rapid reaction set in, and in 50 minutes the sodium metal was completely converted to sodamide. 1-Heptyne (480 g.) containing as an impurity 6% of amyl chloride was dropped into this well-stirred solution during 45 minutes, a liter of ammonia being added during the same time in order to increase slightly the volume of the solution and maintain it in a fluid condition. Amyl chloride (432 g.) was added to the suspension of heptynylsodium, and the autoclave was closed. After stirring for 1 hour, at which time the pressure had reached 160 p.s.i., the reaction mixture was allowed to stand overnight. The autoclave was opened, and the reaction mixture was hydrolyzed with 2 liters of water. The large oily layer that separated was removed, washed with 1:3 hydrochloric acid and then twice with water. It was then dried over calcium chloride and distilled through an efficient column. The fractions collected were as follows:

(1)	33–95°	6 g.
(2)	95–105°	97 g.
(3)	105–115°	67 g.
(4)	115–100° at 15 mm.	18 g.
(5)	100° at 15 mm.	460 g.
(6)	residue	16 g.

The over-all yield of 6-dodecyne corresponds to 59% of the theoretical. Analysis of fraction 2 indicated that 60 g. of 1-heptyne was recovered, thus giving a net yield of 6-dodecyne of 68%. The side reactions previously mentioned all take place, but contamination of the dodecyne with alkyl halide is not a serious problem because of the wide difference in boiling points.

ACKNOWLEDGMENT

Grateful acknowledgment is made of the help of numerous students in conducting portions of the experimental work reported here. Particular thanks are also due Drs. D. B. Killian, J. P. Danehy, A. S. Young and Messrs. P. A. Sartoretto,[29] S. J. Slanina, J. W. Kroeger, T. J. Tobin[30] and M. J. Geerts.[30] The courtesy of the Union Carbide and Carbon Research Laboratories, Inc. in permitting the completion and checking of certain work is also acknowledged.

CONCLUSION

The well-known reaction of metal alkynylides with alkyl halides and sulfates in liquid ammonia has been studied over a wide variety of conditions and has been applied to the synthesis of a large number of mono- and dialkylethynes. The principal disadvantage of this method for preparing 1-alkynes lies in the presence of small amounts of alkyl halides in the product. A new and rapid method for the preparation of metal alkynylides has been developed. The relative reactivities of potassium, sodium, barium, and calcium acetylides to alkyl chlorides, bromides, iodides and sulfates have been studied. A number of by-products, overlooked by other workers in the field, have been isolated and identified.

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[29] SARTORETTO, M. S. Thesis, University of Notre Dame, 1934.

[30] TOBIN AND GEERTS, B. S. Theses, University of Notre Dame, 1936.

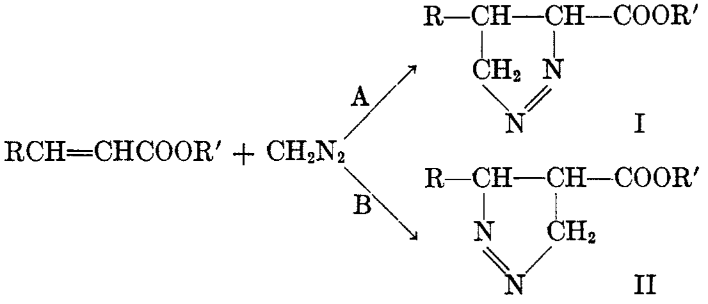
[Contribution from the School of Chemistry of the University of Minnesota]

THE ACTION OF DIAZOMETHANE UPON α,β-UNSATURATED KETONES. I. BENZALACETOPHENONE

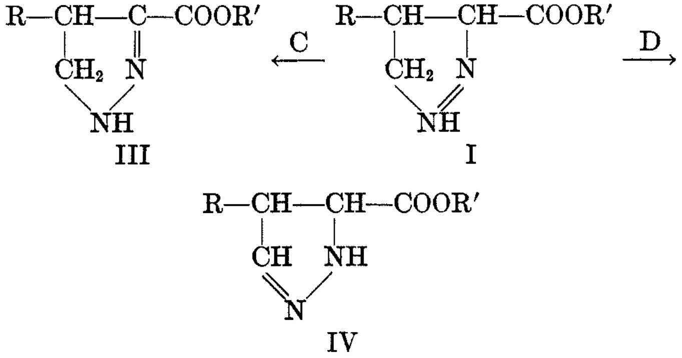
LEE IRVIN SMITH and W. B. PINGS

Received January 26, 1937

It has been shown by von Auwers[1] that the addition of diazomethane to α,β-unsaturated esters proceeds in such a way that the nitrogen atoms become attached to the α-carbon atom, *i.e.*, the reaction follows scheme A rather than B.



von Auwers (*loc. cit.*) also showed that under the influence of certain reagents (such as halogen acids), the Δ^1-pyrazolines first formed could be changed to the isomeric Δ^2-pyrazolines and that, wherever possible, this change resulted in the formation of a conjugated system (reaction C):



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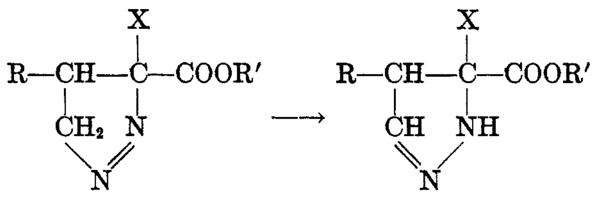
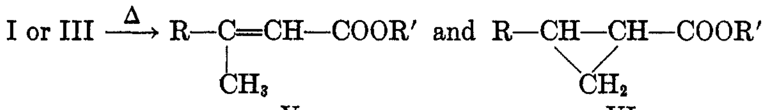
[1] von Auwers, (*a*) *Ann.*, **470**, 284 (1929); (*b*) *ibid.*, **496**,, 27, 252 (1932); (*c*) *Ber.*, **66**, 1198 (1933); see also von Pechmann, (*d*), *Ber.*, **33**, 3590, 3594, 3597 (1900).

However, in the case of substituted pyrazolines, the alternative reaction according to D was found to take place:



Ia IVa

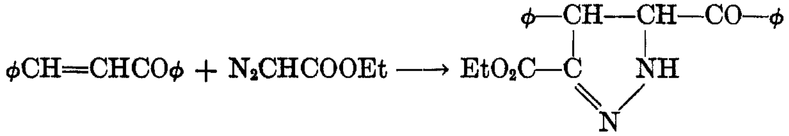
Thermal decomposition of these products led to olefinic esters and cyclopropane derivatives,



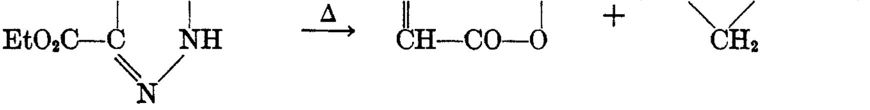
V VI

and the course of this reaction was determined by the complexity of the pyrazoline; the simpler members in general yielding mostly unsaturated compounds.

There is no recorded instance of diazomethane having been added to α,β-unsaturated ketones, but Kohler and Steele[2] in an attempt to prepare substituted cyclopropanes, studied the addition of diazoacetic ester to benzalacetophenone and represented the reaction as taking place in the following manner:



Thermal decomposition of the pyrazoline gave a small yield of the desired cyclopropane, but the reaction led chiefly to the pyrone:



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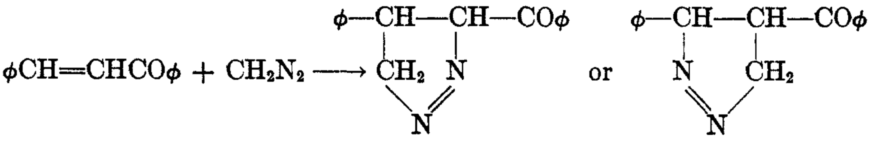
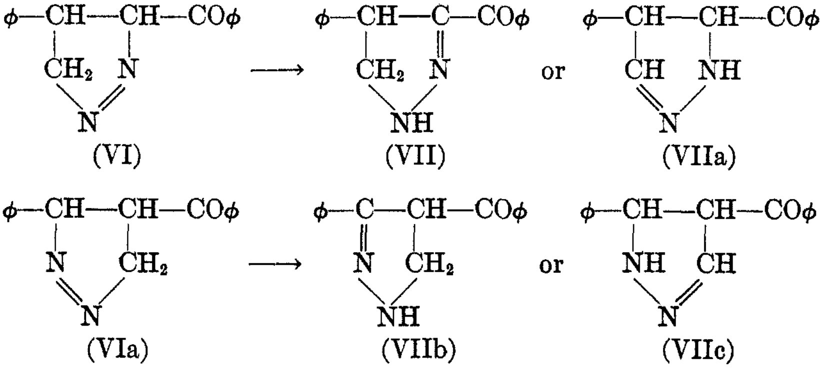
[2] Kohler and Steele, J. Am. Chem. Soc., **41**, 1093 (1919).

Two modes of addition of diazomethane to benzalacetophenone are structurally possible:



(VI) (VIa)

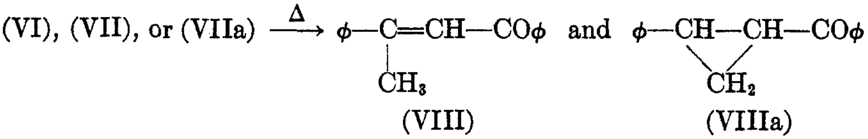
and the change of the Δ^1-pyrazoline primarily formed to the isomeric Δ^2-pyrazoline could then take place according to the following schemes:



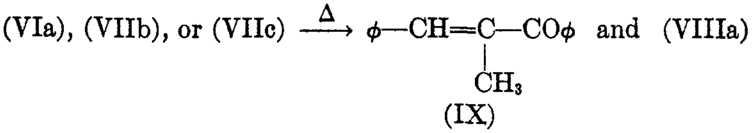
(VI) (VII) (VIIa)

(VIa) (VIIb) (VIIc)

Thermal decomposition of these products should proceed as follows:



(VIII) (VIIIa)

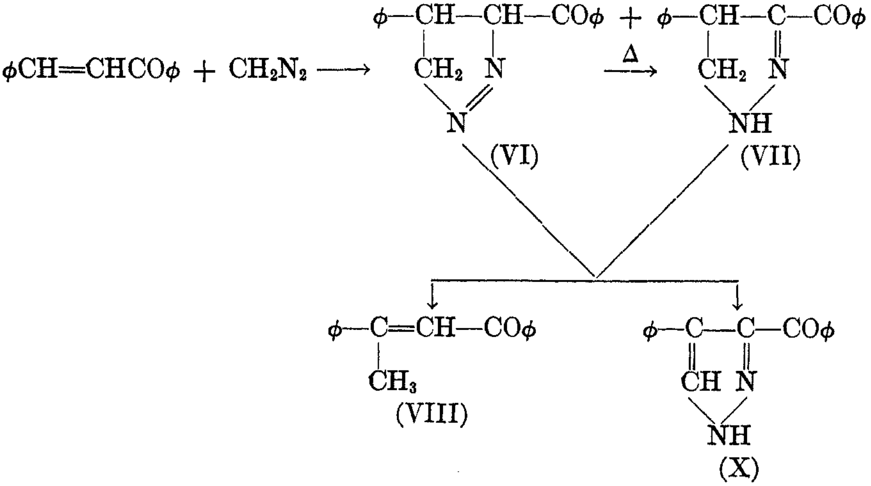


$$\text{(VIa), (VIIb), or (VIIc)} \xrightarrow{\Delta} \phi\text{—CH=}\underset{\displaystyle CH_3}{\text{C}}\text{—CO}\phi \text{ and (VIIIa)}$$

(IX)

In view of the results of von Auwers and Kohler, the primary product to be expected from this reaction is (VI), 3-benzoyl-4-phenyl-Δ^1-pyrazoline, and this was found to be the case. Diazomethane was found to add readily to benzalacetophenone in cold ether solution, giving two isomeric pyrazolines of melting points 92–3° and 127–9°, respectively. The lower-melting product (VI) could be transformed into its isomer (VII) by gentle heating slightly above its melting point. The higher-melting isomer is arbitrarily assigned the structure VII, 3-benzoyl-4-phenyl-Δ^2-pyrazoline, since this structure has a conjugated system (*cf.* von Auwers, *loc. cit.*), although no proof of this formulation has been obtained.

Thermal decomposition of the products was not clean-cut, but in one instance a yellow oil was obtained, which was identified as dypnone (VIII) by the melting point of a mixture of the oxime with dypnone oxime. This shows that the reaction took place in the expected manner, and that the nitrogens are adjacent to the carbonyl group. In another case, the thermal decomposition did not lead to loss of nitrogen, but apparently hydrogen was split off, giving a product represented as (X), 3-benzoyl-4-phenyl-pyrazole. The structure of this product was established by oxidation of 3-benzoyl-4-phenyl-Δ^2-pyrazoline by bromine, which gave the same pyrazole. von Auwers[1b] observed a similar type of reaction in one case. The courses of these reactions are indicated as follows:



The addition of diazomethane appears to be a general reaction of α,β-unsaturated ketones, and further work in this field will be reported in a later paper.

EXPERIMENTAL

Addition of diazomethane to benzalacetophenone. Preparation of 3-benzoyl-4-phenyl-Δ^1-pyrazoline (VI).—To the cold ethereal diazomethane solution prepared from ten grams of nitrosomethylurea (*ca.* 2.8 g. CH_2N_2; 0.067 mole; volume 100 cc.) was added a solution of benzalacetophenone (14.5 g.; 0.07 mole) in 150 cc. of ether. Within five minutes a precipitate formed. After an hour at −14° filtration yielded 13.5 g. of colorless material; m.p. 91–93°. Partial evaporation of the ether gave an additional 3 g. of material; m.p. 78–88°. Final evaporation left 1.0 g. of unchanged benzalacetophenone. The total yield, based on 13.5 g. of benzalacetophenone (0.065 mole), was 100%.

The material may be crystallized from methyl or ethyl alcohol, a mixture of ethyl acetate and petroleum ether, a mixture of chloroform and petroleum ether, or from carbon tetrachloride. The best results were obtained with the use of methyl alcohol. The melting point after two crystallizations was 92–93°.

Anal. Calc'd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.64; N, 11.20; mol. wt. 2.50
Found: C, 76.56, 76.50; H, 5.85, 5.80; N, 11.35, 11.13; mol. wt. (in benzene), 265, 241, 244.

Upon standing for about four months this material decomposed to an oil, from which no crystalline material could be isolated.

Addition of diazomethane to benzalacetophenone. Preparation of 3-benzoyl-4-phenyl-Δ^1-pyrazoline (VI) and 3-benzoyl-4-phenyl-Δ^2-pyrazoline (VII).—To the cold ethereal diazomethane solution prepared from ten grams of nitrosomethylurea (*ca.* 2.8 g. diazomethane; 0.067 mole; volume 100 cc.) was added a solution of benzalacetophenone (14.5 g.; 0.07 mole) in 150 cc. of dry ether. A colorless precipitate formed in the cold solution within a few minutes. A portion removed and purified melted at 92–3°. The reaction mixture was kept in an ice bath (*ca.* −10°) for one hour, then allowed to come to room temperature slowly. The precipitate appeared to redissolve in part, but after standing and upon shaking, a voluminous precipitate separated. This was separated by filtration, giving 8.5 g. of faintly yellow material. The product may be crystallized from the usual organic solvents; m.p. 127–9°.

Anal. Calc'd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.64; N, 11.20; mol. wt. 250
Found: C, 76.76; H, 5.89; N, 11.05; mol. wt. (in benzene), 276, 268, 274.

Action of heat on 3-benzoyl-4-phenyl-Δ^1-pyrazoline (VI). Preparation of 3-benzoyl-4-phenyl-Δ^2-pyrazoline (VII).—The pyrazoline (VI) (0.5 g.) was placed in a small test-tube, a thermometer was immersed in the solid, and the tube was heated gently with a small free flame. At 120° there was an apparent reaction, and the temperature rose to 150° without further heating. The temperature was held between 150–170° for 15 minutes; upon cooling and stirring the mass solidified. After crystallization from ethyl alcohol the melting point was 125–129°.

The pyrazoline (VI) (2.0 g.) was placed in a small test-tube and heated in an oil bath held at 90–97°. The clear yellow solution solidified upon cooling (ten minutes) to a yellow solid, which was crystallized from methyl alcohol to give clear yellow crystals; m.p. 128–9° (1.5 g.).

Thermal decomposition of 3-benzoyl-4-phenyl-Δ^2-pyrazoline (VII). Preparation of dypnone (VIII).—The pyrazoline (VII) (1.5 g.) was placed in a small test-tube, a thermometer was immersed in the solid, which was heated in an oil bath. Gas evolution began at a temperature of 178° and became brisk at 200°. The temperature was held at about 200° as long as any evolution of gas was apparent (1.5 hours). The liquid was a clear orange-red in color. Vacuum distillation yielded 1.0 g. of clear yellow liquid; 197–200°/13 mm.

Oxime.—A few drops of the yellow oil was dissolved in 15 cc. of ethyl alcohol and boiled under reflux for five hours with an excess of hydroxylamine hydrochloride; the solution was then diluted with water and cooled. The solid product which separated was crystallized twice from dilute alcohol, when it melted at 126–8° (softened at 120°). This sample did not depress the melting point of a known sample of dypnone oxime; 126–30° (softened at 121°).

A similar result was obtained with some of the lower melting pyrazoline (VI). Two grams of impure material (m.p. 87–90°) was placed in a test-tube, a thermometer was immersed in the solid, and the tube was heated gently. There was some sign of reaction at about 100°, and at 130–40° a vigorous reaction took place, the temperature rising to 190–200° without further heating. The material was boiled gently for a few minutes (temperature 240–50°), then allowed to cool. The orange-red oil could not be solidified, and was vacuum-distilled; a yellow viscous oil passing over at 185–90° under 13 mm. pressure. The oil did not contain nitrogen.

Thermal decomposition of 3-benzoyl-4-phenyl-Δ^1-pyrazoline (VI). Preparation of 3-benzoyl-4-phenyl-pyrazole (X).—A portion of the pyrazoline (VI) which had started to decompose upon standing for four months was placed in a small sausage-type flask and distilled at atmospheric pressure. The distillate was a yellow oil which solidified upon cooling. The material was taken up in boiling chloroform, and filtered from a small amount of undissolved material (m.p. 215–220°), petroleum ether was added, the solution was cooled, and the colorless, fluffy precipitate was separated by filtration; m.p. 170–73°. Concentration of the filtrate gave a further quantity of colorless material; m.p. 191–193°. After crystallization from ethyl acetate-petroleum ether and ethyl alcohol, the melting point was 193–4°. The two other products were not investigated further.

Anal. (substance of m.p. 193–4°) Calc'd for $C_{16}H_{12}N_2O$: C, 77.42; H, 4.84
Found: C, 76.50, 76.99; H, 5.16, 5.14.

A small amount of colorless material of the same melting point had been noticed previously in the thermal decomposition of the isomeric 3-benzoyl-4-phenyl-Δ^2-pyrazoline (VII).

Action of bromine on 3-benzoyl-4-phenyl-Δ^2-pyrazoline (VII). Preparation of 3-benzoyl-4-phenyl-pyrazole (X).—A small amount of the pyrazoline (VII) was dissolved in carbon disulfide and a solution of bromine in carbon disulfide was added slowly. Two products were obtained: bright yellow crystals, which after crystallization from methyl alcohol, melted (d.) at 120–22° (not investigated further), and a smaller amount of colorless material, m.p. 193–4° after crystallization from ethyl acetate-petroleum ether and dilute ethyl alcohol. The melting point of a mixture with the thermal decomposition product having the same melting point, showed no depression.

SUMMARY

1. Diazomethane has been added to benzalacetophenone, giving two isomeric pyrazolines which are represented as 3-benzoyl-4-phenyl-Δ^1- and -Δ^2-pyrazolines.

2. The lower-melting compound may be changed into its isomer by heating to slightly above its melting point.

3. Thermal decomposition of these pyrazolines gives a number of substances, among which are dypnone and a nitrogen-containing compound represented as 3-benzoyl-4-phenyl-pyrazole.

4. The action of bromine on the higher-melting pyrazoline gives the same pyrazole as is obtained in the thermal decomposition.

[Contribution from the Chemical Laboratories of Yale University and the University of Texas]

BIS-ISOTHIOCYANOMETHYL AND BIS-1-ISOTHIOCYANOETHYL ETHERS*

HENRY R. HENZE, ARTHUR J. HILL, AND LOY B. CROSS†

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The first production of a substituted ether containing the isothiocyanate grouping appears to have been accomplished in 1909 by Johnson and Guest[1] who prepared isothiocyanomethyl methyl ether and the ethyl and isoamyl homologs of this ether. Probably because these mono-isothiocyano ethers occasioned a mild irritation of the skin, even at ordinary temperatures, the series was not investigated further. However, this very property awakened new interest during 1918 in the synthesis of additional mustard oil ethers. Since the vesicatory effect was attributed to the mustard oil grouping, it was to be anticipated that increasing the number of such groupings in an ether should also enhance the power of the latter to cause blistering of the skin.

It is in a report[2] on a study of comparative skin irritation of mustard gas and other agents that there is to be found the only published reference to the existence of a di-mustard-oil ether, namely, bis-isothiocyanomethyl ether (I). Because of the severe vesication which it produces on human skin, work on the proof of structure of this compound was interrupted in 1918, and only recently has it been resumed. In addition to the methyl ether (I), its ethyl homolog has also been prepared and its properties studied with the result that the stability and chemical behavior of the two isothiocyanates have been found to differ widely and are here reported.

$$\underset{\text{I}}{SCN—CH_2—O—CH_2—NCS} \qquad \underset{\text{II}}{SCN—CH(CH_3)—O—CH(CH_3)—NCS}$$

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* This investigation was initiated in 1918 at Field Laboratory 2124Y of the Chemical Warfare Service at Yale University under the direction of Professors Treat B. Johnson and Arthur J. Hill. Permission to publish data concerning bis-isothiocyanomethyl ether has been granted by The Chief, Chemical Warfare Service, U. S. Army.

† From a thesis presented by Loy B. Cross to The Graduate School of The University of Texas in partial fulfillment of the requirements for the degree of Master of Arts, August, 1936.

[1] Johnson and Guest, *Am. Chem. J.*, **41**, 337–44 (1909).

[2] Hanzlik and Tarr, *J. Pharmacol.*, **14**, 221–8 (1919).

For the preparation of the bis-isothiocyanomethyl ether (I) in good yield potassium thiocyanate must be reacted with symmetrical dichloromethyl ether,

$$(R{-}CHCl)_2O + 2MSCN \rightarrow 2MCl + (R{-}CHNCS)_2O$$

but for the production of bis-1-isothiocyanoethyl ether (II) it is necessary to use sodium thiocyanate with the corresponding dichloroethyl ether. Both of the di-mustard-oil ethers respond to all the usual qualitative tests for the presence of isothiocyanate groupings, but the ethyl ether derivative is definitely less stable and, especially, more susceptible to hydrolysis than is its lower homolog. It is to be noted that on the basis of the products of hydrolysis of alkyl isothiocyanates, the results of the hydrolysis of bis-1-isothiocyanoalkyl ethers are not predictable. Whereas the alkyl isothiocyanate yields an amine and thioformaldehyde, the mustard-oil ether forms thiocyanic acid and formaldehyde.

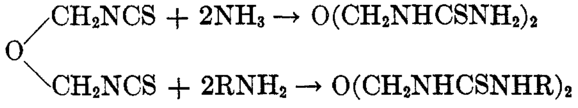
$$CH_3NCS + H_2O \rightarrow CH_3NH_2 + COS \text{ (or } CO_2 + H_2S)$$

$$(SCNCH_2)_2O + H_2O \rightarrow 2HNCS + 2HCHO$$

However, this latter behavior is truly characteristic of the α-dichloroethers from which these isothiocyanates were synthesized:

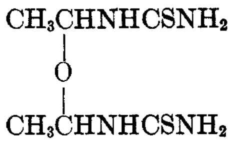
$$(CH_2Cl)_2O + H_2O \rightleftharpoons 2HCl + 2HCHO.$$

Although both of the mustard-oil ethers reacted readily with ammonia, aniline, and *o*-toluidine, respectively, only the substituted methyl ether formed the anticipated thioureas.



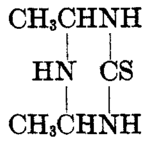
$$O\begin{cases} CH_2NCS + 2NH_3 \rightarrow O(CH_2NHCSNH_2)_2 \\ CH_2NCS + 2RNH_2 \rightarrow O(CH_2NHCSNHR)_2 \end{cases}$$

In contrast, the lesser stability of bis-1-isothiocyanoethyl ether is evidenced by the formation of products of unexpected structure; thus, when it reacted with anhydrous ammonia, simple addition to form a thiourea (III) does not occur, and, instead, Dixon's[3] "diethylidenethiourea" (IV) results.



$$\begin{array}{l} CH_3CHNHCSNH_2 \\ \quad | \\ \quad O \\ \quad | \\ CH_3CHNHCSNH_2 \end{array}$$

III



IV

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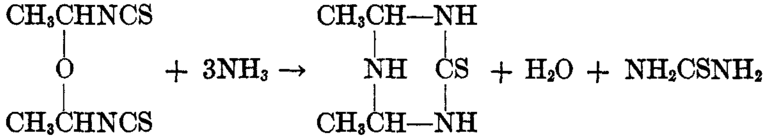
[3] Dixon, *J. Chem. Soc.*, **61**, 509–510 (1892).

Since Dixon prepared the latter by the interaction of thiourea and acetaldehyde-ammonia, it is to be presumed that the ethyl ether derivative ammonolyses and that ammonia then units with the acetaldehyde and isothiocyanic acid formed to yield acetaldehyde-ammonia and thiourea; the water produced in the condensation would facilitate the formation of additional acetaldehyde by hydrolysis of the mustard-oil ether.



II IV

Since ammonia reacts differently with formaldehyde and acetaldehyde, respectively, it is not altogether inconsistent that ammonia should produce different products with the isothiocyanoethers derived from these aldehydes.

Likewise, the reactions of this ethyl ether derivative with aniline and *o*-toluidine yielded unexpected results, in that the chief products isolated from the reaction mixtures were found by analysis to contain no oxygen and were shown to be phenylthiourea and *o*-tolylthiourea. It is probable that here, too, the ether compound was cleaved by the amines and that the arylthioureas formed from the products of fission.

$(CH_3CHNCS)_2O + RNH_2 \rightarrow RNHCSNH_2 + H_2O +$ polymerization products of HNCS.

EXPERIMENTAL

Preparation of bis-isothiocyanomethyl ether.—One hundred eighty-seven grams (4.1 moles) of dry, finely powdered potassium thiocyanate, 350 cc. of anhydrous benzene, and 75 grams (1 mole) of bis-chloromethyl ether were placed in a flask provided with a mechanical stirrer and reflux condenser. The mixture was stirred and heated for six hours in an oil bath at 110°. After cooling, filtration yielded an amount of mixed salts indicating 95% conversion of the reactants. The benzene solution was distilled under diminished pressure, yielding 66 g. of an almost water-white oil; yield, 88%; b.p. 115–116°/5 mm.; redistillation produced 60 g. of bis-isothiocyanomethyl ether, b.p. 101.5–102°/2.5–3 mm.; n_D^{20} 1.6117; d_4^{20} 1.3153; M.R. calc'd 42.43; M.R. obs. 42.27. The mustard oil-ether solidifies in an ice bath, its melting point being 18.5°.

Anal. Calc'd for $C_4H_4N_2OS_2$: N, 17.49; S, 40.04.
Found: N, 17.44; S, 39.97.

The isothiocyano ether gave a positive Feigl test, readily blackened mercuric oxide or aqueous lead acetate solution. On warming with water, hydrolysis of the ether occurred, formaldehyde and thiocyanic acid being identified as products of the reaction.

Bis-thioureidomethyl ether.—In preparing this ammonia derivative, 100 cc. of anhydrous ethyl ether was saturated with anhydrous ammonia in an ice bath. To this mixture was added 5 g. of bis-isothiocyanomethyl ether diluted with 10 cc. of anhydrous ethyl ether. Although very little heat was evolved, a white solid soon separated. Filtration of this product, followed by washing with ethyl ether and drying in air, resulted in a theoretical yield of 6 g. of faintly yellow solid material; m.p. 115–6°. Recrystallization from ethyl alcohol yielded a white, crystalline powder, melting sharply at 147–149° (corr.).

Anal. Calc'd for $C_4H_{10}N_4OS_2$: N, 28.85; S, 33.01.
Found: N, 28.71: S, 32.74.

Bis-phenylthioureidomethyl ether.—Ten grams (0.102 mole) of freshly distilled aniline was added to 50 cc. of anhydrous benzene, and the solution was cooled to 0°, and diluted with a cooled solution prepared by dissolving 8 g. (0.05 mole) of bis-isothiocyanomethyl ether in 50 cc. of anhydrous benzene. Much heat was evolved and cooling was necessary to moderate the reaction, which caused the separation of a white, crystalline solid. After standing at 20° for an hour, the solid was filtered, washed with anhydrous benzene, and dried at 110°; yield 15.5 g., or 89.5%. The product is very sparingly soluble in cold water, acetone or alcohol, but is moderately soluble in these boiling solvents. Recrystallization from acetone yielded a white crystalline powder, m.p. 159.5° (corr.).

Anal. Calc'd for $C_{16}H_{18}N_4OS_2$: N, 16.19; S, 18.53.
Found: N, 16.23; S, 18.42.

Attempts to recrystallize bis-phenylthioureidomethyl ether from boiling alcohol always produce a colorless material melting at 135–136° (corr.). Apparently, alcoholysis of the ether grouping occurs and *N*-ethoxymethyl-*N'*-phenylthiourea is formed. The melting point is 135–136° (corr.) although Johnson and Guest reported m.p. 125–126°[1] for a compound of this structure.

Anal. Calc'd for $C_{10}H_{14}N_2OS$: N, 13.33; S, 15.24.
Found: N, 13.43; S, 15.19.

Bis-o-tolylthioureidomethyl ether.—In preparing this ether, 12 g. (0.112 mole) of freshly distilled *o*-toluidine and 8 g. (0.05 mole) of bis-isothiocyanomethyl ether were mixed as in the preparation of the phenyl analog. The reaction product weighed 16 g., 85.5% yield. This thioureido ether closely resembles its lower homolog in solubilities, hence was recrystallized from hot acetone as a finely crystalline powder, m.p. 169–169.5° (corr.).

Anal. Calc'd for $C_{18}H_{22}N_4OS_2$: N, 14.97; S, 17.13.
Found: N, 14.73; S, 16.93.

This thioureido ether, too, is altered by refluxing it in ethyl alcohol solution and is converted into *N*-ethoxymethyl-*N'*-*o*-tolylthiourea, m.p. 127.5–128.5° (corr.)

Anal. Calc'd for $C_{11}H_{16}N_2OS$: N, 12.50; S, 14.30.
Found: N, 12.72; S, 14.23.

Preparation of bis-1-isothiocyanoethyl ether.—Although potassium thiocyanate reacted smoothly with the dichlormethyl ether to produce the corresponding isothiocyano ether in excellent yield, the use of this salt with bis-1-chloroethyl ether resulted in the formation of much reddish-brown, amorphous, solid material and little or no mustard-oil ether. However, sodium thiocyanate reacted readily with the dichloroethyl ether yielding the desired isothiocyano ether in good yield.

Three hundred seventy-five grams (4.63 moles) of dry, finely powdered sodium thiocyanate, 750 cc. of anhydrous benzene, and 215 g. (1.5 mole) of bis-1-chloroethyl ether were stirred and heated in an oil bath at 110° for 7 hours. The solution assumed a clear golden color, and the thermometer immersed in it registered 84°. After filtration from the solid salts, distillation of the benzene solution yielded 220 g. of a dark-red oil boiling above 45° at 40–45 mm. pressure. By redistillation of 100 g. of this oil, 60 g. of a colorless oil, boiling at 94.5° under a pressure of 2–3 mm. and possessing a refractive index (n_D^{20}) of 1.5540, was obtained. The product quickly assumed an orange color and orange-red solid material soon began to separate.

For further purification, a portion of the freshly distilled mustard oil was cooled at −30° in an ether-alcohol-solid-carbon-dioxide mixture; the solid thus obtained was allowed to warm slowly until approximately two-thirds had melted, and the liquid portion was poured off. The residual solid was melted, and the process of resolidification and fusion was repeated. The ether thus obtained melted at −7°, had a refractive index (n_D^{20}) of 1.5520 and a density (d_4^{20}) of 1.1535. From these data, the observed molecular refraction is 52.236 as compared to the calculated value of 51.669.

Anal. Calc'd for $C_6H_8N_2OS_2$: N, 14.89; S, 34.08.
Found: N, 14.37; S, 33.55.

Action of ammonia on bis-1-isothiocyanoethyl ether.—Three grams of freshly distilled bis-1-isothiocyanoethyl ether was diluted with 10 cc. of anhydrous ethyl ether and added slowly to 100 cc. of ethyl ether which had been saturated at 0° with anhydrous ammonia. A viscous, orange-colored oil separated, which, after an hour, almost completely solidified. This material, weighing two grams, was recrystallized from hot water and then melted at 182–3° (corr.). The compound is practically insoluble in cold water, but is very soluble in hot water, acetone, alcohol and very dilute hydrochloric acid.

Anal. Calc'd for $C_5H_{11}N_3S$: C, 41.33; H, 7.64, N, 28.94; S, 22.08.
Found: C, 41.75; H, 7.98; N, 27.83; S, 22.25.

A sample of diethylidenethiourea ammonia was prepared according to the directions of Dixon.[3] The melting point of a mixture of equal parts of pure diethylidenethiourea ammonia with the product of the ineraction of ammonia and bis-1-isothiocyanoethyl ether was found to be 182.5°. To characterize our product still further, it was converted into its picrate which crystallized from alcohol in fine, hair-like needles, melting with decomposition at 241–245°. The diethylidenethiourea ammonia of known structure was likewise converted into a picrate identical in physical and chemical properties. The melting point of a mixture of the two samples was 241–245°. The conversion of bis-1-isothiocyanoethyl ether unto diethylidenethiourea ammonia represented a yield of 88%.

Action of aniline on bis-1-isothiocyanoethyl ether.—Twelve grams (0.129 mole) of redistilled, water-white aniline was mixed with 50 cc. of anhydrous benzene and cooled in an ice-bath. Ten grams (0.053 mole) of bis-1-isothiocyanoethyl ether was then added slowly; the addition resulted in the evolution of much heat and the separation of a dark-brown oil. After standing at room temperature for a day, the oil deposited a small amount of crystalline solid. It was possible by steam-distillation to remove the oily material from the solid without altering the composition of the latter. Considerably more aniline was recovered from the steam distillate than was added in excess of the amount required for a normal conversion of the mustard oil into the corresponding thiourea. The residual water in the distillation flask was decanted, while hot, from some vicous, gummy, reddish-brown solid material, decolorized with Norite and, on cooling, deposited colorless, monoclinic crystals; m.p. 153–154°. Subsequent recrystallizations from hot water did not alter this melting point.

Anal. Calc'd for $C_7H_8N_2S$: C, 55.23; H, 5.30; N, 1840; S, 21.08.
Found: C, 55.95; H, 5.89; N, 17.85; S, 19.85.

Since the analytical data suggested that phenylthiourea had been obtained, the melting point of a mixture with authentic phenylthiourea[4] was taken and found to be 153–154°. Further to establish the identity of the reaction product, it was acetylated by means of acetic anhydride, and the acetyl derivative recrystallized from diluted alcohol; m.p. 137–138°; resolidification at 145°; refusion at 160–165°. An authentic sample of *N*-acetyl-*N'*-phenylthiourea was prepared,[5] and melted at 137–138°, resolidified at 145°, and remelted at 163–166°. A mixture of the two samples was found to melt at 136–138°, resolidifying at 146°, and remelting at 160–165°.

Anal. Calc'd for $C_9H_{10}N_2OS$: N, 14.43. Found: N, 14.13.

Action of o-*toluidine on bis-1-isothiocyanoethyl ether.*—Twenty grams (0.206 mole) of freshly redistilled *o*-toluidine and 19 g. (0.101 mole) of bis-1-isothiocyanoethyl ether were mixed as described for the action of aniline. Again, more amine was recovered by steam distillation than the amount added in excess of that required for normal thiourea formation. From the hot aqueous solution remaining in the distillation flask, 4 g. of rather large, colorless, monoclinic crystals were obtained; the melting point, 163°, was not altered by subsequent recrystallization.

Anal. Calc'd for $C_8H_{10}N_2S$: C, 57.78; H, 6.07; N, 16.86; S, 19.29.
Found: C, 58.45; H, 6.53; N, 16.49; S, 18.40.

Since these data suggested that the reaction product was *o*-tolylthiourea, an authentic sample of the latter was prepared[6]; m.p. 160–162° (corr.). The melting point of a mixture was 162.5° (corr.). Further confirmation of the identity of the *o*-tolylthiourea was obtained by acetylization. When recrystallized from 50% alcohol, the acetyl derivative formed fine, glistening plates melting at 137–138°, resolidifying at 145° and again melting at 186–188° (corr.). A sample of *N*-acetyl-*N'*-*o*-tolylthiourea was prepared according to the directions of Hugershoff,[7] and found to melt at 138–139°, to resolidify at 148°, and to fuse again at 184–187° (corr.). A mixture of equal parts of the two samples melted at 138°, resolidified at 146°, and remelted at 185–188° (corr.)

Anal. Calc'd for $C_{10}H_{12}N_2OS$: N, 13.46. Found: N, 13.61.

SUMMARY

1. Bis-isothiocyanomethyl ether and bis-1-isothiocyanoethyl ether have been synthesized and their structures established. They are very active skin irritants, rather unstable towards air and water.

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[4] De Clermont, *Ber.*, **9**, 446 (1876).
[5] Hugershoff, *ibid.*, **32**, 3658 (1899).
[6] Dixon, *J. Chem. Soc.*, **61**, 574 (1895).
[7] Hugershoff, *Ber.*, **32**, 3659 (1899).

2. Bis-isothiocyanomethyl ether condenses with ammonia, aniline and *o*-toluidine to form the anticipated thioureas. However, the phenyl- and *o*-tolylthioureido ethers are cleaved by ethyl alcohol, forming the corresponding *N*-ethoxymethyl-*N′*-arylthioureas.

3. Bis-1-isothiocyanoethyl ether reacts with amines in an anomalous fashion; thus with ammonia the mustard oil is converted into diethylidene-thiourea ammonia, while with aniline and *o*-toluidine, respectively, the chief products of reaction are phenylthioura and *o*-tolylthiourea.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

EXCHANGE REACTIONS IN DEUTEROALCOHOL

M. S. KHARASCH, WELDON G. BROWN, AND JOHN McNAB

Received January 30, 1937

INTRODUCTION

It has been evident since the discovery and isolation of the hydrogen isotope that a direct method for the demonstration of the lability of hydrogen in certain types of organic compounds is now available. It consists in determining whether an exchange of light and heavy hydrogen atoms occurs when two compounds of different isotopic composition are brought together in solution at moderate temperatures. The experimental conditions may be adjusted at will from the very mildest to the most severe by a suitable choice of solvent, temperature, and catalytic agents, and the method is, therefore, not only direct but highly flexible.

It so happens that most of the work on exchange reactions which bears on the problem of hydrogen lability in organic compounds has been done with heavy water as the solvent and donor of deuterium. This is a consequence of the fact that the analytical operations are somewhat less complex for water than for other solvents which might be used. But since many of the compounds which are of interest in this connection are insoluble in water, the use of an organic solvent containing labile hydrogen can hardly be avoided in a comprehensive investigation of the exchange method.

The present work is the beginning of such an investigation and in this work we have employed heavy ethyl alcohol as the solvent and contributor of deuterium. The experiments reported at the present time are of an exploratory nature and are designed simply to provide some further orientation with regard to the types of substances which exhibit the exchange reaction.

A number of recorded observations relating to the exchange of hydrogen between water and various organic substances are summarized in Table I. The list comprises a considerable variety of compounds and it will be seen that the exchange reaction is in all cases confined to those hydrogen atoms which we know to be labile on the basis of experience with various other types of reactions, electrolytic dissociation, salt formation, condensation, prototropy, etc. Also in accord with expectations is the rapid exchange of two hydrogen atoms in cyclohexylidene acetonitrile in ethyl alcohol solution containing 0.1 *N* sodium ethylate, recently reported by Ingold, de Salas, and Wilson.[1] It is also of interest to note that the less labile hydrogens of benzene can be made to participate in exchange reactions under appropriate conditions, and that these conditions approach those under which aromatic substitution occurs. Thus it is reported by Klit and Langseth[2] that benzene exchanges hydrogen with hydrogen chloride in the presence of anhydrous aluminum chloride, and by Ingold, Raisin, and Wilson[3] that benzene exchanges hydrogen slowly with 50 per cent. sulfuric acid and more rapidly with 90 per cent. sulfuric acid.

EXPERIMENTAL PROCEDURE AND RESULTS

The occurrence of an exchange reaction between "heavy" alcohol and a substance of natural isotopic composition dissolved in it may be detected either by a decrease in the concentration of deuterium in the solvent or by an increase in the deuterium content of the solute. In these preliminary experiments we have relied entirely on observations of the change in composition of the solvent, and while it would be desirable to check these results by analysis of the solute, this would have necessitated the development of special analytical methods.

Analysis of ethyl alcohol for deuterium.—The analysis of ethyl alcohol for its deuterium content is accomplished by density measurements, using the temperature-float method,[22] on water obtained from the combustion of the alcohol. A 1-cc. sample of alcohol is burned in a small glass lamp containing an asbestos wick, the lamp being inserted in a chamber which is connected to a heated tube containing copper oxide, and this in turn leads to a series of traps where the water is collected. Dry air for the combustion is drawn through the system by suction. The water sample is heated under reflux for thirty minutes after adding a small quantity of potassium permanganate and sodium carbonate, and then distilled three times in high vacuum. It is collected finally in a small tube attached to the line by means of a ground joint. This tube is removed, and after introduction of the quartz float, transferred to a water-bath where the suspension temperature is determined. The movements of the float, which measures about 4 mm. in diameter and about 5 mm. in length, are observed with the aid of a low-power microscope. The temperatures were observed on two Beckmann thermometers which, together, provided a range of nearly ten degrees.

The amount of water required for the analysis is approximately 0.5 cc. This is very much less than is customary, or desirable, in density measurements by this method, but the restriction of operations to such a scale is dictated by practical considerations, such as the time required for the combustion process and the vacuum distillations. The chief difficulty lies in the purification of the water sample, as is evident from the fact that we have not been able to utilize the full sensitivity of the float method except with samples of water which were available in quantities large enough for a preliminary purification by the usual methods. With water obtained from the combustion of alcohol, as described above, the suspension temperatures were ordinarily reproducible to within 0.08° but there were occasionally larger discrepancies apparently due to accidental contamination of the quartz surface.

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[1] INGOLD, DE SALAS, AND WILSON, *J. Chem. Soc.*, **1936**, 1328.

[2] KLIT AND LANGSETH, *Z. phys. Chem.*, **A176**, 65 (1936).

[3] INGOLD, RAISIN, AND WILSON, *J. Chem. Soc.*, **1936**, 915; *Nature*, **134**, 734 (1934).

In the range of deuterium concentration over which our measurements extend, namely from zero to 1.7% deuterium, the relationship between suspension temperature and density or deuterium concentration, departs only slightly from linearity, and the error introduced on assuming such a relationship is less than our experimental

TABLE I

Exchange Reactions Between Water and Organic Compounds

COMPOUND	OBSERVATIONS	REFERENCES
Formaldehyde	No exchange.	4, 5, 6
Acetaldehyde	Slow exchange of 1 H atom, doubtful.	4, 5, 6
Acetone	Slow exchange in neutral solution; rapid in alkaline solution.	4, 5, 7, 8
Acetylacetone (2,4-Pentanedione)	All hydrogens exchange.	4, 5
Acetic acid	Exchange of carboxyl hydrogen only.	9
Sodium acetate	No exchange.	4, 5
Sodium formate	Slight exchange at 100°.	10
Formic acid	Exchange of carboxyl hydrogen only.	10
Monochloroacetic acid	Exchange of carboxyl hydrogen only.	10
Succinic acid	Exchange of carboxyl hydrogen only.	10, 11
Malonic acid	All hydrogens exchange rapidly.	10, 11
Ethylene glycol	Hydroxyl hydrogen atoms exchange rapidly.	12
Sucrose	Hydroxyl hydrogen atoms exchange rapidly.	13
d-Glucose	Hydroxyl hydrogen atoms exchange rapidly.	14
Cellulose	Hydroxyl hydrogen atoms exchange rapidly.	15
Hydroquinone Orcinol Resorcinol Pyrogallol	Instantaneous exchange of hydroxyl hydrogens; slow exchange of nuclear hydrogens.	16
Phloroglucinol	Rapid exchange of all hydrogens.	16

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[4] Klar, *Z. phys. Chem.*, **B26**, 335 (1934).

[5] Bonhoeffer and Klar, *Naturwissenschaften*, **22**, 45 (1934).

[6] Wirtz and Bonhoeffer, *Z. phys. Chem.*, **B32**, 108 (1936).

[7] Schwartz and Steiner, *ibid.*, **B25**, 153 (1934).

[8] Anderson, Halford, and Bates, *J. Am. Chem. Soc.* **56**, 491 (1934); **57**, 663 (1935).

[9] Lewis and Schutz, *J. Am. Chem. Soc.*, **56**, 493 (1934).

[10] Münzberg, *Z. phys. Chem.*, **B31**, 18 (1935).

[11] Halford and Anderson, *J. Am. Chem. Soc.*, **58**, 736 (1936).

[12] Hall, Bowden, and Jones, *ibid.*, **56**, 750 (1934).

[13] Bonhoeffer and Brown, *Z. phys. Chem.*, **B23**, 171 (1933).

[14] Hamill and Freudenberg, *J. Am. Chem. Soc.*, **57**, 1427 (1935).

[15] Bonhoeffer and Rummel, *Naturwissenschaften*, **22**, 45 (1934).

[16] Münzberg, *Z. phys. Chemie*, **B33**, 23, 39 (1936).

TABLE I—*Concluded*

COMPOUND	OBSERVATIONS	REFERENCES
Urea	Exchange of all hydrogens.	18
Hydroxyproline	Exchange of three hydrogens.	18
Barbituric acid	Exchange of four hydrogens.	19
Strychnine	No exchange.	17
Vomicine	Exchange of two hydrogens.	17
Phenacetin	Exchange of one hydrogen.	19
Egg albumin	Exchange of amino hydrogens.	15
Methylamine hydrochloride	Exchange of amino hydrogens.	20
Sodium vinylacetate	Exchange of one hydrogen.	21

error. Moreover, since the absolute magnitude of the deuterium concentration is of no significance in the interpretation of our results, it is not essential that the observed suspension temperatures be transformed to read as actual concentrations. Nevertheless, a calibration of the float was carried out, using as reference points a number of water samples of known density, and it was thereby ascertained that the relationship between suspension temperature and concentration of deuterium was represented fairly well by the equation $t = 1.62 + 3.80\ N$, where t is the temperature reading (arbitrary scale) and N is the concentration of deuterium in mole per cent.

Preparation of "heavy" ethyl alcohol.—Ethyl alcohol, in which a part of the hydroxyl hydrogen was replaced by deuterium, was prepared by mixing deuterium oxide with absolute alcohol, and later removing the water by means of calcium oxide. The absolute alcohol used in this preparation was first refluxed with calcium oxide and finally distilled over metallic sodium through a fractionating column, the fraction boiling at 78.3° being collected. To 194 g. of this product were added 4.2 g. of heavy water (99.5% deuterium). This mixture was allowed to stand for some time at room temperature after which it was refluxed with an excess of freshly ignited lime and finally distilled. From the combustion of samples of this product, water containing 1.52 mole per cent. deuterium was obtained. Assuming that all of this deuterium was present in the alcohol as C_2H_5OD, the concentration of this species can be given as 9.1 mole per cent. This product was used as the solvent in all of the experiments described hereafter.

Exchange experiments.—In all experiments a carefully dried and weighed sample (usually 5 g.) of the compound to be investigated was introduced into a reaction tube which had previously been connected to a vacuum line. After the opening through which the material had been introduced had been sealed, the tube was cooled in a carbon dioxide-acetone bath, and evacuated. A measured quantity (usually 5 cc.) of the solvent alcohol, contained in a vessel attached to the line through a stopcock, was then allowed to distill into the reaction tube and after a further evacuation the

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[17] ERLENMEYER, EPPRECHT, AND LOBECK, *Helv. Chim. Acta*, **19**, 543 (1936).

[18] WILLIAMS, *J. Am. Chem. Soc.*, **58**, 1819 (1936).

[19] ERLENMEYER, EPPRECHT, LOBECK, AND GÄRTNER, *Helv. Chim. Acta*, **19**, 354 (1936).

[20] GOLDFINGER AND LASAREFF, *Compt. rend.*, **200**, 1671 (1935).

[21] IVES AND RYDON, *J. Chem. Soc.*, **1935**, 1735.

[22] A discussion of this and other methods is given by UREY AND TEAL, *Rev. Mod. Phys.*, **7**, 34 (1935).

TABLE II
EXCHANGE REACTIONS IN DEUTEROALCOHOL

COMPOUNDS	CONDITIONS	PERCENTAGE DECREASE IN DEUTERIUM OF ALC. (OBS.)	PERCENTAGE DECREASE IN DEUTERIUM OF ALCOHOL CALCULATED FOR THE EXCHANGE OF		
			1H	2H	3H
Triphenylmethane	Room temp. for 135 days.	0	19		
Triphenylmethane	100° for 150 days	0			
Triphenylmethane	100° for 6 days 0.02 *M* in NaOH.	0			
Diphenylmethane	Room temp. for 147 days.	0	26		
Fluorene	Room temp. for 138 days.	0	26	41	
Fluorene	110° for 28 days.	0			
Fluorene	110° for 8 days 0.02 *M* in NaOH.	35.5			
Fluorene	110° for 2 days 0.02 *M* in NaOH.	34			
Fluorene	110° for 2 days 0.01 *M* in H_2SO_4.	0			
Acenaphthene	110° for 36 hours.	0	28		
Dianisylphenylmethane	110° for 36 hours.	0	15		
Dianisylphenylmethane	110° for 96 hours 0.02 *M* in NaOH.	5.5			
Ethyl acetoacetate	Room temp. for 3 days.	41	31	48	58
Succinimide	110° for 25 hours.	32	36		
2-Methoxynaphthalene	110° for 22 hours.	0	26		
2-Methoxynaphthalene	110° for 22 hours 0.02 *M* in NaOH.	0			
o-Nitrotoluene	110° for 34 hours.	16.5	33	46	60
o-Nitrotoluene	110° for 34 hours 0.02 *M* in NaOH.	31			
p-Nitrotoluene	110° for 48 hours.	Little, if any.	30		
p-Nitrotoluene	110° for 48 hours 0.02 *M* in NaOH.	20			
Quinaldine	110° for 60 hours.	44.5	31	47	58
1,3,5-Trinitrobenzene	110° for 64 hours.	0	22	35	45
1,3,5-Trinitrobenzene	110° for 68 hours 0.02 *M* in NaOH.	40.5			
7,8-Benzoquinaldine	110° for 104 hours.	22	23	38	48
7,8-Benzoquinaldine	110° for 108 hours 0.02 *M* in NaOH.	40			
m-Nitrotoluene	110° for 66 hours.	6	33	46	60
m-Nitrotoluene	110° for 66 hours 0.02 *M* in NaOH.	6			
m-Nitrotoluene	Blank run. Alcohol removed immediately after mixing with *m*-nitrotoluene.	6			

TABLE II—*Concluded*

COMPOUNDS	CONDITIONS	PERCENTAGE DECREASE IN DEUTERIUM OF ALC. (OBS.)	PERCENTAGE DECREASE IN DEUTERIUM OF ALCOHOL CALCULATED FOR THE EXCHANGE OF		
			1H	2H	3H
Dimethylaniline	110° for 96 hours.	17.3	32	49	58
Dimethylaniline	110° for 96 hours 0.02 *M* in NaOH.	14.6			
Dimethylaniline	110° for 96 hours. (P_2O_5 treatment for alc.)	20			
Dimethylaniline	110° for 96 hours 0.01 *M* in H_2SO_4 (P_2O_5 treatment of alc.)	(*a*)52.1 (*b*)54.6			

tube was sealed off. These reaction tubes were fitted with break-seals so that they could be re-attached to the line and opened in vacuum after they had been maintained for various lengths of time at the various temperatures noted hereafter. At the conclusion of the experiment, the reaction mixture is separated into its components by vacuum distillation, the alcohol being collected in a small tube connected to the line with a ground joint. The alcohol is then transferred to the glass lamp for the combustion.

Experimental results.—The experimental results are summarized in Table II, in which the extent to which the exchange reaction has taken place is indicated by the decrease in the deuterium content of the alcohol. The calculated values, corresponding in each instance to the exchange of one, two, and three hydrogen atoms, were derived on assuming a statistical distribution of the deuterium atoms determined solely by the relative molal quantities of solute and alcohol and by the number of replaceable hydrogen atoms in the solute molecule. It is well known that the equilibrium constants in isotopic exchange reactions may deviate considerably from the values to be expected on the basis of a simple statistical distribution and thus that the number of replaceable hydrogen atoms in a compound cannot be determined with certainty by experiments of the type under consideration. Lack of agreement between the observed values and the calculated values may also arise from the fact that the observations now reported do not necessarily relate to equilibrium conditions.

DISCUSSION OF RESULTS

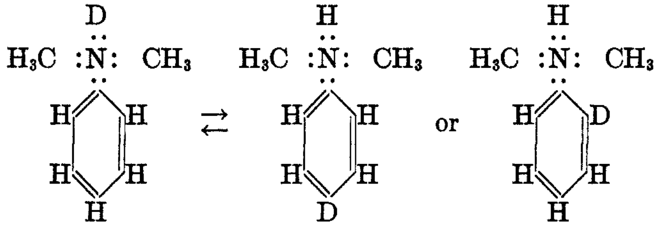
It should be made clear at the outset that in the present study no attempt has been made to establish experimentally true exchange equilibria. Nor in the cases of compounds which did not undergo the exchange reaction can it be said that the range of experimental conditions which might conceivably give rise to exchange has been exhaustively explored. The data presented should be interpreted as implying only that under the conditions recorded exchange reactions either did not proceed at all or did take place to the extent observed. Nevertheless, certain theoretical conclusions are suggested by the facts already revealed.

The exchange reactions in which ethyl acetoacetate and succinimide participated require no special comment. They are of the conventional type. It is of interest that ethyl acetoacetate exchanges two hydrogen atoms even in the absence of alkali.

The reaction of dimethylaniline, however, is of somewhat fresher interest, for in this compound the basic nitrogen atom carries no replaceable hydrogen atoms; exchange cannot be assumed to take place through the simple mechanism of deuteron addition and proton elimination at the basic group as with primary and secondary amines. Neither are "acidic" properties, such as are sometimes attributed to the triarylmethanes, logically ascribable to dimethylaniline. It would seem that this exchange must be related to a different kind of hydrogen lability—that which is manifested in the relatively high reactivity of this compound in nuclear substitution and in condensation reactions. It is, perhaps, significant that in the presence of a small amount of strong acid the exchange observed corresponded roughly to three hydrogen atoms. General chemical evidence supports the assumption that the labilizing effect of the dimethylamino substituent in the benzene nucleus is effective chiefly in the para and the two ortho positions.

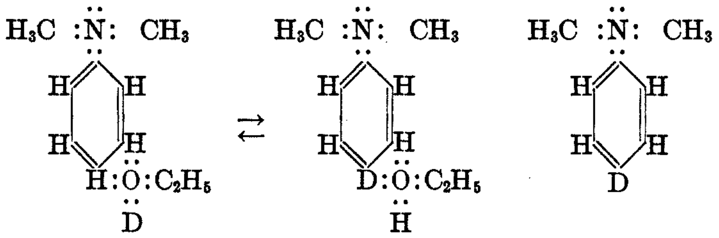
In view of the catalytic effect of acids three possible mechanisms suggest themselves for consideration: (1) deuteron addition at the nitrogen atom, followed by simple molecular rearrangement,

I



(2) intermediate complex formation through a hydrogen bridge, followed by rearrangement and dissociation, or

II



(3) a combination of mechanisms of I and II.

We appreciate the fact that the data on hand are insufficient to evaluate the relative probabilities of these mechanisms, and we contemplate a study of the exchange reactions of deuteroalcohol with diphenylmethylamine and triphenylamine.

Irrespective of the mechanism, however, a strikingly important fact has been demonstrated, namely, the ability of dimethylaniline to exchange a proton even in a solvent such as alcohol. In our opinion this remarkable lability of the ortho and para hydrogen atoms in dimethylaniline arises from the relatively high electronegativity[23] of the *ortho-* and *para-N,N*-dimethylphenyl radicals.* In other words, the electron density in the immediate vicinity of the ortho and para carbon nuclei is greater than around the meta carbon nuclei, or the carbon nuclei of a phenyl radical. We do not suggest that this high electron density can lead to appreciable ionization even in highly polar or protophilic solvents. It might lead, however, to formation of hydrogen bridges, with the consequent labilization of the proton. We would be inclined to regard this type of hydrogen-deuterium exchange as a special case of benzene-ring substitution, and to postulate as special prerequisites: (1) the presence in the ring of a substituent or substituents of the type that greatly increase the electronegativity of the phenyl radical; and (2) the presence in the medium of an acid, which can also serve as a deuteron source.

Whether or not it is an absolute prerequisite, or merely a favorable circumstance, that the benzene ring substituent may serve as a proton or deuteron acceptor, thus enabling the molecule to acquire a positive charge,

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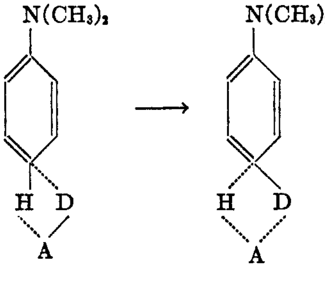
[23] Kharasch and Marker, *J. Am. Chem. Soc.*, **48**, 3130 (1925); Kharasch and Reinmuth, *J. Chem. Educ.*, **5**, 404 (1928); **8**, 1703 (1931); Kharasch, Reinmuth, and Mayo, **11**, 82 (1934); Kharasch and Flenner, *J. Am. Chem. Soc.*, **54**, 674 (1932).

* A rather attractive interpretation of the labilization by acids of the hydrogen atoms of strongly electronegative radicals and their replacement by deuterons, is given in the following highly schematic representation:



The essence of this representation is that there exists an attraction for deuterons by the *o* and *p* carbon atoms due to the high electron-density around these atoms, and that the labilization of the protons is facilitated by the approach of the deuterons. The formulae should not be looked upon as intermediates, but rather as phases of the labilization process.

is perhaps an open question. It is worthy of remark, however, that the substituent groups that we believe to be capable of increasing tremendously the electronegativity of the phenyl radical (the amino, the alkyl- and dialkylamino, the hydroxy and alkoxy groups) are all capable of so serving. The facts that traces of acids accelerate the exchange of the hydrogens for deuterium in dimethylaniline, while small amounts of alkali are essentially without effect, tend to support the first or third mechanisms suggested for this exchange. However, as already indicated, further experiments are necessary to test this hypothesis.

It is of interest to compare the high lability of the protons of dimethylaniline with the lack of lability of the protons of the di- and triarylmethanes in deuteroalcohol under the same conditions. Although the di- and triarylmethanes have been described as "weak acids," on the basis of their reactivity toward alkali metals,[24] it is fairly evident from our data that their proton ionization must be negligible.

From our standpoint, the electron density around the methyl carbon atoms in di- and triphenyl methanes would be very small, (as compared with the carbon atoms of *ortho-* or *para-N,N*-dimethylphenyl radicals), and in our notation we would define them as weakly electronegative radicals. It is possible of course for the electron density around the methyl carbon atom to decrease to a point where the proton may be readily removed by hydroxyl ions. Whether such a state is actually realized in fluorene, or whether the hydrogen atom lability should be ascribed to some peculiarity associated with the five-membered ring, the labilization of the hydrogen atoms by alkali is of considerable theoretical importance. We propose to investigate many other similar five-membered ring systems, particularly in view of the fact that acenaphthene does not undergo any exchange in deuteroalcohol.

Consistent with the interpretation that a low electron density around a carbon atom would facilitate the removal of a proton by hydroxyl ions, is the behavior of the nitrotoluenes and 1,3,5-trinitrobenzene in deuteroalcohol. Unlike the amino group, the nitro group markedly decreases the electronegativity of the phenyl radical.[25] These data are well in accord with observations that direct nuclear substitution proceeds more readily in aromatic hydrocarbons than in the corresponding nitro derivatives. This would imply that trinitrobenzene is a poor proton donor in acid solution. The fact that no exchange takes place when 1,3,5-trinitrobenzene is dissolved in deuteroalcohol is consistent with the view, and the

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[24] WOOSTER AND MITCHELL, *J. Am. Chem. Soc.*, **52**, 688 (1930); CONANT AND WHELAND, *ibid.*, **54**, 1212 (1932); *Cf.* KHARASCH AND REINMUTH, *J. Chem. Educ.*, **8**, 1740 (1931).

[25] KHARASCH AND GRAFFLIN, *J. Am. Chem. Soc.*, **47**, 1948 (1925); KHARASCH AND GLADSTONE, unpublished work.

contrast with the behavior of dimethylaniline is marked. We would predict also that no exchange would occur in the case of trinitrobenzene in deuteroalcohol even in the presence of small quantities of acids. In alkaline solution, however, the entire relationship is changed. The exchange of dimethylaniline hydrogen atoms is unaffected, but with trinitrobenzene and the ortho and para nitrotoluenes, substances which can exist in tautomeric forms, rapid exchange takes place. It is significant that 1,3,5-trinitrobenzene exchanges all three hydrogen atoms, while in *o*-nitrotoluene the exchange is less complete. In the case of the *p*-nitrotoluene an enormous labilization of a hydrogen atom by alkali is definitely demonstrated. In the case of *m*-nitrotoluene no labilization of the hydrogen atoms can be demonstrated in the presence of alkali. It is our belief that the small exchange observed with that substance is due to some impurity.

In quinaldine and 7,8-benzoquinaldine the methyl hydrogen atoms are readily eliminated as protons. The proton labilization in an alcoholic solution of quinaldine must be considerable, and accounts for the ready condensation of the molecule with many proton acceptors (aldehydes, etc.). The increased exchange noted in alkaline solution, and the effects of traces of acids, is under investigation.

In conclusion, we should like to call attention to the fact that in the case of strongly electronegative radicals a certain liminal value in electronegativity must be reached before labilization of a hydrogen atom becomes marked in the absence of high concentration of acid. Thus, 2-methoxynaphthalene does not exchange the hydrogen atom in the 1-position, although the radical is strongly electronegative. Of course, the lack of exchange cannot be attributed entirely to the character of the radical, but is in part due to the fact that deuteroalcohol is a poor deuteron donor. With molecules which supply a large concentration of deuterons, such as sulfuric acid, the exchange would probably take place. With this in mind, the tremendous lability of the dimethylaniline hydrogen atom is most striking.

EXPERIMENTAL DATA

Calibration of the float.—The float was calibrated with reference to normal water (laboratory distilled water) and two known samples of dilute heavy water which had been prepared by the quantitative dilution of a sample containing 12.47 mole per cent. deuterium oxide, this figure having been ascertained through pycnometric measurements of the density. The suspension temperature readings for normal water were: 1.610°, 1.625°, 1.610°, 1.650°; mean 1.625°. The readings for samples of water containing 0.87 mole per cent. deuterium oxide were 4.940°, 4.945°, 4.950°; mean 4.945°. The readings for samples containing 1.65 mole per cent. deuterium oxide were 7.925°, 7.910°, 7.895°, mean 7.910°.

Analysis of stock heavy alcohol.—The suspension temperature readings for water samples obtained on the combustion of the heavy alcohol which was used as the solvent in this work were as follows: 7.380°, 7.380°, 7.485°, 7.365°, 7.375°, 7.325°, 7.425°, 7.325°; mean 7.385°.

Combustion of normal ethyl alcohol.—As a check on the method of combustion and purification a number of analyses were carried through on absolute ethyl alcohol, and the following readings were obtained: 1.605°, 1.625°, 1.655°, 1.610°, 1.620°, 1.645°; mean 1.625° (*cf.* value for normal water).

Exchange experiments.—Experimental data concerning the preparation of the reaction mixtures and the analyses of the alcohol samples removed from these mixtures are recorded hereafter. The figures which follow the description of the experiment are the observed suspension temperatures. The units are degrees Centigrade and the scale, though arbitrary, is consistent throughout.

Triphenylmethane.—The triphenylmethane used in the present work was carefully purified by several crystallizations from alcohol. The compound was dried thoroughly *in vacuo* to remove any traces of water and solvent of crystallization; m.p. 92°.

Experiment 1.—A reaction tube containing 5 g. of triphenylmethane and 5 cc. of deuteroalcohol was allowed to stand at room temperature for 133 days: 7.285°, 7.260°, 7.460°; mean 7.325°.

Experiment 2.—A reaction mixture identical with that of experiment 1 was maintained at a temperature of 100° for 150 days: 7.350°, 7.400°, 7.410°; mean 7.385°.

Experiment 3.—To a reaction mixture of 5 g. of triphenylmethane and 5 cc. deuteroalcohol 0.002 g. NaOH was added. The reaction tube was immersed in an oil bath at 100° for 6 days. The error introduced by exchange of the hydrogen in such a small quantity of alkali is of negligible magnitude: 7.470°, 7.400°; mean 7.435°.

Diphenylmethane.—This compound was purified prior to use by a series of vacuum distillations.

Experiment 4.—The exchange reaction solution of 5 cc. diphenylmethane in 5 cc. deuteroalcohol was allowed to stand at room temperature for 147 days: 7.355°, 7.375°; mean 7.365°.

Fluorene.—A pure sample of this compound was obtained by several crystallizations from alcohol with subsequent drying *in vacuo*; m.p. 112–114°.

Experiment 5.—A reaction tube containing 5 g. fluorene and 5 cc. deuteroalcohol stood at room temperature for 138 days: 7.410°, 7.430°, 7.425°; mean 7.420°.

Experiment 6.—A reaction tube containing 5 g. fluorene in solution in 5 cc. deuteroalcohol at 110° was allowed to stand for 28 days: (*a*) 7.385°; (*b*) 7.285°, 7.325°; mean 7.310°.

Experiment 7.—A reaction mixture of 5 g. fluorene and 5 cc. deuteroalcohol containing 0.002 g. of NaOH was heated to 110° for 8 days: 5.425°, 5.255°; mean 5.340°.

Experiment 8.—A reaction mixture identical with that of experiment 7 was heated to a temperature of 110° for 2 days: 5.510°, 5.375°; mean 5.440°.

Experiment 9.—A reaction mixture of 5 g. fluorene and 5 cc. deuteroalcohol 0.01 molar in H_2SO_4 was maintained at a temperature of 110° for 2 days: 7.395°, 7.465°; mean 7.430°.

Acenaphthene.—A pure vacuum-dried product was prepared for use in this work; m.p. 94–95°.

Experiment 10.—A 5-g. portion of acenaphthene was placed in a reaction tube with 5 cc. deuteroalcohol, and the tube was immersed in an oil bath at 110° for 36 hours: 7.430,° 7.400°; mean 7.415°.

Dianisylphenylmethane.—A quantity of this compound was purified by several crystallizations from a mixture of chloroform and methyl alcohol; drying was effected *in vacuo*; m.p. 100–101°.

Experiment 11.—A reaction mixture of 5 g. dianisylphenylmethane and 5 cc. deuteroalcohol was maintained at a temperature of 110° for 36 hours: 7.340°, 7.370°; mean 7.355°.

Experiment 12.—A reaction mixture of dianisylphenylmethane and deuteroalcohol 0.02 molar in NaOH was heated to a temperature of 110° for 96 hours: 7.060°.

Ethyl acetoacetate.—The product used in this work was purified by several distillations *in vacuo.*

Experiment 13.—A reaction tube containing 5 cc. ethyl acetoacetate and 5 cc. deuteroalcohol was allowed to stand at room temperature for 3 days: 5.125°, 4.940°; mean 5.030°.

Succinimide.—A pure sample of this compound was dried for several hours in an Abderhalden desiccator at 78° prior to use in the exchange experiments; m.p. 124°.

Experiment 14.—A reaction mixture of 5 g. succinimide and 5 cc. deuteroalcohol was maintained at a temperature of 110° for a period of 25 hours: 5.450°, 5.640°; mean 5.545°.

2-Methoxynaphthalene.—A carefully purified sample of this compound was thoroughly dried *in vacuo* for use in the present work; m.p. 70°.

Experiment 15.—A tube containing 5 g. 2-methoxynaphthalene and 5 cc. deuteroalcohol was immersed in an oil bath at 110° for 22 hours: 7.435°, 7.395°; mean 7.420°.

Experiment 16.—A reaction mixture of 2-methoxynaphthalene and deuteroalcohol containing 0.002 g. NaOH was heated to a temperature of 110° for 22 hours: 7.425°, 7.365°; mean 7.395°.

o-*Nitrotoluene.*—This compound was purified by a series of vacuum distillations.

Experiment 17.—A solution of 5 cc. *o*-nitrotoluene in 5 cc. deuteroalcohol was heated to 110° for 34 hours: 6.400°, 6.470°; mean 6.435°.

Experiment 18.—A reaction mixture of *o*-nitrotoluene and deuteroalcohol 0.02 molar in NaOH was maintained at a temperature of 110° for 34 hours: 5.565°, 5.615°; mean 5.590°.

p-*Nitrotoluene.*—A pure sample of this compound was dried thoroughly *in vacuo* prior to use in exchange experiments; m.p. 52°.

Experiment 19.—A reaction tube containing 5 g. *p*-nitrotoluene and 5 cc. deuteroalcohol was immersed in an oil bath at 110° for 48 hours: 7.290°, 7.260°; mean 7.275°.

Experiment 20.—A reaction mixture of *p*-nitrotoluene and deuteroalcohol 0.02 molar in NaOH was heated to 110° for 48 hours: 6.250°, 6.210°; mean 6.230°.

Quinaldine.—A quantity of this compound was purified prior to use by distillation *in vacuo.*

Experiment 21.—A reaction tube containing 5 cc. of quinaldine in solution in 5 cc. deuteroalcohol was heated to a temperature of 110° for a period of 80 hours: 4.795°, 4.845°; mean 4.820°.

1,3,5-Trinitrobenzene.—A pure sample of this compound was throughly dried *in vacuo* for use in the present investigation; m.p. 121–122°.

Experiment 22.—A reaction mixture of 5 g. 1,3,5-trinitrobenzene and 5 cc. deuteroalcohol was maintained at a temperature of 110° for 64 hours: 7.345°, 7.395°; mean 7.370°.

Experiment 23.—A reaction mixture of 1,3,5-trinitrobenzene and deuteroalcohol 0.02 molar in NaOH was heated to a temperature of 110° for a period of 68 hours: 5.075°, 5.015°; mean 5.045°.

7,8-Benzoquinaldine.—Several attempts to crystallize this compound from dilute alcohol were unsuccessful. The compound was finally purified by distillation under very low pressure; m.p. 82°.

Experiment 24.—A reaction mixture of 5 g. 7,8-benzoquinaldine and 5 cc. deuteroalcohol was heated to a temperature of 110° for 104 hours: 6.150°, 6.090°; mean 6.120°.

Experiment 25.—A reaction mixture of 7,8-benzoquinaldine and deuteroalcohol 0.02 molar in NaOH was maintained at a temperature of 110° for 108 hours: 5.050°, 5.120°; mean 5.085°.

m-*Nitrotoluene.*—A quantity of this compound (Kahlbaum product) was purified by a series of vacuum distillations with subsequent drying over anhydrous Na_2SO_4.

Experiment 26.—A reaction tube containing 5 cc. *m*-nitrotoluene and 5 cc. deuteroalcohol was immersed in an oil bath at 110° for 66 hours: (*a*) 7.385°, (*b*) 7.045°, 7.025°; mean 7.035°.

Experiment 27.—A reaction mixture of *m*-nitrotoluene and deuteroalcohol 0.02 molar in NaOH was maintained at a temperature of 110° for 66 hours: 7.015°, 7.055°; mean 7.035°.

Experiment 28.—A control or blank run was made by mixing 5 cc. of *m*-nitrotoluene and 5 cc. deuteroalcohol and then removing the deuteroalcohol immediately by distillation *in vacuo*: 7.045°.

Dimethylaniline.—A quantity of this compound was purified by distillation from sodium, the distillate being allowed to stand over sodium overnight, then redistilled from sodium and a central fraction collected.

Experiment 29.—A reaction tube containing 5 cc. dimethylaniline in solution in 5 cc. deuteroalcohol was heated to 110° for a period of 96 hours: 6.450°, 6.325°; mean 6.390°.

Experiment 30.—A reaction mixture of 5 cc. dimethylaniline and 5 cc. deuteroalcohol 0.02 molar in NaOH was maintained at a temperature of 110° for 96 hours: 6.595°, 6.490°; mean 6.545°.

Experiment 31.—A reaction mixture identical with that of experiment 29 (neutral solution) was heated at 110° for 96 hours. A portion of the deuteroalcohol was distilled from the solution *in vacuo* into a receiver containing anhydrous phosphorus pentoxide. After a short period of standing a portion of this alcohol was removed by a further distillation *in vacuo*: 6.285°.

Experiment 32.—A reaction mixture of dimethylaniline and deuteroalcohol 0.01 molar in H_2SO_4 was maintained at a temperature of 110° for 96 hours. The deuteroalcohol was recovered by the same technique employed in experiment 31: 4.385°.

Experiment 33.—Experiment 32 was duplicated with the exception that the reaction mixture stood 48 hours at room temperature after the treatment at 110° for 96 hours: 4.240°; mean of experiments 32 and 33, 4.315°.

SUMMARY

1. The lability of hydrogen atoms in a number of organic substances has been studied with the aid of deuteroalcohol as the deuteron donor.

2. The theoretical implications of the lability of the hydrogen atoms in acid and alkaline solutions are discussed.

3. The experimental part should be consulted for the details of the analyses and the accuracy of the experimental results.

4. The work is being continued.

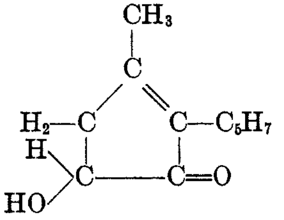
[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, UNITED STATES DEPARTMENT OF AGRICULTURE, WASHINGTON, D. C.]

CONSTITUENTS OF PYRETHRUM FLOWERS. VII.* THE BEHAVIOR OF THE PYRETHRINS ON HYDROGENATION†

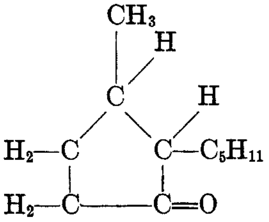
H. L. HALLER AND F. B. LAFORGE

Received February 2, 1937

It has been shown[1] that pyrethrolone (formula I), the cyclic ketonic alcohol common to both of the known pyrethrins, when completely hydrogenated, with elimination of the hydroxyl group and saturation of the side chain and nucleus, is converted into hexahydropyrethrone (formula II).



I



II

This end-product however, is obtained more advantageously by hydrogenation of the ethers or the acetate of pyrethrolone.[1] The hydrogenation of an ester with formation of an acid and a hydrocarbon, although uncommon, has since been observed with other esters.[2]

As the pyrethrins themselves are esters of pyrethrolone with chrysanthemum monocarboxylic acid and chrysanthemum dicarboxylic acid methyl ester, on hydrogenation they should be expected to behave in the same manner as pyrethrolone acetate, and should yield, as the final reaction products, hexahydropyrethrone of formula II and the respective acid components. Thus, pure pyrethrin I should yield hexahydropyrethrone and dihydrochrysanthemum acid (formula III), and pyrethrin II should yield the same hexahydropyrethrone and chrysanthemum dicarboxylic acid monomethyl ester (formula IV), in which the double bond, unlike the one in the monocarboxylic acid, is completely resistant to hydrogenation.

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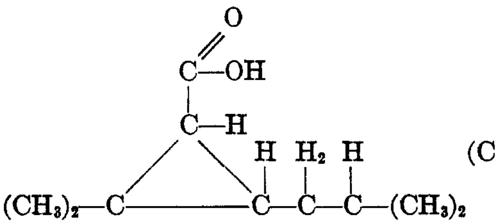
* For article VI of this series see *J. Am. Chem. Soc.*, **58**, 1777 (1936).

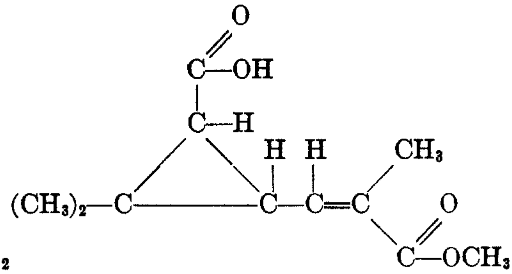
† Presented before the Division of Organic Chemistry at the ninety-third meeting of the American Chemical Society, Chapel Hill, N. C., April 13, 1937.

[1] STAUDINGER AND RUZICKA, *Helv. Chim. Acta*, **7**, 236 (1924).

[2] BURDICK AND ADKINS, *J. Am. Chem. Soc.*, **56**, 438 (1934).



III



IV

That the pyrethrins actually do behave in this manner has now been demonstrated by a large number of experiments.

Since neither pyrethrin I nor pyrethrin II has yet been available in a pure state, the concentrates containing both pyrethrins, but in widely different proportions, described in a previous article,[3] were employed as starting material for these investigations.

Although a pyrethrin II concentrate can be prepared that by analysis contains over 80 per cent. of pyrethrin II and only about 4 per cent. of pyrethrin I, the best pyrethin I concentrate thus far obtained has a content of not more than 55 per cent. of pyrethrin I and about 11–12 per cent. of pyrethrin II. In both these concentrates the rest of the material consists for the most part of unknown substances. The pyrethrin II concentrate, containing the least of these impurities, should evidently be more suitable for the study of the course of hydrogenation than the pyrethrin I concentrate.

In a previous article[4] it was shown that, with the employment of platinum oxide catalyst, the pyrethrin II concentrate was rapidly hydrogenated, and that if the process was interrupted at the proper time, the reaction product, tetrahydropyrethrin II, with a saturated side chain could be readily isolated in good yield as its crystalline semicarbazone. The conditions of this experiment were similar to those employed for the preparation of tetrahydropyrethrolone by hydrogenation of pyrethrolone or its semicarbazone.

It has now been observed that, when the hydrogenation of a pyrethrin II concentrate is prolonged, hydrogen is absorbed at a slower rate for a long time after the first more rapid reaction has taken place.

This first reaction evidently involves the saturation of the side chain of the pyrethrolone component. Cleavage of the molecule, with the formation of tetrahydropyrethrone (dihydrojasmone) (formula V) and

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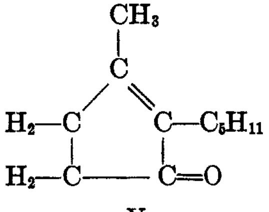
[3] LAFORGE AND HALLER, *ibid.*, **57**, 1893 (1935).

[4] HALLER AND LAFORGE, J. ORG. CHEM., **1**, 38 (1936).

chrysanthemum dicarboxylic acid monomethyl ester, then follows and, finally, the saturation of the remaining double bond in the α,β position in the nucleus of tetrahydropyrethrone with the formation of hexahydropyrethrone (formula II).



V

In actual practice, although the first stage of the hydrogenation was finished in a very short time, the absorption of hydrogen ceased owing to inactivation of the catalyst before the last two stages had reached completion. If the acids were removed and the catalyst renewed, the neutral material could then be further hydrogenated with the production of more acid.

The acid products of the reaction were found to consist almost entirely of chrysanthemum dicarboxylic acid monomethyl ester, which could be freed by steam distillation of small quantities of volatile acids originating from the pyrethrin I, or possibly from the unknown by products present in the concentrate. (Incidentally, the hydrogenation procedure offers the most convenient method for obtaining pure chrysanthemum dicarboxylic acid monomethyl ester.) The neutral reaction products consisted largely of tetrahydropyrethrone (dihydrojasmone) and hexahydropyrethrone, which were separated from nonvolatile impurities by steam distillation and isolated as their semicarbazones.

Hexahydropyrethrone semicarbazone forms more rapidly and is less soluble than the semicarbazone of the tetrahydro compound. The crystalline deposit that first formed, consisting chiefly of this compound, was removed by filtration after 3 or 4 hours.

The semicarbazone of tetrahydropyrethrone separated from the solution on longer standing, and the part remaining in solution was obtained in an impure state by precipitation with water.

A detail worthy of special mention is the fact that tetrahydropyrethrone semicarbazone is easily soluble in cold dilute hydrochloric acid and is precipitated unchanged from the solution by addition of alkali.[5] This property was taken advantage of for its complete separation from noncrystalline byproducts. The semicarbazone of hexahydropyrethrone is

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[5] LaForge and Haller, *J. Am. Chem. Soc.*, (in press).

insoluble in acid and was separated from small quantities of the soluble semicarbazone of the tetrahydro derivative in the same manner.

Under the conditions described, the yield of hexahydropyrethrone semicarbazone was much less than that of the tetrahydroderivative. The former was obtained sometimes in the form that melted at 160° and at other times, under the same conditions and treatment, in the stereoisomeric form melting at 194°.[6]

When palladium charcoal or the Raney nickel catalyst was employed, the results were similar to those obtained with platinum oxide, although in general more of the hexahydropyrethrone was obtained.

As already stated, concentrates of pyrethrin I always contain, besides some pyrethrin II, more than twice as much material other than pyrethrins as does the pyrethrin II concentrate. Consequently, the results obtained on hydrogenation were not so definite as those obtained with the pyrethrin II concentrate. The course of the reaction was similar in both cases. With the pyrethrin I concentrate and the platinum oxide catalyst, the rate of absorption was at first rapid and then continued at a slower rate. To complete the reaction, the acids formed were removed and the neutral material was further hydrogenated with fresh catalyst.

The total acid fraction was distilled with steam and the volatile constituent was separated. This was found, by analysis, titration, and from its physical properties, to consist of dihydrochrysanthemum monocarboxylic acid. The nonvolatile residue was not further examined because of the small quantity.

The neutral fraction was subjected to steam distillation, and the volatile constituents were treated with semicarbazide in the usual manner. A mixture of the semicarbazones of tetrahydro- and hexahydropyrethrone, which was separated with hydrochloric acid, was obtained. The latter was obtained in two forms, one melting at 196° and the other at 160°C.

Theoretically, the quantities of dihydrochrysanthemum acid and of the hydrogenated pyrethrones to be expected from pyrethrin I should be very nearly equal, since the molecular weight of the acid is 170 and that of hydrogenated pyrethrones 166 and 168. Actually, the quantity of acid obtained was about 50 percent. greater than the quantity of pyrethrones as calculated from the yield of their semicarbazones. This discrepancy may be due to incomplete isolation of the semicarbazones, or the excess acid may have been formed by the hydrogenation of some byproduct.

In the experiment described, in which the pyrethrin II concentrate was hydrogenated, the yield of acids exceeded the quantity of reduced pyrethrones, as calculated from the weight of semicarbazones obtained, by only 20 percent., which may be within the experimental error. In

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[6] TREFF AND WERNER, *Ber.*, **66**: 1521 (1933).

both experiments the quantities of acids obtained correspond very closely to the quantities of the pyrethrins in the respective concentrates as determined by analysis, where the method of Seil[7] was used for pyrethrin I and the methoxyl method[8] for pyrethrin II.

Since the reductive cleavage of the pyrethrins with the formation of the corresponding acids is specific for these compounds, the hydrogenation method offers at least the theoretical possibility of the development of a quantitative method based on this behavior.

EXPERIMENTAL

Hydrogenation of pyrethrin II concentrate.—Five grams of a concentrate that contained 80.8 per cent. of pyrethrin II and about 4 per cent. of pyrethrin I,[8] was dissolved in about 35 cc. of ethanol and reduced in an atmosphere of hydrogen with 0.3 gram of reduced platinum oxide catalyst. The absorption of hydrogen was very rapid at first, and about 300 cc. was absorbed in about 20 minutes. The absorption then continued at a slower rate until about 1,200 cc. was taken up in the course of 7 hours, after which the absorption practically ceased. At this stage the solution was filtered and made neutral to phenolphthalein with 5 per cent. potassium hydroxide solution. Water was then added and the solution was twice extracted with petroleum ether. The neutralized aqueous alcoholic solution was then evaporated to a small volume on the steam bath.

The neutral petroleum-ether residue was again subjected to hydrogenation with fresh catalyst and absorbed about 75 cc. in 3 hours.

On completion of the second reduction the reaction products were again separated into acid and neutral fractions.

The alkali-soluble fractions from both hydrogenations were combined, acidified with dilute sulfuric acid, and extracted repeatedly with petroleum ether. On removal of the solvent, 2.15 grams of acid material was obtained. This was subjected to steam distillation to remove the small quantity of chrysanthemum monocarboxylic acid originating from the pyrethrin I in the concentrate. The acids that were not volatile with steam were isolated by extraction with petroleum ether and removal of the organic solvent. The yield was 1.9 grams. The crude product was then distilled and boiled at 145–7° and 1.5 mm., giving 1.5 grams of pure chrysanthemum dicarboxylic acid monomethyl ester.

Anal. Calc'd for $C_{11}H_{16}O_4$: Mol. wt., 212; OCH_3, 14.6.
Found: Equiv. wt. (titration) 211.5; OCH_3, 14.27.

The calculated quantity of chrysanthemum dicarboxylic acid monomethyl ester in the concentrate employed is 2.3 grams.

The neutral reaction product of the experiment consisted of 2.1 grams of oil. This material was subjected to steam distillation, and the volatile constituents that contained the hydrogenated pyrethrones were separated from the nonvolatile impurities. The volatile constituents (1.8 grams) were dissolved in 17 cc. of ethanol and 3 cc. of pyridine, and 2.5 grams of semicarbazide hydrochloride in 3.5 cc. of hot water was added. After standing for 4 hours at room temperature, the separated crystals (0.35 gram) were removed by filtration. A second crop of crystals (0.65 gram) was ob-

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[7] SEIL, *Soap*, **10**, no. 5, 89 (1934).

[8] HALLER AND ACREE, *Ind. Eng. Chem.*, *Anal. Ed.*, **7**, 343 (1935).

tained from the filtrate on standing overnight. Water was then added to the filtrate and a precipitate was obtained that consisted of less pure material. After drying it weighed 0.85 gram. The second crop consisted essentially of tetrahydropyrethrone (dihydrojasmone) semicarbazone. It melted, after one recrystallization from benzene, at 176°, simultaneously with a mixture obtained by mixing it with an equal part of authentic tetrahydropyrethrone semicarbazone.

Anal. Calc'd for $C_{12}H_{21}N_3O$: C, 64.57; H, 9.42.
Found: C, 64.49, 64.85; H, 9.55, 9.50.

The first crop consisted principally of hexahydropyrethrone semicarbazone, the third of an impure mixture of the tetrahydro and hexahydro derivatives. Since the tetrahydro derivative has been shown to be soluble in dilute hydrochloric acid,[5] this property was utilized for their purification. The first crop was suspended in petroleum ether and shaken in the cold with dilute hydrochloric acid (about 4*N*). This treatment removed the tetrahydropyrethrone semicarbazone, leaving an insoluble fraction consisting of the semicarbazone of hexahydropyrethrone that melted after recrystallization from benzene at 160°. A mixture of it with authentic material likewise melted at 160°.

Anal. Calc'd for $C_{12}H_{23}N_3O$: C, 64.0; H, 10.22.
Found: C, 64.64, 64.35; H, 10.41, 10.36.

The third crop was separated by treatment with dilute hydrochloric acid, and the soluble semicarbazone was isolated from the acid solution by addition of alkali. This material was combined with the acid-soluble portion obtained from the first crop and recrystallized from benzene. It was identified by its melting point (176°) and mixture melting point as tetrahydropyrethrone semicarbazone. The acid-insoluble fraction after recrystallization from benzene was shown to be tetrahydropyrethrone semicarbazone melting at 160°. The total yield of hexahydropyrethrone semicarbazone was 0.8 gram, and of tetrahydropyrethrone semicarbazone 1.0 gram. The yield of hydrogenated pyrethrone semicarbazones as calculated from the pyrethrin content of the concentrate was 2.54 grams.

Hydrogenation of a pyrethrin I concentrate.—The same general procedure described above was employed for the hydrogenation of the pyrethrin I concentrate.

Five grams of a concentrate[3] containing 54.4 per cent. of pyrethrin I and 11.5 per cent. of pyrethrin II as determined by analysis was dissolved in about 35 cc. of ethanol and hydrogenated with 0.3 gram of reduced platinum oxide catalyst. In this case about 300 cc. of hydrogen was absorbed in 10 minutes, after which the reduction proceeded until 900 cc. had been absorbed in 7 hours. The solution was then filtered and neutralized, and after addition of water the neutral portion was separated by extraction with petroleum ether. After removal of the solvent the residue was returned to the apparatus and further hydrogenated with a fresh quantity of catalyst. In the second operation 400 cc. of hydrogen was absorbed, and after the reaction had ceased the products were separated as before into neutral and acid fractions and the latter was combined with the first alkaline extract. The solution was concentrated and the organic acids were isolated by addition of dilute sulfuric acid and extraction with petroleum ether; yield, 2 grams. The crude acid was subjected to steam distillation, and the volatile acids were recovered from the distillate; yield, 1.7 grams. The acid distilled at 98° and 0.35 mm.; yield, 1.3 grams. It was identified as dihydrochrysanthemum monocarboxylic acid.

Anal. Calc'd for $C_{10}H_{18}O_2$: Mol. wt., 170; C, 70.60; H, 10.60.
Found: Equiv. wt. (titration) 169.4; C, 70.16; H, 10.63.

Only a very small quantity of acids nonvolatile with steam was obtained, but this was not further examined. The yield of total acids calculated from the total pyrethrin content in the concentrate was 1.74 grams.

The neutral fraction (2.6 grams) was steam-distilled, and the volatile constituents were recovered from the distillate with petroleum ether; yield, 1.65 grams. The oil was converted into the semicarbazones. The proportions of solvent and reagents employed were: ethanol 17 cc., pyridine 3 cc., semicarbazide hydrochloride 2.5 grams in 3.5 cc. of water. After 4 hours the deposit of crystals was removed by filtration. The yield was 0.35 gram and the melting point 185°. After one recrystallization from methanol it melted at 196°. It was compared with authentic hexahydropyrethrone semicarbazone melting at 196° and found to be identical with it.

Anal. Calc'd for $C_{12}H_{23}N_3O$: C, 64.0; H, 10.22.
Found: C, 64.60, 64.70; H, 10.28, 10.40.

A second crop of crystals was deposited from the solution on longer standing; yield, 0.55 gram. This was a mixture of the semicarbazones of tetrahydro- and hexahydropyrethrones. Water was added to the filtrate and precipitated 0.8 gram more of the same mixture. These two mixtures were combined and separated into acid-soluble (0.4 gram) and acid-insoluble fractions (0.8 gram).

The acid-insoluble fraction, after recrystallization from benzene, melted at 160°, and was identified as the other form of the semicarbazone of hexahydropyrethrone by determination of melting point of a mixture with an authentic sample. The acid-soluble fraction was recrystallized from benzene, and then melted at 176°, and was identified as tetrahydropyrethrone semicarbazone. The quantity of hydrogenated semicarbazones, calculated on the basis of the total pyrethrin content of the concentrate, is 2.2 grams.

A large number of experiments were made with other concentrates of various pyrethrin contents and platinum oxide catalyst. Also in several cases the Raney nickel catalyst and palladium charcoal were employed. In general the results obtained were similar to those described in detail above.

SUMMARY

As in the hydrogenation of the acetate of pyrethrolone with the formation of hexahydropyrethrone, the pyrethrins I and II are cleaved on hydrogenation, yielding a mixture of tetrahydro- and hexahydropyrethrone and the respective acid components.

A concentrate in which pyrethrin II predominated yielded tetrahydro- and hexahydropyrethrone, together with chrysanthemum dicarboxylic acid monomethyl ester; one that contained principally pyrethrin I yielded the same pyrethrone derivatives and dihydrochrysanthemum monocarboxylic acid.

These reaction products have been isolated and identified in a series of experiments.

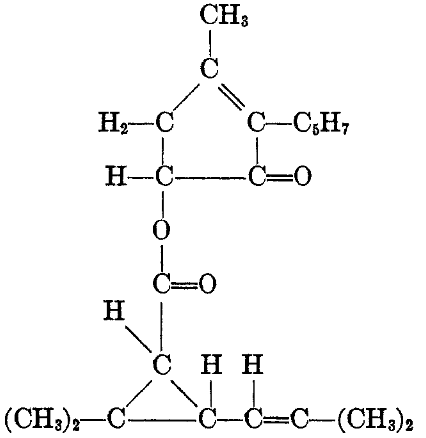
[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, U. S. DEPARTMENT OF AGRICULTURE, WASHINGTON, D. C.]

CONSTITUENTS OF PYRETHRUM FLOWERS. VIII.* THE PRESENCE OF A NEW ESTER OF PYRETHROLONE

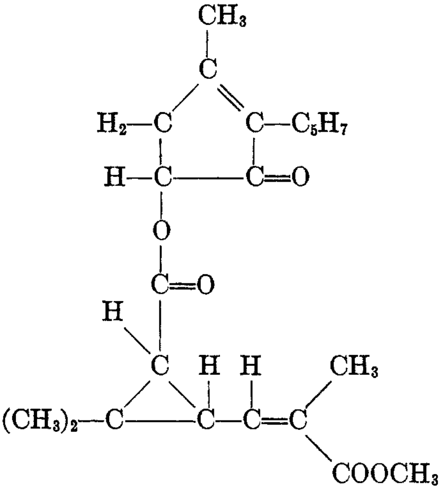
F. B. LAFORGE AND H. L. HALLER

Received February 2, 1937

Pyrethrum flowers are known to contain two insecticidally active compounds, pyrethrin I and pyrethrin II. These have been regarded as the only constituents having insecticidal properties.



Pyrethrin I



Pyrethrin II

Many methods have been devised and are in general use for the quantitative estimation of the pyrethrins. Some of these methods are based on the separation and titration of the acid components, others on the indirect determination of the pyrethrolone component. Comparisons of the values obtained by the various methods usually revealed a lack of concordance. Moreover, attempts to correlate the chemical analyses with toxicity have generally been unsuccessful. The reasons for this failure are many, and among them may be mentioned the lack of definite knowledge of the relative toxicity of pyrethrin I and pyrethrin II, the presence of the chrysanthemum acids, free or combined, and the possible presence in the flowers

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* For article VII of this series see J. ORG. CHEM., **2**, 49 (1937).

of esters of pyrethrolone with acids other than those contained in the known pyrethrins.

Neither pyrethrin I nor pyrethrin II has yet been obtained as a chemically pure individual of unaltered configuration. The isolation of the pyrethrins as their crystalline semicarbazones by Staudinger and Ruzicka[1] made possible the determination of their structures by indirect means, but these authors did not claim to have prepared even these derivatives in a chemically pure state.

In a previous article of this series[2] the semicarbazone of pyrethrin II is described for the first time. Its ease of purification, sharp melting point, and definite elementary composition characterize it indubitably as a chemical individual. However, no method has yet been dicovered by which this derivative can be hydrolyzed to yield pyrethrin II in a pure condition.

The semicarbazone of pyrethrin I, on the other hand, has not been obtained in a state of more than approximate purity. Preparations of it obtained from concentrates of pyrethrin I always exhibit an indefinite melting point even after repeated recrystallization, and they always contain methoxyl. This methoxyl content persists even after repeated purification fails to raise the melting point further.

Another significant difference between the semicarbazones of pyrethrin I and pyrethrin II is the relative instability of the former. Pyrethrin II semicarbazone may be kept over a period of years without any noticeable change, but the semicarbazone of pyrethrin I begins to darken after a few weeks when kept in ordinary containers, and after several months it is badly decomposed.

Since the semicarbazone of pyrethrin II is the more soluble in most reagents, it is strange that it should not be eliminated by recrystallization. Nevertheless, preparations of pyrethrin I semicarbazone melting at 114–120° show a methoxyl content indicating the presence of 8 to 10 per cent. of pyrethrin II semicarbazone. The possibility of the presence of some other methoxyl-containing complex is, of course, not excluded by any evidence at hand.

Saponification of pyrethrin I semicarbazone preparations yielded as the alcoholic component only pyrethrolone semicarbazone. Since the presence of pyrethrin II semicarbazone in the pyrethrin I semicarbazone preparations could be decided by the isolation and identification of chrysanthemum dicarboxylic acid, an examination of the combined acids was made in the manner described below.

A concentrate containing about 50 per cent. pyrethrin I and about 12

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

[2] HALLER AND LAFORGE, J. ORG. CHEM., **1**, 38 (1936).

per cent. pyrethrin II was treated with semicarbazide in the manner already described,[2] and the semicarbazone was purified by two crystallizations from acetone and one from toluene. The material melting at 114–118° was then saponified in methanol solution with one equivalent of sodium methylate to pyrethrolone semicarbazone and the mixture of acids and esters according to the usual procedure.[2] The acid-ester mixture was then completely saponified, and the acids were isolated. Since chrysanthemum monocarboxylic acid is volatile with steam while chrysanthemum dicarboxylic acid is not, a separation of the two could be easily accomplished. The acids obtained were therefore subjected to this process and, as was to be expected, the major fraction was found to be volatile and was identified as chrysanthemum monocarboxylic acid. A considerable proportion of the total acids, however, was found to be nonvolatile with steam, and this acid residue, corresponding to roughly 20 per cent. of semicarbazones other than pyrethrin I in the starting material, was then examined. Chrysanthemum dicarboxylic acid is known to be almost insoluble in petroleum ether. When, however, the nonvolatile acid mixture was extracted with this solvent, a very large proportion of it dissolved. The remaining syrupy acid was then extracted with ether, and the ether-soluble residue, after removal of the solvent, crystallized partly on seeding with chrysanthemum dicarboxylic acid.

Since not all of this acid fraction could be induced to crystallize, and because the direct quantitative isolation of chrysanthemum dicarboxylic acid is practically impossible, its characteristic *p*-phenylphenacyl ester[2] was prepared from a portion of the mixture and thus identified. The yield of the derivative indicated, however, that the mixture contained only about 25 per cent. of the dicarboxylic acid, while the remainder could not be identified.

Chrysanthemum dicarboxylic acid itself was isolated directly from another portion of the mixture and identified by its melting point.

The part of the original acid mixture that was soluble in petroleum ether was obtained, on removal of the solvent, as a slightly yellow oil that solidified on cooling. The crude acid contained small amounts of chrysanthemum dicarboxylic acid, which could be removed by taking advantage of the solubility of the latter in hot water. The purified material was then distilled in a high vacuum. The acid melted at 41°. It decolorized bromine and is therefore unsaturated. With the Denigés reagent it gave a color similar to that of chrysanthemum monocarboxylic acid. A solution of its alkali salt is precipitated by barium chloride.

Although the analyses and titration indicate the formula $C_{16}H_{30}O_2$ it is doubtful that the compound is homogeneous. A *p*-bromoanilide is obtained by treating the acid chloride with *p*-bromoaniline. Analysis of this derivative agrees fairly closely with the derivative of the acid of the above formula but the yield is small. On hydrogenation with platinum oxide catalyst the equivalent of one mol of hydrogen is absorbed and an acid is obtained that melts at 53°. Analysis indicates that the hydrogenated compound corresponds to the formula $C_{16}H_{32}O_2$. However, titration indicates a molecular weight of about 290. It seems probable that the original material is a mixture of two or more fatty acids which may still contain a small quantity of chrysanthemum dicarboxylic acid.

From the data so far obtained, it may be concluded that esters of pyrethrolone with acids other than the chrysanthemum acids are present in pyrethrum flowers and that the semicarbazones of these esters are contained in the highly purified pyrethrin I semicarbazone preparations to the extent of 7 to 8 per cent.

As to the effect of the presence of other pyrethrolone esters in pyrethrum flowers on the analytical results, those methods which are based on pyrethrolone would include them with the total pyrethrins, while those based on the determination of the chrysanthemum acids would be unaffected since the new acid would be eliminated by the precipitation with barium chloride.

EXPERIMENTAL

Saponification of pyrethrin I semicarbazone.—Forty grams of a preparation of pyrethrin I semicarbazone that had been recrystallized twice from acetone and once from toluene, and that melted at 114–118° (clear at 120°), were saponified in 450 cc. of methanol with one mol of sodium methylate. After standing in the ice box for 6 days, the separated pyrethrolone semicarbazone was filtered off and the alcoholic solution was evaporated to a syrup. This was dissolved in about 150 cc. of ethanol to which 15 cc. of 15 per cent. aqueous potassium hydroxide was added, and the solution was refluxed for 10 minutes. The condenser was then removed and the solution was boiled with gradual addition of water until the greater part of the ethanol had been expelled. On cooling, a voluminous deposit of pyrethrolone semicarbazone was obtained. This was removed by filtration and recrystallized by dissolving in a boiling mixture of equal parts of methanol and ethyl acetate and concentrating to about one-third of its volume. The dried material weighed 5.4 grams and melted at 202–203°. It was therefore unaltered pyrethrolone semicarbazone. The main portion of the same material weighed 17.0 grams and melted at 205°. The total yield of semicarbazone was 22.4 grams, or 91.8 per cent. of the theoretical quantity that would result from 40 grams of pure pyrethrin I semicarbazone.

Separation of the acid components.—The aqueous alcoholic solution resulting from the complete saponification of the acid-ester mixture that contained the alkali salts of the total acids was acidified, and the acids were isolated by extraction with ether. The quantity obtained was 16.5 grams. By calculation 40 grams of pure pyrethrin I semicarbazone should yield 17.4 grams of chrysanthemum monocarboxylic acid. The acids obtained were subjected in three equal portions to steam distillation in such a manner that about 700 cc. of distillate was collected from each one in 20 to 25 minutes, after which time the distillate was practically neutral. The three distillates were extracted with petroleum ether. The aqueous solution was neutralized and concentrated to about 30 cc. on the steam bath. It was then acidified and extracted with petroleum ether. The solvent was then evaporated from the combined petroleum ether solutions, leaving 13.0 grams of chrysanthemum monocarboxylic acid, or about 75 per cent. of the theoretical yield calculated from 40 grams of pure pyrethrin I semicarbazone.

After each distillation the nonvolatile acids were extracted several times, first with petroleum ether and then with ether, the extracts being kept separate. The total quantity of acids obtained from the petroleum ether extracts was 1.4 grams, that from the ether extracts 1.7 grams.

The ether extracts consisted of a thick reddish oil, which crystallized partly on seeding with chrysanthemum dicarboxylic acid. Since the crystallization was not complete, 0.45 gram of this material was neutralized with alcoholic alkali and, after addition of the quantity of *p*-phenylphenacyl bromide corresponding to the amount of alkali required, was boiled for 30 minutes. The chrysanthemum dicarboxylic acid di-*p*-phenylphenacyl ester[2] separated from the boiling solution and, after cooling, was filtered off and recrystallized from ethyl acetate. It melted at 153–154° simultaneously with a mixture with an authentic sample of this compound. The yield (0.34 gram) corresponded to about 25 per cent. of the dicarboxylic acid in the crude acid mixture. The rest of the ether residue was boiled with 8 cc. of water, and the insoluble oil was separated by decantation and filtration. The oil was again extracted with a little water in the same manner. The aqueous solution, on standing, deposited crystals which were separated and twice recrystallized from chloroform and petroleum ether. Thus a small quantity of chrysanthemum dicarboxylic acid was obtained as such, melting at 160°. The oily material was not further investigated. The petroleum-ether-soluble acid material obtained by the first petroleum-ether extraction solidified at room temperature and contained a little chrysanthemum dicarboxylic acid. By far the greater part, however, consisted of an acid not heretofore observed in pyrethrum flowers.

The 1.4 grams obtained in the experiment was dissolved in 8 cc. of 10 per cent. potassium hydroxide solution, heated to boiling, transferred to a small separatory funnel with the aid of 2 to 3 cc. of hot water, and was acidified with 6 cc. of hot 10 per cent. hydrochloric acid. The small quantity of chrysanthemum dicarboxylic acid present remained dissolved in the aqueous solution which was drawn off from the main quantity of the insoluble melted acid that floated on the surface. This was washed with hot water and dissolved in petroleum ether. After drying and removal of the solvent, the 1.1 grams of residue was distilled; it passed over between 175° and 185° at 0.7 mm., and solidified on cooling. The yield of distilled product was 0.8 gram. It melted at 41°.

The acid decolorized bromine solution and is therefore unsaturated. A 3 per cent. solution in methanol showed no rotation in a 2-dm. tube.

Anal. Calc'd for $C_{16}H_{30}O_2$: Mol. wt. 254; C, 75.59; H, 11.81.
Found: Equiv. wt. (titration) 260.6, 259.3, 250; C, 75.32; H, 11.56.

The acid chloride was prepared from the acid by treatment with thionyl chloride in petroleum ether solution.

Derivatives of the new acid.—The acid chloride in benzene solution was added to about two mol equivalents of *p*-bromoaniline dissolved in benzene. The solution was heated to boiling, filtered from the *p*-bromoaniline hydrochloride, and extracted first with dilute hydrochloric acid and then with dilute potassium hydroxide. The benzene solution was concentrated to a small volume and on addition of petroleum ether yielded the crystalline reaction product. It was recrystallized from methanol, and melted at 107°. The yield was small.

Anal. Calc'd for $C_{22}H_{34}BrNO$: C, 64.70; H, 8.33; Br, 19.60; N, 3.43.
Found: C, 65.01, 64.82; H, 8.91, 8.88; Br. 20.05; N, 3.43, 3.32.

The methyl ester was prepared by boiling 1 part of the acid in 20 parts of methanol containing 1 part of sulfuric acid. After 2 hours the solution was diluted with water and the ester was extracted with petroleum ether. The solution was washed with water and with sodium carbonate solution and dried. After removal of the solvent the residue was distilled and boiled at 155° and 1.0 mm.

Anal. Calc'd for $C_{17}H_{32}O_2$: C, 76.12; H, 11.95; CH_3O, 11.57.
Found: C, 75.55, 75.33; H, 11.75, 11.95; CH_3O, 11.80, 11.85.

On hydrogenation of 0.45 gram of material with platinum oxide catalyst in ethanol solution, whereby 40 cc. of hydrogen was absorbed in a few minutes. The alcoholic solution was concentrated to about 8 cc., and on addition of water the reaction product was precipitated in crystalline form. After drying in vacuum at 60°C., the solidified acid melted at 53°.

Anal. Found: Equiv. wt. (titration), 290; C, 75.22, 75.40; H, 12.48, 12.63.

A much larger quantity of the new acid was obtained by treating acid mixtures obtained in previous experiments from similar pyrethrin I semicarbazone preparations. When larger quantities were handled, the product obtained by the process just described distilled over a much narrower range (170–172° at 0.35 mm.). If small quantities of chrysanthemum dicarboxylic acid are present, it can be removed by dissolving the acid in petroleum ether and filtering.

SUMMARY

The semicarbazone of pyrethrin I, even after purification by several recrystallizations, is still a mixture. To determine the nature of the semicarbazones that accompany the semicarbazone of pyrethrin I, the products of saponification of a purified preparation have been examined.

The alcoholic component was found to consist only of pyrethrolone semicarbazone, while three acid components were isolated. The larger proportion of these acids consisted of chrysanthemum monocarboxylic acid. Chrysanthemum dicarboxylic acid was also found in much smaller amounts.

The third acid which may be a mixture seems to correspond to the formula $C_{16}H_{30}O_2$ and is unsaturated. Its methyl ester and *p*-bromoanilide have been prepared. It absorbs hydrogen and is converted into a saturated acid that melts at 53°. The results reported show the presence of a new ester of pyrethrolone in pyrethrum flowers.

[Contribution from the Insecticide Division, Bureau of Entomology and Plant Quarantine, U. S. Department of Agriculture]

CROTON RESIN. IV. THE PETROLEUM-ETHER-INSOLUBLE ACIDS*

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The saponification products of the complex mixture of esters known as croton resin may be separated into three groups: a mixture of fatty acids, the composition of which has been previously reported,[1] 30 per cent.; an amorphorus brown acidic mixture insoluble in petroleum ether, 40 per cent.; and water-soluble phenolic constituents, 30 per cent. The percentage composition of the fractions is approximate. This paper is primarily a report of a study of the petroleum-ether-insoluble constituents, which have been shown to consist mainly of amorphous unsaturated polyhydroxy acids.

The saponification products of a croton resin were first separated by Boehm,[2] who recognized the acidic character of the petroleum-ether-insoluble fraction. Wagner[3] found a large percentage of these acids in the saponification products of the resin and suggested that they may be auto-oxidation or polymerization products of linoleic acid known to be present. Flaschenträger and Wolffersdorff[4] reported 6.93 per cent. of petroleum-ether-insoluble acids in the saponification products of croton oil.[5]

In the present study a large quantity of the petroleum-ether-insoluble acids was prepared by careful saponification of croton resin. Precautions

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* Since it appears improbable that the author will have further opportunity for the study of croton resin, it seems worth while to publish the information accumulated up to the present time. The experimental work recorded in this paper was carried out in the Chemistry Department of the University of Maryland. For articles I, II, and III of this series see *J. Am. Chem. Soc.*, **57**, 180–187 (1935).

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[1] Drake and Spies, *J. Am. Chem. Soc.*, **57**, 184–187 (1935).

[2] Boehm, *Arch. Expt. Path. Pharmakol.*, **79**, 138–153 (1915).

[3] Wagner, Inaugural Dissertation, Leipzig, **1929**.

[4] Flaschenträger, and Wolffersdorff, *Helv. Chim. Acta*, **17**, 1444–1452 (1934).

[5] For a review of the recent chemistry of the toxic constituent of croton oil refer to the following articles: Flaschenträger, in Festschrift Heinrich Zangger II. Teil, pp. 857–873, Zurich, Leipzig, and Stuttgart, **1934**; Boehm, Flaschenträger, and Lendle, *Arch. Expt. Path. Pharmakol.*, **177**, 212–220 (1935).

were taken to make the separation from the fatty acids as nearly complete as possible. The substance resisted efforts to obtain crystalline derivatives, and consequently oxidation studies were considered the most likely means of obtaining crystalline degradation products. With this purpose in view the substance was methylated to protect hydroxyl and acid groups. The methylation was carried out in dry dioxane solution with the use of methyl iodide and silver oxide. The first product contained 8.4 per cent. methoxyl. This partially methylated material was further methylated twice with methyl iodide (in which it was now soluble) and silver oxide. The methoxyl content rose to 11.2 and 12.5 per cent., respectively.

Fractional precipitation of the methylated substance was made by dissolving it in dry acetone and effecting partial precipitation by adding petroleum ether to the solution, redissolving the precipitated fraction, and repeating the process twice. In three precipitations 74, 17.6, and 7.8 grams remained in the acetone-petroleum-ether solution. These three fractions were combined, yielding a dark-colored viscous oil (I). The fraction insoluble in acetone-petroleum-ether was freed from solvent, and a light-brown amorphous powder (II), insoluble in cold aqueous alkali and containing 10 per cent. methoxyl, was obtained.

Eighty-nine grams of the liquid (I) was subjected to fractional distillation at 1 mm. pressure in a Podbielniak column, and 34.6 ml. of distillate, representing several fractions, was collected. The undistilled residue was obtained as a dark-colored glass-like substance. From the distilled fractions were identified the methyl esters of caprylic, capric, and lauric acid which have been previously reported.[1] These acids were identified by determination of the saponification equivalents of the esters, as well as by preparation of the corresponding toluidides according to the method of Koelsch and Tenenbaum.[6] In the distillate were also obtained some high-boiling, dark-colored, viscous fractions possessing a green fluorescence which did not yield crystalline toluidides.

In the preparation of toluidides from the fractions consisting of the methyl esters of capric and lauric acids, small quantities of an ether-insoluble crystalline substance were obtained which analysis and molecular-weight determinations showed to have the formula $C_{23}H_{30}N_2O_2$. This corresponds to the toluidide of azelaic acid. Determination of the melting point of a mixture with the toluidide of authentic azelaic acid showed this to be the case. Azelaic acid has not been previously reported in the saponification products of the resin. It may not be present as such, however, but may be formed by the oxidizing action of silver oxide, during

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[6] Koelsch and Tenenbaum, *J. Am. Chem. Soc.*, **55,** 3049–3050 (1933).

methylation, on the oleic acid known to be present. Its derivation from oleic acid would denote the presence of the $\Delta^{9,10}$ isomer.

Saponification of the amorphous petroleum-ether-insoluble ester (II) with 10 per cent. alcoholic alkali yielded a dark-colored noncrystalline acid (III) containing 7.3 per cent. methoxyl, together with some ether-soluble resin. This shows the presence of hydroxyl groups in the molecule. The acid (III) is completely soluble in dilute, but not in concentrated, alkali. Ebulliscopic molecular-weight determinations in methanol gave values of 533 and 524 for II and 420 and 437 for III. A molecular-weight determination by electrometric titration of III gave a value of 512 ± 5. The equivalence point was at pH 8.14, indicating a dissociation equal to that of the usual organic acid.‡

The unsaturated character of the acid (III) was demonstrated by its reaction with alkaline permanganate and the precipitation of a bromide when its acetic acid solution was treated with bromine. This material has not been studied further.

Boehm, Flaschenträger, and co-workers[6] have reported the isolation of phorbol, a crystalline nontoxic polyhydroxy compound obtained by carefully controlled hydrolysis of a toxic constituent of croton oil. This interesting substance reacquires almost the original toxicity of the parent material when acetylated. While the author has not repeated this work, he has observed[7] that methylation of croton resin yields a resinous product containing 11.7 per cent. OCH_3, which is no longer toxic to goldfish or vesicant to man. Since this observation was first reported, an experiment has been carried out to show that this loss of activity was due to masking of the free hydroxyls of the resin and not to any oxidizing action of the silver oxide used in methylation. These facts suggest the possibility of the presence of more than one toxic substance in the resin mixture. An analogy to this loss of toxicity due to masking of hydroxyl groups is furnished by urushiol, the active constituent of both Japan lac. from *Rhus vernicifera* Dc.[8] and poison ivy (*Rhus toxicodendron*)[9], whose vesicant action closely resembles that of croton resin. Urushiol consists of a mixture of unsaturated isomers, which upon hydrogenation yields the single compound, hydrourushiol, or 1-*n*-pentadecyl-2,3-dihydroxybenzene.

Toyama[10] first showed that urushiol dimethyl ether is not vesicant, and while hydrourushiol is less toxic than the unsaturated parent com-

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‡ The author is indebted to S. A. Shrader for the ebulliscopic molecular-weight determinations and to D. H. Wheeler for the electrometric titration.

[7] Spies, *J. Am. Chem. Soc.*, **57**, 182–184 (1935).

[8] Majima, *Ber.*, **55B**, 172–191 (1922).

[9] Hill, Mattacotti, and Graham, *J. Am. Chem. Soc.*, **56**, 2736–2738 (1934).

[10] Toyama, *J. Cutaneous Diseases*, **30**, 157–165 (1918).

pounds, it also becomes inactive upon methylation. Hill and co-workers[9] verified the observations of Toyama regarding the important relation of the hydroxyl groups to toxicity.

This relationship of hydroxyl groups to toxicity indicates the possibility in the case of croton resin, of isolating from the complex mixture the compound or compounds responsible for its physiological activity. Hydrolysis of the methylated resin (11.7 per cent. OCH_3) by alcoholic alkali should leave the methoxyl groups intact, and the component containing them should be more stable and could then possibly be isolated from the saponification products. A preliminary experiment was conducted with this in view. The saponification products of some methylated resin were separated, and the methoxyl content of the fractions was determined as follows: Fatty acids, 5.5 per cent.; petroleum-ether-insoluble acids, 5.5 per cent.; water-soluble constitutents, 13.1 per cent.; an ethereal extract of the aqueous solution of the water-soluble constituents, 8.1 per cent. The acidified aqueous solution of the saponification products of the methylated resin, after removal of the acids, still gives a deep red-violet color with ferric chloride. No crystalline products were obtained.

EXPERIMENTAL

Isolation of croton resin.—The resin used in this study was isolated by the method of Cherbuliez, Ehninger, and Bernhard[11] as modified by the author.[12]

Anal. Found: C, 68.3; H, 8.90; OCH_3,[13] 1.3, 1.4.

Saponification of the resin.—Four hundred eighty grams of resin was refluxed for two hours in 2 l. of 8 per cent. alcoholic potassium hydroxide under an atmosphere of hydrogen gas. The alcohol was evaporated, and the dark-colored residue was dissolved in 1,200 ml. of water over which was stratified 700 ml. of petroleum ether (b.p. 50–70°). The mixture was vigorously stirred mechanically while it was slowly made acid to Congo red with dilute sulfuric acid. The water layer was separated from the petroleum-ether layer, which contained the insoluble acids in suspension. These acids were separated and thoroughly washed with water.

"Purification" of the petroleum-ether-insoluble acids.—For further separation of the fatty acids, the petroleum-ether-insoluble acids were dissolved in about 3 l. of 95 per cent. methanol, and the solution was thoroughly extracted with petroleum ether (b.p. 50–70°) the final portion of which removed 0.2 g. of substance. The methanol-water was evaporated, and the residue was dried by distilling absolute ethanol-benzene from it. The benzene was finally removed by vacuum distillation on the steam bath in a current of hydrogen; yield, 225 g. When thoroughly freed from solvent this substance is obtained as a brown amorphous powder.

Methylation of the petroleum-ether-insoluble acids.—Two hundred twenty-five grams of the dried acids was dissolved in 850 ml. of anhydrous dioxane to which was added 220

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[11] Cherbuliez, Ehninger, and Bernhard, *Helv. Chim. Acta*, **15**, 658–670 (1932).

[12] Spies, Ph.D. Dissertation, University of Maryland, **1934**.

[13] Found by method described by Clark, *J. Assoc. Off. Agr. Chem.*, **15**, 136–140 (1932).

ml. of methyl iodide and 200 g. of silver oxide in small portions. The mixture was stirred mechanically and refluxed for ten hours. The solvents were distilled off on the steam bath under reduced pressure, and the residue was taken up in ethanol and filtered from the silver oxide. The product was again dried by distilling with benzene. The average methoxyl content was 8.43 per cent.

This partially methylated product was methylated twice more, methyl iodide being used as solvent. The methoxyl content was 11.2 and 12.5 per cent., respectively.

Fractional precipitation of the methylated product.—The methylated material (12.5 per cent. OCH_3) was dissolved in 150 ml. of dry acetone, to which solution was added with stirring 600 ml. of petroleum ether (b.p. 50–70°). The addition of the petroleum ether caused precipitation of a dark, tarry mass which was separated from the solution. The acetone-petroleum ether solution contained 74 g. of dissolved ester. This treatment was repeated twice on the insoluble mass, and 17.2 g. and 7.8 g. of it remained in solution on successive treatments.

The combined soluble fractions were obtained as a viscous dark-colored liquid (I).

The solvent was removed from the fraction insoluble in petroleum-ether-acetone in a vacuum desiccator, and 108.5 g. of an amorphous brown powder (II) containing 10.0 per cent. methoxyl was obtained.

Anal. (II). Found: C, 68.00, 67.86; H, 7.57, 7.52.

Alcoholic alkaline saponification of II yielded a dark, amorphous acidic material. This substance was extracted with ether, in which about 20 per cent. was soluble. The insoluble amorphous powder (III) contained 7.3 per cent. methoxyl. Fraction III is completely soluble in dilute, but not in concentrated, aqueous alkali.

Anal. (III). Found: C, 66.85, 66.91; H, 7.04, 7.04.

Bromination.—To a solution of 0.5 g. of III in 25 ml. of glacial acetic acid bromine was added to excess. The amorphous precipitate was filtered off, washed with water, and dried; yield, 0.1 g.

Anal. Found: C, 49.18, 49.67; H, 5.20, 5.33.

The mother liquor was poured into water and another bromine-containing amorphous precipitate was obtained. It was filtered, washed, and dried; yield, 0.47 g. The ester (II) also yields an amorphous bromide.

Effect of silver oxide on the toxicity of croton resin.—Two and three-tenths grams of croton resin dissolved in 50 ml. of absolute ether to which 0.3 ml. of water was added was refluxed with 2 g. of silver oxide for 46 hours. The resin was recovered and its toxicity to goldfish at a concentration of 0.5 mg. per liter at 26.6° was determined. Four fishes were killed by this resin in an average of 20 minutes, while, as previously reported, the methylated resin did not kill fish in stronger concentration in 1740 minutes.**

Identification of azelaic acid.—Eighty-nine grams of the liquid esters (I) was fractionally distilled at 1 mm. pressure with the use of the Podbielniak column. Several fractions were obtained, and, in the preparation of the toluidides of the fractions corresponding to the methyl esters of capric and lauric acids, about 0.7 g. of an ether-insoluble crystalline substance was obtained. When recrystallized to constant melting point from methanol, it melted sharply at 201–202° (a standardized Anschutz thermometer was used). The melting point of the toluidide of azelaic acid is not recorded in the literature, but analysis and molecular-weight determinations corresponded to this substance. The toluidide of authentic azelaic acid melted at 201–202°, and the melting point of a mixture showed no depression.

** The author wishes to thank W. A. Gersdorff for these tests.

Anal. Calc'd for $C_{23}H_{30}N_2O_2$: C, 75.33; H, 8.25; N. 7.65.
Mol. wt., 366.
Found: C, 74.89, 75.09; H, 8.19, 8.28; N, 7.68, 7.85. Mol. wt. (Rast); 338, 335.

SUMMARY

1. The petroleum-ether-insoluble substance obtained by saponification of croton resin has been shown to be a complex mixture of unsaturated polyhydroxy acids of high molecular weight.
2. Azelaic acid has been shown to be present in the saponification products, either as such or derived, by oxidation, from one of the unsaturated fatty acids known to be present. Its derivation from oleic acid would denote the presence of the $\Delta^{9,10}$ isomer.
3. Croton resin does not lose its toxicity to goldfish on prolonged boiling of its moist ethereal solution with silver oxide.
4. An analogous relationship between croton resin and urushiol from poison ivy and Japan lac is pointed out. In both substances the hydroxyl groups are intimately associated with toxicity.
5. Attention is directed to evidence of the presence of more than one toxic substance in the resin mixture.

[Contribution from the Cobb Chemical Laboratory of the University of Virginia]

OXIDATION-REDUCTION POTENTIALS OF A SERIES OF NITROSOBENZENE-PHENYLHYDROXYLAMINE SYSTEMS

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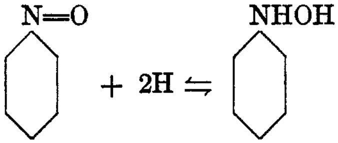
Nitrosobenzene and phenylhydroxylamine under some conditions form a typical reversible oxidation-reduction system that is stable and gives rise to reproducible potentials which can easily be measured.[1]



We have determined the oxidation-reduction potentials of a series of derivatives and have obtained results which, in spite of the sensitivity of many of the compounds involved, are in the main sufficiently accurate and extensive to show the general reversibility of the various reductions, and to show the effect on the potentials of conditions and substitution in the benzene nucleus. These preliminary results are being reported at this time because active work on the problem has been discontinued.

In Table I is listed the series of nitrosobenzene derivatives which have been prepared and used as oxidants, together with the oxidation-reduction potentials of the systems concerned, determined under standardized conditions, namely, 0.1 *N* hydrochloric acid in 50 per cent. acetone-water mixtures at 25°. This solvent was chosen rather than alcohol-water mixtures because the systems studied were relatively unstable in the latter. The measurements of the potentials were made by the method of titration of the oxidant with the reducing agent, titanous chloride, the end- and midpoints being determined graphically and checked by the amounts of standardized reagent consumed. In one instance, namely, *p*-bromonitrosobenzene, the titration results were checked by determination of the potentials directly by the method of mixtures of oxidant and reductant. The curves representing change in potential plotted against increments of reducing agent followed with reasonable accuracy in most cases the theoretical curves calculated from the midpoint in the titration. Few of the systems measured were stable indefinitely and in many cases the titration had to

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[1] Conant and Lutz, *J. Am. Chem. Soc.*, **45**, 1059 (1923).

TABLE I

OXIDATION-REDUCTION POTENTIALS OF THE VARIOUS NITROSOBENZENE-PHENYLHYDROXYLAMINE SYSTEMS IN 50 PER CENT. ACETONE-WATER-0.1 *N* HYDROCHLORIC ACID AT 25°

SUBSTITUENTS OF THE NITROBENZENE DERIVATIVE USED AS OXIDANT		π_0[a]
Alkyl	-(nitrosobenzene, itself)	0.582[c]
	2-methyl	0.598[b]
	3-methyl	0.579[b]
	4-methyl	0.567[b]
	2,5-dimethyl	(0.595)[e]
	2,4-dimethyl	0.587
	3,5-dimethyl	0.579
	2-ethyl	0.589
	4-ethyl	0.560
Halogens	2-chloro	0.598
	3-chloro	0.583
	4-chloro	0.576
	2-bromo	0.592
	3-bromo	0.577
	4-bromo	0.575
	3-iodo	0.582
	4-iodo	0.577
	4-fluoro	(0.574)
Alkoxyl	2-methoxyl	(0.600)
	3-methoxyl	0.573
	4-methoxyl	0.554
	2-ethoxyl	(0.596)
	3-ethoxyl	(0.575)
	4-ethoxyl	0.550[d]
Carboalkoxyl and Nitro	2-nitro	0.672
	2-carbomethoxyl	0.622[b]
	3-carbomethoxyl	(0.593)
	4-carbomethoxyl	0.610
	2-carboethoxyl	0.622[b]
	3-carboethoxyl	(0.586)
	4-carboethoxyl	0.613
	4-carboisopropoxyl	0.607

[a] Values are expressed in terms of the hypothetical normal hydrogen electrode in the same solvent, assuming quinhydrone to be 0.699 v.

[b, c, d] Deviation of the potentials from theoretical at ¼ and ¾ reduction is ±2 mv. unless otherwise indicated as follows: (*b*) deviation is −3 to −4 mv.; (*c*) −5 mv.; (*d*) +3 to +5 mv.

[e] Values in brackets are of questionable accuracy and may be in error by ±3–5 mv. Other values unless indicated are probably accurate to ±1–2 mv.

be carried out rapidly. The determinations which are of questionable accuracy because of instability of the systems are indicated in brackets; the others are accurate to ±1−2 mv. The values are expressed in terms of a hypothetical normal hydrogen electrode, the measurements actually being made against a calomel or quinhydrone electrode, the latter being the real standard of reference. The values listed are expressed as the difference between the potentials of the cell consisting of the oxidation-reduction half-cell and the quinhydrone electrode in the same solvent, subtracted from the value 0.699 v. *assumed* for the quinhydrone electrode in this solvent (we have arbitrarily chosen to use the actual potential of quinhydrone in water, rather than the value in alcohol [*cf.* ref. (1)]). The potentials are significant therefore only in relation to each other and to quinhydrone under the standard conditions we have chosen, and of course are only approximately comparable with potentials of these and other compounds determined in water or other solvents.

TABLE II

THE DIFFERENCES BETWEEN THE OXIDATION-REDUCTION POTENTIALS OF THE NITROSOBENZENE-PHENYLHYDROXYLAMINE SYSTEM AND ITS DERIVATIVES

SUBSTITUENT GROUP		POTENTIAL DIFFERENCE IN MV. RESULTING WHEN GROUP IS		
		ortho	*meta*	*para*
Alkyl	CH_3	+16	−3	−15
	C_2H_5	+7	—	−22
Halogen	F	—	—	−8
	Cl	+16	+1	−6
	Br	+10	−5	−7
	I	—	0	−5
Alkoxyl	OCH_3	+18	−9	−28
	OC_2H_5	+14	−7	−32
Carboalkoxyl and Nitro	$COOCH_3$	+40	—	+28
	$COOC_2H_5$	+40	—	+31
	$COOC_3H_7$	—	—	+25
	NO_2	+90	—	—

The effect of substitution of groups on the potential of the arylnitroso-arylhydroxylamine system is outlined in Table II. Alkyl groups when ortho to the nitroso group raise the potential, when para lower it, and when meta have little effect. The halogens, which are nearly equivalent to each other in effectiveness, in the ortho position also raise the potential, when para lower it, although only slightly, and in the meta position are apparently without appreciable effect. The strongly ortho-para orienting groups, methoxyl and ethoxyl, show close agreement with each other, raising the potential when ortho, lowering it very slightly when meta, and lowering it very considerably when para. It is apparent from these facts that the ortho-para orienting groups when located meta to the nitroso group have very little or no effect on the potential, but when ortho consistently raise it, and when para consistently lower it.

The substitution of the carboxylic ester group in either the ortho or the para position raises the potentials considerably, by 40 mv. when ortho, and 25–31 mv. when para. Ortho nitro-nitrosobenzene, the only nitro compound studied, gave the highest potential, 90 mv. above that of nitrosobenzene itself. The meta carboxylic esters gave somewhat uncertain values which were, however, qualitatively similar to the potential of nitrosobenzene itself, showing the meta substitution to be without significant effect.

From the foregoing results it is evident that both ortho-para and meta orienting groups, located ortho to the nitroso group, raise the potential, the carboxylic ester and nitro groups having the greater effects. In the para position, however, the effects of the two types of groups are opposite, the ortho-para orienting groups lowering and the meta orienting groups raising the potential. Meta substitution has consistently little or no effect on the potential regardless of the nature of the group.

A comparison between nitroso compounds and quinones with respect to the effects of substitution on oxidation-reduction potential is of interest. However, meta and para substitution in nitroso compounds finds no counterpart in substitution in the para quinones. There is some structural analogy between the ortho monosubstituted nitroso compounds and the quinones with substituents β to one of the quinone carbonyl groups; but the adjacency of the substituent to the other carbonyl is a factor which renders comparison of uncertain significance. Chlorine and bromine raise the potential of the quinone-hydroquinone system about 13 mv. This is in degree and direction close to the effect of ortho halogen on the nitrosobenzene potential. Alkyl and alkoxyl in the quinone series, however, lower the potential sharply in contrast to the opposite effect in the ortho nitrosobenzenes. On the other hand such groups as the carboxylic ester in quinone raise the potential in much the same way as in the ortho and para nitrosobenzenes.

Of the many nitrosobenzene drivatives studied, only two, nitrosomesitylene, and *o*-iodonitrosobenzene, failed to give reproducible oxidation-reduction potentials, and were not reduced by titanous chloride under the usual conditions. Common to both of these compounds is heavy substitution ortho to the nitroso group and steric influence is undoubtedly in some way responsible for the phenomenon. These results are consistent with the fact that 2,6-dimethyl and 2,4,6-trimethylnitrosobenzenes do not undergo normal reduction easily as do the other homologs with one or no ortho substituent.[2]

A series of determinations of oxidation-reduction potentials of a number of typical nitroso compounds was made at 35° and at 45° in order to obtain temperature coefficients, but in view of the magnitude of the experimental error, and the uncertainty of many of the measurements at the higher temperatures only a qualitative statement of the results is warranted. It may be said that the temperature coefficients lie between -0.5 and -2.0 mv. per degree, nitrosobenzene and the methyl derivatives having high values (-1.1 to -2.0 mv. per degree) and the carboxylic ester, the *o*-nitro, halogens and the methoxy compounds consistently lower values (-0.8 mv. per degree or less). These values may be compared with the temperature coefficient of -1.1 mv. per degree for quinone.[3]

The effect of hydrogen-ion concentration on the potential of a typical nitroso compound, *p*-bromonitrosobenzene, was studied, but because of the many uncertainties the determinations are only qualitative. Over a range of pH up to approximately 5 the change in potential of the *p*-bromonitrosobenzene-*p*-bromophenylhydroxylamine system very closely parallels the change in the quinhydrone electrode potential with approximately the anticipated "0.6" slope except in the extreme acid range where there appears to be some deviation corresponding perhaps more closely to the "0.9" slope characteristic of systems where the reductant may form salts. The oxidation-reduction potentials could not be followed beyond a pH of about 5 due to increasing instability of the systems under these conditions.

EXPERIMENTAL

Of the nitroso compounds listed in Table I, all but eight are known. Many of them are unstable, particularly when impure. The usual method of preparation, namely, oxidation of the corresponding phenylhydroxylamine with chromic acid, with subsequent steam distillation, was found to be inferior in many cases to the method utilizing ferric chloride where the product can usually be isolated directly in the crude condition and washed free from acids before steam distilling.

The nitrosobenzene homologs were best purified by successive steam distillations, since crystallization from solvents gave relatively unstable products in many cases. Compounds in this series were the least stable, and were stored in an ice box and used as soon as possible after preparation. The carboalkoxy and halogeno derivatives were relatively stable and were handled adequately by ordinary crystallization methods. The alkoxyl derivatives were the most difficult to prepare and were made

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[2] Bamberger and Brady, *Ber.*, **33**, 274 (1900).

[3] Conant and Fieser, *J. Am. Chem. Soc.*, **44**, 2480 (1922).

by oxidation of the corresponding alkoxyaminobenzenes by means of Caro's acid. The ortho compounds were reasonably stable, but the para less so, while the meta compounds decomposed on drying and had to be used immediately after preparation.

o-*Nitrosotoluene*[4] was prepared as follows: 15.6 g. of *o*-nitrotoluene, 24 cc. of water, 42 cc. of ethanol, and 1.5 g. of calcium chloride, heated to boiling, with mechanical stirring, were treated with 20 g. of zinc dust (added slowly). After 10 min. the residue was filtered off and the solution poured into 600 cc. of ice water containing 37 g. of ferric chloride. The *o*-nitrosotoluene separated as a solid and was filtered off, washed on the filter with water, and then steam-distilled twice (yield 20%, m.p. 72.5°).

m- *and* p-*Nitrosotoluenes*[4] *and 2,4- and 2,5-dimethylnitrosobenzenes* were prepared by the above procedure. Three new homologs, namely, *3,5-dimethylnitrosobenzene* (m.p. 59°), o-*ethylnitrosobenzene* (m.p. 61°), and m-*ethylnitrosobenzene* (m.p. 22°), were also obtained by the above procedure from the corresponding nitro compounds in yields of 13–16% of purified material. They were difficult to get into a condition of analytical purity and were not analyzed. They each reacted nearly quantitatively with two equivalents of titanous chloride. In view of the mode of preparation from the corresponding known nitro compounds, their reduction by two hydrogen equivalents of titanous chloride, and their sharp oxidation-reduction potentials which were of the correct order, their structures are certain.

Nitrosomesitylene was prepared by the above method and also by the oxidation of mesidine with Caro's acid.[5, 4b]

The o-, m-, *and* p-*nitrosomethylbenzoates* and o-, m-, *and* p-*nitrosoethylbenzoates* were prepared according to the directions of Alway and Walker.[6]

p-*Nitrosoisopropylbenzoate* (new) was obtained also by this method in a yield of 40%. It melted at 61–62° and reacted practically quantitatively with two equivalents of titanous chloride.

p-*Fluoronitrosobenzene*[7] was prepared by the Alway and Walker[6a] method using however ferric chloride as the oxidizing agent.

o-*Chloronitrosobenzene*.[8]—Nine grams of *o*-nitrochlorobenzene was reduced by adding 10 g. of zinc dust to a boiling solution in 50 cc. of ethanol, 12 cc. of water, and 0.5 g. of calcium chloride, heating being continued for 10 minutes with stirring. The filtered solution was added to a solution of 18.5 g. of ferric chloride in 600 cc. of water and ice, the crude nitrosochlorobenzene being filtered off, washed, and steam-distilled (yield 40%, m.p. 56°).

The m- *and* p-*chloronitrosobenzenes*[4a] were prepared similarly in yields of 29 and 41%, respectively, with melting points of 72° and 89.5°, respectively.

o-*Bromonitrosobenzene*[9] was prepared by reducing 11.5 g. of *o*-nitrobromobenzene in 100 cc. of alcohol, 15 cc. of water, and 0.5 g. of calcium chloride with 10 g. of zinc dust at boiling temperature, and adding the filtered solution to a solution of 18.5 g.

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[4] (*a*) Bamberger, *Ber.*, **28**, 245 (1895); (*b*) von Pechmann and Nold, *ibid.*, **31**, 561 (1898); (*c*) Bamberger and Rising, *Ann.*, **316**, 277 (1901).

[5] Bamberger and Rising, *Ber.*, **33**, 3632 (1900).

[6] (*a*) Alway and Walker, *Ber.*, **36**, 2312 (1903); (*b*) Alway and Pinckney, *Am. Chem. J.*, **32**, 399 (1904).

[7] Rinkes, *Chem. Zentr.*, **1914**, I, 2036.

[8] *cf.* Haworth and Lapworth, *J. Chem. Soc.*, **119**, 768 (1921).

[9] Bamberger, *Ber.*, **28**, 1222 (1895).

of ferric chloride in 600 cc. of water and ice. The crude nitrosobenzene was filtered off, washed, and steam distilled (yield 35%, m.p. 97°).

m- *and* p-*Bromonitrosobenzene*[8, 9] were prepared similarly. p-*Hydroxylaminobromobenzene* was prepared in the usual way in a yield of 47% (m.p. 92°).[9]

o-*Iodonitrosobenzene* (new) was prepared by reducing 14.5 g. of iodonitrobenzene in 200 cc. of alcohol, 15 cc. of water and 0.5 g. of calcium chloride at boiling temperature with 10 g. of zinc dust, the filtered mixture being diluted with 100 cc. of alcohol, boiled for a half hour and filtered. The solution was added slowly to a solution of 18.5 g. of ferric chloride in 600 cc. of water and ice, the crude product being filtered, washed, and steam distilled (yield 30%; m.p. 117°).

Anal. Calc'd for C_6H_4INO: C, 30.9; H, 1.7; I, 54.4.
Found: C, 31.4; H, 1.8; I, 54.6.

m-*Iodonitrosobenzene* (new) was prepared as above (yield 19%; m.p. 77°).

Anal. Calc'd for C_6H_4INO: I, 54.4. Found: I, 54.4.

p-*Iodonitrosobenzene*[4a] was also prepared as above.

o-*Methoxynitrosobenzene* (*o*-nitrosoanisole)[10] was prepared in the following manner: 13.5 g. of potassium persulfate was added to 15 g. of concentrated sulfuric acid in a small mortar and the mixture was ground to homogeneity and allowed to stand for one hour. The solidified product was dissolved in 300 cc. of water and 400 cc. of ice, made alkaline with sodium carbonate and acidified with acetic acid; 6.15 g. of *o*-anisidine was added and the mixture was stirred for 25 min. and filtered, the solid then being washed and steam-distilled (yield 7%; m.p. 101.5°).

m-[11] *and* p-[10]*Methoxynitrosobenzenes* and o-, m- *and* p-*ethoxynitrosobenzenes* (nitrosophenetoles)[12] were prepared in exactly the same way in yields of 13–23%. In the preparation of *p*-ethoxynitrosobenzene the mixture after oxidation was directly steam distilled since the product was low melting (30°). The m- *and* p-*ethoxynitrosobenzenes* are new but were not obtained sufficiently pure for analysis. They reacted with two hydrogen equivalents of titanous chloride and gave oxidation-reduction potentials of the expected order of magnitude.

The apparatus and measurement of potentials.—The usual procedures[1] were followed and need be only briefly summarized here. For the titration half-cell a 400-cc. wide-mouthed bottle was used, fitted with a rubber stopper carrying a mercury-sealed stirrer, an inlet tube for introducing titrating agent and pure nitrogen for sweeping, and an agar-agar-potassium-chloride salt bridge. A thermostat controlled the temperature at 25 ± 0.1°. The electrode was of the platinized platinum type. The standard reference half-cell was either quinhydrone in the standard solvent or calomel which had been checked against quinhydrone during and after use. In many instances both quinhydrone and calomel were used in different runs on the same compound with identical results. The actual runs were made as follows: 0.0005 moles of the nitroso compound was dissolved in 100 cc. of acetone, and 100 cc. of standard hydrochloric acid was added. The apparatus was swept with nitrogen and titration was carried out with standardized titanous chloride, the equilibrium potentials being noted. The variation in concentration of acetone on addition of the aqueous titanous chloride was shown experimentally to have a negligible effect. The necessary small corrections for the change in acid concentration during titration due to the excess of acid in the standardized titanous chloride solution were made, and

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[10] BAEYER AND KNORR, *ibid.*, **35**, 3034 (1902).

[11] BAUDISCH AND FURST, *ibid.*, **48**, 1665 (1915).

[12] RISING, *ibid.*, **37**, 43 (1904).

the results all referred to 0.1 *N* hydrochloric acid solution, the actual average concentration involved in these measurements. The validity of these corrections was checked by controlled experiments on *p*-bromonitrosobenzene by the method of mixtures and titrations under the various conditions actually used in the experiments. The observed potentials were plotted against increments of standardized reducing agent and the midpoints were determined by the graphical method with the amount of reducing agent consumed serving as a check.

SUMMARY

The oxidation-reduction potentials of a series of substituted nitrosobenzene-phenylhydroxylamine systems have been determined, and the effects of substitution of different types of groups in the various positions are discussed and compared with the effects of similar groups on the quinone-hydroquinone potential.

Eight new nitrosobenzene derivatives are described.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE HYDROLYSIS OF CARBON TETRAIODIDE

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INTRODUCTION

Several investigators[1] have reported that carbon tetraiodide yields iodoform and a hypoiodite when treated with alkaline reagents. In spite of the fact that contradictory results are recorded by other investigators, the belief that in carbon tetraiodide one atom of iodine is "positive" is quite widespread among chemists. Waters and Lowry[2] have even suggested the term "inverse substitution" to account for this phenomenon.

From the standpoint of the hypothesis developed by one of us and collaborators, it appeared highly improbable that carbon tetraiodide should yield iodoform and a hypoiodite when treated with an alkali. Our recent investigation has confirmed our *a priori* conviction that "positive" iodine is not eliminated in the hydrolysis of carbon tetraiodide. Furthermore, in view of our findings, and because of the claim that "iodine is even more easily [than bromine] expelled as a positive radical by inverse substitution,"[2] we are inclined to believe that no methane halogen compound eliminates a "positive" halogen upon hydrolysis with alkali. The quotation from Waters and Lowry,[2] in support of the hypothesis of "inverse substitution" that "the ease with which iodine can be expelled is indeed so great that it can be eliminated in an elementary form from the tetrahalogen derivatives without the intervention of alkali," is without foundation, and is based upon erroneous interpretations by the original investigators. We have shown quite conclusively that the elimination of iodine from carbon tetraiodide (in benzene or chloroform) at ordinary temperatures is caused by oxygen of the air.

PREVIOUS WORK

Most of the work on the interaction of carbon tetraiodide with various reagents is quite old. As early as 1874, Gustavson[3] reported the forma-

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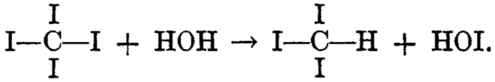
[1] NEF, *Ann.*, **308**, 330 (1889); JONES, see STIEGLITZ, *J. Am. Chem. Soc.*, **44**, 1307 (1922).

[2] WATERS AND LOWRY, "Physical Aspects of Organic Chemistry," D. Van Nostrand Company, Inc., New York, **1936**, p. 223.

[3] GUSTAVSON, *Ann.*, **172**, 173 (1874).

tion of iodoform when carbon tetraiodide was heated in water solution. On the other hand, Moissan[4] was unable to obtain any iodoform by heating carbon tetraiodide with water in a sealed, evacuated tube. The statement is made that the solution possessed no oxidizing properties. Nef,[1] however, claims that iodoform was obtained as a result of the hydrolysis of carbon tetraiodide with alcoholic potassium hydroxide, sodium ethylate, alcoholic potassium cyanide, and with alcohol alone at 100°. The details of the experimental procedure are entirely lacking. Jones[1] claims that treatment of carbon tetraiodide with water produces hypoiodous acid. If the formation of iodoform and hypoiodous acid by the hydrolysis of carbon tetraiodide is to be accepted without question, the presence of a "positive" iodine in carbon tetraiodide may be accounted for by the following schematic representation:



$$\mathrm{I{-}\overset{\displaystyle I}{\underset{\displaystyle I}{C}}{-}I} + \mathrm{HOH} \rightarrow \mathrm{I{-}\overset{\displaystyle I}{\underset{\displaystyle I}{C}}{-}H} + \mathrm{HOI.}$$

DISCUSSION OF RESULTS

Before proceeding with the discussion of our study of the hydrolysis of carbon tetraiodide with various reagents, it is necessary to discuss the results of some of our preliminary experiments. First, we have been unable to effect hydrolysis of carbon tetraiodide with aqueous alkali at room temperature. Hydrolysis was negligible when the reaction mixture was boiled for several hours, and allowed to stand for several months. It is quite likely that the insolubility of the carbon tetraiodide in water is responsible for this apparent lack of reactivity. Second, the decomposition of carbon tetraiodide in various solvents is contingent upon the available oxygen. Thus, solutions in methyl and ethyl alcohol decompose quickly (a matter of minutes) if the solutions are shaken while exposed to air. In a sealed tube, and particularly in evacuated tubes, alcoholic solutions of carbon tetraiodide keep fairly well. Little decomposition is noted in the evacuated tubes at the end of three or four days. The stability of carbon tetraiodide is greatest in tertiary butyl alcohol; a sample sealed with air present in the tubes decomposed only after the solution had stood for twenty days at room temperature and for ten hours at 50°. However, a similar experiment with the air removed from the tube did not show any decomposition of the carbon tetraiodide at the end of the heating period. Again, a benzene solution of carbon tetraiodide, when shaken in air, decomposes to give a quantitative yield of iodine within a few minutes, but shows only slight decomposition at the end of six weeks when

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[4] MOISSAN, *Compt. rend.*, **113**, 20 (1890).

kept in an evacuated tube. Similarly, solutions of carbon tetraiodide in chloroform yield iodine readily when in contact with air, but the tetraiodide can be successfully crystallized from this solvent when air is rigidly excluded. This process can be carried out most conveniently in a highly evacuated system.

TABLE I

Hydrolysis of Carbon Tetraiodide and Iodoform[d]

NO.	IODOMETHANE, MOLES × 10^4	SOLVENT, CC.	HYDROLYTIC AGENT, MOLES[a]	IODIDE,[c] %[b]	CONDITIONS	REACTION TIME, DAYS	REMARKS
Experiments in Water							
1	CI_4 9.61	5	KOH 1.0	0.0	Air	90	No reaction.
2	CHI_3 12.7	5	KOH 1.0	0.0	Air	90	
Experiments in Methanol							
3	CHI_3 5.09	4	KOH 13.0	34.8 V	Air	1	
4	CHI_3 5.09	4	KOH 6.9	58.7 V	Air	2	
5	CHI_3 5.09	50	KOH 6.9	72.9 V	Air	2	
6	CI_4 9.61	50	KOH 6.9	84.7 V	Vac.	1	
7	CI_4 9.61	4	KOH 6.9	74.9 V	Vac.	2	
8	CI_4 3.85	4	KOH 18.5	67.9 V	Air	1	
9	CI_4 9.61	4	KOH 6.9	75.9 V	Air	2	
10	CI_4 9.61	5	KOH 5.0	76.0 V	Air	3	
11	CHI_3 12.7	5	CaO 5.0	0.0 V	Air.	6	
12	CHI_3 12.7	5	CaO 3.5	0.0 V	Vac.	10	
13	CHI_3 12.7	5	CaO 4.0	0.0 F	Vac.	30	
14	CI_4 5.09	5	CaO 5.0	94.0 V	Air.	6	
15	CI_4 5.09	5	CaO 5.0	76.0 V	Vac.	10	Incomplete; CI_4 recovered.
16	CI_4 9.61	5	CaO 4.0	81.2 F	Vac.	30	
17	CHI_3 12.7	5	$NaOC_6H_5$ 4.0	0.0 V	Vac.	2	
18	CHI_3 12.7	5	$NaOC_6H_5$ 4.0	0.0 V	Air	3	
19	CHI_3 12.7	5	$NaOC_6H_5$ 4.4	0.0 F	Vac.	30	
20	CI_4 9.61	5	$NaOC_6H_5$ 5.0	84.9 V	Vac.	2	
21	CI_4 9.61	5	$NaOC_6H_5$ 5.0	84.2 V	Air	3	
22	CI_4 9.61	5	$NaOC_6H_5$ 4.6	98.7 F	Vac.	30	

[a] Per mole iodomethane.

[b] Expressed as percentage of the theoretically possible yield.

[c] Initials indicate whether the Volhard or Fajans titration method was used.

[d] No free iodine was obtained in any of these experiments.

The results of the hydrolysis experiments upon carbon tetraiodide and iodoform with a variety of reagents are given in Tables I and II. The hydrolytic experiments with iodoform are of importance from the standpoint of the mechanism suggested by the earlier workers for the hydrolysis of carbon tetraiodide. Iodoform, it may be recalled, is the intermediate product postulated by these investigators in the hydrolysis of carbon tetraiodide. In Table I, experiments 3 to 10 inclusive indicate that potassium hydroxide is not a suitable reagent for our purpose, for it causes the hydrolysis of both iodoform and carbon tetraiodide, and is not the differential reagent needed for the purpose. Calcium oxide and sodium phenolate, however, are ideal hydrolytic reagents. They do not affect iodoform in alcoholic solution (*cf.* experiments 11–13 and 17–19, inclusive), but cause complete hydrolysis of the carbon tetraiodide (*cf.* experiments 14–16 and 20–22 inclusive). Another experiment, not listed in the table, in which a mixture of iodoform and carbon tetraiodide was hydrolyzed under similar conditions, showed that the stability of iodoform was not affected by any product from the carbon tetraiodide. These experiments prove beyond reasonable doubt that iodoform is not an intermediate product in the hydrolysis of carbon tetraiodide, and that hypoiodites are not formed in the hydrolysis of this substance.

TABLE II

EFFECT OF ALKALI AND AIR ON HYDROLYSIS OF CARBON TETRAIODIDE

NO.	CI_4, MOLES $\times 10^4$	METHANOL		KOH, MOLES[a]	IODIDE,[c] %[b]	IODINE, %[b]	CONDITIONS	REACTION TIME, HOURS	REMARKS
		Conc.[d]	cc.						
1	1.9	60%	5	1	20.8 F	79.2	Air	4	
2	1.9	50%	5	2	58.9 F	41.1	Air	4	
3	1.9	60%	5	3	72.5 F	27.5	Air	4	
4	1.9	60%	5	4	80.7 F	19.3	Air	3	
5	1.9	60%	5	6	98.8 F	0.0	Air	3	
6	1.9	60%	5	1	24.4 F	0.0	Vac.	49	Most of CI_4 recovered.

[a, b, c] Have the same significance as in Table I.

[d] Expressed as percentage of methanol by volume in methanol-water mixture used as solvent.

That our analyses for total iodides are in some cases lower than the calculated values is due in part to incomplete hydrolysis and in part to the use of the Volhard method for the determination of iodides in the reaction mixture. Much better results were obtained by the method of Fajans and Hassel,[5] and therefore the analytical method is indicated for each experiment in the tables.

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[5] FAJANS AND HASSEL, *Z. Elektrochem.*, **29**, 495 (1923).

Table II shows clearly the effect of air and quantity of potassium hydroxide used on the amount of iodine formed by hydrolysis of carbon tetraiodide. When sufficient alkali is used to neutralize all hydriodic (and carbonic) acid formed, no free iodine is formed. When insufficient alkali is used, iodine is liberated in the presence of air, but not in the absence of air (experiment 6), and in the latter case, hydrolysis is negligible after the alkali is used up. The natural explanation, therefore, is that carbon tetraiodide is attacked directly by the oxygen present in the reaction vessels. Calculations have shown that sufficient oxygen was present to effect this reaction. The decrease in the amount of iodine formed from 79 per cent. to 0 per cent. when the proportion of potassium hydroxide was varied from 1 to 6 moles is very striking, but definitely in accord with the above suggestion.

There remains still one unexplained fact, namely, the formation of iodoform reported by the earlier investigators when the carbon tetraiodide is treated with alkali. Our data, as well as our interpretation of the reaction, led us to believe that if the observations of the earlier investigators were correct, the differences in our results are due to the presence of some reducing agents in the solvents used by the earlier investigators. Accordingly, we added small amounts of the corresponding aldehydes to the alcohols used as solvents. Here numerous difficulties were encountered. When insufficient alkali was used, iodine, as expected, was formed, due to oxidation of carbon tetraiodide or intermediate hydrolysis products. With a large amount of alkali and a small amount of aldehyde the normal hydrolysis was faster than the reduction of the carbon tetraiodide to iodoform. The percentage of water in the alcohol is of importance, for water decreases the solubility of the carbon tetraiodide in alcohol. Yet it is possible to choose conditions, even when only minute amounts of the aldehyde are employed, such that substantial conversion of the carbon tetraiodide to iodoform is obtained. Because of the large differences in molecular weight and the small quantities of carbon tetraiodide employed, even a very low concentration of aldehyde in the alcohol would furnish a mole of aldehyde to a mole of carbon tetraiodide. In one experiment with alkali and formaldehyde between 85 per cent. and 100 per cent. of the calculated amount of iodoform was actually isolated. The very large excess of potassium hydroxide was probably unnecessary.

Another phenomenon which may have deceived some earlier investigators, since it temporarily deceived us, is the color change when the dark red carbon tetraiodide is dissolved in an alcohol, with or without alkali, and precipitated immediately with water. The product is a yellow-orange solid, resembling iodoform contaminated with a little carbon tetraiodide much more than it resembles the initial carbon tetraiodide.

We should state further that we are of the opinion that, while the general conclusions drawn concerning Table III are absolutely valid, it will probably be difficult for others to duplicate any given experiment so as to obtain *exactly* the same result as we have recorded. We suspect that such factors as the age and purity of carbon tetraiodide, peroxide content of solvent and aldehyde, alcohol and potassium hydroxide concentration, temperature, illumination, and agitation may be very important in determining both reaction rate and products.

TABLE III

EFFECT OF ALKALI AND ALDEHYDES ON CARBON TETRAIODIDE[d]

NO.	MOLES CI_4 × 10^4	ALCOHOL[e] SOLVENT		ALDEHYDE, MOLES[a]	KOH MOLES[a]	REACTION TIME, HOURS	IODIDE,[c] %[b]	IODINE, %[b]	CHI_3, %[b]
		Conc.	cc.						
1	1.9	40% Methyl	5	Form-, 1	70	12			94
2	2.0	43% Methyl	7	0	50	7	97.4 F	0.0	0
3	2.0	43% Methyl	7	Form-, 1	50	7	96 F	0.0	0
4	2.0	43% Methyl	7	Form-, 5	50	7	33–46 F	0.0	72–89
5	1.9	50% Methyl	6	Form-, 1	2	3	82.5 F	12.7	0
6	1.9	50% Methyl	6	Form-, 2	2	1.5	58.9 F	41.1	0
7	1.9	50% Methyl	6	Form-, 3	2	5	56.8 F	43.2	0
8	1.9	57% Methyl	7	Form-, 0.1	70	6	98 F	0.0	0
9	1.9	40% Ethyl	5	Form-, 1	1	12	26.3 F	51.5	4
10	1.9	40% Ethyl	5	Form-, 1	70	6	99.4 F	0.0	0
11	1.9	40% Ethyl	5	Acet-, 1	35	1	69.2 F	Remainder a mixture of CHI_3 and unchanged CI_4	
12	1.9	40% Ethyl	5	Acet-, 1	70	1	72.3 F		
13	1.9	50% Ethyl	4	Acet-, 1	1	1	29.2 F	62	6
14	1.9	95% Ethyl	4	Acet-, 1	1	0.5	27 F	39.1	33
15	1.9	95% Ethyl	5	Acet-, 1	3	0.17	50.8 F	0.0	47
16	1.9	95% Ethyl	4	Acet-, 2	2	0.25	44.4 F	4.4	59
17	1.9	95% Ethyl	5	Acet-, 3	1	1.5	29.4 F	25.4	20
18	1.9	95% Ethyl	5	Acet-, 3	3	0.17	57.4 F	0.0	32

[a], [b], [c] Have the same significance as in Table I.

[d] All experiments made on shaking machine in glass-stoppered bottles containing air.

[e] Expressed as percentage of alcohol by volume in alcohol-water mixture used as solvent.

Our investigation suggests that the observations of the earlier investigators, that carbon tetraiodide upon treatment with alkali yields iodoform, may be essentially correct. The interpretation of such results, however, is to be sought in the reducing impurities (aldehydes, etc.) which were most likely present either in the solvents or in the alkali used in the experiments.

EXPERIMENTAL

Preparation and properties of carbon tetraiodide.—Carbon tetraiodide was prepared by the method first suggested by Spindler.[6] The modifications recommended by Lantenois[7] were found essential. The carbon tetraiodide prepared by this method could not be successfully crystallized from any organic solvent in air. However, excellent results were obtained by the use of chloroform in a highly evacuated extraction apparatus. We believe that under similar conditions benzene and other low-boiling solvents could be used equally well.

As far as we have been able to find, carbon tetraiodide has not been analyzed successfully, nor have any reproducible physical constants been recorded for that substance. The best analysis for iodine recorded in the literature[8] is 97.0%, while the calculated value is 97.69%. It can be seen very readily that since the proportion of iodine in iodoform is 96.69%, an iodine analysis does not indicate the purity of carbon tetraiodide. We experienced great difficulty with the analysis of carbon tetraiodide for iodine when the usual methods were employed, such as the decomposition of the sample with sodium in liquid ammonia,[9] heating with concentrated nitric acid and silver nitrate,[10] etc. However, a rather unusual method of analysis was discovered which gave very satisfactory results. The method depends on an observation, made by us, that when carbon tetraiodide is treated with benzene and the mixture is shaken, iodine is evolved. Presumably the following reaction takes place:

$$CI_4 + O_2 \rightarrow CO_2 + 2I_2.$$

The iodine thus liberated can be titrated with thiosulfate. Actual experiments gave a value for iodine of 97.4% as compared with a theoretical value of 97.69%.

Carbon tetraiodide when crystallized from chloroform (in a highly evacuated system) separates in minute, ruby-red crystals. In view of the fact that oxygen decomposes the substance, it is not at all unusual that the exact temperature of the decomposition of carbon tetraiodide depends on many factors. Thus we have observed that in the light, carbon tetraiodide shows appreciable decomposition in the range 90-100°. On the other hand, when somewhat protected from light practically no decomposition takes place until the temperature reaches 140°. It is thus obvious that one cannot speak of the melting point of the substance. The decomposition point we have observed as 162-165° in a highly evacuated tube protected from light. However, it is possible that this temperature is not perfectly reproducible because of very minute yet significant quantities of oxygen or impurities contained in the system. When pure, carbon tetraiodide keeps fairly well in air in the dark, but decomposes in a few hours in the light. When dissolved in organic solvents in the presence of air, formation of iodine is evident in a few seconds.

Experimental technique.—The solvent or a solution of the hydrolytic agent was placed in a tube, and frozen in a liquid nitrogen bath. Known quantities of carbon

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[6] Spindler, *Ann.*, **231**, 264 (1885).

[7] Lantenois, *Compt. rend.*, **156**, 1385 (1913).

[8] Mark, *Ber.*, **57B**, 1822 (1924).

[9] Vaughn and Nieuwland, *Ind. Eng. Chem.*, *Anal. Ed.*, **3**, 274 (1931).

[10] Gane and Webster, *Z. angew. Chem.*, **22**, 1059 (1909).

tetraiodide (0.1-0.5 g.) were then introduced. In the experiments where calcium oxide was used, the latter was added at this point. The tube was then evacuated thoroughly with the mercury pump and sealed off. Most of the experiments in Tables I and II, made in the presence of air, were conducted by placing the reactants in tubes which were then sealed in air. The experiments of Table III and a few hydrolysis reactions were carried out in glass-stoppered bottles by shaking on a mechanical shaker. All other experiments were carried out in the dark with only occasional agitation. All experiments (except as otherwise noted) were performed at room temperature.

Analysis.—When hydrolysis was complete (as evidenced by the disappearance of solid carbon tetraiodide and its color from solution) the reaction tube was opened, the contents of the tube were either made up to a standard volume for aliquot division, or they were analysed directly. Free iodine was determined by titration with sodium thiosulfate, iodides either by Fajans' method, using sodium eosin as indicator, and $N/10$ silver nitrate, or by the Volhard method. Both determinations were made on the same sample when the Fajans method for iodides was used, the iodine being converted to iodide by thiosulfate and the total iodides then determined. The first titre subtracted from the second gave the iodide content of the original solution. Iodoform was collected on a sintered glass funnel and weighed.

The solubility of iodoform in water (0.01 g. per 100 cc.) and the ease with which iodoform sublimes introduce possible errors of 10% in its determination. It was identified by melting point in several instances.

SUMMARY

1. It has been shown that the instability of carbon tetraiodide in solvents is due to oxygen.

2. It has been shown that hydrolysis of carbon tetraiodide results in the formation of iodide ions, and that no hypoiodites are formed.

3. Reagents have been found which cause the hydrolysis of carbon tetraiodide but are without effect upon iodoform.

4. It has been shown that the formation of iodoform, when carbon tetraiodide is treated in alcohol with alkali, may be accounted for on the basis of the aldehydes present in the alcohol as impurities.

5. There is no factual basis for the assumption that carbon tetraiodide contains positive iodine.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

RELATIVE REACTIVITIES OF ORGANOMETALLIC COMPOUNDS. XVII. THE AZO LINKAGE

HENRY GILMAN AND J. CLYDE BAILIE

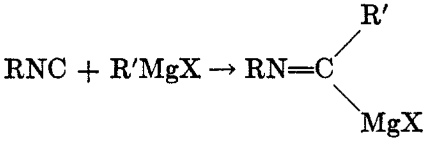
Received March 8, 1937

INTRODUCTION

Moderately reactive organometallic compounds like the Grignard reagents add to unsaturated linkages of three general classes. First, in the most frequently observed type of addition to unsymmetrical unsaturated linkages, the R attaches itself to the relatively less acidic element and the MgX to the relatively more acidic element.

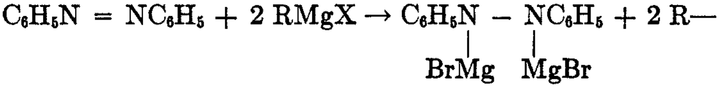
$$R\left\{\begin{matrix} C = O \\ C = S \\ S = O \\ N = O \\ C = N \end{matrix}\right\}MgX$$

Second, with compounds like isocyanides there appears to be some addition to the terminal unsaturated carbon.



$$RNC + R'MgX \rightarrow RN{=}C\begin{matrix} \diagup R' \\ \diagdown MgX \end{matrix}$$

Third, symmetrical unsaturated linkages may or may not add moderately reactive RM compounds. The olefinic and acetylenic linkages do not add Grignard reagents, but will add more reactive organometallic compounds, particularly the organoalkali and some of the more reactive RM compounds of the alkaline earth metals. Another symmetrical unsaturated linkage, the azo linkage, does react with Grignard reagents, and here two MgX groups add, the R groups then undergoing coupling to R·R compounds and disproportionation to R(+H) and R(−H) compounds.[1]



$$C_6H_5N = NC_6H_5 + 2\,RMgX \rightarrow \underset{BrMg}{C_6H_5N} - \underset{MgBr}{NC_6H_5} + 2\,R—$$

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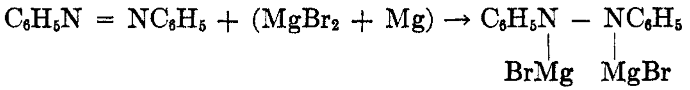
[1] (*a*) FRANZEN AND DEIBEL, *Ber.*, **38**, 2716 (1905); (*b*) GILMAN AND PICKENS, *J. Am. Chem. Soc.*, **47**, 2406 (1925); (*c*) RHEINBOLDT AND KIRBERG, *J. prakt. Chem.*, **118**, 1 (1928).

The structure of the intermediate di-bromomagnesium compound was established by reaction with benzoyl chloride which gave dibenzoylhydrazobenzene. Furthermore, the di-bromomagnesium compound is formed by the reducing action of the Gomberg-Bachmann binary system[2] ($MgBr_2 + Mg$).



$$C_6H_5N = NC_6H_5 + (MgBr_2 + Mg) \rightarrow \underset{BrMg}{C_6H_5N} - \underset{MgBr}{NC_6H_5}$$

Hydrazobenzene, formed by hydrolysis of the di-bromomagnesium compound, is the chief product, but aniline is also obtained in small quantities both from the Grignard reaction[1b] and the binary system.[2] Long years ago, Frankland[3] obtained an 85 per cent. yield of aniline from the reaction between azobenzene and diethylzinc. In view of the general similarities between organozinc and organomagnesium compounds,[4] one might have expected some hydrazobenzene. We have shown that hydrazobenzene as well as aniline result from this reaction, and the high yield of aniline is due, in part, to heating the intermediate zinc complex. This result was confirmed by treating hydrazobenzene with diethylzinc to give the intermediate zinc complex which when heated gave significant quantities of aniline on hydrolysis.

TABLE I

REACTION OF AZOBENZENE AND SOME ORGANOMETALLIC COMPOUNDS

RM COMPOUND	PRODUCTS	YIELD (%)	AZOBENZENE RECOVERED (%)
$(C_2H_5)_2Zn$	Hydrazobenzene	31	
	Aniline	16	50.4
C_2H_5ZnI	Aniline	12.2	66.2
$(C_6H_5)_2Zn$	Aniline	6.8	77.5
C_6H_5MnI	Aniline	53.8	40.5
$(C_6H_5)_2Be$	Hydrazobenzene	55.4	40.0
C_2H_5MgBr	Hydrazobenzene	58.0	35.0
C_6H_5MgBr	Hydrazobenzene	62.5	27.4
C_6H_5Li	Hydrazobenzene	51.8	34.1
C_6H_5Na	Hydrazobenzene	25.1	73.6
C_6H_5CaI	Triphenylhydrazine	18.5	64.4
C_6H_5K	Triphenylhydrazine	38.4	54.9

One of the interesting results of the present report is the formation of a

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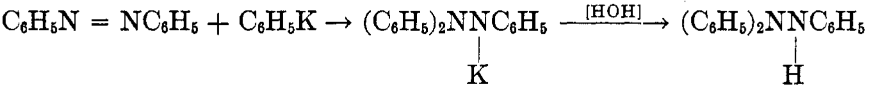
[2] BACHMANN, *J. Am. Chem. Soc.*, **53**, 1524 (1931); GILMAN AND HECK, *Rec. trav. chim.*, **50**, 522 (1931).

[3] FRANKLAND AND LOUIS, *J. Chem. Soc.*, **37**, 560 (1880).

[4] GILMAN AND MARPLE, *Rec. trav. chim.*, **55**, 133 (1936).

third product from the reaction between azobenzene and organometallic compounds. It has been found that some of the highly reactive organometallic compounds, like phenylcalcium iodide and phenylpotassium, add in the following unsymmetrical manner to give triphenylhydrazine.



$$C_6H_5N = NC_6H_5 + C_6H_5K \rightarrow (C_6H_5)_2N\underset{K}{N}C_6H_5 \xrightarrow{[HOH]} (C_6H_5)_2N\underset{H}{N}C_6H_5$$

The general results are given in Table I, and a discussion of them and related studies follows the experimental part.

EXPERIMENTAL

All reactions were carried out under an atmosphere of dry nitrogen and all organometallic compounds were transferred under the same gas. Care was taken to exclude air as much as possible to prevent oxidation in working up the reaction products. The solvents were removed at as low a temperature as possible under reduced pressure and in a stream of inert gas. All experiments were checked.

Diethylzinc.—To a solution of 8 g. (0.065 mole) of diethylzinc in 75 cc. of ether was added dropwise 5.46 g. (0.03 mole) of azobenzene dissolved in 25 cc. of ether. The solution turned dark, and some heat was evolved. The mixture was then refluxed gently for 6 hours and allowed to stand overnight. A yellow precipitate separated during the heating. After hydrolysis by ammonium chloride solution, the ether layer was separated and dried over anhydrous sodium sulfate. Removal of the ether left a residue which upon washing with petroleum ether (b.p., 60–68°) gave 1.1 g. of insoluble hydrazobenzene, confirmed by the melting point of a mixture with an authentic specimen. The residue obtained by evaporation of the washings was shaken with cold 30% acetic acid which removed 0.88 g. of aniline, identified by conversion to benzanilide. The resulting residue was then heated gently with dilute hydrochloric acid to convert remaining hydrazobenzene to benzidine, of which 0.6 g. was obtained as the sulfate. The final, insoluble residue (2.75 g.) was azobenzene.

Ethylzinc iodide.—To a clear ether solution of ethylzinc iodide prepared in 50 cc. of ether from 15.6 g. (0.1 mole) of ethyl iodide and 13 g. of zinc-copper couple, was added 4 g. (0.022 mole) of azobenzene. The mixture was refluxed for 12 hours during which time a small amount of precipitate formed. After hydrolysis by ammonium chloride solution, the ether layer was separated and dried. Removal of the ether left a gummy solid which, after washing with petroleum ether, left a small quantity of tarry substance from which no pure compound was isolated. From the washings there was obtained 0.5 g. of aniline and 2.65 g. of azobenzene. Longer periods of heating did not improve the yield.

Diphenylzinc.—Diphenylzinc was prepared in accordance with recent directions.[5] In most preparations longer periods of heating were necessary in order to complete the reaction. Also, addition of very small quantities of *n*-butylmagnesium bromide facilitated initiation of the reaction. In general, 21.3 g. (0.06 mole) of diphenylmercury and 26.2 g. (0.4 g.-atom) of mossy zinc were refluxed for 24 hours in 150 cc. of xylene previously dried over sodium. The warm xylene solution was forced by

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[5] KOCHESKOV, NESMEYANOV, AND POTROSOV, *Ber.*, **67B**, 1138 (1934). See, also, GILMAN AND MARPLE, *Rec. trav. chim.*, **55**, 133 (1936).

nitrogen pressure through a glass tube, containing a plug of glass wool, into a 500-cc. three-necked flask to which was then added 4 g. (0.022 mole) of azobenzene. The solution was heated at 55–60° for 24 hours, and then hydrolyzed by ammonium chloride solution. The dark red residue obtained after drying and removing the xylene yielded 0.28 g. of aniline by cold dilute acetic acid extraction. There was recovered 3.1 g. of azobenzene.

Practically all the azobenzene was recovered after refluxing an ether or a benzene solution for 40 hours with phenylzinc chloride.

Phenylmanganese iodide.—Phenylmanganese iodide was prepared in accordance with the directions of M. M. Barnett from 15 g. (0.0488 mole) of anhydrous manganous iodide and 0.15 mole of phenylmagnesium iodide. After stirring for 12 hours, the insoluble chocolate-colored manganese compound was washed several times with 200-cc. portions of ether to remove excess Grignard reagent and magnesium salts. The "phenylmanganese iodide" is free of magnesium and analyzes for a mixture of phenylmanganous iodide and diphenylmanganese, but may not contain divalent manganese. Organomanganese compounds and their reactions will be reported later.

To a suspension of the organomanganese compound or compounds in 150 cc. of ether was added 4 g. (0.022 mole) of azobenzene and the mixture was then refluxed with stirring for 12 hours. The products isolated by customary procedures were 2.8 g. of aniline hydrochloride, 1.62 g. of azobenzene and 4.9 g. of diphenyl. Hydrolysis of phenylmanganese iodide gives both diphenyl and benzene. Also, the inflammable organomanganese compound gives diphenyl on moderate pyrolysis.

A mixture of 6.8 g. of manganous iodide and 4 g. of azobenzene in 50 cc. of ether was refluxed for 24 hours. No color change was observed, and the azobenzene was recovered quantitatively.

Diphenylberyllium.—Diphenylberyllium was prepared in accordance with the directions of R. H. Kirby. The etherate of beryllium chloride was first prepared by the slow addition of 50 cc. of ether to 4 g. (0.05 mole) of anhydrous beryllium chloride. The first drops of ether should be added quite slowly because of the vigorous reaction. After stirring for one hour the solution was pale yellow, and a small oily layer had formed at the bottom.

To the etherate was added dropwise 100 cc. of an ether solution containing 0.1 mole of phenyllithium. The mixture was stirred and then allowed to stand overnight. The clear brown solution, from which a gray precipitate had settled, was forced by nitrogen into another flask and 4.55 g. (0.025 mole) of azobenzene added. The mixture was stirred and refluxed for 8 hours prior to hydrolysis by ammonium chloride solution. The products isolated were 2.55 g. of hydrazobenzene, 2.31 g. of diphenyl and 1.82 g. of azobenzene.

Ethylmagnesium bromide.—A yellow precipitate formed promptly when 4 g. (0.022 mole) of azobenzene was added to 0.055 mole of ethylmagnesium bromide. The mixture was refluxed for 6 hours, and after distilling off ether by heating in a water bath, the pink gelatinous mass was heated for an hour. The products obtained, after hydrolysis, were 2.35 g. of hydrazobenzene and 1.4 g. of azobenzene. No aniline was isolated.

Phenylmagnesium bromide.—To a filtered 125-cc. ether solution of phenylmagnesium bromide (0.22 mole) was added 18.2 g. (0.1 mole) of azobenzene in 100 cc. of ether. After refluxing for 8 hours, during which time a heavy yellow precipitate separated, the mixture was cooled in an ice bath and then hydrolyzed by ammonium chloride solution. The products were 11.5 g. of hydrazobenzene, 6.1 g. of diphenyl, 4.5 g. of azobenzene, and a small quantity of tarry residue.

Phenyllithium.—A mixture of 0.1 mole phenyllithium and 0.05 mole of azobenzene in ether was stirred for 40 hours at room temperature. The products, after hydrolysis by ammonium chloride, were 4.77 g. of hydrazobenzene, 4.4 g. diphenyl, 3.1 g. azobenzene and 2 g. of tarry residue.

Phenylsodium.—A suspension of phenylsodium was prepared by stirring 25 g. (0.08 mole) of di-*n*-butylmercury and 6.7 g. (0.3 g. atom) of sodium in 200 cc. of dry benzene for 8 hours, and then allowing to stand overnight. A few drops of mercury were added to insure amalgamation of the excess sodium. The heavy brown suspension was transferred in an inert atmosphere to a flask containing 7.23 g. (0.04 mole) of azobenzene. The mixture was stirred 4 hours at 0°. Higher temperatures or longer periods of reaction resulted in the formation of tarry substances. Subsequent to hydrolysis, there was isolated 1.85 g. of hydrazobenzene, 1.66 g. of diphenyl and 5.3 g. of azobenzene.

Phenylcalcium iodide.—Phenylcalcium iodide was prepared in 150 cc. of ether from 40.8 g. (0.2 mole) of iodobenzene and 12 g. (0.3 g. atom) of calcium turnings. The filtered, dark-red solution together with 12.74 g. (0.07 mole) of azobenzene was refluxed for 12 hours. The products isolated were 3.5 g. of triphenylhydrazine (identified by determination of the melting point of a mixture with an authentic specimen[6]) and 8.2 g. of azobenzene. About 3 g. of a tarry residue remained.

Phenylpotassium.—Phenylpotassium was prepared by the procedure described recently,[7] di-*n*-butylmercury being used instead of diethylmercury. This replacement resulted in a substantial increase in yield. Carbonation of a sample prepared in this manner gave 83.3% of benzoic acid and 2.5% of terephthalic acid (identified as the dimethyl ester). The odor of valeric acid was apparent, and a fluorescein test established the presence of some phthalic acid.

A suspension of phenylpotassium, prepared from 10.83 g. (0.0745 mole) of di-*n*-butylmercury, 3.9 g. (0.1 g. atom) of potassium and 60 cc. of benzene, together with 3.64 g. (0.02 mole) of azobenzene was stirred for 8 hours at 0°. The mixture was hydrolyzed by cautious addition of 10 cc. of butyl alcohol and then 50 cc. of a saturated ammonium chloride solution. The products isolated were 2 g. of triphenylhydrazine and 2 g. of azobenzene.

Hydrazobenzene and diethylzinc.—A solution of 7.5 g. (0.06 mole) of diethylzinc and 4.6 g. (0.025 mole) of hydrazobenzene in 100 cc. of ether was refluxed gently for 12 hours during which time a yellow precipitate settled. The products isolated were 1.33 g. (33%) of aniline and 2.96 g. (53.4%) of hydrazobenzene.

DISCUSSION OF RESULTS

Correlation of types of reaction with relative reactivities of RM compounds.—The unsymmetrical addition to azobenzene of highly reactive phenylmetal compounds to give triphenylhydrazine as contrasted with the symmetrical addition of moderately active RM compounds to give hydrazobenzene is one the very few illustrations of different types of reaction with RM compounds and a selected reactant. Broadly speaking, organometallic compounds show the same reactions but at different rates. On the basis of the results reported, it appears that phenylcalcium iodide

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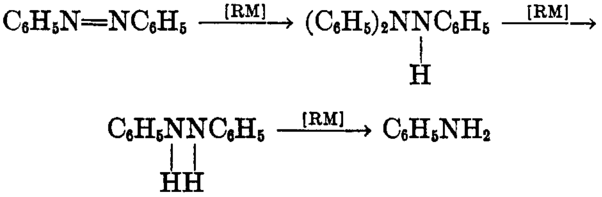
[6] Busch and Hobein, *Ber.*, **40**, 2099 (1907).

[7] Gilman and Kirby, *J. Am. Chem. Soc.*, **58**, 2074 (1936).

is more reactive than phenyllithium and phenylsodium. Previous work has shown that phenylcalcium iodide undergoes reactions peculiar to organoalkali compounds.[8] Unpublished studies by R. H. Kirby on conjugated systems indicate that phenylcalcium iodide and phenylpotassium are more reactive than phenyllithium and phenylsodium. For example, moderately reactive RM compounds like diphenylzinc, triphenylaluminum, phenylmanganese iodide, diphenylberyllium and phenylmagnesium bromide add exclusively 1,4 to a conjugated system like that in benzalacetophenone. Phenylcalcium iodide and phenylpotassium appear to add exclusively 1,2. Phenyllithium and phenylsodium add both 1,2 and 1,4.

There is, accordingly, a very close relationship between the groupings of RM compounds on the basis of their relative reactivities and the types of reaction they undergo with compounds such as azobenzene and benzalacetophenone. A particular exception is phenylmanganese iodide which, with azobenzene, gave aniline and not hydrazobenzene. Although it is quite clear that phenylmanganese iodide is of moderate reactivity, it is known to show occasional special reducing reactions with simple functional groups other than azo. The reactions of organoaluminum compounds will be reported separately, but it might be stated here that the conventional type of addition to most unsaturated linkages is accompanied by condensation and polymerization reactions.

Successive reactions.—It has been suggested that the three chief reaction products may possibly be related in a series of successive reactions.



$$C_6H_5N{=}NC_6H_5 \xrightarrow{[RM]} (C_6H_5)_2N\underset{H}{N}C_6H_5 \xrightarrow{[RM]}$$

$$C_6H_5\underset{H}{N}\underset{H}{N}C_6H_5 \xrightarrow{[RM]} C_6H_5NH_2$$

As we have shown, it is true that the very high yield of aniline which Frankland obtained with diethylzinc is due in part to the intermediate formation of hydrazobenzene which under the experimental conditions is converted to a significant extent to aniline. However, despite the known instability of trisubstituted hydrazines it is quite unlikely that a moderately reactive RM compound first gives a compound like triphenylhydrazine (or its metallic salt) which then is transformed to hydrazobenzene. As a possible explanation for the formation of triphenylhydrazine from β-phenylhydroxylamine and phenylmagnesium bromide,

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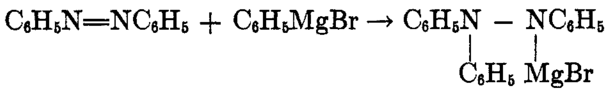
[8] Gilman, Kirby, Lichtenwalter, and Young, *Rec. trav. chim.*, **55**, 79 (1936).

Busch and Hobein[9] suggested that the Grignard reagent added to azobenzene as follows.

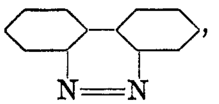


$$C_6H_5N{=}NC_6H_5 + C_6H_5MgBr \rightarrow \underset{C_6H_5}{\underset{|}{C_6H_5N}} - \underset{MgBr}{\underset{|}{NC_6H_5}}$$

If triphenylhydrazine or its magnesium salt is formed transitorily it is *not* converted to hydrazobenzene by heating with a liberal excess of either ethylmagnesium bromide or phenylmagnesium bromide.[10]

Initial formation of complexes.—Whether one has symmetrical or unsymmetrical addition to the azo linkage appears to depend primarily on the relative reactivity of the organometallic compound. However, in all cases the opening of the azo linkage is apparently preceded by the formation of an addition complex or a coördinate compound. Significant quantities of azobenzene were recovered from all reactions even though an excess of RM compound was used. In several cases, particularly with the Grignard reagent, light colored precipitates were formed leaving the supernatant solvent practically colorless. On hydrolysis, the solvent exhibited the typical bright-red color of dissolved azobenzene.

Schlenk and co-workers[11] found that one atom of potassium reacted with one molecule of azobenzene to give a colored complex ($C_6H_5N{=}NC_6H_5\cdot\underset{K}{\underset{|}{C_6H_5N}}{-}\underset{K}{\underset{|}{NC_6H_5}}$), which on hydrolysis gave equimolecular quantities of azobenzene and hydrazobenzene. However, the binary system ($Mg + MgBr_2$) gives a practically quantitative yield of hydrazobenzene,[2] and the cyclic azo grouping in benzocinnolines,



adds two atoms of lithium, sodium and potassium for each molecule of azo compound.[12]

A most interesting case of complex formation is that reported by Taurinš[13] on the reaction between Grignard reagents and hydroxyazo compounds. The observations were made that RMgX compounds are precipitated quantitatively and promptly by hydroxyazo compounds

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[9] Busch and Hobein, *loc. cit.*

[10] Gilman and Adams, *J. Am. Chem. Soc.*, **48**, 2004 (1926).

[11] Schlenk, Appenrodt, Michael, and Thal, *Ber.*, **47**, 485 (1914).

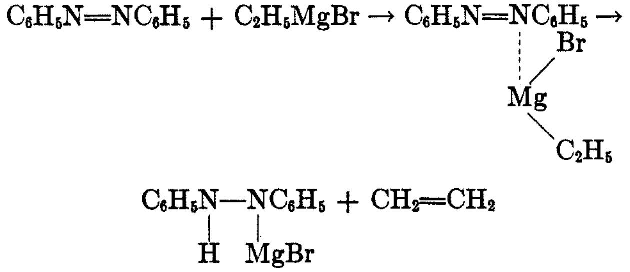
[12] Wittig and Stichnoth, *ibid.*, **68**, 928 (1935).

[13] Taurinš, *Acta Univ. Latviensis, Kim. Fakult. Serija*, **2**, 321 (1934) [*Chem. Abstr.*, **29**, 1400 (1935)].

like benzeneazophenol to give colored products of the general formula $RMgX \cdot C_6H_5N{=}NC_6H_4OH \cdot 2(C_2H_5)_2O$. Related complexes are formed from R_2Mg compounds and from magnesium halides; and an equimolecular mixture of R_2Mg and MgX_2 gives the same complex as does the corresponding RMgX compound. It is somewhat surprising that the RMgX or R_2Mg compounds are not decomposed by the active hydrogen in the hydroxyazo compounds, for in other studies we have shown that even triethylaluminum reacts promptly with benzeneazophenol to liberate ethane.

Reducing action.—The tendency to reduction as evidenced by the formation of hydrazobenzene and aniline appears to be greatest with the less reactive RM compounds and least with the more reactive RM compounds. If there be a relationship between the reduction of the azo linkage and other unsaturated linkages, particularly the carbonyl group, by organometallic compounds, then one may predict that RM compounds of calcium and potassium will show very little reduction of carbonyl compounds to primary or secondary alcohols.

A refined mechanism for the reduction is not clear. There may be several mechanisms depending both on the nature of the metal and the R group. Rheinboldt and co-workers[14] first suggested that the active reducing agent was HMgX.



$$C_6H_5N{=}NC_6H_5 + C_2H_5MgBr \rightarrow C_6H_5N{=}\underset{\underset{\displaystyle Mg\begin{matrix}\diagup Br\\ \diagdown C_2H_5\end{matrix}}{\vdots}}{N}C_6H_5 \rightarrow$$

$$C_6H_5\underset{\underset{\displaystyle H}{|}}{N}-\underset{\underset{\displaystyle MgBr}{|}}{N}C_6H_5 + CH_2{=}CH_2$$

When they later found that not only ethylene but ethane were liberated in about equivalent quantities they apparently abandoned the HMgX interpretation for this particular reduction.[1c] Apart from the restricted application of this concept for reduction of the azo linkage,[1b] it would appear that an equivalent quantity of ethane is actually to be expected. The active hydrogen on the nitrogen of the mono-bromomagnesium compound should react with a second molecule of ethylmagnesium bromide to give ethane and the di-bromomagnesium compound known to be formed.

The mechanism proposed for the reduction of aldazines[1a] by Grignard reagents may warrant confirmation.

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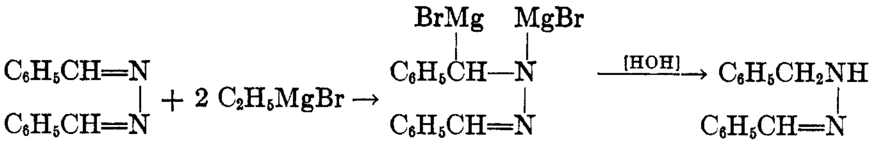
[14] RHEINBOLDT AND ROLEFF, *Ber.*, **57**, 1921 (1924); *J. prakt. Chem.*, **109**, 175 (1925).

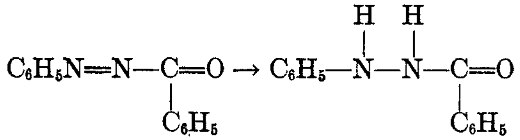


$$\begin{array}{l} C_6H_5CH{=}N \\ C_6H_5CH{=}N \end{array} + 2\,C_2H_5MgBr \rightarrow \begin{array}{l} C_6H_5\overset{BrMg}{\overset{|}{C}}H{-}\overset{MgBr}{\overset{|}{N}} \\ C_6H_5CH{=}N \end{array} \xrightarrow{[HOH]} \begin{array}{l} C_6H_5CH_2NH \\ C_6H_5CH{=}N \end{array}$$

It seems unlikely that the anil linkage would behave like an azo linkage, for anils are known to add RMgX compounds unsymmetrically.

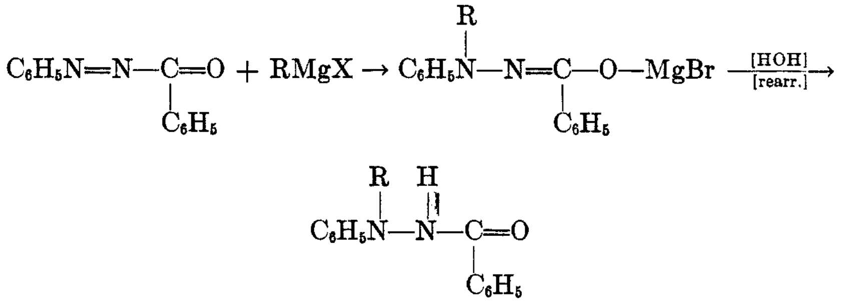
$$C_6H_5CH{=}NC_6H_5 + RMgX \rightarrow C_6H_5\overset{R}{\overset{|}{C}}H{-}\overset{MgBr}{\overset{|}{N}}C_6H_5$$

Possible unsymmetrical addition of less reactive RM compounds.—Stollé and Reichert[15] have examined the reaction of Grignard reagents with azodibenzoyl and benzoylazobenzene. From these compounds having the azo linkage conjugated with the carbonyl group, two products were obtained. One, in lesser amount, was the reduction product which corresponds with hydrazobenzene from azobenzene.



$$C_6H_5N{=}N{-}\underset{C_6H_5}{\underset{|}{C}}{=}O \rightarrow C_6H_5{-}\overset{H}{\overset{|}{N}}{-}\overset{H}{\overset{|}{N}}{-}\underset{C_6H_5}{\underset{|}{C}}{=}O$$

The mechanism of formation of the other product was interpreted by them as an unsymmetrical 1,4 addition.



$$C_6H_5N{=}N{-}\underset{C_6H_5}{\underset{|}{C}}{=}O + RMgX \rightarrow C_6H_5\overset{R}{\overset{|}{N}}{-}N{=}\underset{C_6H_5}{\underset{|}{C}}{-}O{-}MgBr \xrightarrow[\text{[rearr.]}]{\text{[HOH]}} C_6H_5\overset{R}{\overset{|}{N}}{-}\overset{H}{\overset{|}{N}}{-}\underset{C_6H_5}{\underset{|}{C}}{=}O$$

The reaction mechanism was not established. However, the 1,4 addition postulated is much more reasonable than a possible unsymmetrical addition of RMgX which might give the same product. It may be predicted that highly active RM compounds will add predominantly 1,2 to the carbonyl group of a conjugated azo-carbonyl system.

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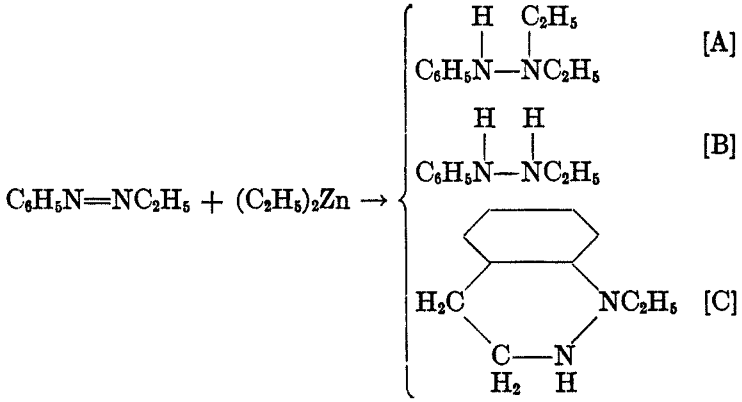
[15] Stollé and Reichert, *J. prakt. Chem.*, **122**, 344 (1929).

It seems unlikely that diethylzinc would add unsymmetrically. However, such addition has been proposed for the reaction with phenylazoethane.[16] The products reported were *N*,*N*-diethyl-*N*′-phenylhydrazine [A], *N*-ethyl-*N*′-phenylhydrazine [B] and ethyltetrahydrocinnoline [C].



The formation of these products was explained as follows. First, unsymmetrical addition gave [A]. Second, *N*,*N*′-diethyl-*N*-phenylhydrazine, formed as an intermediate, underwent ring closure with the loss of two hydrogen atoms to give [C].[16b] Third, the two hydrogen atoms liberated in the formation of [C] reduced some of the original phenylazoethane to give [B].

It is possible that the phenylhydrazone of acetaldehyde, which is readily formed by a 1,3 shift of hydrogen in phenylazoethane,[17] may have been present in the reaction mixture and somewhat altered the course of reaction. The reduction product [B] was very likely formed by symmetrical addition, as in the conversion of azobenzene to hydrazobenzene by diethylzinc.

The possibility of unsymmetrical addition to an azo linkage of moderately reactive RM compounds, and of symmetrical addition of highly reactive RM compounds is not excluded. On the basis of studies now in progress it is reasonable to expect that the direction and extent of reaction with various functional groups can be varied by the introduction of proper substituents in the R groups of both RM compounds and the reactants.

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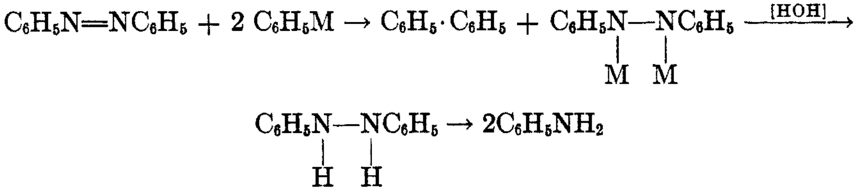
[16] Tichwinski, (*a*) *J. Russ. Phys. Chem. Soc.*, **36**, 1056 (1904) [*Chem. Zentr.*, *I*, 80 (1905)]; (*b*) *ibid.*, **36**, 1052 (1904) [*Chem. Zentr.*, *I*, 79 (1905)].

[17] Fischer, *Ber.*, **29**, 794 (1896); Bamberger and Pemsel, *ibid.*, **36**, 56 (1903).

SUMMARY

1. Three main products are formed from the reaction between azobenzene and phenylmetallic compounds: aniline, hydrazobenzene and triphenylhydrazine.

2. The formation of aniline and hydrazobenzene is due to the symmetrical addition of moderately reactive RM compounds to the azo linkage.



$$C_6H_5N{=}NC_6H_5 + 2\ C_6H_5M \rightarrow C_6H_5{\cdot}C_6H_5 + \underset{M}{C_6H_5N}{-}\underset{M}{NC_6H_5} \xrightarrow{[HOH]}$$

$$\underset{H}{C_6H_5N}{-}\underset{H}{NC_6H_5} \rightarrow 2C_6H_5NH_2$$

3. Triphenylhydrazine results by unsymmetrical addition of the highly reactive phenylcalcium iodide and phenylpotassium.

$$C_6H_5N = NC_6H_5 + C_6H_5K \rightarrow (C_6H_5)_2NNHC_6H_5$$

4. Some reaction mechanisms are discussed.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE ACTION OF DIAZOMETHANE UPON DUROQUINONE*

LEE IRVIN SMITH AND W. B. PINGS

Received February 26, 1937

Until the recent work of Fieser and his students,[1] there had been very little study of the reaction between quinones and aliphatic diazo compounds. v. Pechmann[2] found that two molecules of diazomethane added readily to benzoquinone, and he formulated the product as a dipyrazolinoquinone. Rotter and Schaudy[3] found that diazomethane and xyloquinone gave an unstable, explosive substance which also was formed by addition of two molecules of the diazo compound to one of quinone. Fieser and Peters[1a] found that benzoquinone and diphenyldiazomethane reacted to give a yellow addition product in nearly quantitative yield, but thermal decomposition of this material did not lead to products suitable for further study.

The reaction between 1,4-naphthoquinones and aliphatic diazo compounds produces in general pyrazoloquinones, and Fieser, studying the reaction between 1,4-naphthoquinone and diazoacetic ester, outlined the reaction as involving four steps leading to the pyrazole. Using diphenyldiazomethane (a diazo compound with no hydrogen atoms on the methane carbon atom), Fieser and Peters[1a] were able to obtain the pyrazoline and from this, by thermal decomposition, a cyclopropane derivative as well as 2-benzohydryl-1,4-naphthoquinone. When the quinone nucleus carried substituents however, the reaction with aliphatic diazo compounds was not so regular. Macbeth and Winzor[4] found that 2-methyl-1,4-naphthoquinone was unreactive toward diazomethane, and Fieser and Hartwell[1c] found that this quinone was also unreactive toward hydrazoic acid. However, these authors showed that the analogous 2-benzohydryl-1,4-naphthoquinone readily added diazomethane to give a pyrazoline

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* Abstracted from a thesis by Wilbur Bennett Pings, submitted to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, July, 1936.

[1] FIESER *et al.*, (*a*) *J. Am. Chem. Soc.*, **53**, 4080 (1931); (*b*) *ibid.*, **56**, 2690 (1934); (*c*) *ibid.*, **57**, 1479, 1482 (1935).

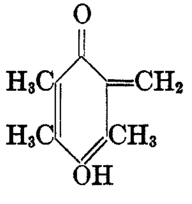
[2] v. PECHMANN, (*a*) *Ber.*, **28**, 855 (1895); (*b*) v. PECHMANN AND SEEL; *ibid.*, **32**, 2292 (1899).

[3] ROTTER AND SCHAUDY, *Monats.*, **47**, 493 (1926).

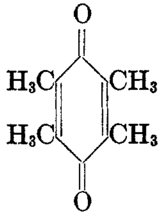
[4] MACBETH AND WINZOR, *J. Chem. Soc.*, **1935**, 334.

which on thermal decomposition, gave 2-benzohydryl-3-methyl-1,4-naphthoquinone. Finally Fieser and Seligman[1b] discovered that two molecules of 2,6-dimethyl-1,4-naphthoquinone reacted with one of diazomethane to produce a dinaphthylmethane derivative.

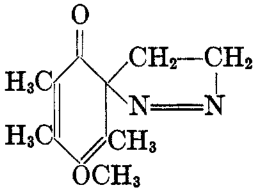
In a series of papers from this laboratory[5] duroquinone (B) has been shown to behave as a pentad-enol system toward various enolates, and to react as though it had the structure A. As yet it has not been possible to prepare any simple derivatives of this structure, and from what is known concerning methylene quinones, it seems likely that any simple reaction involving them, in order to give a definite product, would have to proceed very rapidly or else the methylene quinone would simply polymerize. Formula A, however, represents a hydroxy derivative of a methylene quinone. If, in solutions of duroquinone, there is present a small amount of A together with a very reactive methylating agent, it might be possible to obtain from A a methyl derivative sufficiently stable to investigate, provided the reagent used would react with B extremely slowly or not at all. Although diazomethane reacts with double bonds to form pyrazolines it appeared from the work of others that substituents attached to the quinone nucleus exerted a pronounced hindrance to the addition of the reagent to the double bond and that duroquinone (B) would not, therefore, react to give pyrazolines or pyrazoles. Hence, if a reaction occurred, the quinone would have to react in the form A, or else the reaction would have to involve the carbonyl groups of B. The latter reaction had not been shown to occur in the case of paraquinones, although it is the common reaction in the case of orthoquinones and leads to ethers of the hydroquinone or to spiro ethylene oxide derivatives.[6,1a,b,c,2b] Diazomethane therefore appeared to be a promising reagent to use for the detection of any A in duroquinone, for either the hydroxyl group, or the unsubstituted heterogeneous conjugated system of A would be expected to react with this reagent much more rapidly than the double bonds or the carbonyl groups of B.



A



B



F

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[5] SMITH AND JOHNSON, *J. Am. Chem. Soc.*, **59**, 673 (1937) and previous papers.

[6] (*a*) BILTZ AND PAETZOLD, *Ann.*, **433**, 64 (1923); (*b*) ARNDT, AMENDE, AND ENDER, *Monats.*, **59**, 202 (1932); (*c*) ALLESANDRI, *Atti. R. accad. Lincei* [5] **22**, I, 517 (1913).

Duroquinone reacted slowly but completely with diazomethane in cold ethereal solution, and from the reaction mixture four products were isolated. These consisted of two isomeric compounds $C_{11}H_{14}N_2O_2$ (I, an unstable oil and II, a stable yellow crystalline compound melting at 103–104°) formed by addition of one molecule of the reagent to one of quinone, and two isomeric products $C_{12}H_{16}N_4O_2$ both colorless solids (III melting at 124–125°, decomp., and IV, melting at 143–144°, decomp.) formed by addition of two molecules of the reagent to one of quinone.

TABLE I

PRODUCTS OBTAINED BY ADDITION OF DIAZOMETHANE TO DUROQUINONE

(Diazomethane from 10 g. nitrosomethylurea added to 5.5 g. of duroquinone, at −15°)

SOLVENT	TIME (DAYS)	I + II (G.)	III (G.)	IV (G.)
Ether, 250 cc.	18	4.0	1.35	
Ether, 75 cc.	12	2.3	5.68 (III + IV)	
Ether, 125 cc.	12	2.3	5.39 (III + IV)	
Ether, 100 cc. (absolute)	5	—	3.47	
Benzene, 100 cc.	14	3.2	3.24 (III + IV)	
*Ether, 100 cc. + chloroform, 50 cc	25	2.4 + 1.23 g. from steam distillate + 7.08 g. of quinone.		
Ether 75 cc. + chloroform 20 cc	12	4.0	2.65	
Ether 100 cc. + acetone 50 cc.	11	2.5	1.34	1.55
Ether 100 cc. + ligroïn 50 cc	26	3.0	—	3.45 + 0.5 g. duroquinone
Ether 100 cc. + methanol 10 cc	11	3.0	—	3.43

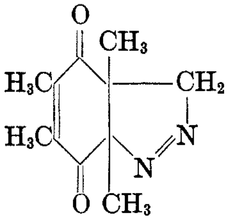
* Eleven grams of quinone used in this experiment with diazomethane from 10 g. nitrosomethylurea.

The mono addition products.—The unstable oily product I was never obtained in a completely pure condition, although analysis agreed well with that required by the composition $C_{11}H_{14}N_2O_2$. Further reaction of I with diazomethane led to IV. The substance I was completely destroyed when oxidized by cold dilute permanganate or by bromine, but when oxidized by ferric chloride, the product was duroquinone (B). Hence the original duroquinone nucleus was intact in I. Attempted acetylation of I gave duroquinone as the only isolable product, and reductive acetylation gave the diacetate of hydroduroquinone. Thermal decomposition of I led to a faintly yellow, stable product (V) melting at 60–61°, having the composition $C_{11}H_{14}O_2$, and which formed a dioxime. The substance

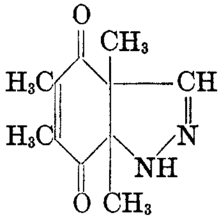
V was unaffected by hydrochloric or sulfuric acid, and was not oxidized by chromic acid or dilute nitric acid. The action of permanganate, or of ozone, upon V caused complete destruction.

In contrast to the behavior of I, the isomeric compound II was completely stable to heat and was recovered unchanged even after it was liquefied and then boiled. The substance (II) was yellow, but it did not have the physical properties characteristic of quinones. It was not volatile with steam, could not be sublimed, and was odorless. Further action of diazomethane upon II, as in the case of I, led to IV. No definite products could be obtained by reduction of II, but the duroquinone skeleton was intact in this compound also, for it gave duroquinone when treated with acetic anhydride followed by sodium bicarbonate, and also when the reduction product was subjected to the action of ferric chloride.

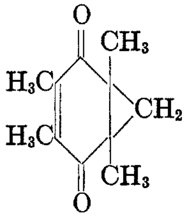
The existence of isomeric mono addition products derived from duroquinone and diazomethane is capable of but two explanations. The compounds might be pyrazolines, in which case the position of the double bond could vary (C and D).



C



D



E

But in this case, conversion of the Δ^1 isomer (C) to the Δ^2 isomer (D) should be possible[7] and such conversion has not been observed for these compounds. Moreover, C and D, by thermal decomposition, should lead to the same product, which is contrary to the observed behavior of I and II. That the decomposition product V obtained from I is not a cyclopropane derivative (E) follows from its stability toward hydrochloric acid, its complete destruction by permanganate and ozone[8] and from the fact that V forms a dioxime.[9] Further evidence against the formulation of I, II and V as C, D, and E respectively is found in the fact that duroquinone can be obtained from either I or II, which would not be the case if these substances were the pyrazolines C and D.

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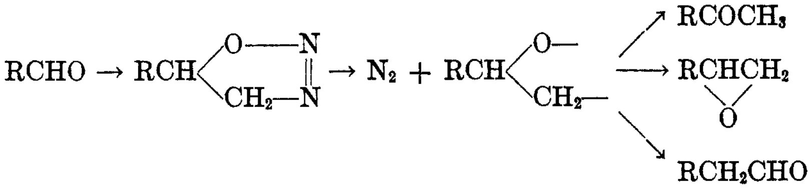
[7] (*a*) v. Auwers and Cauer, *Ann.*, **470**, 284 (1929); (*b*) v. Auwers and Konig, *ibid.*, **496**, 27, 252 (1932); (*c*) v. Auwers and Ungemach, *Ber.*, **66**, 1198 (1933).

[8] Kohler *et al.*, *J. Am. Chem. Soc.*, **39**, 1404, 1699, 2405 (1917); **41**, 1093 (1919).

[9] Kehrmann, *Ber.*, **21**, 3315 (1888).

If I and II are not pyrazolines, they must be formed by a mode of addition of diazomethane which has not yet been observed in the case of paraquinones. Had duroquinone reacted according to formula A, the product would most likely have been a monomethoxy spiro compound, such as F, which not only does not have the composition of I or II, but which, on thermal decomposition, would almost certainly have given a derivative of trimethylethylquinone. No such substances were ever encountered. It follows, then, that the attack of the reagent was confined to the carbonyl groups in the quinone.

Meyer[10] and Schlotterbeck[11] found that certain aldehydes behaved toward diazomethane as though they contained active hydrogen. Nitrogen was evolved, and methyl ketones were formed. Arndt and his collaborators[12] showed that this reaction was not of general application, since in some cases ethylene oxides were formed, the ketone and a homolog of the aldehyde appearing only as by-products. The mechanism put forth by Arndt for these reactions involved a primary 1,3 addition of the reagent to the carbonyl group to give furo-α-β-diazolines which, by loss of nitrogen then gave rise to transient radicals rearranging into the stable products obtained.



Meerwein and Burneleit[13] discovered that although ketones do not react with diazomethane under ordinary conditions, they do so in the presence of certain catalysts (water, alcohols, metallic salts) yielding ethylene oxides and higher ketones. This reaction was formulated as also involving furo-α,β-diazolines as primary products. When applied to cyclic ketones, Mosettig and Burger[14] found that cyclohexanone reacted vigorously with diazomethane in the presence of methanol to give cycloheptanone and even larger ring ketones. Ring expansion in reactions of cyclic dicarbonyl

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[10] Meyer, *Monats.*, **26**, 1295 (1905); *Ber.*, **40**, 847 (1907).

[11] Schlotterbeck, *Ber.*, **40**, 479 (1907).

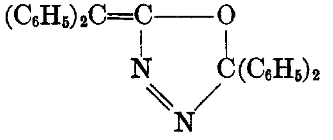
[12] Arndt *et al.*, (*a*) *Z. angew. Chem.*, **40**, 1099 (1927); (*b*) *Ber.*, **60**, 446 (1927); (*c*) *ibid.*, **61**, 1107 (1928); (*d*) *ibid.*, **61**, 1118 (1928); (*e*) *ibid.*, **61**, 1952 (1928); (*f*) *ibid.*, **62**, 44 (1929).

[13] Meerwein and Burneleit, (*a*) *Ber.*, **61**, 1840 (1928); (*b*) *ibid.*, **62**, 999 (1929).

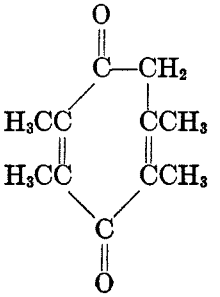
[14] Mosettig and Burger, *J. Am. Chem. Soc.*, **52**, 3456 (1930).

compounds with aliphatic diazo compounds had been noted by others previously.[15]

Although all these reactions between carbonyl compounds and aliphatic diazo compounds were supposed to involve furo-α,β-diazolines, in which a new carbon-to-carbon linkage was established, in no case was the diazoline isolated. Theoretically two modes of addition of aliphatic diazo compounds to carbonyl groups are possible, leading to furo-α,β- and furo-β,β'-diazolines, and it is interesting that in the one case in which the diazoline was actually isolated, Staudinger[16] assigned to it the structure of a furo-β,β'-diazoline (G)

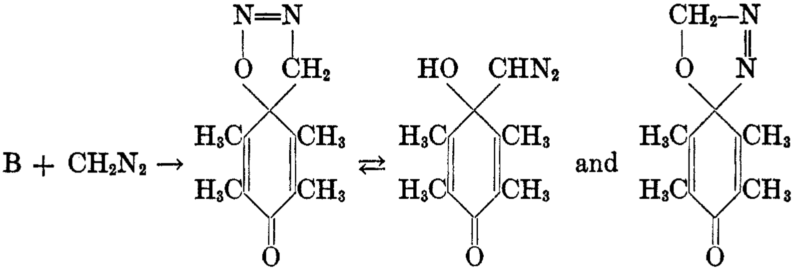


G



V

If the reaction between diazomethane and duroquinone is confined to the carbonyl groups of the quinone, since two modes of addition are possible, two mono addition products should result—the spiro-furo-α,β-diazoline I, and the spiro-furo-β,β'-diazoline II.



I

II

While these structures for the mono addition compounds I and II are of necessity based upon rather indirect evidence, at the present time they best represent the behavior of the substances. Although formulas II and IIa, as well as I and Ia, were considered as structures for compounds I and

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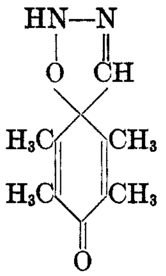
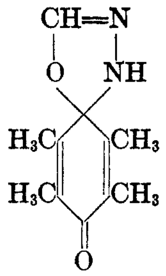
[15] (*a*) Heller, *Ber.*, **52**, 741 (1919); (*b*) *ibid.*, **59**, 704 (1926); (*c*) Hantzsch and Czapp, *ibid.*, **63**, 566 (1930); (*d*) Arndt, *ibid.*, **63**, 1180 (1930).

[16] Staudinger, *Helv. Chim. Acta*, **4**, 3 (1921).


Ia


IIa

II, respectively, formulas I and II were preferred because of the fact that I could not be converted into II, or vice versa, and because of the difference in thermal stability of compounds I and II. The formulas I and II readily account for the persistence of the original nucleus of duroquinone in these compounds. Moreover, I, being a diazo anhydride, would be tautomeric with the β-hydroxy diazomethane derivative as shown. Such a substance should be unstable and should lose the nitrogen, passing into a larger ring ketone via a spiroethylene oxide (or radicals) as is the case with simple ring ketones such as cyclohexanone. The decomposition product (V) of I is therefore assigned the structure 2,3,5,6-tetramethylcycloheptadiene-2,5-dione-1,4.

The thermal stability of compound II indicates that it must have a structure essentially different from that of I. Although no exact analogy can be drawn, it is known that the aromatic disubstituted β-β′-diazoles are very stable substances.[17] While the conversion of II into duroquinone by action of acetic anhydride followed by sodium bicarbonate is rather obscure for such a stable substance, nevertheless a compound of the structure II would be expected to yield duroquinone as a degradation product.

The di addition products (*III and IV*)—Compound III separated from the reaction mixture in clear rectangular prisms melting at 124–125° with evolution of gas. Analysis indicated the composition $C_{12}H_{16}N_4O_2$. Thermal decomposition caused quantitative loss of nitrogen and led to a colorless substance (VI) $C_{12}H_{16}O_2$ which melted at 142–143° and which formed a dioxime. Substance III reacted with hydrochloric acid or hydrobromic acid to give salts which could be titrated; duroquinone was formed when attempts were made to regenerate III from these salts, or when aqueous solutions of the salts were warmed. No oxime was formed from III, but

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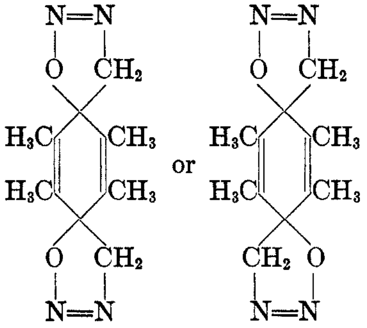
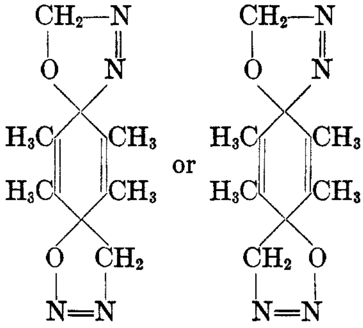
[17] (*a*) PINNER, *Ber.*, **26**, 2130 (1893); (*b*) *ibid.*, **27**, 988, 1006 (1894); (*c*) *Ann.*, **297**, 237 (1897); (*d*) *ibid.*, **298**, 16 (1897); (*e*) GÜNTHER, *ibid.*, **252**, 61, 64 (1889); (*f*) STOLLE, *J. prakt. Chem.*, [2], **68**, 137 (1903); (*g*) *ibid.*, **70**, 395, 414 (1904); (*h*) *ibid.*, **73**, 279 (1906); (*i*) *ibid.*, **74**, 11, 15, 20, 22 (1906); (*j*) *ibid.*, **88**, 317 (1913).

it reacted with phenylhydrazine to give a compound having the composition $C_{18}H_{22}N_6O$. A silver salt was obtained by adding silver nitrate to a solution of III in ammonium hydroxide.

The isomeric compound IV was obtained in clusters of fine needles melting at 143–144° with decomposition. Thermal decomposition of IV was smooth; only about half of the nitrogen was lost, and two unstable isomeric nitrogenous compounds $C_{12}H_{16}N_2O_2$ (VII and VIII) were isolated, along with some duroquinone. Treatment of IV with hydrochloric acid or hydrobromic acid gave salts apparently identical with those obtained from III. Attempts to form an oxime or a semicarbazone from IV gave only duroquinone, and the quinone also resulted when IV was gently warmed with dilute acids. Derivatives were obtained from IV by action of phenylhydrazine or phenylisocyanate, but 1-naphthylisocyanate was without action. A silver salt was obtained from IV in the same manner as from III.

On the basis of these reactions, III is assigned the structure a bisfuro-α,β-diazoline, while IV is given the structure in which one of the hetero rings is a furo-α,β- and the other a furo-β,β'-diazoline. As in the case of compounds I and II, various tautomeric modifications of formulas III and IV (analogous to Ia and IIa) were considered for the di addition products. While the evidence against such formulas for III and IV is much weaker than is the case with compounds I and II—in fact, there is some evidence for such a relationship between III and IV—the bulk of the evidence pointed to two different types of ring structures in substances III and IV and such tautomeric formulas were rejected, at least for the present. Structures III and IV account for the behavior of these compounds upon thermal decomposition, for III, with two unstable furo-α,β-diazoline rings

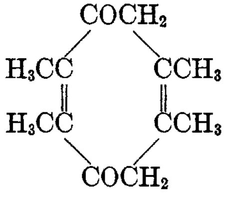

III


IV

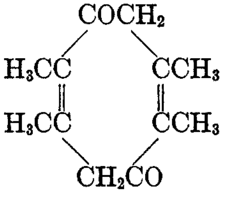
should lose nitrogen quantitatively while IV, with one stable and one unstable ring, should lose only half of the nitrogen. The fact that IV can be obtained by addition of diazomethane to either I or II is also an indication that IV must contain one hetero ring of each kind. The difference in behavior of the two compounds on thermal decomposition is an indication that they cannot be represented simply as a pair of *cis-trans* isomers, although such isomerism is possible in the case of compounds having either structure III or IV. Finally, structures III and IV, as well as I and II, account for the easy conversion of the two substances to duroquinone.

The formation of identical salts from III and IV with hydrochloric acid or hydrobromic acid cannot be explained satisfactorily at present. Analyses of the salts indicated a carbon to hydrogen ratio of 1 to 2, and since III and IV have the composition $C_{12}H_{16}N_4O_2$, it appeared that a reduction had occurred. The formation of silver salts from III and IV is just as obscure, for while it is known that furo-β-β′ diazoles in many cases form double salts with silver nitrate[17] it is not possible to write such a formula consistent with the analyses of the silver salts of III and IV.

In analogy with structure V, the substance VI obtained by thermal decomposition of III is assigned the structure 2,3,6,7-tetramethylcyclooctadiene-2,6-dione-1,4 (VIa) or 2,3,6,7-tetramethylcycloöctadiene-2-6-dione-1,5 (VIb), while the decomposition product of IV

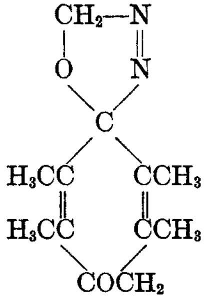


VIa



VIb

is assigned the structure of a spiro-cycloheptadiene-furo-β,β′-diazoline (VII). Two isomeric compounds were obtained by thermal decomposition of IV, but at present the relationship between these is not known. Both VII and VIII were unstable and decomposed on standing to give uncrystal-



(VII)

lizable yellow oils; both reacted with acetic anhydride, giving the same unstable acetyl derivative.

EXPERIMENTAL*

The addition reaction.—The reaction between duroquinone and diazomethane was carried out in a number of solvents. In general either III or IV was obtained, along with varying amounts of the mono addition products I and II. However, it was not possible to predict which of the products would be formed except when methanol was present. Under these circumstances, if any di addition product was obtained, it was invariably IV. In other solvents no such regularity was noticed, and two experiments, apparently identically performed, rarely gave the same results. In general the yields of di addition products ranged from about 30–60%; while the yields of mono addition products ranged from about 75–35%. A typical experiment will be described, and the results of others will be given in tabular form. A solution of diazomethane (2.8 g., 0.067 moles; obtained from 10 g. nitrosomethylurea) in ether (100 cc.) was added to a solution of duroquinone (5.5 g., 0.034 moles) in ether (125 cc.) and methanol (20 cc.). The solution, after standing at −5 to −10° for 11 days, deposited clusters of fine needles (4 g., IV) which were removed, washed with ether, and recrystallized from methanol or chloroform-petroleum ether. The substance (IV) melted at 143–144° with evolution of gas. It was insoluble in cold water, but soluble in hot water, dilute hydrochloric acid, 10% sodium hydroxide, concentrated ammonium hydroxide, and acetic acid. It was decomposed violently by concentrated sulfuric acid.

Anal. Calc'd for $C_{12}H_{16}N_4O_2$: C, 58.04; H, 6.50; N, 22.58.
Found: C, 58.33; H, 6.47; N, 22.77.

Evaporation of the ethereal filtrate from IV and steam distillation of the residue gave only a trace of duroquinone in the distillate. The non-volatile oil (3.2 g., 47%) remaining in the distilling flask was a mixture of I and II.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.04; H, 6.85.
Found: C, 64.63; H, 7.10.

The oils, from four reactions (16 g.) were combined and decomposed by heating gently in a distilling flask. After the vigorous evolution of gas had subsided, water was added and steam was passed through until no more yellow oily material collected in the distillate. The distillate was saturated with salt and extracted with ether. Evaporation of the solvent left a clear yellow oil (2 g.) which solidified on standing. Crystallized several times from dilute acetone, dilute methanol, or low boiling petroleum ether, the substance (V) was nearly colorless and melted at 60–61°. It was insoluble in water, dilute hydrochloric acid, or dilute sodium hydroxide, but was soluble in concentrated sulfuric acid (orange-red solution), and reprecipitated on dilution. Permanganate in dilute acetone was readily reduced by the substance, but bromine in chloroform, as well as acetyl chloride, were without action.

Anal. Calc'd for $C_{11}H_{14}O_2$: C, 74.11; H, 7.92.
Found: C, 74.48; H, 8.11.

The residue remaining after V had been steam-distilled was a dark oil (6.1 g.) which could not be crystallized. When distilled under reduced pressure there was obtained 4.4 g. of a clear yellow oil (b.p. 160–170° 13 mm.) which solidified on cooling. Crystallized from water, dilute methanol, ethanol, acetone, or petroleum ether, the

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* Microanalyses by Mr. J. W. Opie.

substance formed bright-yellow prisms melting at 102–103° (II), and soluble in dilute hydrochloric acid or in concentrated sulfuric acid, insoluble in 10% sodium hydroxide. Cold dilute alkaline permanganate, as well as bromine in chloroform, were instantly decolorized by the substance.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.04; H, 6.85; N, 13.59; mol. wt., 206.
Found: C, 63.74; H, 6.93; N, 13.24, 13.62; mol. wt. (Rast) 221, 212.

The mixture of mono addition products I and II could also be separated by long-continued steam distillation, the yellow product II remaining as a non-volatile residue while the decomposition product (V) of I slowly distilled over.

The di addition product III was obtained by conducting the addition reaction as described above, *omitting the methyl alcohol.* The product (4.26 g., 57%) separated in clear rectangular prisms which were removed and crystallized from methanol. The substance melted at 123° with evolution of gas. It was insoluble in cold water, but soluble in hot water although it decomposed partially, giving a yellow viscous oil. It dissolved in dilute sodium hydroxide, concentrated ammonium hydroxide, and in dilute hydrochloric acid, and was violently decomposed by cold concentrated sulfuric acid.

Anal. Calc'd for $C_{12}H_{16}N_4O_2$: C, 58.04; H, 6.50; N, 22.58.
Found: C, 58.23; H, 6.51; N, 22.64.

The filtrate from III, handled in the say as that from IV, gave a trace of duroquinone and 2.2 g. (35%) of a mixture of the mono addition products I and II.

Addition of diazomethane to II.—The yellow mono addition product II (0.45 g.) in dry ether (25 cc.) was added to diazomethane (0.9 g.) in ether (35 cc.). After standing at 0–5° for 10 days, the products were 0.2 g. of IV, m.p. and mixture m.p. 141–142° (decomp.) and 0.1 g. of unchanged II.

Addition of diazomethane to I.—The oily addition product I (1.8 g.) (from which duroquinone was removed by steam distillation) in ether (25 cc.) and methanol (1 cc.) was added to diazomethane (from 3.5 g. nitrosomethylurea) in ether (30 cc.). After standing at 5–10° for 3 days, the solution deposited colorless needles (0.55 g.) of IV melting at 138–140° (decomp.).

Reactions of I. (*a*) *Ferric chloride.*—The oily product I (0.8 g.) (freed of all volatile material by steam distillation) was dissolved in a little ethanol, and a warm concentrated solution of ferric chloride was added. Gas was evolved, and after standing two hours the yellow precipitate was removed. It weighed 0.33 g., and was duroquinone (m.p. and mixture m.p. 110–111°).

(*b*) *Acetic anhydride.*—The oily product I (0.9 g.) and sodium acetate (1 g.) were dissolved in acetic anhydride (3 cc.) and warmed on the steam bath for 30 minutes. The black solution, when poured into water and made alkaline with sodium hydroxide, precipitated 0.175 g. of duroquinone.

(*c*) *Reductive acetylation.*—The product I (0.92 g.) and sodium acetate (1 g.) were dissolved in acetic acid (10 cc.) and acetic anhydride (5 cc.). The solution was heated to boiling and zinc dust (3 g.) was added in small portions over the course of an hour. The product (0.18 g.) crystallized from ethanol, melted at 197–200° and was the diacetate of hydroduroquinone.

Anal. Calc'd for $C_{14}H_{18}O_4$: C, 67.16; H, 7.25.
Found: C, 67.45; H, 7.09.

The original filtrate from the diacetate was extracted with ether and chloroform. The extracts were washed with bicarbonate solution and dried. Evaporation of the solvents left 0.49 g. of a black intractable oil.

Reactions of V. (*a*) The *oxime*, prepared in the usual way and crystallized from dilute acetone, darkened at 220° and melted at 241–242°.

Anal. Calc'd for $C_{11}H_{16}N_2O_2$ (dioxime): C, 63.42; H, 7.75; N, 13.45.
Found: C, 64.37; H, 7.96; N, 13.21.

No phenylhydrazone or *p*-nitrophenylhydrazone of V could be made. The only product isolated was impure starting material.

(*b*) *Acetylation* of V was unsuccessful, and only unchanged material was recovered after treatment of V in the usual way with acetyl chloride, or with acetic anhydride in the presence or absence of sulfuric acid.

(*c*) *Hydrochloric acid* in ether at −10° failed to react with V in the course of an hour.

(*d*) *Oxidation.*—To a solution of V (178 mg.) in acetone (5 cc.) and water (5 cc.) there was added potassium hydroxide (75 mg.) and then, with cooling, a solution of permanganate (421 mg.) in water (10 cc.) was added dropwise. The color was immediately discharged. A little bisulfite was added, and the solution was extracted with ether. Evaporation of the ether left only a trace of oily residue. The alkaline aqueous layer was evaporated to 15 cc., cooled, acidified with dilute sulfuric acid and saturated with salt. Extraction with ether removed only a trace of oily material.

Repetition of the oxidation with the use of 534 mg. of V, 1.263 g. of permanganate and 223 mg. of potassium hydroxide gave essentially the same results, although a very small amount (about 15 mg.) of material melting at 128–131° was obtained when the alkaline solution was extracted with ether.

Chromic acid (0.5 g.) in acetic acid (1 cc.) and water (0.5 cc.) was without action upon V (0.3 g.) in acetic acid (2 cc.), and even after two days at room temperature the substance was recovered unchanged. Likewise heating of V to 100° for an hour with dilute nitric acid (1:10, 5 cc.) produced no change.

(*e*) *Ozonolysis.*—When subjected to the action of ozonized oxygen (5% O_3) for eleven minutes a cold (−10 to −15°) solution of V (0.5 g.) in carbon tetrachloride (80 cc.) absorbed 85% of the amount of ozone calculated for two double bonds. The ozonide was decomposed by adding the solution dropwise to a boiling mixture of water (100 cc.), zinc dust (2 g.) and a small crystal each of silver nitrate and hydroquinone.[18] The product was a small amount of yellow oil which could not be crystallized and which gave no reaction with *o*-phenylenediamine.

Repetition of the ozonolysis (1 g. of V) with chloroform as the solvent and 3% ozonized oxygen gave only a small amount of yellow oil although 95% of the theoretical amount of ozone was absorbed in 22 minutes. The yellow oil was not oxidized by alkaline hydrogen peroxide, and although the iodoform reaction was immediately positive, no organic acid could be isolated.

In a third experiment, the ozonide from 1.5 g. of V was decomposed by boiling the solution with alkaline hydrogen peroxide with no better results.

Reactions of II.—(*a*) A small amount of II was heated in a test-tube. There was no evolution of gas, even after fusion, followed by boiling of the liquid. The melt solidified on cooling; it was remelted and then boiled for 3 minutes. The substance was recovered completely unchanged.

(*b*) Hydroxylamine hydrochloride (0.5 g.), sodium acetate (0.5 g.), and II (0.34 g.) were dissolved in water (3 cc.) and ethanol (7 cc.), and the mixture was refluxed for 48 hours. The product (45 mg.) was a slightly yellow solid which after several crystallizations first from dilute ethanol and then from chloroform-petroleum ether, melted at 201–203°. (Decomp.) The substance was still impure, but the analysis indicated a monoxime.

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[18] (*a*) WHITMORE AND CHURCH, *J. Am. Chem. Soc.*, **54,** 3711 (1932); (*b*) CHURCH, WHITMORE, AND MCGREW, *ibid.*, **56,** 176 (1934).

Anal. Calc'd for $C_{11}H_{15}N_3O_2$: C, 59.70; H, 6.84; N, 19.00.
Found: C, 58.68, 59.10, 60.21; H, 6.72, 8.30, 7.81; N, 18.92.

(*c*) *Bromination.*—A solution of bromine in chloroform (10%) was added dropwise to a cold solution of II (0.2 g.) in chloroform (10 cc.) until the color of bromine was permanent. The solution after washing with bisulfite and then with water was dried. Evaporation of the solvent left a small amount of yellow oil which solidified when rubbed with a little cold methanol. The solid was crystallized several times; first from dilute methanol, then from dilute acetone, and finally from petroleum ether. It was light yellow and melted at 83–84°.

Anal. Found: C, 47.23; H, 4.83; N, 9.53.

(*d*) *Reduction.*—A solution of II (0.61 g.) in acetic acid (10 cc.) and water (5 cc.) was boiled for three hours with granulated zinc (1.5 g.). The product (0.2 g.) was nearly colorless and melted at 250–256° with some sublimation. Acetylation with acetic anhydride and a drop of sulfuric acid gave 60 mg. of a brown solid melting at 115–125°.

Repetition of the experiment gave a colorless product melting at 198–200° (decomp.). When this product was suspended in a solution of ferric chloride, it was not oxidized to duroquinone nor to II. Acetylation of the compound melting at 198–200° gave a light tan solid (0.17 g.) which melted at 130–138° after it was crystallized twice from dilute methanol.

Reduction of II by stannous chloride and hot hydrochloric acid gave colorless needles which melted at 213–215°. The compound contained no nitrogen, and when oxidized by ferric chloride, the product was duroquinone.

Anal. Found: C, 70.56; H, 7.95.

(*e*) *Acetylation.*—A small amount of II was boiled with acetic anhydride for 5 minutes, and the mixture was poured into ice water. No solid appeared after the anhydride had all decomposed. Excess bicarbonate was added, and the solution, after standing overnight, deposited duroquinone. Boiling saturated bicarbonate solution was without effect upon II, nor was any duroquinone formed when II (0.1 g.) was boiled with acetic anhydride (2 cc.) for 20 minutes, or when water (4 cc.) was added and boiling was continued for 30 minutes longer. But when an excess of bicarbonate was added to this (warm) solution, duroquinone was precipitated immediately.

Reactions of III. (*a*) *Thermal decomposition.*—The reaction was followed quantitatively by measuring the nitrogen evolved, sweeping it out by a current of carbon dioxide and collecting it over 50% potassium hydroxide solution. With chlorobenzene (b.p., 132°) as the solvent, the figures (percentage of the theoretical value for $C_{12}H_{16}N_4O_2$) for the nitrogen evolved were: 100.54; 101.04; 97.88; 96.60. Evaporation of the solvent *in vacuo* left a yellow residue (VI) which partially solidified. The substance was pressed on a clay plate, and the solid was then crystallized several times from dilute ethanol or dilute acetone. It was white, melted at 143–144° and contained no nitrogen. The substance was insoluble in water, dilute sodium hydroxide, and dilute hydrochloric acid. It was soluble in cold concentrated sulfuric acid, and reprecipitated on dilution. The acetone solution of VI did not decolorize permanganate, even when it was boiled. Phenylhydrazine was without action.

Anal. Calc'd for $C_{12}H_{16}O_2$: C, 74.95; H, 8.40; mol. wt., 192.
Found: C, 74.82; H, 8.34; mol. wt., (Rast) 191.

The *oxime* of VI was obtained in 73% yield by the usual procedure. It was white and melted above 260° (very dark at 250°).

Anal. Calc'd for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.60.
Found: C, 64.34; H, 8.23; N, 12.26.

(*b*) *Phenyl isocyanate.*—The substance III (0.2 g.) was heated with several cc. of phenyl isocyanate. No reaction was apparent, but the solid dissolved. The solution was cooled, extracted with ligroïn, and the solvent was evaporated. The residue, crystallized from methanol, melted at 138–139° (decomp.) and was identified as IV by determining the mixture melting point. Repetition of the experiment did not give the same results; instead, a compound melting at 160–161° was obtained which was identical with the product of the action of phenyl isocyanate upon IV. In addition to this product, there resulted a somewhat larger quantity of a colorless solid melting at 127–128° (decomp.) but which was not unchanged III.

Anal. (Substance melting at 127–128°.) Found: C, 67.51; H, 5.39; N, 14.72.

1-Naphthyl islcyanate was without action upon III.

(*c*) *Hydroxylamine* gave no oxime with III; the only product that could be obtained from the reaction was a small amount of red oil.

(*d*) *Phenylhydrazine.*—A solution of III in dilute ethanol gave an immediate precipitate when phenylhydrazine and a little acetic acid were added. The solid, crystallized twice from dilute ethanol, was white and melted at 144–145° (decomp.).

Anal. Calc'd for $C_{18}H_{22}N_6O$ (mono phenylhydrazone): C, 63.87; H, 6.55; N, 24.84.

Found: C, 64.03; H, 6.68; N, 24.60.

(*e*) *Acetylation of III* with acetic anhydride and a drop of sulfuric acid gave a diacetate which melted above 260° after crystallization from ethanol-ethyl acetate.

Anal. Calc'd for $C_{16}H_{20}N_4O_4$: C, 57.80; H, 6.07; N, 16.87.

Found: C, 58.09; H, 6.28; N, 16.57.

(*f*) *Silver salt.*—The substance III (0.5 g.) was allowed to stand with concentrated ammonium hydroxide (15 cc.) until solution was complete. The excess ammonia was removed under reduced pressure, and a solution of silver nitrate (0.7 g.) in water (5 cc.) was added. The light-tan precipitate was filtered and washed with water, ethanol and ether. The product weighed 0.67 g., and melted with decomposition at 128–129°.

Anal. Found: Ag, 34.94, 34.57, 34.59, 34.16.

(*g*) *Hydrochloric acid.*—Concentrated hydrochloric acid (3 cc.) and III (0.1004 g.) were placed on a watch glass and allowed to stand in a vacuum desiccator until the liquid evaporated. The white hygroscopic product weighed 0.1496 g. and melted with decomposition at 112–113°. The material did not depress the melting point of a similar product obtained from IV. The weight of the product indicated a molecular weight of 370. Titration with standard alkali gave values of 328 and 332 for the neutral equivalents, assuming two acid groups were titrated. The titrated solutions gave duroquinone when steam distilled. When hydrochloric acid was allowed to act upon III in the presence of dimedon, the solution did not deposit any precipitate—hence formaldehyde was apparently not eliminated.

(*h*) *Hydrobromic acid.*—By the use of the procedure described above, there was obtained from III (0.1012 g.) and 40% hydrobromic acid (2 cc.), a light-brown solid (0.1734 g.) which darkened at 145° and melted with decomposition at 155–156°. From the quantities of material involved, a molecular weight of 425 was indicated. When the material was suspended in ethanol-ether, it became colorless, and the solid then melted with decomposition at 139–140°. This material did not depress the melting point of a product obtained by the action of hydrobromic acid upon IV.

Anal. (Sample melting at 139–140°.) Found: C, 39.65; H, 6.11; N, 14.52.

Reactions of IV. (*a*) *Thermal decomposition.*—This was carried out as described under III, with bromobenzene (b.p. 156°) as the solvent. The percent of nitrogen evolved in two experiments was 60.65 and 63.28 respectively. The substance IV (2 g.) was decomposed by heating small portions of it in a nickel crucible. Decomposition occurred at 155–160°. When there was no further evolution of gas, the bath was held at 175–180° for 15 minutes. Upon cooling the melt partially solidified. The hot acetone solution filtered, diluted and cooled, deposited 0.27 g. of a light-brown solid melting with decomposition at 128–129°. Four similar thermal decompositions gave the following products: (*a*) 3 g. of IV gave 0.625 g. of nearly colorless material melting at 115°; (*b*) 4 g. of IV gave 0.4 g. of colorless material, melting at 124–127°, and 0.61 g. of buff-colored material melting at 103–105°; (*c*) 5 g. of IV gave 1.15 g. of solid melting at 103–113°; the acetone filtrate, when steam distilled, gave 0.6 g. of duroquinone and 0.8 g. of a black non-volatile residue; (*d*) 5 g. of IV gave 0.51 g. of material melting at 125–129°, 0.38 g. melting at 102–104°, 0.34 g. of duroquinone, and 1.485 g. of non-volatile residue.

Analysis indicated that the two decomposition products (VII and VIII) were isomers, formed by loss of one mole of nitrogen from IV.

Anal. Calc'd for $C_{12}H_{16}N_2O_2$: C, 65.41; H, 7.32; N, 12.72; mol. wt., 220.

Found: (substance melting at 124–127°) C, 65.65; H, 6.87; N, 12.41; mol. wt. (Rast), 250, 258.

Found: (substance melting at 103–113°) C, 65.62; H, 7.33; N, 12.63.

Upon standing, both solids decomposed to yellow oils which could not be solidified. The substance melting at 103–113° (0.2 g.) was heated for 4 hours on the steam bath with acetic anhydride and a drop of sulfuric acid. The solution was diluted, cooled, made alkaline with carbonate and extracted with ether. Evaporation of the ether left 0.16 g. of material melting at 90–117°. Crystallized once from ether-petroleum ether, the substance melted at 138–143°; and when an attempt was made to crystallize this from dilute methanol, the substance decomposed. The decomposition product melting at 124–127° apparently gave the same acetyl derivative, but this also decomposed during attempted recrystallization.

The low-melting isomer (103–113°) gave no oxime when treated with hydroxylamine in the usual manner, nor could any of the starting material be recovered. When the low-melting isomer (0.5 g.) in acetic acid (10 cc.) and water (7 cc.) was boiled for 7 hours with zinc (2 g.) it gave 0.22 g. of material melting at 124–128° and showing no depression in melting point when mixed with the high-melting (124–127°) decomposition product.

(*b*) *2,4-Dinitrophenylhydrazine.*—No phenylhydrazone was obtained by the customary procedure, and from 0.5 g. of IV, 0.38 g. of unchanged material was recovered.

(*c*) *Hydroxylamine.*—The usual procedure for preparation of oximes converted IV (0.4 g.) into duroquinone, and a similar result was obtained when an attempt was made to prepare a semicarbazone of IV.

(*d*) *Methyl sulfate* and alkali completely destroyed IV; only a trace of brown oil could be isolated.

(*e*) *Potassium cyanate.*—To a cold solution of IV (1 g.) in acetic acid (60 cc.) there was added with shaking solid potassium cyanate (5 g.) in small portions. The solution, after standing at 5° for 3 days, was made alkaline with potassium carbonate, and the colorless precipitate was removed. It was dissolved in hot acetic acid, the solution was filtered and the substance was reprecipitated by neutralizing the filtrate with dilute sodium hydroxide. The substance (a urea?)[19] was white, darkened at 245° and melted with decomposition at 251°.

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[19] LOCQUIN AND HEILMAN, *Compt. rend.*, **180**, 1757 (1925).

Anal. Found: C, 49.50; H, 5.62; N, 24.19.

(*f*) *Oxidation.*—A cold (10°) solution of IV (0.5 g.) in sodium hydroxide (10 cc., 10%) and water (40 cc.) was oxidized by addition of permanganate (50 cc., 2%) in 2 cc. portions. The color was immediately discharged. After standing over night at 0°, the precipitated oxides were removed and the alkaline filtrate was extracted with ether and with chloroform. Nothing was removed by the organic solvents. The aqueous solution was acidified with dilute sulfuric acid and again extracted; again nothing was removed. The aqueous layer was then made alkaline and evaporated to dryness. The solid residue (0.5 g.) was dissolved in water (3 cc.), hydrochloric acid (2 drops) was added and the solution was refluxed with *p*-nitrobenzyl bromide (0.5 g.) and alcohol (7 cc.) for 2 hours. The cooled and diluted solution deposited a solid which, when crystallized from alcohol was colorless and melted at 77–78°. The reported melting point of *p*-nitrobenzyl acetate is 78°.[20]

Oxidation of IV (1 g.) in warm (60°) sodium hydroxide (15 cc., 10%) by slow addition of iodine (6.25 g.) in potassium iodide (12.5 g.) and water (50 cc.) gave, when the reaction mixture was diluted with water (15 cc.), a small amount (ca. 15 mg.) of a colorless solid melting at 144–145°, but which was not IV.

Anal. Found: C, 63.58; H, 7.90; N, 24.79.

Extraction of the alkaline filtrate with ether removed 25 mg. of colorless material melting at 106–109°. After crystallizing the substance several times from water, the melting point was 107–108. The water solution, when hot, had a strong phenolic odor.

Anal. Found: C, 49.92; H, 5.95; N, 21.47.

No other products could be isolated.

(*g*) *Phenyl isocyanate.* When heated with several cc. of phenyl isocyanate, the substance IV (0.2 g.) dissolved. Methanol was added to decompose the excess reagent, the hot solution was filtered and the filtrate, on cooling, deposited a colorless solid melting with decomposition at 160–161°. This substance was identical with the substance obtained from III by the same procedure.

Anal. Calc'd for $C_{19}H_{21}N_5O_3$: C, 62.10; H, 5.77; N, 19.06.
Found: C, 62.40; H, 5.82; N, 19.42.

As in the case of III, 1-naphthyl isocyanate was without action upon IV.

(*h*) *Aniline.*—The substance IV (1 g.) was warmed on the steam bath for 5 hours with aniline (0.465 g.) and acetic acid (1.5 cc.). The black liquid was poured into excess sodium bicarbonate, and the solution was extracted with ether. The ether was washed with dilute hydrochloric acid (to remove aniline), then dried and evaporated. The residue was 60 mg. of duroquinone, and steam distillation of the acid washings gave an additional 70 mg. of the quinone. No other material could be isolated, and no triazole was apparently formed.[21]

(*i*) *Silver salt.*—By the same procedure as that used in the case of III, a silver salt (0.45 g.) was prepared from IV (0.5 g.). The substance was a heavy, white solid, which melted at 136–137° with decomposition.

Anal. Found: C, 26.57, 25.99, 25.40, 26.43; H, 3.48, 3.68, 4.42, 3.99; N, 16.78; Ag, 35.20, 34.69, 34.10, 34.53.

The silver salt was unaffected by boiling it for 10 hours with methyl iodide in ether. When methanol was used as the solvent, the product was an orange oil which could not be solidified.

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[20] KAMM, "Qualitative Organic Analysis," John Wiley & Sons, Inc., New York, **1932**, p. 180.

[21] WOLFF, *Ann.*, **325**, 163 (1902); *ibid.*, **394**, 26 (1912).

(*j*) *Hydrochloric acid.*—Substance IV (0.1006 g.) was converted to the hydroscopic salt (0.1511 g.) by the same procedure as that used in the case of III. The salt melted with decomposition at 112–114°, and from the weight of the product, the molecular weight was 373.

Anal. Found: C, 37.53; H, 6.28, N.E. (two acid groups) 300, 312.

When the titrated solutions were steam distilled, duroquinone was obtained. Hydrolysis of the salt to duroquinone by alkali was carried out in the presence of benzaldehyde in an attempt to detect any hydrazine that might have formed. The result was negative, and blanks showed that one drop of dilute hydrazine hydrate gave a positive reaction. Similarly, a test for formaldehyde was made by subjecting IV to the action of hydrochloric acid in the presence of dimedon. This test was also negative, while the blanks were positive.

When IV (0.2 g.) was refluxed for 1.5 hours in alcohol (10 cc.) containing 3–4 drops of hydrochloric acid, the product was duroquinone.

(*k*) *Hydrobromic acid.*—Substance IV (0.1017 g.) was converted to the bromide (0.1765 g.) by the same procedure as that used in the case of III. The crude product, almost white, darkened at 145° and melted with decomposition at 153–154°. When shaken with a mixture of alcohol and ether, cooled, filtered, washed with ether and dried *in vacuo*, the salt was colorless, melted at 139–140° (decomp.) and was identical with the salt obtained by action of hydrobromic acid upon III. From the relative weights of IV and salt, the molecular weight was indicated as 430.

Anal. Found: C, 41.05; H, 5.99; N, 14.46; N.E. (two acid groups) 418, 428; Br. (addition of HNO_3 to the solutions after determining N.E., and titrating for Ag in the usual way), 36.92, 34.58.

When a small amount of the salt was dissolved in water and shaken with freshly precipitated silver oxide, there was an immediate precipitation of silver halide. The silver compounds were removed and the filtrate, after standing for an hour, was extracted with ether. Nothing was removed by the ether. After standing for 4 hours longer, the filtrate deposited a yellow solid which was identified as duroquinone.

SUMMARY

1. Diazomethane has been added to duroquinone, a completely substituted quinone.

2. Four products resulted; two isomeric compounds formed by addition of one molecule of diazomethane to one molecule of the quinone, and two isomeric products formed by addition of two molecules of diazomethane to one of the quinone.

3. The properties and reactions of these substances have been described, and structures have been proposed for them, as well as for the products of their thermal decomposition.

4. The reaction between duroquinone and diazomethane, unlike that of any other *p*-quinone, is confined entirely to the carbonyl groups and no pyrazolines are formed.

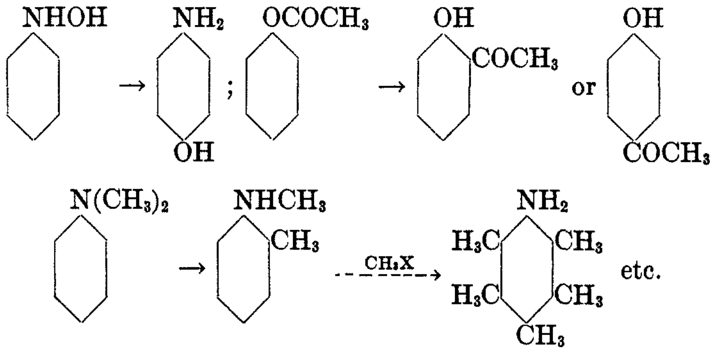
[Contribution from the School of Chemistry of the University of Minnesota]

THE JACOBSEN REACTION. V*

CLARENCE L. MOYLE and LEE IRVIN SMITH

Received March 3, 1937

Many rearrangements of benzene derivatives are known in which a substituent migrates from some hetero element in a side-chain to a carbon atom of the ring; even carbon-to-carbon bonds can be established in this way. Thus:



Rearrangements in which the whole substituent migrates from one position to another in the ring are not so numerous, however. Chief among these are the migration of sulfonic acid groups, as in the well-known transformations of 1-naphthalenesulfonic acid into the 2-isomer; the migration of halogen atoms, and of alkyl groups. In the last case, a carbon-to-carbon bond is broken and another is reëstablished. The discussion which follows will deal with the last two types of rearrangement, and will be restricted to those benzene derivatives containing only halogen atoms, only alkyl groups, or a combination of the two, for these are the substances which undergo what has come to be known as the Jacobsen reaction, or the Jacobsen rearrangement. This name has been given to the rearrangement of the polyalkylbenzenes, the halogenated polyalkylbenzenes and the polyhalogenated benzenes which occurs when these substances are sulfonated and their sulfonic acids are allowed to stand in contact with sulfuric acid. The reaction consists in the migration of an alkyl group and/or halogen

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* Polymethylbenzenes XIX. Paper XVIII, *J. Am. Chem. Soc.* **59** (June, 1937).

atom, and was discovered by Oscar Jacobsen in 1886[1] although Herzig[2] was the first to study the rearrangement of *halogen* compounds in the presence of sulfuric acid. All of these rearrangements may be divided into two general types: (*a*) intramolecular, in which the migrating group moves from one position to another in the same molecule, and (*b*) intermolecular, in which there is a transfer of one or more groups from one molecule to another.

A. HYDROCARBONS

Migrations of alkyl groups in aromatic hydrocarbons are caused chiefly by two reagents: anhydrous aluminum chloride and concentrated sulfuric acid. Rearrangements caused by aluminum chloride do not constitute a phase of the Jacobsen reaction, but they are of interest in this connection because of the opposite orienting effects of the two reagents and because of the possibility of relationships between mechanisms for rearrangements caused by the two reagents. Aluminum chloride gives products in which the vicinal orientation of the substitutents is avoided, while sulfuric acid tends to produce the vicinal arrangement.

1. *Migrations Produced by Aluminum Chloride*

The common method of alkylating benzene by action of alkyl halides upon benzene derivatives in the presence of anhydrous aluminum chloride was discovered by Friedel and Crafts in 1884.[3] Shortly thereafter the methylation of benzene and its homologs was investigated in some detail by a number of workers, particularly by Oscar Jacobsen[4] and by Anschutz.[5] Jacobsen, as a result of his studies, set up the following diagram as representing the methylation of toluene.

$$\begin{tikzcd}
 & \textit{o}\text{-Xylene} \arrow[dr] & & & \\
\text{Toluene} \arrow[ur] \arrow[r] \arrow[ddr] & \textit{p}\text{-Xylene} \arrow[r] & \text{Pseudocumene} \arrow[r] & \text{Durene} \arrow[dr] & \\
 & & & & \text{Pentamethylbenzene} \\
 & \textit{m}\text{-Xylene} \arrow[uur] \arrow[r] & \text{Mesitylene} \arrow[r] & \text{Isodurene} \arrow[ur] &
\end{tikzcd}$$

But Ador and Rilliet[6] could find no *o*-xylene in the product obtained by methylation of toluene, and he reported that this product consisted mainly (95 per cent.) of *m*-xylene together with a little (5 per cent.) *p*-xylene.

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[1] Jacobsen, *Ber.*, **19**, 1209 (1886).

[2] Herzig, *Ber.*, **14**, 1205 (1881).

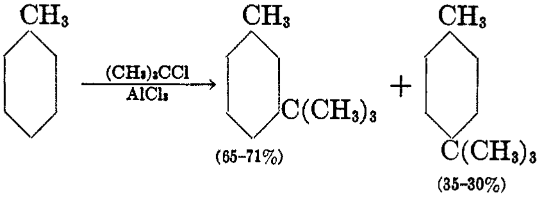
[3] Friedel and Crafts, *Ann. chim. phys.*, **1**, 449 (1884).

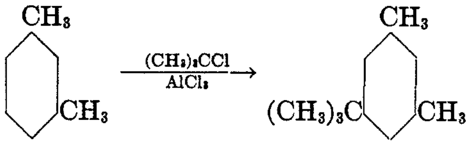
[4] Jacobsen, *Ber.*, **14**, 2624 (1881).

[5] Anschutz, *Ann.*, **235**, 177 (1886).

[6] Ador and Rilliet, (*a*) *Ber.*, **11**, 1627 (1878); (*b*) *ibid.*, **12**, 329 (1879).

There was no hemimellitene (1, 2, 3) among the trimethylbenzenes, and no prehnitene (1, 2, 3, 4) among the tetramethyl benzenes. The latter statement has been verified[7] since a very careful search for prehnitene among the methylation products of (mixed) xylenes showed none present, while blank tests showed that as little as 1 per cent. of prehnitene could have been detected by the method used. There is much evidence—although some of it is conflicting—in other connections that in the Friedel-Crafts synthesis, meta derivatives are largely produced. Shoesmith and McGechen[8] obtained from toluene and *tert*-butyl chloride 65–71 per cent. *m-tert.*-butyltoluene and 35–30 per cent. of the para compound; and the well-known synthesis of 1,3-dimethyl-5-*tert.*-butylbenzene from *m*-xylene[9] is another example of meta alkylation in the Friedel-Crafts reaction. One would expect, in this case, the 1, 3, 4 isomer since this would conform to the usual orienting effects of the methyl groups in *m*-xylene. The production of the 1, 3, 5 isomer must therefore mean either that the methyl groups do not exert their usual directing effects, or that if the 1, 3, 4 compound is the primary product, it is subsequently rearranged to the 1, 3, 5 isomer by aluminum chloride. To decide this point[10] 1,3-dimethyl-4-*tert.*-butylbenzene was synthesized and subjected to the action of aluminum chloride. The only product which could be isolated (45 per cent. yield) was the 1, 3, 5 isomer.





The mechanism of this rearrangement can be viewed as an elimination of alkyl halide (since the Friedel-Crafts alkylation is known to be reversible) followed by a re-synthesis, according to the views of Anschutz[5] on methylation.

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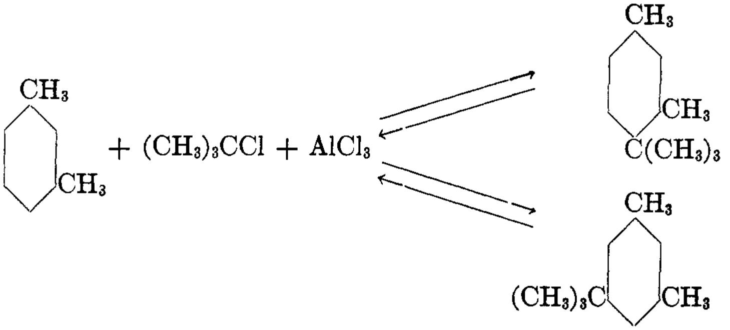
[7] O. W. Case, Ph.D. Thesis, University of Minnesota, **1931**.

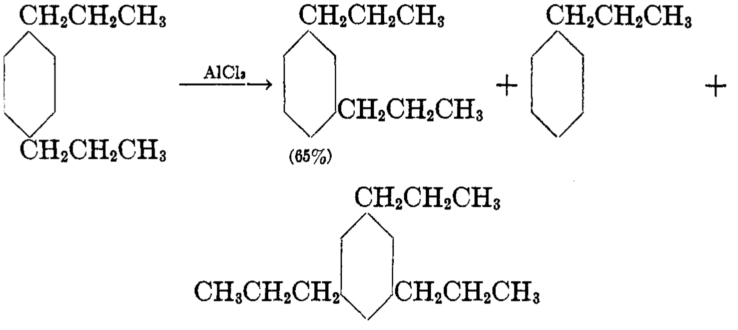
[8] Shoesmith and McGechen, *J. Chem. Soc.*, **1930**, 2231.

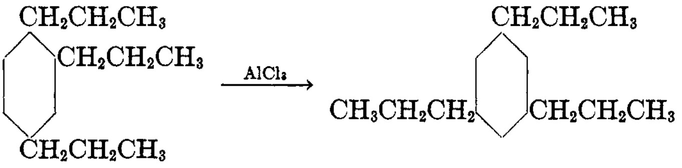
[9] Bauer, *Ber.*, **24**, 2840 (1891).

[10] Unpublished work by H. O. Perry of this laboratory.



But as Baddelcy and Kenner[11] have stated in a recent paper, such a mechanism would also involve the isomerization of the alkyl group in certain cases since, for example, aluminum chloride converts *n*-propyl chloride into isopropyl chloride. Accordingly they synthesized *m*- and *p*-di-*n*-propylbenzenes, as well as 1,2,4-tri-*n*-propylbenzene and subjected these hydrocarbons to the action of aluminum chloride.[12] The results were that the para compound was converted to the extent of about 65 per cent. into the meta compound in two hours at 100°; at the same time some *n*-propylbenzene and some 1,3,5-tri-*n*-propylbenzene were produced. Very little para compound was formed when the meta compound was so treated, but the 1,2,4-tripropyl derivative was largely converted into the 1, 3, 5 compound. In no case was any *isopropyl* derivative produced; hence the mechanism cannot involve the elimination of propyl chloride, either for the intramolecular rearrangement or for the intermolecular transfer of the propyl group.





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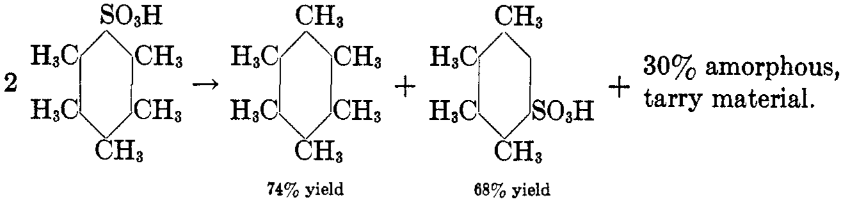
[11] Baddelcy and Kenner, *J. Chem. Soc.*, **1935**, 303.

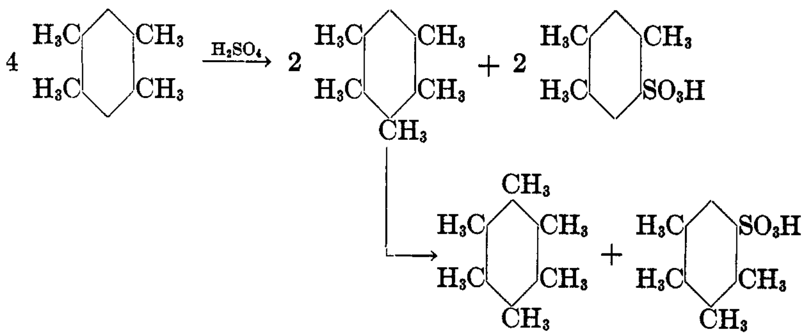
[12] See also Heise and Tohl, *Ber.*, **24**, 768 (1891).

2. Migrations Produced by Sulfuric Acid. (Jacobsen Rearrangements)

Pentamethylbenzene.[13, 14]—When pentamethylbenzene is allowed to stand in contact with concentrated sulfuric acid, the hydrocarbon first undergoes sulfonation, and then the sulfonic acid rearranges. This reaction is intermolecular and there is a transfer of a methyl group from one molecule to another.



Tetramethylbenzenes.[1, 15]—The first recorded rearrangement of a polymethylbenzene by sulfuric acid was reported by Jacobsen in 1886 in the case of durene. Jacobsen reported that durene was sulfonated by sulfuric acid slowly at 15–20° (6–10 hours) and rapidly at 80–100°, but that durenesulfonic acid in the presence of cold concentrated sulfuric acid was completely hydrolyzed to durene. When, however, durene or durenesulfonic acid was left at room temperature in contact with concentrated or fuming sulfuric acid for 4–8 days, or at 100° for 3–5 hours, sulfur dioxide was evolved, the liquid darkened and there was produced prehnitenesulfonic acid, pseudocumenesulfonic acid-5, pseudocumenesulfonic acid-6, and hexamethylbenzene, together with a brown, water-insoluble material. The main product was prehnitenesulfonic acid. On the basis of these facts Jacobsen believed that durene itself rearranged, and he represented the reaction as follows:



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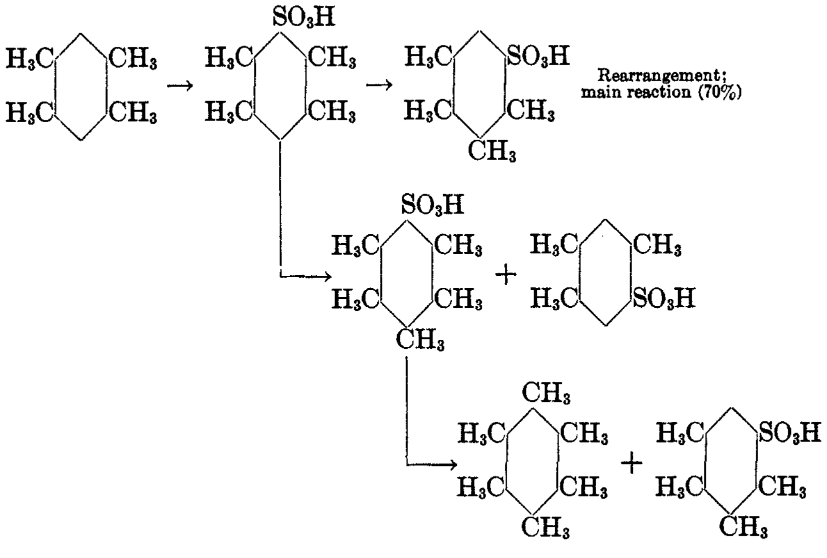
[13] Jacobsen, *Ber.*, **20**, 896 (1887).

[14] Smith and Lux, *J. Am. Chem. Soc.*, **51**, 2994 (1929).

[15] Smith and Cass, *ibid.*, **54**, 1614 (1932).

The maximum yield of prehnitene from durene according to Jacobsen's scheme is 25 per cent. Smith and Cass re-investigated this reaction; they established that prehnitenesulfonic acid was produced in 70 per cent. yield based on a direct mole-for-mole rearrangement of durene to prehnitene. The other products of the reaction were sulfur dioxide (0.356 moles per mole of durene used); CO_2 (0.0201 moles); very small amounts of pseudocumenesulfonic acid-5 and of hexamethylbenzene; and a brown amorphous material which constituted about 30 per cent. of the reaction product. Moreover, durene was found to be stable when refluxed with phosphorus pentoxide, but it rearranged in contact with sulfuric acid. Durenesulfonic acid, either hydrated or anhydrous, rearranged in contact with sulfuric acid or phosphorus pentoxide. Thus it is the sulfonic acid which rearranges, not the hydrocarbon. This is also shown by the fact that pentamethylbenzenesulfonic acid, left in a desiccator over sulfuric acid, rearranged, whereas the hydrocarbon, under the same conditions, did not rearrange. Moreover, it was found that the hydrolysis of durenesulfonic acid to durene by cold concentrated sulfuric acid was not complete until after 30 hours at 12°. Smith and Cass therefore wrote the Jacobsen reaction as follows, with the main reaction involving an intramolecular shift of a methyl group.

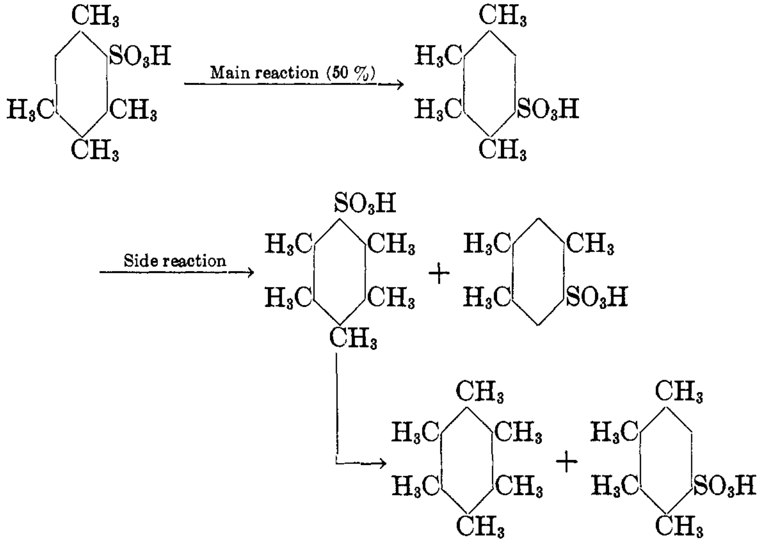


+ amorphous by-product, 15–30%.

These reactions, as well as Jacobsen's; do not account for the large amounts of sulfur dioxide evolved, nor for the amorphous by-products. Smith and

Moyle[16] have shown that the source of the sulfur dioxide is twofold: some comes from the sulfonic acid during rearrangement, and some results from the action of sulfuric acid upon the amorphous by-product.

The rearrangement of isodurene was really discovered by Töhl[17] who however, did not recognize in his isolation of prehnitene that a rearrangement of isodurene had actually occurred. The rearrangement was investigated by Smith and Cass,[15] who found that the rearrangement was quite analogous to that of durene.



+ amorphous by-product (28%)

Prehnitene[15] is merely sulfonated by sulfuric acid, and the sulfonic acid does not rearrange.

No polymethylbenzenes up to the tetramethylbenzenes are rearranged by sulfuric acid or other sulfonating agents: toluene, the three xylenes and the three trimethylbenzenes merely yield sulfonic acids which are quite stable toward sulfuric acid. Hexamethylbenzene was shown by Jacobsen[1] and by Smith and Cass[15] to be stable toward sulfuric acid.

Few ethyl derivatives of benzene have been studied, but Töhl and Karchowski[18] prepared 5-ethylpseudocumene and subjected the hydrocarbon to the action of sulfuric acid. They concluded that no rearrangements

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[16] Smith and Moyle, *ibid.*, **55**, 1676 (1933).

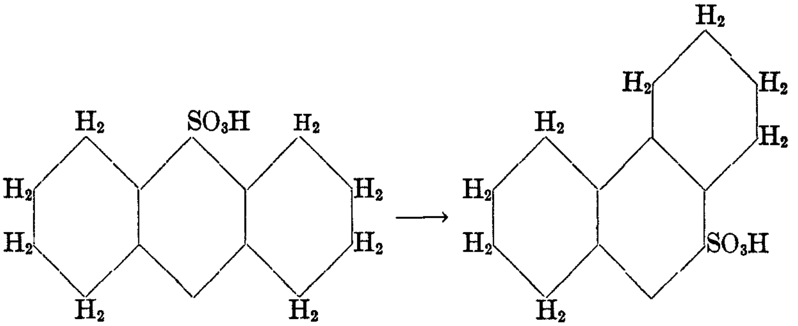
[17] *Ber.*, **21**, 904 (1888).

[18] Töhl and Karchowski, *Ber.*, **25**, 1530 (1892).

occurred, but their conclusion was based upon the fact that the sulfonic acids, when converted to the dibromo compounds, gave compounds which did not show marked depressions in melting points when mixed with each other or with dibromo-5-ethylpseudocumene prepared from the original hydrocarbon. This evidence is of little value as a proof of structure since it has been demonstrated[16] that the perbromopolymethylbenzenes when mixed with each other do not give significant depressions in melting points. Moreover, work in progress in this laboratory[19] indicates that both ethylpseudocumene and ethylmesitylene rearrange, and that the ethyl group is lost during the process.

Pentaethylbenzene was found by Töhl[17] to rearrange, and the rearrangement produced hexaethylbenzene and 1,2,3,4-tetraethyl benzene, analogous to the products obtained from pentamethylbenzene.

Octahydroanthracene.—Schroeter and Götzsky[20] found that this hydrocarbon, in the presence of sulfuric acid, rearranged to give octahydrophenanthrene.



The rearrangement occurred only in sulfuric acid solution; heating the sodium sulfonate merely produced the original hydrocarbon, octahydroanthracene.

B. Halogen Derivatives

1. Iodo compounds.—Neumann[21] observed that aromatic iodo compounds rearranged in the presence of sulfuric acid, and from iodobenzene he obtained *p*-diïodobenzene and benzenesulfonic acid. He claimed that no evolution of iodine or of carbon dioxide occurred, and noticed only small amounts of sulfur dioxide. Similar rearrangements were observed in the case of *o*- and *p*-iodotoluene.

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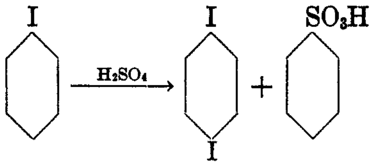
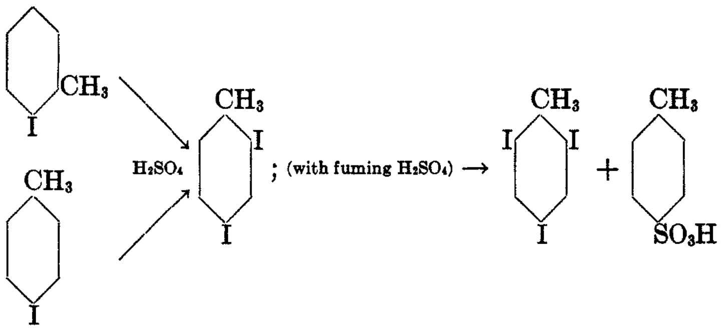
[19] Matthew Kiess, unpublished work.

[20] Schroeter and Götzsky, *Ber.*, **60**, 2035 (1937).

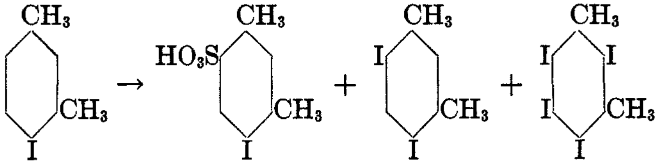
[21] Neumann, *Ann.*, **241**, 33 (1887).





Cass[7] verified Neumann's results in the case of iodobenzene, but he was able to show that both iodine and hydriodic acid were evolved. Boyle[22] stated that *p*-diïodobenzene was converted to a tri- and a tetraiodobenzene by hot fuming sulfuric acid, although no experimental details were given.

Hammerich[23] as well as Töhl and Bauch[24] found that 4-iodo-*m*-xylene, after contact with sulfuric acid for one week, gave polyiodo-*m*-xylenes.



It is interesting to note, in this connection, that no rearrangements have been reported in the case of *o*- and *p*-xylenes or any of their halogen derivatives.

Kurzel[25] investigated the rearrangement of 5-iodopseudocumene in the presence of concentrated or fuming sulfuric acid; he isolated two diïodopseudocumenes, an iodopseudocumenesulfonic acid, and pseudocumenesulfonic acid-5.

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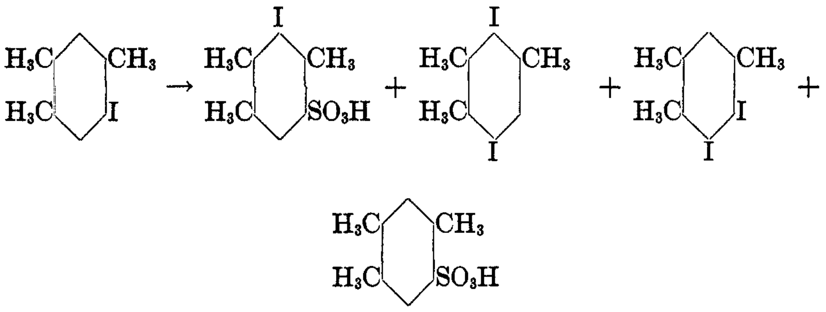
[22] Boyle, *J. Chem. Soc.*, **95**, 1683 (1909).

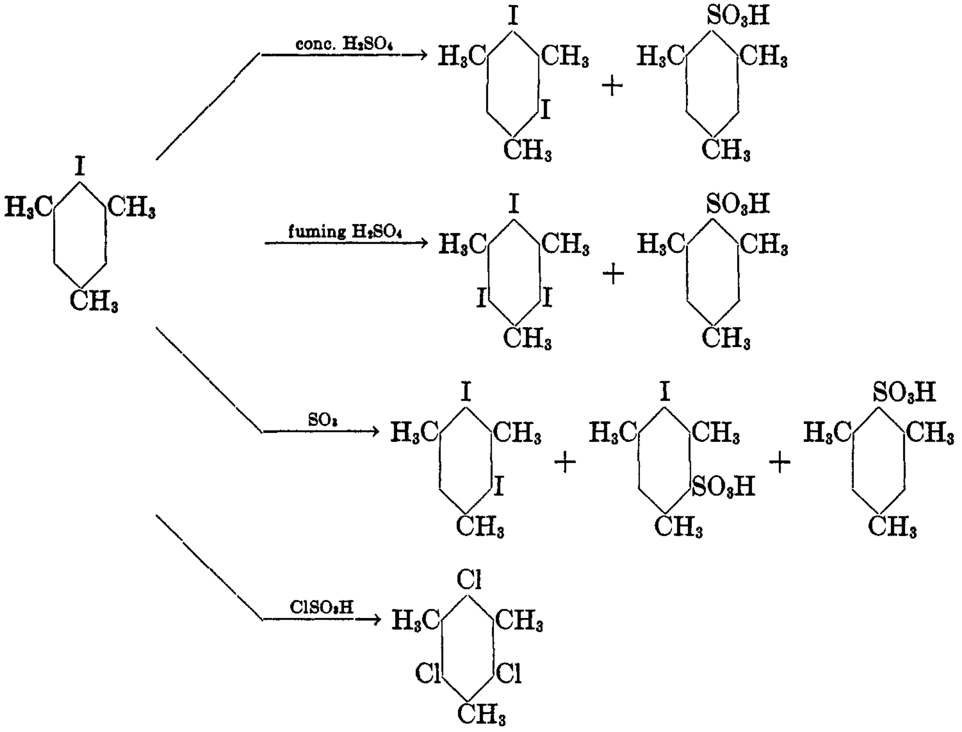
[23] Hammerich, *Ber.*, **23**, 1634 (1890).

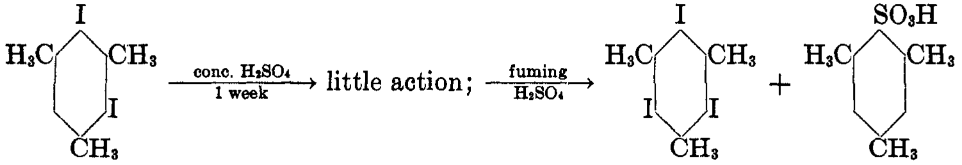
[24] Töhl and Bauch, (*a*) *ibid.*, **23**, 3117 (1890); (*b*) *ibid.*, **26**, 1105 (1893).

[25] Kurzel, *ibid.*, **22**, 1586 (1889).



Iodomesitylene was investigated by Töhl and Eckel[26] who studied the effects produced by varying the reagent.





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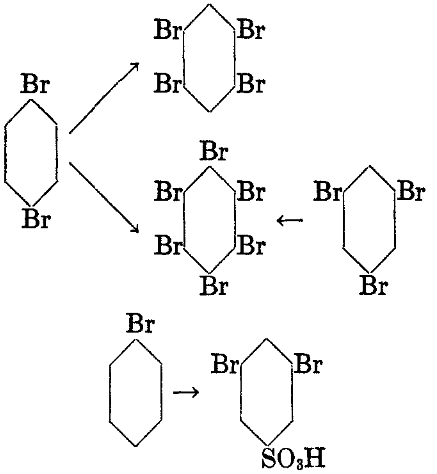
[26] Töhl and Eckel, *ibid.*, **26**, 1099 (1893).

The last reaction is good evidence that sulfonation precedes the rearrangement, for fuming sulfuric acid, required to sulfonate the diïodo compound, is also required to bring about the rearrangement.

Iodopentamethylbenzene was decomposed when subjected to the action of sulfuric acid. Iodine was evolved, and a black tarry decomposition product was formed.[27]

2. Bromo compounds.—Bromobenzene, when refluxed for eight hours with concentrated sulfuric acid, was reported by Herzig[2] to give large amounts of sulfur dioxide and carbon dioxide, together with small amounts of a dibromobenzenesulfonic acid, which Herzig thought was the 1, 3, 5 compound. *p*-Dibromobenzene gave the same gaseous products, together with some 1,2,4,5-tetrabromobenzene and a small amount of hexabromobenzene. From 1,3,5-tribromobenzene, Herzig obtained hexabromobenzene. Herzig explained these transformations by assuming that the halogen was eliminated as nascent bromine, which then acted as a brominating agent.



An attempt by Jackson and Gallivan[28] to nitrate 1,2,4,5-tetrabromobenzene in the presence of sulfuric acid, resulted in the production of hexabromobenzene.

By the action of concentrated sulfuric acid at 230° upon 4,6-dibromo-*m*-xylene, Jacobsen[29] obtained 2,4-dibromo-*m*-xylene. Whether a bromine atom or a methyl group migrated cannot be determined, for the same product would result in either case. The rearrangement of 5-bromo pseudocumene was also investigated by Jacobsen[30] who sulfonated a large

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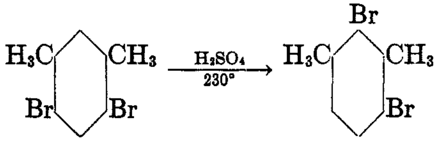
[27] C. L. Moyle, M. S. Thesis, University of Minnesota, 1932.

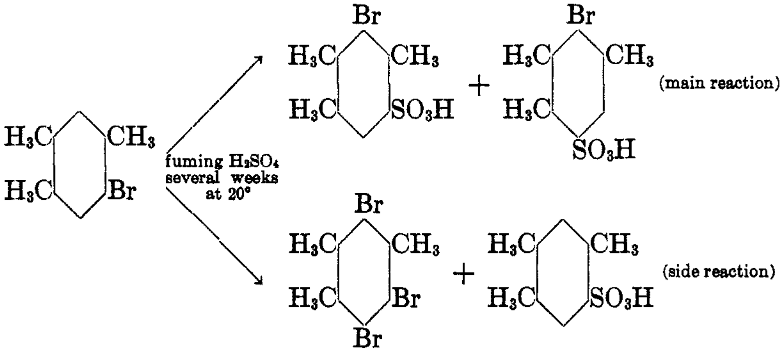
[28] Jackson and Gallivan, *Am. Chem. J.*, **18**, 251 (1896).

[29] Jacobsen, *Ber.*, **21**, 2827 (1888).

[30] Jacobsen, *ibid.*, **22**, 1580 (1889).

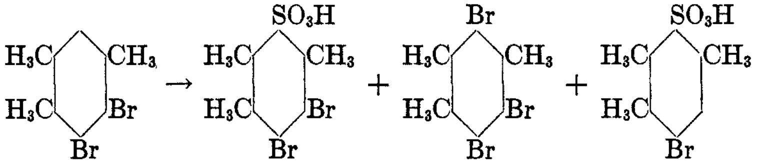
amount (450 g.) of the substance with fuming sulfuric acid (2300 g.) and kept the solution at room temperature for several weeks. The main reaction led to 3-bromopseudocumenesulfonic acid-5, which could have been produced by migration of either a methyl group or a bromine atom.





Smith and Moyle[31] found that 5-bromopseudocumene rearranged largely to 3-bromopseudocumenesulfonic acid-5 together with a small amount of tribromopseudocumene, but contrary to the work of Jacobsen, no pseudocumenesulfonic acid-5 could be found in the product.

When 5,6-dibromopseudocumene was subjected to the action of chlorosulfonic acid[32] the substance was not only sulfonated, but 6-bromopseudocumenesulfonic acid-3 and tribromopseudocumene were obtained.



Töhl and Eckel[26] found that the action of sulfuric acid upon bromomesitylene consisted not only of sulfonation, but that there was a migration of bromine, leading to dibromomesitylenesulfonic acid and mesitylenesulfonic acid as by-products, a point which had been overlooked by Rose.[33]

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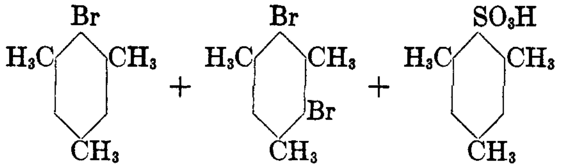
[31] Smith and Moyle, *J. Am. Chem. Soc.*, **58,** 1 (1936).

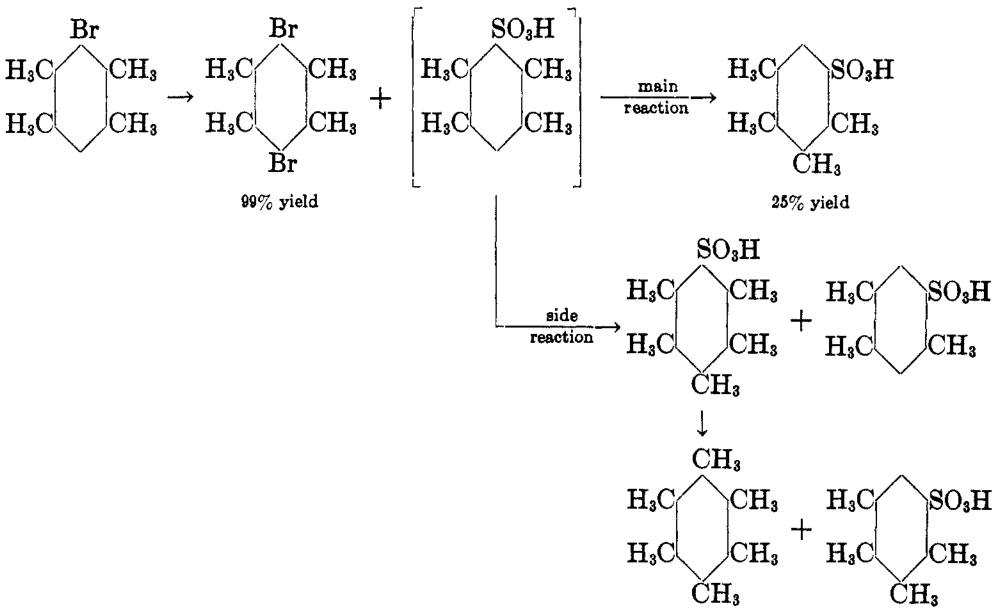
[32] Jacobsen, *Ber.*, **19,** 1221 (1889).

[33] Rose, (*a*) *Ann.*, **164,** 63 (1872); (*b*) *Ber.*, **26,** 1102 (1893).



Smith and Moyle[31] verified the results of Töhl and Eckel concerning the rearrangement of bromomesitylene, but in addition it was found that either dibromo- or tribromomesitylene could be produced, depending upon the temperature.

The Jacobsen reaction of the monobromotetramethylbenzenes[16]—bromodurene,[34] bromoisodurene, and bromoprehnitene[35]—consisted of migration of a bromine atom from one molecule to another to give the corresponding dibromo derivative. Removal of the bromine atom left the sulfonic acid of the hydrocarbon, and since both durene and isodurene rearranged to prehnitene, the final bromine-free product in all three cases was prehnitenesulfonic acid. The dibromo compounds were obtained in excellent yields (80–100 per cent.); prehnitenesulfonic acid resulted in yields of from 25 to 80 per cent. Sulfur dioxide was evolved, and there was produced as usual the insoluble brown amorphous powder which represented 25–30 per cent. of the weight of the total product. The course of these reactions was outlined by Smith and Moyle[16] as follows:



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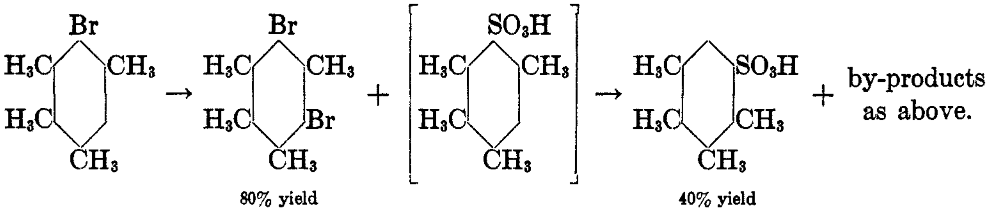
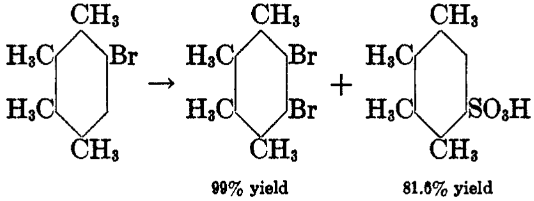
[34] Jacobsen, *Ber.*, **20**, 2837 (1887).

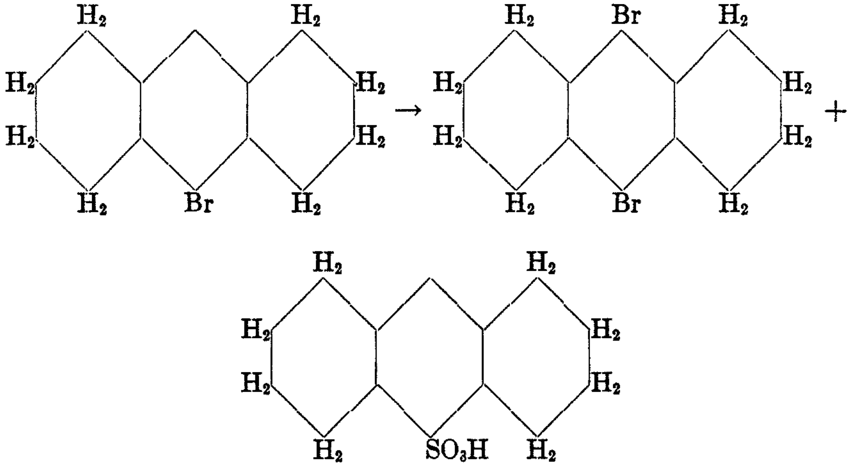
[35] Töhl, *ibid.*, **25**, 1527 (1892).





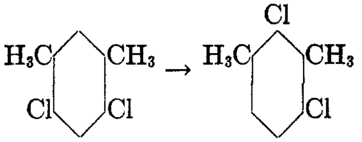
The three isomeric dibromotetramethylbenzenes, as well as bromopentamethylbenzene, did not rearrange when in contact with sulfuric acid, although all underwent a very slow oxidation (decomposition) accompanied by evolution of sulfur dioxide.

Schroeter and Götzky[20] have reported that 9-bromoöctahydroanthracene, when treated with fuming sulfuric acid at 50–60° for a short time, gives the dibromo compound together with a sulfonic acid. The structure of the sulfonic acid was not determined; if, as assumed, it were actually a derivative of octahydroanthracene, it is likely that longer contact with sulfuric acid would have produced octahydrophenanthrenesulfonic acid.

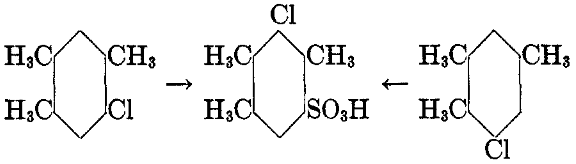


3. Chloro compounds.—Chlorobenzene in contact with sulfuric acid merely sulfonates, and no rearrangement occurs.[7] However, 4,6-dichloro-

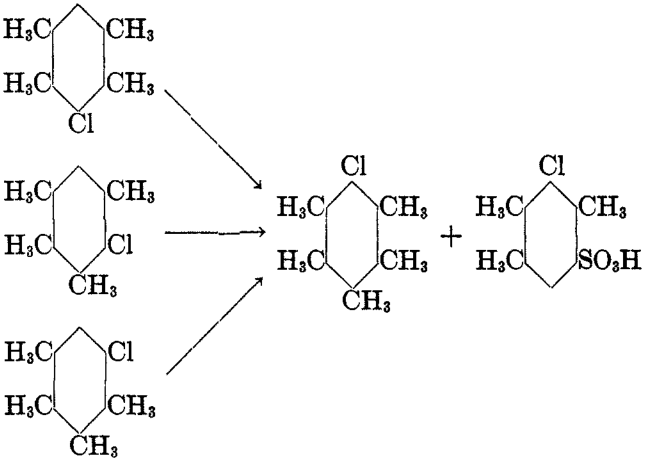
m-xylene[36] behaves in a manner analogous to that of the corresponding dibromo compound and rearranges into 2,4-dichloro-*m*-xylene.



Töhl and Müller[37] observed that 5-chloropseudocumene, when treated with fuming sulfuric acid gave a liquid chloropseudocumene, but they did not determine the structure of the product. Smith and Moyle[31] investigated the action of sulfuric acid upon the three monochloropseudocumenes. They found that 5- and 6-chloropseudocumene rearranged into 3-chloropseudocumene and that the last compound was stable toward sulfuric acid. In these cases, the migrating group was the chlorine atom, and the methyl groups were unaffected.



In the rearrangement of chlorodurene, reported by Töhl[38] a methyl group migrated, and the products were 3-chloropseudocumenesulfonic acid-5 and chloropentamethylbenzene. Smith and Moyle[31] investigated the rearrangements of the three chlorotetramethylbenzenes and found that all of them gave chloropentamethylbenzene and 3-chloropseudocumenesulfonic acid-5.



Thus the rearrangements of the chlorotetramethylbenzenes involve migration of a methyl group, whereas those of the bromotetramethyl-

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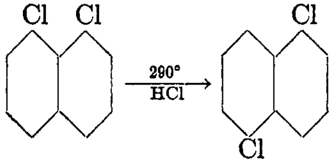
[36] Koch, *ibid.*, **23**, 2318 (1890).

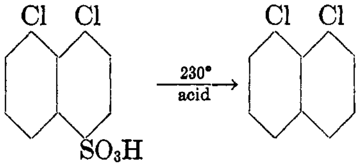
[37] Töhl and Müller, *ibid.*, **26**, 1108 (1893).

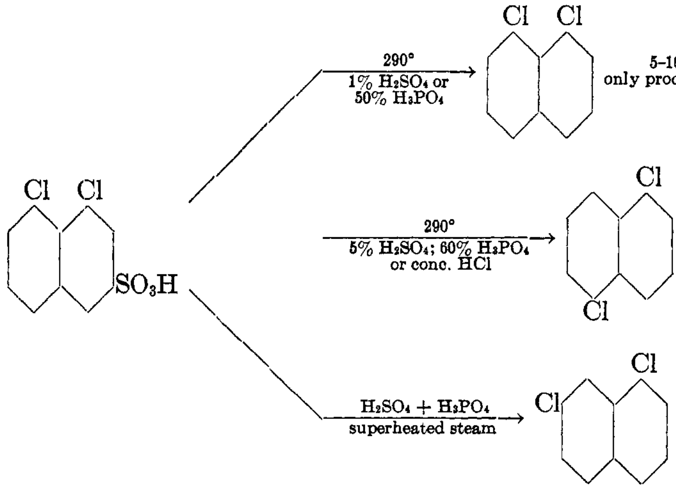
[38] Töhl, *ibid.*, **25**, 1527 (1892).

benzenes involve migration of the halogen atom. It is likely that these migrations constitute, in some cases at least, but the first step and that more than one migration occurs before the final products are reached.

There are some interesting observations in the literature on the migration of chlorine atoms in certain naphthalene derivatives. Thus Armstrong and Wynne[39] found that when 1,8-dichloronaphthalene was heated to 290° with hydrochloric acid, it was converted into 1,5-dichloronaphthalene. This isomerization did not occur below 200°, but it was noticeable at 250° and complete at 290°. No isomerization occurred when the chloronaphthalene was heated alone, with water, or with phosphoric acid at 300°, but it did occur when sulfuric acid was used, and under these conditions there was considerable carbonization. None of the isomeric dichloronaphthalenes showed any tendency to change under any of the conditions used by Armstrong and Wynne. The 4-sulfonic acid of 1,8-dichloronaphthalene when hydrolyzed by acid at 230°, gave only 1,8-dichloronaphthalene, but the 3-sulfonic acid, which could not be hydrolyzed below 285°, gave no less than three isomeric dichloronaphthalenes.







5-10% yield only product obtained.

20% yield much carbon.

40% yield much carbon.

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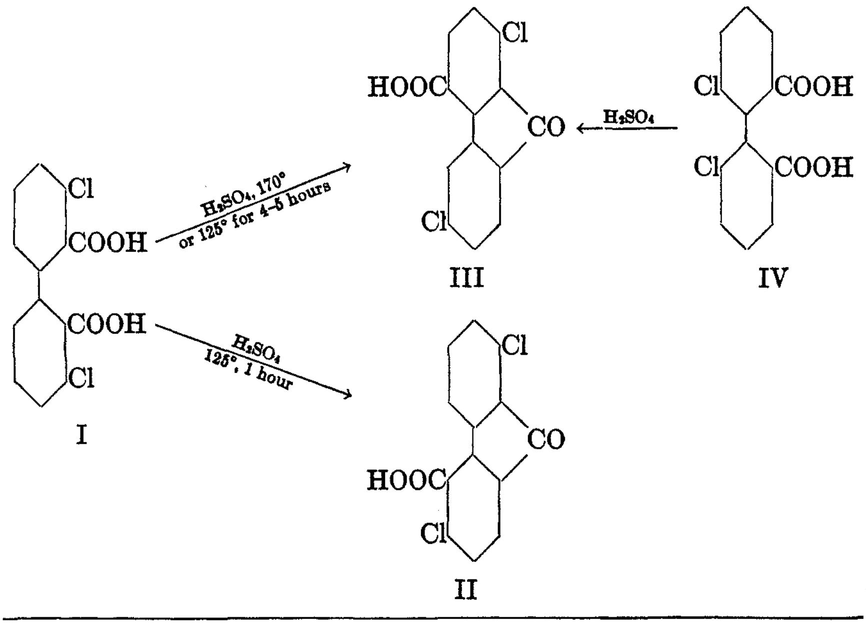
[39] Armstrong and Wynne, *Chem. News*, **76**, 69 (1897).

Of the trichloronaphthalenes, the 1, 2, 8 isomer was the only one which rearranged when heated with hydrochloric acid. The course of the rearrangement was not determined.

Recently, Huntress and his students[40] have investigated the migrations of chlorine atoms which occur when certain dichlorodiphenic acids are heated with sulfuric acid. Thus 3,3′-dichlorodiphenic acid (I) when heated with sulfuric acid at 125° for one hour, gives the expected product, 1,6-dichlorofluorenone-5-carboxylic acid (II) in quantitative yield. But if the time of heating is prolonged (4–5 hours), or if higher temperatures are used, the product is the isomeric 1,6-dichlorofluorenone-4-carboxylic acid (III), a substance which is also obtained from 5,5′-dichlorodiphenic acid (IV). It was also found that both the 1,6- (V) and the 1,8- (VI) dichlorofluorenones, when heated with sulfuric acid gave the rearrangement product, 3,6-dichlorofluorenone (VII). Phosphoric acid does not cause the rearrangement, but does cause the ring closure, giving in every case the expected product. It follows that the rearrangement occurs after the ring closure. The work is still incomplete, but it will be interesting to learn whether or not a sulfonation is involved. If so, the reaction becomes a typical Jacobsen rearrangement of chlorine produced by sulfuric acid; if not, the reaction must be assigned to some other class.



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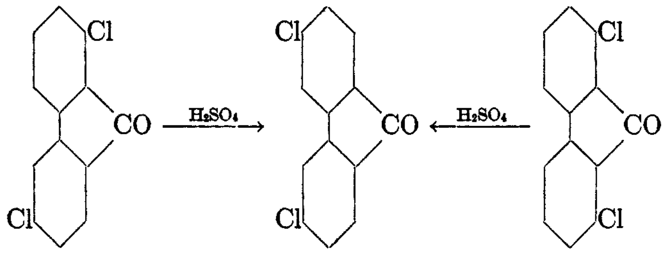
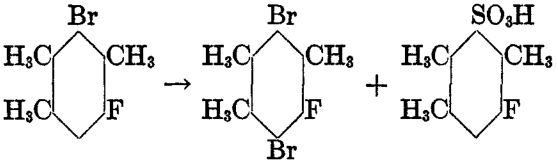
[40] Huntress *et al.*, *J. Am. Chem. Soc.*, **58**, 1514 (1936).

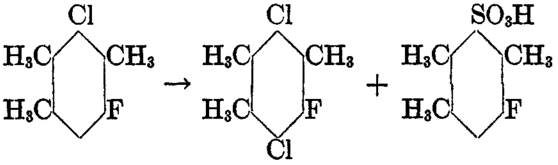


V VII VI

4. Fluoro compounds.—The only fluorine compounds to be investigated so far are studied by Töhl and Müller,[37] and in this group are also the only mixed halogen compound which have been studied. 5-Fluoropseudocumene was sulfonated by sulfuric acid, but the sulfonic acid remained unaffected by sulfuric acid when in contact with it for three months. The action of sulfuric acid upon 3- (or 6-) iodo-5-fluoropseudocumene caused decomposition with evolution of iodine; no rearranged product was found. However, 3- (or 6-) bromo-5-fluoropseudocumene rearranged with migration of the bromine atom:

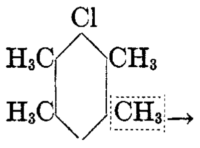


while the corresponding chloro-fluoro compound rearranged with migration of chlorine, and the methyl groups were unaffected.

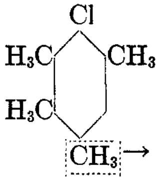


DISCUSSION

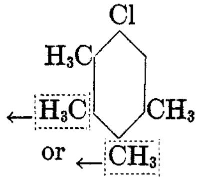
The three chlorotetramethylbenzenes, chlorodurene (I), chlorisodurene (II), and chloroprehnitene (III), rearrange to give the same products, *viz:* chloropentamethylbenzene and 3-chloropseudocumenesulfonic acid-5. In each case a methyl group migrates in such a manner that the same chlorotrimethylbenzene results. These rearrangements can be compared with that of pentamethylbenzene (A) in which a methyl group also migrates. But the situation becomes more involved when the rearrangement of chlorodurene is compared with those of bromodurene (B) and of 3-chloro-5-fluoropseudocumene (C).



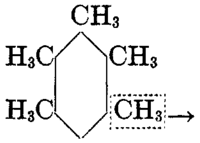
I



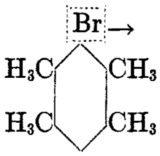
II



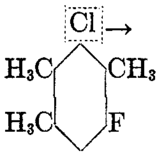
III



A



B

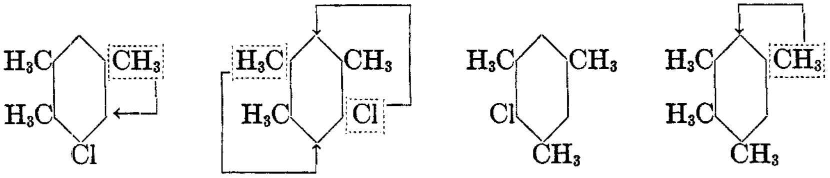


C

It is not known, of course, which methyl group migrates in pentamethylbenzene. In the analogs I and A, a methyl group migrates, while in B and C, the halogen atom is the labile group. The rearrangements of I, B, and C show the different courses which the rearrangement may take when one substituent is replaced by another. In I the methyl group migrates; in B the bromine atom moves, and in C the chlorine atom migrates and leaves a non-vicinal tetrasubstituted benzene, 5-fluoropseudocumene.

A methyl group can be removed from either I or II (as shown) in such a way that 3-chloropseudocumene results directly. But the rearrangement of III is more complex and must involve at least two migrations. If either of the marked methyl groups were to be removed, the product would be a chloropseudocumene which would itself then rearrange into 3-chloropseudocumene. Methyl group 1 cannot be the one removed, because the first product would then be 4-chlorohemimellitene, a substance which does not undergo the Jacobsen rearrangement. No 4-chlorohemimellitene could be found among the rearrangement products of III. Removal of the methyl group at 4 would give 5-chlorohemimellitene as the first product. Unfortunately this compound has not been available for study and hence nothing can be said concerning this possibility.

Two chlorotrimethylbenzenes are unstable toward sulfuric acid, the 6- and the 5-chloropseudocumene both rearranging to 3-chloropseudocumene. On the other hand, 4-chlorohemimellitene and chloromesitylene do not rearrange. If the latter is compared with isodurene, the migration of a methyl group would be expected. However, if the assumption is made that the chlorine atom is the only group in a chlorotrimethylbenzene that can move then chloromesitylene should be a stable substance. This



assumption has some basis in the fact that halogen is the labile group when 3-chloro-5-fluoropseudocumene, bromomesitylene, or 5-bromopseudocumene rearrange.

The rearrangements of two bromotrimethylbenzenes have been investigated—5-bromopseudocumene and bromomesitylene. The former rearranged chiefly to 3-bromopseudocumene, with a small by-product of tribromopseudocumene; the latter rearranged entirely intermolecularly giving mesitylene and polybromomesitylenes.

The Jacobsen reaction does not appear to be an extensive reaction. With few exceptions it is limited to the halogen derivatives of benzene, the halogen derivatives of methylated benzenes, the tetramethylbenzenes (durene and isodurene), pentamethylbenzene, pentaethylbenzene, and possibly to mixed alkyl benzenes. In general, four substituents must be attached to the ring except when halogen alone is present. The substituents which have so far been shown capable of migration are I, Br, Cl, CH_3, C_2H_5 and SO_3H. No Jacobsen rearrangements are known in which an amino, nitro, acetyl, methoxyl or carboxyl group is present in the molecule (except perhaps for the recent work of Huntress). Moreover, the conditions which bring about the rearrangement appear to be quite limited. Many reagents have been tried,[31] but the only reagent of general applicability is some form of sulfuric acid, and it is not possible to replace more than a small proportion of the sulfuric acid by something else. The following table shows some data regarding the effect of changing the reagent upon the products obtained. The material used was a tetramethylbenzene mixture, about 90 per cent. isodurene and 10 per cent. durene both of which give prehnitene on rearrangement. In only three cases was any considerable yield of prehnitene obtained; all the others gave essentially unchanged material.

The ease of rearrangement of various substituents changes with the nature of the compounds. In the case of the monochloro- and monobromotetramethylbenzenes, the data show the relative ease of migration to be Br > CH_3 > Cl, but in the case of halogenated trimethylbenzenes, the halogen always migrates if any rearrangement occurs, and the relative

TABLE

Summary of the Effect of Different Reagents upon Rearrangement of Tetramethylbenzenes[a]

EXPT.	REAGENT AND CONDITIONS	TEMP., °C.	TIME, HRS.	TAR[b] G.	OIL[b] G.	A[c]	B[c]	C[d]	D[d]
1	50 ml. 20% fuming H_2SO_4	86	8	5.0		31.5	7.0	24.0 (48%)	
2	75 ml. 20% fuming H_2SO_4; pass in SO_2 with stirring	85	6	0.5		32.9	12.2	25.8	
3	50 ml. 20% fuming H_2SO_4 to sulfonate; then add 18 ml. water	65	20		18.0	23.0	5.5		34.0
4	75 ml. 20% fuming H_2SO_4 to sulfonate; then add 50 ml. CH_3COOH	85	10	2.0		40.2	4.8		31.5
5	50 ml. 20% fuming H_2SO_4 to sulfonate; then add 50 ml. 100% H_3PO_4	65	20	5.2	16.0	15.2	4.8		24.6
6	50 ml. 20% fuming H_2SO_4 to sulfonate; then add 300 ml. conc. H_2SO_4	80	15	23.5		12.3	3.0	6.6	
7	50 ml. 20% fuming H_2SO_4 to sulfonate; 35 g. Na_2SO_4 in 50 ml. conc. H_2SO_4	65	30	4.2		34.6	6.2	25.2	
8	40 ml. 20% fuming H_2SO_4 to sulfonate; then add 1 g. $HgSO_4$	65	15	5.8		28.0	8.2		21.0

[a] Fifty grams of the mixed tetramethylbenzene filtrate used in each experiment except No. 8, in which 40 g. was used.

[b] The reaction product was poured onto ice and the tar and oil (if any) were separated.

[c] Sulfuric acid was added to the aqueous filtrate from *b*, and the precipitated prehnitene sulfonic acid was filtered off. It was dissolved in water (100 cc.) and sulfuric acid (30 cc.) and hydrolyzed with steam at 145°. Column A gives the weight of crude product in the distillate; column B gives the weight of residue.

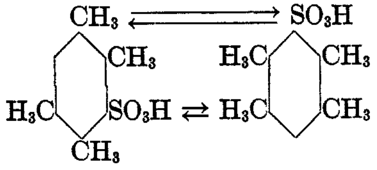
[d] Column C gives the weight of pure prehnitene obtained by fractionation of the oil in the distillate from *c*. Column D gives the weight of mixed tetramethylbenzenes obtained in the experiments in which the Jacobsen rearrangement either did not occur, or was incomplete.

ease of migration appears to be $Br > Cl > CH_3$. But slight changes in conditions and in the nature of the compound may cause great differences in the ease of rearrangement—for example, pentamethylbenzenesulfonic acid rearranges readily, but its methyl ester does not rearrange at all.

Attempts to formulate a mechanism for the reaction, or even to formulate with certainty the course of the reaction, are complicated by the fact that sulfuric acid can act as a reagent in so many different reactions—oxidation, sulfonation, hydrolysis, polymerization, and the like. In all the Jacobsen reactions so far observed, there resulted large amounts of a tarry amorphous solid which accounted for approximately one-third of the starting material. The source of this material is not definitely known, but this by-product resulted only when sulfur dioxide was evolved, and the amount appeared to be roughly proportional to the amount of sulfur dioxide. Rapid rearrangements (chloro- and bromotetramethylbenzenes), accompanied by only small amounts of sulfur dioxide, gave good yields of products and much less of the amorphous by-product than did the slower rearrangements. Moreover, if a substance that rearranged rapidly was allowed to stand in contact with sulfuric acid for a long time, the evolution of sulfur dioxide continued and the longer the time, the smaller the yield of rearranged product and the greater the amount of amorphous material. Hence it appears that the amorphous by-product is a result of the action of sulfuric acid upon all the organic materials present. The source of the sulfur dioxide appears to be not only sulfuric acid, but also the sulfonic acids themselves. The reaction is always accompanied by a series of characteristic color changes: first red, then deepening to reddish-brown, and finally black.

Three mechanisms have so far been suggested for the Jacobsen reaction. Herzig[2] explained the production of dibromobenzene from bromobenzene by assuming the elimination of (nascent) bromine which then acted as a brominating agent. While a plausible explanation for some rearrangements of halogenated compounds, this mechanism fails when attempts are made to apply it to the halogen-free compounds unless by "nascent" groups, one means transient radicals.

Jacobsen[41] suggested that prehnitene resulted from durene through an exchange of a methyl group of one molecule for the sulfonic acid group of another molecule, thus:



This "mechanism" involves exchanges among four groups, and it does not, of course, explain the stability of the final product, prehnitene.

Recently Schroeter and Götzky[20] proposed that the rearrangement takes place because of longitudinal and transversal oscillations within the

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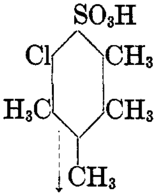
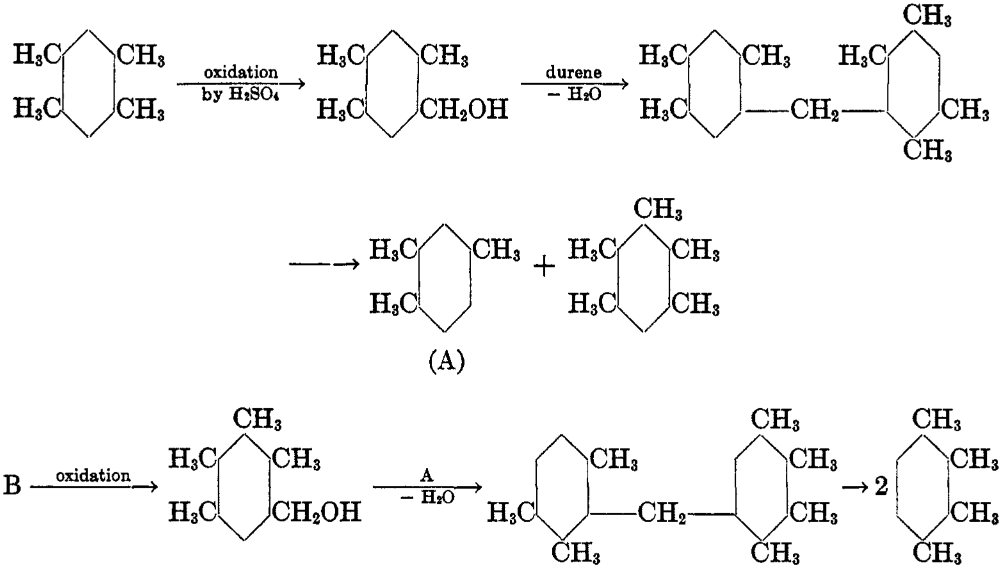
[41] Jacobsen, *Ber.*, **19**, 1215 (1886).

molecules. This idea cannot explain migrations of groups within a molecule, and although it can be applied to pentamethylbenzene, it cannot be used to explain the rearrangement of chloroprehnitene unless the assumption is made that the bond of a substituent in the para position to the sulfonic acid group is also broken by the longitudinal vibrations within the molecule. Schroeter's mechanism cannot be applied to the rearrange-



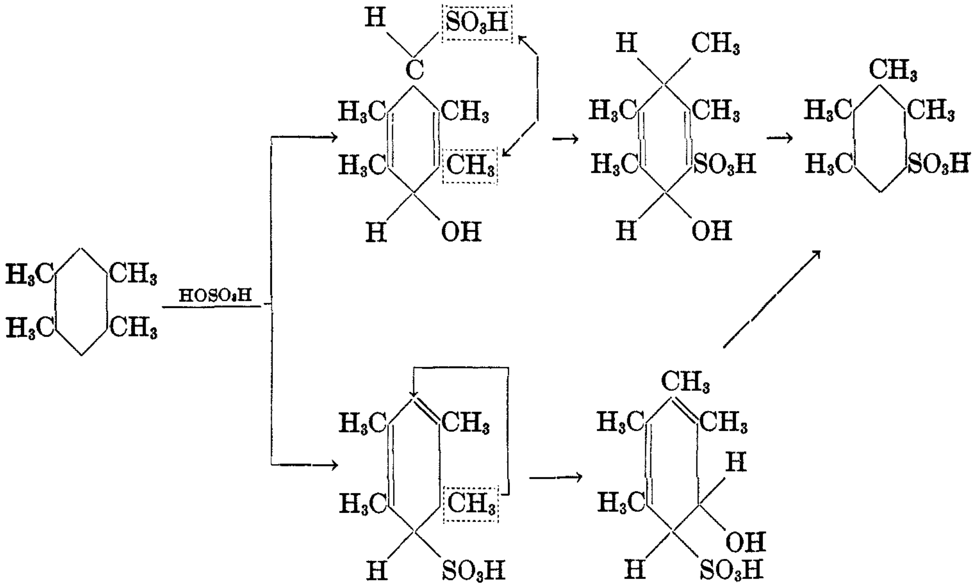
ments of the bromotetramethylbenzenes without considerable modification.

The authors have considered three other formulations of the mechanism of the Jacobsen reaction. The first of these involved formation and subsequent cleavage of diphenylmethane derivatives, thus transferring a methyl group. Applied to durene, the scheme may be outlined somewhat as follows:



By assuming a series of similar intermediates, the other products could be accounted for by means of concurrent reactions. The mechanism of the cleavage was a matter for some speculation, since it involved the addition of two hydrogen atoms. According to this mechanism, a mixture of one mole of pentamethylbenzene and one mole of pseudocumene should lead to two moles of prehnitene. An experiment conducted upon a mixture of pentamethylbenzene (0.338 moles) and pseudocumene (0.417 moles) led to prehnitene (0.125 moles) in an amount no greater than that which would have been obtained from the pentamethylbenzene alone. Enough pentamethylbenzene and pseudocumene were recovered which, together with the other products, accounted for practically all the material used. Hence it does not appear that the mechanism of the transfer of the methyl group can involve chain-ring compounds related to diphenylmethane.

The second scheme involved the addition of sulfuric acid as hydroxyl and SO_3H to ortho or para positions in the benzene nucleus; the quinoid intermediate so produced then rearranged to give the final product.

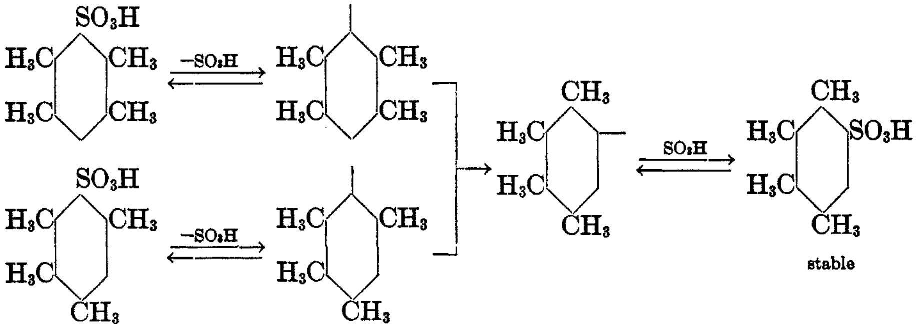


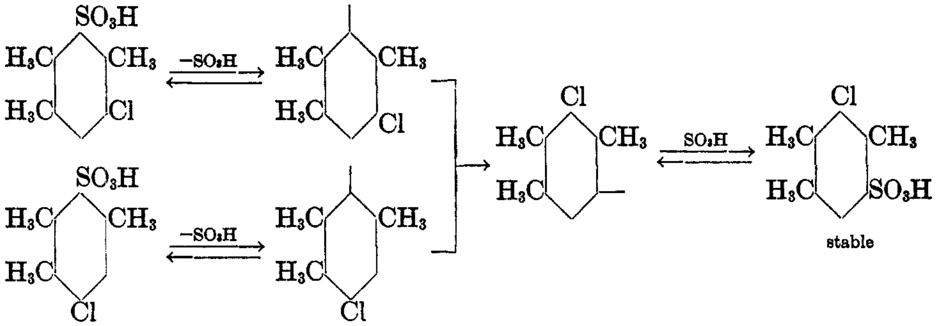
This mechanism has the advantage that it is analogous to the known rearrangements of quinols, and while there are some objections, it has decided possibilities. It does not explain the stability of chloromesitylene or of 5-fluoropseudocumene unless one assumes that these substances do not add sulfuric acid, or if they do, the quinoid intermediate decomposes to give the original products again. Moreover, this mechanism would not hold for the rearrangements of the dry sulfonic acids by phosphorus pentoxide, because in this case formation of addition compounds is impossible unless it is assumed that hydrolysis of the sulfonic acid by traces of water takes place.

No mechanism has been found which will explain satisfactorily all the available data. The main points to be considered in formulating a mechanism are the following:

1. Whether or not, in any given case, a rearrangement will occur, and why.
2. Both the intermolecular and intramolecular types of rearrangement must be explained, and predictions made as to when they will occur.
3. Which groups will migrate in a given compound, and why.
4. The non-rearrangement of chloromesitylene, 5-fluoropseudocumene, 5-aminopseudocumene, 5-nitropseudocumene, *p*-bromodiphenyl, 2,3-dimethylnaphthalene, the xylenes, the trimethylbenzenes, and all the hexasubstituted benzenes.
5. The stability of 3-chloropseudocumene and the other products obtained from the Jacobsen reactions.
6. The rearrangement of certain of the sulfonic acids when the dry substances are mixed with phosphorus pentoxide, and the evolution of sulfur dioxide under these conditions.
7. The inhibiting action of phosphoric and acetic acids when mixed with the sulfuric acid used.
8. The evolution of sulfur dioxide, the colors during the reaction, and the formation of the amorphous by-product as well as its nature.

From the information available at present, the ease with which the sulfonic acids rearrange seems possibly to be related to the ease with which the sulfonic acids can be hydrolyzed. The sulfonic acids of durene, isodurene and pentamethylbenzene (which rearrange) are all easily hydrolyzed at lower temperatures than prehnitene, chloromesitylene and 3-chloropseudocumene (which do not rearrange). How far this generalization will hold is a matter to be determined by experiments. If one invokes transient radicals as intermediates, then the extent of radical formation might logically be connected with the ease with which the sulfonic acids are hydrolyzed. Thus:





The free radicals rearrange to give the most stable structure, and the same stable structure will be obtained from all those radicals which have the same number and kind of substituents attached to the ring. According to this mechanism, 3-chloropseudocumene is a more stable structure than chloromesitylene, even though the latter (because the sulfonic acid does not dissociate into radicals) is not capable of rearrangement. In agreement with the predictions of this theory, all the chlorotrimethylbenzenes which can rearrange give the same product, 3-chloropseudocumene. It would be expected in some cases that the free radicals would combine to give a diphenyl derivative and in two cases such products have been observed: a cómpound having the composition $C_{20}H_{24}Cl_2$ (dichloroöctamethyldiphenyl?) was obtained as a by-product from the rearrangement of chloroisodurene, and from the rearrangement of 6-chloropseudocumene there was obtained a high-melting substance (m.p. 168–169°) which possibly is a diphenyl derivative. Moreover, the free radicals would be susceptible to oxidation and polymerization, which would account for the amorphous by-product.

Finally, in studying the Jacobsen reactions it is necessary that the structures of the reaction products should be established beyond any doubt. In preparing many of these substances for purposes of comparison, sulfonation is often used as one of the steps in the synthesis; since this is also the condition under which the Jacobsen reaction occurs, great care must be taken to show that no rearrangements have occurred during the syntheses. The papers of Smith and Moyle[16, 31] contain detailed experiments which show that mixture melting points of the halogenated polymethylbenzenes cannot be relied upon as a method of identification and the detailed proof of the structure of many of the reaction products is also given in these papers.

SUMMARY

This paper contains a discussion of the Jacobsen rearrangement. The material is reviewed historically and the limits of the reaction, the nature of the products, and the possible mechanisms are discussed. A table is given showing the effect of changes in the nature of the reagent upon the rearrangement of a mixture of durene and isodurene.

RECENT BOOKS

PREPARATION OF SCIENTIFIC AND TECHNICAL PAPERS. *S. F. Trelease*, Columbia University, and *Emma S. Yule*, University of the Philippines. The Williams & Wilkins Co., Baltimore. Third edition, 1936. v + 114 pp. 12.5 × 18.5 cm. $1.25.

"This manual is intended for the use of students who are writing articles on scientific or technical subjects. It is designed primarily as a reference book for senior and graduate students who want information concerning matters of style to be followed in the preparation of papers. . . . No attempt has been made to include rules of grammar and rhetoric."

The authors have succeeded in preparing a useful manual for students in the biological sciences and, to a lesser extent, for students in chemistry. The deficiencies are inherent in any small-sized book that would attempt to cover all sciences. A pertinent illustration is the group of six examples of a literature citation given on page 84 "to illustrate some of the forms used by periodicals." Not one of these conforms with usage of a strictly chemical periodical. However, it is emphasized that "The author should make a careful study of the journal in which his article is to be published, and he should prepare his copy so that it conforms to the best practice illustrated by current issues of the journal." Unfortunately, the book is not wholly consistent, for in the brief section on literature citations used by "many chemical and physical journals" each of the six different illustrations have abbreviations not used by *Chemical Abstracts*, despite the fact that three pages later is the statement that "The chemical journals use the abbreviations given by *Chemical Abstracts* in its list of periodicals abstracted."

Some of the advice on the preparation of a summary of an article would not be helpful for strictly chemical periodicals: "Study as models the abstracts given in the abstract journals, and try to make a summary that an abstractor (one who is as well acquainted with the field as you are yourself) would wish to insert, without alteration, in an abstract journal." Biological abstracts are not chemical abstracts.

The book contains numerous helpful suggestions for all students, particularly if they remember that "Obviously, no set method or arrangement will be suited to all kinds of articles."

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SOME NUCLEUS ALKYL DERIVATIVES OF PHENETHYLAMINE* †

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Received November 28, 1936; revised January 21, 1937

Since Barger and Dale showed that possession of the skeleton of phenethylamine is the primary requirement for the manifestation of sympathomimetic properties,[1] much work has been done to determine the effect of substituents attached either to the nucleus or to the side-chain of the parent molecule. In such study, alkyl groups have received their share of attention when attached to either carbon or nitrogen in the side-chain, but there are few references indeed to the effect of alkyl groups attached directly to the nucleus. The *p*-methyl, *p*-ethyl, and *p*-butyl derivatives of ephedrine have been prepared and were described as more toxic and having less circulatory effect than ephedrine.[2] Likewise, the methyl group in either the meta[3] or para[4] position of phenylpropanolamine is said to lower the activity and increase the toxicity of the base. Simultaneous introduction of methyl and hydroxyl into the nucleus of phenylpropanolamine produced an interesting pair of compounds.[5] The 3-methyl-4-hydroxy derivative was found to be twice as active and about four times as toxic as the parent; the 4-methyl-3-hydroxy isomer was also twice as active but was somewhat less toxic than phenylpropanolamine.

A few other nucleus-alkylated phenethylamines have been reported, but pharmacological data concerning them are lacking. Though the effect of methyl in the nucleus appears to be distinctly unfavorable to pressor activity, it seemed to the authors worth while to conduct a more comprehensive investigation along these lines, and to extend observations to

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† The material in this paper is abstracted from the dissertation presented by John H. Speer to the Faculty of the Graduate School, Yale University, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

‡ Present address: G. D. Searle & Co., Chicago, Ill.

[1] Barger and Dale, *J. Physiol.*, **41**, 19, (1910).

[2] Ehrhart, *Metallboerse*, **20**, 1800, (1930).

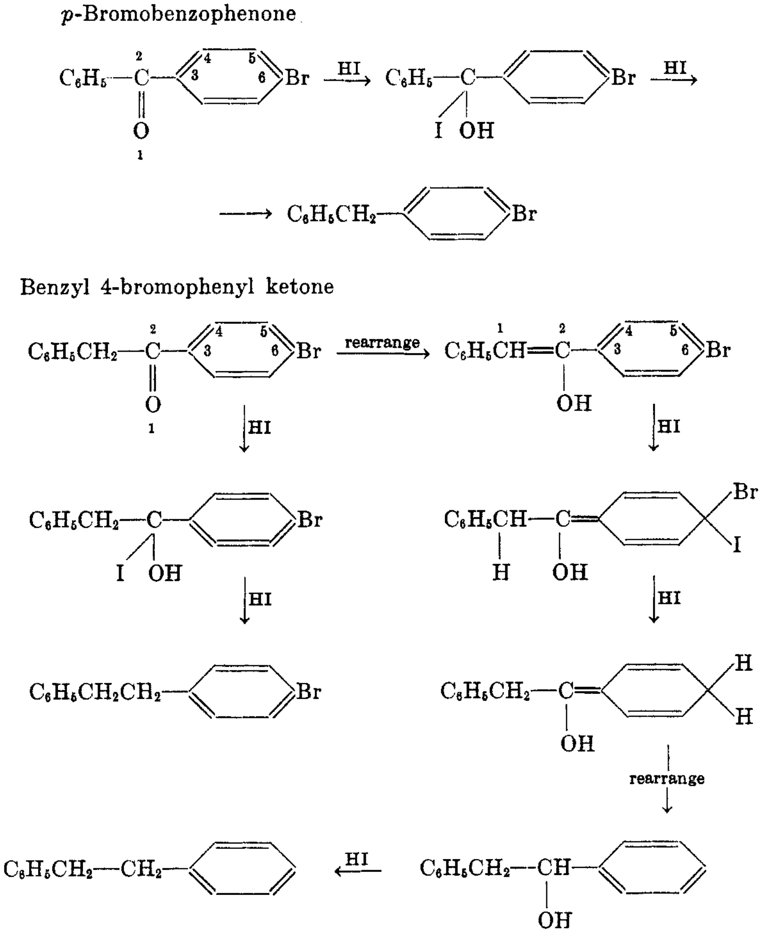
[3] Thompson, Personal communication to Hartung, quoted in *Chem. Rev.*, **9**, 437, (1931).

[4] Hartung and Munch, *J. Am. Chem. Soc.*, **51**, 2262, (1929).

[5] Hartung *et al.*, *ibid.*, **53**, 4149, (1931).

several other types of alkyl groups. Phenethylamine itself, rather than one of its more active substitution products, was chosen as the parent compound of the series in order to avoid any specific influence of other groups, and so to furnish a truer evaluation of the alkyl groups under consideration.

CHART I



In developing a general and practical method of synthesis for such a series of compounds, alkylation of bromobenzene by means of the Friedel-Crafts condensation, with subsequent replacement of the nuclear bromine by an aminoethyl group was selected as the most promising route of approach on account of both smoothness of operation and lack of formation of undesired isomers. Such a synthesis leads entirely to the formation of para-alkylated compounds; the ortho and meta isomers were obtained only in special cases.

Alkylation was accomplished in two steps: (1) formation of a ketone by the action of an acid chloride, and (2) reduction of the ketone. The reduction of ortho and para bromobenzophenones by means of hydriodic acid and red phosphorus proceeded with excellent yields, the bromine being not at all affected by the reducing agent. When the same method of reduction was applied to benzyl 4-bromophenyl ketone, about twenty mole-per cent. of *sym.*-diphenylethane was recovered from the reaction. The increased lability of the bromine atom which was observed in this latter compound may be taken to indicate a partial enolization of the ketone, followed by addition of hydrogen iodide in the 1,6 position to the conjugate system of $C = C$ double bonds (see Chart I). Such addition would form a quinoid ring, labilizing the bromine atom. That such addition does not take place, under the reaction conditions employed, in the 1,6 position in the conjugate system involving the $C = O$ double bond (keto form) is demonstrated by the stability of the bromine atom in bromobenzophenone, which compound can exist only in the keto form. That an aromatic nucleus can form part of a conjugate system with a double bond in the side-chain has been previously observed by Gilman and coworkers[6], and by Kohler and Nygaard.[7]

Replacement of bromine in the nucleus by a β-aminoethyl group was effected in three steps. (1) Ethylene oxide was added to the magnesium derivative of the alkylbromobenzene, forming a phenethyl alcohol. (2) This was converted to the corresponding phenethyl bromide by the action of phosphorus tribromide, and (3) the bromide was condensed with an appropriate amine.

In the Department of Pharmacology and Toxicology, a study of the pressor activity of some of the methyl and ethyl derivatives was made on cats and dogs[8]. None of these was found to be more active than the parent substance (phenethylamine). In primary amines (see Table II) a methyl group in the para position did not appreciably alter activity, but a para ethyl group caused a moderate decrease in the pressor effect. In the *N*-methyl amines, a methyl group in either the para or meta position reduced the activity slightly, an ortho methyl group reduced it greatly, while para ethyl substitution was associated with either a weak pressor action or a definite depressor tendency. The two *N*-ethyl derivatives (meta methyl and para methyl) were depressor. Both of these *N*-ethyl,

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[6] GILMAN *et al.*, *ibid.*, **51**, 2252, (1929).

[7] KOHLER AND NYGAARD, *ibid.*, **52**, 4128, (1930).

[8] HAMBOURGER AND JAMIESON, *J. Pharmacol.*, **58**, 53, (1936).

and also the para ethyl *N*-methyl, compounds caused a reversal of the pressor response normally produced by the other compounds studied. Preliminary trials of the other amines prepared showed all the tertiary amine derivatives to be uniformly depressor, and those derivatives containing a second phenyl ring to be comparatively inactive, with a probable depressor tendency. They were not of sufficient pharamacological interest to warrant further investigation at present.

EXPERIMENTAL

The bromoketones.—*p*-Bromoacetophenone and *o*- and *p*-bromobenzophenone were prepared as described elsewhere in the literature.[9] Benzyl 4-bromophenyl ketone[10] was prepared by the action of 1 mole of phenylacetyl chloride on 2½ moles of bromobenzene in carbon disulfide solution in the presence of 1 mole of aluminum chloride. After decomposition of the aluminum complex with water, the ketone was obtained by fractional distillation. It boiled at 165° at 3 mm. pressure and solidified completely on cooling. It crystallized from alcohol in plates which melted at 114–115°. On oxidation with chromic acid it yielded benzoic and *p*-bromobenzoic acids.

TABLE I

PROPERTIES OF THE PHENETHYL ALCOHOLS

$RC_6H_4CH_2CH_2OH$ R =	B.P., °C.	PRESSURE, MM.	YIELD, %	PHENYLURETHANE		
				M.P., °C.	Per cent Nitrogen	
					Calc'd	Found
2-CH_3[a]	119	16	44	67		
3-CH_3[b]	111–115	15	52			
4-CH_3[a]	115	15	74	112		
4-C_2H_5	98–101	4	70	104.5	5.20	5.23
2-$CH_2C_6H_5$	162	3	68	124	4.23	4.18
4-$CH_2C_6H_5$	172	4.5	50	93	4.23	4.19
4-$CH_2CH_2C_6H_5$[c]	172	3	54	107	4.06	4.07

[a] GRIGNARD, *Compt. rend.*, **141**, 45, (1905).

[b] KLING, *Chem. Zentr.*, **1908**, II, 1863.

[c] Plates from benzene; m.p. 67–68. *Anal*: Calc'd for $C_{16}H_{18}O$: C, 84.91; H,8.00. Found: C, 85.01; H, 7.85.

Anal: Calc'd. for $C_{14}H_{11}BrO$: Br, 29.06. Found: Br, 28.92.

The oxime crystallized from alcohol in needles which melted at 137°.

Anal: Calc'd. for $C_{14}H_{12}BrNO$: Br, 27.55. Found: Br, 27.81.

The alkyl bromobenzenes.—*p*-Bromoethylbenzene[11] was prepared in 38% yield by a Clemmensen reduction of *p*-bromoacetophenone.

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[9] SCHWEITZER, *Ber.*, **24**, 550 (1891);
CATHCART AND MEYER, *ibid.*, **25**, 1498, (1892);
CONE AND LONG, *J. Am. Chem. Soc.*, **28**, 521, (1906).

[10] IVANOFF AND POPOFF, *Bull. Soc. Chem.*, [4], **49**, 1547, (1931).

[11] ASCHENBRANDT, *Ann.*, **216**, 222, (1883).

p-Bromodiphenylmethane was prepared by heating 13 g. of *p*-bromobenzophenone, 13 g. of hydriodic acid (sp. gr., 1.58), and 2.5 g. of red phosphorus in a sealed tube at 160° for 6 hours. After cooling, water was added, and the oil was extracted with ether. The ether extract was washed successively with water, sodium carbonate solution, sodium thiosulfate solution, and water, and dried over sodium sulfate. On distillation, the product was obtained in 92% yield as a colorless oil which boiled at 162° at 13 mm. pressure, or at 128° at 3 mm. pressure.

Anal: Calc'd for $C_{13}H_{11}Br$: Br, 32.35. Found: Br, 32.44.

In a similar way, *o*-bromodiphenylmethane[12] was obtained in 90% yield from *o*-bromobenzophenone. It was a colorless oil which boiled at 165° at 12 mm. pressure. The same method of reduction, when applied to benzyl 4-bromophenyl ketone, gave *p*-bromo-*sym.*-diphenylethane in 60% yield. The compound boiled at 143° at 3 mm. pressure, and solidified on standing to a crystalline mass which melted sharply at 32°. The yield was 60%. Analysis showed it to be about 95% pure (Calc'd. for $C_{14}H_{13}Br$: Br, 30.61. Found: Br, 28.90). From the lower-boiling fraction obtained in the distillation, 22% of *sym.*-diphenylethane was obtained.

The phenethyl alcohols.—The Grignard reagent was formed from the alkyl bromobenzene in the customary manner. The solution was cooled in a freezing bath, and two equivalents of ethylene oxide dissolved in dry benzene were added slowly during stirring. The mixture frequently set to a solid gel before addition was complete. This was allowed to stand a short time in the freezing bath, after which it was warmed to 60° for about three hours. The magnesium complex was decomposed with dilute sulfuric acid, and the ether layer was separated. It was washed with water, sodium carbonate solution, and water, dried over sodium sulfate, and fractionally distilled. The properties of the alcohols and analyses of the corresponding phenylurethanes are recorded in Table I.

As a by-product in the above reaction, a hydrocarbon of the diphenyl series was isolated in each case save that of *o*-bromodiphenylmethane. All of these hydrocarbons were previously known, save the two described below.

4,4'-Dibenzylbiphenyl boiled between 190° and 215° at 5 mm. pressure, and crystallized from alcohol in plates which melted at 113°. This description corresponds exactly to that given by Wolf[13] for x,x'-dibenzylbiphenyl, the empirical formula of which was confirmed by him by analysis.

4,4'-Diphenethylbiphenyl crystallized in the distilling flask after removal of the solvent, but before distillation of the accompanying 4-(phenethyl)phenethyl alcohol. It crystallized from ethanol in platelets which melted at 146°. It is sparingly soluble in hot alcohol, and nearly insoluble in cold alcohol.

Anal: Calc'd for $C_{28}H_{26}$: C, 92.80; H, 7.20.
Found: C, 92.91; H, 6.99.

The phenethyl bromides.—Two and a third equivalents of phosphorus tribromide was dropped rapidly into a solution of three equivalents of the alcohol dissolved in dry benzene and cooled in an ice bath. The mixture was kept in the ice bath about half an hour, then slowly heated to boiling on a steam bath, and boiled until the evolution of hydrogen bromide had ceased. After cooling, the solution was washed several times with water, then once with dilute sodium carbonate solution, and dried over calcium chloride. The three tolylethyl bromides were obtained by fractional distillation; they have been previously described in the literature.[14]

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[12] Clarkson and Gomberg, *J. Am. Chem. Soc.*, **52**, 2887, (1930).

[13] Wolf, *Ber.*, **14**, 2031, (1881).

[14] Shoesmith and Connor, *J. Chem. Soc.*, **129**, 1770, (1927).

1-Ethyl-4-(β-bromoethyl) benzene was a colorless oil which boiled at 84–86° at 3 mm. pressure.

Anal: Calc'd for $C_{10}H_{13}Br$: Br, 37.51. Found: Br, 37.38.

The derivatives of diphenylmethane and of diphenylethane decomposed slightly when distillation was attempted, so they were used in the crude condition without analysis. Their identity is confirmed by the analyses of the amines prepared therefrom. The yields in each case ranged between 60 and 70%.

TABLE II

PROPERTIES OF THE PHENETHYLAMINES

	$RC_6H_4CH_2CH_2Y$		B.P., °C.	PRESSURE, MM.	METHOD OF PREPARATION AND YIELD
	R =	Y =			
1	2-CH_3	$NHCH_3$	99	12	IV, 62%
2	2-CH_3	$N(C_2H_5)_2$	120.5	14	IV, 55%
3	3-CH_3	$NHCH_3$[a]	98–99	12	IV, 53%
4	3-CH_3	NHC_2H_5	100	9	IV, 60%
5	3-CH_3	$N(C_2H_5)_2$	120	15	IV, 60%
6	4-CH_3	NH_2[b]	91–92	10	I, 74%; III, 25%
7	4-CH_3	$NHCH_3$[a]	103–107	16	IV, 67%
8	4-CH_3	NHC_2H_5	107	12	IV, 73%
9	4-CH_3	$NHCH_2C_6H_5$	165–167	4	IV, 90%
10	4-CH_3	$NHCH(C_6H_5)_2$[c]	193–195	2.5	IV, 90%
11	4-CH_3	$NHCH_2CH_2N(C_2H_5)_2$	131–134	3	IV, 77%
12	4-CH_3	$N(C_2H_5)_2$	119	14	IV, 68%
13	4-CH_3	$N(n\text{-}C_4H_9)_2$	120–122	2.5	IV, 90%
14	4-CH_3	$N(CH_2)_5$	118	4	IV, 86%
15	4-C_2H_5	NH_2	97	8	I, 67%
16	4-C_2H_5	$NHCH_3$	90–91	4.5	IV, 70%
17	2-$CH_2C_6H_5$	NH_2	155	4	I, 10%; II, 35%
18	2-$CH_2C_6H_5$	$NHCH_3$	146–148	3	IV, 77%
19	2-$CH_2C_6H_5$	$N(C_2H_5)_2$	157	3	IV, 57%
20	4-$CH_2C_6H_5$	NH_2	178–181	8	I, 80%
21	4-$CH_2C_6H_5$	$NHCH_3$	145–146	3	IV, 81%
22	4-$CH_2C_6H_5$	$N(C_2H_5)_2$	169–170	3	IV, 52%
23	4-$CH_2CH_2C_6H_5$	NH_2[d]	160	2	II, 43%
24	4-$CH_2CH_2C_6H_5$	$NHCH_3$	152–155	2.5	IV, 80%

[a] TITLEY, *J. Chem. Soc.*, **128**, 508, (1926).

[b] CIESIELSKI, *Chem. Zentr.*, **1907**, I, 1793.

[c] Platelets from alcohol; m.p. 73.5°. *Anal*: Calc'd for $C_{21}H_{22}N$: N, 4.86. Found: N, 4.69.

[d] Solidified on standing; m.p. 49°.

In working up the product from the reaction of phosphorus tribromide on 4-(β-hydroxyethyl)-*sym.*-diphenylethane, the washing of the reaction mixture with sodium carbonate solution caused the formation of a copious crystalline precipitate. This was identified as the disodium salt of an acid phosphite ester of the alcohol. It was obtained in about 25% yield. It crystallized from 80% alcohol in leaflets which did not melt below 300°.

Anal: Calc'd for $C_{16}H_{17}Na_2O_3P$: P, 9.30. Found: P, 9.40.

Upon acidification, it yielded the free ester as an oil which was insoluble in water and soluble in the usual organic solvents.

The phenethylamines.—Amines were prepared from the corresponding bromides by four general methods.

I. Fifteen grams of a phenethyl bromide were dissolved in 500 cc. of alcoholic ammonia saturated at 5°, and allowed to stand at room temperature for five to eight days in a tightly stoppered flask. The solution was then evaporated to dryness, and the crystalline residue was decomposed with aqueous alkali. The base was extracted with ether, dried over solid potassium hydroxide, and fractionally distilled. Bases prepared in this way reacted readily with the carbon dioxide of the atmosphere.

TABLE III

PROPERTIES OF THE PHENETHYLAMINE HYDROCHLORIDES

NUMBER, TABLE II	M.P., °C.	CRYST. FORM	SOLVENT[a]	SOL. IN WATER[b]	% NITROGEN		% CHLORINE	
					Calc'd	Found	Calc'd	Found
1	167	Needles	Ac.	v.s.	7.54	7.42	19.14	19.25
2	147.5	Plates	Ac.-Et.	v.s.	6.15	6.09	15.58	15.66
3	143	Plates	Ac.	v.s.	7.54	7.45	19.14	19.12
4	161–162	Platelets	Ac.-Al.	v.s.	7.01	7.07	17.78	17.75
5	148	Leaflets	Ac.	v.s.	6.15	6.13	15.58	15.61
6	217–218	Hex. plates	Al.	m.s.			20.67	20.53
7	192	Leaflets	Ac.	m.s.	7.54	7.47	19.14	19.12
8	203–204	Leaflets	Ac.-Al.	v.s.	7.01	7.09	17.78	17.86
9	232–234	Prisms	95% Al.	sp.s.	5.35	5.26	13.55	13.72
10	256	Prisms	90% Al.	insol.	4.31	4.27		
11	124–125[c]	Plates	Ac.	v.s.	9.12	9.21	23.09	23.20
12	115–116	Plates	Ac.-Et.	v.s.	6.15	6.18	15.58	15.62
13	93	Needles	Ac.-Et.	v.s.	4.93	4.71	12.50	12.50
14	212	Needles	Ac.	v.s.	5.84	6.05	14.81	14.77
15	208[d]	Plates	95% Al.	m.s.	7.54	7.56	19.14	19.15
16	192–193	Plates	Ac.-Al.	v.s.	7.01	6.93	17.78	17.59
17	169–170	Platelets	Al.-Et.	v.s.	5.65	5.52	14.32	14.32
18	180	Leaflets	Al.	v.s.	5.35	5.26	13.55	13.46
19	122	Platelets	Ac.-Et.	v.s.	4.61	4.51	11.69	11.74
20	222–224	Leaflets	Al.	sp.s.	5.65	5.63	14.32	14.29
21	192	Plates	Al.	m.s.	5.35	5.37	13.55	13.56
22	136.5	Leaflets	Ac.	v.s.	4.61	4.68	11.69	11.66
23	213–215	Needles	95% Al.	sp.s.	5.35	5.29	13.55	13.49
24	197	Leaflets	Al.	m.s.	5.08	5.06	12.87	13.03

[a] Solvents: Ac. = acetone; Al. = absolute alcohol; Et. = anhydrous ether.

[b] Solubilities in water (approx.): v.s. = over 8%; m.s. = 1% to 8%; sp.s. = less than 1%; all at 25°C.

[c] Dihydrochloride.

[d] Sinters at 200°.

II. One equivalent of a phenethyl bromide was heated at 180° for 4 hours with 1.1 equivalents of potassium phthalimide. The melt was boiled for a few minutes with water, filtered hot, and the alkylphthalimide was dried and weighed. It was hydrolysed without further purification by the method of Ing and Manske,[15] using hydrazine hydrate.

III. Equal weights of potassium phthalimide and of β-*p*-tolylethyl bromide were refluxed together in absolute alcohol for 48 hours. The solution was cooled, the alcohol diluted with one quarter its volume of water, and the alkylphthalimide filtered. It crystallized from alcohol in leaflets which melted at 117°. The yield was 45%.

Anal: Calc'd for $C_{17}H_{15}NO_2$: N, 5.28. Found: N, 5.11.

TABLE IV

PROPERTIES OF THE PHENETHYLAMINE PICRATES

NUMBER, TABLE II	M.P., °C.	CRYST. FORM[a]	SOLVENT	% NITROGEN	
				Calc'd	Found
1	114–115	Needles	Water	14.81	14.67
2	110	Needles	Water	13.33	13.26
3	127	Plates	Water	14.81	14.74
4	133	Needles	Water	14.28	14.18
5	95	Plates	Ac.-Et.	13.33	13.48
6	155[b]				
7	135[b]				
8	126	Leaflets	Water	14.28	14.14
9	125	Rhomboids	Alcohol	12.33	12.23
10	155	Needles	70% Al.	10.83	10.90
11	Not made				
12	132	Needles	Water	13.33	13.32
13	62–63	Needles	Alcohol	11.76	11.73
14	144	Needles	Water	12.95	12.92
15	168	Needles	Water	14.81	14.78
16	Oil				
17	178–179	Plates	40% Al.	12.72	12.50
18	169–171	Rhomboids	Water	12.33	12.20
19	143–144	Needles	50% Al.	11.29	11.26
20	154–155	Needles	50% Al.	12.72	12.63
21	93–94	Plates	Alcohol	12.33	12.36
22	Oil				
23	135	Needles	80% Al.	12.33	12.25
24	115–116	Leaflets	50% Al.	11.96	12.02

[a] Color in each case was some shade of orange-yellow.

[b] TITLEY, *J. Chem. Soc.*, **128,** 508, (1926).

The *p*-tolylethylphthalimide thus obtained was dissolved in the calculated volume of half-normal alcoholic potassium hydroxide and boiled for five minutes. On cooling, the solution was diluted with an equal volume of water to complete the precipitation of β-*p*-tolylethylmonoamide of phthalic acid. The amide crystallized from 25% alcohol in leaflets which melted at 150°C. The yield was quantitative.

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[15] ING AND MANSKE, *ibid.*, **128,** 2348, (1926).

Anal: Calc'd for $C_{17}H_{17}NO_3$: N, 4.98. Found: N, 4.87.

β-Tolylethylphthalamide was boiled for 15 hours with excess 20% hydrochloric acid. On cooling, the solution was filtered, the precipitate was washed with warm water, and the combined filtrates were concentrated to a small volume. The base was liberated and distilled in the usual manner. The yield was 54%, calculated from the phthalamide, or 25% calculated from the original bromide.

IV. One equivalent of a phenethyl bromide was heated at 100° (in a sealed tube if necessary) with five equivalents of a primary amine, or three equivalents of a secondary amine, for six to eight hours. (Methylamine and ethylamine were used as a 50% solution in absolute alcohol; the time of heating was extended to 24 hours.) On cooling, the solution was made strongly alkaline, and the base was extracted and distilled in the usual manner.

The properties of all the bases are recorded in Table II.

The Amine Hydrochlorides were prepared by passing a stream of dry hydrogen chloride into a solution of the base in 25 times its weight of dry ether, and crystallizing the amorphous precipitate from an appropriate solvent. In the case of some of the larger molecules, the pure crystalline hydrochloride could be obtained directly by passing dry hydrogen chloride into a solution of the base in six times its volume of absolute alcohol without cooling until the solution had become acid in reaction, and then cooling in an ice box.

The properties of the hydrochlorides are recorded in Table III.

The Amine Picrates were prepared by mixing cold aqueous solutions of equivalent weights of the amine hydrochloride and of picric acid. The picrate frequently separated as an oil which usually solidified upon standing over night. It was crystallized from an appropriate solvent.

The properties of the picrates are recorded in Table IV.

SUMMARY

1. A series of derivatives of phenethylamine, bearing methyl, ethyl, benzyl or phenethyl groups substituted in the nucleus, has been prepared, and the hydrochlorides and picrates of the bases, as well as a number of intermediate compounds, are described.

2. Those bases bearing either a methyl or ethyl group in the nucleus, and not more than one methyl group on the nitrogen atom, show pressor activity in general similar in kind to, but less in degree than, phenethylamine. Compounds bearing two phenyl rings, or a tertiary nitrogen atom are either inactive or depressor in circulatory effect.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GOODYEAR TIRE AND RUBBER CO.]

REACTIONS IN THE THIAZOLE SERIES. I. REACTIONS OF 2-CHLOROBENZOTHIAZOLES WITH THIOUREAS

WINFIELD SCOTT AND GEORGE W. WATT

Received February 23, 1937

Rather extensive studies involving the addition compounds of alkyl halides with thiourea have been pursued for the purpose of elucidating the structures of thiourea, of its addition compounds, and of basic substances derived therefrom[1–6]. The formation of aliphatic mercaptans by the decomposition of addition compounds of this type indicates that the hydrocarbon group is attached to sulfur. While such reactions in the aliphatic series were observed by Claus[7] at an early date, a survey of the literature reveals that these studies have been extended to halogen compounds of the aromatic and heterocyclic series in but a few instances. Furthermore, with but one exception[8, 9] no attempts have been made to determine the relative reactivities of substituted thioureas toward the various types of organic halides.

Of a number of chloropolynitrobenzenes investigated, only 1-chloro-2,4-dinitrobenzene and picryl chloride have been found reactive toward thiourea[10, 11], the former yielding bis (2,4-dinitrophenyl) disulfide, and the latter dipicryl sulfide. Rosenhauer, Hoffman, and Heuser[12] have shown that thiourea and certain chloroquinolines react to form either mercaptans, sulfides, or disulfides. Their observations support the view that the primary reactions consist in the formation of definite additive compounds.

Experiments described in the following pages show that analogous reactions occur when 2-chlorobenzothiazoles and thiourea are refluxed, or are

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[1] BERNTHSEN AND KLINGER, *Ber.* **11**, 492–5 (1878); **12**, 574–6 (1879).

[2] RATHKE, *ibid.*, **14**, 1774–80 (1881).

[3] WILL, *ibid.*, **14**, 1489–92 (1881); **15**, 338–48 (1882).

[4] WILL AND BIELSCHOWSKI, *ibid.*, **15**, 1309–18 (1882).

[5] WERNER, *J. Chem. Soc.*, **57**, 283–304 (1890).

[6] LECHER AND HEUCK, *Ann.*, **438**, 169–84 (1924).

[7] CLAUS, *Ber.*, **7**, 235–7 (1874); **8**, 41–4 (1875); *Ann.*, **179**, 146–7 (1875).

[8] GOLDSCHMIDT AND GRINI, *Z. Elektrochem.*, **19**, 226–34 (1913).

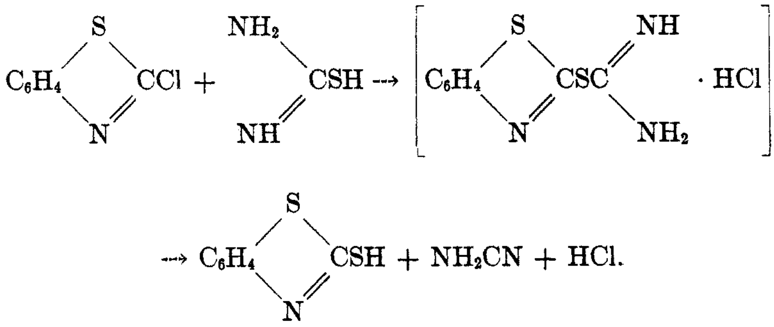
[9] GOLDSCHMIDT AND HOUGEN, *ibid.*, **22**, 339–49 (1916).

[10] WILLGERODT, *Ber.*, **10**, 1686–9 (1877); Private Communication to "Beilstein", II, Third Edition, p. 816.

[11] TAYLOR AND DIXON, *J. Chem. Soc.*, **125**, 243–50 (1924).

[12] ROSENHAUER, HOFFMAN, AND HEUSER, *Ber.*, **62B**, 2730–6 (1929).

allowed to stand for some time at room temperature, in alcoholic solution. The interaction of 2-chlorobenzothiazole and thiourea may be represented by the equations,



The instability of the intermediate addition compound is apparently such that it decomposes spontaneously, even at room temperature, resulting in the formation of 2-mercaptobenzothiazole, cyanamide, and hydrogen chloride. Both 2-mercaptobenzothiazole and cyanamide have been identified, the latter in the form of its silver salt, and the formation of hydrogen chloride is indicated by the fact that an aqueous solution of the reaction product is acid to litmus and exhibits reactions characteristic of hydrochloric acid. Similar reactions occur with monosubstituted thioureas, while the disubstituted compounds may result in the formation of mercaptans or stable addition compounds, depending upon the nature of the substituent groups and upon the lability of the halogen atom in the 2-position in the thiazole ring. In certain cases the disubstituted compounds are unreactive.

EXPERIMENTAL

With the exceptions noted below, materials used in this investigation were prepared and purified by methods ordinarily employed, or consisted of carefully purified commercial products. All analytical data presented herein were obtained by standard procedures and are averaged values.

Preparation of 2-chlorobenzothiazole.—The method employed for the preparation of 2-chlorobenzothiazole is essentially that due to Clifford[13] and is generally applicable to the preparation of 2-chlorobenzothiazoles.

One hundred fifty grams of sulfur monochloride (10% excess) was added in small portions and with stirring to 167 g. (1 mole) of commercial grade 2-mercaptobenzothiazole contained in a three liter flask provided with an air reflux condenser. When the initial exothermic reaction had subsided, the reaction mixture was heated cautiously until frothing ceased, then refluxed on the sand bath for one and one-half hours and allowed to stand overnight. The black liquid was transferred to a Claisen

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[13] CLIFFORD, *U. S. Pat.* 2,043,948, June 9, 1936.

flask and distilled; the fraction boiling at 150–70° (55–65 mm.) being collected. This material was washed thoroughly with 10% sodium carbonate solution, washed with water, separated, and dried over anhydrous sodium sulfate. Redistillation of the dried product gave a 72% yield (117 g.) of clear colorless 2-chlorobenzothiazole; b.p., 158-62°/50 mm.

Preparation of s-*dicyclohexylthiourea.*—One-half mole of *N*-methylenecyclohexylamine (55 g.) in a 500 cc. flask was melted on the steam bath. Small portions of sulfur were then added to the melt until 31.8 g. had been added. The reaction mixture darkened, heat was liberated, and there was a copious evolution of hydrogen sulfide. After heating under reflux (air condenser) for five minutes, the mixture was distilled under reduced pressure. The pale yellow oily distillate which solidified upon cooling was recrystallized from alcohol; white crystals of *s*-dicyclohexylthiourea; m. p. 179–80°. The melting point of a mixture with a specimen prepared as described by Skita and Rolfes[14] was not depressed. Yield, 22 g. or 37%.

Anal. Calc'd for $C_{13}H_{24}N_2S$: N, 11.7; S, 13.3.
Found: " 11.5; " 13.4.

Various modifications of the foregoing procedure resulted in no marked increase in yield, the maximum obtained being 44%. The crude reaction product may be distilled at atmospheric pressure without materially altering either the yield or the quality of the product. Insofar as we have been able to determine, *s*-dicyclohexylthiourea has previously been prepared only by the method of Skita and Rolfes.

Attempt to prepare s-*dipentamethylenethiourea.*—In view of the results obtained in the reaction between *N*-methylenecyclohexylamine and sulfur, it seemed probable that the preparation of *s*-dipentamethylenethiourea might be accomplished through the interaction of 1,1′-methylenebispiperidine and sulfur. It was found, however, that such interaction results in the formation of relatively low yields of piperidine pentamethylenedithiocarbamate, hydrogen sulfide, piperidine hydrosulfide, and variable amounts of tarry products.

Since the reaction was found to be a very violent one, the procedure finally adopted involved the use of xylene as the reaction medium, the following being a description of a typical case. Ninety-two grams of 1,1′-methylenebispiperidine, 36.4 g. of sulfur, and 100 cc. of xylene were placed in a three-liter flask equipped with an air condenser tube, the top section of which was bent at a forty-five degree angle and which led into a one-liter Erlenmeyer flask immersed in an ice bath. (The condenser tube should have an inside diameter of at least 1.6 cm.) The purpose of this apparatus is to obviate loss of the product during the violently exothermic reaction when much of the reaction mixture will be forced out through the condenser tube and lost if these precautions are not observed.

The reaction vessel was warmed gently until the reaction began. Cold water was then allowed to flow over the surface of the flask in order to keep the reaction under control. When vigorous boiling ceased, that portion of the reaction mixture which was trapped in the Erlenmeyer flask at the exit to the condenser tube was returned to the reaction vessel, and the whole was refluxed for 20 minutes. The system was then arranged for distillation at atmospheric pressure in the usual manner, using an air condenser. The greater portion of the reaction mixture was distilled over, including the solvent xylene, and collected in a cooled receiver. The white crystalline product was separated by filtration and recrystallized from methyl alcohol. White

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[14] SKITA AND ROLFES, *Ber.*, **53B**, 1247 (1920).

crystals of piperidine pentamethylenedithiocarbamate; m. p., 172–3°; yield, 42 g. or 34%.

Anal. Calc'd for $C_{11}H_{22}N_2S_2$: N, 11.4; S, 26.0.
Found: " 11.1; " 26.3.

The melting point of a mixture with an authentic specimen of the piperidine salt prepared from piperidine and carbon bisulfide in the usual manner showed no depression.

During refluxing, piperidine hydrosulfide condensed on the walls of the condenser assembly, and a smaller quantity volatilized in the early stages of the distillation. While our experience with this reaction is not sufficiently extensive to warrant speculation as to the mechanism of the formation of the products obtained, it is possible that the anticipated product, *s*-dipentamethylenethiourea, was formed as an intermediate in the production of the dithiocarbamate.

Reactions of 2-chlorobenzothiazole.—Seventeen grams of 2-chlorobenzothiazole and 7.6 g. of thiourea were refluxed for one hour in 100 cc. of ethyl alcohol. The clear alcoholic solution was poured into 500 cc. of ice water, whereupon a white crystalline solid separated. This material was filtered off and washed with water. The crude product, 2-mercaptobenzothiazole, weighed 16.8 g. (100% yield) and melted at 175–6°. After recrystallization from alcohol it melted at 176–7° and this melting point was not depressed when a sample was mixed with an equal weight of 2-mercaptobenzothiazole prepared by an entirely independent method.[15]

TABLE I

REACTIONS WITH 2-CHLOROBENZOTHIAZOLE

THIOUREA	YIELD, %	M. P., °C.
Thiourea	100	175–6
Allyl-	100	170–3
Phenyl-	78	170–3
o-Tolyl-	79	169–74
s-Diphenyl-	0	
s-Dicyclohexyl-	0	
N,*N*-Dimethyl-*N*′-phenyl-	0	
N,*N*-Pentamethylene-*N*′-phenyl-	0	

Anal. Calc'd for $C_7H_5NS_2$: N, 8.4; S, 38.3.
Found: " 8.3; " 38.4.

The filtrate was made distinctly alkaline with ammonium hydroxide and treated with aqueous silver nitrate. A small quantity of yellow silver cyanamide, m. p., 200° (dec.) was precipitated.

Equimolar quantities of 2-chlorobenzothiazole and thiourea in alcohol solution were allowed to stand overnight at room temperature in a tightly stoppered container. When the solvent alcohol was allowed to evaporate without application of heat, a theoretical yield of 2-mercaptobenzothiazole was obtained.

In Table I are presented yield data relative to reactions of 2-chlorobenzothiazole with a number of thioureas. The melting points of the *crude* products are included in the table since they serve as an index to the purity of 2-mercaptobenzothiazole

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[15] KELLY. *U. S. Pat.* 1,631,871, June 7, 1927.

produced in these reactions. In each case one-tenth molar quantities of 2-chlorobenzothiazole and the designated thiourea were refluxed for one hour in 100 cc. of alcohol.

Monosubstituted thioureas.—After reactions involving monosubstituted thioureas, a different method was required for the isolation of the mercaptan, due to the presence of insoluble monosubstituted cyanamides. When the alcoholic solutions were poured into ice water, there separated not definitely crystalline products such as are obtained when thiourea itself is used, but rather soft semi-solid materials which only partially solidified upon standing in the aqueous medium in the cold. When these products were purified by crystallization from organic solvents, unavoidable purification losses led to yield values appreciably lower than actually formed in the reactions. Accordingly, the crude products were filtered off, dried, and the melting points were estimated; the products were then extracted three times with 50 cc. portions of cold 10% sodium hydroxide solution. 2-Mercaptobenzothiazole was then precipitated from the combined extracts by acidification with dilute hydrochloric acid. After recrystallization from 50% alcohol, 2-mercaptobenzothiazole isolated in this manner melted at 175-7° and its identity was confirmed by mixture melting points in each case.

The residues remaining after the alkali extractions were examined in some detail and in every case were found to consist of a mixture of products. For example, in the case of the reactions with phenylthiourea, fractional crystallizations of the alkali-insoluble material from alcohol, ether, and ethyl acetate resulted in the isolation of very small quantities of white solids having melting points of 40-45° and 183-5° (after softening at 160°). These substances have properties similar to those exhibited by phenylcyanamide (m. p. 47°),[16] and triphenylisomelamine (m. p., 185°).[17]

Disubstituted thioureas.—As shown in Table I, 2-mercaptobenzothiazole is not formed when 2-chlorobenzothiazole is refluxed with disubstituted thioureas in alcohol for one hour. Neither is it formed when such solutions are refluxed for periods up to 40 hours, nor when disubstituted thioureas are refluxed for several hours in an excess of 2-chlorobenzothiazole (b. p., 247°). With exception of the latter case, when the disubstituted thioureas undergo partial decomposition during the refluxing at high temperatures, the greater part of the starting materials may be recovered unchanged.

In one instance, a stable addition compound was formed between 2-chlorobenzothiazole and a disubstituted thiourea. Seventeen grams of 2-chlorobenzothiazole and 15 g. of *N,N'-o*-phenylenethiourea (thiobenzimidazolone) were refluxed for one hour in 100 cc. of alcohol. The insoluble gray solid was filtered off and washed with alcohol and benzene. It weighed 27.5 g. (86% yield) softened at 220-2° and melted with decomposition at 233-4°. This substance is insoluble in ordinary organic solvents and has been shown by analysis to consist of a simple addition compound.

Anal. Calc'd for $C_{14}H_{10}ClN_3S_2$: N, 13.1; S, 20.0; Cl, 11.1.
Found: " 13.0; " 19.9; " 11.9.

Trisubstituted thioureas.—No reactions occurred when the trisubstituted thioureas listed in Table I were refluxed with 2-chlorobenzothiazole in alcohol, and the starting materials were recovered.

Reactions of 2-chloro-6-nitrobenzothiazole.—Ten and six-tenths grams of 2-chloro-6-nitrobenzothiazole and 3.8 g. of thiourea were refluxed for one hour in 75 cc. of

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[16] HOFFMAN, *Ber.*, **18**, 3221 (1885).

[17] HOFFMAN, *ibid.*, **18**, 3223 (1885).

alcohol. After refluxing for a few minutes, the solution assumed an orange-yellow color and crystals of 2-mercapto-6-nitrobenzothiazole having a like color separated. The reaction mixture was cooled; the crystals were separated by filtration, washed with cold alcohol, and dried. The filtrate and washings were poured into 500 cc. of ice water, and the yellow crystals which separated were isolated as described above. Thus, 9.9 g. was obtained by direct crystallization from the reaction mixture, and 0.6 g. by dilution with water, or a total of 10.5 g. which represents a quantitative yield; m. p., 225–7°.

Anal. Calc'd for $C_7H_4N_2O_2S_2$: N, 13.2; S, 30.3.
Found: " 13.2; " 30.1.

Data contained in Table II represent results obtained when 1/20 mole each of 2-chloro-6-nitrobenzothiazole and the indicated thiourea were refluxed in 75 cc. of alcohol for the given periods of time. As in Table I, the melting points given are those of the crude products.

Monosubstituted thioureas.—The procedure used in isolating 2-mercapto-6-nitrobenzothiazole from reactions involving monosubstituted thioureas differed from that described above only in that the product obtained by dilution with water was extracted with an excess of 10% sodium hydroxide and filtered, and the mercaptan was precipitated by addition of dilute hydrochloric acid. The rate of formation of 2-mercapto-6-nitrobenzothiazole from 2-chloro-6-nitrobenzothiazole and monosubstituted thioureas is noticeably slower than when thiourea is used, as judged by the elapsed time between the beginning of refluxing and the appearance of the mercaptan in the form of insoluble orange-yellow crystals. This difference in rate of reaction becomes quite apparent when a reaction with a monosubstituted thiourea and one employing thiourea are carried out simultaneously.

TABLE II

REACTIONS WITH 2-CHLORO-6-NITROBENZOTHIAZOLE

THIOUREA	TIME, (HRS.)	YIELD, %	M.P., °C.
Thiourea	1	100	255–7
Allyl-	1	94	248–50
Phenyl-	1	92	249–52
o-Tolyl-	1	93	254–6
s-Diphenyl-	12.5	49	225–30
s-Dicyclohexyl-	1	94	251–3
N,*N*-Dimethyl-*N'*-phenyl-	50	0	

Disubstituted thioureas.—Upon completion of refluxing, the solid products isolated as previously described were combined, and the mercaptan extracted in 10% sodium hydroxide solution. As shown in Table II, the reaction with *s*-diphenylthiourea was very slow, while that with *s*-dicyclohexylthiourea appeared to proceed at a rate only slightly lower than similar reactions with monosubstituted thioureas. The alkali-insoluble material from the reaction involving *s*-dicyclohexylthiourea was boiled with toluene to remove soluble impurities. There remained 4.0 g. of a grayish-white solid which after recrystallization from alcohol consisted of white crystals of *s*-dicyclohexylurea; m.p., 229–30°.

Anal. Calc'd for $C_{13}H_{24}N_2O$: N, 12.5. Found: N, 12.1.

The formation of this substance may be readily explained. When a disubstituted thiourea reacts with an organic halide in the manner described in the foregoing pages, there is formed not cyanamide, but rather the disubstituted diimide, RN:C:NR. This, in turn, may react with any water present in the hot alcoholic reaction medium to form the corresponding urea.

It is significant that the crude products from reactions involving disubstituted thioureas had a marked odor of mustard oils. The appearance of such products is indicative of decomposition of the thioureas during refluxing.

Trisubstituted thioureas.—In the only case studied, namely that of *N*,*N*-dimethyl-*N*'-phenylthiourea, we have been unable to identify 2-mercapto-6-nitrobenzothiazole as a product of the reaction. However, by extraction with aqueous sodium hydroxide and acidification of the clear alkaline extract, there was isolated 8.4 g. of a pale tan solid, m.p., 80–110°. Repeated recrystallization of this material from glacial acetic acid (in an effort to isolate the mercaptan) resulted in a progressive lowering of the melting point to a value of 67–9° after the fourth crystallization. This behavior is indicative of a progressive acetylation. The final product was small in amount and was found by analysis to contain 8.5% nitrogen and 17.6% sulfur. This product has not been identified.

The alkali-insoluble fraction (10.0 g.) was recrystallized from toluene. It consisted mainly of bright yellow crystals of 2-dimethylamino-6-nitrobenzothiazole; m.p., 197.5–199°.

Anal. Calc'd for $C_9H_9N_3O_2S$: N, 18.8; S, 14.3.
Found: " 18.4; " 14.5.

During the prolonged refluxing to which the reactants concerned were subjected (50 hours) the trisubstituted thiourea was apparently decomposed, and dimethylamine was thereby liberated. The free amine must then have reacted with the 2-chloro-6-nitrobenzothiazole with elimination of hydrogen chloride to form the 2-dimethylamino derivative.

DISCUSSION

The foregoing data indicate that there is a definite gradation in the reactivity of thiourea and its substituted derivatives toward 2-chlorobenzothiazoles, the corresponding mercaptans being produced most readily by thiourea, more slowly and less completely by monosubstituted thioureas, and slowly if at all by disubstituted compounds. In no case was a reaction of this type observed with a trisubstituted thiourea.

Since it is logical to assume that the primary reaction consists in the formation of an addition compound, the efficiency of a given thiourea may be thought of in terms of the ease with which it forms such addition compounds. Goldschmidt and co-workers[8, 9] have studied the rates of formation of addition compounds between methyl and ethyl iodides and thiourea, its mono- and disubstituted derivatives. Largely from conductivity data they have established the following order of decreasing reactivity,

$$\text{thiourea} > \text{mono-} > \text{di-} > \text{trisubstituted},$$

this order being identical with that found in the present study.

The difference in yields of mercaptans obtained with the various types of thioureas cannot be attributed to differences in the techniques employed in the isolation of the products. In each instance the method used insured the complete removal of any mercaptan formed in the reaction. The method employing alkali extraction might conceivably result in high yields in terms of mercaptan in the case of reactions with 2-chloro-6-nitrobenzothiazole, since any unchanged chloro compound would probably be at least partially converted to 2-hydroxy-6-nitrobenzothiazole by the action of sodium hydroxide. The hydroxy compound would, in this event, appear along with the mercaptan upon acidification of the aqueous solution of the combined sodium salts. However, no such complication was encountered in the present studies, since, when there appeared to be any reaction whatever, sufficient time was allowed for the complete utilization of the chloro compound.

The markedly greater reactivity of 2-chloro-6-nitrobenzothiazole as compared with 2-chlorobenzothiazole, as evidenced by results obtained in reactions with disubstituted thioureas, and by relative yields of mercaptans with monosubstituted thioureas, provides further evidence as to the effect of a nitro group in the 6-position upon the lability of the halogen atom in the 2-position in the thiazole ring.[18] Another factor concerned in the apparent reactivities of the two halides lies in the relative solubilities of the corresponding mercaptans in alcohol. The nitro-substituted mercaptan is almost insoluble in hot alcohol whereas 2-mercaptobenzothiazole is very soluble under the same conditions and appreciably soluble at room temperature. Hence, should the reactions in question involve an equilibrium situation, those producing mercaptans of low solubility would be expected to occur the more readily.

Mercaptobenzothiazoles produced by the interaction of 2-chlorobenzothiazoles and thiourea are of a degree of purity limited only by the purity of the starting materials. 2-Mercaptobenzothiazole prepared by the usual method[15] possesses a yellow color which is extremely difficult if not impossible to remove by the ordinary methods of purification. However, when this material is prepared as described in this paper, it is perfectly white and of a high degree of purity.

A study of reactions of halides of the type used in this investigation with thiourea in aqueous media has led to results which seem worthy of further study. Accordingly, these reactions will be described in a later communication.

SUMMARY

1. It has been shown that the interaction of 2-chlorobenzothiazoles and thiourea leads to the formation of high yields of the corresponding mercaptans, and a mechanism for the reaction has been suggested.

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[18] *Cf.* Teppema and Sebrell, *J. Am. Chem. Soc.*, **49**, 1780–1 (1927).

2. A brief study of the relative reactivities of a number of substituted thioureas has indicated the following order of decreasing reactivity,

thiourea > mono- > di- > trisubstituted.

3. Methods for the preparation of 2-chlorobenzothiazoles and of s-dicyclohexylthiourea have been described.

4. The reaction between 1,1′-methylenebispiperidine and sulfur has been shown to result in the formation of piperidine pentamethylenedithiocarbamate.

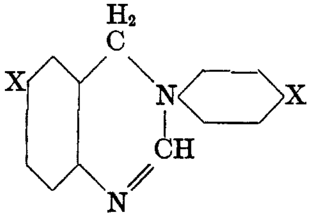
[Contribution from the John Harrison Laboratory of Chemistry of the University of Pennsylvania]

CONDENSATIONS OF AROMATIC AMINES WITH FORMALDEHYDE IN MEDIA CONTAINING ACID. VI. THE USE OF FORMIC ACID IN THE PREPARATION OF 3,6-DISUBSTITUTED DIHYDROQUINAZOLINES FROM PARA-SUBSTITUTED AMINES, AND FROM THEIR BIS(ARYLAMINO)-METHANES AND SCHIFF BASES

E. C. WAGNER

Received March 2, 1937

Quinazolines of the type shown (I) have been obtained from para-substituted arylamines by condensation with formaldehyde in aqueous acid solution[1], and by treatment of *N*-(2-aminobenzyl)-arylamines with formic acid or ethyl orthoformate[2]. The first procedure gives small yields of dihydroquinazoline as one of several products whose separation may be troublesome and wasteful. The second method, involving a familiar ring-closure, appears to be dependable but presents the disadvantage that the required aminobenzylarylamines are obtainable only by a slow and cumbersome method[3]. These considerations, and others discussed below, made it appear that a satisfactory method for the preparation of dihydroquinazolines (I) might be based upon a combination of the two methods, *i.e.*, by starting with the amine and formaldehyde, or with other precursors of the aminobenzylarylamine and by operating under conditions favorable to formation of the aminobenzylarylamine, and in presence of formic acid to ensure the final ring-closure. This paper



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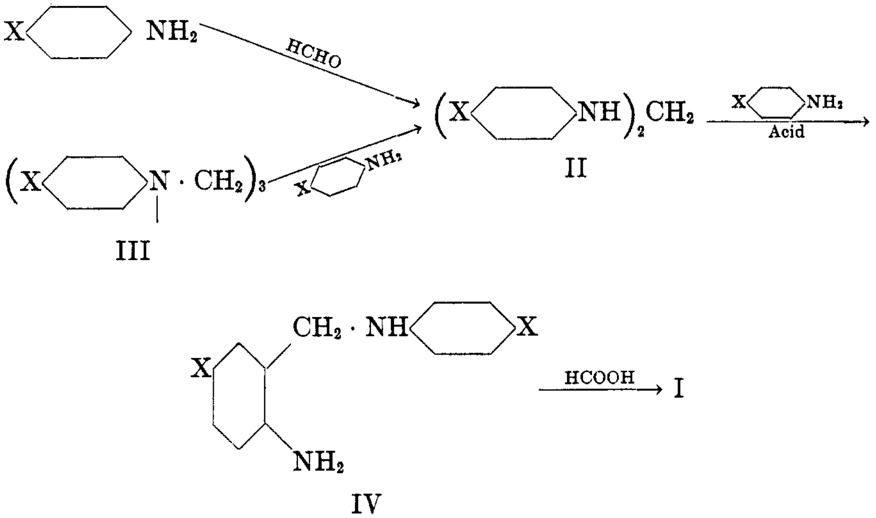
[1] See the preceding paper of this series [Wagner and Eisner, *J. Am. Chem. Soc.*, **59**, 879 (1937)] for recent work and literature.

[2] v. Walther and Bamberg, *J. prakt. Chem.*, [2], **73**, 209 (1906).

[3] *Ger. Pat.*, **105**, 797; *Friedl.* **5**, 84.

describes experiments in which this possibility was tested, and which showed that dihydroquinazolines may be obtained conveniently from para-substituted arylamines, their methylenebisarylamines or their trimeric Schiff bases, as shown in the reaction scheme.



The compounds used as starting materials were *p*-toluidine, *p*-anisidine, *p*-phenetidine, *p*-chloroaniline, and *p*-bromoaniline, and corresponding methylenediarylamines (II) and Schiff bases (III). The final step has been realized independently for the bases (IV) obtained from *p*-toluidine[2], *p*-chloroaniline, and *p*-bromoaniline[1].

1. Dihydroquinazolines from para-substituted amines.—With the amine and formaldehyde as initial reactants, yielding first the methylenebisarylamine (II), conversion of the last-named to the aminobenzylarylamine (IV) requires acid and amine, usually provided as amine hydrochloride. It was found that the formic acid added to effect ring-closure with IV would serve also as the acid needed for formation of the latter from II; the needed amine was supplied presumably by hydrolysis of some II by the aqueous acid. After the reaction considerable amine was present as the formyl derivative, and it is likely that this or other formyl derivative was instrumental in the ring-closure[4].

Interaction of amine, formaldehyde and formic acid at water-bath temperature yielded in each case the expected dihydroquinazoline, present in the residue left after the reaction mixture was made strongly alkaline

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[4] See *e.g.*, PAAL AND BUSCH, *Ber.*, **22**, 2686 (1889); *Ger. Pat.* **51**, 712, *Friedl.* **2**, 125; NIEMENTOWSKI, *J. prakt. Chem.*, [2] **51**, 564 (1895); KULISCH, *Chem. Zentr.* **1899**, I, 847.

(to decompose formylamine) and steam-distilled. Yields averaged 20 to 30 per cent., except in the case of *p*-bromoaniline, which gave a 10 per cent. yield. Results appear in Table I.

The steam-volatile material was found, in the cases examined, to consist of the original amine and its methyl and dimethyl derivatives. Methylation is to be expected in such reactions[5], but in these experiments was due in part to the reducing action of formic acid[6], as shown by the characteristic effervescence and by the extent of the methylation.

2. Dihydroquinazolines from methylenediarylamines.—Cairncross and Bogert[7] reported a single trial of this method, using the ethyl ester of methylene-N,N′-bis(*p*-aminobenzoic acid), but under strongly hydrolyzing conditions, and obtained a 9 per cent. yield of the corresponding dihydroquinazoline. In the present study the procedure used by Cairncross and Bogert was not tested with other methylenebisarylamines, for a consideration of the reactions involved indicated the advisability of different conditions.

TABLE I

PREPARATION OF DIHYDROQUINAZOLINES FROM PARA-SUBSTITUTED AMINES, FORMALDEHYDE, AND FORMIC ACID

AMINE	AMINE, G.	HCOOH, EQUIV.[a]	HCHO, EQUIV.	STEAM-VOLATILE, G.	DIHYDROQUINAZOLINE	
					G.	%[b]
p-Toluidine	25	2.1	0.5	12.7	5.7	20.6
	25[c]	2.1	1.0	6.0	7.2	26.3
	25	3.4	0.5	11.8	6.3	22.8
	25	1.3 + 1.7	0.5	9.6	6.8	24.7
p-Anisidine	12.3[d]	1 + 2	0.6	0.7	3.0	22.0
p-Phenetidine	10	2.1	0.6	4.0	2.4	22.2
	10	2.1	1.1	3.9	3.3	30.5
p-Chloroaniline	10.6	1 + 2	0.5	5.1	2.4	20.9
p-Bromoaniline	17.2	1 + 2	1.0	6.8	1.9[e]	10.4

[a] When two quantities are given the formic acid was added in two stages.

[b] Yields are calculated on ratio 2 amine: 1 quinazoline.

[c] Average of 4 experiments.

[d] Average of 2 experiments.

[e] Product was isolated through the recrystallized hydrochloride, probably with considerable loss. This experiment, gave also 1.5 g. of the base of m.p. 134–5° previously reported (Ref. 1) as one product of the condensation of *p*-bromoaniline and formaldehyde in dilute hydrochloric acid solution.

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[5] MAFFEI *et al.*, Ref. I; EISNER AND WAGNER, *J. Am. Chem. Soc.*, **56**, 1938 (1934).

[6] CLARKE, GILLESPIE, AND WEISSHAUS, *J. Am. Chem. Soc.*, **55**, 4571 (1933); *cf.* EISNER AND WAGNER, *ibid.*, **56**, 1941 (1934); footnote.

[7] CAIRNCROSS AND BOGERT, *Coll. Czechoslovak. Chem. Comm.*, **7**, 57 (1936).

The intermediate formation of the aminobenzylarylamine (IV) from the methylenebisarylamine (II) requires amine, amine-salt and conditions not strongly hydrolytic. In preliminary experiments methylenebis(*p*-toluidine) and *p*-toluidine, with formic acid somewhat more than equivalent to the latter, were warmed together to promote formation of *o*-amino-*m*-xylyl-*p*-toluidine (IV); a moderate excess of formic acid was added and the heating was continued. Yields of dihydroquinazoline averaged 21.7 per cent.

At this stage of the work there became available the results of Simons' study[8] of the reactions in the system including methylenebisarylamine and amine salt, found to yield the dihydroquinazoline and also its precursors (IV and the tetrahydroquinazoline), as well as free amine, either split out during the reactions or left residually. All the other compounds present are convertible to dihydroquinazoline: aminobenzylarylamine by formic acid, free amine by joint action of formaldehyde and formic acid, and (as shown in the experimental part) tetrahydroquinazoline by action of formic acid. The procedure developed to take advantage of these apparent possibilities for obtaining the dihydroquinazoline involved heating methylenebisarylamine and amine hydrochloride in the molecular ratio of five to one for an hour on the water-bath, addition of some formaldehyde and a moderate excess of formic acid, and continuation of the heating. Yields of the dihydroquinazolines ranged from 27 to 38 per cent. Results are presented in Table II.

TABLE II

PREPARATION OF DIHYDROQUINAZOLINES FROM METHYLENEBISARYLAMINES

METHYLENEBISARYLAMINE	AMINE, G.	AMINE-HCL, EQUIV.	HCHO, EQUIV.	HCOOH, EQUIV.	STEAM-VOLATILE, G.	DIHYDROQUINAZOLINE	
						G.	%[a]
$(CH_3C_6H_4NH)_2CH_2$	11.3	0.2	0.12	4	0.5	3.5	27.0
	11.3	0.2	0.5	4	2.3	3.9	30.0
$(CH_3OC_6H_4NH)_2CH_2$	5.20[b]	0.3	1.2	8	1.2	2.29	36.7
$(C_2H_5OC_6H_4NH)_2CH_2$	5.70	0.3	1.2	8	1.5	2.31	33.7
$(ClC_6H_4NH)_2CH_2$	1.00	0.65	1.7	10	0.17	0.52	37.6
$(BrC_6H_4NH)_2CH_2$	4.00	0.65	2.2	14	0.67	1.72	31.6

[a] Yields are calculated on the assumption that methylenediarylamine and amine hydrochloride are both convertible to dihydroquinazoline.

[b] Average of 2 experiments.

3. Dihydroquinazolines from trimeric Schiff bases.—The method used was based on the preceding, and on consideration of the fact that the

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[8] SIMONS, *J. Am. Chem. Soc.*, **59**, 518 (1937).

initial step is the formation of the methylenediamine, a change which requires presence of free amine:

$$\frac{1}{3}\,(Ar \cdot N \cdot CH_2)_3 + ArNH_2 = ArNH \cdot CH_2 \cdot NHAr.$$

For the first stage of the reaction there was heated a mixture of the Schiff base and free amine in a molar ratio of about one to three, and in presence of amine hydrochloride in amounts well above the minimum found effective by Simons[8]. There were then added formaldehyde and formic acid, and the heating was continued. By this procedure the yields of dihydroquinazolines varied from 22 to 39 per cent. Results appear in Table III.

Methods 2 and 3 gave better yields and less resinous material than the first method, and a smaller proportion of methylated products. The methylenediamines and Schiff bases are readily obtained as starting materials and may be used without careful purification.

TABLE III

PREPARATION OF DIHYDROQUINAZOLINES FROM TRIMERIC SCHIFF BASES

SCHIFF BASE	BASE, G.	AMINE-HCL, EQUIV.[a]	AMIEN, EQUIV.[a]	HCHO, EQUIV.[a]	HCOOH, EQUIV.[a]	STEAM-VOLATILE, G.	DIHYDROQUINAZOLINE	
							G.	%[b]
$(CH_3C_6H_4NCH_2)_3$	1.80	1.4	3	5	30	0.48	1.44	32.6
$(CH_3OC_6H_4NCH_2)_3$	4.50	0.56	3	1.1	18	0.20	2.50	25.4
$(C_2H_5OC_6H_4NCH_2)_3$	5.00	0.58	3.4	2.2	17.6		3.42	29.2
$(ClC_6H_4NCH_2)_3$	5.00	0.51	3.3	2.1	16.3		2.43	21.6
$(BrC_6H_4NCH_2)_3$	2.10	1.3	3.9	6.5	40		2.20	39.1

[a] The equivalencies given are calculated with reference to the trimeric Schiff base, and do not properly suggest the reaction relationships.

[b] Calculations of percentage yields are based on the assumption that all starting materials (Schiff base, amine and amine-HCl) are convertible to dihydroquinazoline.

EXPERIMENTAL

Methylenebisarylamines.—These starting compounds were made from amine and formaldehyde (0.5 equivalent) in presence of ethyl alcohol and potassium hydroxide.[11] The reaction mixture was heated on the water bath for several hours, and was then cooled and saturated with carbon dioxide. Alcohol was added to dissolve the product, which was obtained in several crops by chilling and progressive dilution with water. Methylenebis(*p*-anisidine) could not be recrystallized from either dilute alcohol or ether, as it was recoverable only as trimeric methylene-*p*-anisidine. The exceptional instability of this diamine was mentioned by Bischoff and Reinfeld[9]. The other compounds were crystallizable, though with considerable loss. Methylenebis(*p*-toluidine) and methylenebis(*p*-anisidine) have been characterized satisfactorily[11]. Methylenebis(*p*-chloroaniline) was obtained from ligroïn as a nearly

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[9] BISCHOFF, *Ber.*, **31**, 3244 (1898); BISCHOFF AND REINFELD, *ibid.*, **36**, 41 (1903); LEPETIT, *Atti. accad. Lincei*, [5], **26**, I, 172 (1917).

white crystal meal of m.p. 59–60°. Bischoff and Reinfeld[12] reported acceptable analytical results for this compound, but no molecular weight, so this was determined. Calculated for $C_{13}H_{12}N_2Cl_2$: mol. wt., 267. Found: mol. wt. (benzene), 252, 257.

Methylene-N,N′-*bis(p-phenetidine).*—White crystal meal from dilute alcohol or from ligroïn; m.p. 75° obs.

Anal. Calc'd for $C_{17}H_{22}N_2O_2$: C, 71.33; H, 7.76; N, 9.78; mol.wt., 286.

Found: C, 71.55; H, 7.94; N, 9.73, 9.72; mol.wt. (benzene), 293, 297. In molten camphor there were obtained the molecular weight values 218 and 228, indicating fission at 175°.

It appears that the compound of m.p. 89° previously reported by Bischoff[9] to be this diamine was the trimeric Schiff base described below. Bischoff's analytical values for carbon, hydrogen and nitrogen represent a total deficiency of 1.26% and do not well support the diamine formula; the values for hydrogen and nitrogen would be acceptable for the Schiff base. Bischoff reported no molecular-weight determination.

Methylene-N,N′-*bis*(p-*bromoaniline).*—This compound was obtained in white crystalline clumps from dilute alcohol. The yield was 80%, and the m.p. 92° obs.

Anal. Calc'd for $C_{13}H_{12}Br_2N_2$: C, 43.84; H, 3.37; N, 7.86; Br, 44.91; mol. wt., 356.

Found: C, 43.88, 43.93; H, 3.39, 3.50; N, 7.42, 7.51, 7.51; Br, 44.61, 44.76; mol. wt. (benzene), 366, 343. In molten camphor the indicated molecular weight values were 306 and 318, indicating instability at 175°.

Houben and Arnold[10] designated as methylenebis(*p*-bromoaniline) a base of m.p. 181° (decomp.) obtained from *p*-bromoaniline and methyl chloromethyl sulfate. Their complete analysis appears to be unexceptionable, but they report no molecular weight, and the melting point seems to be entirely too high for the compound named. As shown in a previous paper[1] the trimeric Schiff base melts at 169° (turbid), but the possibility that this is the base described by Houben and Arnold appears to be excluded by their analytical values for carbon and bromine.

That the base of m.p. 92° described above is methylenebis(*p*-bromoaniline) may be inferred from the fact that it was obtained in 80% yield from *p*-bromoaniline and 0.5 equivalent of formaldehyde. The identification is supported by the analytical values given, and by the results of the two chemical tests of structure which follow.

(1) Cleavage by reduction.—Cleavage of diamines by strong reduction[13] yields primary and secondary amines as principal products, with not more than a small amount of tertiary amine, the last obtained no doubt as a result of incidental methylation by some formaldehyde formed from the diamine by hydrolysis. The base of m.p. 92°, when split by reduction, gave the results just stated. Three grams of the compound was ground with 6 g. of zinc dust, and the mixture was added in small portions to 40 cc. of concentrated hydrochloric acid kept at 0°. After about an hour the excess zinc was dissolved by gentle warming, and the clear solution was made alkaline and steam-distilled. The steam-volatile oil was examined by the Hinsberg-Kessler procedure. There were obtained 2.05 g. of *N*-(*p*-bromophenyl)benzene-

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[10] Houben and Arnold, *Ber.*, **41**, 1565 (1908).

[11] Eberhardt and Welter, *ibid.*, **27**, 1804 (1894); Bischoff, Ref. 9; Bischoff and Reinfeld, Ref. 9.

[12] Bischoff and Reinfeld, *Ber.*, **36**, 46 (1903).

[13] Miller and Wagner, *J. Am. Chem. Soc.*, **54**, 3698 (1932), and unpublished results.

sulfonamide (m.p. 135° obs.), equivalent to 1.13 g. of *p*-bromoaniline; 0.80 g. of the secondary amine derivative (m.p. 74–75° obs.), equivalent to 0.46 g. of methyl-*p*-bromoaniline; 0.15 g. of dimethyl-*p*-bromoaniline picrate (m.p. 138° obs.), equivalent to 0.07 g. of the tertiary amine.

(*2*) *Conversion to trimeric Schiff base by formaldehyde.*—Treatment of diamines with excess formaldehyde converts them into Schiff bases[14]. The base of m.p. 92° (1.78 g.) was dissolved in alcohol and treated with formaldehyde (5 cc. of 37% formalin). The mixture was allowed to stand for some hours, and water was added to incipient turbidity. The mixture on further standing deposited an amorphous material, viscous at first but later solid which was separated and crystallized from dilute alcohol. The product (0.68 g.) was crystallized from ligroïn. It melted at 166° (turbid); a mixture with trimeric methylene-*p*-bromoaniline melted at 165.5° obs. (turbid).

The foregoing evidence establishes the base of m.p. 92° as methylenebis(*p*-bromoaniline).

*Methylene-*p*-phenetidine.*—This Schiff base was made by the general method[13]. The yield was 88% crude, and 69% after crystallization from ligroïn. Like the corresponding compound from *p*-bromoaniline[1], this base crystallized in long flexible needles, much matted; m.p. 90° obs.

Anal. Calc'd for $(C_9H_{11}NO)_3$: C, 72.48; H, 7.38; N, 9.39; mol. wt., 450.

Found: C, 72.64, 72.48; H, 7.51, 7.29; N, 9.23, 9.31; mol. wt. (benzene), 435, 450. In molten camphor there were obtained molecular weight values of 291 and 288, indicating partial depolymerization at 175°.

The designation of this compound as cyclic trimeric methylene-*p*-phenetidine was supported by the results of cleavage[15]. Reduction of 2.00 g. of the base by zinc dust and cold concentrated hydrochloric acid gave 1.40 g. of steam-volatile oil, which by the Hinsberg procedure yielded derivatives of primary and secondary amines, and 0.19 g. of a tertiary amine of m.p. 35°. This was found by mixture melting point test to be identical with dimethyl-*p*-bromoaniline (m.p. 35°) made by methylation of *p*-bromoaniline with methyl sulfate. The picrates (m.p. 141° obs.) likewise were shown to be identical.

Preparation of Dihydroquinazolines

Isolation procedure.—The manner in which the reaction mixtures were worked up was fairly uniform for all the experiments. When the heating period was at an end the mixture was made strongly alkaline with sodium hydroxide and was submitted to steam-distillation. The basic products in the distillate were in some experiments taken up in ether, and the extract was dried with sodium sulfate, was filtered into a tared beaker, and the mixture of bases was weighed after evaporation of the ether. In some cases the mixture was examined by the Hinsberg-Kessler procedure to obtain evidence of methylation.

The residue not volatile with steam was generally yellow and liquid or soft while hot, but became solid on cooling. It was removed, air-dried, and then extracted with ether to remove the sticky, resinous material which made unsatisfactory the direct crystallization of the dihydroquinazoline after dissolving the mass in alcohol or ligroïn. The dihydroquinazolines considered in this paper are very slightly soluble in cold ether. The simpler extraction procedure was to cover the solid with ether in a small beaker and to press and disintegrate the mass by manipulation with

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[14] Ingold and Piggott, *J. Chem. Soc.*, **123**, 2745 (1923).

[15] Wagner, *J. Am. Chem. Soc.*, **54**, 660 (1932); Miller and Wagner, Ref. 13.

a glass rod with flattened end. As the resins dissolved the dihydroquinazoline remained as a finely granular residue. After chilling of the beaker in ice, the solid was collected in a small Buchner funnel, and beaker and product were washed with small portions of chilled ether. Alternatively the crude residue from the steam distillation was extracted with ether in a Soxhlet apparatus. Extraction of the dihydroquinazoline was slow, but the product crystallized out in large part in the flask. The operation was checked at a time when nearly all the ether was in the extraction chamber, with only enough in the flask to hold the resins in solution. The crystals were filtered off and washed sparingly with chilled ether. The first procedure was much the more rapid. The crude dihydroquinazolines isolated in these ways were in many experiments white or nearly so, and practically pure. They were recrystallized from hot alcohol suitably diluted.

The quantity of resinous material was greatest in experiments in which amine was taken as starting material, and in some cases represented a large part of the original amine. The resins were examined for isolable compounds in several experiments, but with little success. They appeared to be mixtures of bases, some of moderate molecular weights and others gluey and intractable. The resins dissolved in hot dilute hydrochloric acid, and on chilling the solution or on adding excess of concentrated hydrochloric acid precipitates of hydrochlorides were obtained. In alcohol solutions of the resins picric acid produced heavy precipitates of picrate mixtures of indefinite melting points. In several experiments with *p*-toluidine various treatments of the resinous material yielded three distinct picrates, of m.p. 210°, 203° and 187° obs., not identified. The last was not identical with the picrates of *p*-toluidine or Tröger's base, both of which melt near 187°.

1. Dihydroquinazolines from amines, formaldehyde, and formic acid.—The amine was treated with 0.5 to 1 equivalent of 37% formalin, and about 2 equivalents of 90% formic acid was added while the mixture was cooled under the tap. The deep red solution was heated for several hours on the water-bath. A more or less brisk effervescence, indicative of methylation[6] was sustained for a time. In some experiments the amine was first treated with 1 equivalent of formic acid and 0.5 to 1 equivalent of formaldehyde, and the mixture was heated, this procedure being designed to favor formation of the diamine and then the aminobenzylarylamine. There were then added more formaldehyde and an excess of formic acid, and the heating was continued. This procedure showed no superiority over the first. Results of trials by these methods appear in Table I.

2. Dihydroquinazolines from methylenebisarylamines.—The methylenebisarylamine was mixed with one-fifth equivalent or more of amine hydrochloride and the mixture was heated on the water bath for an hour. A quantity of formaldehyde nearly equivalent to the amine and amine salt taken initially was added, followed by formic acid in excess, and the mixture was heated further for about two hours. Results of the trials are given in Table II.

3. Dihydroquinazolines from trimeric Schiff bases.—A mixture of the methylenearylamine with 3 equivalents of the corresponding amine and one-half equivalent or more of the amine hydrochloride was heated for an hour on the water bath. The preparation was completed as in the preceding method, by addition of formaldehyde and formic acid, followed by further heating. Results by this method appear in Table III.

*3-(*p*-Anisyl)-6-methoxy-3,4-dihydroquinazoline.*—This compound, not previously described, was obtained in colorless plates of m.p. 136° obs., or 138° corr.

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.44; CH_3O, 23.1; mol. wt. 268.
Found: C, 71.68, 71.69; H, 5.83, 6.04: N, 10.42, 10.49; CH_3O, 22.9; mol. wt. (camphor), 265, 271.

Picrate.—An alcohol solution of 0.50 g. of the base was mixed with a saturated solution of 0.90 g. of picric acid in cold alcohol (0.86 g. is two equivalents). The picrate weighed 0.94 g., a theoretical yield of the 1:1 picrate. Crystallization from alcohol gave 0.77 g. of pure picrate, of m.p. 209° obs., or 214° corr.

3-(p-Anisyl)-6-methoxy-1,2,3,4-tetrahydroquinazoline.—This compound was prepared from the dihydroquinazoline by hydrogenation using sodium and alcohol: 2.04 g. of dihydroquinazoline gave 1.18 g. (58%) of tetrahydroquinazoline. After recrystallization from dilute alcohol the compound melted at 133° obs., or 135° corr. This is close to the melting-point of the dihydroquinazoline, but a mixture of the two melted around 122°.

Anal. Calc'd for $C_{16}H_{18}N_2O_2$: N, 10.37. Found: N, 10.34, 10.30, 10.26.

Picrate of 3-(p-phenetyl)-6-ethoxy-3,4-dihydroquinazoline.—This derivative was made as outlined for the anisyl compound: 0.25 g. of the dihydroquinazoline and 0.43 g. of picric acid (more than 2 equivalents) were separately dissolved in the least possible alcohol, and the solutions were mixed. The picrate weighed 0.44 g., a 99.2% yield of the 1:1 picrate. After crystallization from alcohol the compound melted at 182° obs., or 185.7° corr.

Conversion of 3-(p-tolyl)-6-methyl-1,2,3,4-tetrahydroquinazoline to the dihydroquinazoline by action of formic acid.—The tetrahydroquinazoline (3.5 g.) and formic acid (5.5 cc. of 90%) were sealed in a tube, and the mixture was heated for two hours at 150°. After suitable treatment there was isolated 2.7 g. (79%) of 3-(*p*-tolyl)-6-methyl-3,4-dihydroquinazoline; m.p. 156–7°, identified by mixture melting point test. By action of formic acid at water-bath temperature the tetrahydroquinazoline was less extensively attacked, only a small amount of the dihydroquinazoline being obtained as picrate.

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SUMMARY

Methods are described for preparation of 3,6-disubstituted dihydroquinazolines from para-substituted amines, and from their methylenebisarylamines and trimeric Schiff bases, with the aid of formic acid. Preparation from the amines gave in general smaller yields, more resinous material, and a higher proportion of methylated products, than by the other two methods. With the methylenebisarylamines or trimeric Schiff bases as starting materials the yields ranged from 25 to 39 per cent., calculated on the assumption that all bases taken were available for formation of

dihydroquinazoline. By proper selection of the starting compound and of experimental conditions yields of over 30 per cent. of the dihydroquinazolines can be assured.

Compounds not previously reported which are described in the experimental section are methylenebis(*p*-phenetidine) (m.p. 75°; the compound hitherto designated as methylenebis(*p*-phenetidine)[9] was found to be the trimeric Schiff base, m.p. 90°), methylene-*N*,*N'*-bis(*p*-bromoaniline) (m.p. 92°; this name was incorrectly assigned by Houben and Arnold[10] to a compound of m.p. 181°), trimeric methylene-*p*-phenetidine (m.p. 90°), 3-(*p*-anisyl)-6-methoxy-3,4-dihydroquinazoline (m.p. 138°), and its picrate (m.p. 214°), 3-(*p*-anisyl)-6-methoxyl-1,2,3,4-tetrahydroquinazoline (m.p. 135°), and the picrate of 2-(*p*-phenetyl)-6-ethoxy-3,4-dihydroquinazoline (m.p. 185.7°).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

A PROPOSED MECHANISM FOR MERCURY CATALYSIS IN ACETYLENE ADDITION REACTIONS*

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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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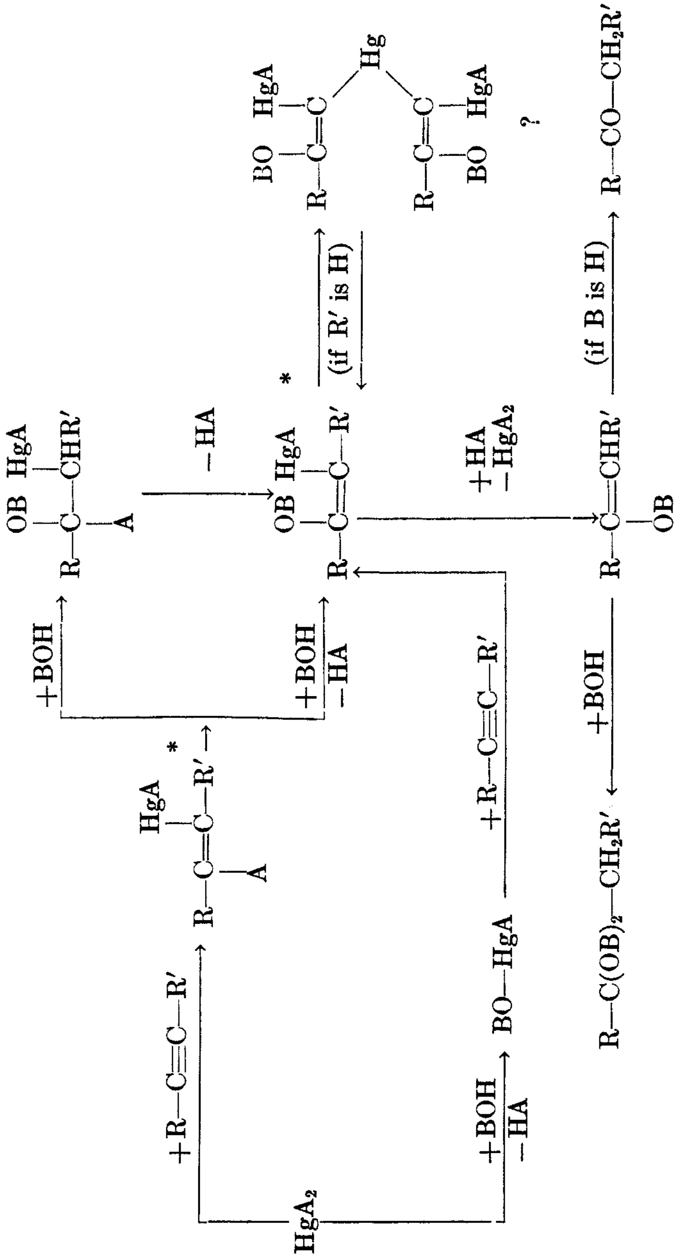
[3] VAUGHN, *Proc. Ind. Acad. Sci.*, **42**, 129 (1933).

[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 DABNEY CHEMICAL LABORATORY OF THE UNIVERSITY OF TENNESSEE]

PARACHOR STUDIES AT VARIOUS TEMPERATURES

C. A. BUEHLER, THOMAS S. GARDNER, AND MILTON L. CLEMENS, JR.

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The parachor, P, as derived by Sugden, has been stated in the form

$$P = \frac{M\gamma^{\frac{1}{4}}}{D - d},$$

where M is the molecular weight, γ the surface tension, and D and d are the densities of the liquid and vapor respectively at the same temperature.

*The CH_2 group.**—By applying the above formula to hundreds of organic compounds and fixing, as a standard for comparison, the covalent bond at zero, Sugden[1] arrived at an average value of 39.0 for the CH_2 group. This value has been the subject of much discussion ever since. Mumford and Phillips[2], from a study of high-molecular-weight compounds, concluded that the CH_2 group should be given a value of 40.0, Vogel[3], from parachor determinations on the methyl and ethyl esters of *n*-dibasic acids, obtained 40.3, and Desreux[4], from the higher members of the paraffin and normal alkyl fluoride and chloride series, found values which varied but slightly from 39.9. More recently Sugden[5] has been inclined to accept the value of 39.6 for the CH_2 group.

These variations at once detract from the usefulness of the parachor in any quantitative approach to the determination of structure. Although the differences were at first thought to be due to impurities or inaccurate measurements, it now appears that they are of a more fundamental nature. As Desreux pointed out, they doubtless indicate that the atomic parachors are not strictly additive. In fact the CH_2 values of Desreux for the paraffins and alkyl fluorides and chlorides are unique in their constancy.

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* Shortly after the submission of this manuscript Bayliss, *J. Am. Chem. Soc.*, **59**, 444 (1937), by the method of least squares, found the CH_2 value to be 39.92.

[1] SUGDEN, "The Parachor and Valency," George Routledge & Sons, Ltd., London, **1930**, p. 35.

[2] MUMFORD AND PHILLIPS, *J. Chem. Soc.*, **1929**, 2112.

[3] VOGEL, *J. Soc. Chem. Ind.*, **53**, 85 (1934).

[4] DESREUX, *Bull. soc. chim. Belg.*, **44**, 249-287 (1935).

[5] SUGDEN, *J. Chem. Soc.*, **1935**, 1550.

Of the numerous determinations made in this laboratory on purified compounds, those for the acetates in Table I and benzene and its homologues in Table II will illustrate the variation shown in the CH_2 group values even in the same homologous series. To make certain that there was no temperature effect, the determinations were carried out at several temperatures, and from these the mean parachors, to be used in finding the CH_2 values, were obtained. In the acetate series, if the first member be excluded, it is to be noted that the values agree very well with the more recent parachors for the CH_2 group. However, the benzene series not only shows a fluctuation from member to member, but the CH_2 parachors are lower than is to be expected on the basis of the newer determinations. It is apparent from these results, which are typical, that, in using the parachor, it is necessary either to employ a mean value, as Sugden did, or to regard the constant value of Desreux as being normal.

TABLE I

PARACHORS OF THE ACETATES

COMPOUNDS	TEMP., °C.		D	d	γ	PARACHORS			
	Obs.	Corr.				Obs.	Litr.	Calc'd[a]	CH_2
Ethyl acetate	40.0	40.0	0.8744	0.0009	21.16	216.2	215.7[b]	216.0	
	50.0	50.1	0.8615	0.0013	20.10	216.8			
					Mean	216.5			
Propyl acetate	40.0	40.0	0.8638	0.0005	22.39	257.2	257.1[c]	255.0	
	50.0	50.1	0.8529	0.0007	21.20	257.0			
	60.0	60.2	0.8414	0.0009	19.97	256.7			
					Mean	257.0			40.5
n-Butyl acetate	40.0	40.0	0.8579		23.18	296.9		294.0	
	50.0	50.1	0.8480		21.96	296.3			
	60.0	60.2	0.8379	0.0005	20.92	296.5			
					Mean	296.6			39.6
n-Amyl acetate	40.0	40.0	0.8541		23.65	335.9		333.0	
	60.0	60.2	0.8342		21.68	336.6			
	70.0	70.3	0.8250		20.59	336.0			
	100.0	100.9	0.7943	0.0010	17.70	336.4			
					Mean	336.2			39.6

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[a] In all calculated parachors, unless otherwise noted, the original atomic and structural parachors of SUGDEN, ref. 1, p. 38, have been used.

[b] *Brit. Assoc. Advancement Sci. Rep.*, 265–83 (1932).

[c] SUGDEN, *J. Chem. Soc.*, **125**, 1183 (1924).

The temperature effect and the coördinate link.—In the original studies of

Sugden[6] on the influence of temperature on the parachor, a small but steady rise, to which no significance was attached, was recorded for the coördinate compounds, dimethyl sulfate, diethyl sulfate and triethyl phosphate. Later similar differences were observed in this laboratory with phenol-amines under conditions which appeared to exclude dissociation.[7] More recently Ray[8] has reported a like effect with azoxy compounds, which are now represented with the oxygen attached by a coördinate bond.

TABLE II

PARACHORS OF BENZENE HYDROCARBONS

COMPOUNDS	TEMP., °C.		D	d	γ	PARACHORS			
	Obs.	Corr.				Obs.	Litr.[a]	Calc'd	CH_2[b]
Benzene	40.0	40.0	0.8530	0.0007	26.41	207.6	205.7	207.1	
	50.0	50.1	0.8421	0.0010	24.97	207.4			
					Mean	207.5			
Toluene	50.0	50.1	0.8361	0.0005	24.94	246.2	245.0	246.1	
	60.0	60.2	0.8271	0.0006	24.01	246.6			
	70.0	70.3	0.8158	0.0008	22.76	246.7			
					Mean	246.5			39.0
Ethylbenzene	40.0	40.0	0.8489		27.20	285.4	284.0	285.1	
	60.0	60.2	0.8302		24.80	285.1			
	100.0	100.9	0.7935	0.0010	20.71	285.6			
					Mean	285.4			38.9
Butylbenzene	40.0	40.0	0.8554		28.10	361.0	361.7	363.1	
	60.0	60.2	0.8390		25.81	360.3			
	70.0	70.3	0.8306		24.83	360.4			
	100.0	100.9	0.8036	0.0005	21.84	361.0			
					Mean	360.7			(2×)37.7
Amylbenzene	40.0	40.0	0.8564		28.47	399.5	402.0	402.1	
	60.0	60.2	0.8405		26.56	400.1			
	70.0	70.3	0.8328		25.53	399.8			
	100.0	100.9	0.8084		22.74	400.1			
					Mean	399.1			39.2

[a] *Brit. Assoc. Advancement Sci. Rep.*, 265–83 (1932).

[b] With no details, DESREUX, ref. 4, states that the CH_2 group varies from 38.58 to 40.32 in this homologous series.

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[6] SUGDEN, *ibid.*, **127**, 1539 (1925).

[7] BUEHLER AND SPREEN, *J. Am. Chem. Soc.*, **56**, 2061 (1934).

[8] RAY, *J. Indian Chem. Soc.*, **13**, 194 (1936).

TABLE III
Parachors of Coördinate Compounds

COMPOUNDS	TEMP., °C.		D	d	γ	k[a]	PARACHORS			P (OBS.)−P (CALC.)
	Obs.	Corr.					Obs.	Litr.	Calc'd[b]	
Ethyl nitrate	30.0	30.0	1.0928	0.0005	26.52	1.73	189.2	189.6[c]	190.8	−1.6
	40.0	40.0	1.0784	0.0007	25.30		189.5			−1.3
	50.0	50.1	1.0642	0.0009	24.57		190.6			−0.2
	60.0	60.2	1.0479	0.0013	23.15		190.8			0.0
Ethyl sulfite	40.0	40.0	1.0605		27.15	2.07	297.3	299.7[d]	298.4	−1.1
	70.0	70.3	1.0262		24.56		299.7			1.3
	100.0	100.9	0.9890	0.0008	21.55		301.2			2.8
	130.0	130.4	0.9521	0.0018	18.51		301.5			3.1
Ethyl sulfate	40.0	40.0	1.1563		31.28	1.90	315.3	313.8[d]	318.4	−3.1
	70.0	70.3	1.1239		28.66		317.3			−1.1
	100.0	100.9	1.0883		26.13		320.2			1.8
	130.0	130.4	1.0561	0.0006	23.29		320.8			2.4
Benzenesulfonyl chloride	40.0	40.0	1.3556		40.66	2.19	328.9		332.5	−3.6
	70.0	70.3	1.3242		37.48		329.9			−2.6
	100.0	100.9	1.2905		34.67		332.0			−0.5
	130.0	130.4	1.2583		31.38		332.1			−0.4
Methyl *p*-toluenesulfonate	40.0	40.0	1.2087		41.10	2.05	389.9		393.3	−3.4
	70.0	70.3	1.1823		38.63		392.5			−0.8
	100.0	100.9	1.1552		35.56		393.5			0.2
	130.0	130.4	1.1282		33.11		395.8			2.5
p-Toluenesulfonyl chloride	100.0	100.9	1.2336		33.26	2.08	371.0	367.8[e]	371.5	−0.5
	130.0	130.4	1.2051		30.64		372.0			0.5
	150.0	150.4	1.1837		28.88		373.2			1.7
	175.0	174.8	1.1526		26.61		375.5			4.0
Sulfuryl chloride	30.0	30.0	1.6443	0.0013	32.53	1.99	196.2	193.3[d]	196.8	−0.6
	40.0	40.0	1.6218	0.0018	31.08		196.7			−0.1
	50.0	50.1	1.5899	0.0025	29.75		198.6			1.8

[a] Ramsay-Shields-Eötvös constant.

[b] Sugden's original value of −1.6 for the coördinate bond has not been included.

[c] Sugden, *J. Chem. Soc.*, **125**, 1186 (1924).

[d] Sugden, Reed, and Wilkins, *ibid.*, **127**, 1526 (1925).

[e] Freiman and Sugden, *ibid.*, **1928**, 264.

Because of these irregularities it seemed of interest to study the effect of temperature more fully. Coördinate compounds were chosen as one type since some uncertainty has existed over the parachor value for the coördinate bond in these compounds. Sugden[9] originally obtained a mean of −1.6 from a series of widely varying values for this bond. In more recent years the same investigator[5] has advanced a value of 0 in agreement with that of the normal covalent bond.

The parachors as found for the purified coördinate compounds are given in Table III. It is apparent that the values are not constant over any considerable range of temperature. At the lower temperatures, as compared to Sugden's calculated parachors, there is a negative anomaly which usually becomes positive at higher temperatures. Under the circumstances it appears that we can only arrive at an approximate value for the coördinate bond in these compounds. Since zero values have been obtained in all the compounds investigated, save one, this value may be accepted as an approximation. It is of interest to point out that this variation with temperature, at least for the compounds studied, will permit a distinction to be made between the coördinate and the normal covalent bond.

Although the parachor is constant for many liquids regardless of the temperature, it does exhibit, as a rule, a steady increase with temperature for associated liquids. Because of this there has been a tendency to attribute such temperature variations to association. In the present instance such an explanation will not suffice. The compounds studied do not possess the characteristics of associated liquids; in addition, although the validity of the Ramsay-Shields-Eötvös constant, k, in Table III is open to question, it is interesting to note that most of these compounds give values near 2.12 in agreement with the great majority of non-associated liquids.

The temperature effect and the hydrogen bridge.—Sidgwick and Bayliss[10] have determined the parachors of certain chelate compounds and their isomers. Assuming the parachor to be uninfluenced by temperature, these investigators found the value for the link of the hydrogen bridge used in closing the chelate ring to be −14.4 units.

In Table IV we have recorded the parachor results obtained at various temperatures on a series of compounds very similar to those investigated by Sidgwick and Bayliss. The ortho compounds are singular in giving values much lower than their meta and para isomers. If we assume that the former contain a chelate bond, its value varies from −10.8 to −14.2. Thus, whatever the nature of this bond may be, it differs from the coördinate bond in the compounds previously described in having no temperature coefficient and, if we accept Sugden's original parachor values, in being decidedly negative. Of interest, too, is the fact that the chelate, ortho compounds may, as a rule, be distinguished from their meta and

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[9] SUGDEN, ref. 1, p. 116.

[10] SIDGWICK AND BAYLISS, *J. Chem. Soc.*, 2027-34 (1930).

TABLE IV

Parachors of Chelate Compounds and Their Isomers

COMPOUNDS	TEMP., °C.		D	d	γ	PARACHORS			P (OBS.) − P (CALC'D)
	Obs.	Corr.				Obs.	Litr.[a]	Calc'd	
o-Nitrophenol	60.0	60.2	1.2776		40.46	274.5	274.7	289.1[b]	
	100.0	100.9	1.2333		35.34	274.9			
	130.0	130.4	1.2000	0.0005	31.66	275.0			
	150.0	150.4	1.1846	0.0007	30.06	275.0			
					Mean	274.9			−14.2
m-Nitrophenol	130.0	130.4	1.2539		40.96	280.5	283.3	283.0	−1.5
	150.0	150.4	1.2334		39.25	282.2			−0.8
	175.0	174.8	1.2209		38.16	283.1			0.1
	190.0	191.6	1.1950		36.66	286.3			3.3
p-Nitrophenol	130.0	130.4	1.2640		45.36	285.5	283.2	283.0	2.5
	150.0	150.4	1.2462		43.15	286.0			3.0
	175.0	174.8	1.2201		41.31	288.9			5.9
	190.0	191.6	1.2088		40.33	289.9			6.9
Methyl salicylate	30.0	30.0	1.1739		38.82	323.3	322.1	337.0[b]	
	60.0	60.2	1.1436		34.95	323.3			
	100.0	100.9	1.1000		29.94	323.4			
	130.0	130.4	1.0735		27.13	323.3			
					Mean	323.3			−13.7
m-Methyl hydroxybenzoate	100.0	100.4	1.1528		37.77	327.0		330.9	−3.9
	130.0	130.4	1.1271		34.93	328.0			−2.9
	150.0	150.4	1.1077		33.52	330.3			−0.6
	175.0	174.8	1.0850		30.96	330.6			−0.3
	190.0	191.6	1.0711		29.50	330.9			0.0
p-Methyl hydroxybenzoate	150.0	150.4	1.1097		34.61	332.4	331.8	330.9	1.5
	175.0	174.8	1.0893		32.47	333.2			2.3
	190.0	191.6	1.0691		30.42	334.0			3.1
o-Hydroxybenzaldehyde	30.0	30.0	1.1483		41.71	270.1	268.0	281.2[b]	
	60.0	60.2	1.1190		37.83	270.5			
	100.0	100.9	1.0799		32.81	270.5			
	130.0	130.4	1.0495	0.0006	29.23	270.6			
					Mean	270.4			−10.8
m-Hydroxybenzaldehyde	130.0	130.4	1.1179		40.43	275.3	274.5	275.1	0.2
	150.0	150.4	1.1011		38.11	275.4			0.3
	175.0	174.8	1.0780	0.0007	36.23	278.0			2.9
	190.0	191.6	1.0683	0.0009	35.10	278.3			3.2

TABLE IV—*Concluded*

COMPOUNDS	TEMP., °C.		D	d	γ	PARACHORS			P (OBS.)− P (CALC'D)
	Obs.	Corr.				Obs.	Litr.[a]	Calc'd	
p-Hydroxybenzaldehyde	130.0	130.4	1.1171		42.71	279.3[c]	278.2	275.1	4.2
	150.0	150.4	1.1119		41.59	278.8			3.7
	175.0	174.8	1.0914		39.11	279.7			4.6
	190.0	191.6	1.0860		38.38	279.7			4.6
o-Hydroxyacetophenone	30.0	30.0	1.1191		40.87	307.4		320.2[b]	
	60.0	60.2	1.0914		37.15	307.8			
	100.0	100.9	1.0544		32.45	308.0			
	130.0	130.4	1.0259		29.15	308.2			
					Mean	307.9			−12.3
p-Hydroxyacetophenone	130.0	130.4	1.0920		40.06	313.5		314.1	−0.6
	150.0	150.4	1.0765		38.28	314.4			0.3
	175.0	174.8	1.0557		35.71	315.1			1.0
	190.0	191.6	1.0428		34.78	316.9			2.8

[a] SIDGWICK AND BAYLISS, ref. 10, p. 2031.

[b] In this value, 6.1 has been included for the six-membered ring.

[c] A noticeable coloration during the heating process may account for the abnormality shown by *p*-hydroxybenzaldehyde.

para isomers not only by their lower parachor values, but by the fact that they show no variations with the temperature. Such results might be anticipated on the basis of association alone, for it is well known that the chelate compounds present a striking contrast[11] to their meta and para isomers in possessing little or no association.

EXPERIMENTAL

The liquids, which were mostly Eastman Kodak Company's best products, were fractionated two or three times through a "cold point" column packed with Lessing contact rings. The solids also largely Eastman products, were purified either by fractionation or recrystallization from various solvents. The boiling and melting points, both corrected, follow:

Ethyl acetate, b. p. 76.1–76.4° (740 mm.)
Propyl acetate, b. p. 100.7–101.2° (740 mm.)
n-Butyl acetate, b.p. 124.3–125.2° (740 mm.)
n-Amyl acetate, b.p. 146.5–148.5° (743 mm.)
Benzene, b. p. 79.6° (742 mm.)
Toluene, b. p. 109.3–109.6° (742 mm.)
Ethylbenzene, b. p. 135.1–135.3° (740 mm.)
Butylbenzene, b. p. 182.6–185.6° (743 mm.)

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[11] SIDGWICK, "The Electronic Theory of Valency," Oxford University Press, London, **1929**, p. 146.

Amylbenzene, b. p. 201.7–203.7° (743 mm.)
Ethyl nitrate, b. p. 86.9–87.1° (744 mm.)
Ethyl sulfite, b. p. 157.0–157.2° (746 mm.)
Ethyl sulfate, b. p. 77.8–78.0° (6 mm.)
Benzenesulfonyl chloride, b. p. 143.0–143.4° (25 mm.)
Methyl *p*-toluenesulfonate, b. p. 144.6–145.2° (5 mm.)
p-Toluenesulfonyl chloride, m.p. 68.0–68.2°
Sulfuryl chloride, b. p. 68.4–68.5° (742 mm.)
o-Nitrophenol, m. p. 45.3–45.7°
m-Nitrophenol, m. p. 97.2–98.0°
p-Nitrophenol, m. p. 114.9–115.6°
Methyl salicylate, b. p. 221.2–221.5° (744 mm.)
m-Methyl hydroxybenzoate, m. p. 72.2–72.4°
p-Methyl hydroxybenzoate, m. p. 127.7–128.3°
o-Hydroxybenzaldehyde, b. p. 194.0–194.6 (744 mm.)
m-Hydroxybenzaldehyde, m. p. 104.9–105.3°
p-Hydroxybenzaldehyde, m. p. 115.8–116.1°
o-Hydroxyacetophenone, b. p. 219.0–219.5° (744 mm.)
p-Hydroxyacetophenone, m. p. 110.2–110.4°

Physical measurements.—Surface tension determinations were made by the maximum bubble pressure method of Sugden[12] in which a glass bubbler was employed. A cathetometer was used to find the manometer levels, and highly purified benzene was the standardizing liquid for determining the apparatus constant from the diameter of the smaller bubbler tube as measured by a filar micrometer. Densities of the compounds were found with a 10-cc. pycnometer; the densities of the vapor, d, were calculated from the relation[13]:

$$\log_{10} d/d_b = 5\ (T/T_b - 1)$$

where T is the absolute temperature, T_b, the boiling point at 760 mm. in degrees absolute, and d_b, 0.0122 M/T_b, in which M is the molecular weight. Vapor density values less than 0.0005 were disregarded.

SUMMARY

The parachor of the CH_2 group is usually not constant even in the same homologous series.

An increase in the parachor with a temperature rise does not always indicate association.

The coördinate bond in the compounds studied has a value of approximately zero; however, this value increases with the temperature.

The bond of the hydrogen bridge employed in forming the chelate ring differs from the above coördinate bond in having a pronounced negative value which is unaffected by the temperature. These chelate compounds differ from their meta and para isomers in that the latter possess higher parachors and, like other associated compounds, show a parachor variation with the temperature.

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[12] SUGDEN, ref. 1, p. 208.

[13] SUGDEN, *ibid.*, p. 205.

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

SALTS OF NITRO COMPOUNDS. I. PREPARATION, ALKYLATION AND ACYLATION OF SALTS OF PHENYLNITROACETONITRILE

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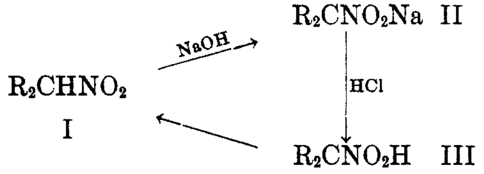
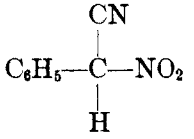
Secondary nitro compounds (I) are interesting chiefly because of their remarkable property of forming salts (II), which, upon acidification, may yield either the original nitro compound or an aci-form (III). The latter may then tautomerize to the normal nitro-form (I).

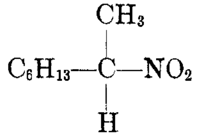


Elucidation of the structures of the salts depends principally on the nature of the derivatives obtained from them by alkylation and acylation. In the special case that the carbon atom holding the hydrogen atom involved in the tautomerization is asymmetric, the optical properties of the salt may aid in indicating its structure. In the present study, a compound of this type—phenylnitroacetonitrile (IV)—has been used. This particular compound was of interest, since both the cyano and the phenyl group are known to promote the mobility of the hydrogen atom, and would enable comparisons to be made with secondary nitro compounds in which only alkyl groups are present, such as 2-nitroöctane (V).



$$C_6H_5{-}\overset{\overset{\large CN}{|}}{\underset{\underset{\large H}{|}}{C}}{-}NO_2$$

IV



$$C_6H_{13}{-}\overset{\overset{\large CH_3}{|}}{\underset{\underset{\large H}{|}}{C}}{-}NO_2$$

V

OPTICAL PROPERTIES

The observation that salts of *d*- and *l*-2-nitrobutane[1] and *d*- and *l*-2-nitroöctane[2] were optically active has led to the search[3] for further exam-

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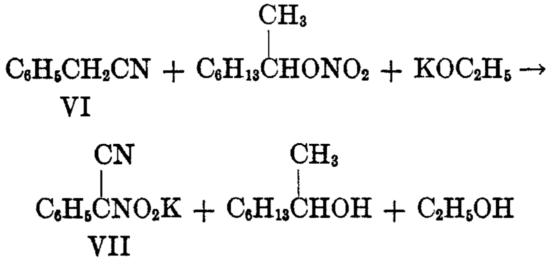
[1] KUHN AND ALBRECHT, *Ber.*, **60**, 1297 (1927).

[2] YOUNG AND SHRINER, *J. Am. Chem. Soc.*, **52**, 3332 (1930).

[3] PARKER AND SHRINER, *ibid.*, **55**, 1242 (1933); HORNE AND SHRINER, *ibid.*, **55**, 4652 (1933); THURSTON AND SHRINER, *ibid.*, **57**, 2163 (1935).

ples of such optically active salts. In the case of phenylnitroacetonitrile, it is not certain whether optically active salts exist. Although the resolution of phenylnitroacetonitrile by brucine, and conversion of the brucine salt into an optically active sodium salt was reported,[4] recent attempts by the same authors to obtain optically active salts have been unsuccessful. It was, therefore, interesting to determine whether optically active sodium salts could be obtained by means of an asymmetric synthesis.[3] Accordingly, phenylacetonitrile (VI) was treated with *d*- and *l*-2-octyl nitrate in the presence of potassium ethoxide. However, the potassium salt (VII)

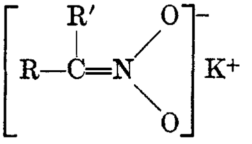


$$\underset{\text{VI}}{C_6H_5CH_2CN} + C_6H_{13}\overset{\overset{CH_3}{|}}{C}HONO_2 + KOC_2H_5 \rightarrow$$

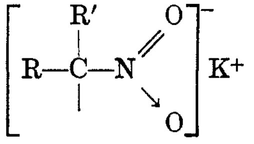
$$\underset{\text{VII}}{C_6H_5\overset{\overset{CN}{|}}{C}NO_2K} + C_6H_{13}\overset{\overset{CH_3}{|}}{C}HOH + C_2H_5OH$$

proved to be optically inactive. The reaction was repeated several times, with changes in the temperature, the ratio, and order of addition of the reactants, but in each case the salts showed no optical activity. One reason for the optical inactivity of the salts may be deduced by a consideration of the factors, which determine whether or not salts of secondary nitro compounds may be optically active.

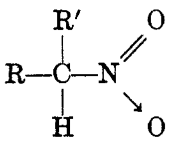
In order to explain both the optical properties and conductivity data on salts of nitro compounds, it was suggested[2] that two forms of the salt



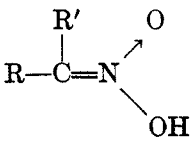
VIII



IX



X



XI

exist, VIII and IX, the latter being the form responsible for the optical activity. Treatment of the salt with acid converts the optically active

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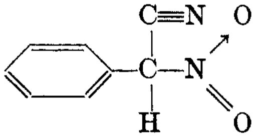
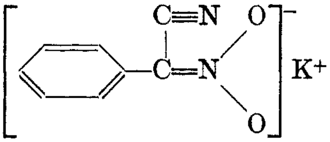
[4] MILLS, *J. Soc. Chem. Ind.*, **51**, 750 (1932).

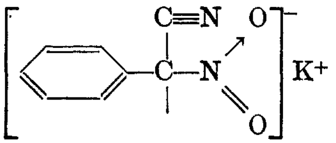
anion (IX), into the optically active nitro form (X), whereas the aci-ion (VIII), yields the inactive aci-modification (XI). Optical activity of the salts is, therefore, dependent on which form of the salt is produced, and this would be determined in part by the character of the R groups. If they are saturated alkyl groups, as in the case of 2- nitrobutane and 2-nitroöctane, both forms would be about equally stable. However, if the R groups contain unsaturated linkages, then forces tending to produce conjugated systems come into play. In the case of phenylnitroacetonitrile (XII),



XII



XIII



XIV

the salt with the aci-structure (XIII) contains a conjugated system, whereas the carbanion (XIV) does not. From studies on many organic reactions, it is known that tautomeric changes and rearrangements tend to produce the conjugated system. Stated in different terms, the resonance of the electrons in these salts would be such as to favor XIII and make the existence of XIV in an optically stable condition rather improbable. No such resonance is possible in the purely aliphatic nitro compounds.

Since the salts were optically inactive, it seems reasonable that, under the conditions of the experiment, the salt possessed the conjugated aci-structure, (XIII). Further evidence bearing out this point was obtained by the alkylation and acylation of this salt.

ALKYLATION

The term alkylation, as used in the present discussion, refers to the treatment of the sodium, potassium, or silver salt of the nitro compound with an alkyl halide. The aci-ion, (VIII), would be expected to produce *O*-alkylation, leading to a nitronic ester; and the carbanion (IX) should produce *C*-alkylation, forming a tertiary nitro compound.

Previous studies on the alkylation of silver salts of secondary nitro compounds have shown that both types of alkylation occur, but the data are somewhat confusing. Nef[5] alkylated 1,1-dinitroethane, and obtained

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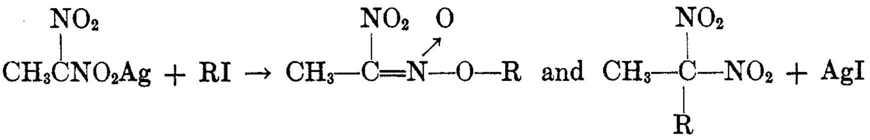
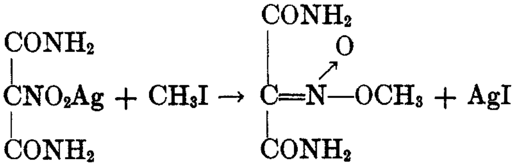
[5] Nef, *Ann.*, **280**, 263 (1894).

both *O*- and *C*-alkylation, whereas Duden[6] reported only *C*-alkylation in the case of dinitromethane.



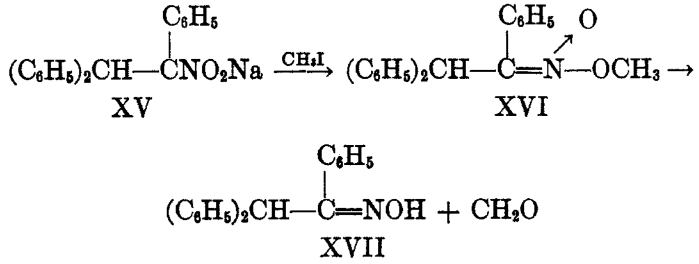
$$CH_3\overset{\overset{NO_2}{|}}{C}NO_2Ag + RI \rightarrow CH_3{-}\overset{\overset{NO_2}{|}}{C}{=}\overset{\overset{O}{\nearrow}}{N}{-}O{-}R \text{ and } CH_3{-}\underset{\underset{R}{|}}{\overset{\overset{NO_2}{|}}{C}}{-}NO_2 + AgI$$

Ratz[7a] on the other hand, obtained *O*-alkylation upon treatment of silver nitromalonamide with methyl iodide, but Ulpiani[7b] reports *C*-alkylation in the case of ammonium nitromalonic ester.



$$\underset{\underset{CONH_2}{|}}{\overset{\overset{CONH_2}{|}}{C}}NO_2Ag + CH_3I \rightarrow \underset{\underset{CONH_2}{|}}{\overset{\overset{CONH_2}{|}}{C}}{=}\overset{\overset{O}{\nearrow}}{N}{-}OCH_3 + AgI$$

Kohler and Stone[8] obtained no evidence for *C*-alkylation upon treating sodium triphenylnitroethane (XV) with methyl iodide. The product was the oxime (XVII), indicating *O*-alkylation to the nitronic ester (XVI) as the intermediate, since this decomposition of the nitronic ester to the oxime and aldehyde or ketone had been shown to be characteristic of this structure.[9] Nenitzescu and Isacescu[10] obtained fluorenone oxime by alkylation of potassium 9-nitrofluorene, and later isolated the methyl nitronic ester. The silver salt of 2-bromo-9-nitrofluorene also undergoes *O*-alkylation to produce a nitronic ester.[3]



$$\underset{XV}{(C_6H_5)_2CH{-}\overset{\overset{C_6H_5}{|}}{C}NO_2Na} \xrightarrow{CH_3I} \underset{XVI}{(C_6H_5)_2CH{-}\overset{\overset{C_6H_5}{|}}{C}{=}\overset{\overset{O}{\nearrow}}{N}{-}OCH_3} \rightarrow$$

$$\underset{XVII}{(C_6H_5)_2CH{-}\overset{\overset{C_6H_5}{|}}{C}{=}NOH} + CH_2O$$

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[6] Duden, *Ber.*, **26**, 3008 (1893).

[7] (*a*) Ratz, *Monatsh.*, **25**, 55 (1904); (*b*) Ulpiani, *Atti. acad. Lincei, Rom.*, [5], **13**, II, 346 (1904).

[8] Kohler and Stone, *J. Am. Chem. Soc.*, **52**, 761 (1930).

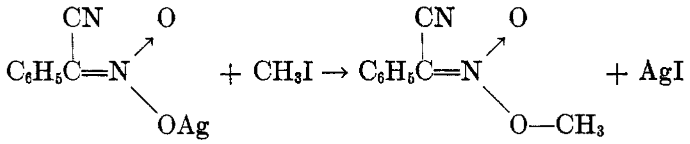
[9] Arndt and Rose, *J. Chem. Soc.*, **1935**, 1.

[10] Nenitzescu and Isacescu, *Ber.*, **63**, 2484 (1930); *Bull. soc. chim. Rom.*, **14**, 53 (1932).

Wislicenus and Elvert[11] obtained the nitronic ester from the silver salt of *p*-bromophenylnitroacetonitrile, whereas Wieland and Höchtlen[12] report *C*-alkylation of phenylnitroacetonitrile by treatment of the silver salt with diphenylbromomethane and triphenylchloromethane.

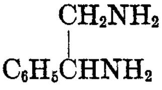
A survey of these previous studies shows that there are no consistent differences obtained when the sodium, potassium or silver salts are used, and no correlation with the presence or absence of conjugated systems.

In the present investigation it was found that the action of methyl iodide on silver phenylnitroacetonitrile (XVIII) at 0° produced the nitronic ester (XIX). The structure of this nitronic exter was established by catalytic reduction of it in acetic anhydride. The reduction product was the diacetyl derivative of phenylethylenediamine (XX). If *C*-alkylation had taken place, the reduction product should have been 2-phenyl-1,2-propylenediamine (XXI).



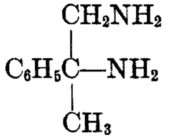
$$C_6H_5C(CN){=}N(\rightarrow O)OAg + CH_3I \rightarrow C_6H_5C(CN){=}N(\rightarrow O){-}O{-}CH_3 + AgI$$

XVIII XIX



$$C_6H_5CH(NH_2)CH_2NH_2$$

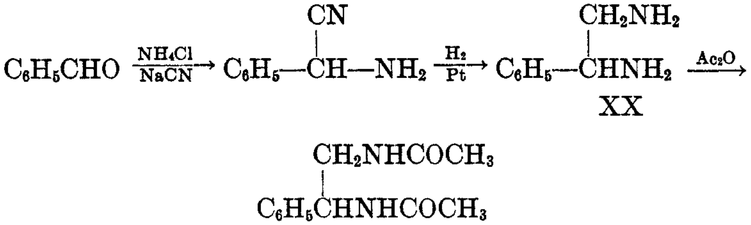
XX



$$C_6H_5C(CH_3)(NH_2){-}CH_2NH_2$$

XXI

The diacetyl derivative (XXII) of phenylethylene diamine (XX) was characterized by comparison with a synthetic sample prepared by the following reactions:



$$C_6H_5CHO \xrightarrow[NaCN]{NH_4Cl} C_6H_5{-}CH(CN){-}NH_2 \xrightarrow[Pt]{H_2} C_6H_5{-}CH(CH_2NH_2)NH_2 \xrightarrow{Ac_2O} C_6H_5CH(NHCOCH_3)CH_2NHCOCH_3$$

XX

XXII

Treatment of silver phenylnitroacetonitrile with benzyl chloride produced a very unstable nitronic ester (XXIII) which could not be isolated,

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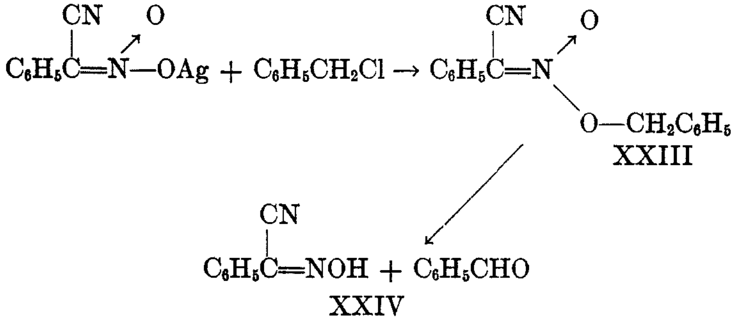
[11] Wislicenus and Elvert, *Ber.*, **41**, 4121 (1908).

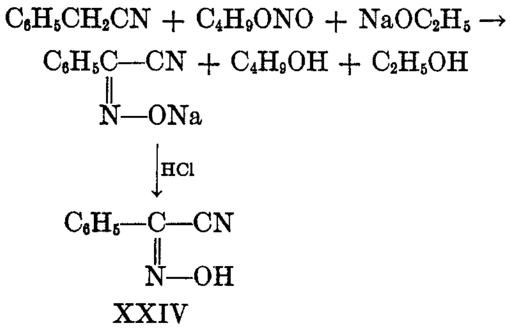
[12] Wieland and Höchtlen, *Ann.*, **505**, 237 (1933).

since it immediately decomposed into benzoyl cyanide oxime (XXIV) and benzaldehyde. The latter was characterized by its phenylhydrazone, and



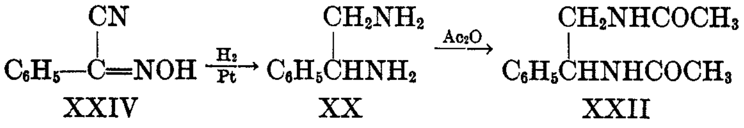
$$C_6H_5\overset{\overset{CN}{|}}{C}{=}\overset{\overset{O}{\nearrow}}{N}{-}OAg + C_6H_5CH_2Cl \rightarrow \underset{XXIII}{C_6H_5\overset{\overset{CN}{|}}{C}{=}N(\rightarrow O){-}O{-}CH_2C_6H_5} \rightarrow \underset{XXIV}{C_6H_5\overset{\overset{CN}{|}}{C}{=}NOH} + C_6H_5CHO$$

the former by comparison with an authentic sample synthesized as follows:



$$C_6H_5CH_2CN + C_4H_9ONO + NaOC_2H_5 \rightarrow C_6H_5\underset{\underset{N-ONa}{\|}}{C}{-}CN + C_4H_9OH + C_2H_5OH \xrightarrow{HCl} \underset{XXIV}{C_6H_5{-}\underset{\underset{N-OH}{\|}}{C}{-}CN}$$

Catalytic reduction of benzoyl cyanide oxime (XXIV) in acetic anhydride yielded the diacetyl derivative (XXII) of phenylethylenediamine (XX). This reduction not only confirms the structure of the benzoyl



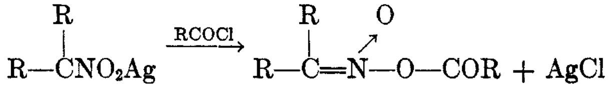
$$\underset{XXIV}{C_6H_5{-}\overset{\overset{CN}{|}}{C}{=}NOH} \xrightarrow[Pt]{H_2} \underset{XX}{C_6H_5\overset{\overset{CH_2NH_2}{|}}{C}HNH_2} \xrightarrow{Ac_2O} \underset{XXII}{C_6H_5\overset{\overset{CH_2NHCOCH_3}{|}}{C}HNHCOCH_3}$$

cyanide oxime, but furnishes another independent synthesis of diacetylphenylethylenediamine (XXII) described above.

In both of these alkylations the alkyl group appeared on the oxygen atom, and not on the carbon atom, indicating that the silver salt of phenylnitroacetonitrile had the structure XVIII derived from XIII; *i.e.*, the conjugated aci-structure was the preferred form. The only indication that the other structure, XIV, may also be present is the *C*-alkylation obtained by Wieland and Höchtlen[12] by the action of diphenylbromomethane and triphenylchloromethane on the silver salt. This reaction is now being studied.

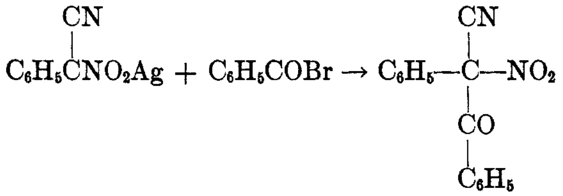
ACYLATION

Several investigators have acylated the salts of secondary nitro compounds. Nef[5] obtained the acyl derivatives of silver 1,1-dinitroethane, and Nenitzescu and Isacescu[10] prepared the acetyl and benzoyl derivatives



$$R-\overset{\overset{\displaystyle R}{|}}{C}NO_2Ag \xrightarrow{RCOCl} R-\overset{\overset{\displaystyle R}{|}}{C}=\overset{\overset{\displaystyle O}{\nearrow}}{N}-O-COR + AgCl$$

of 9-nitrofluorene from the potassium 9-nitrofluorene. These acyl derivatives were indicated as having the acyl group attached to oxygen, but no proof of structure was given other than hydrolysis. Wieland and Höchtlen[12] treated silver phenylnitroacetonitrile with benzoyl bromide, and ascribed the structure XXV to the acyl derivative, which is an example

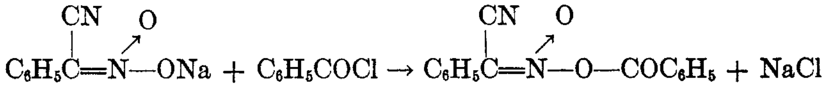


$$C_6H_5\overset{\overset{\displaystyle CN}{|}}{C}NO_2Ag + C_6H_5COBr \rightarrow C_6H_5-\underset{\underset{\underset{\underset{\displaystyle C_6H_5}{|}}{\displaystyle CO}}{|}}{\overset{\overset{\displaystyle CN}{|}}{C}}-NO_2$$

XXV

of *C*-acylation; in fact, it is the only example of *C*-acylation of a salt of a secondary nitro compound. The only evidence for its structure was the fact that it was readily cleaved by alkalies to sodium benzoate and sodium phenylnitroacetonitrile. The structure XXV would certainly be expected to be unstable to alkalies, but the alternative structure XXVI, the *O*-acylation product, would also cleave upon treatment with alkali. Hence, alkaline hydrolysis cannot be used as a method for distinguishing between the two possibilities.

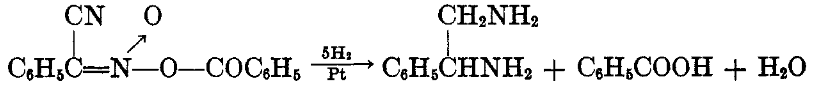
In the present work, the benzoyl derivative of phenylnitroacetonitrile was prepared by the action of benzoyl chloride on both the sodium and silver salts of the nitro compound. Its structure was definitely established



$$C_6H_5\overset{\overset{\displaystyle CN}{|}}{C}=\overset{\overset{\displaystyle O}{\nearrow}}{N}-ONa + C_6H_5COCl \rightarrow C_6H_5\overset{\overset{\displaystyle CN}{|}}{C}=\overset{\overset{\displaystyle O}{\nearrow}}{N}-O-COC_6H_5 + NaCl$$

XXVI

as that of the *O*-acylated compound (XXVI) by catalytic reduction with platinum and hydrogen at room temperature in acetic anhydride. The reduction products were shown to be benzoic acid and the diacetyl deriva-

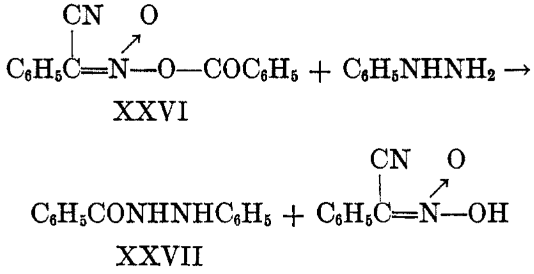


$$C_6H_5\overset{\overset{\displaystyle CN}{|}}{C}=\overset{\overset{\displaystyle O}{\nearrow}}{N}-O-COC_6H_5 \xrightarrow[Pt]{5H_2} C_6H_5\overset{\overset{\displaystyle CH_2NH_2}{|}}{C}HNH_2 + C_6H_5COOH + H_2O$$

XX

tive (XXII) of phenylethylenediamine (XX), previously obtained by catalytic reduction of the methyl nitronic ester. These reduction products could not be obtained from a structure such as XXV under the mild conditions employed for the reduction. The water produced in the reduction was taken up by the acetic anhydride used as the solvent, hence hydrolysis of XXV and then reduction to XX is precluded.

Moreover, treatment of the benzoyl derivative in chloroform solution with phenylhydrazine at 20° did not produce a hydrazone of the ketone (XXV), but instead cleaved the product to β-phenyl benzhydrazide (XXVII). This behavior is further evidence in favor of the *O*-benzoyl linkage, XXVI, since this structure is essentially that of a mixed anhydride of the nitronic acid and benzoic acid.



$$C_6H_5\overset{\overset{CN}{|}}{C}{=}\overset{\overset{O}{\nearrow}}{N}{-}O{-}COC_6H_5 + C_6H_5NHNH_2 \rightarrow$$

XXVI

$$C_6H_5CONHNHC_6H_5 + C_6H_5\overset{\overset{CN}{|}}{C}{=}\overset{\overset{O}{\nearrow}}{N}{-}OH$$

XXVII

The benzoyl derivative of phenylnitroacetonitrile, therefore, possesses the structure XXVI, and, like the two alkyl derivatives, is derived from the aci-structure XIII.

EXPERIMENTAL

Potassium salt of phenylnitroacetonitrile.—One gram of potassium was dissolved in 10 cc. of absolute alcohol and 30 cc. of absolute ether. The solution was cooled to 0°, and a solution, consisting of 3 g. of benzyl cyanide, 6.7 g. *dl*-2-octyl nitrate, 25 cc. absolute ether and 25 cc. petroleum ether was added slowly with stirring. The potassium salt started to precipitate after about one-third of the solution had been added. The precipitated salt was filtered, washed twice with 30-cc. portions of equal parts of ordinary ether and low-boiling petroleum ether, and finally recrystallized by dissolving in 30 cc. of methyl alcohol, then pouring into a solution composed of 50 cc. of ordinary ether and 100 cc. of low-boiling petroleum ether. The slightly yellow potassium salt, obtained in yields of 80 per cent. of the theoretical amount, decomposed at 265°.

Anal. Calc'd for $C_8H_5KN_2O_2$: K, 19.54. Found: K, 19.27.

The above procedure was repeated, using both *d*-2-octyl nitrate ($[\alpha]_D^{25}$ +15.37°) and *l*-2-octyl nitrate ($[\alpha]_D^{25}$ −15.00°), prepared as previously described, and in each case absolute alcohol solutions of the salts showed no sign of optical activity. The order of mixing the reactants was changed, and also the molar ratio, but no optically active salts were produced.

Salt from *d*-2-octyl nitrate:

Anal. Calc'd for $C_8H_5KN_2O_2$: K, 19.54. Found: K, 19.45.

Salt from *l*-2-octyl nitrate:

Anal. Calc'd for $C_8H_5KN_2O_2$: K, 19.54; N, 14.00.
Found: K, 19.52; N, 14.27.

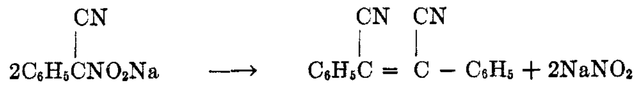
On acidification of a cold, dilute, aqueous solution of the potassium salt with acetic acid, the aci-form separated as a yellow, pasty solid. A solution of this solid in alcohol gave a brownish color with ferric chloride. The aci-form, on standing, changed to an oil, the free nitro form, which did not give a color with ferric chloride. This oil was extracted with ether, the solution dried and the ether distilled. An alcohol solution of the residual phenylnitroacetonitrile showed no optical activity.

Treatment of an absolute alcohol solution of the potassium salt from the preparations in which *d*- and *l*-2-octyl nitrate were used with one mole of bromine produced an oil which Wislicenus and Schafer[13] have shown to be phenylbromonitroacetonitrile. An alcohol solution of this derivative was also optically inactive.

Attempted alkylation of potassium and sodium salts.—Treatment of the potassium or sodium salts of phenylnitroacetonitrile with alkyl halides gave no alkyl derivatives. Decomposition products were produced, among which were benzoyl cyanide oxime and the aldehyde corresponding to the alkyl group. However, treatment of 5 g. of the sodium salt with 4 g. of methyl sulfate and 1.3 g. of sodium hydroxide in 75 cc. of methanol at room temperature for three weeks gave a crystalline precipitate. Recrystallization produced yellow needles melting at 161–162°. This compound was finally identified as dicyanostilbene,[14] and the melting point of a mixture with a synthetic sample showed no depression.

Anal. Calc'd for $C_{16}H_{10}N_2$: N, 12.17. Found: N, 12.00.

This compound resulted from the decomposition of the sodium salt.



$$2C_6H_5\overset{\overset{CN}{|}}{C}NO_2Na \longrightarrow C_6H_5\overset{\overset{CN}{|}}{C}=\overset{\overset{CN}{|}}{C}-C_6H_5+2NaNO_2$$

Silver salt of phenylnitroacetonitrile.—To 7 g. of the potassium salt dissolved in 250 cc. of distilled water was slowly added, with stirring, an aqueous solution of silver nitrate prepared by dissolving 6 g. of silver nitrate in 100 cc. of water. The precipitated salt was washed three times with alcohol, and finally with ether. A yield of 9 g., which was nearly quantitative, was obtained.

Methyl aci-*phenylnitroacetonitrile.*—To 12 g. of the silver salt was added ten times the theoretical amount (68 g.) of methyl iodide, diluted with an equal volume of ether. During the addition of the methyl iodide, the pasty mass was stirred and cooled in an ice-salt bath. After standing one and one-half hours at this temperature, the reaction mixture was shaken for fifteen hours at room temperature. The excess methyl iodide and the ether solution of the methylated compound were filtered from the silver iodide. The solvent and methyl iodide were removed under vacuum at room temperature, leaving a heavy oil. Ten cubic centimeters of ether was added and warmed slightly. On cooling in an ice-salt mixture and diluting with low-boiling petroleum ether, the product crystallized in the form of colorless needles. These darkened on standing, and finally turned to a heavy oil. The crystals melted at 41 to 42°, and weighed 3.5 g., which corresponds to a yield of 50 per cent.

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[13] Wislicenus and Shafer, *Ber.*, **41**, 4169 (1908).

[14] Wislicenus and Enders, *ibid.*, **35**, 1755 (1902).

Anal. Calc'd for $C_9H_8N_2O_2$: N, 15.91. Found: 16.10.

The nitronic ester was unstable, and decomposed on standing to form an oil which possessed an odor of formaldehyde. This type of decomposition has been noted by Nenitzescu and Demitrie,[10] and by Arndt and Rose.[9]

Catalytic reduction of methyl aci-*phenylnitroacetonitrile.*—A solution of 1.5 g. of the nitronic ester in 35 cc. of acetic anhydride and 0.15 g. of platinum oxide were shaken with hydrogen under three atmospheres pressure. After fifteen hours, five molecular equivalents of hydrogen had been absorbed. The mixture was filtered, the filtrate poured into 50 cc. of 30 per cent. sodium hydroxide solution, and the product extracted with chloroform. Evaporation of the chloroform left an oil which crystallized on standing. Recrystallization from ethyl acetate gave colorless crystals which melted sharply at 155 to 155.5°.

Anal. Calc'd for $C_{12}H_{16}N_2O_2$: N, 12.72. Found: 12.30.

Since the melting point of the diacetyl derivative of phenylethylenediamine is given as 152° in the literature,[15] a sample was synthesized for comparison.

Synthesis of diacetyl derivative of phenylethylenediamine.—The intermediate phenylaminoacetonitrile was prepared by vigorously stirring a mixture of 20 g. of benzaldehyde, 50 g. of sodium cyanide and 54 g. of ammonium chloride dissolved in 350 cc. of water. After three hours, an equal volume of water was added, and the oil was extracted with two 75-cc. portions of benzene. The combined benzene extracts were shaken with two 75-cc. portions of hydrochloric acid (1:1), which were then poured into 500 cc. of 20 per cent. sodium hydroxide solution. The phenylaminoacetonitrile was extracted with ether, and the ether evaporated. Nine grams of the product was dissolved in 75 cc. of acetic anhydride and reduced with hydrogen in the presence of 0.26 g. of platinum oxide. The reduction mixture was filtered, and the filtrate poured into 100 cc. of 30 per cent. sodium hydroxide solution to decompose the excess acetic anhydride. Extraction with chloroform by distillation gave a gummy solid. After several recrystallizations from ethyl acetate, colorless crystals which melted at 155–155.6° were obtained. The melting point of a mixture with the diacetyl phenylethylenediamne, obtained by reduction of the methyl nitronic ester described above, showed no depression.

Anal. Calc'd for $C_{12}H_{16}N_2O_2$: N, 12.72. Found: N, 12.30.

Benzylation of the silver nitro salt.—By warming at 40–50°, a suspension of 8 g. of the silver salt in 7.5 cc. of benzyl chloride and 15 cc. of ether for one and one-half hours, then filtering and evaporating the solvent at diminished pressure, an oily residue was obtained. This residue was taken up in 10 cc. of low-boiling petroleum ether and cooled in an ice-salt bath. The crystals which separated were purified by recrystallization from hot water. Colorless plates which melted at 129° were obtained. The melting point of a mixture with benzoyl cyanide oxime, prepared as described below, showed no depression.

Anal. Calc'd for $C_8H_6N_2O$: N, 19.19. Found: N, 19.19.

Treatment of the petroleum ether solution from the above crystallization with phenylhydrazine gave the phenylhydrazone of benzaldehyde, which melted at 156.5°, and the melting point of a mixture with an authentic specimen showed no depression.

Benzoyl cyanide oxime.—To 2.3 g. of freshly cut sodium in 25 cc. of absolute alcohol was added 11.7 g. of benzyl cyanide, followed by 10.3 g. of butyl nitrite. The yellow sodium salt immediately precipitated and, after thirty minutes, it was filtered,

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[15] FEIST AND ARNSTEIN, *ibid.*, **28**, 426, 3172 (1895).

washed with ether and dried in a desiccator. The yield was 8.5 g. or 69 per cent of the theoretical. The free oxime was obtained by acidification of an aqueous solution of the salt. After recrystallization from water, the crystals melted at 129.5°, which checked the value given by Zimmerman.[16]

Reduction of benzoyl cyanide oxime.—A solution of 3.7 g. of the oxime in 35 cc. of acetic anhydride was shaken with 0.3 g. of platinum oxide and hydrogen under pressure. The reduction proceeded very slowly, and forty-eight hours was required for absorption of four molecular equivalents of hydrogen. A very low yield of the diacetyl derivative of phenylethylene diamine was isolated by the same procedure given above and found to melt at 155–155.5°.

Benzoylation of the salts of phenylnitroacetonitrile.—Three methods were used in order to obtain the benzoyl derivative.

(*A*) To 1.25 g. of the sodium nitro salt in 10 cc. of water was added 2 cc. of benzoyl chloride. After shaking for a few minutes and keeping the solution alkaline by addition of 10 per cent. sodium hydroxide solution, the product was filtered, washed with alcohol and recrystallized from benzene and low-boiling petroleum ether. The colorless solid melted at 116°, while the recorded melting point[12] is 118°.

Anal. Calc'd for $C_{15}H_{10}N_2O_3$: N, 10.51. Found: N, 1055.

(*B*) To 5 g. of the sodium nitro salt, suspended in 25 cc. of dry benzene, was added 4 cc. of benzoyl chloride. After shaking for thirty-six hours, the filtrate was evaporated under diminished pressure, and the remaining 15 cc. of solution was poured into low-boiling petroleum ether. The precipitate, after recrystallization from ethyl acetate, melted at 116° and gave no depression in melting point when mixed with the product prepared above.

(*C*) The best yield of the benzoylated derivative was obtained as follows. To 8 g. of the silver salt, suspended in 50 cc. of dry benzene, was added 4.5 g. of benzoyl chloride. After vigorous stirring for three hours, the benzene was filtered, concentrated under diminished pressure, and the yellow product recrystallized from ethyl acetate. The yield of colorless prisms melting with decomposition at 116° was 6.8 g., or 85 per cent. of the theoretical amount. The melting points of mixtures with the benzoylated derivatives described above gave no depression.

Properties of the benzoyl derivative.—This compound failed to yield an oxime or semicarbazone, even after standing three months with the reagents.

Treatment of a chloroform solution of the benzoyl derivative with phenylhydrazine gave pale yellow crystals of a compound which melted at 170° after recrystallization from alcohol. This product was identified as β-phenylbenzhydrazide by means of a mixture melting-point comparison with an authentic sample prepared according to the method of Fischer.[17]

Treatment of the benzoyl derivative with warm, 5 per cent. sodium hydroxide hydrolyzed it to benzoic acid and phenylnitroacetonitrile.

Catalytic reduction of the benzoyl derivative.—A solution of 4 g. of the benzoyl-*aci*-phenylnitroacetonitrile in 35 cc. of acetic anhydride absorbed five molecular equivalents of hydrogen in nine hours when shaken with hydrogen and 0.25 g. of platinum oxide. The catalyst was removed by filtration, and the solution was poured into 50 cc. of 30 per cent. sodium hydroxide solution. The product was extracted with ether, and the ether was removed by distillation. Recrystallization of the residue from benzene gave colorless crystals of diacetylphenylethylenediamine, which melted at

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[16] Zimmerman, *J. prakt. Chem.*, **66**, 353 (1902).

[17] Fischer, *Ann.*, **190**, 125 (1877).

155–155.5°, and did not depress the melting point of the samples of this compound described above.

The above sodium hydroxide solution was acidified and cooled. Crystals of benzoic acid, melting at 120°, were obtained.

SUMMARY

Treatment of benzyl cyanide with *d*- and *l*-2-octyl nitrates in the presence of potassium or sodium ethoxide yielded the potassium or sodium salts of phenylnitroacetonitrile, which were optically inactive.

The silver salt of phenylnitroacetonitrile reacted with methyl iodide to yield the methyl nitronic ester whose structure was established by catalytic reduction to phenylethylenediamine.

Benzyl chloride and the silver salt yielded benzoyl cyanide oxime and benzaldehyde.

Both the sodium and silver salts reacted with benzoyl chloride to produce a benzoyl derivative whose structure as an oxygen acylated derivative was established by catalytic reduction to benzoic acid and phenylethylenediamine.

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

THE PEROXIDE EFFECT IN THE ADDITION OF HYDROGEN BROMIDE TO ETHYLENE COMPOUNDS. XIV. THE ADDITION OF HYDROGEN BROMIDE TO THE HIGHER ALKENES

M. S. KHARASCH and WM. M. POTTS

Received April 20, 1937

INTRODUCTION

The addition of hydrogen bromide to ethylene and acetylene compounds, in the presence and absence of peroxides, has been investigated in this laboratory.[1] It has been shown that in the absence of peroxides (and/or oxygen), hydrogen bromide adds to unsaturated compounds to yield secondary bromides. On the other hand, in the presence of peroxides the normal bromides are formed. Our previous studies were confined to the lower alkenes. It was of interest and of considerable theoretical moment to determine whether or not the same generalizations would apply to higher alkenes containing terminal double bonds. Through friendly coöperation Mr. A. P. Kozacik and Prof. E. Emmet Reid, of Johns Hopkins University, supplied us with a number of long-chain hydrocarbons, containing terminal double bonds, and identified the primary bromides by the preparation of crystalline derivatives. The quantities of these unsaturated substances were not very large, and an exhaustive study with each individual compound was impossible. However, the results obtained with nonene-1, tridecene-1, undecene-1 and pentadecene-1 prove that the generalizations evolved as a result of the study of the short-chain unsaturated compounds, apply to the higher alkenes also.

DISCUSSION OF RESULTS

The results obtained, in the addition of hydrogen bromide to the higher alkenes, are given in Table I. We have recorded the results obtained with all the samples sent us. The available quantities of some of them, however, were so small, and the purification of the resulting bromides so difficult, that we have serious doubts whether any significance should be attached to the experiments with heptadecene-1, nonadecene-1, 4-phenylbutene-1, and 6-phenylhexene-1. The data obtained are included along with our

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[1] Kharasch and others, *J. Am. Chem. Soc.*, **55**, 2468, 2521, 2531, (1933); **56**, 244, 712, 1212, 1243, 1425, 1643, 1782 (1934); **57**, 2463 (1935).

other results, because Mr. Kozacik and Prof. Reid have prepared solid condensation products of these bromides with phenolic compounds.

The addition of hydrogen bromide to the first five unsaturated compounds recorded in Table I is very fast, under "peroxide" as well as under "antioxidant" conditions. These high rates of addition, coupled with the presence of quantities of peroxides in the unsaturated compounds, make it extremely difficult to direct the addition so as to obtain quantitative yields of either the primary or the secondary bromides.

Unfortunately, since we had no ready analytical method to determine the percentage of primary and secondary bromide in our "peroxide" experiments, we were unable to adjust the conditions properly to take into account the enormously high rate of the "normal" addition. Had we been aware of that, we would have employed larger quantities of peroxides, and introduced the hydrogen bromide into the reaction mixture at a very slow rate. The results given in Table I, therefore, are to be looked upon not as a record of what may be accomplished, but rather as a report of what the first trial experiments have yielded. One may complain of the yields, but the results obtained show conclusively that primary bromides are formed from the unsaturated compounds in the presence of peroxides, and that, therefore, the Markownikow rule applies not only to the short-chain unsaturated substances, but to the higher alkenes. The yields of the primary bromides given in the table are supplied by personal communication from Kozacik and Reid. It should be emphasized that the 82 per

TABLE I

ADDITION OF HYDROGEN BROMIDE TO HIGHER ALKENES

HYDROCARBON	"ANTIOXIDANT" CONDITIONS		"PEROXIDE" CONDITIONS		PER CENT PRIMARY BROMIDE ESTIMATED (KOZACIK AND REID)
	B. P.	n_D^{20}	B. P.	n_D^{20}	
1. Nonene-1.......	63- 67°/4 mm.	1.4542	71- 75°/6 mm.	1.4529	82+
2. Undecene-1.....	100-101°/5 mm.	1.4567	98- 99°/5 mm.	1.4557	65+
3. Tridecene-1.....	129-131°/5 mm.	1.4574	121-123°/5 mm.	1.4568	41+
4. Pentadecene-1..	142-147°/6 mm.	1.4604	130-131°/6 mm.	1.4592	60+
5. Allylbenzene...	98-102°/6 mm.	1.5457	91- 93°/6 mm.	1.5449	
6. Heptadecene-1..	163-165°/6 mm.	1.4616	158-160°/6 mm.	1.4608	
7. Nonadecene-1...	191-195°/6 mm.		185-186°/6 mm.		
8. 4-Phenylbutene-1........	108-109°/6 mm.	1.5392	102-103°/6 mm.	1.5358	
9. 6-Phenylhexene-1.........	129-133°/6 mm.	1.5273	115-118°/6 mm.	1.5280	

cent. of the primary bromide from nonene-1, 65 per cent., 60 per cent. and 41 per cent. from undecene-1, pentadecene-1 and tridecene-1, respectively, are the amounts of the primary bromides which they isolated and are less than the amounts which are formed when hydrogen bromide is added to the unsaturated compounds under peroxide condition.

Better results, than those given in the table, were obtained by us recently in the addition of hydrogen bromide to tridecene-1.* The precaution was taken to insure the presence of about 10 per cent. of peroxides in the reaction mixture. The hydrogen bromide was introduced slowly in accordance with the procedure used by Kharasch and Hinckley.[2] Under these conditions a product was obtained, which contained over 85 per cent. of the primary bromide. The identification was first attempted through the conversion of the bromides obtained from "peroxide" and "antioxidant" experiments to the corresponding mercury compounds. No decisive results were obtained. The melting points of the mercury compounds of the primary and secondary bromides were very close, (88° and 90° respectively), although each depressed the melting point of the other (79°–80°). The identification was finally made through the condensation of the Grignard reagent of the bromide with phenyl isocyanate. An anilide was obtained which melted at 80°–82°, and the melting point of it was not depressed by the addition of a synthetic sample of myristic anilide.

SUMMARY

1. It has been shown that the addition of hydrogen bromide to the higher alkenes, containing terminal double bonds, results in the formation of primary bromides, whenever "peroxides" are present in the reaction mixture, while secondary bromides are formed in the presence of "antioxidants."
2. The Markownikow rule as applied to unsaturated hydrocarbons has been put on a firm experimental basis.

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* This result is reported separately in order not to cause confusion with the first sample analyzed by Kozacik and Reid, and to be recorded in their publication.

[2] KHARASCH AND HINCKLEY, *Ibid.*, **56**, 1212 (1934).

[16, WESTLANDS AVENUE, NORTON, STOCKTON-ON-TEES, CO. DURHAM, ENGLAND]

MECHANISM OF THE DIAZOAMINOBENZENE CONVERSION

H. VINCENT KIDD

Received April 29, 1937

1. PRESENT CONTROVERSIAL POSITION

A recent paper by Earl[1] revives the question of the mechanism underlying the conversion of diazoaminobenzene, and its derivatives, to aminoazo compounds. The nature of this mechanism has been debated since the introduction of diazoaminobenzene by Griess[2] in 1862; and the controversial state of the question is evidenced by the more recent literature on the subject[3]. While Earl's last paper[1] refers to dynamic isomerism involving mobilitiy of the hydrogen in certain reactions cited[4], it is not clear whether this is intended to support his previous interpretation of the reaction, which postulated the formation of benzenediazoaminoazobenzene as an intermediary[3].

2. NEW RESULTS NOT EXPLAINED BY A PREVALENT THEORY[5]

Early in 1933 the author obtained experimental results while working at University College, London, which throw further light on the probable mechanism of this reaction; and the recurring interest in the subject makes their publication seem desirable. The following results were obtained, using an aqueous or alcoholic solution of diazoaminobenzene.

(*a*) Over 90 mole-per cent. of the diazobenzene constituent in a sample of diazoaminobenzene was recovered from an acidic solution of the latter, in the form of its β-naphthol compound, 2-naphthol-1-azobenzene. This

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[1] EARL, *J. Soc. Chem. Ind.*, **55**, 192 (1936).

[2] GRIESS, *Ann.*, **121**, 258 (1862).

[3] GOLDSCHMIDT, JOHNSEN, AND OVERWIEN, *Z. physikal. Chem.*, **110**, 251 (1924); INGOLD, SMITH, AND VASS, *J. Chem. Soc.*, **1927**, 1245; ROSENHAUER AND UNGER, *Ber.*, **61B**, 392 (1928); EARL, *J. Proc. Roy. Soc. N.S.W.*, **63**, 83 (1929); **64**, 96 (1930); *Ber.*, **63B**, 1666 (1930); ROSENHAUER, *ibid.*, **64B**, 1438 (1931).

[4] MELDOLA AND STREATFIELD, *J. Chem. Soc.*, **51**, 27, 109 (1887); *Cf.* NOELTING AND BINDER, *Bull. soc. chim.*, **42**, 336, 341; *Ber.*, **20**, 3004.

[5] COHEN, "Organic Chemistry", **1931** Ed., p. 420; *Cf.* also C. W. PORTER, "Molecular Rearrangements," Am. Chem. Soc. Mon. No. 45, p. 69.

reaction has been carried out qualitatively by Friswell and Green[6], and recently by Earl[1].

(*b*) Aniline was isolated from the aqueous solution from (*a*), equivalent to over 90 mole-per cent. of its content (in combined form) in the sample of diazoaminobenzene used. No mention has been found of a previous attempt to isolate aniline from an acidified solution of diazoaminobenzene.

(*c*) Phenyldiazonium chloride has been directly combined with aniline under homogeneous conditions, the resulting aminoazobenzene separating out of the solution in the form of its hydrochloride, free from diazoaminobenzene or other intermediate product. This result has not previously been accomplished, although Friswell and Green[6] attempted the combination by "varying the conditions in every possible way."

(*d*) After a strong hydrochloric acid solution of diazoaminobenzene had been kept at 0–2° for 288 hours, approximately 75 per cent. of the original compound had undergone irreversible chemical change (100 per cent. after 92 days). Only 14 per cent. had been converted to aminoazobenzene. The difference between this figure and the amount of diazoaminobenzene which had undergone change could be accounted for reasonably well by the appearance of phenol and aniline. In a complementary experiment, the rate at which the phenyldiazonium chloride arising from fission of the diazoaminobenzene disappeared was shown to be sensibly linear.

It is considered that a prevalent view of the mechanism of the diazoaminobenzene conversion[5], originated by Goldschmidt and his collaborators[7], is inadequate to explain these results. On the other hand, it is felt that the explanation of the mechanism considered in section 5, far from excepting the experimental results upon which Goldschmidt's theory is based, serves to harmonize these with the present results, and those of other workers.

3. GOLDSCHMIDT'S THEORY OF RESIDUE INTERCHANGE

The intermolecular nature (*Cf.* "The Benzidine Rearrangement"[8]) of the conversion of diazoaminobenzene to aminoazobenzene seems never to have been in doubt since Kekulé first effected the change[9], and treated it as a double decomposition. Further evidence of the intermolecular character of the reaction was soon provided by Baeyer and Jaeger[10],

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[6] Friswell and Green, *J. Chem. Soc.*, **47**, 917 (1885); **49**, 746 (1886).

[7] Goldschmidt, *Ber.*, **24**, 2317 (1891); Goldschmidt and Bardach, *ibid.*, **25**, 1347 (1892); Goldschmidt and Reinders, *ibid.*, **29**, 1369, 1899 (1896).

[8] Ingold and Kidd, *J. Chem. Soc.*, **1933**, 984; *Ann. Repts.*, **1933**, 178.

[9] Kekulé, *Z. Chem.*, **2**, 688 (1866).

[10] Baeyer and Jeager, *Ber.*, **8**, 151 (1875).

Nietzki[11], and Jaenke[12]. Meanwhile, however, the actual details of the mechanism were attracting the attention of investigators; and in 1891 Goldschmidt began the series of experiments which has been extended by himself and his collaborators[7], over a number of years, in support of the theory to which reference has been made.

This theory postulates the formation of an additive compound, $(ArNH)_2NCl$, (I), and the para-combination of this with a molecule of the basic solvent, forming the compound $(ArNH)_2N \cdot Ar'NH_2$, (II), which then breaks down to $ArNH_2$ and $ArN{:}N \cdot Ar'NH_2$, the aminoazo-compound. The ArNH residue of I may be replaced by other basic residues from the solvent (aniline, toluidine, etc.) before II is formed. In this way the different products from a number of reactions were explained; but it was not certain when residue exchange might be expected, nor why it occurred. This is illustrated by two typical reactions considered in section 5, which were advanced by Goldschmidt and collaborators in 1892 as inconsistencies on the basis of the theory considered in section 4. It will be shown in section 5, when it will be necessary to refer to I and II, that these very examples reveal a weakness in Goldschmidt's theory.

It is important to note here, that while Goldschmidt postulates the addition of one molecule of hydrochloric acid to diazoaminobenzene in the initial formation of I, the author has observed that the white crystalline precipitate thrown out of an ethereal solution of diazoaminobenzene by anhydrous hydrochloric acid contains two moles of hydrochloric acid per mole of diazoaminobenzene. This observation finds a consistent explanation in the theory discussed directly.

4. FRISWELL AND GREEN'S THEORY OF PRIMARY FISSION

In 1885 Friswell and Green[6] had put forward an extremely simple theory of the mechanism of this conversion; but this was soon engulfed by the flood of careful experimental work from Goldschmidt's laboratories in support of the above theory. Friswell and Green's explanation was not recognized again until Meyer[13] re-advanced the idea of fission in 1921: and afterwards, Rosenhauer and Unger[3] drew long-overdue attention to the work of Friswell and Green. Earl's 1929 and 1930 papers[3] again revert to the idea of a nuclear condensation, which fails to meet the demands of the majority of the mechanistic aspects of the reaction which have been observed.

Friswell and Green contended that the first stage in this conversion in the presence of hydrochloric acid was a primary fission of diazoamino-

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[11] NIETZKI, *ibid.*, **10**, 662, (1877).

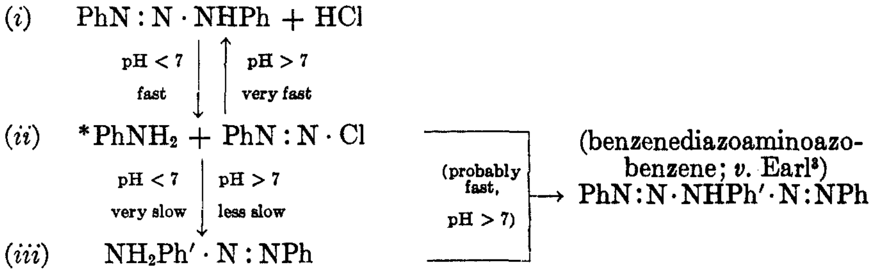
[12] JAENKE, *ibid.*, **21**, 548 (1888).

[13] MEYER, *ibid.*, **54B**, 2265 (1921).

benzene to benzene (*i.e.*, phenyl) diazonium chloride and aniline. This was held to be a rapid and reversible reaction, while aminoazobenzene was said to be formed from the products of the fission by a slow and irreversible reaction. It is this theory, with some additions, which the author regards as giving the most likely, and certainly the most comprehensive, explanation of this conversion and the chemical phenomena which have been observed to accompany it.

5. ELECTRONIC INTERPRETATION OF MECHANISM

(*A*) *General view of system.*—Accepting Friswell and Green's postulation of a primary fission (which is in agreement with Goldschmidt's cryoscopic results[7]), the simplest case of this reaction—namely, when taking place in alcohol or water containing appreciable quantities of hydrochloric acid—may be formulated thus:



$$\begin{tikzcd}
(i)\ \mathrm{PhN:N\cdot NHPh + HCl} \arrow[d, shift right, "\substack{\mathrm{pH} < 7\\ \text{fast}}"'] & & \\
(ii)\ {}^*\mathrm{PhNH_2 + PhN:N\cdot Cl} \arrow[u, shift right, "\substack{\mathrm{pH} > 7\\ \text{very fast}}"'] \arrow[d, "\substack{\mathrm{pH} < 7\\ \text{very slow}}"', "\substack{\mathrm{pH} > 7\\ \text{less slow}}"] \arrow[rr, "\substack{\text{(probably}\\ \text{fast,}\\ \mathrm{pH} > 7)}"] & & \substack{\text{(benzenediazoaminoazo-}\\ \text{benzene; } v. \text{ Earl}^{8})\\ \mathrm{PhN:N\cdot NHPh'\cdot N:NPh}} \\
(iii)\ \mathrm{NH_2Ph'\cdot N:NPh} \arrow[urr] & &
\end{tikzcd}$$

This system will be seen to provide an excellent example of the conflicting advantages that sometimes arise in an interdependent series of reactions. The reaction (*ii*) to (*iii*) is aided by the same conditions of basicity as favour the much more rapid reaction (*ii*) to (*i*). The $\mathrm{pH} > 7$ necessary for the production of the parents of aminoazobenzene, actually militates against the formation of this compound from them, for the reason discussed in *B*.

The experiments reported in section 6 were carried out in aqueous medium in order to establish the points given in section 2; but aniline (or toluidine) is normally used as reaction medium, under which conditions the effect of the solvent cannot be ignored. While reaction (*ii*) to (*i*) will be greatly favoured by the presence of the base, the formation of aminoazobenzene by the irreversible reaction (*ii*) to (*iii*) will eventually reflect the mass law action of the solvent molecules. The effect becomes appreciable when diazoaminobenzene is heated for some hours in aniline containing aniline hydrochloride. The reaction is also favorably affected,

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* The aniline will probably be largely in the form of its hydrochloride; and this, and also the phenyldiazonium chloride, partially dissociated.

in general, by the greater stability of phenyldiazonium chloride in aniline, than in an aqueous medium.

It may be noted that benzenediazoaminoazobenzene, which Earl[3] postulated as an intermediary, is formed as a natural consequence of the presence of phenyldiazonium chloride arising from fission, the latter reacting with aminoazobenzene. This view is supported by experimental work on the reaction of phenyldiazonium chloride and aminoazobenzene[14]. The author has observed the presence of benzenediazoaminoazobenzene in crude diazoaminobenzene prepared from aniline sulfate and nitrous acid.

(*B*) *The prototropic system; an analogy with the mobility and fission of keto-enol systems.*—The prototropic system[15] —N═N—NH— may become operative by the direct attraction of an alkaline catalyst for the ionising proton[16]; or indirectly by addition or electrostriction of an acidic catalyst†, in such a way as to increase the positive field of the atom from which the proton separates, by increasing the attraction of its shared electrons to another center in the system[17]. In the case of the diazoaminobenzene conversion, which is effected under acidic conditions, the mobility of the system must be due to the latter electromeric effect. Another familiar example of the same effect is found in Meyer's work on the equilibrium system of ethyl malonate[18], in which it is shown that the enol content of the freshly-acidified system changes from about 3 per cent. enol to nil in one minute.

It appears likely that fission of the diazoaminobenzene follows as a consequence of the electron mobility of the system; and here, again, one finds an analogy in the aceto-acetic ester type of system. Hydrolysis of these esters by dilute alkalies—when the ester molecule is known to contain a mobile ionic system[16]—leads to the familiar "ketonic hydrolysis". Dilute acids give the same result, and it may be assumed that it is fission of the enolic form (*i.e.*, $Me \cdot C(OH){=}CH \cdot COOEt$) which occurs, giving rise in the first place to the enolic form of the ketone (*i.e.*, $Me \cdot C(OH){=}CH_2$)[19]. The slower reaction with acids, during which only the electromeric effect would influence the keto-enol equilibrium, lends support to this view; and

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[14] Vignon, *Compt. rend.*, **140,** 92; *Bull. soc. chim.*, [3], **33,** 232; Nietzki and Diesterweg, *Ber.*, **21,** 2144.

[15] Lowry, *J. Chem. Soc.*, **123,** 822 (1923).

[16] Ingold and Shoppee, *ibid.*, **1929,** 447; **1930,** 968.

† Since this paper was written, an interesting paper bearing on this point has appeared: *vide* Hunter, *J. Chem. Soc.*, **1937,** 320.

[17] Baker, *ibid.*, **1928,** 1583, 1979; Lowry, *ibid.*, **1925,** 1371; *Cf.* Ingold and Ingold, *ibid.*, **1926,** 1310; Robinson and others, *ibid.*, **1926,** 401.

[18] Meyer, *Ber.*, **45,** 2843 (1912).

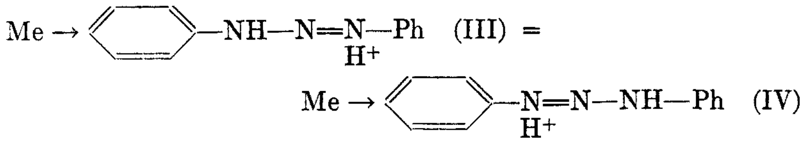
[19] Lapworth, *J. Chem. Soc.*, **85,** 41 (1904).

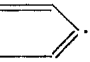
the fact that a much higher temperature (boiling) is required to effect fission of the mobile carbon system, as compared with the ease of fission of the mobile nitrogen system, is quite understandable.

The $PhNH_3^+$ ion has been advanced as the active catalyst in the diazoaminobenzene conversion; but even if it were allowed that this ion could play a part in the early stages of the reaction, its presence to any appreciable extent would certainly retard para-recombination in the later stage. The deactivating effect of a positive pole attached to the benzene nucleus on the latter, and especially on the ortho, and para, positions is well known. The present importance of the activity of the para position is well illustrated by the rapid combination of PhN:N·Cl with $(Me)_2NPh$, or PhO^-. It is, therefore, reasonable to suppose that even in a distinctly acidic solution of diazoaminobenzene, the second stage involving *p*-combination of PhN:N·Cl with $ArNH_2$, takes place with the free base in the equilibrium mixture, $ArNH_2 \cdot HCl = ArNH_2 + HCl$.

(*C*) *Secondary effect of solvent medium.*—The conversion of diazoaminobenzene in aqueous, alcoholic, or aniline solution, can give rise to only the one simple aminoazocompound, aminoazobenzene, even if proton transference should occur. Such is not the case, however, with benzenediazoaminotoluene, a consideration of which will serve to illustrate the various examples around which the controversy of this mechanism has centered. In this case one has, in addition to the influence of the acidic catalyst on the prototropic system, a permanent inductive effect within the molecule[20]. Equation (*iv*) represents the two forms of diazo compound.

(*iv*)



Ignoring secondary factors, a preponderence of IV might be expected in the equilibrium mixture. Fission of IV and para-recombination would give rise, when carried out in *toluidine* solution, to Me·  ·N=N·  ·NH_2·(Me), as Goldschmidt observed[7]; and IV would arise from a solution of diazoaminobenzene in toluidine containing acid, by the reactions indicated in (*A*) and (*iv*) above. In seeking a congruous explanation of the many results that have been reported, however, the influence of the solvent cannot be ignored; and this is illustrated by examining two typical results which Goldschmidt thought to be inconsistent with a theory of fission[7].

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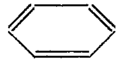
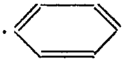
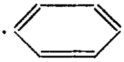
[20] *Ann. Repts.*, **23**, 140 (1926).

(*a*) Me ·  · N=N · NH ·  · Me, in *aniline*, gave Me ·  · N=N · NH · Ph, and Me ·  · N=N ·  · NH_2, but not Ph · N=N · NH · Ph. The first two compounds follow directly from the reactions of section (*A*), and for the reason discussed in the previous paragraph, the latter would not be expected. (*b*) Ph · N=N · NH ·  · Me, in *aniline*, gave Ph · N=N ·  · NH_2, but not Me ·  · N=N ·  · NH_2. The first compound is again explained by the reactions of section (*A*), but the absence of the latter compound casually appears to be at variance with the reaction which might have been expected from equation (*iv*); *i.e.* Me ·  · N=N ·  · NH_2 might have been expected by the formation of IV from the starting compound, followed by fission, and para-recombination. In reaction (*b*) the solvent is aniline; and should the equilibrium mixture have tended to establish itself in the direction of IV, the fission of IV in aniline—itself an equilibrium—would have been suppressed by the effect of the preponderating aniline (solvent) molecules. Fission of the starting material will therefore take place preferentially, giving a reaction mixture very much richer in phenyldiazonium, than in tolyldiazonium, chloride; and one must consequently expect to find essentially phenyldiazo, and not tolyldiazo compounds in the product of conversion.

Examination of a number of similar apparent contradictions of the fission theory, in the literature, has shown that these lend themselves to a satisfactory explanation on the basis discussed in sections (*A*) and (*B*), provided that account is taken of all factors affecting the system during conversion.

It is interesting to apply Goldschmidt's results (*a*) and (*b*) to his own theory (section 3). In (*b*) the Me ·  · NH— residue was preferentially ejected from his postulatory compound II, when only one such residue could have been present in the compound. On the other hand, his postulatory compound I, which would arise in the initial stages of (*a*), must be assumed to contain two Me ·  · NH— residues; and yet neither of these was displaced by the aniline molecules present in large excess, in that stage where residue exchange is most to be expected. The author feels that such elucidating experimental results as those just considered require no more complex interpretation than that of a simple fission and para-recombination; and the side-reactions which make this type of conversion system chemically complex also provide the evidence of its simple (and familiar) mechanism for producing aminoazo compounds.

6. EXPERIMENTAL PROCEDURE AND RESULTS

(*a*) *Preparation of diazoaminobenzene, and preliminary tests.*—The diazoaminobenzene used in these experiments was prepared by standard methods[21], and after several recrystallizations from ethanol containing a trace of ammonium sulfide, it melted sharply at 98°. When this compound was shaken with an 18% aqueous solution of hydrochloric acid at 0°, and the solution was kept for 3 days below 2°, a purple solid was obtained; if the solution were allowed to warm the solid which resulted was sticky. On treating the purple solid with dilute ammonia, and crystallizing the product from petroleum ether, the latter was shown to be aminoazobenzene; m.p., 125°; m.p. of mixture with authentic aminoazobenzene (127°), 126°.

Analysis, found: C, 73.2; H, 5.6; N, 21.6. Aminoazobenzene requires: C, 73.1; H, 5.6; N, 21.3.

This result was repeatable with different concentrations of aqueous acid, the yield of product—always small—being greater with weaker acidity, within limits.

When anhydrous hydrogen chloride was passed into an ethereal solution of pure diazoaminobenzene, avoiding excess hydrogen chloride, a white crystalline precipitate was obtained. The same result was obtained with an alcoholic solution, by shaking out with ether, after passing hydrogen chloride.

Analysis of the "crude" solid gave the following results. Found: C, 52.6; H, 4.6; Cl, 26.3. Required by equimolecular proportions of phenyldiazonium chloride and aniline-hydrochloride: C, 53.2; H, 4.8; Cl, 26.3.

When crude diazoaminobenzene was used for this experiment, the solid precipitated was partially colored (reddish). On filtering this by suction, and washing the solid with a large quantity of cold water, a clean yellow solid remained; m.p., without recrystallization, 119–120°, sharp. The melting point of benzenediazoaminoazobenzene is 119.5°; and it has been shown in section 5(*A*) how this compound would arise in the preparation of diazoaminobenzene.

(*b*) *Quantitative isolation of the diazobenzene constituent of diazoaminobenzene.*—To 1.3 g. of diazoaminobenzene, 60 cc. of concentrated hydrochloric acid added with periodical vigorous shaking, and maintaining the temperature below 0°. An hour later 100 cc. of water at 0° was added, and the solution was filtered. The filtrate was stirred slowly into a solution of 1 g. of β-naphthol in excess caustic soda. The mixture was made slightly acidic, and filtered at 0°, the filtrate being preserved for subsequent examination. The solid was washed with cold water, cold dilute caustic, then cold dilute hydrochloric acid and water; yield of β-naphthol derivative, 1.5 g., or 91% of that theoretically possible. It melted without recrystallization at 128°, and mixed with pure 2-naphthol-1-azobenzene (130.5°) at 129°. This reaction is examined more fully under (*e*).

(*c*) *Quantitative isolation of aniline from acid solution of diazoaminobenzene.*—The acid filtrate and first aqueous washings from the precipitate of β-naphthol derivative in (*b*) were made alkaline, cooled, and well extracted with ether. This extract was filtered of scum, dehydrated for four days, and refiltered. Anhydrous hydrogen chloride precipitated from the ether a white crystalline solid, which melted at 196°.

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[21] GRIESS, *Ann.*, **137**, 58 (1866); STAEDEL AND BAUER, *Ber.*, **19**, 1952 (1886).

Mixed with pure aniline hydrochloride (198°), it melted at 197°. Yield of aniline hydrochloride, 0.82 g., or 96% of that theoretically possible. The oil obtained by neutralization gave positive reactions for aniline by standard qualitative tests.

(*d*) *Direct formation of aminoazobenzene from phenyldiazonium chloride and aniline.*—One mole (15 g.) of freshly-distilled aniline was stirred into 2 moles (11.8 g.) of hydrogen chloride in 450 cc. of water. To this solution at −2°, 0.5 mole (5.57 g.) of dissolved sodium nitrate was added slowly with stirring, keeping the temperature below 0°. The resulting solution, which was definitely acid to litmus, showed no sign of cloudiness; after 10 minutes at 0° it had turned red, but remained perfectly clear. This solution was stored in the dark in a glass-stoppered flask at 0-2°. After 17 hours the solution was a deep clear red; and the first sign of a solid—in the form of fine, dark-purple, metallic-looking needles—was observed 21 hours after the commencement of the experiment. When the flask was held in reflected light the small glinting crystals could be seen suspended in the red solution. After 48 hours, the bottom of the flask was covered with fine, sharply-defined, crystals, and the supernatant liquid was clear save for innumerable tiny particles suspended in it; *i.e.* it was not opaque. Thus this solution behaved in all respects like a slowly crystallizing solution of a pure compound. The experiment was allowed to stand for 7 days at 0-2°, during which time the crop of crystals grew slowly, but fairly steadily, and the color of the body of the solution deepened to a bluish-red. The solution was then suction-filtered through a cold funnel into a flask surrounded by ice. The clear filtrate was immediately replaced in cold storage. The crystals were washed with 75 cc. of water at 2°; yield, 0.2 g. On treatment with dilute ammonia, these yielded a light-brown solid which melted at 126° sharply, after crystallization from petroleum ether; m.p. of mixture with pure aminoazobenzene (126°), 126°.

A further 0.22 g. of clean, lustrous, purple crystals was obtained after 8 more days. This filtrate again yielded a third small lot of crystals after standing for another 23 days in the cold; but these showed a definite stickiness on filtering, and possessed an odor of phenol. The body of the liquid was intensely colored by this time, and was slightly opaque.

(*e*) *Behavior of acid solution of diazoaminobenzene on prolonged standing at low temperature.*—Five separate 0.5-g. samples of finely-powdered diazoaminobenzene were stirred slowly into separate 25-cc. lots of concentrated hydrochloric acid cooled to 0°, in small glass-stoppered flasks. The flasks were then shaken vigorously, which resulted in almost complete solution of the solid; at this stage the flasks were stored in the dark at 0-2°. Subsequently 25 cc. of water at 0° was added to each flask. Addition to number 1 flask was made after an hour, and just before examining its contents; and to flasks 2-5, addition was made after 20 hours. At different times the contents of individual flasks were examined for phenyldiazonium chloride content by filtering the solution and adding the filtrate gradually to a cold solution of β-naphthol in excess caustic soda. The resulting 2-naphthol-1-azobenzene was shown to be reasonably pure, in each case, by a melting-point determination upon a mixture with a pure specimen of this compound.

The results are summarized in Table I, in which column 2 gives the time elapsed before examining the contents of the flask in question, and column 5 gives the per cent of phenyldiazonium chloride calculated from the β-naphthol derivative, and based on that which could arise theoretically from the diazoaminobenzene originally taken.

These results indicate essentially: (a) the presence of phenyldiazonium chloride in practically theoretical amount in a freshly acidified solution of diazoaminobenzene; and (b) the slow disappearance of the former, due to irreversible *p*-combination with the aniline arising from fission, and to its slow decomposition and side reactions. The course of the latter is shown roughly by the following semi-quantitative experiment.

Powdered diazoaminobenzene (14.4 g.) was shaken vigorously with 150 cc. of concentrated hydrochloric acid, and after standing for 12 days in the dark at 0–2°, 400 cc. of water at 0° was added without temperature rise. The content of the flask was filtered cold and the solid collected was washed with ether. The solid was crude aminoazobenzene hydrochloride, as shown by neutralization with ammonia, and recrystallization of the resulting yellow compound from petroleum ether, giving a product m.p., 126°; m.p. of mixture with pure specimen, 126°. The yield of crude product accounted for approximately 14% of the diazoaminobenzene used.

The ether washings were added to an ether extract of the acidic filtrate, which was filtered of scum and dried. Thus, phenol corresponding to about 15% of the diazoaminobenzene was recovered; b.p., 175°; white ppt. with bromine water (m.p., 91°); violet color with ferric chloride; characteristic odor.

The aqueous portion from the ether extract was stirred periodically, and allowed to stand until the traces of ether had evaporated. It was then made alkaline, and a dark mass separated on the surface; when filtered, washed with cold water, and dried, this solid accounted for 40% by weight of the original diazoaminobenzene. It was an impure mixture of brown crystals, with some green ones, and attempts to effect a separation were unsuccessful. The mixture melted sluggishly in the region of 90°, and decomposed with a puff when heated further, suggesting the presence of an appreciable proportion of reformed diazoaminobenzene.

TABLE I

EXPT. NO.	TIME IN HOURS	β-NAPHTHOL DERIVATIVE, G.	M. P. CRUDE	% PHENYLDIAZONIUM CHLORIDE
1	1	0.61	129°	97
2	74	0.47	127°	74
3	215	0.24	128°	38
4	309	0.15	129°	24
5	2200	0.00		00

The alkaline filtrate and washings yielded, on ether extraction, aniline corresponding to nearly 20% of the original diazoaminobenzene; b.p., 178–80°; basic odor; sparingly soluble sulfate; violet hypochlorite reaction.

A small amount of *p*-hydroxyazobenzene was also detected in this system; m.p., crude, 145°; crystallized from petroleum ether, 152°; m.p. of mixture with a pure specimen of *p*-hydroxyazobenzene, 151.5°. Per cent. N, found, 13.8; required by *p*-hydroxyazobenzene, 14.1.

ACKNOWLEDGMENT

The author wishes to acknowledge with appreciation assistance received from Professor C. K. Ingold, F. R. S., in whose laboratories at University College, London, the experimental work was carried out.

SUMMARY

(1) The controversial position of the question of the diazoaminobenzene conversion mechanism has been reviewed.

(2) A prevalent theory of the mechanism of conversion of diazoamino compounds, which postulates unstable intermediary complexes, has been examined briefly. This has been shown to be less satisfactory in explaining certain results than a theory of primary fission and subsequent para-combination.

(3) Other experimental results are reported for which the former theory is inadequate. These include the isolation of phenyldiazonium chloride, and also aniline, in sensibly theoretical amounts from an acidic solution of diazoaminobenzene, and success in effecting the direct combination of phenyldiazonium chloride with aniline (in acidic medium) to give aminoazobenzene.

(4) The important rôle of the solvent medium has been discussed.

(5) Attention has been drawn to the analogy between the prototropic mobility and consequent fission of diazoamino, and keto-enol, systems.

RECENT BOOKS

DISTILLATION. *Joseph Reilly,* D.Sc., F.Inst.P., F.R.C., Sc.I., F.I.C., Professor of Chemistry, National University of Ireland, Methuen & Co., Ltd., London, 1936. vii + 118 pp. 41 figs., 10 x 16.5 cm. Price in America $1.25, through The Chemical Publishing Co. of New York City. Stated price in England 2*s* 6*d*, net each.

This book is one of a series by Methuen & Co. Ltd. of London on chemical subjects and therefore apparently conforms to other books in this series in scope and purpose, namely to present the salient facts of a particular narrow subject in a concise yet authoritative manner, so as to serve as a convenient handbook either for specialists in the field covered or for persons of technical training to explain the principles of the subject plus selected practical examples.

The author has been successful in condensing and correlating a considerable amount of difficult fractional distillation theory in the space available to him. The examples of fractionating columns and equipment given are up to date and the additional references given to the literature are well selected and helpful. The section on "Azeotropic Mixtures" is authoritatively written with a special emphasis on refining alcohol by azeotropic agents with which the author is especially familiar. The subject of vacuum distillation in the laboratory is well covered. Destructive distillation and sublimation are passed over fairly briefly.

The author's job of selection from the wide field of fractional distillation topics has been a very difficult one and doubtless no two men's opinions could be expected to check even closely on such selection. The reviewer would have preferred somewhat less material on vacuum fractionation in favor of more discussion of the theoretical and practical effects of varying the number of plates in a column on the results and in consideration of various types of applications. Also a brief survey of the extremely important applications of fractional distillation in the petroleum industry would perhaps have been desirable. In the section on Azeotropes there should have been included brief descriptions of the azeotropic distillation of acetic acid and instances if not a table of still other azeotropic agents. Aside from these suggestions rather than criticisms the book seems to be well worth reading and keeping on the desk for handy reference on the fundamentals of fractional distillation and on azeotropic alcohol distillation.

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COLLOID CHEMISTRY, PRINCIPLES AND APPLICATIONS. *Jerome Alexander,* M.Sc., National Research Council. 4th ed. D. Van Nostrand Company, Inc., New York City, 1937. xviii + 505 pp. 43 figs. 15 x 24 cm. $4.50.

Jerome Alexander's brief introduction to COLLOID CHEMISTRY, whose first edition was published in 1918, has grown beyond recognition in this imposing fourth edition, of 1937. It now affords an unequalled assembly of the most various fields of knowledge illustrating colloid behavior. The author has had the advantage of being editor of the comprehensive survey of colloid chemistry, compiled by many of the active workers in the subject, in four large volumes. He now gives his own personal conspectus of all the interesting items which appear to have any relevance to colloid systems. His avowed object is "... to form a broad mosaic which gives a coherent picture of nature...." and "... breaking down the artificial mental barriers arising from scientific specialization...." "Observable facts are stressed, theoretical considerations being incidentally invoked so that the facts may be better coördinated and their import understood."

The book makes fascinating reading as it is filled with the most interesting information, some of it very topically up-to-date. It is addressed to the general reader as well as to the student. It is not a text in the ordinary sense. For the most part it dispenses with mathematical theory and with tabulations of data. The industrialist in whatsoever field, the medical man, or the biologist, chemist, or physicist will find references to facts of his own knowledge placed in intriguing juxtaposition to others from diverse or highly specialized fields. Naturally, each will wish to pause and study in greater detail the considerations which are only touched upon with regard to his particular interest, but this stimulus is one of the main purposes of the book.

The book covers so much ground that it is of little avail to quote the chapter headings of its four hundred fifty-four pages which are followed by a bibliography, a glossary, and full author and subject indexes. The historical portions and the general introductions and general properties are dealt with in the first one hundred fifty-eight pages, then follow practical applications, finally extending into biology, medicine, genetics, hormones, vitamins, physiology, pathology, bioelectricity, and lastly a twenty-fourth chapter describing simple experiments which the general reader can attempt for himself to illustrate some of the chief principles which have been discussed.

The printing and make-up of the book are excellent.

JAMES W. MCBAIN

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ORGANIC CHEMISTRY. *Frank C. Whitmore*, Dean of the School of Chemistry and Physics, Pennsylvania State College. First Edition, D. Van Nostrand Co., Inc., New York City, 1937. x + 1080 pp. 14 x 21.5 cm. $7.50.

This book describes the facts and generalizations of organic chemistry. It does this without the dreariness characteristic of reference books. The author steers a happy mean between a college textbook and a reference book. The text is very reliable and up-to-date. Much discussion of the theoretical aspects of the science would be beyond the scope of the book, and the author shows, in general, commendable restraint in avoiding such topics. Occasionally even greater restraint might have been exercised. For instance, all reference to the theory of resonance in organic compounds might have been omitted. Actually it is often used to explain facts, though no adequate account of the theory and its implications are given. The reviewer doubts whether the changes of position of hydrogen atoms implied in the resonances suggested for pyrazole and imidazole are consistent with the theory of resonance.

The book fills a real need, and should achieve the high measure of success that it deserves on its own merits.

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[Contribution from the Chemical Laboratories of Columbia University]

THE ANHYDRIDES OF *N*-ARYLANTHRANILIC ACIDS. II

J. STEIGMAN and G. POWELL

Received January 25, 1937

Compounds of unknown constitution, analyzing as anhydrides, have often been reported in dealing with anthranilic acids, salicylic acids, and related compounds[1]. While working with *N*-phenylanthranilic acid and *N*,*N*-diphenylanthranilic acid the authors observed that the action of benzenesulfonyl chloride on pyridine solutions of these acids did not lead to *N*-benzenesulfonyl derivatives of the acids, but to yellow anhydrides. These anhydrides were observed to give rise to acridones on heating, and to rearrange to compounds of a peptide type if a hydrogen atom was still available on the nitrogen for rearrangement. To the yellow anhydride, by virtue of its reaction with ammonia and alkalies, was acribed the acyl anhydride formula[2], hitherto unrecognized among such amino-acids. The present communication describes further results with substituted *N*-arylanthranilic acids. The reaction appears to be a general one for *N*-arylanthranilic acids. Attempts have been made to obtain the peptide type of compound from *N*-arylanthranilic acids by other methods not involving the possibility of anhydride formation in the synthesis. These have been so far unsuccessful and the preparation of *N*-arylanthranoyl-*N*-arylanthranilic acids is at present limited to the method described above.

EXPERIMENTAL

A. Acyl anhydrides

1. N-o-*Ethoxyphenylanthranilic anhydride.*—By the addition of benzenesulfonyl chloride to a pyridine solution of *N*-*o*-ethoxyphenylanthranilic acid. Crystallized from alcohol or by the addition of alcohol to a chloroform solution of the crude anhydride; m. p. 135°–137°; yellow needles.

Anal. Calc'd: C, 72.55; H, 5.68; N, 5.64.
Found: C, 72.70; H, 5.68; N, 5.5.

2. N-o-*chlorphenylanthranilic anhydride.*—Yellow needles melting near 170°, only

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[1] (*a*) Heller and Lauth, *Ber.* **52B**, 2295 (1919).
(*b*) Spallino, *Gazz. chim. ital.*, **37**, (11) 151 (1907).
(*c*) Meyer, *Ann.*, **351**, 267 (1907).

[2] Goodman, Arbiter, and Powell, *J. Am. Chem. Soc.*, **55**, 4294 (1933).

slowly changed by treatment with acetic acid, but converted into a compound of the B type by heating for a short time with dilute alcoholic solutions of alkalies.

Anal. Calc'd: N, 5.87. Found: N, 6.08.

3. N-o-*tolylanthranilic anhydride.*—Yellow needles, m. p. 164°–166° (from alcohol). Gives an acridone and *o*-tolylanthranilic acid on heating to 190° for five minutes, and is converted into a compound of the B type by refluxing with acetic acid containing sodium acetate for a short time.

Anal. Calc'd: N, 6.42. Found: N, 6.75.

4. N, N-*di*-o-*tolylanthranilic anhydride.*—Yellow needles, m. p. 188°–191°. Gives no compound of the B type on treatment with acetic acid, and is hydrolysed by alcoholic alkalies.

5. N-*mesitylanthranilic anhydride.*—*N*-mesitylanthranilic acid was prepared, and the yellow anhydride was obtained in the usual way; m. p. 200°C–203°.

B. Compounds of the Peptide Type

1. From *N*-*o*-ethoxyphenylanthranilic anhydride by treatment with glacial acetic acid; colorless; m. p. 188–190°. Soluble in dilute ammonia.

Anal. Calc'd: C, 72.55; H, 5.68; N, 5.64.
Found: C, 72.57; H, 5.74; N, 5.5.

2. From *N*-*o*-tolylanthranilic anhydride in the same manner; colorless; n . p. variable; probably not pure.

3. From *N*-*o*-chlorphenylanthranilic anhydride by heat with alcoholic alkalies for a short time; colorless; m. p. near 225° with decomposition.

SUMMARY

The preparation of substituted *N*-arylanthranilic anhydrides is described. The reaction appears to be a general one for *N*-arylanthranilic acids.

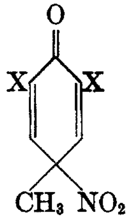
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

THE ACTION OF NITROUS ACID ON THE BROMINE SUBSTITUTION PRODUCTS OF SOME PHENOLS

L. CHAS. RAIFORD AND JOHN HOWE SCOTT

Received May 17, 1937

By oxidation of tetrachloro-*p*-cresol with nitric acid Schneider[1] obtained a tetrachloro cyclic ketone without loss of halogen. Following the same method, Auwers[2] prepared from 2,6-dibromo-*p*-cresol a product of composition $C_7H_5Br_2NO_3$, while Zincke[3] obtained a similar product from the corresponding chlorine compound. The last two substances were represented as shown below:



Meanwhile, in attempts to prepare the analogous nitroso compounds Zincke and students[4] tested a number of the bromine substitution products of the cresols toward nitrous acid. In all cases they obtained nitro compounds which were formed by the replacement of hydrogen or bromine by the nitro radical. Zincke[5] summarized the results as follows: "In the meta series this reaction gives products in which the halogen atom para to hydroxyl is replaced by the nitro group, while in the ortho and para series the ortho halogen is replaced". Raiford and others[6] found that in most cases with this method of nitration the ortho and meta series give isomeric mononitro compounds, and that the method is selective to the extent that chlorine is not replaced.[7]

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[1] SCHNEIDER, Dissertation, Marburg (1896), p. 29.

[2] AUWERS, *Ber.*, **35**, 457 (1902).

[3] ZINCKE, *Ann.*, **328**, 289 (1903).

[4] FOSTER, Dissertation, Marburg (1898); WAGNER, *ibid.*, (1899).

[5] ZINCKE, *J. prakt. Chem.*, [2], **61**, 565 (1900).

[6] RAIFORD, *J. Am. Chem. Soc.*, **44**, 158 (1922).

[7] RAIFORD AND MILLER, *ibid.*, **55**, 2131 (1933).

In the present work this study has been extended. It has been found that when an acetic acid solution of 2,4,6-tribromo-*sym*-xylenol[8] was treated with sodium nitrite, as previously explained,[9] there was obtained a product that decomposed at about 147°. By fractional crystallization this material was separated into two substances, (1) and (2), that melted at 172–173° and 172° respectively. When a mixture of these products was heated it liquefied between 130° and 145° and underwent at least partial decomposition.

At first it was thought that these compounds might be the expected isomeric mononitrodibromoxylenols neither of which was found on record. Analysis of product (1) gave figures that agree with such a composition, and further study of it showed that the nitro radical was in position 4 (OH = 1). The position was determined in the following way. The substance was reduced to the corresponding amino compound, and this was converted into the mixed acetyl-benzoyl derivatives by introduction of the radicals in both possible orders. Isomeric mixed diacyl derivatives were obtained, and no rearrangement was observed, which shows that the nitro radical in compound (1) is not in the ortho position as respects hydroxyl.* This view is supported also by the behavior of the compound when oxidized. When it was treated with fuming nitric acid as directed by Kohn and Rabinowitsch[10] it gave the corresponding dibromo-*m*-xyloquinone previously obtained by Jacobsen[11] by oxidation of dibromomesitol. These relations are indicated on the following page.

Qualitative tests of compound (2) indicated the absence of nitrogen, and a mixture of it and the xyloquinone specified above melted without depression. It was further identified by a study of its derivatives. Reduction of it gave a compound which, though not entirely colorless, was proved to be the required hydroquinone. The latter was easily converted into diacyl derivatives that were colorless and readily crystallized.

It is of particular interest here to note the behavior of this quinone toward amino compounds. Attempts to prepare the oxime, the phenylhydrazone and the semicarbazone gave, in each case, the hydroquinone

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[8] Nölting and Forel, *Ber.*, **18**, 2679 (1885).

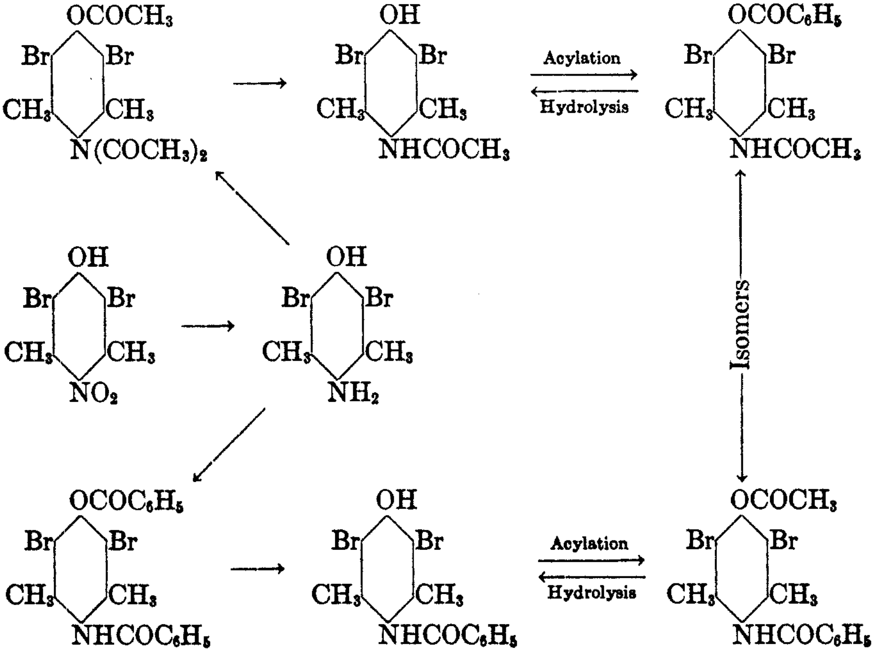
[9] Raiford, *Am. Chem. J.*, **46**, 426 (1911).

* It has been shown by Raiford and others [*J. Am. Chem. Soc.*, **56**, 1586 (1934)] that when two different acyl radicals derived from carboxylic acids are introduced into an ortho aminophenol, only one mixed diacyl derivative can usually be obtained, and in this product the heavier and more acidic radical is attached to nitrogen. To meet this requirement the migration of acyl from nitrogen to oxygen must occur in one of these reactions.

[10] Kohn and Rabinowitsch, *Monatsh.*, **48**, 360 (1927).

[11] Jacobsen, *Ann.*, **195**, 273 (1879).

Proof of structure of 2,6-dibromo-4-nitro-*sym*-xylenol



in yields of 81, 83, and 94%, respectively, and nothing else was isolated from the reaction mixtures.† These relations are shown on page 216.

The second compound studied was the tribromo derivative of resorcinol monomethyl ether. When this product was nitrated[12] it gave a high yield of a mononitrodibromo compound that melted at 126–127°.‡ Reduction of this product (III) (see accompanying diagram) gave an aminophenol (IV) which was readily converted into the corresponding diacyl derivatives (V) and (IX). Partial hydrolyses of these products gave the phenolic substances (VI) and (VIII), respectively, which must have had the remaining acyl groups attached to nitrogen. When these products, in turn, were acylated with the required reagents they gave the acetyl-benzoyl derivatives (VII) and (X), which melted at 186° and 170–171°, respec-

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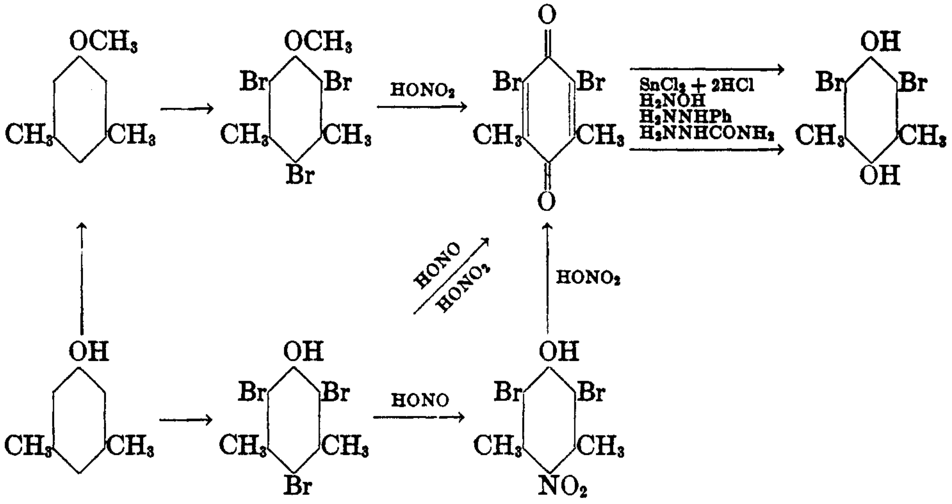
† This behavior agrees with the observations of Nef [*Ann.*, **237**, 12 (1887)] who was unable to obtain an oxime from duroquinonecarboxylic acid, and of Kehrmann [*Ber.*, **21**, 3320 (1888)] who found that tetrasubstituted quinones, such as chloranil, give no oximes. These authors did not test their products toward phenylhydrazine and semicarbazide, and the formation of a hydroquinone was noted in only one case.

[12] Raiford and Grosz, *J. Am. Chem. Soc.*, **53**, 3422 (1931).

‡ Kohn and Löff [*Monatsh.*, **45**, 594 (1924)] recorded 122° for a product that should have the structure of this one.

Behavior of 2,4,6-tribromo-*sym*-xylenol toward nitrous and nitric acids



tively, and which depressed each other's melting points profoundly. This showed that the positions of the acyl radicals could not have been the same in the two products (see page 217). But, inasmuch as the partial hydrolysis of these compounds gave the same benzoylaminophenol, product (VIII), it follows that in the latter reaction the benzoyl radical in product VII migrated from oxygen to nitrogen.§

Acknowledgment. We are indebted to Mr. Donald W. Kaiser of this Laboratory for assistance with certain portions of the experimental work.

EXPERIMENTAL PART

*2,4,6-Tribromo-*sym*-xylenol (OH = 1).*—Thöl[13] gave 162.5° as the melting point of a product which he regarded as having this structure, but he described no method of preparation and recorded no analytical data. In the present work, Anselmino's[14] method, modified in certain details, was used. To a solution of one molecular proportion (122 g.) of *sym-m*-xylenol in 800 cc. of acetic acid there was slowly added three molecular proportions of bromine dissolved in 150 cc. of acetic acid, with continual stirring. The solution was at room temperature when reaction was started; by the time all bromine was in it was near the boiling point of acetic acid. The pasty mass that formed as the mixture cooled was allowed to stand overnight and was then poured with stirring into ten volumes of dilute solution of sodium acid sulfite. The yield was nearly quantitative. Crystallization from carbon tetra-

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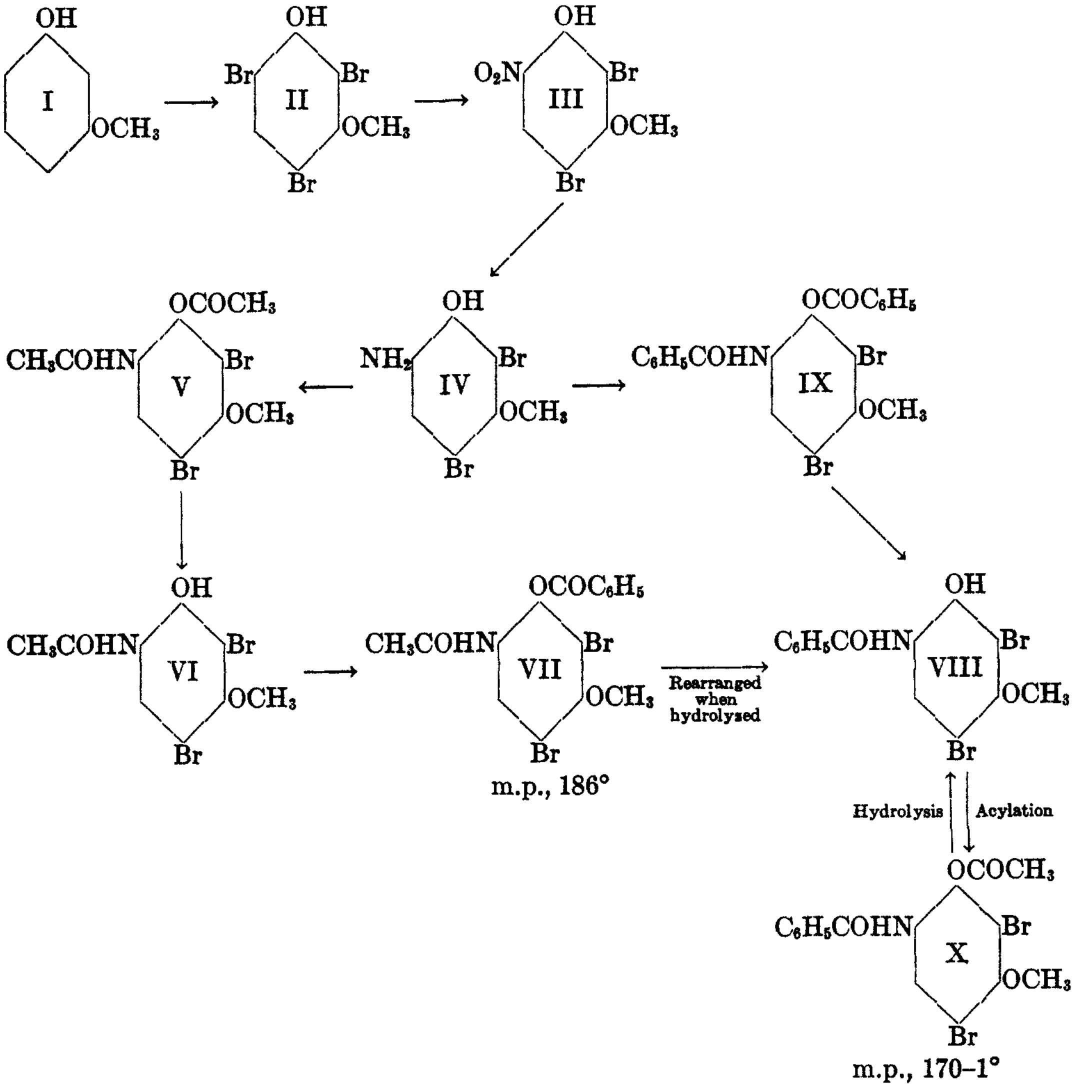
§ This behavior has previously been noted by Raiford and Couture [*J. Am. Chem. Soc.*, **46**, 2307 (1924)] in the study of other ortho aminophenols.

[13] Thöl, *Ber.*, **18**, 362 (1885).

[14] Anselmino, *ibid.*, **35**, 147 (1902).

Derivatives of 2,4-dibromo-3-methoxy-6-nitrophenol



chloride gave colorless, silky needles that melted at 166°, which agrees with Anselmino's value.*

Nitration of tribromo-sym-*xylenol.*—A suspension of 100 g. of the tribromo compound in 700 cc. of acetic acid at room temperature was stirred for one and one-half hours while 2.5 molecular proportions of sodium nitrite was added. No attempt was made to control the temperature. The mixture was allowed to stand overnight and was then poured with stirring into 10 volumes of water. A yield of 89% was obtained. One crystallization from carbon tetrachloride gave a mass of fine yellow crystals that seemed to decompose at about 147°, suggesting a mixture. Several repeated crystallizations finally gave pale lemon-colored clusters of tablets that decomposed at 172–173°. The yield of purified material was 58%. This compound, designated above as product (1), was identified as 2,6-dibromo-3,5-dimethyl-4-nitrophenol.

Anal. Calc'd for $C_8H_7Br_2NO_3$: Br, 49.23.
Found: Br, 48.92.

2,6-Dibromo-3,5-dimethyl-4-aminophenol.—Twenty grams of the above nitro compound, dissolved in 125 cc. of boiling acetic acid, was reduced by means of stannous chloride and hydrochloric acid. The yield of purified amine hydrochloride[15] was 59%.

Anal. Calc'd for $C_8H_{10}Br_2ClNO$: N, 4.22.
Found: N, 4.26.

A portion of the hydrochloride was made into a paste with water and treated with ammonium carbonate solution to obtain the aminophenol, which was almost colorless when freshly prepared. Crystallization from benzene gave pale brown needles that melted with decomposition at 207°.

Anal. Calc'd for $C_8H_9Br_2NO$: Br, 54.23.
Found: Br, 53.94.

2,6-Dibromo-3,5-dimethyl-4-diacetylaminophenyl acetate.—When a portion of the required aminophenol, mixed with anhydrous sodium acetate, was warmed with the theoretical amount of acetic anhydride the product obtained had a melting range of 120–135° and could not be purified by crystallization. By the use of excess of acetic anhydride a single compound was obtained. Crystallization from alcohol gave colorless plates that melted at 153–154°. The yield of purified material was 81%. Analysis indicated the presence of three acetyl radicals.†

Anal. Calc'd for $C_{14}H_{15}Br_2NO_4$: Br, 38.00.
Found: Br, 37.99.

Hydrolysis of this product with caustic alkali caused the loss of acyl from oxygen and one of these groups from nitrogen to give the corresponding acetylaminophenol. Analytical data and other properties for this and related acyl derivatives are given in Table I.

2,6-Dibromo-m-*xyloquinone.*—This compound, designated above as product (2), melted at 172°, which is two degrees lower than that reported by Jacobsen. Analysis of the product here under consideration indicated that it was nearly pure.

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* It is of interest here to note that attempts to alkylate this phenol were unsuccessful. The failures may be due to steric hindrance.

[15] RAIFORD, *Am. Chem. J.*, **46**, 419 (1911).

† The formation of such triacetyl derivatives has previously been noted by PFOB [*Monatsh.*, **18**, 475 (1897)] and by RAIFORD AND COUTURE [*J. Am. Chem. Soc.*, **46**, 2313 (1924)].

Anal. Calc'd for $C_8H_6Br_2O_2$: Br, 54.42.
Found: Br, 54.33.

*2,6-Dibromo-*m*-xylohydroquinone.*—In the first attempt to obtain this product a dilute alcoholic solution of the quinone was saturated with sulfur dioxide. A dark-colored product, probably a quinhydrone, was formed, but this was not changed by fifteen hours' further treatment with the gas. In a second experiment a solution of 10 g. of stannous chloride (30% excess) in 10 cc. of concentrated hydrochloric acid was added gradually through a return condenser to a boiling solution containing 10 g. of the quinone in 50 cc. of acetic acid. The mixture became dark colored at first but was nearly colorless after all stannous salt had been added. Heating was continued for fifteen minutes, and the liquid was allowed to cool, which caused a portion of the product to separate in pale brown needles. The mixture was filtered, and concentrated hydrochloric acid was added to the filtrate, which caused an additional portion of hydroquinone to crystallize out. The total yield was 96%. In this condition the compound decomposed when heated to about 211°. Attempts to recrystallize it were not successful. Its identity was established by a study of its derivatives.‡

TABLE I

ACYL DERIVATIVES OF 2,6-DIBROMO-3,5-DIMETHYL-4-AMINOPHENOL

POSITION OF ACYL RADICAL	YIELD, %	CRYSTAL FORM[b]	M.P., °C.	COMPOSITION	ANALYSES, HALOGEN	
					Calc'd	Found
Acetalyminophenol	88[a]	Colorless rhombohedra	243–244	$C_{10}H_{11}Br_2NO_2$	47.47	47.34
N-Acetyl-*O*-benzoyl[c]	69	Colorless needles	252–253	$C_{17}H_{15}Br_2NO_3$	36.28	35.98
N-Benzoyl-*O*-benzoyl	82	Colorless amorphous powder	[d]	$C_{22}H_{17}Br_2NO_3$	31.80	31.57
Benzoylaminophenol		Colorless needles	257–258	$C_{15}H_{13}Br_2NO_2$	40.10	39.89
N-Benzoyl-*O*-acetyl	90	Colorless needles	210	$C_{17}H_{15}Br_2NO_3$	36.28	36.09

[a] These figures refer to purified material.

[b] These products were crystallized from a mixture of equal volumes of acetone and toluene.

[c] The Schotten-Baumann method gave poor results here, but that described by Einhorn and Hollandt [Ann., 301, 101 (1898)] was quite satisfactory.

[d] Did not melt below 276°.

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‡ CLAUS AND RUNSCHKE [*J. prakt. Chem.*, [2], 42, 124 (1890)] used stannous chloride to reduce the corresponding dichloroquinone and stated that they obtained a product that melted at 224°. The compound was not analyzed and is not listed in Richter's Lexikon, nor in Stelzner's Register. The authors assumed that the substance was a hydroquinone, because they were able to oxidize it into the quinone with which they started, and for which they obtained analytical data.

The diacetyl derivative.—A mixture of 10 g. of the hydroquinone, 3 g. of fused anhydrous sodium acetate and 15 cc. of acetic anhydride was gently warmed for three-fourths hour, and the cooled mixture was extracted with water. The residue was crystallized from alcohol, from which it separated in colorless needles that melted at 215–216°. The yield of purified material was 86%.

Anal. Calc'd for $C_{12}H_{12}Br_2O_4$: Br, 42.10.
Found: Br, 41.76.

The dibenzoyl derivative was obtained by treatment of the hydroquinone with benzoyl chloride by the Schotten-Baumann method. Crystallization of the product from *n*-amyl alcohol gave fine colorless needles that melted at 249–250°. A 76% yield of purified material was obtained.

Anal. Calc'd for $C_{22}H_{16}Br_2O_4$: Br, 31.74.
Found: Br, 31.70.

2,4,6-Tribromoresorcinol monomethyl ether (*OH = 1*).—Benedikt[16] found 99° as the melting point for a product he obtained by the action of excess of bromine on an acetic acid solution of resorcinol monomethyl ether, and which he designated as a tribromo compound. He recorded no analytical data, and did not study the product further. Tiemann and Parrisius[17] found 104° for a compound prepared by treatment of an ether solution of the same starting material with bromine as long as decolorization took place, and for which they obtained a satisfactory analysis. Neither of these workers recorded the yield of product.

TABLE II

ACYL DERIVATIVES OF 2,4-DIBROMO-3-METHOXY-6-AMINOPHENOL

POSITION OF ACYL GROUP	YIELD, %	M.P., °C.	FORMULA	HALOGEN ANALYSES, %	
				Calc'd	Found
Acetylaminophenol..........	67	157–158[a]	$C_9H_9Br_2NO_3$	47.19	47.40
Benzoylaminophenol	71	146–147	$C_{14}H_{11}Br_2NO_3$	39.90	39.90
N-Benzoyl-*O*-benzoyl	69	169–170	$C_{21}H_{15}Br_2NO_4$	31.68	31.50
N-Benzoyl-*O*-acetyl..........		170–171[b]	$C_{16}H_{13}Br_2NO_4$	36.11	35.80
N-Acetyl-O-benzoyl[c].........	22	186–186.5[b]	$C_{16}H_{13}Br_2NO_4$	36.11	36.10

[a] These products were purified by crystallization from benzene.

[b] A mixture of these melted with pronounced depression.

[c] Hydrolysis of this product caused rearrangement, and gave the benzoylaminophenol melting at 146–147°.

In the present work bromination was carried through by following Benedikt's general directions modified to the extent that somewhat more than three molecular proportions of bromine were employed, and when the reaction seemed to be complete the mixture was poured into four volumes of water containing sodium acid sulfite. Best results were obtained by working with 25-g. portions of starting material. When larger quantities were used the product was more difficult to purify. A yield of 80% was obtained. Crystallization from alcohol gave short colorless needles that melted at 104–105°.

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[16] BENEDIKT, *Monatsh.*, **1**, 368 (1880).

[17] TIEMANN AND PARRISIUS, *Ber.*, **13**, 2364 (1880).

2,4-Dibromo-3-methoxy-6-nitrophenol.—To a solution of the above tribromo compound in acetic acid there was gradually added with stirring 2.5 molecular proportions of sodium nitrite, while the temperature was held between 12° and 15°. After standing overnight the solution was poured into about 5 volumes of water, stirred well and allowed to remain until the precipitate had settled. The yield was 95%. Repeated crystallization from alcohol gave yellow needles that melted at 126–127°. Kohn and Löff[18] reported 122° for a product which probably has this composition, though their analytical data did not indicate a pure substance. Also, while the present work was in progress Hodgson and Nixon[19] reported 128° for a compound obtained in an attempt to alkylate 2,4-dibromo-3-fluoro-6-nitrophenol, which they regarded as having the same structure as the one here under consideration.

Anal. Calc'd for $C_7H_5Br_2NO_4$: Br, 48.92.
Found: Br, 48.70.

2,4-Dibromo-3-methoxy-6-aminophenol.—When the nitro compound just described was reduced with a mixture of stannous chloride and hydrochloric acid[20] the corresponding amine hydrochloride was obtained in nearly quantitative yield.

Anal. Calc'd for $C_7H_8Br_2ClNO_2$: Hal, 58.62.
Found: Hal., 58.59.

A portion of this salt was mixed into a paste with water, the solution was treated with the calculated amount of ammonium carbonate, and filtered, and the residue was washed with several small portions of cold water. A yield of more than 90% was obtained. Crystallization from ligroïn gave pale brown needles that melted at 105–106.5°.

Anal. Calc'd for $C_7H_7Br_2NO_2$: Br, 53.87.
Found: Br, 53.99.

The diacyl derivatives.—The simple and mixed diacyl derivatives were obtained by standard methods. Analytical data and other properties of the products are given in Table II.

SUMMARY

When *sym*-tribromo-*m*-xylenol was subjected to the action of nitrous acid as directed by Zincke there was obtained a mixture of 2,6-dibromo-4-nitro-*m*-xylenol and 2,6-dibromo-*m*-xyloquinone. When 2,4,6-tribromoresorcinol monomethyl ether was treated in the same way, 2,4-dibromo-3-methoxy-6-nitrophenol was formed. The relative positions of the hydroxyl and nitro radicals in these compounds were determined by reduction to the corresponding aminophenols and study of the mixed acetylbenzoyl derivatives of these products. From the aminoxylenol isomeric mixed diacyl derivatives were obtained and no rearrangement was observed, which showed that the amino and hydroxyl groups were not ortho to each other. The migration of acyl previously found to be characteristic of *o*-aminophenol derivatives was found to occur in the product obtained from resorcinol monomethyl ether.

[18] KOHN AND LÖFF, *Monatsh.*, **45**, 594 (1924).

[19] HODGSON AND NIXON, *J. Chem. Soc.*, **1932**, 274.

[20] RAIFORD, *Am. Chem. J.*, **46**, 419 (1911).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF McGILL UNIVERSITY]

SOME LIMITATIONS OF 2,4-DINITROPHENYLHYDRAZINE AS A REAGENT FOR CARBONYL GROUPS

C. F. H. ALLEN* AND J. H. RICHMOND

Received May 21, 1937

Since the appearance of our earlier paper[1] the use of 2,4-dinitrophenylhydrazine as a reagent for identification of aldehydes, ketones and ketone derivatives has been generally adopted. In addition to the many isolated instances in which the derivatives have been prepared as reference compounds for new substances, there have been numerous papers dealing with carbonyl group reagents.[2] The many discrepancies in the melting points as recorded in various laboratories for the same substances are noteworthy; the variation is frequently too great to be explained on the ground of insufficient purification. The purpose of this paper is to describe certain observations made in this laboratory over a period of years, which may be of assistance to others, as well as accounting for some of the discrepancies.

There are two modifications of the general procedure for the preparation of the derivative—one employing hydrochloric and the other sulfuric acid. The latter is applicable in a few instances where the former has not been useful, but, in our opinion, the ease of purification of the derivative is greater when hydrochloric acid is the catalyst. Traces of sulfuric acid persist through several recrystallizations, and, if secondary reactions are possible, as is frequently the case, lead to increasing difficulty in purification. Brady's[3] objection that the hydrochloride of the reagent is less soluble, is unimportant if one adds the acid before the carbonyl compound, though this is only necessary in a very few extreme instances.

Acetaldehyde, as is well-known, gives dinitrophenylhydrazones that seem to exist in two modifications, one melting at 147° and the other at 164°. In half a dozen comparable runs, the use of hydrochloric acid in every instance gave a crude product melting at 157° or higher, whereas sulfuric acid gave the low-melting form each time. Whether these are true isomers or one an impure form of the other is under controversy.

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[1] ALLEN, *J. Am. Chem. Soc.*, **52**, 2955 (1930).

[2] (*a*) STRAIN, *ibid.*, **57**, 758 (1935); (*b*) COWLEY AND SCHUETTE, *ibid.*, 3463 (1935); (*c*) CAMPBELL, *Analyst*, **61**, 391 (1936); (*d*) RODUTA AND QUIBILAN, *Rev. Filipina med. farm.*, **27**, 123 (1936) [*Chem. Abstr.*, **31**, 98 (1937)].

[3] BRADY, *J. Chem. Soc.*, **133**, 756 (1931).

Bryant[4] assumes that the two are polymorphs, whereas in Campbell's[2c] experience it is a case of insufficient purification.

An alternative explanation, rejected by both authors, is that of geometrical isomerism. Bredereck[5] demonstrated the occurrence of this in the furan series, and it might be encountered with other aldehydes. The change of one form into the other is catalyzed by acidic reagents, and would be more probably encountered in the sulfuric acid procedure, in which the acid is less readily removed during purification. However, this explanation cannot account for the discrepancies recorded for the melting points of dinitrophenylhydrazones of symmetrical ketones.

The separation of the dinitrophenylhydrazones from the unused reagent is difficult. It is advisable *always to use a slight excess of the carbonyl compound* and thus avoid this complication. In our opinion, many of the discrepancies in melting points in the literature may be accounted for by contamination of the derivative with the reagent.

The nature of the solvent selected for purification may be of importance. When it can be used, alcohol is preferable to all others, but when the derivative is too sparingly soluble some substitute is necessary. Acetic acid and acetone must be avoided for obvious reasons; dioxane, aromatic hydrocarbons, or esters are usually suitable. In our experience, chloroform is usually to be avoided, since it does not give a good separation of mixtures; the melting point is often unchanged after successive crystallizations, yet subsequent use of another solvent at once raises it. As a rule, the substances are too soluble in nitrobenzene, and it is not easily removed from the crystals owing to its high boiling point. *In every case the derivative should be recrystallized to the same constant melting point from two different solvents.*

Frequently the derivative obtained does not correspond to the substance started with. This is unimportant, provided the same procedure always gives the same product. The most noticeable instances are the ketonic acids,[2a, b] which give esters so rapidly that alcohols, as media for the reaction, are to be avoided. In the case of keto esters, the possibility of radical interchange on recrystallization from an alcohol should be kept in mind.

The dinitrophenylhydrazine of benzoylformic acid, prepared in water solution, melts at 196°[6] and that of the methyl ester at 171°,[1] but the ethyl ester gives a product, m.p. 158°, that has lost alcohol; it is probably a pyridazine.

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[4] Bryant, *J. Am. Chem. Soc.*, **58**, 2335 (1936).

[5] Bredereck, *Ber.*, **65**, 1833 (1932); Bredereck and Fritzsche, *ibid.*, **70**, 802 (1937).

[6] Corson, Sanborn, and Van Ess, *J. Am. Chem. Soc.*, **55**, 3463 (1935).

TABLE

Properties of 2,4-Dinitrophenylhydrazones*

CARBONYL COMPOUND	CORRECTED M.P., °C.	COLOR	FORMULA	CALCULATED, %			FOUND, %		
				C	H	N	C	H	N[a]
Hydrocinnamic aldehyde[b]	149	Yellow	$C_{15}H_{14}N_4O_4$			17.8			17.7
$C_6H_5C{\equiv}CCHO$	190	Yellow	$C_{15}H_{10}N_4O_4$			18.1			18.2
Di-*i*-propyl ketone[c]	88	Orange	$C_{13}H_{18}N_4O_4$			19.1			19.0
Di-*i*-butyl ketone[c]	66	Orange-red	$C_{15}H_{22}N_4O_4$			17.4			17.1
Hexadecane-2,15-dione[d]	117	Yellow	$C_{28}H_{38}N_8O_8$	54.7			54.9	6.0	
3-Methylcyclohexanone	155	Yellow	$C_{13}H_{16}N_4O_4$			19.1			18.9
Dibenzyl ketone	100	Yellow	$C_{21}H_{18}N_4O_4$			14.3			14.5
p-Chloroacetophenone	231	Scarlet	$C_{14}H_{11}ClN_4O_4$			16.7			16.7
p-Bromoacetophenone	230	Scarlet	$C_{14}H_{11}BrN_4O_4$	44.3	2.9		44.6	3.0	
p-Methylacetophenone	248	Claret	$C_{15}H_{14}N_4O_4$			17.8			17.9
p-Methoxyacetophenone	220	Red	$C_{15}H_{14}N_4O_5$			17.0			17.1
Phenacyl chloride	212	Orange	$C_{14}H_{11}ClN_4O_4$	50.3	3.3		50.5	3.4	
Benzylacetophenone	180	Orange	$C_{21}H_{18}N_4O_4$	64.6	4.6		64.8	4.6	
Vanillalacetone	230	Carmine	$C_{17}H_{16}N_4O_5$			15.7			15.7
Ethyl benzoylformate	158	Or-yellow	$C_{14}H_8N_4O_5$			17.9[e]			17.7, 17.6
Benzalacetophenone	245	Red-orange	$C_{21}H_{16}N_4O_4$[e]			14.4			14.5
(Pyrazoline from)	175	Red-orange	$C_{21}H_{16}N_4O_4$			14.4			14.4
Desoxybenzoin	204	Orange	$C_{20}H_{16}N_4O_4$			14.9			14.9

[a] Semi-micro Dumas method, Allen and Young, *Can. J. Res.*, **14**, 216 (1936).

[b] This substance, and *p*-tolualdehyde, were supplied by Compagnie Parento Ltd.

[c] By sulfuric acid procedure.

[d] This substance, and methyl vinyl ketone were donated by E. I. Dupont de Nemours Inc.

[e] Calc'd for a pyridazine; a DNPH, $C_{16}H_{14}N_4O_6$, would have 15.6% N; it gave a negative Zeisel test.

* Some of these substances were prepared in connection with other work by Miss M. R. Gilbert, and Messrs. J. C. W. Evans, J. Henderson, J. A. McWha, R. V. V. Nicholls, and C. G. Eliot. Their assistance is gratefully acknowledged.

Benzalacetophenone might give isomeric dinitrophenylhydrazones or a pyrazoline derivative. Actually it gives mixtures of two substances the relative amounts depending on the time of contact with the acid. A high-melting form, which decolorizes permanganate rapidly, is probably the open-chain derivative. The low-melting isomer reacts only slowly with the hot oxidizing agent and is presumably the pyrazoline; the latter results by simple recrystallization of the hydrazone in the presence of a trace of mineral acid. These results indicate that mixtures may be expected with unsaturated ketones. We have, so far, been unable to recrystallize satisfactorily the derivative from methyl vinyl ketone.

Diacetone alcohol loses water during the short time of preparation of the dinitrophenylhydrazone, so that the derivative is that of mesityl oxide; hydroxycitronellal shows a similar behavior.

Although chloral has been reported as giving a derivative,[2d] in our hands the reactivity of the chlorine atoms has led to mixtures, so that the reaction cannot be considered convenient or easily reproducible.

Finally, regeneration of the carbonyl compound from the dinitrophenylhydrazones cannot be said to be satisfactory. The procedure involving simple reversal of the reaction by which they are formed has been successful in a very few instances.[7] Replacement by a different carbonyl compound has not been as valuable a method as might be anticipated. Strain[2a] recommends the use of the relatively inaccessible glyoxals or diacetyl, while Rupe[8] suggests a five-hour treatment with alcoholic *m*-nitrobenzaldehyde. Picryl chloride has been used in a few instances.[9] Collatz and Neuberg[7] observed that heating in a pressure bottle with a large excess of acetaldehyde, acetone, or furfural enabled them to regenerate substances like glyceric aldehyde and dihydroxyacetone. Since 2,4-dinitrophenylhydrazine is unstable to alkaline reagents,[2a, 10] the use of the latter has led to success in some instances.[11]

EXPERIMENTAL

The dinitrophenylhydrazones in the table were obtained by the general procedure using hydrochloric acid, unless otherwise noted, when sulfuric acid gave a better result. Neither modification gave useful products with chloral, bromal, methyl *n*-heptyl ketone, methyl *n*-octyl ketone, methyl vinyl ketone, di-*n*-butyl ketone, vinyl phenyl ketone, phenacyl bromide, β-chloropropiophenone, or dimethyl pyrone.

As examples of the failure of chloroform as a solvent for purification may be cited these instances: (*a*) *p*-tolualdehyde gave a product, m.p. 214–215°C. unchanged by

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[7] Collatz and Neuberg, *Biochem. Z.*, **255**, 27 (1932).

[8] Rupe and Gassmann, *Helv. Chim. Acta*, **19**, 574 (1936).

[9] Cuisa, *Gazz. ital. chim.*, **37**, [ii], 301 (1907).

[10] Macbeath and Price, J. Chem. Soc., **1934**, 1637.

[11] Private Communication, G. F. Wright, McGill University.

recrystallization from this solvent, but one treatment with dioxane raised it 12°. In the preparation, the reagent is completely dissolved, so contamination of the product by the former seems unlikely. (*b*) The mixtures of dinitrophenylhydrazone and pyrazoline from benzalacetophenone are usually unchanged by recrystallization from chloroform, but at once separated by the use of dioxane. These mixtures, secured under apparently identical conditions, melt anywhere from 204 to 240°C. One of them, m.p. 208°C. seems to behave like a single substance, and has been mistaken for the pure dinitrophenylhydrazone.[1] The pure high-melting isomer, which is thought to be the hydrazone, when boiled 15-20 minutes in alcohol with a trace of sulfuric acid, gave this mixture. It is well known that pyrazolines are formed by the action of mineral acids on phenylhydrazones of α,β-unsaturated ketones.

SUMMARY

Attention is called to limitations in the application of 2,4-dinitrophenylhydrazine as a reagent for identifying carbonyl compounds, and suitable precautions are suggested to circumvent these. The avoidance of an excess of reagent is emphasized; a procedure and solvents are recommended; and the nature of certain secondary products is illustrated.

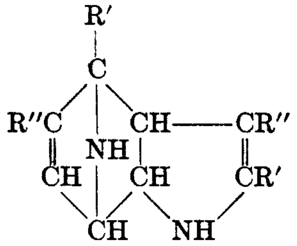
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF McGILL UNIVERSITY]

THE STRUCTURE OF DIPYRROLES

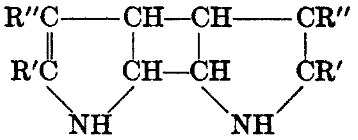
C. F. H. ALLEN,[*] M. R. GILBERT, AND D. M. YOUNG[†]

Received May 21, 1937

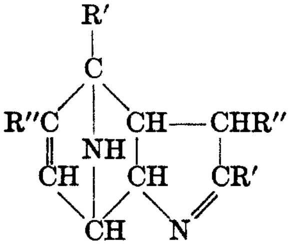
By analogy with the structures assigned to the dimeric forms of diphenylcyclopentadienone[1] and dicyclopentadiene[2] a few years ago, it was suggested at that time[1] that the dipyrroles had a similar ring system, formed by a diene synthesis, and should be represented as I, instead of being written as one of the possible cyclobutane derivatives, II, in current use. The position of the linkage of the carbon rings is, of course, unaffected by the usual tautomerism of unsaturated nitrogen compounds, as in Ib.



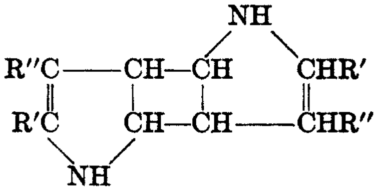
Ia



IIa



Ib



IIb

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[*] Present address, Eastman Kodak Co., Rochester, N. Y.

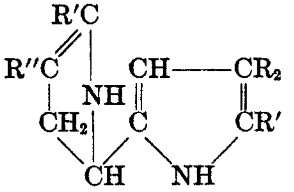
[†] Acknowledgment is hereby made of a bursary and studentship granted by the National Research Council of Canada.

[1] ALLEN AND SPANAGEL, *J. Am. Chem. Soc.*, **55**, 3773 (1933).

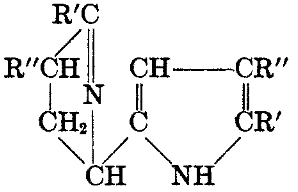
[2] ALDER AND STEIN, *Ann.*, **485**, 223 (1931); **496**, 204 (1932).

From Diels' work[3] it is known that pyrroles do not enter into the diene synthesis in the usual way, but like any substance of the type HA, they add to the conjugated system of the other reactant. If there is nothing else present for the pyrrole to combine with, it should add to itself. Since pyrroles can be kept unchanged for long periods of time, this tendency cannot be very great; the addition, however, is brought about by the action of strong acids, which form salts with the dipyrrole, thus removing it from the equilibrium.*

In the case at hand, this situation would give rise to one of the five tautomeric forms of substance III†



IIIa



IIIb

The difference between formulas I and III is not great; in fact, the latter would be a very probable intermediate in the formation of Ia in a stepwise diene synthesis.

Dipyrrole salts are formed by the action of acids on dry, ethereal solutions of pyrroles.[4] The free bases are liberated by alkali. The dimers of pyrroles which are substituted unilaterally may be distilled unchanged, and converted into indoles with loss of ammonia‡ but otherwise they are depolymerized by heat.§

Pyrroles seldom form salts with acids, and methiodides are practically unknown. The dipyrroles form salts with one equivalent of acid, indicat-

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[3] Diels, Alder, and Winter, *ibid.*, **486**, 211 (1931).

* Indole formation from pyrroles and dipyrroles may take place in the same way, the loss of ammonia removing the latter as fast as formed; this subject will be considered in a subsequent paper.

† Only two possibilities are illustrated, since the others present no new complication.

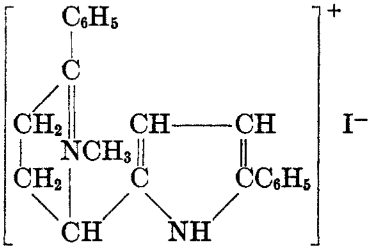
[4] Fischer, *Ber.*, **48**, 401 (1915); Fischer and Orth, "Die Chemie des Pyrrole." Akad. Ver. Ges. M.B.H., Leipzig, **1934**, Bd. I. s. 38.

‡ An apparent exception is H. Fischer's 2-methyl-5-carboxy- (or carbethoxy-) pyrrole-3-propionic acid [Fischer and Hussong, *Ann.*, **492**, 128 (1931)] which loses the carboxy group in the process, and hence is equivalent to a pyrrole with groups in one side of the ring only.

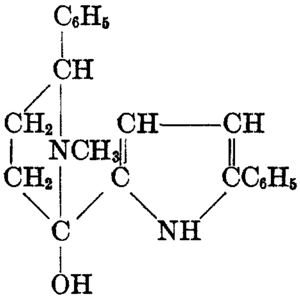
§ Pyrrole gives tripyrrole except under special conditions [Schmitz-Dumont, *Ber.*, **62B**, 226 (1929)]; on being heated, indole, pyrrole, and ammonia result [Dennstedt and Voigtlander, *ibid.*, **27**, 476 (1894)].

ing that at least one nitrogen atom is different and that the characteristic pyrrole linkage has disappeared. On inspection of the formulas I, II, and III, it is seen that both nitrogen atoms are alike in II but different in the others; II can thus be excluded from consideration. A pyrrole system is still present in III, and monoacidic salts would be expected, but in the absence of our knowledge of substances like I, it is not possible to predict the behavior of the nitrogen atoms.

With a view to securing solid substances and thus facilitating manipulation and simplifying the identification of degradation products, 2-phenylpyrrole was used in the work described in this paper. It does not give a methiodide but readily forms a dipyrrole; the latter gave salts with three acids, as well as a mono-methiodide. This methylation involved refluxing in methyl iodide as a solvent (over twenty equivalents.) With sodium hydroxide an oil resulted, which again added methyl iodide to give a salt, insoluble in water, and unaffected by potash. Refluxing with a suspension of silver oxide in aqueous alcohol brought about a decomposition and deposition of silver iodide, but it was impossible to recognize any of the organic material. Pyrroles do not form methiodides, whereas the reduced derivatives are completely methylated by excess methyl iodide; this behavior makes it possible to exclude all the possible tautomeric forms of diphenyldipyrrole (I and III) except those of the type IIIb. In this, the nitrogen atoms are unlike; one is still a pyrrole, incapable of forming salts, whereas the other is like a Schiff base, and could add once (IV).[5] On treatment with a strong base, the iodine could be replaced by OH to yield a pseudo base such as V.* The new substance could again add methyl iodide to yield a methyl methiodide.



IV



V

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[5] Decker, *Ann.*, **395**, 390 (1913).

* This structure was suggested by Dr. A. H. Corwin. We did not isolate a corresponding substance but methylated the oil obtained from the action of sodium hydroxide.

Thus, these reactions serve to establish the skeletal structure of dipyrroles, and indicate that the nitrogen atom is connected to an adjacent carbon by a double bond. The phenyl group is placed at the top by analogy with the reaction of 2-methylpyrrole to form 2,4-dimethylindole with mineral acid. Further, the only recognizable oxidation product was benzoic acid, pointing to the attachment of the phenyl group to a doubly-bound carbon. None of the cyclobutane structures, II, have possibilities in agreement with the above evidence, and these should be discarded. It was always difficult to explain indole formation from them, whereas all that is necessary with the new structure is to have the diene synthesis continue, to give a substance of type I. Since nothing like the former is yet known, its properties cannot be predicted, but by analogy with the furan-maleic anhydride addition products, which lose water easily to give an aromatic ring[6] this (I) could equally well lose ammonia to yield an indole.

Finally, no tri- or tetrasubstituted pyrrole has ever been converted into an indole. The diphenyldipyrrole, described in this paper, could not be converted into a diphenylindole; this behavior is in favor of structure III. Two diphenylindoles have been prepared, so it is known that they are capable of existence.

EXPERIMENTAL

A. Preparation and Properties of 2-Phenylpyrrole, and Related Substances.

1. Preparation.—2-Phenylpyrrole was obtained by rearrangement of *N*-phenylpyrrole,[7] which in turn was secured by heating aniline mucate.[8] By introducing slight variations into the specified procedures a better yield or quality of product resulted. In the case of the *N*-phenylpyrrole, the crude distillate from 170 g. of aniline mucate was treated with ether and the insoluble diphenylurea was removed by filtration. The ether solution was then shaken twice with 10 per cent. hydrochloric acid to remove the aniline present, followed by two washings with water. On evaporation, the crude *N*-phenylpyrrole was crystallized from about 150 cc. of a 3:1 alcohol-water mixture. The yield was 23 g., with an additional 4 g. obtained by addition of water to the filtrate; the total yield was 43 per cent. of the theoretical amount. The melting point was 60–1°.

For the isomerization, a Pyrex combustion tube, heated to dull redness, was employed; the pyrrole was passed through at the rate of 50 g. per hour. The distillate was fractionally crystallized using 500 cc. of Skelly-Solve C, the 2-phenylpyrrole being less soluble and separating first. It required three or four treatments to raise the melting point to 129°, the value given in the literature for the pure substance. The conversion was in the neighborhood of 35 per cent. Approximately 90 per cent. of the unchanged *N*-phenylpyrrole could be recovered and used in a later run; *i.e.*;

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[6] VanCampen and Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).

[7] Pictet and Crepieux, *Ber.*, **29**, 1904 (1895).

[8] Köttnitz, *J. prakt. chem.*, **6**, 136 (1872); Feist, *Ber.* **35**, 1654 (1902); Pictet and Steinmann, *ibid.*, **35**, 2529 (1902).

the loss on each isomerization treatment was 10 per cent., deposited in the hot tube as a tar.

Plancher[9] obtained 2-phenylpyrrole by heating potassium pyrrole and bromobenzene in a sealed tube for 7 hours at 150°. When we heated *N*-phenylpyrrole in a similar manner, there was no formation of 2-phenylpyrrole, which would indicate that in the instance cited there was no intermediate formation of *N*-phenylpyrrole.

2. Other attempts to synthesize 2-phenylpyrrole.—(*a*) In view of the high yield of 2,5-dimethylpyrrole obtained by treating acetonylacetone with ammonium carbonate[10] the same procedure was considered for securing 2-phenylpyrrole. This procedure would require β-benzoylpropionaldehyde. Burcker[11] claimed to have obtained this substance by the action of chromyl chloride on butyrophenone, but gave no means of identification, nor could he obtain a bisulfite addition product. All our attempts at repetition gave an addition product of the ketone with the reagent, which on hydrolysis gave back unchanged ketone. As a reference compound the 2,4-dinitrophenylhydrazone was prepared; it separated from benzene in red plates, m.p. 187°.[12]

(*b*) Stephen's aldehyde synthesis[13] is reported to give good results with many aliphatic nitriles. To obtain β-benzoylpropionaldehyde, β-cyanopropionphenone is necessary, and was readily obtained by the addition of hydrogen cyanide to vinyl phenyl ketone in the presence of sodium cyanide. To a solution of 85 g. of β-chloropropiophenone in 200 cc. of hot alcohol was added 50 g. of potassium acetate, and, after cooling, the potassium chloride was removed by filtration. A solution of 50 g. of sodium cyanide in 150 cc. of water was added to the filtrate with stirring; there was a marked temperature rise. The nitrile that separated from the cold solution was filtered and crystallized from alcohol; it formed leaflets, m.p. 76°. The yield was 50 g. or 65 per cent.

Anal. Calc'd for $C_{10}H_9NO$: N, 8.8. Found: N, 9.1.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner, separated from benzene in yellowish-orange leaflets, m.p. 141°.

Anal. Calc'd for $C_{16}H_{13}N_5O_4$: N, 20.6. Found: N, 20.3.

The nitrile was easily hydrolyzed by mineral acids to β-benzoylpropionic acid; m.p. 116°, showing no depression on admixture with a sample at hand. The acid forms a 2,4-dinitrophenylhydrazone, deep orange leaflets from *n*-butyl alcohol, m.p. 190°.

Anal. Calc'd for $C_{16}H_{14}N_4O_6$: N, 15.6. Found: N, 15.7.

Although the structure of the nitrile is certain, it could not be reduced by Stephen's method, nor were any variations useful. The method was checked by reduction of benzonitrile to benzaldehyde.

(*c*) Pyrolysis of mixed calcium salts of formic and β-benzoylpropionic acids. The only product that could be isolated from the tarry distillate was acetophenone, identified by the boiling point, refractive index, and 2,4-dinitrophenylhydrazone. Its formation is unexplained.

3. Properties and reactions.—2-Phenylpyrrole was recovered unchanged after 8 hours' refluxing in alcohol with mineral acid; it did not form a 2,4-dinitrophenyl-

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[9] Plancher and Ghigi, *Gazz. chim. ital.*, **55**, 757 (1925).

[10] Allen and Young, *Organic Syntheses*, **16**, 25.

[11] Burcker, *Ann. chim. phys.*, [5], **26**, 463 (1882).

[12] Allen and Young, *Can. J. Research*, **B14**, 216 (1936).

[13] Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).

hydrazone, indicating no ring opening. It gave neither a picrate nor a methiodide, but yielded 2-phenyl-4,7-dimethylindole when treated with acetonylacetone.

Unless completely substituted, pyrroles rapidly turn red or purple on keeping; this has usually been attributed to oxidation. 2-Phenylpyrrole is no exception, and has a decided purplish tinge when crystallized in the ordinary manner, the color becoming very deep, even though the work be done in an atmosphere of nitrogen. However, when the solution was treated with decolorizing carbon, white crystals were obtained. These remained white for two months; in sunlight they acquired a faint pink tinge which soon changed to brown. Solutions exposed to sunlight showed the same color changes, but a dark tan solid separated in 3 weeks; this was found to contain a little diphenyldipyrrole.

Four sample tubes of the pyrrole, that had been freshly decolorized and recrystallized in air in an amber-glass beaker, were prepared as follows:* one in dry air, one in dry nitrogen, one in moist nitrogen, and one in nitrogen plus one drop of hydrochloric acid. These were placed in direct sunlight for 3 weeks (April). The last three turned a pale pink in a few minutes but the color changed to tan in a day; the first one became tan without a pink color. There was no further visible change except with the last one, the container wall of which appeared much browner. The melting point of each except the last had dropped about 5 degrees; all were found to be essentially unchanged 2-phenylpyrrole by mixture melting points, whereas admixtures with the diphenyldipyrrole were depressed over 20°. A specimen in an open beaker (amber glass) exposed to all the laboratory fumes for three weeks, acquired a faint pink tinge. From these observations it is concluded that the production of color is associated with traces of an impurity that is affected by light.

B. Diphenyldipyrrole (IIIb, $R' = C_6H_5$, $R'' = H$)

The 2-phenylpyrrole was recrystallized in an atmosphere of nitrogen† and the saturation with hydrogen chloride was performed in the same apparatus.

A solution of 10 g. of 2-phenylpyrrole in 50 cc. of dry peroxide-free ether was saturated with hydrogen chloride, the gas being passed through at the rate of one bubble per second, while the reaction flask was cooled in ice-water. After closing the flask and allowing it to stand overnight the ether was decanted from 9.8 g. of a brownish resinous deposit. After several washings with acetone, 5.4 g. of a yellow hydrochloride remained. It was purified by crystallization from a mixture of alcohol and acetone, from which it separated in shiny, yellow-bronze leaflets, m.p. 202–203° with decomposition.

Anal. Calc'd for $C_{20}H_{19}ClN_2$: N, 8.7; Cl, 11.0; HCl, 11.3.
Found: N, 8.6; Cl, 11.1; HCl 11.3.

The actual yield was variable, the above being an average value, whether done in

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* The effect of light, air, moisture, and acid was studied in part by Mr. W. J. Poyner. His assistance is gratefully acknowledged.

† The apparatus for working in an atmosphere of nitrogen was built by Mr. W. J. Poyner. Commercial nitrogen from a cylinder was passed successively over heated copper gauze, and through absorption towers containing Fieser's solution, lead acetate, sulfuric acid, and Dessichlora, and finally bubbled through sodium benzophenone in *p*-cymene. The hydrogen chloride was generated by dropping concentrated sulfuric acid into concentrated hydrochloric acid, dried by passage through concentrated sulfuric acid, and passed over heated copper gauze.

air or nitrogen. The presence of moisture may be beneficial, for the best yields were obtained from air-dried pyrrole; a specimen from the same lot carefully dried in a Fischer pistol for 3 hrs. and run at the same time under the same conditions gave no salt. The resinous by-product is greater if the ether contains peroxide, or if the pyrrole contains *N*-phenylpyrrole.

The free base was liberated nearly quantitatively by treatment with slightly over the calculated amount of 10% alcoholic potash, followed by ether extraction and crystallization of the dipyrrole from alcohol. It formed fine, buff needles, m.p. 140°.

Anal. Calc'd for $C_{20}H_{18}N_2$: C, 83.9; H, 6.3; N, 9.8.
Found: C, 84.1; H, 6.4; N, 9.8.

The hydrochloride was reobtainable by the use of alcoholic hydrochloric acid, while dilute sulfuric acid formed a sulfate (m.p. 210-211° with decomposition; no solvent for crystallization found) and picric acid yielded a picrate. The latter separated from alcohol in yellow leaflets, m.p. 184° with decomposition.

Anal. Calc'd for (A) $C_{20}H_{18}N_2 \cdot H_2SO_4$: N, 7.3; (B) $C_{26}H_{21}N_5O_7$: N, 13.6.
Found (A) 7.4; (B) 13.5.

The methiodide IV resulted from an hour's refluxing of 1 g. of the dipyrrole in 5 cc. of methyl iodide; 1.1 g. (75%) of buff needles were isolated after washing with ether. It was purified by dissolving in a minimum of acetone and adding Skelly-Solve B to cloudiness. It formed needles, very soluble in alcohol, slightly in acetone and dioxane, but insoluble in ether, benzene, and petroleum ether; m.p. 210–11° with decomposition.

Anal. Calc'd for $C_{21}H_{21}IN_2$: C, 58.9; H, 4.9; N, 6.5; I, 29.7.
Found: C, 59.0; H, 4.9; N, 6.4; I, 29.9.

The methiodide was mixed with an equivalent amount of alcoholic potassium hydroxide, diluted with water, and extracted with ether. On evaporation, an oil, presumably the free amine, was left; this turned green on standing in the air and gave a tar when picrate formation was attempted. However, it readily added methyl iodide (0.4 g. from 1 g. of the first methiodide) that separated as microscopic needles, softening at 206° and melting over the range 206–225°.

Anal. Calc'd for $C_{22}H_{23}IN_2$: N, 6.2. Found: N, 6.2.

The second methiodide was insoluble in water, and was unaffected by an aqueous suspension of silver oxide. After substituting alcohol as a solvent and refluxing for 2 hours, silver iodide was observed; the solid was filtered from the cooled mixture and the alcohol allowed to evaporate. On heating, the residue, a fishy odor was noticed, but could not be identified. All the gas in the apparatus was swept into alcoholic phenyl isothiocyanate but no derivative resulted. The residue did not give a picrate.

Other reactions of diphenyldipyrrole.—The dipyrrole formed a black oil when treated with phthalic anhydride. It was unaffected by dilute aqueous or alcoholic sulfuric acid, being recovered unchanged after many variations in procedure. There was no evidence for depolymerization; this point was investigated carefully. If any 2-phenylpyrrole, which is volatile with steam, had been formed it would have been found. When the acid concentration was increased, tars resulted, from which no picrate could be prepared.

The dipyrrole (1 g.) in 50 cc. of acetone decolorized 3.4 g. of powdered permanganate, but the only product identified was benzoic acid. Ozone gave a tar and sodium peroxide was without action. There was no reaction with pure phenyl azide, aniline, phenol or benzene. Impure phenyl azide, which might have contained any of the last three substances, gave a solid (8.1% N), but did not react at all with 2-phenylpyrrole.

A sulfur dehydrogenation by Morton's method[14] gave nothing useful. A mixture of 1.5 g. of dipyrrole, 4 g. of sulfur and 25 cc. of toluene was heated at 140° for 50 hours. Assuming the loss of 2 atoms of hydrogen per molecule of dipyrrole, one-third of the calculated amount of hydrogen sulfide was evolved. After a tedious separation from sulfur, 1 g. of a grey lustrous solid was obtained, which became a dull yellow after several recrystallizations from acetone. It melted with decomposition at 268° and contained sulfur and nitrogen; the molecular weight (Rast) was found to be 636, probably indicating polymerization. It was not further studied.

When the dipyrrole (1 g.) was heated for an hour at 230–250° one-eighth of the calculated amount of ammonia was given off; the residual solid was an unstable yellow substance that after an alcohol extraction and recrystallization from acetone melted at 260° with decomposition. It turned greenish after a few days in the air. A molecular weight determination (Rast) gave the value 272, and nitrogen determination, 9.9% (calc'd for $C_{20}H_{15}N$: M.W., 269; N, 5.2%). Presumably this is some kind of a polymer that dissociates at the melting point of camphor; it did not form a picrate. The alcoholic extract gave a trace of a picrate, m.p. 198–200°, dec.

We are indebted to Dr. A. H. Corwin for valuable criticism in the preparation of this paper.

The work has been assisted by a grant from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

SUMMARY

2-Phenylpyrrole and the corresponding diphenyldipyrrole have been prepared and certain of their chemical properties determined. Based on these, a new type of structure for dipyrroles has been suggested.

β-Benzoylpropionitrile has been synthesized.

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[14] MORTON AND HORVITZ, *J. Am. Chem. Soc.*, **57**, 1860 (1935).

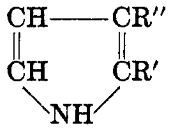
[Contribution from the Chemical Laboratory of McGill University]

INDOLE FORMATION FROM PYRROLES

C. F. H. ALLEN,* D. M. YOUNG,† and M. R. GILBERT

Received July 21, 1937

About fifty years ago Dennstedt[1] found that certain pyrroles dimerized when treated with mineral acids in the absence of water, and that a subsequent treatment with dilute sulfuric acid brought about the loss of ammonia with the formation of an indole. Since these reactions were observed only with pyrroles that were substituted unilaterally (I)‡ the cyclobutane structure (II) was assigned to the dipyrrole. The position of the substituent groups in the indole (III) was not proved by an independent synthesis, but assigned on the basis of ring splitting as indicated in formula II.



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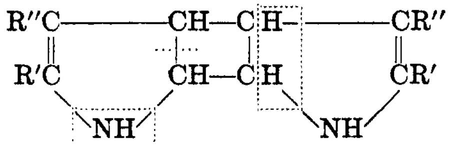

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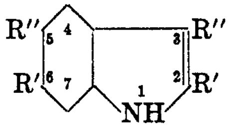

III

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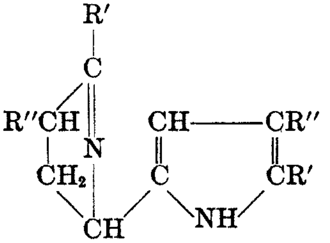
* Present address, Eastman Kodak Co., Rochester, N. Y.

† Acknowledgment is hereby made of a bursary and studentship granted by the National Research Council of Canada.

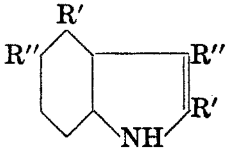
[1] Dennstedt, *Ber.*, **21**, 3429 (1888); **22**, 1930 (1889); **24**, 2559 (1891); Dennstedt and Zimmermann, *ibid.*, **20**, 850 (1887); **21**, 1478 (1888).

‡ Dialkylpyrroles with one substituent on each side of the ring have not been observed to give dipyrroles, but under conditions of indole formation yield condensation products of unknown structure that have lost one molecule of ammonia for every two molecules of pyrrole. Some tri- and tetrasubstituted pyrroles give dipyrrole picrates; the free bases dissociate on heating. In no case has indole formation from these dipyrroles been observed.

Since it was shown in an earlier paper[2] that a dipyrrole has the structure IV, an indole obtained from it would be expected to have the arrangement of groups shown in V.



IV



V

Conversely, from the location of the groups in the indole, it would be possible to place them in the dipyrrole. In the previous work in which 2-phenylpyrrole was used, it was not possible to convert the corresponding dimer into an indole, hence the position occupied by the phenyl group on the pyrroline ring was uncertain. It was tentatively placed on the top carbon atom (R′ in IV) because at that point it would be expected to offer a hindrance to the necessary ring closure, and because of its analogy with the corresponding product from 2-methylpyrrole. Before discussing the latter, it is necessary to consider the conditions for indole formation in this series.

These are (1) from the pyrroles by long heating with zinc salts and acetic acid, (2) from the dipyrrole and sulfuric acid, and (3) a method closely related to the first, which employs acetonylacetone and pyrroles. The yields are low by all procedures.

Starting with the dimethyldipyrrole from 2-methylpyrrole, Dennstedt[3] prepared a dimethylindole, and represented the latter as the 2,6 isomer, on the assumption that the reactions followed the course I–III above. Plancher[4] suggested that the formation of an indole involved a preliminary hydrolysis of one molecule of pyrrole to ammonia and a 1,4-dicarbonyl compound; the latter then condensed with a second molecule of pyrrole. In favor of this is the known ease of ring opening of 2,5-dimethylpyrrole by acids, and the reaction between acetonylacetone and pyrrole to give 4,7-dimethylindole[5]. This latter reaction is apparently more general

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[2] ALLEN, GILBERT AND YOUNG, THIS JOURNAL, **2**, 227 (1937).

[3] DENNSTEDT, *Ber.*, **21**, 3429 (1888).

[4] PLANCHER AND CIUSA, *Atti. accad. Lincei*, [5], **15**, (ii), 447 (1906); through *Zentr.*, **10**, II, 1847 (1906), and *J. Chem. Soc.*, (1807), i, 80.

[5] PLANCHER, *Atti. accad. Lincei*, [5], **11**, (ii), 210 (1902); *Zentr.*, **6**, II, 1472 (1902); PLANCHER AND CARAVAGGI, *ibid.*, **14**, (i), 157 (1905); *J. Chem. Soc.*, (1905), **i**, 298.

than originally suspected, for it forms 4,7-dimethylindoles with many pyrroles, the only exception noted being the 2-acetyl derivative, Table I. If this mechanism were applied to 2-methylpyrrole, 2,4- or 2,7-dimethylindole would be expected. Plancher synthesized a dimethylindole from acetone *m*-tolylhydrazone identical with the one obtained from 2-methylpyrrole itself. This synthesis could give either a 2,4- or 2,6-dimethylindole, the 2,4- being favored since it is common to both Plancher's mechanism and synthesis. He concluded that his indole was "probably" identical with Dennstedt's[4], from which it follows that the dipyrrole must have first dissociated into the monomeric form, if this mechanism is correct.

TABLE I

REACTIONS OF PYRROLES

PYRROLE USED	HCl IN DRY ETHER	DIPYRROLE AND H_2SO_4	2,4-DINITROPHENYLHYDRAZINE AND DIL. ALC. H_2SO_4[a]	ZINC ACETATE AND ACETIC ACID	DITTO, PLUS ACETONYLACETONE
Pyrrole	Tripyrrole		No DNPH[b]	Trace of 2-acetylpyrrole	Indole
2-CH_3-	Dipyrrole	Indole	No DNPH	Indole	Indole
2-$(CH_3)_2CH$-[c]	Dipyrrole	Indole	Not tried	Not tried	Not tried
2-C_6H_5-	Dipyrrole	None	No DNPH	None	Indole
2-$COCH_3$-	None		DNPH	None	None
3-CH_3	Dipyrrole	Indole	Not tried	Not tried	Not tried
2,3-di-CH_3-	Dipyrrole	Indole	Not tried	Not tried	Not tried
2-CH_3-3-COOR	Not tried	Not tried	No DNPH	Not tried	Indole

[a] 2,4-Dimethyl- and 2,4-dimethyl-3,5-dicarbethoxypyrroles also used, but did not give derivatives.

[b] DNPH = 2,4-Dinitrophenylhydrazone.

[c] This was erroneously thought to be the 3 isomer.

We have prepared the dimethylindoles in question by both procedures and have found that they are identical. Finally, we have synthesized all the other dimethylindoles from the corresponding aceto-*o*-xylidides[6] and have found that the Dennstedt-Plancher substance is different from each, and by exclusion must be the 2,4-dimethylindole. Hence there is no longer any support for Dennstedt's dipyrrole structure.

Plancher's mechanism, which involved (1) dissociation of the dipyrrole to the monomer, and (2) hydrolysis of the latter, is capable of being tested, for it should be possible to find out whether dipyrroles do dissociate and whether the pyrroles themselves are hydrolyzed under the conditions

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[6] SALWAY, *J. Chem. Soc.*, **103**, 1990 (1913); VERLEY, *Bull. soc. chim.*, [4], **35**, 1039 (1924); **37**, 189 (1925).

for indole formation. Plancher's argument was supported only by the analogy with the acetonylacetone reaction.

There is no evidence in favor of the dissociation of the dipyrrole. We have examined both dimethyl- and diphenyldipyrrole under the conditions of indole formation, heating them in the presence of acid in an apparatus arranged for simultaneous steam distillation. With the diphenyl derivative only water was found in the distillate, the dipyrrole being recovered unchanged; hence there is no dissociation. The dimethyl homolog, however, gave the indole at once—a matter of minutes. This forms excellent evidence that the dipyrrole is an intermediate product, because it requires fifteen hours to get the same indole from the pyrrole itself under the same conditions.

To establish the ring-opening reaction as the mechanism it should be shown that pyrroles are hydrolyzed under the conditions necessary for ring formation. With a view to securing evidence on this point, a considerable variety of pyrroles has been treated in acid solution under such conditions in the presence of 2,4-dinitrophenylhydrazine. This reagent was selected because it is known to combine with carbonyl compounds with great rapidity and because of the relative insolubility of the expected products[7]. As the formation of an indole from pyrrole and acetonylacetone is a slow reaction, one would expect to be able to detect any hydrolysis product (carbonyl compound) produced by ring opening. The necessary conditions involved 24–48 hours of refluxing, during which time most of the reactants were lost by tar formation; by interrupting after varying intervals it was impossible to isolate unchanged pyrrole and hydrazine. Only in one instance, that of 2,5-dimethylpyrrole, was there detectable ring opening. When a mineral acid was used, the bis-dinitrophenylhydrazone of acetonylacetone was formed instantly[8]; the rate was slower in acetic acid, but the product was the same. The ketones 2-acetyl- and 2,4-dimethyl-3-acetyl-5-carbethoxypyrroles gave dinitrophenylhydrazones without ring opening, but the others were unaffected (Table I). Finally, 2-methylpyrrole was converted into 2,4-dimethylindole with the same yield in the presence and absence of dinitrophenylhydrazine. Thus there is not the slightest indication that ring opening is a step in the reaction.

The validity of the reasoning depends on the assumption that the pH most favorable for reaction is the same for dinitrophenylhydrazone and indole formation. Pyrroles are so easily resinified by moderate concentrations of acid that it is impractical to operate in other than dilute solutions.

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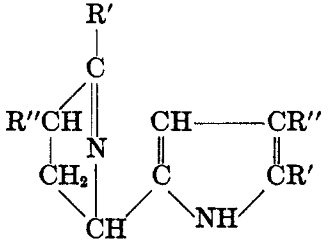
[7] Allen, *J. Am. Chem. Soc.*, **52**, 2955 (1930).

[8] Allen and Young, *Can. J. Research*, **10**, 771 (1934).

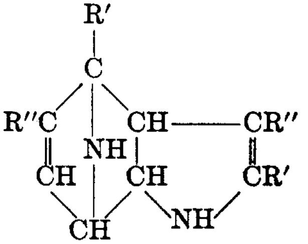
However, under these conditions carbonyl compounds actually form dinitrophenylhydrazones, and in the absence of proof to the contrary, the above assumption seems reasonable. 2,5-Dimethylpyrrole is hydrolyzed, to be sure, but as it does not form an indole, this behavior cannot be interpreted in favor of the hydrolysis mechanism.*

It would appear, therefore, that an indole is formed directly from a dipyrrole, and that the latter is an intermediate step in the reaction, starting from a simple pyrrole. There is no evidence requiring an assumption of depolymerization, or ring opening.

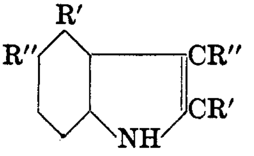
The question then arises, as to how indoles are formed from dipyrroles. An inspection of the formulae



IV



VI



V

reveals that if the diene synthesis, begun in IV, were completed, a substance VI would result. This structure is analogous to the furan-maleic anhydride addition products, which lose water to give an aromatic structure[9], to members of the tropane series, which give dienes on exhaustive methylation[10], and to carbonyl bridge compounds which lose carbon monoxide relatively easily[11]. No substances like VI are known, hence

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* Since the sparingly soluble bis-dinitrophenylhydrazones form almost instantly and quantitatively with most dicarbonyl compounds, and since the reaction is essentially non-reversible it seems fairly certain that any ketone, if ever formed, would be detected. The regeneration of carbonyl compounds from these derivatives has been accomplished in a very few instances. For references, see Allen and Richmond, This Journal, **2**, 227 (1937).

[9] VanCampen and Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).

[10] Willstätter, *Ber.*, **30**, 721 (1897); **31**, 1534 (1898).

[11] Allen and Spanagel, *J. Am. Chem. Soc.*, **55**, 3773 (1933); Allen and Sheps, *Can. J. Research*, **11**, 171 (1934).

their properties can be predicted only by analogy with the instances cited. Now, if IV and VI were in an equilibrium, which normally favors IV, indole formation by loss of ammonia from VI would displace the equilibrium, and the reaction would proceed to the right. The procedures for securing indoles involve treatment with mineral acids or zinc salts, both of which enter into chemical combination with the ammonia, thus favoring the direction of reaction leading to an aromatic structure. Owing to the many possibilities for side reactions, a low yield would be anticipated.

As mentioned above, it was not found possible to convert 2-phenylpyrrole into an indole. In order to make sure that this was not due to the instability of the expected indole, a synthesis was performed by Bischler's[12] method, and two diphenylindoles prepared. In the one from *p*-xenylamine the phenyl groups are in the 2 and 5 positions, but the synthesis from *m*-xenylamine is ambiguous; while not definitely established, by analogy with the dimethyl series the phenyl radicals are presumably in the 2 and 4 positions. These diphenylindoles are high-melting, unreactive solids. They do not form picrates or methiodides.

EXPERIMENTAL

I. Preparation of Starting Materials and Related Substances

Most of the pyrroles were secured without great difficulty by directions already published, but no satisfactory procedure was found for 2-methylpyrrole. Hydrolysis and decarboxylation of Benary's ester[13] gave the best results. In recent papers, Jurjew[14] described the conversion of furans into pyrroles by passage with a current of ammonia over an aluminum oxide catalyst. We obtained but a 5% yield of the desired pyrrole using 2-methylfuran;* most of the latter was recovered, but some was converted into tarry oils.

2,5-Diphenylpyrrole was obtained by the usual ring closure method from dibenzoylethane. The latter was secured by a modification of Lutz' reduction method[15,†] as follows: a solution of 15 g. of dibenzoylethylene, 250 g. of 95% acetic acid and 200 cc. of alcohol was refluxed for an hour with 100 g. of zinc dust. It was filtered while hot into 300 cc. of water; the solid was separated by filtration after standing overnight, and was crystallized from a benzene-alcohol (4:7) mixture. A yield of 7 g. of pure dibenzoylethane, m.p. 144°, was obtained. The bis-2,4-dinitrophenylhydrazone VII formed orange-yellow needles, m.p. 250°, with decomposition, from a nitrobenzene-alcohol mixture; it is insoluble in the common solvents except aniline and tetralin.‡

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[12] BISCHLER, *Ber.*, **25**, 2860 (1892).

[13] BENARY, *ibid.*, **44**, 495 (1911).

[14] JURJEW, *ibid.*, **69**, 440, 1003 (1936).

* We are indebted to Dr. G. F. Wright for this substance.

[15] LUTZ, *J. Am. Chem. Soc.*, **51**, 3008 (1929).

† Preliminary work by Mr. A. Rose.

‡ All melting points are corrected. All analyses are collected in Table III.

A 90% yield of the pyrrole resulted on 8 hours' heating at 150–160° with saturated alcoholic ammonia in an autoclave; m.p. 143°. The diketone was unaffected by heating with ammonium carbonate, but a difficultly separable mixture of pyrrole and starting material could be obtained by the use of ammonium acetate. The product from the pressure method is much better to manipulate.

II. Procedures Used with the Pyrroles

A. Acid hydrolysis.—A mixture of 1 g. of the pyrrole, 0.5 g. of 2,4-dinitrophenylhydrazine, and 25 cc. of alcohol was heated to boiling and 2 cc. of 10% sulfuric acid was added. If no solid precipitated within a few minutes, the whole was refluxed for 40 hours, being interrupted from time to time to enable any derivative or unchanged reagent to be detected. In nearly all cases this long acid treatment led to the destruction of the reactants, with production of tars or amorphous solids, usually black. The results are summarized in Table I. There was no reaction with 2-phenyl-, 2,5-diphenyl-, and 2,4-dimethyl-3,5-dicarbethoxypyrroles; after 8 hours the starting materials were recovered unchanged. 2-Acetyl- and 2,4-dimethyl-3-acetyl-5-carbethoxypyrroles gave 2,4-dinitrophenylhydrazones instantly, without ring-opening[8]. The derivative, VIII, of the former was insoluble in the common solvents, but crystallized in reddish-brown needles from dioxane, m.p. 297° with decomposition. When refluxed without the reagent for 48 hours, an amorphous resin was formed from 2-acetylpyrrole; this did not form a phenylhydrazone and decomposed when heated on metal foil. 2-Acetylpyrrole did not form a dipyrrole. As previously described[8] 2,5-dimethylpyrrole gave the bis-2,4-dinitrophenylhydrazone of acetonylacetone. It is of interest to note that 2,5-diphenylpyrrole is not opened by hydroxylamine.

The bis-2,4-dinitrophenylhydrazones of levulinic aldehyde and of acetonylacetone are very sparingly soluble in a large excess of glacial acetic acid, and are precipitated by addition of a small amount of water. They are insoluble in dilute alcoholic or aqueous sulfuric acid. Hence if ever formed, it is believed they would be detected. They separate practically quantitatively in one minute when prepared in 90% acetic acid.

B. Indole formation; use of zinc acetate in acetic acid.—A mixture of 3 g. of the pyrrole, 5 g. of zinc oxide or acetate and 20 cc. of 90% acetic acid was refluxed for 24–48 hours, and then submitted to steam distillation. The acid in the distillate was neutralized by sodium hydroxide and any organic product filtered or extracted with ether. In the case of pyrrole, a small amount of 2-acetylpyrrole was obtained, but there was no trace of indole.

With 2-methylpyrrole, 2,4-dimethylindole was isolated from the steam distillate and converted into a picrate, which recrystallized from dilute alcohol in red-brown needles as described by Plancher[4]. The procedure was repeated in the presence of 2,4-dinitrophenylhydrazine; the same indole picrate resulted. There was no reaction with 2-phenyl- or 2-acetylpyrrole.

C. Acetonylacetone treatment.—A mixture of 3 g. of the pyrrole, 5 g. of zinc acetate, 5 g. of acetonylacetone* and 20 cc. of acetic acid was refluxed for 48 hours and then steam distilled. A small amount of solid was removed by filtration, and after neutralization of the acid in the distillate, ether extraction yielded a little more of the same solid, which, in the case of pyrrole, agreed with Plancher's description of 4,7-dimethylindole[5]; it had a faint, disagreeable indole-like odor, and melting point of 101–2°; the yield was 0.25 g. or 4 per cent.

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* The acetonylacetone was very kindly supplied by Shawinigan Chemicals Limited.

2-Acetylpyrrole was unaffected, but indoles were obtained with 2-methyl-, 2-phenyl-, and 2-methyl-3-carbethoxypyrroles. 2,4,7-Trimethylindole (IX) resulted from 2-methylpyrrole; the picrate was obtained as reddish-brown needles from dilute alcohol; m.p. 175–6°.

2,4,7-Trimethyl-3-carboxyindole (X) was formed when 2-methyl-3-carbethoxypyrrole was used, the ester being hydrolyzed during the process. After steam distillation, the solid in the flask was easily dislodged from a tar clinging to the walls by a swirling motion and recrystallized from dilute alcohol, separating as tan-colored needles, m.p. 153–5°. It dissolved in sodium carbonate, but did not form a picrate.

2-Phenyl-4,7-dimethylindole was obtained in a similar manner from 2-phenylpyrrole; a small quantity of unchanged pyrrole was also isolated from the steam distillate. The ether extract of the non-volatile fraction gave an oil, which formed a picrate (XI); the latter separated from dilute alcohol in reddish-brown needles; m.p. 171–2°.

Since this indole was previously unknown, it was synthesized by Bischler's method[12], from *p*-xylidine and phenacyl bromide. The first step, the formation of phenacyl *p*-xylidide (XII), was accomplished by warming gently a mixture of 1 g. of phenacyl bromide, 1.2 g. of *p*-xylidine and 5 cc. of alcohol. The solid was separated by filtration, washed, and crystallized from dilute alcohol; the yield was quantitative. It separated in buff colored rods, m.p. 105°. To obtain the indole, a solution of 4 g. of *p*-xylidine and 1 g. of this xylidide was refluxed for an hour and poured into 100 cc. of dilute hydrochloric acid. The oil was extracted with ether, and after evaporation of the solvent, and solution in alcohol was at once converted into a red picrate, identical with the one mentioned above; there was no depression of melting points on admixture.

III. Acid Treatment of Dipyrroles

As described in the previous paper, there was no reaction with diphenyldipyrrole, the latter being recovered unchanged. When submitted to the same procedure, dimethyldipyrrole gave the indole at once—it was unnecessary to prolong the time as indicated by Dennstedt and the yield was much greater. The indole distilled with the steam, was extracted with chloroform, and identified as the picrate. No 2-methylpyrrole could be detected in the distillate by Diels' procedure[16].

A mixture melting point of the above picrate and the one prepared from 2-methylpyrrole, as described at the end of section B was not depressed, indicating their identity. Their color and crystal form were indistinguishable.

IV. Synthesis of Dimethylindoles

These were prepared by Solway's procedure[6], or, better, by Verley's technique[6] from the corresponding aceto-*o*-xylidides. The non-availability of 1,2-dimethyl-3-aminobenzene prevented the synthesis of the 2,4-isomer in this way; all the picrates were made for comparison.

V. Work with Xenylamines

With the view of securing some diphenylindoles for purposes of comparison, the three xenylamines (aminobiphenyls) were treated with phenacyl bromide, to obtain

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[16] Diels, Alder, and Winter, *Ann.*, **486**, 221 (1931).

derivatives suitable for a synthesis by Bischler's method.* The ortho isomer did not react, but pale yellow phenacyl derivatives were obtained from the others. On purification, the meta (XIII) separated as leaflets, m.p. 134°, while the para (XIV) formed rods, m.p. 148°. The picrate (XV) of the latter separated from the alcohol in prisms, m.p. 130–1°. Phenacyl chloride reacted much less rapidly than the bromide.

TABLE II

PROPERTIES OF DIMETHYLINDOLES

XYLIDINES USED			POSITION OF CH_3–	M.P., °C.	B.P.	PICRATES	
CH_3	CH_3	NH_2				Color	m.p., °C.
1	2	3	2,4		180/20[3,4]	Brick-red	158[3,4]
1	3	4	2,5	114[6,17]		Dark red	155
1	4	5	2,6[b]	86		Dull red[c]	132
1	3	2	2,7	35	129–131/2 mm.[a]	Carmine[d]	149

[a] Micro boiling point by Dr. G. F. Wright

[b] Substance XXI.

[c] Substance XXII.

[d] Substance XXIII.

TABLE III

ANALYSES

NUMBER OF SUBSTANCE	FORMULA	CALC'D % N	FOUND[a]
VII	$C_{28}H_{22}N_8O_8$	18.7	18.5
VIII	$C_{12}H_{11}N_5O_4$	24.2	24.1
IX	$C_{17}H_{16}N_4O_7$	14.4	14.3
X	$C_{12}H_{13}NO_2$	6.9	6.9
XI	$C_{22}H_{18}N_4O_7$	12.4	12.2
XII	$C_{16}H_{17}NO$	5.9	5.9
XIII	$C_{20}H_{17}NO$	4.9	4.7
XIV	$C_{20}H_{17}NO$	4.9	4.9
XV	$C_{26}H_{20}N_4O_8$	10.8	10.7
XVI	$C_{20}H_{15}N$[b]	5.2	5.3
XVII	$C_{20}H_{15}N$	5.2	5.1
XVIII	$C_{18}H_{14}N_4O_7H_2O$	13.5	13.5
XIX	$C_{18}H_{14}N_4O_7$	14.1	13.9
XX	$C_{18}H_{14}N_4O_7$	14.1	13.9
XXI	$C_{10}H_{11}N$	9.7	9.6
XXII	$C_{16}H_{14}N_4O_7$	15.0	15.0
XXIII	$C_{16}H_{14}N_4O_7$	15.0	15.2, 15.2

[a] Semi-micro Dumas: ALLEN AND YOUNG, *Can. J. Research*, **B14**, 216 (1936).

[b] Calc'd C, 89.2; H, 5.6. Found: C, 88.8; H, 5.6.

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* Generous samples of *o*- and *p*-xenylamines were kindly furnished by the Monsanto Chemical Co. The meta isomer was secured by the directions in the literature [JACOBSON AND LOEB, *Ber.*, **36**, 4082 (1903); FICHTER AND SULZBERGER, *ibid.*, **37**, 878 (1904)].

[17] RASCHEN, *Ann.* **239**, 227 (1887).

The indoles were obtained as follows: a mixture of 12 g. of the xenylamine and 17 g. of the phenacyloxenylamine were heated in a sealed tube at 300° for an hour. The solid was extracted with ether, and the residue, after removal of the solvent, taken up in chloroform, decolorized by Nuchar, and diluted with methanol. Both substances separated in white prisms faintly tinged with yellow. The 2,4-diphenylindole (XVI) melted at 209–9°, while the 2,5-isomer (XVII) melted at 192–3°. Neither isomer formed a picrate nor a methiodide, and were recrystallized unchanged from acetyl chloride and acetic anhydride, but both slowly gave purple colors by the pine shaving test, and a pale pink color with Ehrlich's reagent, becoming yellow with nitrous acid.

For purposes of recognition, on the assumption that the indoles would add picric acid, the picrates of the xenylamines were prepared. The derivatives from the ortho XVIII and meta XIX isomers separated from alcohol in yellow prisms, m.p. 163–4° and 196° respectively, while the para XX formed needles, m.p. 198–9°.

ACKNOWLEDGMENT

The work has been assisted by a grant from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

SUMMARY

It is shown that the dimethylindoles described by Dennstedt and by Plancher are identical.

The 2,3- and 2,7-dimethylindoles have been synthesized and their picrates prepared. A comparison of these, Salway's 2,5 isomer and the Dennstedt-Plancher substance, shows that the latter is different, and, by exclusion, it must be 2,4-dimethylindole.

This arrangement of groups confirms the structure of the dipyrroles assigned in the previous paper. Dennstedt's formula is no longer tenable.

The mechanism of formation of indoles from pyrroles is discussed. The evidence seems to favor intermediate dipyrrole formation. There is no indication of ring opening of pyrroles, as suggested by Plancher, nor detectable dissociation of the dipyrrole.

[COMMUNICATION No. 627 FROM THE KODAK RESEARCH LABORATORIES]

CONFIGURATIONS ABOUT SINGLE BONDS*

ARNOLD WEISSBERGER

Received May 27, 1937

In 1887, that is, exactly fifty years ago, J. Wislicenus published a paper "On the Spatial Arrangement of Atoms in Organic Molecules,"[1] wherein he propounded the theory of geometric isomerism. This states that only two stable configurations exist about double bonds, the *cis* and the *trans* form of the molecule. Errera[2] has shown that the electric moments of the two forms are different. The *trans* forms of simple molecules, *e.g.*, *trans*-dichloroethylene are centrosymmetrical and have no moment, whereas the *cis* forms exhibit finite dipole moments, *e.g.*, *cis*-dichloroethylene, $1.7D$. The reason for the rigidity of the double bonds given by Wislicenus is that "it is impossible for tetrahedra to rotate with respect to one another if they are attached edge to edge." In the same paper, the different behavior of single bonds is stated: "Two carbon atoms linked together by one valency only are able to rotate about the axis formed by this link. Free rotation due to thermal agitation will occur unless special influences either fix definite configurations rigidly, or at least make them preferred ones."

With this statement of Wislicenus, the problem was set of investigating whether and where free rotation exists and what forces interfere where it does not exist.

We shall use the terms *cis* and *trans* for configurations about single bonds in analogy to usage with double bonds and shall reckon the angle of rotation θ so that 0° indicates the *cis*, and 180°, the *trans* positions. The term free rotation will mean equal probability for all configurations from 0 to 2π.

The classical *chemical* method for investigation is limited in a field of this type. This method consists in the isolation of isomers, and it can

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* Contribution to the Symposium on Dipole Moments conducted by the Division of Physical Chemistry at the ninety-third meeting of the American Chemical Society, Chapel Hill, N. C., April 15, 1937.

[1] WISLICENUS, "*Über die räumliche Anordnung der Atome in organischen Molekülen,*" *Abhandlungen der Kgl. Sächs Gesellschaft der Wissenschaften,* Vol. XIV, Leipzig, 1887.

[2] ERRERA, *Phys. Z.*, **27**, 764 (1926).

help only where isomers exist long enough without interchange to be observed as individuals. If only one individual corresponding to a structural formula is found, the chemical method cannot answer the question whether this is due to the existence of only one rigid form or to the coëxistence of a number of configurations which interchange. In the special case of biphenyl and some other compounds, *stereo*chemical investigations lead a step farther. Here, two optically active forms can be prepared if the substituents in the position ortho to the biphenyl link are too big to pass each other. Thus, proof is given for restricted rotation about single bonds due to the size of the ortho substituents.

The following discussion reviews the information about configurations around single bonds which has been obtained through the determination of *dipole moments.* First, some instances will be given whereby we can find out whether free rotation exists or not. Then, we shall analyze some examples of restrained rotation and investigate the restricting forces.

Let us assume that a single bond is an ideal axis for rotation, with a certain direction which determines the distance of the connected groups but not their configuration about this axis. Preference for special configurations can then be caused: (1) by *mutual influences* of the two groups, and (2) by the *shape of the whole molecule.* We shall neglect the second point at present and discuss it at the end of the paper.

Mutual influences may be the volume effect, Coulomb forces, and dispersion forces. They will diminish as the separation of the connected groups increases, the Coulomb forces decreasing most slowly. L. Meyer[3] has pointed out that such influences are negligible, if the energy between the groups is smaller than $1/10\ kT$. The energy between dipoles of about $1D$ each is, at room temperature, below this limit, if the groups are more than 3 Å. apart. The distance apart of substituents in the para positions in benzene is almost double this value. Thus, we can expect that groups which occupy the para positions in a benzene nucleus will not interfere with each other's free rotation.

Let us assume that the moments of two identical groups form angles θ with the axis of rotation. J. W. Williams[4] showed that if free rotation exists, the resultant moment of the molecule equals $\sqrt{2}\cos\theta$.

The moment of *p*-xylylene chloride $ClH_2C \cdot C_6H_4 \cdot CH_2Cl$ is $2.2_8\ D$.[5] It is composed of the moments of two chloromethyl groups. The magnitude of each of these moments and the angle it makes with the rotation

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[3] L. Meyer, *Z. physik. Chem.*, **8B,** 27 (1930).

[4] Williams, *ibid.*, **138A,** 75 (1928).

[5] Weissberger and Sängewald, *Physik. Z.*, **30,** 792 (1929).

axis can be obtained from the moments of benzyl chloride and *p*-chlorobenzyl chloride;[6] the calculated value for *p*-xylylene chloride under conditions of free rotation is found to be 2.2_9D.[7] Thus, there is good agreement between the experimental result and the moment calculated on the assumption that there is free rotation of the groups in the positions para to each other.

If we (hypothetically) remove the benzene nucleus from the *p*-xylylene chloride, we obtain ethylene chloride. Here, the two chloromethyl groups are close to each other; the distance between the two carbon atoms is now 1.54 Å., instead of 4.76 Å. As Williams[4] has shown, the *moment* for this compound *is smaller* than would be expected with free rotation of the chloromethyl groups.

Further evidence of the mutual influence of the two parts of the molecule comes from the observation of dipole moments at *different temperatures*. As already stated, the probabilities for all configurations around a single bond become practically identical, if the interfering energy is smaller than $1/10\,kT$. If, on the other hand, such interferences exist, and the temperature of measurement is increased we can expect the observed value to alter and to approach that for free rotation. Sänger[8] and Zahn[9] observed this effect with ethylene chloride and various other molecules in the gaseous state. Smyth, Dornte, and Wilson[10] observed it for solutions of ethylene chloride, and calculated the potentials which are due to Coulomb forces between the two chloromethyl groups over a whole revolution about the ethane link. They found a potential trough of about 12×10^{-14} erg in favor of the *trans* position, whereas, the value of kT at room temperature is about 4×10^{-14} erg. One may, therefore, expect to find more of the molecules in the *trans* position than in any other configuration, which is in qualitative agreement with the observed moment.

The question, "free rotation or not," was approached from another angle by dipole determinations of *stereoisomers*. A substance with two identically substituted asymmetric atoms exists in two enantiomorphic optical antipodes, their mixture, and the intramolecularly compensated inactive meso form. If there is free rotation, the moments of the meso form and of the enantiomorphic forms ought to be identical. Nonidentity of their dipole moments, on the other hand, shows the absence of freedom about the single C-C link. The three groups of substances of this type

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[6] BERGMANN AND ENGEL, *Z. physik. Chem.*, **15B**, 85 (1932).

[7] WEISSBERGER AND SÄNGEWALD, *ibid.*, **20B**, 147 (1933).

[8] SÄNGER, *Physik. Z.*, **32**, 21 (1931).

[9] ZAHN, *Phys. Rev.*, **38**, 521 (1931).

[10] SMYTH, DORNTE, AND WILSON, *J. Am. Chem. Soc.*, **53**, 4242 (1931).

which have been investigated are the *stilbene chlorides*,[11] *the hydrobenzoins*,[12] and the *diethyl tartrates*.[13]

Stilbene chlorides...	$C_6H_5 \cdot CHCl \cdot CHCl \cdot C_6H_5$	α	1.2_7D	β	2.7_5D
Hydrobenzoins......	$C_6H_5 \cdot CHOH \cdot CHOH \cdot C_6H_5$	meso	$2.3D$	*dl*	$2.7D$
Diethyl tartrates....	$C_2H_5O_2C \cdot CHOH \cdot CHOH \cdot CO_2C_2H_5$	meso	3.6_5D	*dl*	3.1_0D

Their moments show by their differences the absence of free rotation for at least one form of each pair.

Let us consider in more detail the moments of the stilbene chlorides. If, with the more symmetrical meso form, two identical substituents are in the *trans* position—which would give no dipole moment—the other substituents must also be in the *trans* position. With the optically active form, however, no entirely symmetrical configuration of the molecule can be obtained. The moments of the stilbene chlorides, therefore, were interpreted as indicating that the lower value corresponded to the meso and the higher value to the *dl* form. We see, however, that the difference between the moments of the stereoisomers is smaller with the hydrobenzoins, and that the order is reversed with the diethyl tartrates. To be on safe ground with the coördination of the formulas to α- and β-stilbene chlorides, it, therefore, appeared worthwhile to synthesize the optically active stilbene chlorides, and to check which form, the α or the β, is the *dl* or the meso. The synthesis went from the α-amino-β-hydroxybibenzyls, over the α-amino-β-chlorobibenzyls, to the stilbene chlorides, clearing up the interrelation of the stereoisomers of these substances and of the α,β-diphenylethyleneimines.[14] It proved that the correlation given above is correct; the compound with the smaller moment is the meso form.

To explain why the difference between the moments of the stereoisomers becomes smaller with the hydrobenzoins and why the order is reversed with the diethyl tartrates, let us consider the moments of the three dimethoxybenzenes. With identical atoms or linear groups, the order of the moments is para < meta < ortho. This order is reversed with the dimethoxybenzenes which contain two angular groups.[5]

o-Dimethoxybenzene 1.3_1D
m-Dimethoxybenzene 1.5_9D
p-Dimethoxybenzene 1.8_1D

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[11] WEISSBERGER AND SÄNGEWALD, *Z. physik. Chem.*, **9B**, 133 (1930).

[12] HASSEL AND NAESHAGEN, *Tidskr. Kjemi Berg.*, **10**, 93 (1930); *Z. physik. Chem.*, **14B**, 232 (1931).
WEISSBERGER AND SÄNGEWALD, *ibid.*, **12B**, 399 (1931).

[13] WOLF, *Trans. Faraday Soc.*, **26**, 315 (1930).

[14] WEISSBERGER AND BACH, *Ber.*, **64**, 1095 (1931); **65**, 631 (1932).

The obvious reason is the mutual orientation of the angular groups. In the para compound, free rotation is established. The closer the groups come to one another, however, the more their mutual orientation tends to diminish the moment of the molecule. A corresponding effect decreases the difference in the moments of the hydrobenzoins which have an angular hydroxyl group on each ethane carbon atom; and with the diethyl tartrates, where each ethane carbon atom is substituted with two angular groups, we have an inversion of the order of the moments similar to that with the dihydroxybenzene ethers.

By analogy with the observations on ethylene chloride and *p*-xylylene chloride, we should expect that any effects due to Coulomb forces, and still more those due to the volume of the substituents, would vanish with increasing distance of the groups in question. If, therefore, we put a benzene nucleus into the middle of the stilbene chlorides, we should expect the moments of the meso form and the racemic form to become identical with each other, and with the value calculated for free rotation, *viz.*, 2.43 *D*.

The two stereoisomeric 1,4-bis(α-chlorobenzyl)benzenes, $C_6H_5 \cdot CHCl \cdot C_6H_4 \cdot CHCl \cdot C_6H_5$, were synthesized, starting with terephthalaldehyde, and going over the 1,4-bis(α-hydroxybenzyl)benzenes, the stereoisomers of which were separated by means of the acetates, and then converted to the chlorides. The moments of the two chlorides (meso and *dl* forms) were found to be 2.2_8 and 2.4_8.[15] We see that the difference between the moments of the two stereoisomers has decreased greatly, and that they have come to close agreement with the calculated value for free rotation.

This result has two further points of interest: (1) there appears to be still some difference between the moments; and (2) the observed values and the value calculated for free rotation of the bis(chlorobenzyl)benzenes are lower than the observed value for *dl*-stilbene chloride, which is 2.7_5 *D*.

This fact: *viz.*, that the moment of *dl*-stilbene chloride is higher than that which would be expected for free rotation deserves some attention, since it cannot be explained by the volume effect or Coulomb forces. Both these influences could only depress the moment below the value for free rotation. To provide for an increase, forces must be acting to keep the main component dipoles at an angle, θ, lower than 90°.

To find out more about this influence under unambiguous circumstances, the dichlorobiphenyls were investigated.[16] The moment of *p,p′*-di-

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[15] Weissberger and Bach, *Ber.*, **65**, 24 (1932); Weissberger and Sängewald, *Z. physik. Chem.*, **20B**, 145 (1933).

[16] Weissberger, Sängewald, and Hampson, *Trans. Faraday Soc.*, **30**, 884 (1934); Weissberger and Sängewald, *Z. physik. Chem.*, **20B**, 145 (1933); Hampson and Weissberger, *J. Am. Chem. Soc.*, **58**, 2111 (1936).

chlorobiphenyl is 0, and requires no further attention. The moment of *m,m'*-dichlorobiphenyl is 1.80 *D*, which is in quite fair agreement with the moment calculated for free rotation. With *o,o'*-dichlorobiphenyl where the two chlorine atoms collide with each other, the *cis* position and a large amplitude around it are excluded from the probable configurations. Since these are the positions with high moments, *o,o'*-dichlorobiphenyl would be expected to have a moment considerably lower than that calculated for free rotation. The moment—1.9_1 *D*—is, however, higher, and even higher than that of the *m,m'* compound. This shows that forces are active between the chlorine atoms favoring configurations of an angle, θ, less than 90°.

These forces may be the dispersion forces studied by London. The potential energy of the molecule in the different positions about the C-C link was, therefore, evaluated, including the Coulomb forces and the London forces. The dotted line in the diagram gives the electrostatic potential alone and shows a marked increase of potential with small angles θ. However, the volume of the chlorine cuts out practically all positions with θ smaller than 62°, where the Cl-Cl distance is 3 Å., and the remaining configurations have almost identical probabilities at room temperature. Thus the volume effect of the chlorines, and Coulomb forces would provide for a small moment. If, however, we take into consideration the London forces, the configurations close to the *cis* position are largely favored. The solid line in the diagram—U_1+L—shows the sum of the electrostatic and London potentials. The dispersion forces reverse the shape of the curve entirely and the configurations with small angles θ are, in fact, preferred.

From these data, the probability distribution under the action of Coulomb and London forces was calculated, which, in combination with the C-Cl moment, allows the evaluation of the moment of the substance itself. To that end, however, definite assumptions about the steric repulsion forces must be made, and it provides a good test of the theory to see whether these assumptions are reasonable. In a first approximation, we can take the quantum-mechanical repulsion as a rigid barrier, and see where the distribution curve must be cut by a straight line to give the right moment. This value proves to be $\theta = 62°$, corresponding to a Cl-Cl distance of 3.0 Å., and is in good agreement with the value to be expected from X-ray and electron diffraction data. Fair agreement is also obtained if the repulsion is assumed to obey an exponential law, as postulated by Born and Mayer,[17] with constants not very different from those they calculated for Cl^-.

We have now distinguished, as forces regulating configurations about

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[17] Born and Mayer, *Z. Phys.*, **75**, 1 (1932).

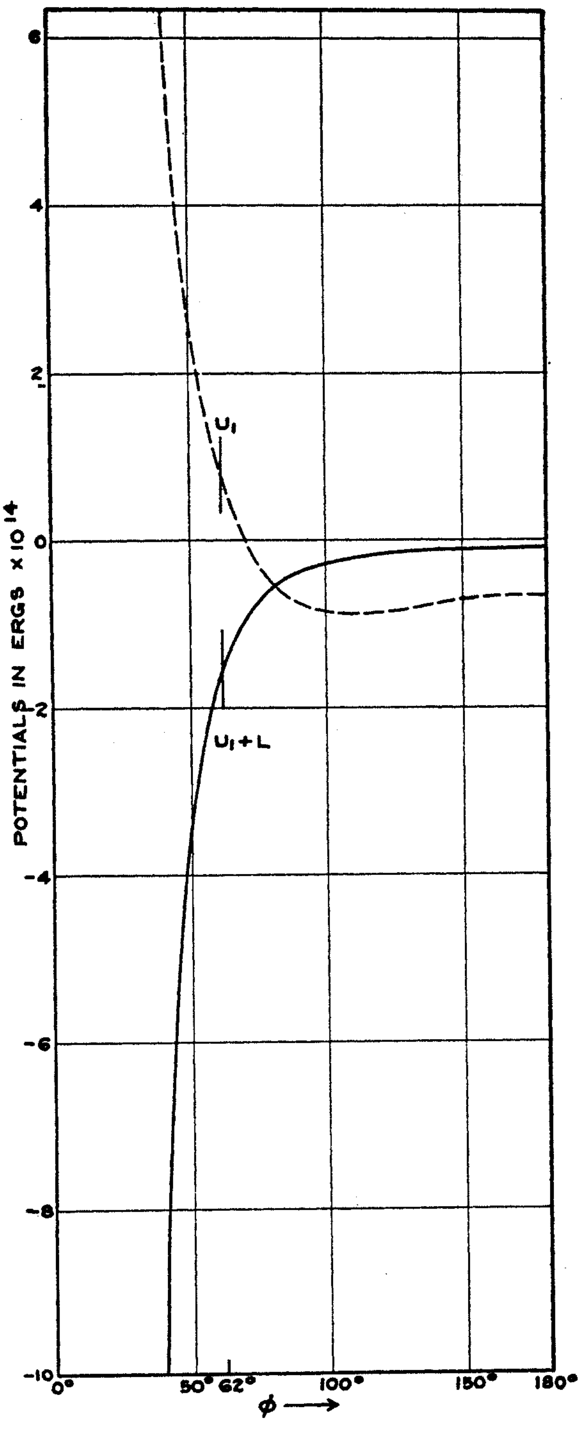
POTENTIALS IN ERGS × 10^14
6
4
2
0
-2
-4
-6
-8
-10
0°
50°
62°
100°
150°
180°
φ ⟶
U₁
U₁ + L

FIG. 1

single bonds, the quantum-mechanical repulsion forces, the Coulomb forces, and the London dispersion forces. The model of the stilbene chlorides from which we started shows that all three factors influence the moments of these compounds, and we understand now the high dipole moment found for the *dl* form.

One word remains to be said about an effect which has been discussed by Lennard-Jones and Pike,[18] and by Altar.[19] These authors suggest that for calculations of intramolecular configurations, one should not simply apply a Boltzman formula in order to obtain the probability distribution from the potentials, but one should weigh each individual configuration according to its moment of inertia by multiplying with an appropriate weight factor. Altar calculated the weight factor for ethylene chloride for the whole revolution. If we remember, however, that the variation of the moment of inertia with *o,o'*-dichlorobiphenyl will be smaller than with ethylene chloride, and that the configurations with ϕ smaller than 60° will be eliminated, we are justified in having neglected this effect with the dichlorobiphenyls. It can have a bearing, however, on the moments of the two 1,4-bis(α-chlorobenzyl)benzenes whose difference, small though it is, can hardly be accounted for by volume effects, Coulomb forces, or London forces. It would seem worth while to remeasure these moments to make the experimental data certain, and then to go through the calculation suggested by Altar. The effect discussed by him might show itself with these substances, the shape of which provides for great differences in the moments of inertia over one revolution about the axial link. If not clear, the effect could be increased by appropriate substitution of the angular groups.

One further point should be mentioned. We have assumed hitherto that a single bond is an ideal axis for rotation but does not bend in itself. However, Wislicenus has indicated that this is a possibility, too, and has represented it by distorted tetrahedra. One can get a rough idea of the energy necessary for a deflection of linkage by the comparison of the combustion heats of compounds with strained and unstrained rings. The data thus obtained are not very reliable, but show that a deflection of the order of one degree could be produced by kT at room temperature. This is the order of magnitude we have just been dealing with, and thus, it appears that this idea of Wislicenus also has a sound basis.

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[18] LENNARD-JONES AND PIKE, *Trans. Faraday Soc.*, **30**, 830 (1934).

[19] ALTAR, *J. Chem. Phys.*, **3**, 460 (1935).

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF BUFFALO]

THE REACTIONS OF ORTHO ESTERS WITH CERTAIN ACID ANHYDRIDES*

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Years ago Sawitsch reported that ethyl orthoformate had reacted with acetic anhydride[1] to give, not methylidene acetate ($CH(OOCCH_3)_3$) as had been expected, but instead formic acid and ethyl acetate. Undoubtedly ethyl formate was formed at the same time.

Later Claisen made use of acetic anhydride in the reaction between ethyl orthoformate and ethyl acetoacetate.[2, 3] In this reaction the product was ethyl α-ethoxymethyleneacetoacetate and it has been tacitly assumed that the function of the acetic anhydride was to remove ethyl alcohol, thus permitting the reaction to proceed. This type of reaction works equally well with acetylacetone[2] or with diethyl malonate,[2] although in the latter case Claisen used zinc bromide as a catalyst.

More recently Sah extended this type of condensation to prepare the corresponding products using, instead of the orthoformate the orthoacetate and the orthobenzoate.[4] These reactions were also carried out in the presence of acetic anhydride.

Similar products were formed as a result of the action of ethyl orthoformate on diethyl acetonedicarboxylate,[5] on ethyl cyanoacetate[6, 7, 8] and on ethyl benzoylacetate.[9]

However, the action of acetic anhydride might not be as simple in these reactions as had been supposed. It might, for example, react first with the orthoester since previous work has shown that orthoesters undergo spontaneous, reversible decomposition to a slight extent even at room temperatures.[10] Many reactions of acid anhydrides can be readily ex-

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* Abstracted from the thesis presented by the second author to the faculty of the University of Buffalo in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[1] SAWITSCH, *Jahresberichte*, **1860**, 391.

[2] CLAISEN, *Ber.*, **26**, 2729 (1893).

[3] CLAISEN, *Ann.*, **279**, 19 (1897).

[4] SAH, *J. Am. Chem. Soc.*, **53**, 1836 (1931).

[5] ERRERA, *Ber.*, **31**, 1682 (1898).

[6] DE BOLLEMONT, *Compt. rend.*, **128**, 1338 (1899).

[7] DE BOLLEMONT, *Bull. soc. chim.*, [3], **25**, 18 (1901).

[8] DE BOLLEMONT, *ibid.*, [3], **25**, 1828 (1901).

[9] WEIS AND WOIDICH, *Monatsh.*, **47**, 427 (1926).

[10] POST AND ERICKSON, *J. Am. Chem. Soc.*, **55**, 3851 (1933).

plained on the basis of a similar reversible, spontaneous decomposition, and, combining the two concepts, it was easy to predict a possible interaction between orthoester and acid anhydride, thus:

I. $HC(OC_2H_5)_3 \rightleftharpoons (HC(OC_2H_5)_2)^+ + (OC_2H_5)^-$

II. $(CH_3CO)_2O \rightleftharpoons (CH_3COO)^- + (CH_3CO)^+$

III. $(CH_3COO)^- + (HC(OC_2H_5)_2)^+ \rightarrow CH_3COOCH(OC_2H_5)_2$

IV. $(CH_3CO)^+ + (OC_2H_5)^- \rightarrow CH_3COOC_2H_5$

This reaction would have to be carried out at room temperatures or at least with very moderate heating, as Sawitsch reported nothing but esters and acids as the final products when ethyl orthoformate and acetic anhydride were heated.[1] If the above assumptions could be proven correct it might even be possible to show that these dialkoxyalkyl esters were intermediates in Sawitsch's reaction.

It was at first thought advisable to determine whether or not ethyl orthoformate would react with ketene, inasmuch as this compound, in a sense is an anhydride of acetic acid. But all attempts in this direction failed. True, diphenylketene reacts with ethyl orthoformate[11] but apparently ketene itself is unreactive.

However, ethyl orthoformate was found to react with acetic anhydride at room temperature, according to the equation:

V. $(CH_3CO)_2O + HC(OC_2H_5)_3 \rightleftharpoons CH_3COOC_2H_5 + CH_3COOCH(OC_2H_5)_2$

The main product of this reaction, diethoxymethyl acetate, is a clear, colorless liquid, formed in 41 per cent. yield on mixing the two reactants. The reaction is slow in the attainment of equilibrium.

As the second step in the development of the concept, diethoxymethyl acetate was allowed to react with ethyl acetoacetate, also at room temperature, as a result of which ethyl α-ethoxymethyleneacetoacetate was formed, probably according to the following series of equations:

VI $CH_3COOCH(OC_2H_5)_2 + CH_3COCH_2COOC_2H_5 \rightleftharpoons$
$CH_3COOH + CH_3COCH(CH(OC_2H_5)_2)COOC_2H_5$

VII $CH_3COCH(CH(OC_2H_5)_2)COOC_2H_5 \rightleftharpoons$
$C_2H_5OH + CH_3COC(=CHOC_2H_5)COOC_2H_5$

VIII $CH_3COOH + C_2H_5OH \rightleftharpoons HOH + CH_3COOC_2H_5,$

and was isolated in 40 per cent. yield, together with ethyl acetate. The

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[11] BERT, *Bull. soc. chim.*, [4], 37, 1408 (1925).

water formed may have reacted to decompose some of the complex acetate according to the equation:

$$\text{IX}\quad CH_3COOCH(OC_2H_5)_2 + HOH \rightarrow CH_3COOC_2H_5 + HCOOC_2H_5 + C_2H_5OH$$

Ethyl orthoformate also reacts with propionic anhydride in like manner, giving a 32 per cent. yield of diethoxymethyl propionate. Indecisive results were obtained with butyric anhydride. If the expected butyrate was obtained at all it had a boiling point so close to that of butyric anhydride that separation of the two was practically impossible. Furthermore, an approximately 34 per cent. yield of ethyl butyrate was obtained together with 20 per cent. of ethyl formate. Hence it seemed that in all probability diethoxymethyl butyrate was formed, and decomposed thus:

$$\text{X}\quad C_3H_7COOCH(OC_2H_5)_2 \rightarrow C_3H_7COOC_2H_5 + HCOOC_2H_5$$

Finally the reaction between ethyl orthoacetate and acetic anhydride was studied under the same conditions. Here, however, evidence was obtained leading to the conclusion that the reaction does not stop at a stage analogous to that reached in each of the preceding reactions but rather that alcohol is almost immediately lost from the complex acetate to produce α-ethoxyvinyl acetate and that this compound reacts to a certain extent with the original $\alpha\alpha$-diethoxyethyl acetate to produce 1,3,3-triethoxy-1-butenyl acetate according to the equations:

$$\text{XI}\quad (CH_3CO)_2O + CH_3C(OC_2H_5)_3 \rightleftharpoons CH_3COOC_2H_5 + CH_3COOC(CH_3)(OC_2H_5)_2$$

$$\text{XII}\quad CH_3COOC(CH_3)(OC_2H_5)_2 \rightleftharpoons C_2H_5OH + CH_3COOC(OC_2H_5){=}CH_2$$

$$\text{XIII}\quad CH_3COOC(CH_3)(OC_2H_5)_2 + CH_3COOC(OC_2H_5){=}CH_2 \rightleftharpoons CH_3COOH + CH_3COOC(OC_2H_5){=}CHC(CH_3)(OC_2H_5)_2$$

EXPERIMENTAL

Ketene, $CH_2{=}CO$, was prepared by the well-known method consisting of the pyrolysis of acetone. It was not liquefied.

Acetone, CH_3COCH_3, was purchased and purified. Crystalline potassium permanganate was added with intermittent shaking over a period of twenty-four hours, after which the acetone was directly distilled, then dried over calcium chloride. The second distillation then yielded a water-white acetone with a boiling point of 55.5° at 741 mm.

Ethyl orthoformate, $HC(OC_2H_5)_3$, was purchased from the Eastman Kodak Co. Constants found: b.p. 60°/30 mm.; n_D^{20} 1.3900. Literature constants: b.p. 60°/30 mm.; n_D^{20} 1.3915.[10]

Ethyl orthoacetate, $CH_3C(OC_2H_5)_3$, was purchased from the Eastman Kodak Co. and redistilled. Constants found: b.p. 66.5°/41 mm.; n_D^{20} 1.3980.

Acetic anhydride, $(CH_3CO)_2O$, was a commercial product, redistilled; b.p. 139°.

Propionic anhydride, $(C_2H_5CO)_2O$, was purchased from the Eastman Kodak Co., redistilled; b.p. 63°/13 mm.; n_D^{20} 1.4048.

Butyric anhydride, $(C_3H_7CO)_2O$, was purchased from the Eastman Kodak Co., redistilled; n_D^{20} 1.4070.

Diethoxymethyl acetate, $CH_3COOCH(OC_2H_5)_2$, was first prepared in one of the attempts to induce a reaction between ketene and an orthoformate when the use of catalysts was tried, among others, acetic anhydride. But instead of the expected product from the ketene the substituted methyl acetate was obtained. Then on subsequent runs the new ester was prepared on a much larger scale. The two compounds, ethyl orthoformate and acetic anhydride were simply mixed in 0.5 molar amount each and allowed to stand at 22° for four days in the dark. The reaction mixture was then distilled through a Widmer column. The properties of the compound were then determined; b.p. 79–80°/24 mm., 85–87°/30 mm., 170–172°/743 mm.; n_D^{20} 1.3959; d_4^{20} 0.9919.

Anal. Calc'd for $C_7H_{14}O_4$: C, 51.8; H, 8.7.
Found: C, 52.2; H, 8.9.

N (assuming molecular weight) = 39.28 (found), 39.46 (calc'd). The saponification equivalent was determined as the equivalent weight of the ester in its reaction with sodium hydroxide according to the equation,

$$\text{XIV} \quad CH_3COOCH(OC_2H_5)_2 + 2NaOH = CH_3COONa + HCOONa + 2C_2H_5OH,$$

and was found to be 82.60 as against the theoretical 81.05. The maximum yield was 41%, obtained, however, on a subsequent run by doubling the amount of acetic anhydride with respect to orthoformate, and making use of gentle heating, which distilled off the ethyl acetate as fast as it was formed. The chemical properties of the compound were determined and can best be represented by the use of equations. The reaction with water has already been mentioned (Equation X) and others follow.

$$\text{XV} \quad CH_3COOCH(OC_2H_5)_2 + NaOH(5\%, \text{cold}) = CH_3COONa + HCOOC_2H_5 + C_2H_5OH \text{ (exothermic)}$$

$$\text{XVI} \quad CH_3COOCH(OC_2H_5)_2 + NaHCO_3(5\% \text{ cold}) = CH_3COONa + HCOOC_2H_5 + C_2H_5OH + CO_2$$

The ester is readily soluble in dilute acids, reacts with cold neutral potassium permanganate, but does not react with bromine in carbon tetrachloride. It is easily and quickly hydrolyzed by cold dilute acids, which is to be expected as it is really an orthoester. With aniline it reacts as does the orthoformate:

$$\text{XVII} \quad CH_3COOCH(OC_2H_5)_2 + 3C_6H_5NH_2 = HC(NHC_6H_5)_3 + CH_3COOH + 2C_2H_5OH$$

This derivative melted at 137°–138° (corr.), and its identity was shown by determination of the melting point of a mixture with the product from the reaction of ethyl orthoformate with aniline.[12]

$$\text{XVIII} \quad HC(OC_2H_5)_3 + 3C_6H_5NH_2 = 3C_2H_5OH + HC(NHC_6H_5)_3$$

The mixture also melted at 137°–138° (corr.).

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[12] GRACOLONE, *Gazz. chim. ital.*, **62**, 577 (1932).

Ethyl α-ethoxymethyleneacetoacetate, $CH_3COC(=CHOC_2H_5)COOC_2H_5$, was prepared by the action of diethoxymethyl acetate on ethyl acetoacetate. The latter was purchased from the Eastman Kodak Co., and after drying over sodium sulfate and distillation through a Widmer column had a boiling point of 75° at 15 mm. The esters were mixed in the proportion of 0.33 moles of ethyl acetoacetate to 0.25 moles of diethoxymethyl acetate, and slowly heated under reflux to gentle boiling. The solution rapidly turned yellow, then brown, to dark coffee-brown at which point the reaction mixture was distilled. The product, ethyl α-ethoxymethyleneacetoacetate corresponded to Claisen's product.[13, 14] It was a colorless oil, rather thick and heavy. Constants found: b.p. 146°/11 mm.; n_D^{20} 1.4730; d_4^{20} 1.0669. Literature constants: b.p. 149–151°/15 mm.; d^{15} 1.0737.[13, 14]

Anal. Calc'd for $C_9H_{14}O_4$: C, 58.0; H, 7.6.
Found: C, 57.8; H, 7.6.

The product reacted with 2,4-dinitrophenylhydrazine in alcoholic solution with a trace of hydrochloric acid to give a crystalline derivative, probably a pyrazolone. Ethyl α-ethoxymethyleneacetoacetate turns brown on standing, perhaps with polymerization.

Diethoxymethyl propionate, $C_2H_5COOCH(OC_2H_5)_2$, was prepared in the same manner as was the preceding acetate, *i.e.*, by the mixing of ethyl orthoformate (0.6 mole) with propionic anhydride (0.5 mole). The product was a colorless, oily liquid with a rather sharp odor in addition to the typical odor of an ester. Properties were determined: b.p. 70–72°/10 mm., 177–179°/751 mm.; d_4^{20} 0.9857; n_D^{20} 1.4052. Saponification equivalent 87.15 (found), 88.56 (calc'd). N (assuming molecular weight) = 43.80 (found), 44.08 (calc'd).

Anal. Calc'd for $C_8H_{16}O_4$: C, 54.5; H, 9.2.
Found: C, 54.2; H, 9.2.

The compound hydrolyzes readily in water but not as rapidly as does the corresponding acetate. Trianilidomethane resulted from the action of aniline, its identity demonstrated by the method of mixture melting points.

Diethoxymethyl butyrate, $C_3H_7COOCH(OC_2H_5)_2$, was assumed to be present in the reaction mixture when 0.5 mole of butyric anhydride and 0.5 mole of ethyl orthoformate were mixed and allowed to react exactly as above. The ester was not isolated but certain other compounds were isolated which could be assumed to be decomposition products of the expected compound. In this reaction there were isolated 0.1 mole of ethyl formate and 0.17 mole of ethyl butyrate.

α,α-Diethoxyethyl acetate, $CH_3COOC(CH_3)(OC_2H_5)_2$, was prepared but not isolated, by the same method, namely, the interaction of 0.5 mole each of acetic anhydride and ethyl orthoacetate. On distillation large quantities of ethyl acetate were obtained. Another fraction, probably the desired product, boiled from 65° to 80° at 16 mm. It condensed as a colorless liquid but on standing turned a distinct violet in 15 minutes, the color deepening later to reddish-brown.

α-Ethoxyvinyl acetate, $CH_3COOC(OC_2H_5)=CH_2$, was isolated from the fraction mentioned above which boiled from 65° to 80° at 16 mm. On redistillation, this fraction gave ethyl acetate, a trace of acetic acid and a fraction (7 cc. of a total 31 cc.) which boiled at 130–133° and which reacted very rapidly with bromine in carbon tetrachloride. The saponification number of this material was found to be 64.46 as compared with the value calculated for α-ethoxyvinyl acetate of 65.04.

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[13] CLAISEN, *Ann.*, **295**, 303 (1897).

[14] CLAISEN, *Ber.*, **28**, 39 (1893).

1,3,3-Triethoxy-1-butenyl acetate, $CH_3COOC(OC_2H_5)=CHC(OC_2H_5)_2CH_3$, was isolated from the distillation process described in the preceding paragraph, boiling at 87–88° at 13 mm. Other properties determined were n_D^{20} 1.4462; d_4^{23} 0.9817.

Anal. Calc'd for $C_{12}H_{22}O_5$: C, 58.5; H, 9.0.
Found: C, 58.2, 58.4; H, 9.2, 9.0.

It crystallized at 20–21° to large rectangular plates. It was insoluble in water but soluble in the usual organic solvents, decolorized bromine in carbon tetrachloride very rapidly. The values for C and H check only for the formula $C_{12}H_{22}O_5$ hence it is assumed the compound is 1,3,3-triethoxy-1-butenyl acetate.

CONCLUSIONS

The experimental work herein presented indicates that in the reaction between an alkyl orthoformate and an aliphatic acid anhydride there is first formed a dialkoxyalkyl ester (Equation V), and that the formation of this compound is the first of a series of two consecutive reactions leading to the final group of simple esters. This statement has been verified for the reaction of ethyl orthoformate with acetic anhydride and with propionic anhydride and is probably true with butyric anhydride.

In the reaction between ethyl orthoformate and ethyl acetoacetate in the presence of acetic anhydride, the function of the anhydride is not, as may be supposed, to remove ethyl alcohol. The present results show that the anhydride reacts with the orthoester to produce the dialkoxyalkyl ester and that this compound then reacts with ethyl acetoacetate to produce the alkoxymethylene derivative. Diethoxymethyl acetate was found to react with ethyl acetoacetate, yielding ethyl α-ethoxymethyleneacetoacetate (Equations VI, VII, VIII).

The reaction between ethyl orthoacetate and acetic anhydride could not be made to yield the expected ester, corresponding in structure to those previously isolated. Instead, another compound, α-ethoxyvinyl acetate was found and it is assumed that α,α-diethoxyethyl acetate lost ethyl alcohol to form this compound (Equations XI, XII). A higher-boiling fraction was obtained which was probably formed by the interaction of α,α-diethoxyethyl acetate and α-ethoxyvinyl acetate with loss of acetic acid, namely, 1,3,3-triethoxy-1-butenyl acetate (Equation XIII).

SUMMARY

1. A new type of compound is presented as the product of the action of ethyl orthoformate on both acetic and propionic anhydrides. Evidence is also presented for the existence of a similar compound resulting from the action of ethyl orthoformate on butyric anhydride.

2. Diethoxymethyl acetate reacts with ethyl acetoacetate to give ethyl

α-ethoxymethleneacetoacetate, the same product as is formed by the interaction of ethyl orthoformate and ethyl acetoacetate in the presence of acetic anhydride. It is proposed that diethoxymethyl acetate is the intermediate in this reaction.

3. The reaction of ethyl orthoacetate with acetic anhydride gives an unstable product which later loses alcohol to form α-ethoxyvinyl acetate, this product later reacting with the original compound, α,α-diethoxyethyl acetate to give 1,3,3-triethoxy-1-butenyl acetate.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CINCINNATI]

A MECHANISM FOR THE REACTION OF ORGANIC HALIDES WITH SULFIDES. SULFONIUM COMPOUNDS. I

FRANCIS EARL RAY AND IRVING LEVINE

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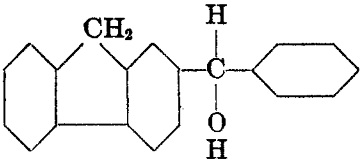
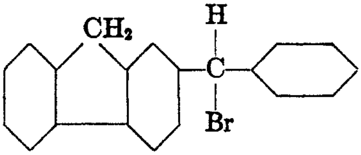
Although Oefele discovered the sulfonium compounds in 1864[1] when he obtained triethylsulfonium iodide by treating diethyl sulfide with ethyl iodide, the course of the reaction that occurs when more complex compounds react is still imperfectly understood.

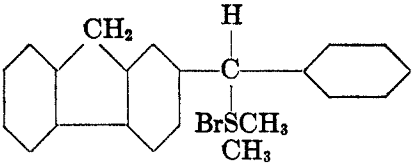
When we attempted to prepare phenyl-2-fluorylmethyldimethylsulfonium bromide, III, by heating phenyl-2-fluorylbromomethane, II, with excess dimethyl sulfide, the desired compound was not obtained. Instead we isolated trimethylsulfonium bromide and phenyl-2-fluorylmethyl methyl sulfide, IV.[2,3]



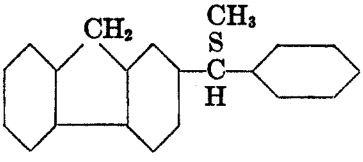
I



II



III



IV

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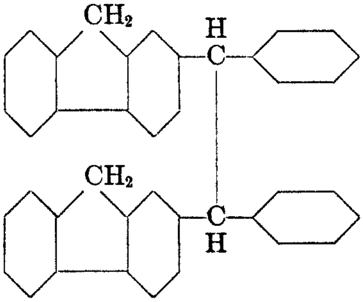
[1] OEFELE, *Ann.*, **132**, 82 (1864).

[2] Phenyl 2-fluoryl ketone was first prepared by FORTNER, *Monatsh.*, **23**, 921 (1902); **25**, 443 (1904).

[3] Phenyl-2-fluorylcarbinol, I, was first prepared by G. HARROLD, Ph. D. Thesis, University of Cincinnati, **1934**.



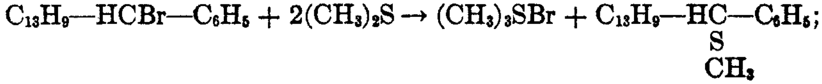
V

Even when equimolar quantities of the bromide and methyl sulfide were used, one-half mole of trimethylsulfonium bromide was formed, and one-half mole of the original bromide was recovered. This suggested the possibility of treating the sulfide, IV, with methyl iodide to obtain the desired sulfonium compound. From this reaction we obtained trimethylsulfonium iodide, a hydrocarbon, and much free iodine. The hydrocarbon was identified as the dimer, V, by comparing it with the product of the same melting point obtained by a Würtz reaction on the bromide, II.

In order to determine more exactly the course of the reaction phenyl-2-fluorylmethyl methyl sulfide, IV, was treated with excess ethyl iodide. This time methyldiethylsulfonium iodide was isolated, and much free iodine was obtained.

If we attempt to write the equations we are struck with the apparent anomaly of these reactions:

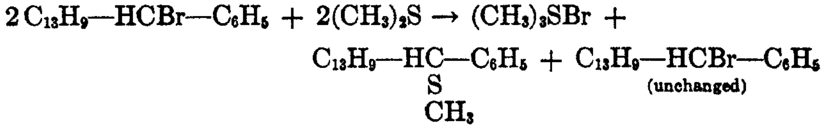
using excess methyl sulfide,

(A)


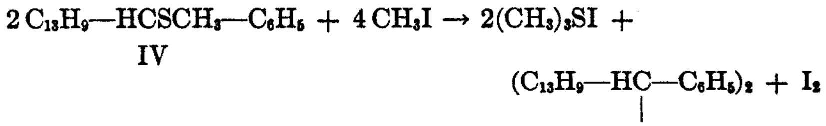
$$\mathrm{C_{13}H_9{-}HCBr{-}C_6H_5 + 2(CH_3)_2S \rightarrow (CH_3)_3SBr + C_{13}H_9{-}\underset{\substack{S\\ CH_3}}{HC}{-}C_6H_5};$$

II III

using equimolar quantities,

(B)


$$\mathrm{2\,C_{13}H_9{-}HCBr{-}C_6H_5 + 2(CH_3)_2S \rightarrow (CH_3)_3SBr +}$$
$$\mathrm{C_{13}H_9{-}\underset{\substack{S\\ CH_3}}{HC}{-}C_6H_5 + \underset{\text{(unchanged)}}{C_{13}H_9{-}HCBr{-}C_6H_5}}$$

(C)


$$\mathrm{2\,\underset{IV}{C_{13}H_9{-}HCSCH_3{-}C_6H_5} + 4\,CH_3I \rightarrow 2(CH_3)_3SI +}$$
$$\mathrm{\underset{V}{(C_{13}H_9{-}\underset{|}{HC}{-}C_6H_5)_2} + I_2}$$

$$\text{(D)}\ 2\,C_{13}H_9\text{—}HCSCH_3\text{—}C_6H_5 + 4\,C_2H_5I \rightarrow 2\,CH_3(C_2H_5)_2SI + (C_{13}H_9H\underset{|}{C}\text{—}C_6H_5)_2 + I_2$$

In reactions (A) and (B) the phenylfluorylmethyl radical has apparently displaced a methyl group from one molecule of methyl sulfide; the methyl bromide which is also formed, then combines with unchanged methyl sulfide to give the trimethylsulfonium bromide. Reaction (B) shows that when this has occurred the phenyl-2-fluorylbromomethane does not react further with the sulfide, IV.

Reaction (C) is the *reverse* of that cited above. Here the methyl group of methyl iodide has replaced the phenyl-2-fluorylmethyl radical of phenyl-2-fluorylmethyl methyl sulfide, IV, to produce first, dimethyl sulfide and phenyl-2-fluoryliodomethane. The dimethyl sulfide at once combines with unchanged methyl iodide to give trimethylsulfonium iodide, and the fluorylphenyliodomethane liberates iodine to give the dimer, V.

TABLE I

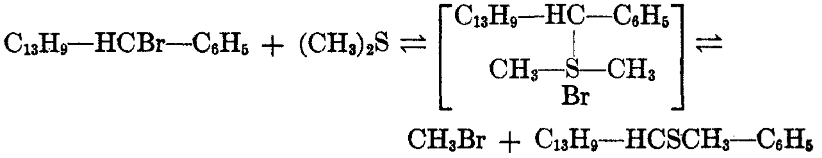
USED	GRAMS	MILLIMOLES	MOLAR RATIO
Dimethyl sulfide	0.846	13.6	2.00
Phenyl-2-fluorylbromomethane	4.560	13.6	2.00
PRODUCTS			
Phenyl-2-fluorylmethyl methyl sulfide, mercuric chloride	4.01	6.8	1.00
Trimethylsulfonium bromide	1.10	7.0	1.03
Phenyl-2-fluorylmethoxymethane	2.13	7.4	1.09

That this picture is correct is shown by the reaction (D) where the resulting sulfonium compound contains two ethyl groups and one methyl group.

It is obvious that these reactions are reversible and it is now necessary to express the mechanism in such a manner that all reactions and products (ours as well as those of other investigators) are accounted for.

This can be done if we assume that the sulfonium compound theoretically expected is produced as an intermediate, and that this intermediate is capable of dissociation (when it is unsymmetrical) in more than one way. This gives a series of equilibria which are displaced in the direction of the most stable sulfonium compound, *i.e.*, that containing alkyl groups of low molecular weight.

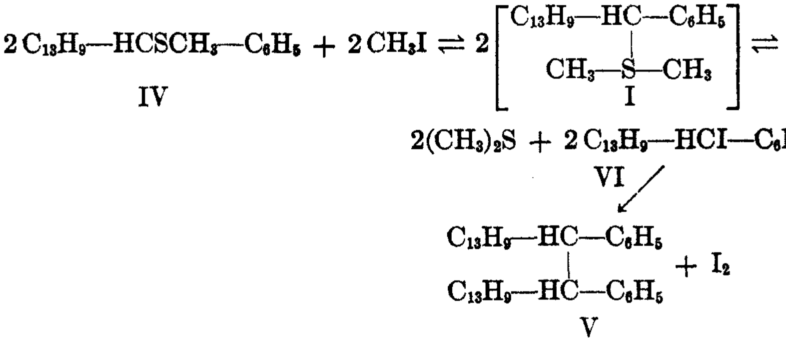
(A′)



$$C_{13}H_9{-}HCBr{-}C_6H_5 + (CH_3)_2S \rightleftharpoons \left[\begin{array}{c} C_{13}H_9{-}HC{-}C_6H_5 \\ | \\ CH_3{-}S{-}CH_3 \\ Br \end{array}\right] \rightleftharpoons CH_3Br + C_{13}H_9{-}HCSCH_3{-}C_6H_5$$

The CH_3Br then reacts with the $(CH_3)_2S$ to form the stable trimethylsulfonium bromide. A similar equation could be written for (B), the reacting substances being in molecular proportion.

(C′)



$$2\,\underset{IV}{C_{13}H_9{-}HCSCH_3{-}C_6H_5} + 2\,CH_3I \rightleftharpoons 2\left[\begin{array}{c} C_{13}H_9{-}HC{-}C_6H_5 \\ | \\ CH_3{-}S{-}CH_3 \\ I \end{array}\right] \rightleftharpoons 2(CH_3)_2S + 2\,\underset{VI}{C_{13}H_9{-}HCI{-}C_6H_5} \rightarrow \underset{V}{\begin{array}{c} C_{13}H_9{-}HC{-}C_6H_5 \\ | \\ C_{13}H_9{-}HC{-}C_6H_5 \end{array}} + I_2$$

Here again (C′) the dimethyl sulfide and the methyl iodide combine to form the trimethylsulfonium ion, while the formation of the hydrocarbon, V, and iodine renders this irreversible, so that no sulfide, IV, is obtained. We have prepared the iodide, VI, and find it to decompose as shown in the equation. A similar equation could be written for (D) with the decomposition of VI accounting for the absence of the other expected product, phenyl-2-fluorylmethyl ethyl sulfide.

On the basis of this generalization we are able to account for the varied and sometimes conflicting results of previous investigators who studied the reactions leading to the formation of various sulfonium compounds. While limitations of space prevent a comprehensive survey of the literature of sulfonium compounds[4], we can, however, point out a few of the applications of this mechanism.

In their pioneer work Oefele[1], Cahours[5], and Schöller[6] all obtained results similar to ours which can only be logically explained by our mechanism.

Schöller treated benzyl sulfide with methyl iodide. Contrary to his

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[4] For such a survey see, IRVING LEVINE, Ph.D. Thesis, University of Cincinnati, **1937**.

[5] CAHOURS, *Ann.*, **135**, 354 (1865); **136**, 151 (1865); *Compt. rend.*, **60**, 620, 1174 (1865); **80**, 1317 (1875); **81**, 1163 (1875).

[6] SCHÖLLER, *Ber.*, **7**, 1274 (1874).

expectations he obtained no dibenzylmethylsulfonium iodide. Instead he isolated benzyldimethylsulfonium iodide and trimethylsulfonium iodide.

If we assume the formation of dibenzylmethylsulfonium iodide as an intermediate we have a clear explanation of this reaction

$$(C_7H_7)_2S + CH_3I \rightleftharpoons [(C_7H_7)_2CH_3SI] \rightleftharpoons C_7H_7SCH_3 + C_7H_7I$$

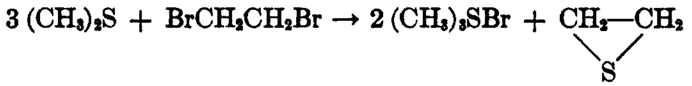
The benzylmethyl sulfide can react with methyl iodide to give benzyldimethylsulfonium iodide. This in turn partly dissociates to benzyl iodide and dimethyl sulfide, which is the source of the trimethylsulfonium iodide.

$$C_7H_7SCH_3 + CH_3I \rightleftharpoons C_7H_7(CH_3)_2SI \rightleftharpoons (CH_3)_2S + C_7H_7I$$

This then gives a satisfactory picture of the complete reaction as written by Schöller.

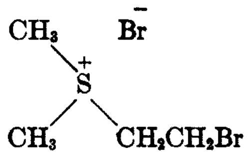
$$2\,(C_7H_7)_2S + 5\,CH_3I \rightarrow (CH_3)_3SI + (CH_3)_2C_7H_7SI + 3\,C_7H_7I$$

Cahours found that when dimethyl sulfide and dibromoethane were heated together he obtained trimethylsulfonium bromide and ethylene sulfide.

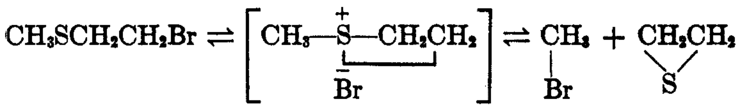


$$3\,(CH_3)_2S + BrCH_2CH_2Br \rightarrow 2\,(CH_3)_3SBr + \underset{S}{CH_2{-}CH_2}$$

This puzzling reaction is readily explained by assuming that the addition product, VII, is first formed. This may dissociate either into its original constituents or into methyl bromide and $CH_3SCH_2CH_2Br$. As before, the methyl bromide reacts with unchanged dimethyl sulfide to give the trimethylsulfonium bromide. The remainder of the reaction is as follows:



VII



$$CH_3SCH_2CH_2Br \rightleftharpoons \left[CH_3{-}\overset{+}{S}{-}CH_2CH_2 \; \overset{-}{Br} \right] \rightleftharpoons \underset{Br}{CH_3} + \underset{S}{CH_2CH_2}$$

An interesting extension of our mechanism aptly elucidates another reaction reported by Cahours[6]. He found that ethyl mercaptan reacted with hydriodic acid to give triethylsulfonium iodide and hydrogen sulfide. Cahours' equation is as follows:

$$3\,C_2H_5SH + HI \rightarrow (C_2H_5)_3SI + 2\,H_2S$$

Here again a logical explanation appears if we assume the formation of hypothetical addition products of the nature of sulfonium compounds.

$$2\,C_2H_5SH + 2\,HI \rightleftharpoons \left[2\,C_2H_5\underset{H}{\overset{H}{S}}I\right] \rightleftharpoons 2\,C_2H_5I + 2\,H_2S$$

$$C_2H_5SH + C_2H_5I \rightleftharpoons [(C_2H_5)_2SHI] \rightleftharpoons (C_2H_5)_2S + HI$$

$$(C_2H_5)_2S + C_2H_5I \rightleftharpoons (C_2H_5)_3SI$$

The diethyl sulfide thus reacts with ethyl iodide to give the final stable product, triethylsulfonium iodide. The summation of our equations is the same as the results Cahours obtained by quantitative measurements.

We have observed that when phenyl-2-fluoryl-bromomethane, II, is allowed to react with the higher mercaptans, an intense red color is produced. On warming, hydrogen bromide is driven off and the red color simultaneously fades. This color is due, we believe, to the formation of an unstable compound of the type R_2SHBr[*].

The subsequent development work by a host of chemists adds further evidence to support our theory[7].

The difficulties that arose in the stereochemical investigation of the sulfonium compounds[8] led to the belief that quadrivalent sulfur had a planar configuration and that the three covalences were not equivalent.

It was not until late in 1900 that Pope and Peachy[9] succeeded in isolating the first optically active sulfonium compound and definitely established the tetrahedral character of sulfur. The difficulties attending this work are well explained by our mechanism, which would allow racemization to take place.

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[*] Brand and Leyerzapf, *Ber.*, **70B**, 284, 296 (1937), and Wood and Bost, *J. Am. Chem. Soc.*, **59**, 1012 (1937), mention the appearance of similar phenomena.

[7] Dehn, *J. prakt. Chem.*, [2], **14**, 108 (1876); *Ann.*, IV, Suppl., 83 (1865–66); Crum Brown and Blaikie, *J. prakt. Chem.*, [2], **23**, 395 (1881); Ferrer, *Ann. soc. espan. fis. quim.*, **16**, 724 (1918); Klinger, *Ber.*, **10**, 1880 (1877); Renshaw, Bacon, and Robyler, *J. Am. Chem. Soc.*, **48**, 517 (1926); Bennett and Hock, *J. Chem. Soc.*, **127**, 2671 (1925); **130**, 2496 (1927); Wegscheider and Schreiner, *Monatsh.*, **40**, 325 (1919); Smiles, *J. Chem. Soc.*, **77**, 163 (1900); Courtot and Freukiel, *Compt. rend.*, **199**, 557 (1934).

[8] Kruger, *J. prakt. Chem.*, [2], **14**, 207 (1876); Nasini and Scala, *Gazz. chim. ital.*, **18**, 67 (1888); Klinger and Maassen, *Ann.*, **243**, 193 (1888); **252**, 241 (1889); Strömhölm, *Ber.*, **33**, 823 (1900).

[9] Pope and Peachy, *J. Chem. Soc.*, **77**, 1072 (1900).

While the hypothesis we have proposed is, of course, implicit in the work of the previous investigators, this is the first time a comprehensive reaction mechanism has been proposed that explains the many results reported in the literature.

In general, sulfonium compounds of the type RR′R″SX may be prepared in three ways.

$$\begin{array}{l} \mathrm{RX + R'R''S} \searrow\!\!\nwarrow \\ \mathrm{R'X + RR''S} \rightleftharpoons \mathrm{RR'R''SX} \\ \mathrm{R''X + RR'S} \nearrow\!\!\swarrow \end{array}$$

It follows that the sulfonium compound may decompose in three ways and each of the new alkyl halides may theoretically react with the sulfides produced, to give six new sulfonium compounds, which are in turn capable of dissociation, etc. But as the stability of these varies with the molecular complexity, the equilibrium is displaced in the direction of the simplest alkylsulfonium compound.

EXPERIMENTAL

Phenyl-2-fluoryl ketone.—This compound was first prepared by Fortner's method[2], but the application of Perrier's[10] modification produces a purer product. From alcohol one obtains white microscopic crystals melting at 122°; yield 61%.

Phenyl-2-fluorylcarbinol, I.—This was prepared from the ketone by reduction with zinc dust in the presence of either alcoholic ammonia or alcoholic potassium hydroxide. It crystallizes from alcohol, in which it is somewhat more soluble than the ketone, as a fine white powder melting at 116°; yield 82%[3].

Phenyl-2-fluorylchloromethane.—Three grams of phenyl-2-fluorylcarbinol was dissolved in 30 cc. of glacial acetic acid. Ten cc. of concentrated hydrochloric acid was added and the mixture was shaken and warmed. On cooling fine crystals separated, which were dried over sodium hydroxide. The melting point was 122°, which is the same as that of the ketone, but a mixture melting point gave 98–112°.

Anal. Calc'd for $C_{20}H_{15}Cl$: Cl, 12.22. Found: Cl, 12.19.

Phenyl-2-fluorylbromomethane, II.—This was prepared by passing hydrogen bromide into a glacial acetic acid suspension of the carbinol. The proportions were 155 g. of carbinol to a liter of acetic acid. The carbinol first dissolves, and then the bromide precipitates. It is freed from hydrogen bromide and carbinol by boiling with dry ether in which the bromide is only very slightly soluble. It may be recrystallized from isopropyl ether or high-boiling petroleum (110–120°). It melts at 118.5°, and the yield is 50%. It reacts with water, alcohols and mercaptans to form the corresponding carbinol, ethers and sulfides.

Anal. Calc'd for $C_{20}H_{15}Br$: Br, 23.85. Found: Br, 23.67.

Phenyl-2-fluoryliodomethane.—When an attempt was made to prepare this compound by treating the bromide with potassium iodide, much free iodine was obtained, together with a hydrocarbon melting at 284–5°. This was identical with the higher-melting compound obtained in the Würtz synthesis of *sym*-diphenyl-di-2-fluoryl-

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[10] PERRIER, *Bull. soc. chim.*, [3], **31**, 859 (1904).

ethane and is probably the racemic form. The significance of this decomposition has been discussed earlier.

The iodide was eventually obtained by dissolving the bromide in methyl iodide and allowing the solution to stand several days, protected by a drying tube. The precipitate melted at 126–7°. It is much more reactive than the bromide, readily losing iodine to give the dimer, V.

Anal. Calc'd for $C_{20}H_{15}I$: I, 33.2. Found: I, 32.5.

Phenyl-2-fluorylmethoxymethane.—Methyl alcohol was saturated at its boiling point with the bromide, II, and the heating was continued for half an hour. On cooling shining white plates were deposited, melting at 92°. It is slightly soluble in cold methyl and ethyl alcohols, soluble in acetone, chloroform, ether, and glacial acetic acid.

Anal. Calc'd for $C_{21}H_{18}O$: C, 88.06; H, 6.34.
Found: C, 88.33; H, 6.33.

On oxidation with potassium dichromate in glacial acetic acid we obtained benzoyl-2-fluorenone-9, melting at 177°.[2]

Phenyl-2-fluorylethoxymethane.—This compound was prepared as described above for the methoxy derivative, to which it was quite similar, but somewhat less soluble in organic solvents. It melted at 80°.

Anal. Calc'd for $C_{22}H_{20}O$: C, 87.94; H, 6.72.
Found: C, 88.06; H, 6.52.

*Phenyl-2-fluoryl-*n*-propoxymethane.*—This compound crystallized from alcohol in white needles melting at 53°.

Anal. Calc'd for $C_{23}H_{22}O$: C, 87.84; H, 7.06.
Found: C, 88.26; H, 7.16.

*Phenyl-2-fluoryl-*n*-butoxymethane.*—This compound was somewhat more difficult to purify than the lower homologues. It was recrystallized from a mixture of ether and alcohol; melting point, 68°.

Anal. Calc'd for $C_{24}H_{24}O$: C, 87.74; H, 7.37.
Found: C, 88.20; H, 7.47.

Phenyl-2-fluorylmethyl ethyl sulfide.—Ethyl mercaptan was saturated with phenyl-2-fluorylbromomethane, and the solution was refluxed for 2–3 hours. The excess mercaptan was evaporated, and the residue was crystallized from ethyl alcohol. Fine white crystals melting at 68–70° were obtained. The material was slightly soluble in methyl and ethyl alcohols, and soluble in ether, chloroform and benzene.

Anal. Calc'd for $C_{22}H_{20}S$: S, 10.20. Found: S, 10.13.

*Phenyl-2-fluorylmethyl-*n*-propyl sulfide* was prepared from the bromide, II, and *n*-propyl mercaptan in a similar manner. A bright red color appeared, but faded out as the reaction proceeded. The product was crystallized from a mixture of alcohol and ether. White needles melting at 51° were obtained. The solubility was similar to that of the ethyl homologue.

Anal. Calc'd for $C_{23}H_{22}S$: S, 9.69. Found: S, 9.73.

*Phenyl-2-fluorylmethyl-*n*-butyl sulfide* was prepared in a similar manner from the bromide, II, and *n*-butyl mercaptan. It also shows the characteristic red color while reacting. The solubility of these compounds is similar but decreases slightly with increasing molecular weight. The butyl derivative melts at 81°.

Anal. Calc'd for $C_{24}H_{24}S$: S, 9.29. Found: S, 9.26.

The sym-*diphenyldi-2-fluorylethanes.*—Five grams of the bromide, II, and 10 g. of sodium wire were refluxed with 200 cc. of dry ether for 24 hours. Excess sodium was removed and the solid compound that had separated as found to melt, after purification, at 168°. A mixture melting point proved to be identical with the compound obtained from the decomposition of phenyl-2-fluoryliodomethane. The mother liquor was worked up and yielded the diastereoisomer melting at 274–280°. A mixture melting point with the substance obtained from the reaction of the bromide, II, with potassium iodide showed them also to be identical.

Anal. Calc'd for $C_{40}H_{30}$: M. W., 510. Found: M. W., 508.

Phenyl-2-fluorylmethyl phenyl sulfide.—Thiophenol was warmed with the bromide, II, until a vigorous reaction occurred. The sulfide crystallized in shining plates melting at 149°.

Anal. Calc'd for $C_{26}H_{20}S$: S, 8.79. Found: S, 8.83.

Phenyl-2-fluorylmethyl methyl sulfide.—Three grams of the bromide, II, was heated with 10 cc. of dimethyl sulfide in a sealed tube for 6.5 hours. The precipitate was filtered off and the water-soluble portion proved to be trimethylsulfonium bromide melting at 200°.

Anal. Calc'd for $(CH_3)_3SBr$: Br, 50.89. Found: Br, 51.00.

The portion insoluble in water was crystallized from alcohol at room temperature. It is also soluble in ether, benzene, and acetone. It melted at 109.5° and proved to be phenyl-2-fluorylmethyl methyl sulfide.

Anal. Calc'd for $C_{21}H_{18}S$: S, 10.59. Found: S, 10.48.

The sulfide described above was allowed to stand in a sealed tube with excess methyl iodide for two days. The water-soluble precipitate was crystallized from water. It melted at 203°, the value given in the literature[5] for trimethylsulfonium iodide. The water-insoluble material melted at 160° and proved to be identical with the lower-melting form of *sym*-diphenyldi-2-fluorylethane. Free iodine was present in considerable quantities.

Quantitative experiment.—In this run 0.846 g. of dimethyl sulfide and 4.56 g. of phenyl-2-fluorylbromomethane were heated in a sealed tube at 100° for 14 hours. The contents were boiled with methyl alcohol to convert any unchanged bromide into the methyl ether. The mixture was evaporated to dryness and then extracted with water to obtain the trimethylsulfonium bromide. The water-insoluble residue was then treated with alcoholic mercuric chloride to form the addition product of phenyl-2-fluorylmethyl methyl sulfide. This was evaporated to dryness and extracted with ether. The mercuric chloride addition product melts at 128°. The results, given in Table I, show that the requirements of equation (B) are fulfilled.

SUMMARY

A mechanism for the reaction between organic halides and sulfides and the decomposition of sulfonium salts, which unifies and explains the hitherto imperfectly understood course of the reactions between organic halides and sulfides, has been proposed.

This mechanism postulates that in all such reactions, a sulfonium salt is first formed; this may decompose in one, two or three ways, depending on the complexity of the salt, to give halides and sulfides, which, in turn, can combine to form the same or other sulfonium salts. The tendency is for that salt having the smallest organic radicals to be the final product of the reaction.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE CONSTITUTION OF THE METHYL IONONES*

GEORGE WILLIAM POPE† AND MARSTON TAYLOR BOGERT

Received July 8, 1937

Inasmuch as the methyl ionones are now products of considerable importance to the perfume industry, and are marketed under a great variety of trade names, their chemical nature becomes a matter of interest.

In the usual method of preparation, citral (I) is first reacted with methyl ethyl ketone. Assuming the terpinolene form for citral, and ignoring the question of stereoisomers (geranial and neral), the structure of the resultant methyl pseudoionone will be governed by whether the aldehydic CO condenses with the methylene or the methyl group of the ketone. That this condensation must occur with a methyl or methylene group adjoining the ketonic CO, follows from the fact that the ionones so formed yield ionenes when dehydrated, a reaction which could scarcely occur if our interpretation[1] of its mechanism be correct. (See flow sheet no. 1.)

There exists, therefore, the possibility of the formation of two structurally different methyl pseudoionones (II and III), from each of which an *alpha*- (IV, V) and a *beta*- (VI, VII) methyl ionone may arise by cyclization.

The presence of these four isomers in commercial methyl ionone was claimed in Haarmann and Reimer's original patent.[2]

As Tiemann[3] has shown, the cyclization of pseudoionone by phosphoric acid yields mainly *alpha*-ionone, whereas with concentrated sulfuric acid the product is chiefly the *beta* isomer. Similarly, the methyl pseudoionone mixture, when cyclized by phosphoric acid gave as the major products two methyl ionones[4] (IV and V), which were identical with the compounds obtained by the condensation of *alpha*-cyclocitral and methyl ethyl ketone;[5] and with sulfuric acid, the main products were two other isomers (VI and

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* Presented in abstract before the Division of Organic Chemistry, at the Chapel Hill, N. C., Meeting of the American Chemical Society, April 13, 1937.

† Fritzsche Fellow, Columbia University, 1935-1936.

[1] (*a*) BOGERT AND FOURMAN, *J. Am. Chem. Soc.*, **55**, 4670 (1933).
(*b*) FOURMAN, Dissertation, Columbia University, 1933.

[2] HAARMANN AND REIMER, *German Patent*, 75120; *Friedländer*, III, 890 (1894).

[3] (*a*) TIEMANN, *Ber.*, **31**, 870 (1898); (*b*) *ibid.*, **33**, 3708 (1900).

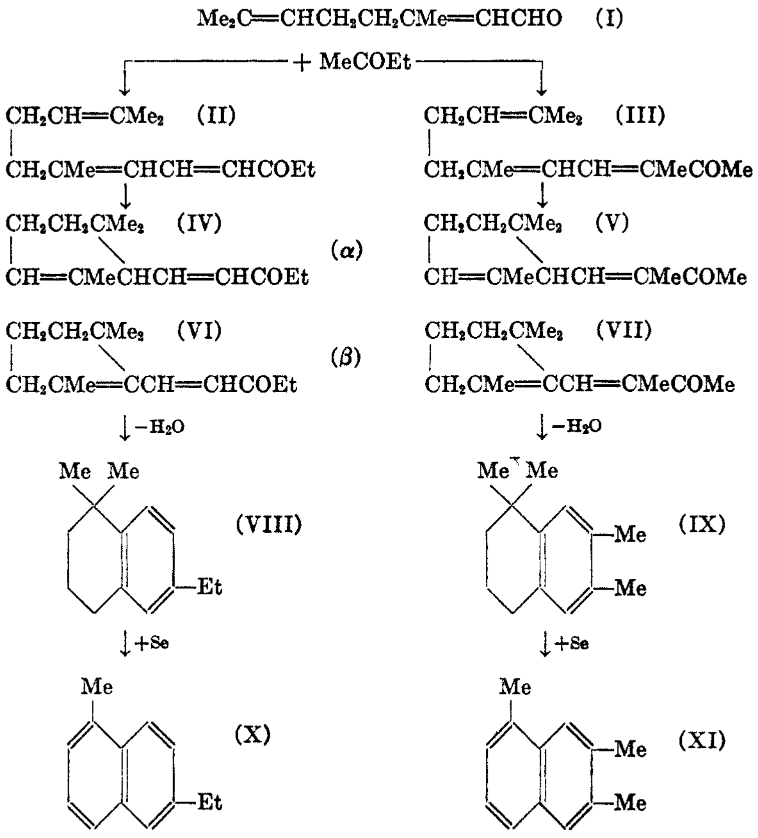
[4] HAARMANN AND REIMER, *German Patent*, 127,424; *Chem. Zentr.*, **1902**, I, 235.

[5] HAARMANN AND REIMER, *German Patent*, 133,758; *Chem. Zentr.*, **1902**, II, 613.

VII), identical with those resulting from the interaction of *beta*-cyclocitral and methyl ethyl ketone. In neither case, however, was it determined which isomer possessed formula IV and which V, or which of the two *beta* forms was VI and which VII.

In a later patent,[6] Haarmann and Reimer described a separation of these various isomers based upon their behavior with sodium bisulfite solution. According to this patent, the methyl pseudoionone mixture obtained by the condensation of citral with methyl ethyl ketone, when refluxed for two days with sodium bisulfite solution, dissolved the ethyl ketone (II), but not the isomer (III). The latter was removed from the bisulfite solution by extraction with ether.

FLOW SHEET No. 1



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[6] Haarmann and Reimer, *German Patent*, 150,827; *Chem. Zentr.*, **1904**, I, 1379.

This process was then applied by them to the separation of the methyl ionone mixture which resulted from the cyclization of the methyl pseudoionone mixture with phosphoric acid. Digestion of the product with the bisulfite solution, dissolved the *alpha* methyl ionone (IV), but not the isomer (V). The latter was collected with ether and purified by distillation under reduced pressure or with steam. The bisulfite solution containing the isomer (IV) was then distilled with steam, which decomposed the hydrosulfite derivative of any *beta* isomer (VI) present and removed it. The undecomposed hydrosulfite of (IV) was then treated with alkali and the liberated (IV) driven over with steam.

Cherbuliez and Hegar,[7] however, have reported concerning the utilization of this method for the separation of the isomeric methyl ionones, that "le procédé proposé (transformation partielle du mélange des cétones 'A' et 'B' en combinaisons bisulfitiques) ne donne aucun renseignment sur la constitution des deux isomères obtenus." They also attempted to prepare the two methyl pseudoionones independently by synthesis; but, of the three methods attempted, only one gave the desired products, and this in such poor yields that, taken together with the uncertainty of the physical constants and the failure to obtain characteristic derivatives, they discontinued the investigation.

Quite recently, Köster,[8] of the Haarmann and Reimer laboratories, has reported on the isolation and identification of the four methyl ionones, by the fractional crystallization of their semicarbazones, discriminating between the derivatives of the two antecedent methyl pseudoionones (II and III) by the iodoform reaction, those giving a positive test being assigned the R—$COCH_3$ structure (V and VII), and those giving a negative one the R—COC_2H_5 structure (IV and VI). The physical constants recorded were in good agreement with those previously reported[6] from these same laboratories.

Our experience in the ionene field[1, 9] suggested a different line of approach to the goal and one which seemed likely to prove interesting. Since we have found that *alpha*- and *beta*- ionones give one and the same ionene when catalytically dehydrated by distillation in the presence of minute amounts of iodine, it was reasonable to assume that the methyl ionones would behave similarly. If so, the isomers IV and VI should both yield the 1,1-dimethyl-6-ethyltetralin (VIII), and V and VII the 1,1,6,7-tetramethyltetralin (IX). These results would be practically independent of the proportions of *alpha* and *beta* isomers present, and thus of the cycli-

[7] Cherbuliez and Hegar, *Helv. Chim. Acta*, **15**, 191 (1932).

[8] Köster, *J. prakt. Chem.*, [2], **143**, 249 (1935).

[9] (*a*) Bogert, Davidson and Apfelbaum, *J. Am. Chem. Soc.*, **56**, 959 (1934). (*b*) Bogert and Apfelbaum, *Science*, n.s., **79**, 280 (1934).

zing agent used, but would be determined entirely by the structures of the antecedent methyl pseudoionones (II or III).

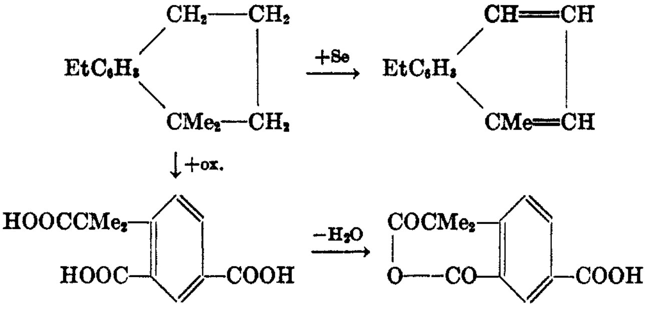
The results of these experiments have shown that when citral and methyl ethyl ketone are condensed, in an alkaline medium, the methyl pseudoionone formed has the structure shown by formula (II). If any of the isomer (III) is also produced, it must be present in relatively small quantity, for it escaped detection, and this is the chief point in which our work differs from that of the Haarmann and Reimer laboratories. Our findings are, however, in entire accord with those of Hibbert and Cannon,[10] who made an extensive study of such citral condensations, and found that they occurred only when the ketone contained a $—COCH_3$ group.

The first task was the synthesis and characterization of the tetralins (VIII and IX). 1,1-Dimethyl-6-ethyltetralin (VIII) was built up by the steps indicated in Flow Sheet No. 2.

FLOW SHEET NO. 2

$m\text{-EtC}_6\text{H}_4\text{Br} \rightarrow \text{EtC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OH} \rightarrow$

$\text{EtC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{Br} \rightarrow \text{EtC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{CH(OH)CHMe}_2 \rightarrow$



(X)

(XII) (XIII)

Flow Sheet No. 3 outlines the similar method of preparation and the oxidation product of 1,1,6,7-tetramethyltetralin (IX) (see flow sheet no. 3).

These syntheses accomplished, and the products characterized by dehydrogenation, oxidation, and the determination of their physical constants, a number of samples of commercial methyl ionone, as well as one we prepared from citral ourselves, were examined by conversion into the tetralin. In every case, as already stated, the only product isolated was the 1,1-dimethyl-6-ethyltetralin (VIII).

Acknowledgments.—Our grateful thanks are due to the generous assist-

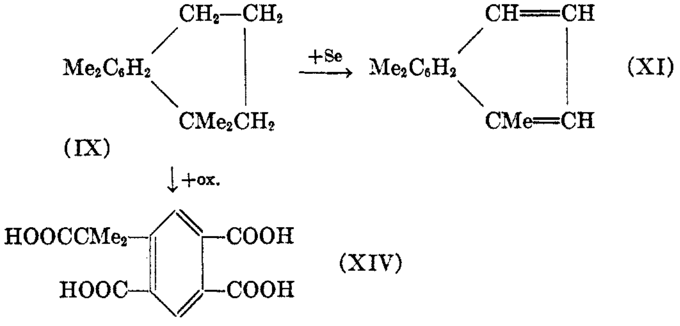
[10] HIBBERT AND CANNON, *J. Am. Chem. Soc.*, **46**, 119 (1924).

ance of the following friends in the perfume industry, who supplied us with various chemicals required for this investigation: Fritzsche Bros., Inc., of New York; Givaudan-Delawanna, Inc., of New York; Naugatuck Chemical, of Naugatuck, Conn.; and the Florasynth Laboratories of New York.

FLOW SHEET NO. 3

$(1,2)Me_2C_6H_3Br(4) \rightarrow Me_2C_6H_3CH_2CH_2OH \rightarrow$

$Me_2C_6H_3CH_2CH_2Br \rightarrow Me_2C_6H_3CH_2CH_2CH(OH)CHMe_2 \rightarrow$



(IX) (XI) (XIV)

EXPERIMENTAL

A. *Synthesis of 1,1-Dimethyl-6-ethyltetralin*

m-*Bromoethylbenzene.*—*m*-Aminoacetophenone was converted into the bromoacetophenone by the diazo reaction, and the latter reduced by Martin's modification[11] of the Clemmensen method; yield, 75–80%; b.p. 100–102°/30 mm. Physical constants of a redistilled sample: b.p. 92°/24 mm.; n_D^{25} 1.5407, d_4^{25} 1.3287; M_D calc'd 43.31, M_D obs. 43.85.

Anal. Calc'd for C_8H_9Br: C, 51.87; H, 4.90.
Found: C, 52.25; H, 5.06.

Oxidized with sodium dichromate and sulfuric acid, it gave *m*-bromobenzoic acid in long thin white needles, m.p. 154–155° (corr.), which melting point was unaltered when the product was mixed with an authentic sample of *m*-bromobenzoic acid of a different origin.

A less satisfactory process for the preparation of the *m*-bromoethylbenzene was the following (with Olga N. Jitkow).

Ethylbenzene was nitrated and the resultant mixture of *o*- and *p*-nitro isomers was reduced to the amines; the amine mixture was acetylated, the mixture of acetyl derivatives brominated, the acetyl group removed, and finally the amino group. When carried through this series of reactions, both *o*- and *p*-nitro ethylbenzene give the *m*-bromoethylbenzene; yield, based on the amount of initial ethylbenzene,

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[11] MARTIN, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

10-15%. The product obtained by this process boiled at 95-97°/26 mm., and 203-205° at atmospheric pressure.

beta-(m-*Ethylphenyl*)*ethanol*.—By the usual Grignard reaction, employing an iodine-activated magnesium, this alcohol was obtained from *m*-bromoethylbenzene and ethylene oxide; b.p. 115-118°/7 mm.; yield, 60%. Physical constants of a redistilled sample: b.p. 110-111°/4 mm.; n_D^{25} 1.5220, d_4^{25} 0.9938; M_D calc'd 46.30, M_D obs. 46.04.

Anal. Calc'd for $C_{10}H_{14}O$: C, 79.94; H, 9.40.
Found: C, 79.88; H, 9.42.

Phenylurethane.—Long thin white needles, m.p. 57.5-58° (corr.).

Anal. Calc'd for $C_{17}H_{19}NO_2$: N, 5.20.
Found: N, 5.31.

3,5-Dinitrobenzoate.—Small pale yellow plates, m.p. 79-79.5° (corr.).

Anal. Calc'd for $C_{17}H_{16}O_6N_2$: N, 8.14.
Found: N, 7.75.

beta-(m-*Ethylphenyl*)*ethyl bromide* was prepared from the above alcohol, either by the action of hydrobromic and sulfuric acids, or of phosphorus tribromide; yields, 80% by the former, and 81% by the latter method; b.p. 99-104°/4 mm. Physical constants of a redistilled sample: b.p. 105-106°/6 mm.; n_D^{25} 1.5413; d_4^{25} 1.2766; M_D calc'd 52.54, M_D obs. 52.45.

Anal. Calc'd for $C_{10}H_{13}Br$: C, 56.33; H, 6.15.
Found: C, 55.87; H, 5.98.

2-Methyl-5-(m-*ethylphenyl*)*pentanol-3* was obtained from the foregoing bromide and isobutyraldehyde, by the Grignard reaction; b.p. 125-129°/2 mm.; yield, 61%. Physical constants of a redistilled sample: b.p. 132-133°/4 mm.; n_D^{25} 1.5047; d_4^{25} 0.9393; M_D calc'd 64.77, M_D obs. 64.70.

Anal. Calc'd for $C_{14}H_{22}O$: C, 81.55; H, 10.76.
Found: C, 81.46; H, 10.77.

Neither a crystalline phenylurethane nor a 3,5-dinitrobenzoate could be secured from this alcohol.

1,1,-Dimethyl-6-ethyltetralin (VIII).—This methyl ionene resulted when the above alcohol was heated with phosphorus pentoxide; yield, 84%. Distilled over sodium, its constants were as follows: b.p. 104-105°/4 mm., n_D^{25} 1.5220; d_4^{25} 0.9304; M_D calc'd 61.05, M_D obs. 61.62; E_M 0.57.

Anal. Calc'd for $C_{14}H_{20}$: C, 89.29; H, 10.71.
Found: C, 89.48; H, 10.79.

Dinitro derivative.[1] —Pale yellow thin needles, m.p. 111-112° (corr.).

Anal. Calc'd for $C_{14}H_{18}N_2O_4$: C, 60.40; H, 6.52.
Found: C, 60.32; H, 6.73.

Sulfonamide.—This was prepared by the process of Bogert, Davidson and Apfelbaum[9]; or the hydrocarbon was converted into its sulfonyl chloride by the action of chlorosulfonic acid, and this chloride then changed to the amide by digestion for 24 hours with concentrated ammonium hydroxide solution. Recrystallized twice from alcohol-water mixtures, it formed small white lustrous plates, m.p. 129-130° (corr.); yield, 55%, by either method.

Anal. Calc'd for $C_{14}H_{21}NO_2S$: C, 62.88; H, 7.92.
Found: C, 63.09; H, 8.12.

alpha-(*2,4-Dicarboxyphenyl)isobutyric acid* (XII).—When the dimethylethyltetralin (VIII) was oxidized with alkaline potassium permanganate, the tricarboxylic acid (XII) was obtained in fine white needles (from water). These softened at about 160°, with loss of water and formation of the anhydride (XIII), which then melted at 214–215° (corr.). Dried in a vacuum desiccator over phosphorus pentoxide, to free it from two molecules of water of crystallization, the *acid* was analyzed.

Anal. Calc'd for $C_{12}H_{12}O_6$: C, 57.12; H, 4.80.
Found: C, 57.06; H, 4.96.

Acid equivalent: calc'd, 84; found, 84.3 and 84.4.

The *anhydride* (XIII), prepared from the acid by 10 hours' heating at 110°, gave the following results:

Anal. Calc'd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.31.
Found: C, 61.58; H, 4.17.

The tetralin, when oxidized by dilute nitric acid under pressure,[12] gave the same acid (XII), in better yield (0.5 g. of purified acid from 1 g. of the hydrocarbon), and free from oily contaminants. Sodium dichromate and sulfuric acid proved still more convenient as an oxidizing agent, although the yield was slightly less (0.8 g. from 2 g. of the tetralin), for the reaction was complete after 3 hours' refluxing.

This acid (XII) has been obtained by the permanganate oxidation of ionene, by Tiemann and Krüger,[13] and by Tiemann,[14] who called it "ioniregentricarboxylic acid," and stated that it lost water at 150°, and recorded the melting point of its anhydride as 214°; and by Bogert and Fourman,[1] who reported 217° as the melting point of the anhydride.

1-Methyl-6-ethylnaphthalene (X).—When the tetralin (VIII) was heated with powdered selenium for 40–45 hours at 300–320°, this naphthalene derivative was the product; b.p. 146°/14 mm.; yield, 90%. *Picrate*, m.p. 80–81° (corr.); *styphnate* m.p. 88.5–89.5° (corr.). Harvey, Heilbron and Wilkinson[15] have reported the boiling point of this compound as 140° at 12 mm., and the melting point of its picrate as 82°.

B. Synthesis of 1,1,6,7-Tetramethyltetralin

beta-(*3,4-Xylyl)ethanol,* from 4-bromo-*o*-xylene, iodine-activated magnesium and ethylene oxide; b.p. of crude product, 115–118°/7 mm.; yield, 58–63%. Physical constants of a redistilled sample: b.p. 109–110°/3 mm., n_D^{25} 1.5300; d_4^{25} 0.9935; M_D calc'd 46.30, M_D obs. 46.62.

Anal. Calc'd for $C_{10}H_{14}O$: C, 79.94; H, 9.40.
Found: C, 79.54; H, 9.39.

Phenylurethane.—White rosettes of thin white needles, m.p. 108–108.5° (corr.).

Anal. Calc'd for $C_{17}H_{19}NO_2$: N, 5.20.
Found: N, 5.44.

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[12] Boes, *Ber. deut. pharm. Ges.*, **12**, 222 (1902); *Chem. Zentr.*, **1902**, II, 1119.

[13] Tiemann and Krüger, *Ber.*, **26**, 2675 (1893).

[14] Tiemann, *ibid.*, **31**, 873 (1898).

[15] Harvey, Heilbron, and Wilkinson, *J. Chem. Soc.*, **1930**, 430.

3,5-Dinitrobenzoate.—Small pale yellow flat plates, m.p. 145–146° (corr.).

Anal. Calc'd for $C_{17}H_{16}O_6N_2$: N, 8.14.
Found: 7.97.

3,4,3′,4′-Tetramethyldiphenyl, separated as a by-product in the preparation of the ethanol, formed small white needles (from alcohol), m.p. 76–77° (corr.), in agreement with the literature.[16]

beta-*(3,4-Xylyl)ethylbromide,* prepared from the corresponding ethanol, concentrated sulfuric, and 48% hydrobromic acids, by the method of Kamm and Marvel,[17] was obtained as a fraction, b.p. 110–113°/6 mm.; yield, 80–86%. Physical constants of a redistilled sample: b.p. 106–107°/4 mm.; n_D^{25} 1.5503; d_4^{25} 1.2868; M_D calc'd 52.54, M_D obs. 52.72.

Anal. Calc'd for $C_{10}H_{13}Br$: C, 56.33; H, 6.15.
Found: C, 56.51; H, 6.21.

2-Methyl-5-(3′,4′-xylyl) pentanol-3.—From the above bromide, activated magnesium, and isobutyraldehyde, this alcohol was obtained in yields of 58–64%, and a b.p. of 130–135°/4 mm. Redistilled, it showed the following physical constants: b.p. 127–128°/3 mm.; n_D^{25} 1.5113; d_4^{25} 0.9501; M_D calc'd 64.77, M_D obs. 64.98.

Anal. Calc'd for $C_{14}H_{22}O$: C, 81.55; H, 10.76.
Found: C, 81.65; H, 10.79.

No crystalline phenylurethane or 3,5-dinitrobenzoate could be obtained from it.

1,1,6,7-Tetramethyltetralin (IX).—In the cyclodehydration of the above alcohol, phosphorus pentoxide gave 90% or better yields of the tetralin, whereas with sulfuric acid the yields were only 20–25%. Distilled over sodium, the hydrocarbon possessed these physical constants: b.p. 103–104°/4 mm., n_D^{25} 1.5280; d_4^{25} 0.9392; M_D calc'd 61.05, M_D obs. 61.64; E_M 0.59. This exaltation compares with those of the isomer (VIII), 0.57, and of ionene itself, 0.65,[9] 0.70,[1] and 0.75.[15]

Anal. Calc'd for $C_{14}H_{20}$: C, 89.29; H, 10.71.
Found: C, 89.23; H, 10.77.

Dinitro derivative.—No crystalline derivative could be obtained.

Sulfonamide.—This was prepared as described for the isomeric 1,1-dimethyl-6-ethyltetralin, or by the process used by Bogert, Davidson and Apfelbaum[9] in the case of ionene; yield, 65% by the first method, 55% by the second. Recrystallized twice from alcohol by the careful addition of water, it formed small white flat plates, m.p. 137–138° (corr.).

Anal. Calc'd for $C_{14}H_{21}NO_2S$: C, 62.88; H, 7.92.
Found: C, 63.23; H, 7.93.

alpha-*(2,4,5-Tricarboxyphenyl)isobutyric acid* (XIV).—Oxidation of 1,1,6,7-tetramethyltetralin (IX) by either alkaline potassium permanganate, or dilute nitric acid under pressure, resulted in the formation of this acid. Sodium dichromate and sulfuric acid proved unsatisfactory. The crude product was purified by solution in absolute ethanol and precipitation by the addition of benzene. Crystallized from a mixture of ethanol and benzene, it formed microscopic white needles which, after being dried *in vacuo* over phosphorus pentoxide, melted in a sealed tube at

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[16] Crossley, *ibid.*, **99**, 726 (1911).

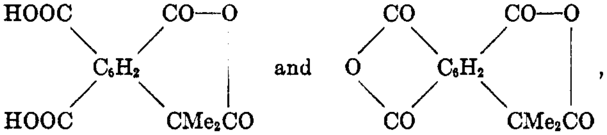
[17] Kamm and Marvel, *Organic Syntheses*, Collective Vol. I, p. 28 (1932).

267–269° (corr.). The resolidified acid showed the same melting point. The yield by the permanganate method was 0.2 g. of the acid from 2 g. of the hydrocarbon; by the nitric acid method, 0.4 g. from 1. g. of the tetralin.

Anal. Calc'd for $C_{13}H_{12}O_8$: C, 52.69; H, 4.09.
Found: C, 52.51; H, 3.87.

Acid equivalent: calc'd, 74; found, 74.1, 74.3.

When heated in an open tube, this acid lost water, with formation of a mixture of the two possible anhydrides,



which were not isolated in sufficient quantity to be purified satisfactorily.

2,3,5-Trimethylnaphthalene (XI).—A mixture of 3 g. of tetramethyltetralin with 4.5 g. of powdered selenium was refluxed for 40–45 hours at 300–320° and the trimethylnaphthalene was then distilled as a pale yellow liquid, b.p. 140°/12 mm. (literature[19] 138°/12 mm.); yield, 92%.

Picrate.—Small orange-red needles; m.p., 125–126° (corr.). The melting point is given in the literature as 122°,[18] 122.5°,[19] and 125°.[20]

Styphnate.—Golden-yellow needles; m.p., 147.5–148.5° (corr.); literature gives 146°,[19] 148–149°,[18] and 149°.[20]

C. Synthesis of "Methyl Ionone" from Citral

The procedure of Hibbert and Cannon,[10] with minor modifications, was found entirely suitable for our purpose. The important features of this synthesis are the careful purification of the citral and the methyl pseudoionone, and the protection of all products, especially during distillations, against oxidation.

The citral was purified as recommended by Tiemann,[21] and by Hibbert and Cannon;[10] average yield, 53%; b.p. 108–111°/12 mm. The rectifications were conducted in an atmosphere of nitrogen. Hibbert and Cannon[10] gave the boiling point at this pressure as 107–112°, and Bogert and Fourman[22] as 110–112°.

"Methyl pseudoionone" (II).—The method followed in this condensation was essentially that employed by Stiehl,[23] and by Hibbert and Cannon[10] for the preparation of other pseudoionones. The product was twice distilled in an atmosphere of nitrogen; average yield, 65%; b.p. 135–140°/3 mm. The methyl pseudoionone so obtained was then purified by the method used by Tiemann[24] for pseudoionone itself. A mixture of 40 g. of the methyl pseudoionone, 80 cc. of 35% sodium bisulfite solution, and 40 cc. of water, was refluxed for 5 hours, a clear yellow solution resulting in less than 3 hours. This solution was extracted with ether (which extract left no residue

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[18] Wilkinson, *J. Chem. Soc.*, **1931**, 1331.

[19] Ruzicka and Ehmann, *Helv. Chim. Acta*, **15**, 159 (1932).

[20] Barnett and Sanders, *J. Chem. Soc.*, **1933**, 434.

[21] Tiemann, *Ber.*, **31**, 3319, 3339 (1898).

[22] Bogert and Fourman, *Am. Perfumer*, **28**, 345 (1933).

[23] Stiehl, *J. prakt. Chem.* [2], **58**, 79 (1898).

[24] Tiemann, *Ber.*, **31**, 808 (1898).

on evaporation), and the separated aqueous layer was decomposed by the addition of a 10% sodium hydroxide solution. The methyl pseudoionone thus liberated was immediately collected with ether, the ether solution washed repeatedly with tartaric acid solution and with water, dried over anhydrous sodium sulfate and distilled in nitrogen, collecting the fraction boiling at 133–137° at 4 mm.; yield, 32%, calculated to the citral.

Anal. Calc'd for $C_{14}H_{22}O$: C, 81.55; H, 10.76.
Found: C, 81.79; H, 10.98.

Haarmann and Reimer[6] have claimed that digestion with sodium bisulfite solution effects a separation of the two isomeric methyl pseudoionones (II and III), by dissolving isomer (II), while (III) remains undissolved. As noted above, our product, when subjected to the bisulfite treatment gave a perfectly clear solution in less than 3 hours.

"alpha-*Methyl ionone*" (IV).—The methyl pseudoionone (II) was cyclized by the action of 85% phosphoric acid at 30°, which is the reagent used in the Haarmann and Reimer patent,[6] and which is reported[4] to give mainly the *alpha* methyl ionone. The crude product was purified by steam distillation, followed by distillation in nitrogen, collecting the fraction which boiled at 108–111° at 4 mm.; yield, 75%. The physical constants of a re-distilled sample were as follows: b.p. 112–113°/6 mm.; n_D^{25} 1.4984; d_4^{52} 0.9104. Previously reported:[25] b.p. 135–140°/15 mm.; n^{20} 1.5009; d^{20} 0.927. As noted by Tiemann and Krüger[13] in the case of pseudoionone and ionone, the molecular refraction of this methyl ionone is likewise abnormally high.

Anal. Calc'd for $C_{14}H_{22}O$: C, 81.55; H, 10.76.
Found: C, 81.23; H, 10.61

Semicarbazone.—Small white plates, from 60% alcohol, m.p. 146–147° (corr.). Previously reported: m.p. 144°,[6] and 146°.[8]

Anal. Calc'd for $C_{15}H_{25}ON_3$: C, 68.39; H, 9.57.
Found: C, 68.12; H, 9.53.

"*Methyl ionene*" (*1,1-Dimethyl-6-ethyltetralin*) (VIII).—Dehydrated by two distillations with 1% of its weight of iodine, the "*alpha* methyl ionone" gave a 75% yield of 1,1-dimethyl-6-ethyltetralin, whose analysis and physical constants are recorded in the Table of Methyl Ionenes given later.

It was further identified by the preparation of its *sulfonamide* (m.p. and mixture m.p., 129–130°, corr.), and *dinitro derivative* (m.p. and mixture m.p., 111–112°, corr.), and by *oxidation* with dilute nitric acid under pressure. The *alpha*-(2,4-dicarboxyphenyl)isobutyric acid (XII) so produced (yield, 0.4 g. from 1 g. of the hydrocarbon), gave the following figures upon analysis:

Anal. Calc'd for $C_{12}H_{12}O_6$: C, 57.12; H, 4.80.
Found: C, 57.40; H, 4.75.

Its *anhydride*, prepared by 10 hours' heating of the acid at 110°, melted at 214–215° (corr.), and gave these results:

Anal. Calc'd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.31.
Found: C, 61.70; H, 4.36.

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[25] HAARMANN AND REIMER, *German Patent*, 127,424; *Chem. Zentr.*, **1902**, I, 235.

TABLE OF METHYL IONENES ($C_{14}H_{20}$)

METHYL IONENES	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	CALC'D
C(%)	89.51	89.35	89.29	89.11	89.58	89.12	89.48	89.23	89.29
H(%)	10.81	10.78	10.88	10.81	10.76	10.71	10.79	10.77	10.71
b.p.	98–100°	99–101°	98–100°	98–100°	99–101°	98–99°	104–105°	103–104°	
Pressure (mm.)	2	2	2	2	3	2	4	4	
n_D^{25}	1.5211	1.5220	1.5215	1.5216	1.5205	1.5215	1.5220	1.5280	
d_4^{25}	0.9297	0.9314	0.9292	0.9306	0.9282	0.9287	0.9304	0.9393	
M_D obs.	61.59	61.55	61.66	61.55	61.66	61.69	61.62	61.64	61.05
E_M	0.54	0.50	0.61	0.50	0.61	0.64	0.57	0.59	
Dinitro deriv., m.p.	111–112°	111–112°	111–112°	111–112°	111–112°	111–112°	111–112°		
Sulfonamide, m.p.	129–130°	129–130°	129–130°	129–130°	129–130°	129–130°	129–130°	137–138°	
Dehydrogenation Product (Alkylnaphthalene)($C_{13}H_{14}$)									
Picrate, m.p.	80–81°	80–81°	80–81°	80–81°	80–81°	80–81°	80–81°	125–126°	
Styphnate, m.p.	89–90°	89–90°	89–90°	88–89°	89–90°	89–90°	88.5–89.5°	147.5–148.5°	

No *alpha*-(2,3,4-tricarboxyphenyl)isobutyric acid (XIV) was detected as an oxidation product of this methyl ionene.

Dehydrogenation by selenium yielded the 1-methyl-6-ethylnaphthalene, which was identified by its *picrate* (m.p. and mixture m.p., 80–81°, corr.), and *styphnate* (m.p. and mixture m.p., 89–90°, corr.).

D. Examination of Commercial "Methyl Ionones"

Having completed the foregoing syntheses and the characterization of the products, five different commercial samples of "methyl ionones," provided by the courtesy of the firms mentioned in the introductory part of this paper, were investigated.

Attempts to separate the components of these ionones by fractional distillation in an atmosphere of nitrogen, using a Widmer column, were unsatisfactory. Fractions were collected which boiled within the range of 143–153° at 17 mm. in yields which averaged 75%. A solid semicarbazone could not be secured from any one of the five samples, but only oils resulted which refused to crystallize even when seeded with crystals of the semicarbazone prepared from our synthetic methyl ionone.

The purified commercial samples, b.p. 143–153° at 17 mm., were dehydrated by distillation with iodine, and the products purified by two distillations over sodium, followed by a fractional distillation in nitrogen with a Widmer column. The yields averaged 70–75%, and the product in every case was the 1,1-dimethyl-6-ethyltetralin. The results of the examination of these products are shown in the accompanying table.

In the Table, samples (1), (2), (3), (4), and (5), were prepared from the commercial "Methyl Ionones." No. (6) was the methyl ionene whose synthesis from citral is described in the foregoing pages. No. (7) was the synthetic 1,1-dimethyl-6-ethyltetralin (VIII) obtained from *m*-bromoethylbenzene; and No. (8) the 1,1,6,7-tetramethyltetralin (IX) synthesized from 4-bromo-*o*-xylene.

Some preliminary work on the dehydration of commercial methyl ionone by distillation with iodine, and the nitration of the methyl ionene so formed, was conducted in these laboratories by Dr. Fourman[1] a few years ago, but pure products were not isolated.

SUMMARY

1. 1,1-Dimethyl-6-ethyl (VIII) and 1,1,6,7-tetramethyltetralin (IX) have been prepared synthetically, and characterized by their physical constants and the properties of certain of their derivatives.

2. The methyl ionone obtained from citral and methyl ethyl ketone has been shown, by dehydration to VIII, to have resulted from the condensation of the aldehyde with the —$COCH_3$ and not with the —CH_2CH_3 group.

3. Five commercial brands of "Methyl Ionone" have been examined and, in every case, after dehydration by distillation with iodine, the only methyl ionene isolated was this same tetralin (VIII). From which it follows that in the manufacture of these products also the citral must have condensed wholly, or chiefly, with the —$COCH_3$ group of the methyl ethyl ketone.

4. These results are somewhat at variance with those of the Haarmann and Reimer laboratories, whose experts have reported the presence of all four possible isomeric methyl ionones in the commercial product.

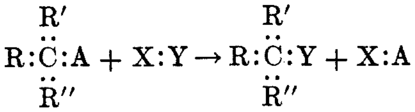
[Contribution from the Chemical Laboratory of the University of Illinois]

OPTICALLY ACTIVE QUATERNARY AMMONIUM SALTS FROM *d*- AND *l*-2-OCTYL *p*-BROMOBENZENESULFONATE AND TERTIARY AMINES

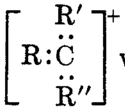
R. C. CARY, J. F. VITCHA and R. L. SHRINER

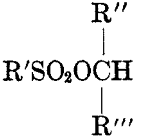
Received July 30, 1936

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),



$$\mathrm{R}:\overset{\mathrm{R'}}{\underset{\mathrm{R''}}{\ddot{\underset{\cdot\cdot}{\mathrm{C}}}}}:\mathrm{A} + \mathrm{X}:\mathrm{Y} \rightarrow \mathrm{R}:\overset{\mathrm{R'}}{\underset{\mathrm{R''}}{\ddot{\underset{\cdot\cdot}{\mathrm{C}}}}}:\mathrm{Y} + \mathrm{X}:\mathrm{A}$$

the residue would be a carbonium ion  $\left[\mathrm{R}:\overset{\mathrm{R'}}{\underset{\mathrm{R''}}{\ddot{\underset{\cdot\cdot}{\mathrm{C}}}}}\right]^+$ 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



$\mathrm{R'SO_2O}\overset{\mathrm{R''}}{\underset{\mathrm{R'''}}{\mathrm{CH}}}$ 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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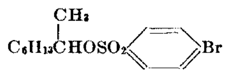
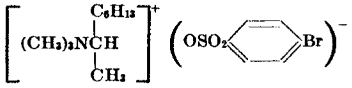
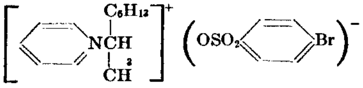
[1] Phillips, *J. Chem. Soc.*, **123**, 44 (1923); *ibid.*, **125**, 399 (1925); *ibid.*, **127**, 2552 (1927); Kenyon and Phillips, *ibid.*, **1930**, 1676; *Trans. Faraday Soc.*, **26**, 451 (1930); Kenyon, Phillips and Pittman, *J. Chem. Soc.*, **1935**, 1072; Kenyon, Phillips and Shutt, *ibid.*, **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.

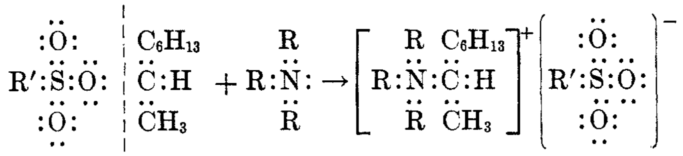
$$R'SO_2O\overset{R''}{\overset{|}{C}}HR''' + R_3N \rightarrow \left[R_3N\overset{R''}{\overset{|}{C}}HR'''\right]^+ (R'SO_2O-)^-$$

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,



I II III IV V

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.

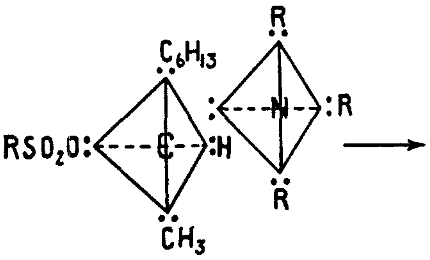


Fig. 1

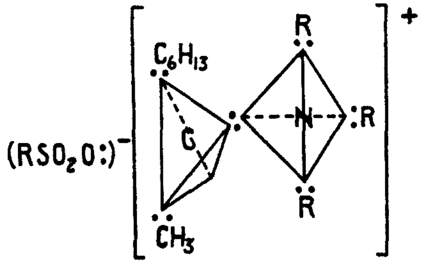


Fig. 2

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-bromooöctane 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°; $[\alpha]^{25}_{D}$ 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.

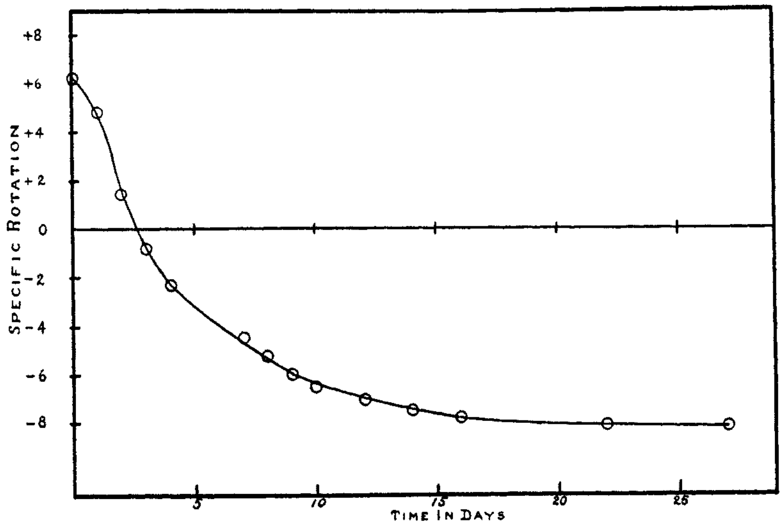

FIG. 3

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 GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

THE PEROXIDE EFFECT IN THE ADDITION OF REAGENTS TO UNSATURATED COMPOUNDS. XV. THE ADDITION OF HYDROGEN BROMIDE TO 1- AND 2-BROMO- AND CHLOROPROPENES

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Received July 30, 1937

INTRODUCTION

The purpose of this investigation was twofold: first, to correlate the structures of ethylene compounds with susceptibility to the "peroxide effect"; second, to extend our knowledge of the intermediates formed in the addition of two moles of hydrogen bromide to methylacetylene under "antioxidant" and "peroxide" conditions.[1] Both objectives seemed attainable in a study of the addition of hydrogen bromide and hydrogen chloride to 1- and 2-bromo- and chloropropenes.

It has been established, by investigators in this laboratory and elsewhere, that excellent yields of either of the two possible products of the addition of one mole of hydrogen bromide to unsaturated compounds may be obtained with the following substances: propene[2], 1-butene[3], 2-methylpropene[4], 1-pentene[5], 4,4-dimethyl-1-pentene[6], 1-nonene[7], 1-undecene[7], 1-tridecene[7], 1-pentadecene[7], vinyl chloride[8], vinyl bromide[9], allyl bromide[10], allyl chloride[11], butadiene[12], vinylacetic acid[13], allylacetic acid[13, 14],

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[1] KHARASCH, MCNAB, AND MCNAB, *J. Am. Chem. Soc.*, **57**, 2463 (1935).

[2] KHARASCH, MCNAB, AND MAYO, *ibid.*, **55**, 2531 (1933); KHARASCH AND MCNAB, *ibid.*, **56**, 1425 (1934); BROUWER AND WIBAUT, *Rec. trav. chim.*, **53**, 1001 (1934).

[3] KHARASCH AND HINCKLEY, *J. Am. Chem. Soc.*, **56**, 1212 (1934).

[4] KHARASCH AND HINCKLEY, *ibid.*, **56**, 1243 (1934); KHARASCH AND POTTS, *ibid.*, **58**, 57 (1936).

[5] KHARASCH, HINCKLEY, AND GLADSTONE, *ibid.*, **56**, 1642 (1934).

[6] KHARASCH, HANNUM, AND GLADSTONE, *ibid.*, **56**, 244 (1934).

[7] KHARASCH AND POTTS, *J. Org. Chem.*, **2**, 195 (1937).

[8] KHARASCH AND HANNUM, *J. Am. Chem. Soc.*, **56**, 712 (1934).

[9] KHARASCH, MCNAB, AND MAYO, *ibid.*, **55**, 2521 (1933).

[10] KHARASCH AND MAYO, *ibid.*, **55**, 2468 (1933).

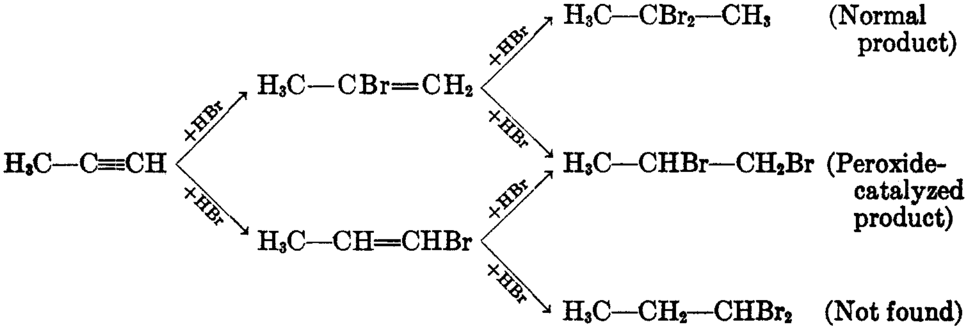
[11] SHANE, Ph.D. Dissertation, University of Chicago, **1933**.

[12] KHARASCH, MARGOLIS, AND MAYO, *J. Org. Chem.*, **1**, 393 (1936).

[13] LINSTEAD AND RYDON, *J. Chem. Soc.*, **1934**, 2001.

[14] KHARASCH AND MCNAB, *J. Soc. Chem. Ind.*, **54**, 989 (1935).

undecenoic acid[15], ethyl undecenoate[16], undecenyl acetate[16], undecynoic acid[17], and butylacetylene[18]. It has not been possible, however, to alter the relative proportion of addition products from 2-penene[19] or undecylenic acid[20] by the use of antioxidants or peroxides, or to obtain more than one product with styrene[21], propenylbenezene[22], undecenol[16], acrylic acid[23], bromomaleic acid[23], bromofumaric acid[23], bromocrotonic acid[23], crotonic acid[23]. A study of the structures of the compounds known to show a "peroxide effect" discloses that they all have a terminal double bond. Obviously, it is of importance to determine whether the presence of two hydrogen atoms on the terminal carbon atom is essential, or whether one of them may be replaced by another atom, such as a halogen atom. Incidentally, a study of the addition of hydrogen bromide to chloro- and bromopropenes not only answers this question, but may be of value in the determination of the intermediate product in the addition of two moles of hydrogen bromide to methylacetylene[1] in the presence of peroxides, as can be seen from the following schematic representation of the reaction.



PREVIOUS WORK

2-Bromo- and 2-chloropropene and the cis and trans forms of 1-chloro- and 1-bromopropene have been described, and some of their physical constants have been recorded. Reboul[24] is the only author who has re-

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[15] Ashton and Smith, *J. Chem. Soc.*, **1934**, 435.

[16] Ashton and Smith, *ibid.*, **1934**, 1308.

[17] Harris and Smith, *ibid.*, **1935**, 1572.

[18] Young, Vogt, and Nieuwland, *J. Am. Chem. Soc.*, **58**, 1806 (1936).

[19] Kharasch, Hinckley, Beck, and Mayo, unpublished work.

[20] Harris and Smith, *J. Chem. Soc.*, **1935**, 1108.

[21] Kharasch, Mayo, and Hammond, unpublished work.

[22] Kharasch and White, unpublished work.

[23] Kharasch and McNab, unpublished work.

[24] Reboul, *Ann. chim.*, [5], **14**, 453 (1878).

ported the addition of hydrogen bromide to these unsaturated compounds. However, the conclusions he draws from his experimental data are open to serious objection. Thus, he records that 1-bromopropene, when treated with four to five volumes of saturated aqueous hydrobromic acid, yields a dibromide. From the fact that the dibromide boiled over a wide temperature range (8°), he assumed that it was a mixture of 1,2- and 1,1-dibromopropane, with a predominance of the former product. He was unable, however, to isolate any pure 1,1-dibromopropane from the reaction mixture, though he predicts that the compound would boil at 131–3°. However, a critical examination of the data suggests that the low-boiling compound obtained by Reboul in the above addition was not 1,1-dibromopropane, but 2,2-dibromopropane. Reboul prepared his 1-bromopropene by treating a mixture of 1- and 2-bromopropene with hydrogen bromide. The method depends upon the observation that the 2- derivative adds hydrogen bromide faster than the 1- compounds. A mixture rich in the 1- form could thus be obtained, and Reboul considered the substance to be pure 1-bromopropene when the boiling point of the material did not change upon further treatment with hydrogen bromide. It is evident, however, that the material must contain a mixture of 1- and 2-bromopropene in quantities approximately inversely proportional to their reactivities. His evidence that 1,1-dibromopropane is formed by the addition of hydrogen bromide to 1-bromopropene is therefore inconclusive.

Reboul records that when a concentrated aqueous solution of hydrogen bromide is added to 2-bromopropene, 2,2-dibromopropane is formed exclusively.

Reboul also studied the addition of concentrated aqueous hydrobromic acid to 1- and 2-chloropropene. He states that 1-chloropropene yielded a mixture of products, but that 1-bromo-1-chloropropane predominated, and that only a small amount of 1-chloro-2-bromopropane was formed. In this case, the criticism of the purity of the initial material is perhaps not valid, for the 1-chloro compound is reported to have been prepared from 1,1-dichloropropane, and should therefore be free from isomers. Careful perusal of Reboul's paper, however, fails to yield any satisfactory proof that his addition product was pure.

Reboul claims to have obtained 2-bromo-2-chlorpropane exclusively by addition of hydrogen bromide to 2-chloropropene.

ADDITION OF HYDROGEN BROMIDE TO BROMO- AND CHLOROPROPENES UNDER "PEROXIDE" AND "ANTIOXIDANT" CONDITIONS

As is recorded in Table I, the "normal" product of the addition of hydrogen bromide to 2-bromopropene is 2,2-dibromopropane. This product is formed *in vacuo* in the presence of "antioxidants". The fact

TABLE I

THE ADDITION OF HYDROGEN BROMIDE TO 2-BROMOPROPENE

EXPT. NO.	MOLES[a] HBr	PEROXIDE OR ANTIOXIDANT, MOLES[a]	TECHNIQUE	REACTION TIME AT ROOM TEMP.	YIELD[b]		% 2, 2- ADDITION PRODUCT[c]	REMARKS
					Minimum, %	Estimated, %		
2	1.5	None	Air, 1	20 hours		100	96	Estimated from b.p.
15	2.1	None	Air, 1	28 hours	75		85–90	
13	1.7	Ascaridole, .06	Air, 2	5 hours	79		17	Checked
33	1.5	Ascaridole, .08	Air, 8	6 hours		81	17	
5	1.5	Diphenylamine, .03	Vacuum, 1	44 hours		100	100	
34	1.5	Diphenylamine, .04	Vacuum, 8	27 hours		92	99	
16	1.5	Thiophenol, .04	Vacuum, 2	21 days	42		98	

[a] On basis of halogenated propylene used.

[b] The "minimum yield" is calculated from the weight of pure dihalide mixture isolated after the final distillation. Low yields are often due to losses from incomplete condensation in vacuum distillations. "Estimated yields" are based on the weight of crude reaction product after removal of solvent, catalyst and hydrogen bromide, or on the presence or absence of unreacted halogenated propylene.

[c] Remainder was other possible addition product.

TABLE II

THE ADDITION OF HYDROGEN BROMIDE TO 2-CHLOROPROPENE

EXPT. NO.	MOLES[a] HBr	PEROXIDE OR ANTIOXIDANT, MOLES[a]	TECHNIQUE	REACTION TIME AT ROOM TEMP.	YIELD[b]		% 2, 2- ADDITION PRODUCT[c]	REMARKS
					Minimum, %	Estimated, %		
58	1.5	None	Air, 1	41 hours	92	100	100	Checked
83	1.7	Ascaridole, .06	Air, 8	7 hours	86	<100	26	
54	1.5	Ascaridole, .02	Air, 3	9 days	71	100	18	
60	1.5	Benzoyl peroxide, .01	Air, 1	5 hours	98		82	
82	1.5	Diphenylamine, .03	Vacuum, 6	40 hours		70	100	
56	1.5	Diphenylamine, .03	Vacuum, 3	7.5 days	43	100	100	

[a, b, c] Have the same significance as in Table I.

that the same product is formed in air, and in the presence of the small amounts of peroxides, formed from the unsaturated compound and oxygen, indicates that this reaction is not particularly sensitive to small amounts of peroxides. However, in the presence of an added peroxide (ascaridole) 80 to 90 per cent. of 1,2-dibromopropane is readily obtained.

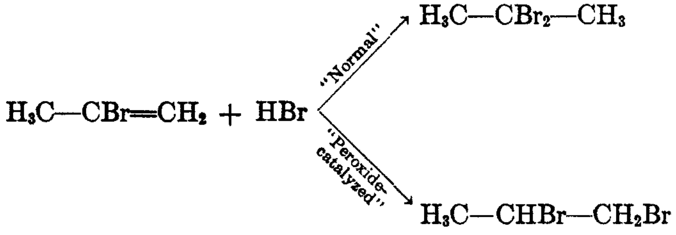


Table II shows that the behavior of 2-chloropropene towards hydrogen bromide is in all respects similar to that of 2-bromopropene. In the presence of air, or in the presence of antioxidants *in vacuo*, the product is pure 2-bromo-2-chloropropane. When an organic peroxide is added to the reaction mixture, 1-bromo-2-chloropropane is the major reaction product. It is of considerable importance that even the "normal" addition of hydrogen bromide to either 2-bromo- or 2-chloropropene is comparatively rapid, and usually complete within a day or two.

The results of addition of hydrogen bromide to the 2-halopropenes are thus in accord with our previous experience and theoretical predictions. The situation is much more complicated in the case of addition of halogen acids to the 1-halopropenes. Here significant differences have been observed in the case of the 1-chloro and 1-bromopropene. In view of the precautions taken in this work the differences observed cannot be dismissed as consequences of experimental error. We believe rather that they have an important and significant theoretical background. It is easy to perceive, on the basis of the hypothesis developed by one of us and collaborators, that in the 2-halopropenes, insofar as electron distribution at the double bond is concerned, that both the methyl groups and the halogen atoms tend to produce a similar electronic distribution, and their individual effects thus reinforce each other. In the 1-halopropenes, there is a distinct opposition of the two effects, and, we believe that the differences observed with 1-chloro- and 1-bromopropene find their explanation in the relative effectiveness of these halogen atoms when in opposition to a methyl group.

Tables III and IV record our observations of the addition of hydrogen bromide to 1-chloro- and 1-bromopropene, respectively. We ordinarily used mixtures of the *cis* and *trans* forms of these halides, but in the tables

TABLE III
The Addition of Hydrogen Bromide to 1-Chloropropene

EXPT. NO.	MOLES[a] HBr	PEROXIDE OR ANTIOXIDANT, MOLES[a]	TECHNIQUE	REACTION TIME[d]	YIELD[b] Minimum, %	YIELD[b] Estimated, %	% 1, 2-ADDITION PRODUCT[c]	REMARKS
57	1.5	None	Air, 1	41 hours	95	100	100	Checked.
67	2.0	None	Air, 4*b*	6 months		<5		42% aq. HBr.
66	1.8	None	Air, 4*b*	5 days	60		100	70% aq. HBr, checked twice.
97	1.54	None	Vac., 9	68 hours	85	90	98	*Cis;* complete in 2 days.
72	1.5	Ascaridole, .05	Air, 6	1 hour		21	100	Checked.
78	1.5	Ascaridole, .025	Air, 7	24 hours		98	100	Checked.
95	1.58	Ascaridole, .03	Air, 9	19 hours	61		90–100	Complete in 1 hour.
59	1.5	Bz_2O_2, .015	Air, 1	5 hours	90		100	
76	1.5	Ph_2NH, .025	Vac., 6	24 hours		3		
79	1.5	Ph_2NH, .03	Vac., 8	4 days		24		
55	1.5	Ph_2NH, .025	Vac., 2	7 days	53		100	
63	1.5	Catechol, .04	Vac., 3	23 hours	86	100	100	Checked
80	1.5	PhSH, .035	Vac., 6	24 hours		6		
96	1.56	PhSH, .045	Vac., 9	40 days	57	65	67	*Trans*
102	1.59	PhSH, .045	Vac., 9	36 days	65	70	63	*Cis*
94	1.61	PhSH, .06	Vac., 9	67 hours	29		35 ±10	.34 *t*-BuNC[a] added.
100	1.54	PhSH, .05	Vac., 9	9.5 days	66	79	71	.18 *t*-BuNC added.
99	2.01	PhSH, .05	Vac., 10	10.5 days	84	88	79	1.00 AcOH[a] added.
98	2.01	EtSH, 1.00	Vac., 9	10.5 days	54		56	Side-reaction.
93	1.58	Anh. $FeCl_3$, .006	Vac., 9 (0°)	2 hours	83	96	8	
101	1.65	Anh. $FeCl_3$, .003	Vac., 9 (0°)	2 hours	15			
103	1.55	Anh. $FeCl_3$, .018	Vac., 9 (0°)	13 hours	91		5	Complete in 8 min.
	MOLES HCl							
90	2.0	Anh. $FeCl_3$, .04	Air, 6	2 days		90	90–100	Checked twice.

[a, b, c] Have the same significance as in Table I.

[d] At room temperature except in last three experiments.

TABLE IV
THE ADDITION OF HYDROGEN BROMIDE TO 1-BROMOPROPENE

EXPT. NO.	MOLES[a] HBr	PEROXIDE OR ANTIOXIDANT, MOLES[a]	TECHNIQUE	REACTION TIME[d]	YIELD[b] Minimum, %	YIELD[b] Estimated, %	% 1, 2-ADDITION PRODUCT[c]	REMARKS
1	1.5	None	Air, 2	20 hours			100	
35	7.5	None	Air, 4*b*	2 months	70		100	65% aq. HBr.
14	2.5	Ascaridole, .04	Air, 2	3 hours	84		100	Checked.
3	1.5	Bz_2O_2, .02	Vac., 1	20 hours			100	
39	3.0	None	Air, 5*b*	5 days	70		100	2.0 H_2O – 0.02 $FeCl_3 \cdot 6H_2O$ added[a].
30	1.5	Ph_2NH, .04	Vac., 8	19 days		62	100	Checked.
25	1.5	$FeSO_4 \cdot 7H_2O$, .07	Vac., 4*a* (0°)	39 hours	70		100	
26	1.5	Ph_2NH, .04 $FeSO_4 \cdot 7H_2O$, .07	Vac., 2 (0°)	41 hours	70		100	
31	1.5	PhSH, .04	Vac., 6	24 hours		5		
18	2.0	PhSH, .04	Vac., 2	5 months	75	100	100	Checked.
41	1.59	PhSH, .04	Vac., 9	18 days	90	91	97	*Trans;* complete in 10 days.
42	1.50	PhSH, .04	Vac., 9	18 days	83	91	97	*Cis;* complete in 14 days.
9	2.4	PhSH, .04	Vac., 4*a*	88 hours	60		100	1.0 AcOH added[a], checked.
43	2.03	PhSH, .04	Vac., 10	11 days	93		99	*Cis;* 1.0 AcOH added.
48	2.19	PhSH, .04	Vac., 10	8 days	93		99	1.0 AcOH added.
20	2.0	PhSH, .04	Vac., 2	4½ days	80		100	0.2 EtCN added[a].
21	2.0	PhSH, .04	Vac., 2	4½ days	80		100	0.2 MeNC added.
45	1.53	PhSH, .04	Vac., 9	13 days	88	98	92	0.15 *t*-BuNC added; complete in 8 days.
38	2.0	*p*-MeC_6H_4SH, .05	Vac., 8	6 days	70		100	0.5 *t*-BuNC added.
44	1.74	EtSH, .50	Vac., 9	9 days	63		94	Side-reaction.
40	1.62	Anh. $FeCl_3$, .006	Vac., 9 (0°)	2 hours	90	95	67	
47	1.52	Anh. $FeCl_3$, .01	Vac., 9 (0°)	45 min.	91		67	Complete in 5 min.
	MOLES HCl							
49	1.62	Anh. $FeCl_3$, .016	Vac., 9 (0°)	15 hours	61	95	65	Complete in 4 hours.

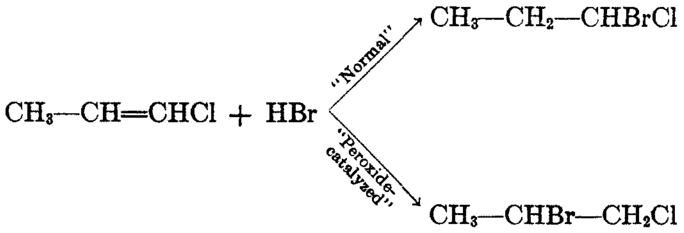
[a, b, c] Have the same significance as in Table I.

[d] At room temperature except as noted.

we include a few experiments in which the pure geometrical isomers were used without significant differences in the results.

In the presence of air and/or added peroxides, 1-chloropropene adds hydrogen bromide rapidly to give 1-chloro-2-bromopropane exclusively. In the absence of air, the addition is slower, but the product is the same. The first experiments *in vacuo* with antioxidants gave the same results, but the reaction appeared to proceed at a still slower rate. The implications involved in this decrease in rate of addition under antioxidant conditions were clear to us, and in experiments 96 and 102 extreme precautions were taken to exclude oxygen and/or peroxides. We also used freshly prepared 1-chloropropene. Under such strict "antioxidant" conditions the rate of addition is exceedingly slow. Thus, in 36 to 40 days, only about 60 to 75 per cent. of the 1-chloropropene reacted to give an addition product of which about one-third was 1,1- and two-thirds was 1,2-dihalopropane. Approximately the same addition mixture, however, can be obtained in a shorter time in the presence of substances which have been shown to accelerate the "normal" addition of hydrogen bromide; *e.g.*, glacial acetic acid[10], or tertiary butyl isocyanide.[9] The use of ethyl mercaptan as a combined solvent and antioxidant gave an accelerated addition and still more 1,1-dihalide, but with the complication of a side reaction mentioned in the experimental part. The last three experiments with hydrogen bromide in Table III show that in the presence of anhydrous ferric chloride (which thus far[9,10] is known to catalyze only the "normal" addition of hydrogen bromide), and in the absence of air, more than 90 per cent. of the 1,1-dihalide is obtained in a few minutes at 0°.

These results suggest that the "peroxide-catalyzed" addition of hydrogen bromide to 1-chloropropene yields 1-chloro-2-bromo-propane exclusively, and that the "normal" addition yields 1-chloro-1-bromopropane. However, the "normal" addition is so slow that it has thus far been impossible to eliminate completely the "peroxide-catalyzed" reaction. We believe, however, that higher yields of the "normal" product, than recorded by us, can be obtained by a more rigorous exclusion of oxygen and/or peroxides.



In substantiation of our conclusion as to the course of the "normal" and "peroxide-catalyzed" reaction with 1-chloropropene, we may cite our experience with the addition of hydrogen chloride to this substance. No peroxide effect has ever been observed with hydrogen chloride[25], and complications from that source are thus eliminated. Unfortunately, hydrogen chloride does not add to 1-chloropropene at an appreciable rate at ordinary temperatures. In the presence of ferric chloride, however, a rapid reaction takes place even at 0°. In three experiments we obtained, within the limits of error of our analytical method, the 1,1-dichloropropane exclusively. We believe, that in this instance the function of the ferric chloride is to accelerate the "normal' adddition, a conclusion justified by our past experience in the use of this reagent as a catalyst in addition reactions.

The results of addition of hydrogen bromide and hydrogen chloride to 1-bromopropene are recorded in Table IV. As mentioned before, the interpretation of these data is much more difficult, but the implications have great interest.

In the absence of air and in the presence of ferric chloride at 0°, 1-bromopropene adds hydrogen bromide in a few minutes to give a mixture of one-third 1,1-dibromopropane and two-thirds 1,2-dibromopropane. *In vacuo* and in the presence of antioxidants, up to 8 per cent. of 1,1-dibromopropane is obtained in the presence of accelerators of the reaction. The latter result is close enough to our admitted experimental error to be of doubtful significance. Under all other conditions, the only addition product obtained was 1,2-dibromopropane, but, as with 1-chloropropene, removing air and adding antioxidants greatly decreased the rate of reaction. We have thus no indication that the normal addition of hydrogen bromide to 1-bromopropene would give more 1,1-dibromide than was obtained in the ferric chloride experiments (33 per cent.). On the contrary the results with antioxidants indicate that this may be the limiting amount of 1,1-dihalide obtainable in the absence of ferric chloride and air, as the peroxide effect is eliminated more completely than has yet been found possible. As a further check of this assumption, we investigated the addition of hydrogen chloride to 1-bromopropene in the presence of ferric chloride at 0°. While, in the case of 1-chloropropene a quantitative yield of the 1,1-dichloropropane was obtained, the 1-bromopropane yielded a mixture of the 1,1 and 1,2 isomers, in an approximate ratio of 1 to 2, respectively. It is to be noted that the same ratio was obtained in the addition of HBr to the 1-bromopropene in the presence of ferric chloride.

For ease of comparison, the behavior of the 1-bromo- and 1-chloropropenes with different reagents is summarized in Table V.

The interpretation of the results recorded in Table V is a matter of

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[25] KHARASCH AND MAYO, unpublished work; ABRAHAM AND SMITH, *J. Chem. Soc.*, **1936**, 1605.

considerable importance. We believe it is established now beyond a reasonable doubt that for each halopropene there is a "normal" and "abnormal" addition, the latter catalyzed by peroxides, and that the composition of the product can readily be controlled by a proper appreciation of these factors. One is forced to admit, therefore, a striking difference in behavior toward halogen acids of the 1-chloro- and 1-bromopropenes. The difference is intimately connected with the general question of formation of two products as a result of a "normal" addition of a halogen acid to an unsaturated molecule. Furthermore, as has been already pointed out by Kharasch and Reinmuth[26], the only substituted ethylene compounds which show this behavior are those in which the two opposing groups are about equal in electronegativity. The striking difference toward halogen acids of the 1-chloro- and 1-bromopropenes may thus be readily accounted for. The broad general problem, however, of the significance of the formation of two products as a result of a "normal" addition remains unanswered. As we perceive it, there are numerous verbalistic variations of the speculative interpretations of this phenomenon that may be offered. If mechanistic details are omitted, however, they would all seem to be reducible to two alternatives. Either (*1*) such compounds exist in a dynamic equilibrium of two forms*, or (*2*) in one form in which the double bond is so slightly polar that the energy changes involved in addition in either direction are nearly equal (as they are presumably exactly equal for such symmetrical molecules as ethylene itself). The implications involved in these ways of viewing the facts are obvious

TABLE V

SUMMARY OF THE ADDITION OF HYDROGEN BROMIDE AND HYDROGEN CHLORIDE TO 1-CHLORO- AND 1-BROMOPROPENES

HALOGEN ACID ADDED	CONDITIONS	% 1, 1-DIHALIDE FROM 1-HALOPROPENE*	
		Chloro-	Bromo-
HBr	Peroxides and/or air present.	0	0
HBr	Air absent, antioxidant present.	20–60	0–10
HBr	Air absent, $FeCl_3$ catalyst.	90–100	33
HCl	$FeCl_3$ catalyst.	90–100	35

* The remainder was the other possible addition product (1,2-).

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[26] KHARASCH AND REINMUTH, *J. Chem. Educ.*, **8**, 1703 (1931).

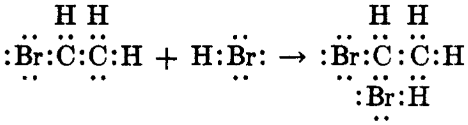
* A consequence of this assumption is that one form "normally" adds halogen acids to give the 1,1-dihalopropane and is susceptible to a "peroxide effect", the other "normally" gives the 1,2- isomer, and is not susceptible to a "peroxide effect" except for acceleration without reversal of addition.

and thought-stimulating, but speculations concerning them can lead nowhere, without further experimental evidence. We hope to review in the near future all the available data relating to formation of two isomers as a result of a "normal" addition of halogen acids to unsaturated compounds.

MECHANISM OF THE PEROXIDE EFFECT

Our tentative hypothesis of the nature of this effect is presented at this time in response to urgent requests of many investitators. In accounting for the remarkable effect of peroxides (and/or oxygen) on the nature of addition of hydrogen bromide to unsaturated molecules, it is important to bear in mind that no reversal has been obtained for hydrogen chloride[25] or sulfuric acid.[†, 27]

To explain this "abnormal" effect it is necessary to dwell for a moment upon the normal reaction. In an earlier article by Kharasch and Reinmuth[26] it was postulated that in an unsaturated molecule of the type R—CH═CH$_2$ the "extra" electron-pair of the double bond would be displaced away from the carbon atom carrying the most electronegative radicals. A highly schematic representation of the "normal" addition of hydrogen bromide to vinyl bromide according to this hypothesis is given below.



$$:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{Br}}}:\overset{\mathrm{H}}{\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{C}}}}:\overset{\mathrm{H}}{\overset{\cdot\cdot}{\mathrm{C}}}:\mathrm{H} + \mathrm{H}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{Br}}}: \rightarrow :\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{Br}}}:\overset{\mathrm{H}}{\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{C}}}}:\overset{\mathrm{H}}{\underset{:\underset{\cdot\cdot}{\mathrm{Br}}:\mathrm{H}}{\overset{\cdot\cdot}{\mathrm{C}}}}:\mathrm{H}$$

This representation in the light of what we now know of the "peroxide effect," is in much better agreement with the facts than the one advanced by Lucas[28] and also by Robinson[29]. It is of interest to note that the chemically important essentials of the formulation are contained in the resonance formulae of the chloroethylenes postulated by Pauling, Brockway, and Beach.[30]

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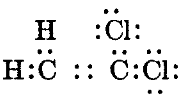
† The possibility of a peroxide effect in case of the other reagents mentioned in our first article[10] is still under investigation in this laboratory, as well as a further study of the addition of hydrogen iodide to unsaturated derivatives, under conditions which would be most likely to effect reversal.

[27] Kharasch and Klaas, unpublished work; Brooks, *J. Am. Chem. Soc.*, **56**, 1998 (1934).

[28] Lucas and Jameson, *J. Am. Chem. Soc.*, **46**, 2475 (1924).

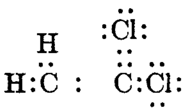
[29] Robinson, "Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions," The Institute of Chemistry of Great Britain and Ireland, London, **1932**.

[30] Pauling, Brockway, and Beach, *J. Am. Chem. Soc.*, **57**, 2693 (1935).



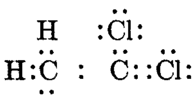
$$\mathrm{H}:\overset{\mathrm{H}}{\ddot{\mathrm{C}}}::\overset{:\ddot{\mathrm{Cl}}:}{\ddot{\mathrm{C}}}:\underset{\cdot\cdot}{\ddot{\mathrm{Cl}}}:$$

I



$$\mathrm{H}:\overset{\mathrm{H}}{\ddot{\mathrm{C}}}:\overset{:\underset{\cdot\cdot}{\ddot{\mathrm{Cl}}}:}{\ddot{\mathrm{C}}}:\underset{\cdot\cdot}{\ddot{\mathrm{Cl}}}:$$

II

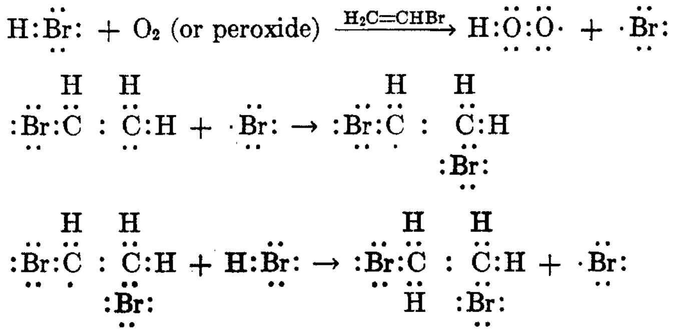


$$\mathrm{H}:\underset{\cdot\cdot}{\overset{\mathrm{H}}{\ddot{\mathrm{C}}}}:\overset{:\ddot{\mathrm{Cl}}:}{\ddot{\mathrm{C}}}::\ddot{\mathrm{Cl}}:$$

III

These authors interpret their electron diffraction data on the dichloroethylenes in terms of resonance of the double bond among three possible positions in which the relative time spent in each position can be determined from the percentage of double (14 per cent.) and single (86 per cent.) carbon-to-chlorine bonds. Forms II and III are richer in energy than I. It is clear that although our notations are different, as would be expected of systems designed to interpret different phenomena, we arrive at essentially similar electronic structures for the terminal carbon atoms of the reactive forms of the haloethene molecules.

The effect of "peroxides" on the addition of hydrogen bromide to such an unsaturated molecule may be described by the following highly schematic representation.



$$\mathrm{H}:\underset{\cdot\cdot}{\ddot{\mathrm{Br}}}: + \mathrm{O_2}\text{ (or peroxide)} \xrightarrow{\mathrm{H_2C{=}CHBr}} \mathrm{H}:\underset{\cdot\cdot}{\ddot{\mathrm{O}}}:\underset{\cdot\cdot}{\ddot{\mathrm{O}}}\cdot + \cdot\underset{\cdot\cdot}{\ddot{\mathrm{Br}}}:$$

$$:\underset{\cdot\cdot}{\ddot{\mathrm{Br}}}:\overset{\mathrm{H}}{\ddot{\mathrm{C}}}:\overset{\mathrm{H}}{\underset{\cdot\cdot}{\ddot{\mathrm{C}}}}:\mathrm{H} + \cdot\underset{\cdot\cdot}{\ddot{\mathrm{Br}}}: \rightarrow :\underset{\cdot\cdot}{\ddot{\mathrm{Br}}}:\underset{\cdot}{\overset{\mathrm{H}}{\ddot{\mathrm{C}}}}:\underset{:\underset{\cdot\cdot}{\mathrm{Br}}:}{\overset{\mathrm{H}}{\ddot{\mathrm{C}}}}:\mathrm{H}$$

$$:\underset{\cdot\cdot}{\ddot{\mathrm{Br}}}:\underset{\cdot}{\overset{\mathrm{H}}{\ddot{\mathrm{C}}}}:\underset{:\underset{\cdot\cdot}{\mathrm{Br}}:}{\overset{\mathrm{H}}{\ddot{\mathrm{C}}}}:\mathrm{H} + \mathrm{H}:\underset{\cdot\cdot}{\ddot{\mathrm{Br}}}: \rightarrow :\underset{\cdot\cdot}{\ddot{\mathrm{Br}}}:\underset{\mathrm{H}}{\overset{\mathrm{H}}{\ddot{\mathrm{C}}}}:\underset{:\underset{\cdot\cdot}{\mathrm{Br}}:}{\overset{\mathrm{H}}{\ddot{\mathrm{C}}}}:\mathrm{H} + \cdot\underset{\cdot\cdot}{\ddot{\mathrm{Br}}}:$$

The essential features of these representations are that, in the addition of hydrogen bromide to vinyl bromide under "antioxidant" conditions, the *bromide ion* is directed toward the carbon atoms with the lowest electron density to yield 1,1-dibromoethane, and that under "peroxide" conditions the *bromine atom* is directed toward the carbon atom with the greater electron density to yield a 1,2-dibromoethyl free radical. This free radical then reacts with hydrogen bromide to yield 1,2-dibromoethane and another bromine atom, which is responsible for the propagation of the chain reaction. According to this mechanism, the function of peroxides or oxygen is to initiate a chain reaction which supplies bromine atoms. Upon the basis of this mechanism it is easy to understand why there is no "peroxide effect" in the addition of hydrogen chloride or sulfuric acid to unsaturated molecules. We hope to elaborate this hypothesis more fully in a later paper.

EXPERIMENTAL

Preparation of halopropenes.—1- and 2-Bromopropenes were prepared by the reaction between propylene bromide and alcoholic sodium ethylate. The product was washed with ice-cold 1-molar sulfuric acid, and with cold water, then dried with calcium chloride. The product was then distilled through a 1-meter column filled with glass beads. The constants obtained are listed in Table VI. Only a portion of the 1-bromopropene was resolved into the *cis* and *trans* forms.

1- and 2-Chloropropenes were prepared similarly from propylene chloride. The halopropenes were then isolated by distillation through a Podbielniak[31] column. This column could effect a separation of the *cis*- and *trans*-1-halopropenes, but most of the 1-halopropenes were used as mixtures in the proportions in which they were found. The constants obtained are listed in Table VI.

Preparation and analysis of reaction mixtures.—The techniques used in the addition of hydrogen bromide to the halogenated propylenes were those described by Kharasch and Mayo[10] for air and vacuum experiments. In general, 0.05 mole of bromopropene or 0.8 mole of chloropropene was used in each experiment, except that 0.1 of the unsaturated compound was usually employed when the product was to be distilled through the Podbielniak Column. At the proper time, the bomb tubes were cooled at about −80°, opened, and allowed to warm up to room temperature to permit escape of the free hydrogen bromide. Several procedures were used in working up the addition products. The numbers correspond to those used in Tables I–IV. (*1*) Products were distilled directly at atmospheric pressure. (*2*) Products were distilled first at 20–30 mm., then at atmospheric pressure. (*3*) Products were warmed in bomb tube to determine whether any unsaturated compound remained, then distilled at atmospheric pressure. (*4*) Products were poured into ice water, washed with water, dilute sodium bicarbonate, and twice more with ice water. The washed product was then dried over (*a*) calcium chloride or (*b*) sodium sulfate, and distilled at 20–30 mm. pressure. (*5a* and *b*) Same as *4a* and *b* except that products were distilled at atmospheric instead of reduced pressure. (*6*) Bomb tube containing products evacuated to about 50 mm. at 0° and shaken to remove unsaturated compound and halogen acid; product weighed to determine yield, then distilled at 10 mm. (*7*) Same as *6*, but washed with water and dried with Na_2SO_4 after weighing and before final distillation. (*8*) Same as *6*, but distilled at atmospheric pressure. (*9*) Product distilled at 20 mm. pressure and then fractionally distilled through Podbielniak column at 50 mm. or 75 mm. (*10*) Products poured onto ice, washed with water and cold bicarbonate solution, dried over anhydrous potassium carbonate and distilled through Podbielniak column as in *9*.

The unsaturated compound was removed from the addition product in the above distillations, and the composition of the addition product was determined by index of refraction with an Abbé refractometer. The boiling point observed in the distillation served to check the latter observation. We estimate the precision of the "estimated yield" and composition of the addition product at ±5%. This yield is thus a "minimum yield" while the actual yield might have been close to 100% when no "estimated yield" is given. See note (*b*), Table I. In some experiments, the rate of addition was measured roughly by the volume decrease of the reaction mixture, which amounted to about 12% at −80° for 100% addition, using about 1.5 moles of

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[31] PODBIELNIAK, *Ind. Eng. Chem., Anal. Ed.*, **5**, 119 (1933).

hydrogen bromide and no solvent. When such measurements furnished additional information, the conclusions are mentioned in the remarks columns of the tables.

Isolation of pure addition products.—Near the completion of the above work, the appropriate addition products were combined and distilled through a Podbielniak column in order to isolate and determine the physical constants of pure samples of

TABLE VI

PHYSICAL CONSTANTS OF HALOGENATED PROPENES AND PROPANES

HALIDE	THIS PROJECT			LITERATURE					
	B. p., °C.	Pressure, mm.	n_D^{20}	B. p., °C.	Pressure, mm.	Reference	n_D	Temp., °C.	Reference
1-Br-propene (cis)	58.6– 58.7	748	1.4544	57.8	760	*32*	1.4564	16.2	*32*
1-Br-propene (trans)	64.2– 64.4	748	1.4532	63.25	760	*32*	1.4549	15.75	*32*
2-Br-propene	48.4	748	1.4440	48.35	760	*32*	1.44665	15.75	*32*
1-Cl-propene (cis)	32.0– 32.2	744	1.4055	32.8	760	*35*			
1-Cl-propene (trans)	36.7	747	1.4054	37.4	760	*35*			
2-Cl-propene	21.7– 21.8	743	1.3949	22.6	760	*35*			
1,1-di-Br-propane	135.3–135.7	740	1.5100	131–133		*24*			
	57.6– 57.8	50		(estimated)					
1,2-di-Br-propane	140.7–140.8	740	1.5200	140	760	*33*	1.5203	20	*33*
	61.8	50							
2,2-di-Br-propane	114.2–114.4	740	1.4988	114.0–114.5	740	*24*	1.4977	20	*1, 34*
	38.4– 39.4	50							
1-Br-1-Cl-propane	111.7–112.0	740	1.4703	110–112	760	*24*			
	47.8	75							
1-Br-2-Cl-propane	117.6–118.0	740	1.4778	117.5–117.8	756	*36*	1.47449	20	*36*
	52.2– 52.8	75							
2-Br-1-Cl-propane	117.2–117.3	740	1.4795	117.5–118.0	756	*36*	1.47447	20	*36*
	52.0	75		115–117	746	*11*	1.4795	20	*11*
2-Br-2-Cl-propane	91.0– 91.2	740	1.4575	93.0– 93.5	745	*24*			
	34.6– 34.8	100							
1,1-di-Cl-propane	87–88	750	1.4295	87	760	*33*			
1,2-di-Cl-propane				96.8	760	*33*	1.4388	20	*33*

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[32] CHAVANNE, *Compt. rend.*, **158**, 1698 (1914).

[33] *International Critical Tables*, Vol. I, McGraw-Hill Book Co., New York, **1928**.

[34] GLADSTONE, Ph.D. Dissertation, University of Chicago, 1936.

[35] TIMMERMANS, *Bull. soc. chim. Belg.*, **36**, 502 (1927).

[36] DEWAEL, *ibid.*, **39**, 87 (1930).

all the possible addition products. Our constants are compared with those of previous workers in Table VI. Only a few grams of the 1,1-dihalides and of 1-bromo-2-chloropropanes could be obtained by this procedure because of the small quantity of starting materials available, and their indices of refraction are subject to an uncertainty of perhaps ±0.0005, with a corresponding effect on the accuracy (but not the precision) of the composition of the addition products. The probable impurity in the 1,1-dihalides is of course the 1,2-dihalide of higher index of refraction; in the 1-bromo-2-chloropropane, the 2,2-dihalide of lower refractive index.

The side-reaction with ethyl mercaptan.—Experiments 44 in Table IV and 98 in Table III were carried out with 0.100 mole of halopropene in the presence of 0.050 and 0.100 mole of ethyl mercaptan, respectively. In each experiment, in addition to the products noted in the tables, close to 4.0 g. of liquid of b.p. 85–110°/22 mm. was obtained. The two products were almost identical. By qualitative tests, each contained sulfur and bromine but no chlorine. The bromine was easily removable by shaking with excess aqueous alcoholic silver nitrate for two or three minutes, after which no more silver bromide precipitated. Rough titration of the remaining silver nitrate by the Volhard method showed that the substances contained between 25% and 30% of active halogen. (Calc'd for $C_3H_6(Br)SC_2H_5$: Br. 43.7%.) When treated with aqueous alcoholic sodium hydroxide for half an hour at room temperature and then with dilute sodium nitroprusside solution, neither substance gave any indication of the presence of ethyl mercaptan. Hence, we conclude that the bromine and thioethoxyl radicals cannot be on the same carbon atom. The mixtures probably contain the diethyl ether of propylene dithioglycol and a bromopropyl ethyl sulfide, formed by the reaction of 1,2-dihalopropane with ethyl mercaptan and/or the addition of ethyl mercaptan to 1-halopropene. Since halogen and thioethoxyl groups are not on the same carbon atom, the presence of this side reaction has not reduced the proportion of 1,1-dihalopropane formed in the normal addition of hydrogen bromide but may have removed some 1,2-dihalopropane formed by the "peroxide-catalyzed" addition. Further investigation of the by-product was discouraged by the small quantity of material available and its lack of homogeneity.

SUMMARY

1. The "normal" addition of hydrogen bromide to 2-bromo- or 2-chloropropane yields the 2,2-dihalide. The "peroxide-catalyzed" addition yields the 1,2-dihalide.

2. The "peroxide-catalyzed" addition of hydrogen bromide to 1-bromo- or 1-chloropropane gives the 1,2-dihalide exclusively.

3. It is concluded that the "normal" addition of hydrogen bromide to 1-chloropropene gives mostly the 1,1-dihalide while 1-bromopropene gives only about one-third 1,1-dihalide and two-thirds 1,2-dihalide. These results are confirmed by the study of the addition of hydrogen chloride to these unsaturated halides and are explained by the differing directing influences of chlorine and bromine atoms when opposed to a methyl group.

4. A mechanism involving bromine atoms is proposed to explain the "peroxide effect."

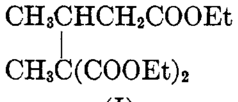
5. New physical constants are given for several dihalogenated propanes.

ON THE COURSE OF THE ADDITION OF MALONIC ENOLATES TO α,β-UNSATURATED ESTERS

ARTHUR MICHAEL

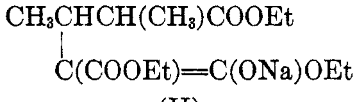
Received July 17, 1937

Michael and Ross[1] found that crotonic and methylmalonic ethyl esters, catalysed by a small amount of alcoholic sodium ethylate, form the 1,2 addition product (I) with migration of the malonic α-hydrogen; while the crotonic ester and the methylmalonic ester enolate yield, by 1,2 addition with migration of the malonic methyl group, the dicarbethoxy enolate (II).



$$\begin{array}{l}CH_3CHCH_2COOEt\\ \quad\;\;|\\ CH_3C(COOEt)_2\end{array}$$

(I)

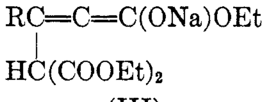


$$\begin{array}{l}CH_3CHCH(CH_3)COOEt\\ \quad\;\;|\\ \quad\;\;C(COOEt){=}C(ONa)OEt\end{array}$$

(II)

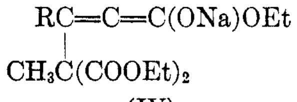
In enolate additions to α,β-Δ-esters the reaction follows the course leading to the possible maximum neutralization of the sodium.[2] In compound (II) this condition is realized by the formation of a dicarbethoxy enolate; the migration of the malonic methyl group to the α-Δ-carbon of the crotonic ester being facilitated by the loosening influence of the poorly neutralized, strongly positive sodium upon the affinity of the methyl group for the carbon to which it is attached in the original methylmalonic enolate.[3]

Recently[4] it was shown that the sodium enolates of malonic and methylmalonic esters "in non-polar solvents" react with α,β-acetylenic esters to form, with migration of the sodium to the monocarbethoxy group, the relatively inert, colored, monocarbethoxy enolates III and IV. The mech-



$$\begin{array}{l}RC{=}C{=}C(ONa)OEt\\ \;|\\ HC(COOEt)_2\end{array}$$

(III)



$$\begin{array}{l}\quad\;\;RC{=}C{=}C(ONa)OEt\\ \quad\;\;\;|\\ CH_3C(COOEt)_2\end{array}$$

(IV)

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[1] Michael and Ross, *J. Am. Chem. Soc.*, (*a*) **52**, 4598 (1930); (*b*) **53**, 1150 (1931); (*c*) **55**, 1632 (1933).

[2] Michael. See 1*a* and 1*b* for literature.

[3] Michael, *Ber.*, **39**, 2142 (1906); *J. Am. Chem. Soc.*, **32**, 997 (1910).

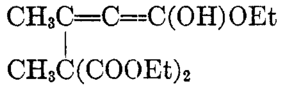
[4] (*a*) Gidvani, Kon, Wright, *J. Chem. Soc.*, **1932**, 1027; (*b*) Gidvani and Kon, *ibid.*, **1932**, 2443; (*c*) Farmer, Ghosal, and Kon, *ibid.*, **1936**, 1804.

anism of these 1,4 additions is similar to that of the addition of potassium cyanide to α,β-Δ-esters.[5]

No theoretical explanation has been advanced for this anomalous behavior of the acetylenic esters in forming monocarbethoxy enolates; nor, for the singular properties of the addition products. The English chemists[4] believe that α,β-ethylenic and α,β-acetylenic esters should react similarly from a valence viewpoint. However, an acetylenic group exerts a far greater negative influence than an ethylenic upon an attached carbonyl. This shows itself in the enormously greater K values of the acetylenic than of the corresponding ethylenic acids (*e.g.*, 2×10^{-5} and 246×10^{-5} for crotonic and tetrolic acids, respectively), in the formation of monocarbethoxy enolates from acetylenic esters, while ethylenic esters yield malonic enolate derivatives, and in that the sodium in the acetylenic addition products is far less reactive, *i.e.*, intramolecularly better neutralized, than in the corresponding ethylenic, malonic ester enolates.[6]

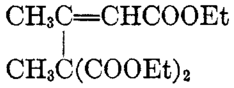
It is evident that the apparently abnormal enolate addition to α,β-acetylenic esters is due to better neutralization, in the addition products, of the sodium in the mono- than in the dicarbethoxy enolate grouping. This conclusion is confirmed by the normal synthesis, through the catalytic process, of 1,2-addition products from malonic and methylmalonic esters with both α,β-acetylenic and α,β-ethylenic esters: the α-hydrogen and the residual radicals of the malonic esters function as addenda in the reactions. Furthermore, the course of addition of methylmalonic ester enolate to α,β-acetylenic esters cannot afford a valid deduction with regard to the mechanism of the entirely different mode of enolate addition to the corresponding ethylenic esters.

Unexplained, also, is the observation[4c] that sodium acts upon an ether solution of the free ester, isolated from IV, to yield the colorless, reactive malonic enolate (VII). An ethylenic ester of the type produced by



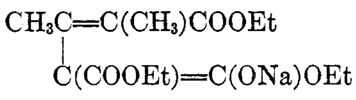
$$\begin{array}{l} CH_3C{=}C{=}C(OH)OEt \\ \quad\;\; | \\ CH_3C(COOEt)_2 \end{array}$$

(V)



$$\begin{array}{l} CH_3C{=}CHCOOEt \\ \quad\;\; | \\ CH_3C(COOEt)_2 \end{array}$$

(VI)



$$\begin{array}{l} CH_3C{=}C(CH_3)COOEt \\ \quad\;\; | \\ \quad\;\; C(COOEt){=}C(ONa)OEt \end{array}$$

(VII)

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[5] Michael and Weiner, *J. Am. Chem. Soc.*, (*a*) **59**, 744 (1937); (*b*) *ibid.*, **59**, 749 (1937).

[6] (*a*) Michael, *Ber.*, **38**, 3222 (1905); (*b*) Michael and Ross, *J. Am. Chem. Soc.*, **53**, 2394 (1931).

change of the labile monocarbethoxy enol (V) to the stable ketonic form[7], (VI), does not react with sodium to yield the corresponding monocarbethoxy enolate[5b,8], but the above chemical system can attain the maximum energy degradation by formation of dicarbethoxy enolate (VII). Expulsion of the α-hydrogen of VI, with migration of the γ-methyl to the α-Δ-carbon occurs; the latter, a forced positional change, is analogous to that observed in the formation of II from crotonic and sodium enol methylmalonic esters[1a].

Anamalous, also, is the behavior of monocarbethoxy enolate (III) towards ethyl iodide in boiling alcohol[4c]; γ-alkylation results with migration of γ-hydrogen to the α-Δ-carbon. The sodium in III is so neutralized that a mineral acid is required to liberate the mother-substance easily[4c]; α-alkylation under the experimental conditions is, therefore, impossible[6]. However, an alkylation may take place indirectly, *i.e.*, by union of the enolate sodium with the iodine of the iodide, intramolecular shifting of the reactive, malonic γ-hydrogen of III to the α-Δ-carbon, and attachment of the ethyl group in the liberated γ-position. Such a *rearrangement-substitution* does not occur in the action of ethyl iodide upon enolate IV; in this reaction, as in alkylacetoacetic ester syntheses, the ethyl group assumes the α-position. Obviously, far more energy is required to overcome the chemical hindrance to the separation of the γ-methyl of IV, than the reactive γ-hydrogen of III, from the attached carbon. The first fission may be effected in a suitably constituted compound by metallic sodium, through its great chemical potential for unsaturated oxygen, but not under mild conditions by the relatively weak affinity of the iodine of the iodide for the comparatively well-neutralized sodium of enolate IV.

Attention was also called[4c] to the isomerization of I to II by sodium ethylate, but, since I is thus retrograded to methylmalonic ester enolate and crotonic ester[9], the conversion follows inevitably from the interaction of these compounds[1a].

Although no reasons are adduced to support the opinion, Farmer, Ghosal, and Kon[4c] believe, with Holden and Lapworth[10], that in the methylmalonic ester addition reactions, "the α,β-dimethyl ester is in all cases produced by the rearrangement of the β,γ-esters primarily formed" and that "*unless* an equivalent of sodium ethoxide is present", the β,γ-

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[7] MICHAEL [*J. prakt. Chem.*, **49**, 20 (1894)] and FEIST [*Ann.*, **345**, 82 (1906)] had previously examined the action of sodium malonic ester upon α,β-acetylenic esters and concluded that the esters liberated from the addition products have normal structures.

[8] MICHAEL, *Ber.*, **33**, 3766 (1900).

[9] MICHAEL, *Ber.*, **33**, 3749 (1900); INGOLD, *J. Chem. Soc.*, **119**, 1976 (1921).

[10] HOLDEN AND LAPWORTH, *J. Chem. Soc.*, **1931**, 2368.

dimethyl ester, $EtOOCCH_2CH(CH_3)C(CH_3)(COOEt)_2$ (VIII) is formed. The latter statement is not probable; when more ethylate is present than is essential for catalysis, an amount of enolate corresponding to the excess of ethylate should be formed. Indeed, a small amount of enolate should appear under the usual catalytic conditions of the addition and undoubtedly it is this, not the ethylate, that really serves as the catalyst[11]. The assumption that the β,γ-dimethyl ester is always the primary product is also improbable. The addition was carried out with methylmalonic ester enolate and crotonic ester in ether solution[1a] and, from their viewpoint, as the enolate contains no α-hydrogen, the monocarbethoxy enolate corresponding to VIII should be mainly the primary product. This course of addition would proceed with migration of the sodium from a dicarbethoxy enolate group to form a much less neutralized, monocarbethoxy enolate derivative. This supposition is as probable as to assume that an aqueous solution of equivalent amounts of crotonic acid ($K = 2 \times 10^{-5}$) and sodium methylmalonate contains mainly sodium crotonate and free methylmalonic acid ($K = 87 \times 10^{-5}$).

It may be assumed that a small proportion of the monocarbethoxy enolate of VIII, existing in balanced equilibrium with the dicarbethoxy enolate[12], undergoes the series of chemical changes postulated by Holden and Lapworth[10] to explain the γ-methyl migration. Accordingly, the mono-carbethoxy enolate of VIII would undergo alcohol elimination spontaneously, forming a 4-membered ring derivative, which would then add alcohol, with ring-fission occurring in such a manner that the dicarbethoxy enolate of the desired α,β-dimethyl derivative would appear. Although it has been shown[1c] that these assumptions are chemically impossible, it may now be mentioned that the reactions were carried out in dilute ethereal solution and ring fission by the theoretical amount of alcohol in very dilute ether solution at room temperature is too improbable to accept; especially, as rings in cyclic enolates are quite stable towards pure alcohol under far more drastic conditions. Further, the implied assumption[10] that the supposed intermediate, cyclic monocarbethoxy enolate would not rearrange mainly to the much better neutralized enolate, containing the sodium at the oxygen of the keto group, is parallel to assuming that the unknown, labile $CH_3COCH{=}C(ONa)OEt$ would not, spontaneously, largely change to the known keto-enolate. The labile cyclic enolate in Lapworth's scheme could rearrange by migration of sodium to a carbonyl of the dicarbethoxy group, the shift of the γ-methyl to the α-Δ-carbon being followed by a series of successive reformations

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[11] MICHAEL, *J. prakt. Chem.*, **60**, 475 (1899).

[12] For literature see reference 6*b*.

and rearrangements. This speculation, however, would be merely a complicated and very improbable modification of the interpretation advanced by Michael and Ross[1a].

The course of most addition reactions involving enolates is so dependent upon the energy and chemical affinity relationships, *i.e.*, the chemical potential, exerted intermolecularly between certain atoms in the original chemical systems, that they cannot be explained rationally solely from valence viewpoints.

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

CONSTITUENTS OF PYRETHRUM FLOWERS. X. IDENTIFICATION OF THE FATTY ACIDS COMBINED WITH PYRETHROLONE

FRED ACREE, JR., AND F. B. LAFORGE

Received August 4, 1937

The active principles of pyrethrum flowers are usually isolated as semicarbazones from concentrates obtained from petroleum ether extractives that have been subjected to certain purifications and separations as described in previous publications[1, 2]. The semicarbazone of pyrethrin II can be obtained as a chemical individual with definite physical and chemical properties. The semicarbazone of pyrethrin I, on the other hand, never has been prepared in a state of similar purity, and preparations of this derivative always exhibit an unsharp melting point, even after repeated recrystallizations, and they always contain methoxyl.

It is evident that such preparations consist of mixtures which cannot be separated by ordinary means.

Pyrethrin I semicarbazone has already been studied, and the results have been reported.[3] The procedure consisted in examining the products of the hydrolysis of a purified semicarbazone preparation.

By saponification carried out in the usual manner, only pyrethrolone semicarbazone was obtained as the neutral alcoholic component. The acid products, however, were found to consist of a mixture in which, as was to be expected, chrysanthemum monocarboxylic acid strongly predominated. The remaining acid products not volatile with steam comprised chrysanthemum dicarboxylic acid and one or more acids of the fatty series. The fatty acids could be separated from the dicarboxylic acid and, after distillation, consisted of a semi-solid product which by analysis and titration seemed to correspond to the formula $C_{16}H_{30}O_2$. Its methyl ester (b. p. about 155° at 1 mm.) was also prepared, and its analysis and methoxyl content were found to agree with the formula $C_{17}H_{32}O_2$. The acid product absorbed one mol of bromine and, on hydrogenation, took up one mol of hydrogen; therefore it was unsaturated. When this product was treated with thionyl chloride, an acid chloride was

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[1] LAFORGE AND HALLER, *J. Am. Chem. Soc.*, **57**, 1893 (1935).

[2] HALLER AND LAFORGE, J. ORG. CHEM., **1**, 38 (1936).

[3] LAFORGE AND HALLER, *ibid.* **2**, 56 (1937).

obtained which, when treated with *p*-bromoaniline, gave a small yield of a bromoanilide melting at 109–110°. On analysis this derivative agreed with the corresponding derivative of an acid of the above formula. The results described led to the conclusion that the acid had the formula $C_{16}H_{30}O_2$. A discordant fact was observed in the case of the hydrogenated material of m. p. 53°, the titration of which indicated it to have a molecular weight of about 290.

The data so far reported show that preparations of pyrethrin I semicarbazone consist of mixtures containing more or less of pyrethrin II semicarbazone together with the semicarbazone of at least one pyrethrolone ester in which the acid component is an unsaturated fatty acid.

Owing to the uncertainty of the nature of the fatty acid component, further study of the subject was indicated.

The petroleum ether extractives of pyrethrum flowers always contain free fatty acids, which are removed in the course of the purification of the concentrates. It was surmised that these fatty acids might contain larger quantities of the acid which was combined with pyrethrolone. Therefore, a considerable quantity of the crude acid mixture was esterified with methanol, and the esters were subjected to repeated fractionation to obtain that fraction boiling around 130–150° at 0.5 mm. This material had about the same properties as the fatty acid ester obtained from pyrethrin I semicarbazone. It was observed, however, that a part separated in crystalline form from a methanol solution on cooling in a freezing mixture. By this means a sharp separation into two fractions could be made. The crystalline ester, boiling at 130–135° at 0.5 mm., m. p. 27–28°, was identified, by the mixture melting-point method, as the methyl ester of palmitic acid.

The ester that was obtained from the methanol solution was subjected to fractionation at 0.5 mm. About 80 per cent. of it boiled at 140–146°. Analysis and methoxyl determination indicated the formula $C_{19}H_{34}O_2$. The ester was unsaturated, and absorbed two moles of hydrogen. The free acid was prepared by saponification of the ester. It boiled at 170–175° at 0.5 mm. The molecular weight was found by titration to be 282. The crystalline tetrabromide was prepared and melted at 112–113°. These properties of the acid and its derivatives are in agreement with those recorded for linoleic acid and its corresponding derivatives.

On hydrogenation of the free acid, two moles of hydrogen were absorbed and the resulting saturated acid melting at 69° was identified as stearic acid. The methyl ester of the unsaturated acid on hydrogenation yielded methyl stearate, which was identified as such by the mixture melting-point method.

The original fraction therefore consisted of a mixture of palmitic and linoleic acids.

Since the acid mixture obtained from the methyl ester fraction of b.p. 130–150° resembled so closely the fatty acid component obtained from pyrethrin I semicarbazone, it seemed probable that the latter also might consist of a mixture of the same fatty acids. Therefore, more of this material was prepared from pyrethrin I semicarbazone. The method employed for the separation of the acid components differed from that recorded in the first article[3] on this subject. The total acid material obtained on saponification of the semicarbazone was converted completely into the methyl esters. The methyl ester of chrysanthemum monocarboxylic acid and the dimethyl ester of chrysanthemum dicarboxylic acid have much lower boiling points than the esters of the fatty acids. Therefore, a separation could be made readily by fractionation of the total esters. The fraction boiling at 130–150° and 0.5 mm. was isolated in this manner. It was found that a methanol solution of this fraction also crystallized partly on cooling, and could be separated into solid and liquid components. The liquid ester was saponified to the free acid. On hydrogenation of the acid, two moles of hydrogen were absorbed, and the resulting saturated acid was identified as stearic acid by its melting point and titration. Finally the *p*-bromoanilide* was prepared from palmitic acid and found to agree as to properties and mixture melting point with the original *p*-bromoanilide obtained from the acid mixture as described in the previous article[3]. Attempts to prepare the *p*-bromoanilide of linoleic acid have been unsuccessful.

Therefore, the acid products other than the chrysanthemum acids obtained from the pyrethrin I semicarbazone consist mainly of a mixture of palmitic and linoleic acids, and these are present combined with pyrethrolone semicarbazone in all preparations of pyrethrin I semicarbazone.

EXPERIMENTAL

Preparation of acids.—The potassium carbonate solutions, obtained during the purification of 8 pounds of pyrethrum oleoresin, were extracted with petroleum ether. The carbonate solutions were then acidified, and the free fatty acids were removed by extraction with the same solvent. The petroleum ether solution was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed, yielding 105 grams of acid mixture.

The acids thus obtained were converted into their methyl esters by boiling under reflux for two hours in 20 parts of methanol and 1 part of concentrated sulfuric acid. The methanolic solution was concentrated to a small volume under reduced pressure pressure, diluted with several parts of water, and extracted with petroleum ether. The petroleum ether solution was washed with sodium carbonate solution, then with water, and dried over anhydrous sodium sulfate. On removal of the sol-

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* No reference to this compound has been found in the literature.

vent, 112 grams of mixed methyl esters was obtained, which was distilled at 0.5 mm. The fraction boiling at 135–150° was collected; it weighed 42 grams.

Palmitic acid methyl ester.—This ester fraction was dissolved in 3 parts of methanol and cooled for 4 hours at −6°. The 14.5 grams of material that crystallized was removed by filtration in the cold. This crystalline material partly melted at room temperature. By distilling 6.7 grams of the material at 0.5 mm., 6.3 grams was obtained, boiling at 130–135°. It again crystallized on cooling and was found to melt sharply at 28°.

Anal. Calc'd for $C_{17}H_{34}O_2$: CH_3O, 11.48; m. w., 270.
Found: CH_3O, 11.4, 11.2; m. w. 271, 276.

Palmitic acid.—One gram of the crystalline ester was saponified by dissolving in 10 cc. of alcohol and boiling under reflux for one and one-half hours with 12 cc. of 0.5 *N* alcoholic potassium hydroxide. The alcoholic solution was diluted with water, and most of the alcohol was removed by boiling. After cooling, the alkaline solution was extracted with ether and then acidified. The free fatty acid was removed with ether, which was washed with water and dried over anhydrous sodium sulfate. The solvent was then removed and gave 0.9 gram of crystalline material which, when recrystallized from methanol, melted at 62–63°. A mixture melting point made with an authentic sample of palmitic acid showed no depression.

Anal. Calc'd for $C_{16}H_{32}O_2$: m. w., 256.
Found: Equiv. wt. (titration) 256, 261.

Linoleic acid methyl ester.—The methanol solution, from which the palmitic acid methyl ester had been removed, was freed from solvent by evaporation and the 27 grams of residue was subjected to fractional distillation at 0.5 mm. Twenty grams distilled at 140–146°; $n_D^{25} = 1.4621$; $n_F^{25} - n_C^{25} = 0.009$.

Anal. Calc'd for $C_{19}H_{34}O_2$: CH_3O, 10.53.
Found: CH_3O, 10.54, 10.73.

One gram of ester was hydrogenated in acetic ester solution with platinum oxide catalyst. It absorbed 155 cc. (two moles) of hydrogen and gave 1 gram of a crystalline product. On recrystallization from methanol it melted at 38° and showed no depression in the melting point when mixed with an equal quantity of authentic methyl stearate.

Linoleic acid.—On saponification by boiling under reflux for two hours with 80 cc. of 0.5 *N* alcoholic potassium hydroxide and subsequently removing any unreacted ester, 5.6 grams of the ester yielded 5.5 grams of acid that boiled at 170–175° at 0.5 mm.; $n_D^{27} = 1.4690$; $n_F^{27} - n_C^{27} = 0.009$.

Anal. Calc'd for $C_{18}H_{32}O_2$: m. w., 280.
Found: Equiv. wt. (titration) 283, 281.

On the addition of 4 atoms of bromine, 0.5 gram of the acid was converted into the crystalline tetrabromide, yield 0.3 gram. After recrystallization from petroleum ether it melted at 112–113°. The recorded melting point for tetrabromolinoleic acid is 113–114°.

On hydrogenation in acetic ester solution with platinum oxide catalyst, the acid absorbed two moles of hydrogen. The crystalline reduction product, after recrystallization from alcohol, melted at 69°. There was no depression in the melting point when this was mixed with an equal quantity of authentic stearic acid.

Preparation of acids from pyrethrin I semicarbazone.—A quantity of twice-recrystallized pyrethrin I semicarbazone was saponified in the usual manner.[2] After filtration from the crystalline pyrethrolone semicarbazone, the total acids were isolated from the alcoholic alkaline mother liquor by the usual procedure.

Ten grams of these acids was converted into their methyl esters by boiling under reflux for two hours in 200 cc. of methanol containing 10 grams of concentrated sulfuric acid. After most of the methanol had been removed under reduced pressure, the residue was strongly diluted with water and extracted with petroleum ether. The petroleum ether solution was washed with water, dilute potassium hydroxide, and again with water. After being dried over anhydrous sodium sulfate, the solvent was removed. The yield of mixed methyl esters was 10.4 grams.

Separation of methyl esters.—Twenty-two grams of mixed methyl esters was distilled at 19 mm. Eighteen grams distilled at 90–100° and consisted essentially of chrysanthemum monocarboxylic acid methyl ester together with some chrysanthemum dicarboxylic acid dimethyl ester. The remainder of the material was distilled at 0.5 mm. Of this 1.8 grams boiled at 110–135° and 0.6 gram boiled at 135–145°. There was some material that would not distill readily.

Palmitic acid methyl ester.—The material from another experiment comparable to this higher-boiling fraction was converted to the free acid, from which the acid chloride was prepared. The latter was treated with *p*-bromoanaline and gave a crystalline *p*-bromoanilide. The compound, twice recrystallized from methanol, melted at 109–110°. It showed no depression when mixed with an equal quantity of an authentic sample of the *p*-bromoanilide of palmitic acid. The yield of the *p*-bromoanilide was small, but it corresponded to a quantity of methyl palmitate proportionate to the amount of crystalline methyl ester obtained by freezing the methanolic solution of mixed methyl esters of b. p. 135–145° as described below.

p-Bromoanilide of palmitic acid.—One gram of palmityl chloride dissolved in 10 cc. of dry benzene was slowly added, with stirring, to a solution of 1.5 grams of *p*-bromoaniline in 10 cc. of the same solvent. After standing for 30 minutes, the crystalline material that immediately separated was filtered and washed with benzene, dilute hydrochloric acid, and water. After recrystallization from alcohol it melted at 114°. It weighed 1.3 grams. A mixture with a sample of the *p*-bromoanilide of melting point 109–110° obtained from the acid isolated as a pyrethrolone ester melted at 111–112°.

Linoleic acid methyl ester.—The 0.6 gram of liquid esters obtained from pyrethrin I semicarbazone of b. p. 135–145° at 0.5 mm. was dissolved in 3 parts of methanol and subjected to a temperature of −6°. Two-tenths of a gram of impure palmitic acid methyl ester deposited and was filtered and washed with a little cold methanol. From the methanolic filtrate, after removal of the solvent, 0.4 gram of oily material was obtained. This material was shown to be linoleic acid methyl ester by its conversion in good yield to the free acid. The acid was reduced catalytically with the absorption of two moles of hydrogen to stearic acid. The recrystallized reduction product of melting point 68° was identified by the melting point, 68–69°, of a mixture with authentic stearic acid.

Anal. Calc'd for $C_{18}H_{36}O_2$; m. w., 284.
Found: equiv. wt. (titration), 289.

Quantity of fatty acids present in a mixture of pyrethrin semicarbazones as pyrethrolone esters.—One hundred thirty grams of partly purified pyrethrum concentrate was converted to the mixture of pyrethrin I and pyrethrin II semicarbazones.[2] The dried material, twice recrystallized from benzene and washed with petroleum ether, weighed 31.6 grams. It was saponified in the usual manner, and the crystalline pyrethrolone semicarbazone was separated by filtration. The alcoholic mother liquor was concentrated to a small volume under reduced pressure and diluted with an equal volume of water. An additional quantity of pyrethrolone semicarbazone crystallized and was removed from the solution by filtration. The filtrate was made strongly alkaline and boiled under reflux for one hour. After being cooled, the solution was acidified and the acids were removed by extraction with petroleum ether. The petroleum ether solution was washed with water, dried over anhydrous sodium sulfate, and evaporated. Ten and one-tenth grams of acids was recovered. They were dissolved in 70 cc. (10 per cent. excess) of normal sodium hydroxide and diluted to 200 cc. with water. After the addition of 1 gram of Filter-cel, 25 cc. of a 10 per cent. solution of barium chloride was added, and the solution was thoroughly mixed. The precipitated barium salts were collected by filtration, washed, suspended in dilute hydrochloric acid, and decomposed by vigorous shaking. The free acids were extracted with petroleum ether, and the solution was washed with water and dried over anhydrous sodium sulfate. The solvent was removed, leaving 0.3 gram of free fatty acids originally combined as pyrethrolone esters.

SUMMARY

The semicarbazone of pyrethrin I as ordinarily prepared from concentrates consists of a mixture of the semicarbazones of pyrethrins I and II together with the semicarbazones of the esters of pyrethrolone with palmitic and linoleic acids. This has been established by the isolation and identification of chrysanthemum mono- and dicarboxylic acids and palmitic and linoleic acids from the acid products of saponification of purified preparations of pyrethrin I semicarbazone. It is practically impossible to prepare pure pyrethrin I semicarbazone by recrystallization.

Palmitic and linoleic acids are contained in the free state in the oleoresins of pyrethrum flowers and may be isolated by fractional distillation of the mixture of the methyl esters of the total free acids. The recrystallized crude semicarbazone mixture obtained from pyrethrum concentrates yields fatty acids on saponification.

[Contribution from the Chemical Laboratory of Northwestern University, Evanston, Illinois]

THE NON-REACTION OF ACETYLKETENE AND MALEIC ANHYDRIDE, AND SOME NOTES REGARDING MALEIC ACID

CHARLES D. HURD, ARTHUR S. ROE, and JONATHAN W. WILLIAMS

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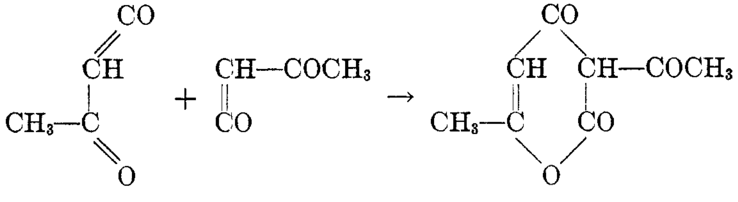
It has been established[1] that acetylketene represents the structure of the dimer of ketene. The polymerization of acetylketene to dehydroacetic acid which involves the addition of a double bond (as in II) to the ends of



I II

a conjugated system (as in I) may be regarded as a reaction of the Diels-Alder type. Therefore, it was of interest to see if acetylketene would undergo other Diels-Alder reactions such as with maleic anhydride by addition to I, or with furan by addition to II. Actually, it did neither.

A reaction product was obtained, however, with maleic anhydride. It melted at 137° and seemed to be identical to the unidentified 137°-material obtained by Trephilieff[2] from maleic acid, acetic anhydride, and acetoacetic ester. Trephilieff believed his substance to be a monobasic acid, $C_{11}H_{14}O_5$. The close relationship between acetylketene and acetoacetic ester made it seem reasonable to think that the same substance should be formed in both experiments. As it turned out, however, this relationship had nothing to do with the reaction product. The reaction involved was merely one of hydration of the maleic anhydride with the trace of water which was present. The 137°-material was shown to be maleic acid.

The generally-accepted[3] melting point of maleic acid is 130.5°. A survey of recent studies which have dealt with supposedly pure maleic

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[1] Hurd and Williams, *J. Am. Chem. Soc.*, **58**, 962 (1936).

[2] Trephilieff, *Ber.*, **40**, 4389 (1907); *J. Russ. Phys.-Chem. Soc.*, **39**, 1618 (1908).

[3] Kempf, *Ber.*, **39**, 3725 (1906); *J. prakt. Chem.*, [2] **78**, 239 (1908). This temperature is selected by *International Critical Tables*.

acid has revealed melting points ranging from 130° to 140°, but no explanation of such a wide variation has been given. Sessions[4] prepared maleic acid, m.p. 138.5–140°, by vapor-phase, catalytic oxidation of furfural at 200–300°. He reported it to melt at 138–139° if crystallized from water, but found the melting point to drop to 130–131° after a few recrystallizations from benzene. Rinkes[5] also recorded 138.5–140° as the melting point. Terry and Eichelberger[6] prepared maleic acid by dissolving pure maleic anhydride in water without mentioning the melting point, but this method was used by Olson and Hudson[7] who reported 134.5°. Vaidya[8] also reported 134°.

The value of 131° is reported in recent work by Ashton and Partington.[9] Pure maleic acid was prepared by Conant for Parks and Huffman[10] by dissolving distilled maleic anhydride in water and crystallized by concentration *in vacuo*. Conant states: "This is the only method which gives a really pure maleic acid free from fumaric. The melting point given in the literature is 130–131°. If slowly heated in the ordinary melting-point apparatus the acid I am sending you melts at this temperature. It shows a somewhat higher melting point if rapidly heated. Personally, I am inclined to think that this higher value may be nearer the truth, in spite of statements in the literature."

That the 137°-material (III) from maleic anhydride and acetylketene or acetoacetic ester was maleic acid was demonstrated by its neutralization equivalent and by other tests. Similar material [(IV), m.p. 136°] was obtained by adding water to a solution of maleic anhydride. When either III or IV was melted, cooled, and remelted the temperature of the second fusion of both was about 130°. When III and IV were mixed, the melting point was not depressed. Also, both compounds yielded the same derivatives with toluidine or anisidine.

It seemed reasonable to believe that the substance melting at 137–138° was pure maleic acid. To account for the lowered melting point in the 130°-material, it was assumed that an impurity was present. The two most obvious impurities to consider were fumaric acid and maleic anhydride. No maleic anhydride was found, but evidence was obtained which shows that about 3 per cent. of fumaric acid was present. The fumaric acid was detected in the maleic-fumaric mixture by extracting the maleic

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[4] SESSIONS, *J. Am. Chem. Soc.*, **50**, 1696 (1928).

[5] RINKES, *Rec. trav. chim.*, **45**, 822 (1926).

[6] TERRY AND EICHELBERGER, *J. Am. Chem. Soc.*, **47**, 1410 (1925).

[7] OLSON AND HUDSON, *ibid.*, **55**, 1410 (1933).

[8] VAIDYA, *Proc. Roy. Soc.*, (London), **A129**, 299 (1930).

[9] ASHTON AND PARTINGTON, *Trans. Faraday Soc.*, **30**, 598 (1934).

[10] PARKS AND HUFFMAN, *J. Am. Chem. Soc.*, **52**, 4381 (1930).

portion of the mixture with a saturated aqueous solution of fumaric acid. The undissolved portion was fumaric acid. The reliability of this procedure was demonstrated with several known mixtures.

It was shown that fumaric acid is produced from maleic acid fairly rapidly at the melting point. The reason why the melting point becomes depressed no further than 130° on one or more fusions is the slight solubility of fumaric acid in the fused mass.

EXPERIMENTAL

Acetylketene was prepared by polymerization of ketene.[1] The furan, maleic anhydride (m.p. 55°), and maleic acid (m.p. 130°) were commercial specimens.

Acetylketene and furan.—Two grams of acetylketene, 4.4 g. of furan, and 5 cc. of benzene were refluxed for three hours. On distillation, the three components were recovered: 30-80°, 5.4 cc.; 80-120°, 3.1 cc.; 120-125°, 1.2 cc. No addition product was found.

Acetylketene and maleic anhydride.—One gram of maleic anhydride, 1 g. of acetylketene and 10 cc. of dry benzene were refluxed for two hours. After standing for a day, a small yield of white crystals (A) separated; m.p., 137°.

Neutr. Equiv. Calc'd for maleic acid: 58.0. Found: 58.6.

When 2.2 g. of freshly distilled acetylketene (b.p. 37° 19 mm.) and 2.0 g. of maleic anhydride were mixed a cooling effect was noticed. Then 0.6 g. of water was added. After twenty-four hours, the crystalline solid (B) was collected on a filter and dried over sulfuric acid in a vacuum desiccator: m.p., 137.5-138°; yield, 1.1 g. If remelted, after cooling, the new m.p. value was 130°.

The same substance was formed merely by adding 0.7 cc. of distilled water to 2 g. of maleic anhydride. The appearance of the white solid gradually changed, and in four hours, it was placed in the vacuum desiccator (over sulfuric acid) for twenty-four hours. The yield of this material (C) was 1.2 g. and the m.p., 136°.

If the maleic anhydride (0.5 g.) was dissolved in 15 cc. of benzene before the addition of 0.36 g. of distilled water, the crystals (D) which separated melted also at 136°; yield, 0.86 g. The m.p. of a mixture of A and D was 136°. After cooling, the m.p. was found to have dropped to 130-131°.

Experiments with ethyl acetoacetate.—When ethyl acetoacetate (2.6 g.), maleic anhydride (2.0 g.) and acetic anhydride (2 cc.) were refluxed for eight hours, no precipitation occurred. On standing for six months in a tightly stoppered bottle, there was still no separation.

In a second experiment, 2.6 g. of the ester and 2.0 g. of maleic anhydride were mixed and a cooling effect was noted. To facilitate solution of the anhydride, the mixture was warmed on a steam bath. After four hours, no precipitation or other visible evidence of reaction had occurred. Then, 0.4 cc. of water was added. Gradually, during twenty-four hours, there separated 1.5 g. of crystals (E) which, after standing in the evacuated desiccator, melted at 137.5-138°. A mixture of A and E melted at 137°. When E was melted, cooled, and remelted, the value obtained was 130-131°.

Derivatives with arylamines.—One gram of maleic acid (m.p. either 130° or higher) was refluxed with 2.5 g. of acetic anhydride for an hour. Then the acetic acid and excess of acetic anhydride were distilled off in a stream of dry air under reduced pressure. The residual maleic anhydride was dissolved in chloroform, and this solution was divided in two parts. To one was added a solution of 0.5 g. of *p*-toluidine in 10 cc. of chloroform. There was obtained 1.02 g. of *N*-*p*-tolylmaleamic acid, $CH_3C_6H_4NHCO{-}CH{=}CH{-}COOH$, m.p. 195°, with decomposition. The m.p. was unchanged by repeated crystallizations from hot acetone, or by solution in sodium hydroxide solution, followed by acidification with sulfuric acid. Dunlap and Phelps[11] listed the m.p. as 201° but we were unable to confirm this value. To the other part was added 0.6 g. of *p*-anisidine in 10 cc. of chloroform. The yield of *N*-4-methoxyphenylmaleamic acid, $CH_3OC_6H_4NHCOCH{=}CHCOOH$, was 0.70 g. The product may be purified by crystallization from hot acetone solution, but better results were obtained by adding chloroform to the hot solution to cause precipitation. The crystals melted with decomposition at 186–186.5°. This is 6° higher than the m.p. given by Piutti.[12]

TABLE

ANALYSIS OF MIXTURES OF MALEIC AND FUMARIC ACIDS

MALEIC ACID			FUMARIC ACID ADDED		INSOL. PORTION, g.	FUMARIC ACID FOUND, %
Source	m.p., °C.	g.	g.	%		
—	—	—	—	—	0.0001	—
—	—	—	0.5726	100.0	.5758	100.6
(*a*)	130	0.7367	—	—	.0243	3.3
(*a*)	130	.8699[b]	.1356	16.3[b]	.1644	16.4
(*c*)	133	.5321	—	—	.0026	0.4
(*d*)	134	.3962	—	—	.0001	0.0
(*e*)	137	.1000	—	—	.0001	0.0
(*d*)	134	.2634	.0036	1.35	.0040	1.5
(*d*)	134	.2777	.0080	2.8	.0081	2.8
(*d*)	134	.4295	.0198	4.4	.0223	4.9

[a] Technical material, thrice crystallized from water.

[b] The true maleic acid content is 0.8412 g. since 3.3% of the 0.8699 g., or 0.0287 g., is fumaric acid. The 16.3% includes 0.0287 + 0.1356 g., or 0.1643 g.

[c] From maleic anhydride and water.

[d] From maleic anhydride in benzene, and water.

[e] This run is typical of five runs which were made with A, B, C, D, and E. The samples taken weighed 0.1–0.2 g. and the maximum insoluble residue (from a 0.2 g. run) was 0.0003 g.

This procedure for preparing the toluidine and anisidine derivatives was used with each of the above five specimens of maleica cid (A–E) which melted at 136–138°. With each specimen, the toluidide was found to melt at 195° and the anisidide at 186°, and the yields in all cases were comparable to the yields mentioned above. Since compounds of the same purity were obtained from the 130°- or the 138°-material, it appears that the fumaric acid content of the former does not interfere.

Analysis of mixtures of maleic and fumaric acids.—Known quantities of the two acids were mixed. A saturated solution of fumaric acid was prepared, the solution

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[11] DUNLAP AND PHELPS, *Am. Chem. J.*, **19**, 494 (1897).

[12] PIUTTI, *Atti. accad. Lincei*, [5] **18**, II, 314 (1909).

being kept in a thermostat at 25°. A weighed quantity of the mixture and 50 cc. of the fumaric acid solution were placed in a small beaker. The latter was kept in the thermostat at 25°. The mixture was stirred for five minutes, after which it was filtered through a weighed filter paper, and washed with a little of the fumaric acid solution. The filter paper containing the undissolved fumaric acid was dried in a desiccator and weighed. Representative data are tabulated.

Behavior of maleic acid on fusion.—Mention has been made of several instances wherein the melting-point value of pure maleic acid dropped from 138° to 130° after the first fusion. This effect was studied quantitatively.

Five grams of maleic acid was prepared by adding water to a solution of maleic anhydride in benzene. The melting point (capillary tube method) was 134–135°. The 5-g. specimen was melted, cooled (F), and a sample of it was remelted. For the most part liquefaction occurred at 132° but a portion of it refused to melt even at 150°. Analysis of 0.2097 g. of F revealed 0.0111 g., or 5.3%, of fumaric acid.

The rest of F was remelted. The temperature was carried to 145° but still about one-fifth of it did not melt. When cool (G), the m.p. of a portion of the solid was determined again by the capillary tube method. The value obtained was 129–130° but there was considerable unmelted material. Analysis of 0.1108 g. of G showed 0.0089 g., or 8.0% of fumaric acid.

It is evident, therefore, that repeated fusions bring about an increased formation of fumaric acid, but because of its comparative insolubility at the fusion temperature this does not cause an increased lowering of the melting point.

A portion of G was tested for maleic anhydride by extracting it with chloroform (in which the anhydride is soluble) and adding to the filtrate a solution of *p*-toluidine in chloroform. No precipitate of *N*-*p*-tolylmaleamic acid occurred, although it was established that 93-96% of the anhydride in synthetic mixtures containing 1 to 9% of maleic anhydride in maleic acid could be accounted for by this method.

SUMMARY

There is no reaction between acetylketene and furan, acetylketene and maleic anhydride, or between acetoacetic ester and maleic anhydride, although a slight separation of maleic acid may occur from the last two mixtures. This maleic acid, and that obtained by adding water to the mixtures, melts at 137–138° instead of 130° which is commonly accepted. This accounts for the unidentified 137°-material obtained by Trephilieff from maleic acid, acetic anhydride and acetoacetic ester.

The 130°-material is not pure maleic acid, but contains about 3 per cent. of fumaric acid. The isomerization occurs on fusion. An analytical method was developed for mixtures of maleic and fumaric acids. Maleic acid may be converted readily with acetic anhydride and arylamines into *N*-arylmaleamic acids, which are satisfactory derivatives.

[Contribution from the Department of Chemistry, Brooklyn College]

THE ACTION OF AMMONIA ON BENZIL

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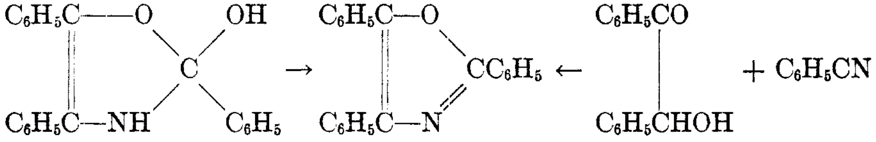
Interest in the action of ammonia on benzil dates back nearly a century to the observation of Zinin,[1] who found that the reaction in aqueous alcoholic medium at 70° yielded ethyl benzoate and a colorless, glistening, crystalline product which he named *Azobenzil.* Soon afterward, Laurent[2] made a more systematic study of the reaction in alcoholic solution, and isolated three substances termed by him *Imabenzil, Benzilimide,* and *Benzilam.* At the suggestion of Zincke,[3] Henius[4] reinvestigated the reaction. He identified Zinin's azobenzil with Laurent's benzilam, and found that in alcoholic solution at 130° imabenzil disappeared after one hour, and on continued heating the remaining benzilimide-benzilam mixture gave way to a mixture of benzilam and lophine.

In the meantime, Japp[5] had also attacked this problem and published the first reliable analyses of Laurent's products. He suggested the following structures for benzilimide (I) and benzilam (II); structures which



I II

are presumably accepted at the present time. For imabenzil ($C_{35}H_{28}N_2O_3$) no structure was proposed by Japp, but he showed it to be converted by acids into one mole each of benzilimide, benzil, and ammonia. Somewhat later, Pinner[6] repeated part of Japp's work and proposed III as the structural formula for imabenzil.

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[1] Zinin, *Ann.*, **34**, 190 (1840).

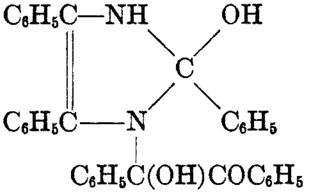
[2] Laurent, *J. prakt. Chem.*, **35**, 461 (1845).

[3] Zincke, *Ber.*, **16**, 889 (1883).

[4] Henius, *Ann.* **228**, 339 (1885).

[5] Japp, *J. Chem. Soc.*, **43**, 11 (1883); *Ber.*, **15**, 2410 (1882); **16**, 2636 (1883); Japp and Wynne, *J. Chem. Soc.*, **49**, 473 (1886).

[6] Pinner, *Ber.*, **35**, 4131 (1902).

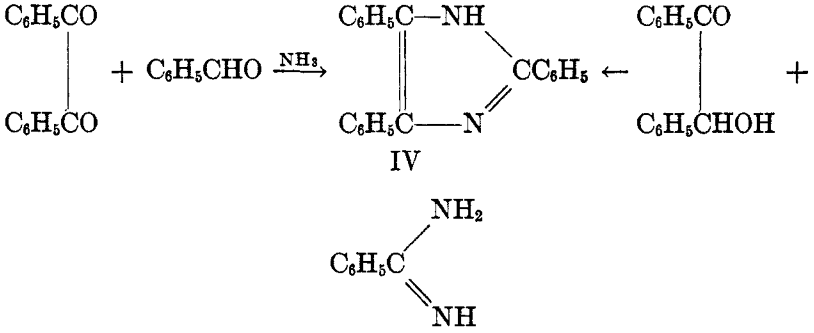


III

The present paper proposes a revision of the structure of benzilimide, suggests a more rational formula for imabenzil, offers a mechanism for the action of ammonia on benzil, and adds an improved procedure for the preparation of glyoxalines derived from benzil. It will be helpful first to review briefly the evidence for the structures of the products obtained from benzil by the action of ammonia, discussing these substances in the reverse order in which they appear in practice.

LOPHINE

Although lophine (IV), m.p. 275°, has been obtained in many complex reactions, two methods of preparation are especially significant in structural discussions. The first is Radziszewski's[7] classic synthesis from benzil, benzaldehyde, and ammonia, while the second is Kulisch's[8] synthesis from benzoin and benzamidine. The latter particularly points to 2,4,5-triphenylglyoxaline as the structure for lophine.



IV

BENZILAM

Benzilam (II), m. p. 116°, occurs not only among the products of the action of ammonia on benzil; both imabenzil and benzilimide are converted into it by the action of sulfuric acid. It has also been reported as result-

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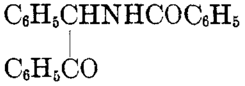
[7] Radziszewski, *ibid.*, **15**, 1493 (1882).

[8] Kulisch, *Monatsh.*, **17**, 300 (1896). See Franklin, *Chem. Rev.*, **16**, 315 (1935).

ing from the action of fused ammonium acetate[9] or ammonium formate[10] on benzil, accompanied by a small amount of lophine. Japp[5] assigned an oxazole structure to benzilam, which he confirmed by a synthesis from benzoin and benzonitrile.[11]

BENZILIMIDE

Japp's structure for benzilimide (I) was based on its dehydration to benzilam (II). Since the latter is best represented as an oxazole, benzilimide was written as a *hydrated* oxazole, or, specifically, as 2-hydroxy-2,4,5-triphenyloxazoline. Henius[4] described benzilimide as occurring in white, asbestos-like needles, melting at 137–139°. In 1913, McKenzie and Barrow[12] benzoylated desylamine and obtained a product consisting of rosettes of slender, colorless needles which melted at 139–140° and yielded benzilam (II) with concentrated sulfuric acid according to Robinson's method of producing oxazoles.[13] In the present work, the preparation of Laurent's benzilimide and of McKenzie and Barrow's benzodesylamide (*N*-desylbenzamide) (V) were repeated, and the products were



$$\begin{array}{l} C_6H_5CHNHCOC_6H_5 \\ \quad\;\;| \\ C_6H_5CO \end{array}$$

V

found to be identical in crystalline form (rosettes of asbestos-like needles) melting point (141°), and chemical behavior (conversion to cyclic bases by ammonia, aniline, or dehydration). Japp's formula for benzilimide, should, therefore, be superseded by *N*-desylbenzamide (V), the structure of which is established by the synthesis of McKenzie and Barrow. In harmony with this formulation benzilimide forms an oxime (m. p. 200°).

THE MECHANISM OF THE ACTION OF AMMONIA ON BENZIL

To explain the formation of benzilimide or benzilam, Japp[5] assumed that one molecule of benzil is split by ammonia into benzaldehyde and benzoic acid. The latter fragment may appear as ethyl benzoate or benzamide depending on circumstances,[14] while the benzaldehyde reacts with

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[9] JAPP AND WILSON, *J. Chem. Soc.*, **49**, 825 (1886), recommended fused ammonium acetate as more convenient than alcoholic ammonia.

[10] LEUCKART, *J. prakt. Chem.*, [2], **41**, 330 (1890).

[11] JAPP AND MURRAY, *J. Chem. Soc.*, **63**, 469 (1893).

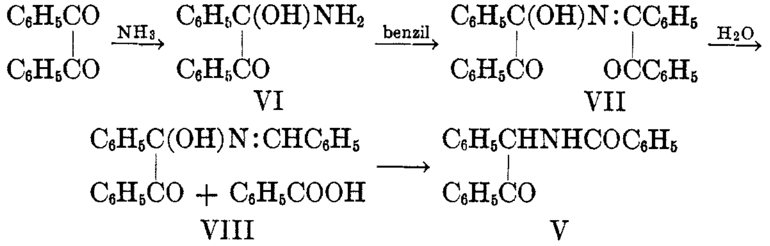
[12] McKENZIE AND BARROW, *ibid.*, **103**, 1331 (1913).

[13] ROBINSON, *ibid.*, **95**, 2167 (1909); ROBINSON AND LISTER, *ibid.*, **101**, 1297 (1912).

[14] SCHÖNBERG, *Ber.*, **54B**, 242 (1921), obtained ammonium benzoate in aqueous ammonia at 120°.

a second molecule of benzil to form benzilimide or benzilam. As Japp recognized, the inherent weakness of this mechanism lies in the fact that, as Radziszewski[7] had shown, a mixture of benzaldehyde and benzil reacts with ammonia in alcohol at 40° to form lophine exclusively. Furthermore, benzil does not undergo the supposed scission when treated with derivatives of ammonia such as primary amines (Zincke[3]). It appears necessary, therefore, to devise a reaction scheme which does not involve benzaldehyde. What follows is proposed as a working hypothesis for the course of this reaction.

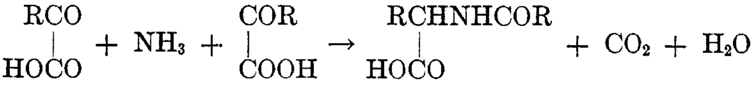
1. Benzil adds ammonia to form the hypothetical benzil-ammonia (VI).
2. Benzil-ammonia condenses with benzil to form another hypothetical intermediate, desylidenebenzil-ammonia (VII).
3. Such a structure (VII), it is proposed, possesses a particularly labile C—C bond between the azomethine carbon atom and the adjacent carbonyl group, which is subject to solvolysis (hydrolysis, alcoholysis, or ammonolysis). This results in the production of benzoic acid or a derivative (ethyl benzoate or benzamide) and a third hypothetical intermediate, benzylidenebenzil-ammonia (VIII).
4. Benzylidenebenzil-ammonia undergoes a form of internal Cannizzaro reaction leading to the benzoyl derivative of desylamine [*N*-desylbenzamide (V)].
5. Sufficiently activated molecules of V undergo spontaneous cyclodehydration to benzilam (II).



$$\begin{array}{c}C_6H_5CO\\|\\C_6H_5CO\\\end{array} \xrightarrow{NH_3} \begin{array}{c}C_6H_5C(OH)NH_2\\|\\C_6H_5CO\\\text{VI}\end{array} \xrightarrow{\text{benzil}} \begin{array}{c}C_6H_5C(OH)N{:}CC_6H_5\\|\qquad\qquad|\\C_6H_5CO\qquad OCC_6H_5\\\text{VII}\end{array} \xrightarrow{H_2O}$$

$$\begin{array}{c}C_6H_5C(OH)N{:}CHC_6H_5\\|\\C_6H_5CO + C_6H_5COOH\\\text{VIII}\end{array} \longrightarrow \begin{array}{c}C_6H_5CHNHCOC_6H_5\\|\\C_6H_5CO\\\text{V}\end{array}$$

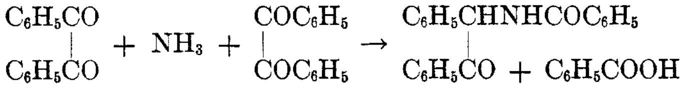
The recognition of benzilimide as *N*-desylbenzamide clarifies the action of ammonia on benzil by bringing to light the close analogy between this reaction of ammonia on an alpha-diketone and its action on alpha-ketoacids. Erlenmeyer, Jr.[15] found that acids of the type RCOCOOH were converted by ammonia to alpha-acylaminoacids of the type RCONHCHRCOOH and carbon dioxide thus:



$$\begin{array}{c}RCO\\|\\HOCO\end{array} + NH_3 + \begin{array}{c}COR\\|\\COOH\end{array} \rightarrow \begin{array}{c}RCHNHCOR\\|\\HOCO\end{array} + CO_2 + H_2O$$

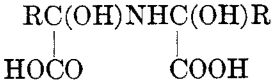
[15] Erlenmeyer, Jr. and Kunlin, *ibid.*, **35**, 2438 (1902).

beside which may be written



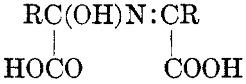
$$\begin{array}{c} C_6H_5CO \\ | \\ C_6H_5CO \end{array} + NH_3 + \begin{array}{c} COC_6H_5 \\ | \\ COC_6H_5 \end{array} \rightarrow \begin{array}{c} C_6H_5CHNHCOC_6H_5 \\ | \\ C_6H_5CO \end{array} + C_6H_5COOH$$

In both reactions an active carbonyl group is converted to an acylated carbinamine group at the expense of a second molecule of the carbonyl compound. Erlenmeyer's mechanism for his reaction involved the intermediate IX. His concept is brought into line with that discussed above in the benzil case by considering this substance to dehydrate to X, which contains the azomethine grouping known to labilize the C—COOH bond and permit decarboxylation.[16] A subsequent rearrangement would yield the final aminoacid derivative.



$$\begin{array}{ccc} RC(OH) & NH & C(OH)R \\ | & & | \\ HOCO & & COOH \end{array}$$

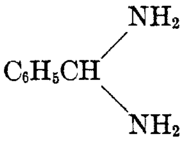
IX



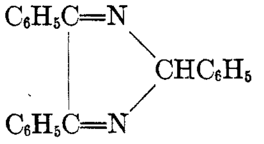
$$\begin{array}{ccc} RC(OH) & N: & CR \\ | & & | \\ HOCO & & COOH \end{array}$$

X

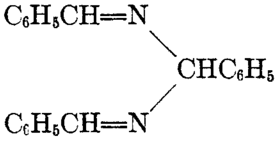
This picture of the mechanism of the action of ammonia on benzil accounts for the apparent (but not actual) scission of benzil. It remains to explain the formation of lophine when ammonia acts on a mixture of benzaldehyde and benzil in alcohol (Radziszewski[7]). Here it may be assumed that the reaction begins with the conversion of benzaldehyde to a diamine (XI), which condenses with benzil to form XII, which then undergoes a Cannizzaro reaction yielding lophine. The formation of the supposed intermediate XII is analogous to the formation of hydrobenzamide (XIII) by the action of ammonia on benzaldehyde alone.



XI



XII



XIII

The formation of lophine in Henius' experiments[4] mentioned above is to be traced to benzilimide, since it is known that such acylated aminoketones react with ammonia to yield glyoxalines.[17] This account for Henius' observation of the disappearance of benzilimide and the appearance of lophine as the action of ammonia was continued. In the present study it was found that benzilam was completely unaffected under conditions which converted benzilimide (*N*-desylbenzamide) quantitatively to lophine.

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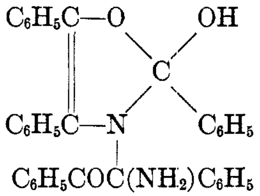
[16] LANGENBECK, *Z. angew. Chem.*, **45**, 97 (1932); *Ber.*, **70B**, 367 (1937).

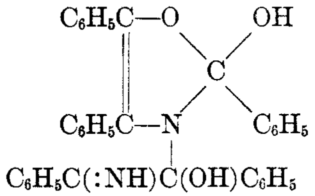
[17] EVEREST AND MCCOMBIE, *J. Chem. Soc.*, **99**, 1746 (1911).

IMABENZIL

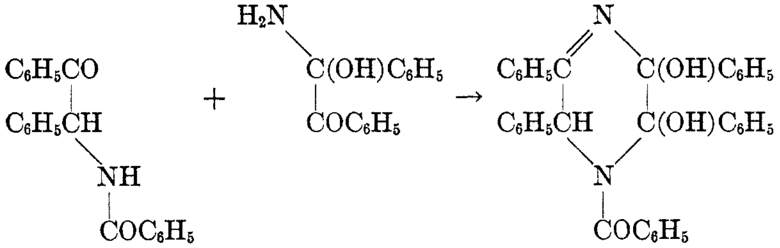
Another aspect of the reaction under discussion which requires clarification is the nature of imabenzil. Imabenzil, the first product to separate in the action of ammonia on benzil, gradually disappears as the action is continued. Hence, Henius considered it the primary product but both Henius and Japp were unable to assign it a structure. Pinner's formula (III) hardly explains the conversion of imabenzil to benzilimide and benzilam, and led Strain[17] to suggest two alternative formulas (XIV or XV). Since these structures were based on Japp's cyclic conception of benzilimide, they also require revision. The essential facts that a structural formula for imabenzil must indicate are its composition ($C_{35}H_{28}N_2O_3$) and its scission by acid into benzilimide, benzil, and ammonia. In harmony with the mechanism of the action of ammonia on benzil presented above the simplest assumption to be made is that imabenzil is a condensation product of benzil-ammonia (VI) and benzilimide (V); namely, 1-benzoyl-5, 6-dihydroxy-2, 3, 5, 6-tetraphenyl-1, 2, 5, 6-tetrahydropyrazine (XVI).



XIV



XV



V VI XVI

GLACIAL ACETIC ACID AS A MEDIUM FOR THE ACTION OF AMMONIA ON BENZIL

The present paper is part of a research program including the study of the action of ammonia in glacial acetic acid on carbonyl compounds. This work was stimulated by the observation of Davidson[18] that glacial acetic acid is an excellent medium for the conversion of alloxantine to murexide

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[18] Davidson, *J. Am. Chem. Soc.*, **58**, 1821 (1936).

by ammonia.[9] When a gram of benzil is refluxed for an hour in 25 cc. of glacial acetic acid containing 5 g. of ammonium acetate, all the benzil reacts, forming over 90 per cent. of the theoretical yield of lophine together with a subordinate amount of benzilam.

Does this result indicate that the action of ammonia on benzil is essentially different in glacial acetic acid from that observed in aqueous or alcoholic medium where little (if any) lophine is formed in the same length of time, and benzilam is the principal final product? Such is apparently not the case. The principal difference between glacial acetic acid and other media is that it is particularly suitable for the conversion of acyl derivatives of desylamine, such as *N*-desylbenzamide (V) to glyoxalines by ammonia. This has been demonstrated by treating benzilimide with ammonium acetate in glacial acetic acid, thus effecting its smooth conversion to lophine. *N*-Desylacetamide behaves similarly. Under the same conditions benzilam is completely unchanged by the reagent. When aniline is employed in place of ammonia, the ring closures lead to *N*-phenyl glyoxalines.

It is worthy of note that at elevated temperatures, fused ammonium acetate[9] or formate[10] convert benzil mainly to benzilam. These results may be reconciled with that described just above by invoking postulate five of the mechanism proposed in an earlier section of this paper. In accordance with this idea, a larger proportion of labile molecules of benzilimide would be formed at the higher temperatures, and would undergo cyclodehydration to the oxazole before they could react with ammonia to form lophine.

A MODIFIED RADZISZEWSKI SYNTHESIS OF GLYOXALINES

If an equimolecular mixture of benzaldehyde and benzil is refluxed for an hour in glacial acetic acid containing insufficient ammonium acetate to convert benzil alone to lophine, a quantitative yield of lophine is obtained. Hydrobenzamide may be substituted for the benzaldehyde. The advantage of the acetic acid medium over Radziszewski's alcoholic ammonia is seen clearly in the case of 4,5-diphenylglyoxaline. This compound was first prepared by Japp[19] by the action of alcoholic ammonia on a mixture of formaldehyde and benzil. Pinner[6] obtained very little of the desired product by Japp's method, the reaction yielding mainly the well-known products of the action of ammonia on benzil alone. Later, Pinner[20] somewhat improved the yield of 4,5-diphenylglyoxaline by working in the cold. This complication prompted Biltz[21] to study the indirect pro-

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[19] JAPP, *J. Chem. Soc.*, **51**, 559 (1887).

[20] PINNER, *Ber.*, **38**, 1536 (1905).

[21] BILTZ, *ibid.*, **40**, 2630 (1907); BILTZ AND KREBS, *Ann.*, **391**, 201, 203 (1912).

duction of this substance from 2-chloro and 2-mercapto derivatives. Pinner's difficulty disappears, however, when glacial acetic acid is employed and hexamethylenetetramine is utilized as a convenient source of formaldehyde, a quantitative yield of Japp's product being obtained. A similar result is experienced with a mixture of paraldehyde and benzil, which leads to 2-methyl-4,5-diphenylglyoxaline.[5]

EXPERIMENTAL

Preparation of Laurent's benzilimide.—Ammonia gas was passed into a solution of 25 g. of benzil in 500 cc. of ethanol at 30–40° until the gain in weight amounted to nine grams. Fine colorless needles of imabenzil soon appeared. After 24 hours the crop, amounting to 0.55 g., melting at 188° (corr.), was collected by filtration, and the filtrate was boiled down in vacuum in two stages to approximately 200 and 100 cc. respectively, further crops of imabenzil of 2.1 g., m. p. 208° (corr.), and 0.8 g., m.p. 193° (corr.), being obtained. The final liquor, on standing, deposited 9.2 g. of a mixture of benzilimide and benzilam melting at about 100°, from which 3 g. of benzilimide, m.p. 141° (corr.), was separated by fractional crystallization from ethanol. No depression of the melting point was observed when this material was mixed with the *N*-desylbenzamide prepared as described below.

N-*Desylbenzamide from desylamine.*—A suspension of 9.2 g. of desylamine stannochloride[22] in 100 cc. of water was covered with 200 cc. of benzene containing 4 cc. of benzoyl chloride. The mixture was stirred and maintained at 5–10° while 80 cc. of 10% sodium hydroxide was slowly dropped in. Stirring was then continued for thirty minutes at room temperature, the benzene layer was separated, the benzene removed, and the residue was crystallized from 60 cc. of ethanol. The yield was 5.0 g. (80% theoretical) of colorless, asbestos-like needles, melting at 141° (corr.). Like benzoin, this substance gives a yellow solution in alcoholic alkali, but, unlike benzoin, does not develop a deep purple color.

Benzilimide oxime.—This was obtained by refluxing 0.32 g. of benzilimide with 0.14 g. of hydroxylamine hydrochloride and 0.16 g. of sodium acetate in 10 cc. of ethanol for 16 hours or by refluxing the amide and hydroxylamine hydrochloride in 3 cc. of pyridine for two hours. In both cases the product was thrown out with water and crystallized from methanol, from which it was obtained in the form of needles, melting at 197–203° (corr.), depending on the rate of heating.

Anal. Calc'd for $C_{21}H_{18}N_2O_2$: C, 76.4; H, 5.5; N, 8.5.
Found: C, 75.9; H, 5.7; N, 8.9.

The mother liquors contained a much more soluble product (m.p. 140°) which may be an isomeric oxime. Identical products were obtained from the *N*-desylbenzamide prepared from desylamine.

Action of ammonia in acetic acid on N-*desylamides.*—*Lophine from* N-*desylbenzamide.*—Benzilimide (0.32 g.) was refluxed for one hour with 1.5 g. of ammonium acetate in 10 cc. of acetic acid. Dilution of the hot solution with water yielded 0.28 g. (93% of theory) of colorless needles, melting at 270° (corr.). Recrystallization from a mixture of pyridine and water raised the melting point to 275° (corr.). Under the same conditions benzilam was recovered quantitatively and unchanged. Substitution of one cc. of aniline for the ammonium acetate yielded *tetraphenyl glyoxaline*,[17] melting at 221° (corr.) (from methanol). This has previously been reported as melting at 215°. Identical results were obtained from *N*-desylbenzamide prepared from from desylamine. Replacement of the *N*-desylbenzamide in the experiments de-

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[22] Pschorr and Bruggemann, *Ber.*, **35**, 2740 (1902).

scribed above by *N*-desylacetamide, the preparation of which is reported below, yielded entirely similar results leading to *2-methyl-4,5-diphenylglyoxaline*, m.p. 243° (corr.) and *2-methyl-1,4,5-triphenylglyoxaline*, m.p. 197° (corr.).

N-*Desylacetamide.*—To a mixture of 20 cc. of dry pyridine and 4 cc. of acetic anhydride surrounded by an ice bath 9.1 g. of desylamine stannochloride was gradually added with stirring. The stirring was continued for an hour at room temperature and the mixture was then poured into chilled dilute hydrochloric acid. This precipitated an oil which soon solidified. Crystallization from methanol gave large, clear prisms, melting at 137° (corr.) in practically quantitative yield.

Anal. Calc'd for $C_{16}H_{15}NO_2$: N, 5.5. Found: N, 5.6.

Action of ammonia on benzil in acetic acid.—A solution of 1.05 g. of benzil and 5.0 g. of ammonium acetate in 25 cc. of glacial acetic acid was refluxed for one hour. Twenty cc. of water was then added. This precipitated 0.05 g. (7% of theory) of benzilam, m.p. 110° (115° after crystallization from ethanol). Dilution of the original mother liquor to 250 cc. precipitated 0.70 g. (94% of theory) of crude lophine, m.p. 250°, which after solution in hot pyridine (10 cc.) and precipitation by addition of hot water (7.5 cc.) melted at 275° (corr.).

A modified glyoxaline synthesis.—Preparation of 4,5-diphenylglyoxaline.—A mixture of 1.05 g. of benzil, 0.13 g. of hexamethylenetetramine, 3.0 g. of ammonium acetate and 25 cc. of glacial acetic acid was refluxed for an hour and then diluted to 250 cc. A slight turbidity was removed by means of Darco and the glyoxaline was precipitated by adding ammonia; yield, 1.00 g. (91% of theory) of a product melting at 228° (corr.). Crystallization from 5 cc. of hot pyridine by addition of 5 cc. of boiling water yielded large, glistening needles, m.p. 232° (corr.).

Anal. Calc'd for $C_{15}H_{12}N_2$: N, 12.7. Found: N, 12.6.

Similar reactions in which the formaldehyde derivative was replaced (*a*) by paraldehyde (0.3 cc.) gave *2-methyl-4,5-diphenylglyoxaline*, m.p. 244° (corr.) in 96% yield; or (*b*) by benzaldehyde (0.5 cc.) or by hydrobenzamide (0.5 g.) gave *lophine*, m. 272° in 90–95% yields.

SUMMARY

1. Laurent's benzilimide is identical with the benzodesylamide (*N*-desylbenzamide) of McKenzie and Barrow.

2. 1-Benzoyl-5,6-dihydroxy-2,3,5,6-tetraphenyl-1,2,5,6-tetrahydropyrazine is suggested as the structure of Laurent's imabenzil.

3. A mechanism for the action of ammonia on benzil which avoids the scission of benzil as a step and relates the reaction to the formation of alpha-acylaminoacids by the action of ammonia on alpha-ketoacids is proposed.

4. *N*-Desyl derivatives of acid amides are converted smoothly into glyoxalines by the action of ammonia in acetic acid.

5. Ammonia in acetic acid converts benzil to lophine accompanied by a small amount of benzilam.

6. The preparation of glyoxalines from benzil, aldehydes, and ammonia is improved by the use of glacial acetic acid. Ammonia derivatives or reversible polymers of the aldehydes may be employed in place of the aldehydes themselves.

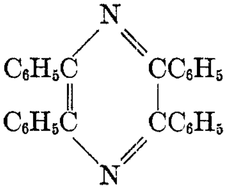
[Contribution from the Department of Chemistry, Brooklyn College]

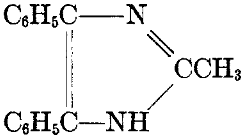
THE ACTION OF AMMONIA ON BENZOIN

DAVID DAVIDSON, MARVIN WEISS, and MURRAY JELLING

Received August 23, 1937

The action of ammonia on benzoin has been studied previously by Laurent,[1] Erdmann,[2] and Japp and Wilson.[3] These investigators found that the reaction leads to three products—amarone ($C_{28}H_{22}N_2$, m.p. 245°) [also called benzoinimide (Erdmann) and ditolane-azotide (Japp and Wilson)], benzoinam ($C_{28}H_{23}N_2O$, m.p. 190°–220° depending on the rate of heating), and benzoinidam ($C_{28}H_{23}NO_2$, m.p. 199°). With fused ammonium acetate at elevated temperatures, Japp and Wilson obtained a fair yield of amarone (55%), while with ammonium formate at 230° Leuckart[4] reported a quantitative yield of amarone with only traces of by-products such as lophine and benzaldehyde. Of the products mentioned above only amarone has been assigned a structural formula. This Japp and Wilson[3] represented as tetraphenylpyrazine (I).


I


II

The present paper deals with an examination of the action of ammonia in acetic acid on benzoin.[5] In this medium it is found that benzoin yields mainly amarone (I) and 2-methyl-4,5-diphenylglyoxaline (II) together with dihydroamarone. Some light is thrown on the mechanism of this reaction by studying other acids particularly formic, and, further by testing the action of ammonia in acetic acid on *esters* of benzoin. This latter

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[1] Laurent, *J. prakt. Chem.*, [1], **36**, 5 (1845).

[2] Erdmann, *Ann.*, **135**, 181 (1865).

[3] Japp and Wilson, *J. Chem. Soc.*, **49**, 825 (1886).

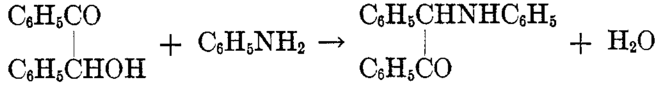
[4] Leuckart, *J. prakt. Chem.*, [2], **41**, 330 (1890).

[5] Previous papers from this laboratory dealing with the action of ammonia in acetic acid on carbonyl compounds: (*a*) Davidson, *J. Am. Chem. Soc.*, **58**, 1821 (1936); (*b*) Davidson, Weiss, and Jelling, J. Org. Chem., **2**, 319 (1937).

reaction produces good yields of oxazoles (accompanied by subordinate amounts of glyoxalines), thus furnishing a new method of producing such cycles.[6]

THE MECHANISM OF THE ACTION OF AMMONIA ON BENZOIN

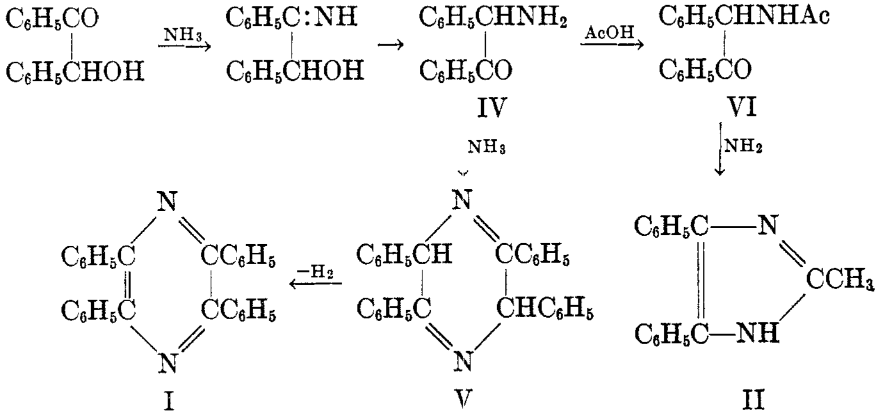
Since it is known that aniline converts benzoin into *N*-desylaniline[7] (III), it is reasonable to assume that the primary product of the action



$$\begin{matrix} C_6H_5CO \\ | \\ C_6H_5CHOH \end{matrix} + C_6H_5NH_2 \rightarrow \begin{matrix} C_6H_5CHNHC_6H_5 \\ | \\ C_6H_5CO \end{matrix} + H_2O$$

III

of ammonia on benzoin is desylamine (IV). In this reaction it is probably the carbonyl group which is converted to the carbinamine group, the process involving condensation followed by tautomerization, thus:



Desylamine, in turn, may react in two ways: (1) undergo autocondensation[8] to dihydroamarone (V); or (2) condense with acetic acid to form *N*-desylacetamide (VI). The latter has been shown to react with ammonia in acetic acid to form 2-methyl-4,5-diphenylglyoxaline (II),[5b] while Gabriel[8] has reported that dihydropyrazines resembling V are readily oxidized to pyrazines.

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[6] Oxazoles derived from benzoin have previously been prepared by (*a*) cyclodehydration of *N*-desylbenzamide, McKenzie and Barrow, *J. Chem. Soc.*, **103,** 1331 (1913); (*b*) the condensation of benzoin with nitriles, Japp and Murray, *ibid.*, **63,** 469 (1893).

[7] A recent study of this reaction has been made by Cameron, *Trans. Roy. Soc. Can.*, [3], **23,** Sect. 3, 53 (1929); **25,** Sect. 3, 145 (1931).

[8] Compare the behavior of other alpha-aminoketones, Gabriel, *Ber.*, **41,** 1127 (1908); Hildesheimer, *ibid.* **43,** 2796 (1910).

The formation of tetraphenyldihydropyrazine in the reaction of ammonia on benzoin in acetic acid is evidenced by the orange color which sets in soon after refluxing of the reaction mixture is begun. That air plays a rôle in its conversion to amarone is indicated by the following experiments (Table I) in which the heating was carried out (1) with air bubbling through the solution, (2) under normal conditions, and (3) in a closed tube. The amarone produced was separated by filtration, and the dihydroamarone remaining in the mother liquors was determined by adding nitric acid until the orange color was discharged, whereupon a second crop of amarone precipitated, while a fugitive green color was observed.*

TABLE I

AIR AS A FACTOR IN THE PRODUCTION OF AMARONE

(In each experiment, 1.06 g. of benzoin, 10.0 g. of ammonium acetate, and 25 cc. of acetic acid were refluxed for one hour.)

CONDITIONS	YIELD OF AMARONE		
	1st crop, g.	2nd crop (by HNO_3), g.	Total, g.
Air bubbled thru solution	0.41	0.14	0.55
Normal refluxing	0.35	0.20	0.55
Closed tube	0.27	0.24	0.51

TABLE II

EFFECT OF AMMONIUM ACETATE ON YIELDS

(In each experiment 1.06 g. of benzoin was refluxed for one hour in 25 cc. of acetic acid with the amount of ammonium acetate indicated.)

AMMONIUM ACETATE EMPLOYED, G	YIELD OF AMARONE			YIELD OF GLYOXALINE, G.
	1st crop, g.	2nd crop, g.	Total, g.	
3	0.22	0.09	0.31	0.24
5	0.31	0.12	0.43	0.36
10	0.35	0.20	0.55	0.28

Table II displays the influence of the ammonia concentration on the total yield of amarone and the yield of the glyoxaline derivative.

The mechanism outlined above is supported by an experiment in which benzoin was replaced by an equivalent quantity of desylamine hydrochloride, without influencing the yields of amarone and 2-methyl-4,5-

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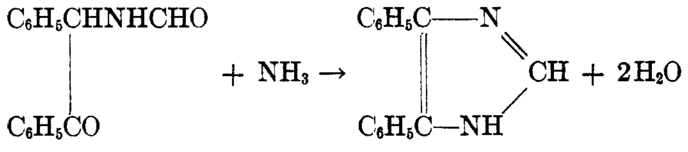
* Unpublished studies in this laboratory indicate that the evanescent green color is due to the action of nitrous acid on a colorless reduction product of amarone. This suggests that part of the dihyroamarone formed in the reaction disproportionates to amarone and the above-mentioned reduction product.

diphenylglyoxaline. Replacement of the acetic acid by propionic acid did not affect the yield of amarone materially but led, of course, to another imidazole derivative; *i.e.*, 2-ethyl-4,5-diphenylglyoxaline.

THE ACTION OF AMMONIA ON BENZOIN IN THE PRESENCE OF FORMIC ACID

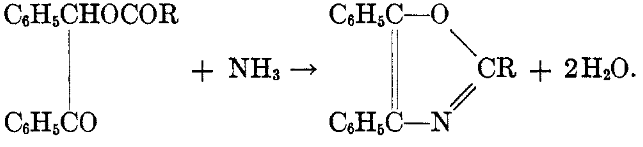
In the presence of formic acid, the formation of pyrazines by the action of ammonia on benzoin was suppressed. Beside the expected 4,5-diphenylglyoxaline there appeared a fair amount of *N*-desylformamide (VII). This result stands in sharp contrast to that of Leuckart[4] who obtained only amarone from the action of ammonium formate on benzoin at 230°. *N*-Desylformamide may be prepared by refluxing desylamine with formic acid. Like other *N*-desylamides,[5b] *N*-desylformamide is smoothly converted to the corresponding glyoxaline (VIII) by treatment with ammonia in acetic acid.



VII VIII

THE ACTION OF AMMONIA IN ACETIC ACID ON ESTERS OF BENZOIN

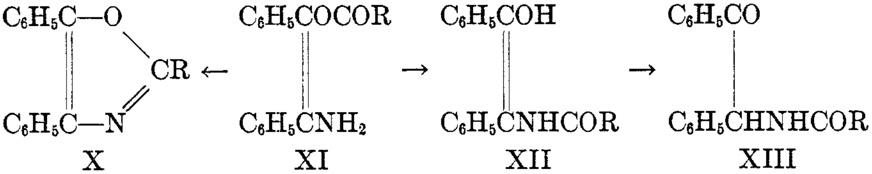
To test the idea that it is the carbonyl group in benzoin which is attacked by ammonia rather than the carbinol group, the latter function was esterified, and the resulting desyl esters were submitted to the action of ammonia in acetic acid. The conversion of *N*-desylamides to glyoxalines illustrated above suggested that the closely related desyl esters (IX) would yield the corresponding oxazoles (X) according to the equation:



IX X

Tests of desyl acetate and benzoate demonstrate that oxazoles are formed in yields of better than 80 per cent., accompanied by the related glyoxalines. The oxazoles and glyoxalines may have a common intermediate (XI) which either undergoes cyclodehydration or suffers acyl migration from oxygen to nitrogen. In the second instance an enol form (XII) of an

N-desylamide (XIII) would be formed; the latter could give rise to the glyoxaline.



EXPERIMENTAL

The action of ammonia on benzoin in acetic acid.—Example: A mixture of 1.06 g. of benzoin, 10 g. of ammonium acetate, and 25 cc. of glacial acetic acid was refluxed for one hour. The solution turned deep orange in color almost at once, and the precipitation of amarone began within ten minutes. The cooled mixture was filtered, and the yellow precipitate was washed with small amounts of glacial acetic acid until the washings were practically colorless. This precipitate weighed 0.35 g. (36% theoretical) and melted at 251° (corr.). It gave in concentrated sulfuric acid the orange-red color characteristic of amarone. The combined liquors were treated with concentrated nitric acid until the orange-red solution changed to yellow, and a crystalline precipitate of amarone appeared; m.p. 246°; yield 0.20 g. (21% theoretical). This was separated, washed with acetic acid and then liberally with water. When recrystallized twice from glacial acetic acid, the amarone was obtained as large, colorless needles, m.p. 252° (corr.).

Anal. Calc'd for $C_{28}H_{20}N_2$: N, 7.3. Found: N, 7.1.

A total of 100 cc. of water was added to the mother liquor. This threw out a little oily matter which was removed by extracting twice with 25 cc. portions of benzene.[†] The final aqueous layer was clarified by filtering through a wet, folded filter, and then heated nearly to boiling and rendered alkaline with concentrated ammonia, producing a precipitate of colorless needles of 2-methyl-4,5-diphenylglyoxaline melting at 237° (corr.); yield, 0.28 g. (24% theoretical). After recrystallization from a mixture of pyridine and water it melted at 240°; its melting point was not depressed by an admixture of the glyoxaline prepared from benzil and paraldehyde.[5b]

The action of ammonia on benzoin in propionic acid.—To a solution of 5 g. of ammonium carbonate in 25 cc. of propionic acid was added 1.06 g. of benzoin. The mixture was refluxed for one hour and worked up as in the previous experiment. The precipitates of amarone weighed 0.28 g. (29% theoretical) and 0.20 g. (21% theoretical) and melted at 250° and 249° respectively. The glyoxaline precipitate weighed 0.16 g. (13% theoretical) and melted at 210° (corr.). After recrystallization from pyridine and water, it melted at 215° (corr.).

Anal. Calc'd for $C_{17}H_{16}N_2$: N, 11.3. Found: N, 11.4.

The action of ammonia on desylamine in acetic acid.—A mixture of 1.24 g. of desylamine hydrochloride,[9] 10 g. of ammonium acetate, and 25 cc. of glacial acetic acid was treated as in the case of benzoin (see above). The amarone precipitates weighed 0.39 g. (41% theoretical) and 0.16 g. (17% theoretical), and melted at 252° and 247°, respectively. The glyoxaline fraction weighed 0.25 g. (21% theoretical) and melted at 237° (corr.).

[†] This oily by-product may contain 2-methyl-4,5-diphenyloxazole.

[9] Pschorr and Bruggemann, *Ber.*, **35**, 2740 (1902).

The action of ammonia on benzoin in the presence of formic acid.—To 10 cc. of formic acid (85–90%) was added 7.5 cc. of acetic anhydride, the heat of the reaction being moderated by means of a cold-water bath. Three grams of ammonium carbonate was then added to the resulting mixture of anhydrous acetic and formic acids. After dissolution was complete, 1.06 g. of benzoin was added, and the mixture was refluxed for three hours. The addition of 100 cc. of water precipitated an oil which was removed by two extractions with 25 cc. portions of benzene. The aqueous layer was rendered ammoniacal, whereupon 0.40 g. (36% theoretical) of 4,5-diphenylglyoxaline, m.p. 232° (corr.), separated. Its melting point was unchanged by recrystallization from dilute pyridine or by mixing with a sample of the glyoxaline prepared from benzil and hexamethylenetetramine.[5] A mixture with 2-methyl-4,5-diphenylglyoxaline, however, melted at 205° (corr.).

Evaporation of the benzene extract left 0.72 g. of a yellow oil from which there was obtained by three extractions with 100 cc. portions of boiling water, 0.34 g. (28% theoretical) of colorless crystals, m.p. 116–118°. Recrystallization from a mixture of anhydrous ethyl acetate and ligroïn yielded large, clear, hexagonal plates, melting at 122°. This product was identified as *N*-desylformamide by conversion to 4,5-diphenylglyoxaline as described below.

Anal. Calc'd for $C_{15}H_{13}NO_2$: N, 5.9. Found: N, 5.5.

The residual oil was not identified, but may have contained 4,5-diphenyloxazole since it possessed the characteristic pepper-like odor of the oxazoles.

Preparation of N-*desylformamide.*—A mixture of 1.24 g. of desylamine hydrochloride,[9] 1.0 g. of sodium acetate, and the solution resulting from the addition of 7.5 cc. of acetic anhydride to 10 cc. of formic acid (85–90%) was refluxed for three hours. The addition of 100 cc. of water precipitated an oil which soon solidified. Yield, 0.91 g. (75% theoretical), melting at 120°. On crystallization from a mixture of anhydrous ethyl acetate and ligroïn it was obtained in large, clear, hexagonal plates, melting at 122°. It is easily soluble in the common organic solvents except light petroleum fractions, and slightly soluble in boiling water. Like other *N*-desylamides its alcoholic solution turns yellow on the addition of 10% sodium hydroxide. Its conversion to 4,5-diphenylglyoxaline is described below.

Conversion of N-*desylformamide to 4,5-diphenylglyoxaline.*—A solution of 0.24 g. of *N*-desylformamide (see just above) and 1.5 g. of ammonium acetate in 10 cc. of acetic acid was refluxed for one hour. Dilution with 100 cc. of water yielded a light precipitate (0.007 g.) which appeared to be crude amarone. From the mother liquor, ammonia precipitated glistening, white crystals, weighing 0.21 g. (95% theoretical) and melting at 231° (corr.) (mixture melting point).

When the experiment was repeated with the *N*-desylformamide obtained from the action of ammonia on benzoin in the presence of formic acid (see above), 0.19 g. (86% theoretical) of 4,5-diphenylglyoxaline, m.p. 228° (corr.) was obtained.

The action of ammonia on desyl esters.—Conversion of desylbenzoate (benzoylbenzoin) to triphenyloxazole (benzilam).—A mixture of 1.58 g. of benzoylbenzoin,[10] 3.0 g. of ammonium acetate, and 25 cc. of acetic acid was refluxed for one hour and then diluted with 20 cc. of water, whereupon benzilam separated as a crystalline precipitate, which was collected by filtration and washed with 60% acetic acid (9 cc.); yield, 1.38 g. (93% theoretical); m.p. 116° (mixture melting point).

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.8.

The filtrate was diluted with 50 cc. of water and clarified by filtering through a

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[10] ZININ, *Ann.*, **104**, 116 (1857). In the present study, the preparation of benzoyl benzoin was improved by employing pyridine as a solvent.

wet folded filter. Ammonia precipitated 0.05 g. (3% theoretical) of crude lophine, melting at about 250°, which when crystallized from a pyridine-water mixture melted at 275° (corr.).

Conversion of desylacetate (acetylbenzoin) to 2-methyl-4,5-diphenyloxazole.—A mixture of 6.35 g. of acetylbenzoin,[11] 10.0 g. of ammonium acetate, and 25 cc. of acetic acid was refluxed for one hour. The addition of 100 cc. of water threw out an oil which was extracted with three 25-cc. portions of benzene. The benzene extract was filtered through a dry filter, the benzene was removed, and the residue was distilled in vacuum; yield, 4.8 g. (82% theoretical) of a viscous oil, b.p. 210–213° at 18 mm. (Japp and Murray[6] reported the b.p. of 2-methyl-4,5-diphenyloxazole as 214° at 17 mm.)

Anal. Calc'd for $C_{16}H_{13}NO$: N, 6.0. Found: N, 5.9.

From the aqueous layer, ammonia precipitated 0.74 g. (13% theoretical) of 2-methyl-4,5-diphenylglyoxaline; m.p. 243° (corr.).

SUMMARY

1. The action of ammonia on benzoin in boiling acetic acid yields amarone, dihydroamarone, and 2-methyl-4,5-diphenylglyoxaline.
2. Desylamine is assumed to be an intermediate product in this reaction. It behaves like benzoin toward ammonia in acetic acid.
3. In the presence of formic acid the formation of pyrazines is suppressed, the isolated products being *N*-desylformamide and 4,5-diphenylglyoxaline.
4. In propionic acid, the behavior of benzoin toward ammonia is similar to that in acetic acid, amarone, dihydroamarone, and 2-ethyl-4,5-diphenylglyoxaline being obtained.
5. Esters of benzoin react with ammonia in acetic acid to form mainly 2-alkyl-4,5-diphenyloxazoles accompanied by subordinate amounts of the corresponding glyoxalines.

[11] CORSON AND SALIANI, *Organic Syntheses*, **12**, 1 (1932).

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

THE NATURE OF THE STEROLS IN COTTONSEED OIL

EVERETT S. WALLIS AND P. N. CHAKRAVORTY*

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Cottonseed oil has recently engaged the attention of chemists as a convenient source of vitamin E (α-tocopherol). Little is known, however, about the other constituents in the unsaponifiable fraction. In the earlier papers the various investigators who have reported upon the composition of the unsaponifiable matter usually have described their products by giving the melting points of the sterols, and in some cases of their acetates. Bömer and Winter[1] isolated a sterol having a melting point of 136–137°. Siegfeld[2] described a product which melted at 138.8–139.8°, and which gave an acetate melting at 131.5–132.5°. König and Schluckebier[3] obtained a sterol which melted at 137–138°. Its acetate after five recrystallizations melted at 125–128°.

That the unsaponifiable matter in cottonseed oil contains no stigmasterol was first shown by Heiduschka and Gloth[4] who employed the method of Windaus and Hauth[5]. From the dibromoacetate a sterol was obtained which melted at 136°. Wagner and Clement[6] later confirmed the observation that cottonseed oil contains no stigmasterol. They did claim, however, to have been able to separate the sterol residues into two fractions, the one melting at 139°, and its acetate melting at 125°; the other at 130–131°, giving an acetate of a melting point of 120°. Similar results have been reported by Anderson and Moore.[7] By fractional crystallization these investigators also claimed to have been able to separate the phytosterols of cottonseed oil into two fractions that differed slightly in melting point and optical rotation. According to them one fraction melted at 134–135°, and had a specific rotation $[\alpha]_D^{20} = -33.61$. Its acetate melted at 119°. From the mother liquors there was isolated what

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* Research Assistant on Special Funds from the American Philosophical Society.

[1] BÖMER AND WINTER, *Z. Nahr. Genuss*, **4**, 865 (1901).

[2] SIEGFELD, *ibid.*, **7**, 581 (1904).

[3] KÖNIG AND SCHLUCKEBIER, *ibid.*, **15**, 653 (1908).
See also MATHES AND HEINZ, *Archiv Pharm.*, **247**, 161 (1909).

[4] HEIDUSCHKA AND GLOTH, *Pharm. Zentr.*, **49**, 863 (1908).

[5] WINDAUS AND HAUTH, *Ber.*, **39**, 4378 (1906); *ibid.*, **40**, 3682 (1907).

[6] WAGNER AND CLEMENT, *Z. Nahr. Genuss.*, **17**, 266 (1909).

[7] ANDERSON AND MOORE, J. *Am. Chem. Soc.*, **45**, 1944 (1923).

was considered to be another sterol of melting point 138–139°; $[\alpha]_D^{20} = -34.19$. This product gave an acetate which melted at 124°. They doubted, however, the purity of their products, and from their experiments concluded that it was doubtful whether these two compounds could "ever be separated into homogeneous substances by simple recrystallization." It should be pointed out that apparently no saturated sterol was obtained by them.

With the increase in our knowledge of sitosterol mixtures since the above investigations were made, it seemed desirable to reinvestigate the nature of the phytosterols of cottonseed oil. The present investigation was also undertaken in connection with previously published work from this laboratory on α-sitosterol from wheat-germ oil[8] in which it was shown that the α-sitosterol of Anderson[9] is a mixture of at least two sterols, both of which are doubly unsaturated and precipitable with digitonin; α_1-sitosterol being an isomer of stigmasterol, and α_2-sitosterol presumably being a homologue, $C_{30}H_{50}O$. A richer source of these two sterols was greatly desired in order to obtain sufficient amounts for a complete determination of their structures. The observation of Thompson[10] that the phytosterols of cottonseed oil are free from γ-sitosterol suggested that one might be able to get these two sterols with less difficulty from this source rather than from the sterol fraction of wheat-germ oil which is known to contain both β-, and γ-sitosterols. Accordingly, a very intensive systematic fractionation of the crude sterols from cottonseed oil and certain of their derivatives was carried out for the purpose of obtaining the sterols present in a pure and homogeneous state.

In the experimental part of this paper experiments are described which show that, unlike wheat-germ oil, not only does cottonseed oil contain no γ-sitosterol as was observed by Thompson[10], but both α_1- and α_2-sitosterols also appear to be absent. Examination of the bottom fraction for the more soluble α_1- and α_2- sitosterols by the method of Wallis and Fernholz[8] failed to disclose the presence of these latter sterols even in small amounts. It was possible to isolate from this fraction only the dinitrobenzoate of β-sitosterol. No α_1- and α_2- sitosteryl dinitrobenzoate could be obtained. In this fraction we did observe the presence of appreciable amounts of a low-melting wax. It was not a sterol, however, but seemed to be of the nature of a hydrocarbon. As yet it has not been further investigated.

Since previous investigators did not observe the presence of saturated sterols in cottonseed oil it seemed advisable to examine the unsaponifiable

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[8] WALLIS AND FERNHOLZ, *ibid.*, **58**, 2446 (1936).

[9] ANDERSON, SHRINER, AND BURR, *ibid.*, **48**, 2987 (1926).

[10] See SPRING, *J. Chem. Soc.*, **1930**, 2664.

material for such sterols. For this purpose the top fraction was used, and the method of Schoenheimer[11] was employed. Decomposition of the digitonide thus obtained gave a sterol which on further purification with acetic anhydride and sulfuric acid had the physical properties of stigmastanol. It melted at 136–137°, and gave an acetate of melting point 129–130°; $[\alpha]_D^{25} = +14.9$. The saturated sterol content in this top fraction is 0.9%.

Thus, from our experiments it is to be concluded that β-sitosterol constitutes the greater part of the sterols in cottonseed oil. Since it contains only small amounts of a saturated sterol, and no detectable amounts of α_1-, α_2-, or γ-sitosterol the unsaponifiable matter of cottonseed oil is an excellent source for pure β-sitosterol. The physical constants of the β-sitosterol so obtained together with those of certain of its derivatives are listed in Table I. The melting points recorded were taken with a standard thermometer calibrated by the Bureau of Standards. No corrections for stem exposure were made.

TABLE I

TYPE OF COMPOUND	MELTING POINT, °C.	SPECIFIC ROTATION $[\alpha]_D^{25}$
Free sterol	136–137	−36.6
Acetate	125–126	−41.0
Benzoate	146–147	−13.8
m-Dinitrobenzoate	202–203	−10.4

EXPERIMENTAL

Five hundred grams of the crude sterols† isolated from cottonseed oil (m.p. 130–133°) were subjected to an intensive systematic fractional crystallization (triangle scheme) from a mixture of benzene and alcohol in such a manner as to obtain eight fractions. Approximately one hundred crystallizations were made. The melting points and specific rotations of the eight fractions so obtained are listed in Table II.

Analysis of fraction 2. Calc'd for $C_{29}H_{50}O$: C, 83.98; H, 12.16.
Found: C, 83.89, 83.85; H, 12.25, 12.16.

Isolation of the saturated sterols from fraction 1.—Thirteen grams of sterol was dissolved in one liter of hot ethyl alcohol. The solution was then placed in a freezing mixture of ice and salt. When the solution reached 20° a cold, normal alcoholic solution of bromine was added drop by drop. The addition was continued (with shaking) until the solution acquired a permanent yellow color. At 5° a precipitate formed but this disappeared on standing at room temperature. After about 2.5 hours an excess of 1% solution of digitonin (1.29 grams) was added. The mixture was kept in the

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[11] Schoenheimer, *Z. physiol. Chem.*, **192**, 81–84 (1930).

† The crude cottonseed oil sterols used in these experiments were furnished by the Merck and Company, Inc., Rahway, New Jersey, and were obtained from the unsaponifiable matter in cottonseed oil.

dark for two days until precipitation of the digitonide was complete. Occasionally small amounts of an alcoholic solution of bromine were added to keep the color of the supernatant liquid faintly yellow. The digitonide so formed was filtered, washed with alcohol, ether, and dried at 80°. It was then decomposed in the usual manner with pyridine. The yield of saturated sterol was 0.124 g., corresponding to 0.9%. Since the Liebermann reaction was not entirely negative this sterol was further purified by treatment with acetic anhydride and concentrated sulfuric acid. The acetate so obtained melted at 129–130°, $[\alpha]_D^{25} = +14.8$ (20.3 mg. in 2 cc. of chloroform solution gave α_D^{25} +0.15, 1 dm. tube).

Hydrolysis of the acetate with a 5% alcoholic potassium hydroxide solution gave a purified sterol which melted at 135.5–137°. The sterol and its acetate did not give depressions of the melting point when mixed with the corresponding stigmastanol derivatives. Depressions of the melting point were observed with β-sitosterol and its acetate.

Isolation of β-sitosterol from fraction 1.—The alcoholic filtrate from the precipitation of the digitonide described above was poured into a large amount of water and the dibromositosterol was filtered. Debromination with zinc in acetic acid solution gave a product which after four recrystallizations from ethyl acetate melted at 136–137°.

TABLE II

FRACTION	MELTING POINT, °C.	SPECIFIC ROTATION $[\alpha]_D^{25}$
1	136–136.5	−34.9
2	136–137	−36.6
3	135–136	−35.9
4	135	−34.5
5	136–136.5	−36.3
6	135.5–136.5	−34.0
7	136.5–137	−35.2
8 (residue)	128–131 (Softened at 120, waxy, contained coloring materials)	−26.2

β-Sitosterol from fraction 2.—Attempts were made at further purification of fractions 2 and 5 by fractional crystallization of their acetates, benzoates, and *m*-dinitrobenzoates. No evidence was found that these fractions contained any other sterol than β-sitosterol. A description of one of several experiments is given here. Twenty grams of sterol from fraction 2 was dissolved in acetic anhydride and heated for two hours on the water bath. The solution was then boiled for 15 minutes and allowed to cool. The product was worked up in the usual manner, and the acetate so obtained was recrystallized from alcohol several times, and from acetone and methyl alcohol with no detectable change in melting point and in optical rotation. The crystals melted at 125–126°; $[\alpha]_D^{25} = -41$ (19.1 mg. in 2 cc. of chloroform solution gave α_D^{25} −0.39).

Anal. Calc'd for $C_{31}H_{52}O_2$: C, 81.51; H, 11.48.
Found: C, 81.49, 81.60; H, 11.59, 11.55.

The mother liquors from the above crystallizations were evaporated to dryness. The product so obtained without a recrystallization melted at 119°–122°. Since Anderson and Moore[7] from their experiments believed that cottonseed oil contained a second sterol whose acetate melted at 119° this product was further examined as described below.

Preparation of β-sitosteryl benzoate.—Five grams of β-sitosteryl acetate (m. p. 125–126°) obtained in the above experiment was hydrolyzed with a 5% alcoholic solution of potassium hydroxide. The free sterol so obtained (m.p. 136–137°) was converted into the benzoate by treatment with benzoyl chloride in pyridine solution. Crystallization from benzene and alcohol gave a product which melted at 146–147°; $[\alpha]_D^{25} = -13.8$ (23.1 mg. in 2 cc. of chloroform solution gave α_D^{25} −0.16).

Anal. Calc'd for $C_{36}H_{56}O_2$: C, 83.33; H, 10.50.
Found: C, 83.36, 83.54; H, 10.65, 10.46.

The acetate residues from the mother liquors (m.p. 119–122°) were also hydrolyzed in a wholly similar manner, and the free sterol so obtained (m.p. 135–136°) was converted into the benzoate. Crystallization of this benzoate from benzene and alcohol gave crystals in well defined leaflets which melted at 146°, and showed no appreciable difference in optical rotation; $[\alpha]_D^{27} = -13.3$.

A sample of the benzoate was also prepared from the free sterol of fraction 2. It melted at 146–146.5°.

Preparation of β-sitosteryl dinitrobenzoate.—Two grams of β-sitosteryl benzoate (m.p. 146–147°; $[\alpha]_D^{25} = -13.8$) was hydrolyzed in the usual manner. The free sterol so obtained was dissolved in pyridine and treated with 2 grams of *m*-dinitrobenzoyl chloride. The mixture was kept on a boiling water bath for one hour. The dinitrobenzoate was taken up in ether, washed free of pyridine, and decolorized with charcoal. Evaporation of the solvent gave a crystalline residue which crystallized from ethyl acetate in the form of white leaflets with a yellowish tint; m.p. 202–203°; $[\alpha]_D^{25} = -10.4$ (25.0 mg. in 2 cc. of chloroform solution gave α_D^{25} −0.13).

Anal. Calc'd for $C_{36}H_{52}N_2O_6$: C, 71.02; H, 8.61.
Found: C, 71.12, 71.14; H, 8.56, 8.71.

In a similar manner the benzoate (m.p. 146°; $[\alpha]_D^{27} = -13.3$) and the residue from its mother liquor, prepared from the acetate of m.p. 119–123°, were hydrolyzed and converted into the *m*-dinitrobenzoate. A product was obtained which on recrystallization from ethyl acetate also melted at 202–203°. Evaporation of the filtrate to dryness gave a residue which melted at 198–200°.

Before concluding the description of this experiment it should be pointed out that a similar experiment was carried out on fraction 5 with the result that here again we could obtain no evidence for the presence of sterols other than β-sitosterol.

Analysis of fractions 7 and 8 for the presence of α_1- and α_2-sitosterols.—These two fractions were examined for the presence of these more soluble sterols by the method used by Wallis and Fernholz[8] in their examination of the sterols in wheat-germ oil. Thirty-five grams of material was dissolved in 150 cc. of pyridine and treated in the usual manner with benzoyl chloride. The benzoate so formed was taken up in ether, and crystallized from a mixture of benzene and alcohol. Twenty-eight grams of β-sitosteryl benzoate was obtained; it melted at 145–146°. The filtrate was evaporated to dryness and hydrolyzed with a 5% alcoholic potassium hydroxide solution. The free sterol was converted into the *m*-dinitrobenzoate, and after decolorization of the ether solution with charcoal it was evaporated. Crystallization from ethyl acetate gave a product which melted at 201–202°; $[\alpha]_D^{25} = -9.9$ (20.4 mg. in 2 cc. of chloroform solution gave $\alpha_D^{25} = -0.10$, 1 dm. tube).

Anal. Calc'd for $C_{36}H_{52}N_2O_6$: C, 71.02; H, 8.61; N, 4.60.
Found: C, 70.94, 70.89; H, 8.48; 8.58; N, 4.68.

An examination of the mother liquors failed to give any evidence of the presence of α_1- or α_2-sitosterol.

The above-described *m*-dinitrobenzoate was hydrolyzed with 5% alcoholic potassium hydroxide solution and portions of the free sterol so obtained were converted into the acetate and benzoate. Their melting points and specific rotations are listed below.

Derivative	Melting Point	$[\alpha]_D^{25}$
Free sterol	136.5–137.1°	−35.6
Acetate	126–127°	−42.0
Benzoate	144–145°	−14.0

We wish to express our thanks to the American Philosophical Society for a grant-in-aid for this work, to Merck and Company, Inc., Rahway, New Jersey, for all the analyses in this article, and for the crude sterols obtained from cottonseed oil which were used in this investigation, and to Mr. E. Gilmore Ford, who helped us in the determination of some of the physical constants.

SUMMARY

An examination has been made of the nature of the sterols present in cottonseed oil.

Evidence is submitted which shows that the chief part of the sterols present is β-sitosterol. No evidence for the presence of a second phytosterol could be obtained.

The absence of γ-sitosterol and stigmasterol is confirmed.

The absence of both α_1- and α_2-sitosterols is demonstrated.

An analysis of the saturated sterols by the method of Schoenheimer[11] shows that stigmastanol is present to an extent of less than 1%.

Cottonseed oil is an excellent source for β-sitosterol.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

THE STRUCTURE OF β-SITOSTEROL, AND ITS PREPARATION FROM STIGMASTEROL

SEYMOUR BERNSTEIN* AND EVERETT S. WALLIS

Received August 30, 1937

It is known that, whereas the structural formulas of cholesterol, ergosterol, and stigmasterol are well established, our knowledge of sitosterol in some respects is still unsatisfactory. This is due to the fact that this plant sterol as obtained from most sources is not a homogeneous substance but contains various amounts of other sterols which can be separated only with great difficulty. This was first clearly demonstrated by Anderson and his co-workers,[1] who isolated from wheat-germ oil three varieties of sitosterol which they named α-, β-, and γ-sitosterol. Recently it was shown in this laboratory[2] that the α-sitosterol of Anderson is in reality a mixture of at least two new sterols α_1-, and α_2-sitosterol which are doubly unsaturated. α_1-Sitosterol is an isomer of stigmasterol; α_2-sitosterol is probably a homologue, $C_{30}H_{50}O$.

The early investigators[3] employed for sitosterol from natural sources the empirical formula $C_{27}H_{46}O$. The formula, $C_{29}H_{50}O$, was later proposed by Sandqvist and Bengtsson,[4] and this latter formulation was confirmed by Windaus, Werder and Gschaider.[5] That the ring system in dihydrositosterol is the same as that in dihydrocholesterol was first shown by Ruzicka and Eichenberger.[6] Oxidation of a dihydrositosteryl acetate (source, wheat germ oil) with chromic acid gave the same hydroxyketone as is obtained from dihydrocholesterol. Similar conclusions can also be deduced from the work of Dalmer *et al.*[7] who oxidized dibromositosteryl acetate with chromic acid, and isolated from the reaction mixture, dehydroandrosterone. That sitosterol contains at least twenty-three carbon

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* Research Assistant on Special Funds from the Rockefeller Foundation.

[1] ANDERSON, SHRINER, AND BURR, *J. Am. Chem. Soc.*, **48**, 2987 (1926). See also ANDERSON, *ibid.*, **46**, 1450 (1924).

[2] WALLIS AND FERNHOLZ, *ibid.*, **58**, 2446 (1936).

[3] ANDERSON AND MOORE, *ibid.*, **45**, 1944 (1923). References to other papers are given in this article.

[4] SANDQVIST AND BENGTSSON, *Ber.*, **64B**, 2167 (1931).

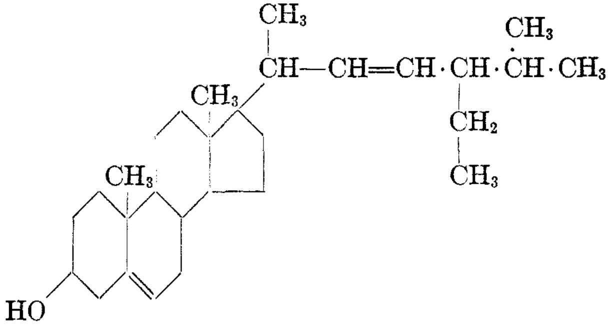
[5] WINDAUS, WERDER, AND GSCHAIDER, *ibid.*, **65B**, 1006 (1932).

[6] RUZICKA AND EICHENBERGER, *Helv. Chim. Acta*, **18**, 430 (1935).

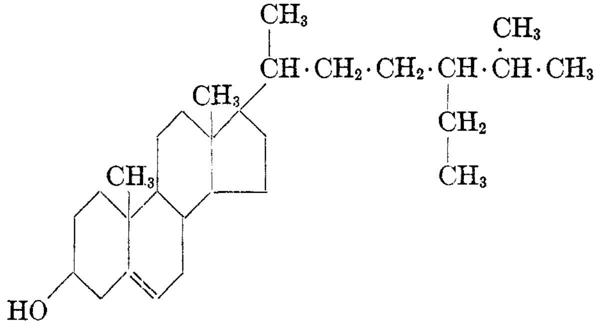
[7] DALMER *et al.*, *Ber.*, **68B**, 1814 (1935).

atoms of the same arrangement as in cholesterol was also shown by degradation studies of Chakravorty.[8] On degradation sitosterol gives 3-oxynorallocholanic acid. It should be stated, however, that in this and other studies it is not always certain that the same variety of sitosterol in a completely homogeneous state is employed. The published physical constants of the particular material used vary, and in some cases suggest that a mixture of more than one sitosterol was employed.

In this paper we wish to report on certain experiments which have a direct bearing on the structure of β-sitosterol, and which were suggested by some experimental results of Bengtsson.[9] Bengtsson compared derivatives of β-sitostanol with stigmastanol, and after a thorough study came to believe that these two compounds are identical. His conclusions seemed to us to have a high degree of probability, and if we assume them to be correct it follows that β-sitosterol is in reality 22-dihydrostigmasterol.



Stigmasterol



22-Dihydrostigmasterol*

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[8] Chakravorty, Diss. Göttingen (1935).

[9] Bengtsson, *Z. physiol. Chem.*, **237**, 46 (1935).

* We wish at this time to call attention to an error made in printing the formula for this compound in the article of Wallis and Fernholz.[2] Readers of that article should make the appropriate correction.

Obviously this latter statement is subject to experimental proof, provided that in some way one can selectively hydrogenate the double bond in the side chain of stigmasterol. Accordingly, a study was made of the selective hydrogenation of the double bonds in the sterol, and as a result we have found that under certain conditions it is possible to hydrogenate the side chain of stigmasterol without hydrogenating to a great extent the double bond in the 5,6 position. The 22-dihydrostigmasterol so obtained did contain small amounts of sterols hydrogenated in the 5,6 position. They were easily removed, however, by taking advantage of the relatively great difference in the rate of hydrolysis of the corresponding *p*-toluenesulfonates—a method which suggests itself in the light of certain observations of Stoll[10] who found that, whereas the *p*-toluenesulfonate of cholesterol easily and rapidly reacted with water and with alcohols to give the free sterol, and the corresponding ethers respectively, the *p*-toluenesulfonates of the saturated sterols were more stable, and after two hours heating with methyl alcohol did not form ethers. The hydrolyzed 22-dihydrostigmasterol was precipitated with digitonin, and the digitonide was worked up in the usual manner. The following table gives the melting points and specific rotations of the 22-dihydrostigmasterol so obtained, together with those of some of its derivatives. The melting points recorded were taken with a standard thermometer, calibrated by the Bureau of Standards. No corrections were made for stem exposure. A comparison with the corresponding compounds of β-sitosterol obtained from cottonseed oil and described by Wallis and Chakravorty in the preceding paper is also made. From these data it is evident that β-sitosterol and 22-dihydrostigmasterol are one and the same compound.

TABLE

DERIVATIVE	22-DIHYDROSTIGMASTEROL		β-SITOSTEROL	
	m. p., °C.	$[\alpha]_D^{25}$	m. p., °C.	$[\alpha]_D^{25}$
Sterol	136.5–137.5	−37	136–137	−36.6
Benzoate	146	−13.5	146–147	−13.8
m-Dinitrobenzoate	202–203	−10.3	202–203	−10.4

As a concluding experiment we hydrogenated a portion of the above-described β-sitosterol, and obtained a saturated sterol of melting point and specific rotation wholly in agreement with those recorded by Bengtsson[9] for stigmastanol.

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[10] Stoll, *Z. physiol. Chem.*, **207**, 147 (1932); *ibid.*, **246**, 1 (1937).

EXPERIMENTAL

Preparation of 22-dihydrostigmasterol.—One and five-tenths grams of stigmasteryl acetate (m. p. 140–141°) was dissolved in ethyl acetate and hydrogenated at room temperature and atmospheric pressure with a palladium catalyst prepared according to the method of Willstätter, and previously saturated with hydrogen. Measurements of the rate of hydrogen absorbtion showed that the double bonds in the compound were being selectively hydrogenated, for hydrogenation progressed very slowly after the absorption of one equivalent of hydrogen. Accordingly, the hydrogenation was stopped when 1.2 equivalents of hydrogen had been used up, in order to be certain that no stigmasteryl acetate remained in the reaction mixture. The hydrogenated product was hydrolyzed to the free sterols with 5% alcoholic potassium hydroxide. The sterols so obtained were converted into their corresponding *p*-toluenesulfonates with pyridine and *p*-toluenesulfonyl chloride. The sulfonates, carefully freed from pyridine, were dissolved in acetone containing water and boiled for 2.5 hours. The solution was then evaporated to dryness and the solid material was taken up in hot ethyl alcohol (90%). The hydrolyzed sterol was precipitated with digitonin, and the digitonide was worked up in the usual manner. A sterol was obtained which after two crystallizations from alcohol melted at 136.5–137.5°, and had a specific rotation $[\alpha]^{25}_{D} = -37°$ (23.1 mg. in 2 cc. chloroform solution gave $[\alpha]^{25}_{D} = -0.43°$, 1 dm. tube). It gave no melting point depression when mixed with crystals of β-sitosterol obtained from cottonseed oil.

A benzoate was prepared by heating a pyridine solution of the free sterol with benzoyl chloride for one hour on the water bath. After the product had been worked up in the usual manner crystals were obtained in the form of well-defined leaflets from a mixture of benzene and alcohol. These crystals melted at 146°; $[\alpha]^{25}_{D} = -13.5$ (23.6 mg. in 2 cc. chloroform solution gave α^{25}_{D} −0.16°, 1 dm. tube).

Preparation of 22-dihydrostigmasteryl dinitrobenzoate.—A pyridine solution of 22-dihydrostigmasterol was treated with an excess of *m*-dinitrobenzoyl chloride. This mixture was kept on a boiling water bath for one hour. The dinitrobenzoate so formed was taken up in ether and worked up in the usual manner. On decolorization with animal charcoal and evaporation of the solvent a product was obtained which after two crystallizations from hot ethyl acetate gave white crystals of a yellowish tint of m. p. 202–203°; $[\alpha]^{25}_{D} = -10.3$ (23.3 mg. in 2 cc. chloroform solution gave α^{25}_{D} −0.12°, 1 dm. tube). The melting point of a mixture with β-sitosteryl dinitrobenzoate showed no depression.

Anal. Calc'd for $C_{36}H_{52}N_2O_6$: C, 71.0; H, 8.61; N, 4.60.
Found: C, 70.85, 71.05; H, 8.44, 8.61; N, 4.71.

Hydrogenation of β-sitosterol from cottonseed oil.—Three grams of β-sitosterol (m. p. 136–137°) was dissolved in ethyl acetate which contained some acetic acid, and was hydrogenated at room temperature and at atmospheric pressure with a platinum oxide catalyst prepared according to the method of Adams. Since the Liebermann reaction was not completely negative the hydrogenated product was converted into its acetate and treated with acetic anhydride and concentrated sulfuric acid to remove unsaturated impurities. Recrystallization of the acetate from ethyl acetate and alcohol gave a product which melted at 129–129.5°; $[\alpha]^{25}_{D} = +15.4°$ (27.3 mg. in 2 cc. of chloroform solution gave α^{25}_{D} +0.21°). Hydrolysis with a 5% alcoholic solution of potassium hydroxide gave a free sterol which after three crystallizations from ethyl alcohol melted at 136–137°, and has the properties of stigmastanol described by Bengtsson; $[\alpha]^{25}_{D} = +23.8$ (20.1 mg. in 2 cc. of chloroform solution gave α^{25}_{D} +0.24°, 1 dm. tube).

We wish to take this opportunity to express our thanks to the Rockefeller Foundation for a grant-in-aid for this work, to Merck and Company, Inc. of Rahway, New Jersey for the analysis of 22-dihydrostigmasteryl dinitrobenzoate, and to Dr. E. Fernholz of the Research Laboratories of Merck and Company for kindly furnishing us the stigmasteryl acetate used in these experiments.

SUMMARY

22-Dihydrostigmasterol has been prepared from stigmasterol by selectively hydrogenating stigmasteryl acetate with a palladium catalyst. Its benzoate and dinitrobenzoate have also been prepared.

Evidence is submitted which shows that β-sitosterol obtained from cottonseed oil and 22-dihydrostigmasterol are identical.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

NITRATION OF ACYL DERIVATIVES OF 4,5-DIBROMO- AND 4,5,6-TRIBROMOGUAIACOL

L. CHARLES RAIFORD AND RALPH E. SILKER

Received September 15, 1937

Armstrong and Harrow[1] found that when 2,4,6-tribromophenol is gradually added to concentrated nitric acid (relative amounts of material and temperature not specified) 2,4-dinitro-6-bromophenol is obtained. If the tribromophenol is dissolved in acetic acid, one molecular proportion of nitric acid is added, and the mixture is heated on a steam bath, the para bromine atom only is replaced and 2,6-dibromo-4-nitrophenol is obtained. In a similar way Claus and Hirsch[2] converted *sym*-tribromo-*m*-cresol into 2,6-dibromo-4-nitro-*m*-cresol.

In later work Zincke and students[3] showed that nitrous acid reacts with bromine substitution products of phenols to replace hydrogen or halogen from an ortho or para position with respect to hydroxyl to give a mononitro compound. Raiford[4] and others found that in most cases this method of nitration gives isomeric mononitro derivatives and that the method is selective[5] to the extent that chlorine is not replaced. More recently Raiford and Scott[6] studied the behavior of the tribromo derivative of resorcinol monomethyl ether. When this product was subjected to the action of nitrous acid under the conditions indicated by Zincke and modified by Raiford and Grosz[7] it gave a high yield of 2,4-dibromo-3-methoxy-6-nitrophenol in which a halogen atom ortho to hydroxyl had been replaced by the nitro radical.

In view of the last-named observations it was of particular interest to study the behavior of related compounds in which the substituents had somewhat different positions. For this purpose 4,5-dibromo- and 4,5,6-tribromoguaiacol (OH = 1) were selected. When these compounds were subjected to the action of nitrous acid, in accordance with the general

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[1] ARMSTRONG AND HARROW, *J. Chem. Soc.*, **29**, 477 (1876).

[2] CLAUS AND HIRSCH, *J. prakt. Chem.*, [2], **39**, 61 (1889).

[3] ZINCKE, *ibid.*, [2], **61**, 561 (1900); ZINCKE AND JANNEY, *Ann.*, **398**, 361 (1913) These papers contain important references to the authors' other work in this field.

[4] RAIFORD AND WOOLFOLK, *J. Am. Chem. Soc.*, **46**, 2253 (1924).

[5] RAIFORD AND MILLER, *ibid.*, **55**, 2131 (1933).

[6] RAIFORD AND SCOTT, J. ORG. CHEM., **2**, 213 (1937).

[7] RAIFORD AND GROSZ, *ibid.*, **53**, 3422 (1931).

method of Zincke, no reaction product could be isolated. With cold fuming nitric acid a vigorous reaction went on but no product was obtained. Possibly complete oxidation took place. Failure to obtain a nitro compound by these methods suggested study of the acyl derivatives.

It has been shown in several cases that acylation of a phenol suppresses the directive influence of the substituent involved, and that if the compound under consideration contains some other *o,p*-directing radical the latter may determine in large measure the position to be occupied by the entering group. Thus, nitration of guaiacol with red fuming nitric acid has been reported to give a mixture of 4-nitro-, 6-nitro- and 4,6-dinitroguaiacol[8], but when acetylguaiacol is used the 5-nitro derivative is obtained[9]. Nitration of vanillin (CHO = 1) gives 5-nitrovanillin in about 95 per cent. yield[10], while the acetyl derivative gives a 75 per cent. yield of the 2-nitro compound[11]. Similarly, when *p*-cresol (OH = 1) is nitrated a 51 per cent. yield of the 2-nitro derivative, along with some dinitro compound[12], is produced, while nitration of *p*-cresyl carbonate gives a very good yield of the 3-nitro compound[13]. Introduction of halogen follows the same course. Bromination of vanillin gives an 85 per cent. yield of the 5-bromo compound[14], while acetylvanillin gives the 6-bromo derivative in 87 per cent. yield and nothing else can be isolated from the reaction mixture[15]. *o*-Cresol reacts with bromine to give a 66 per cent. yield of the 4-bromo derivative[16], but when 2-methoxyphenyl carbonate (guaiacol carbonate) is used, an almost quantitative yield[17] of the 5-bromo compound is obtained. Apparently in the second example in each of the above cases the position taken by the entering group is determined by alkyl or alkoxyl.

In the present work the acetyl and benzoyl derivatives of the above bromoguaiacols have been examined.

The dibromoguaiacol that melts at 94–95°, which was prepared by

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[8] Klemenc, *Monatsh.*, **33**, 701 (1912).

[9] Cardwell and Robinson, *J. Chem. Soc.*, **107**, 256 (1915).

[10] Vogl, *Monatsh.*, **20**, 384 (1899).

[11] Pschorr and Sumuleanu, *Ber.*, **32**, 3408 (1899). This was confirmed by Raiford and Stoesser [*J. Am. Chem., Soc.*, **50**, 2558 (1928).] who found that about 5% of the 6-nitro isomeride is also formed in this experiment. Raiford and Milbery [*ibid.*, **56**, 2727 (1934)] obtained similar results with benzoylvanillin.

[12] Staedel, *Ann.*, **217**, 53 (1883).

[13] German Pat., 206638; *Frd.*, **9**, 151 (1908).

[14] Dakin, *Am. Chem. J.*, **42**, 493 (1909).

[15] Raiford and Stoesser, *J. Am. Chem. Soc.*, **49**, 1079 (1927).

[16] The method followed was outlined by Claus and Jackson [*J. prakt. Chem.*, [2], **38**, 324 (1888)] who recorded no yield. This was determined by Miller [Thesis, Iowa (1930) p. 40] who had occasion to repeat the work.

[17] Hindmarsh, Knight, and Robinson, *J. Chem. Soc.*, **111**, 942 (1917).

Cousin[18], and in which the halogen atoms have been oriented in positions 4 and 5[17], failed to give a definite product when attempts were made to nitrate it. Accordingly, its acyl derivatives were studied. Treatment of the acetyl compound (II) with fuming nitric acid as described below gave two nitro compounds, (III*a* or III*b*, and VI). The formation of III*a* or III*b* involved the replacement of a bromine atom by the nitro radical and the product must have one of the structures shown. Since it has been proved in other cases that —OCH_3[8] has a more pronounced directing influence than —$OCOCH_3$, at least when hydrogen is replaced, it seems probable that the product in hand had structure III*a*. Hydrolysis of this compound gave the corresponding bromonitroguaiacol (IV*a* or IV*b*), that melted at 118–119°. This product may be identical with that described by Meldola and Streatfield[19], which melted at 120°, but it seems improbable that it can have the structure they assigned, *viz.*, 2-methoxy-4-bromo-6-nitrophenol. Their structure is based in part on the observation that the compound formed a deep red sodium salt which suggested an ortho nitrophenol. They also argued that hydroxyl and the nitro radical have in this compound the same structural relations as in the nitrobenzoylguaiacol, m.p., 88–89°, which was isolated by them and in which they claim that the nitro group and the benzoyloxy radical are adjacent to each other, though they established no direct experimental relations between these compounds. Doubt concerning the structure of this benzoyl derivative has been raised by Oxford[20] who found 88–89° for the melting point of the benzoate of that nitroguaiacol obtained by treatment of acetylguaiacol with acetyl nitrate, which latter was shown by Pictet and Khotinsky[21] to give high yields of ortho nitro derivatives, especially when the alkoxyl group is present. This indicates that the compound in question is 2-methoxy-3-nitrophenyl benzoate, and its formation agrees with the observations of Cardwell and Robinson[22] who noted that methoxyl has a far greater orienting effect than acyloxyl. In the present work nitration of II was effected with nitric acid, which may be expected to give the para isomeride (III*a*) as the chief product. Hydrolysis of this must lead to IV*a* which is the most likely structure for our product, and also for that of Meldola and Streatfield.

This view is supported by other facts. In the nitrobromoguaiacol isolated by us it seems almost certain that the bromine atom and the nitro

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[18] Cousin, *Ann. chim. phys.*, [7], **29**, 63 (1903).

[19] Meldola and Streatfield, *Proc. Chem. Soc.*, **12**, 125 (1896), and *J. Chem. Soc.*, **73**, 689 (1898).

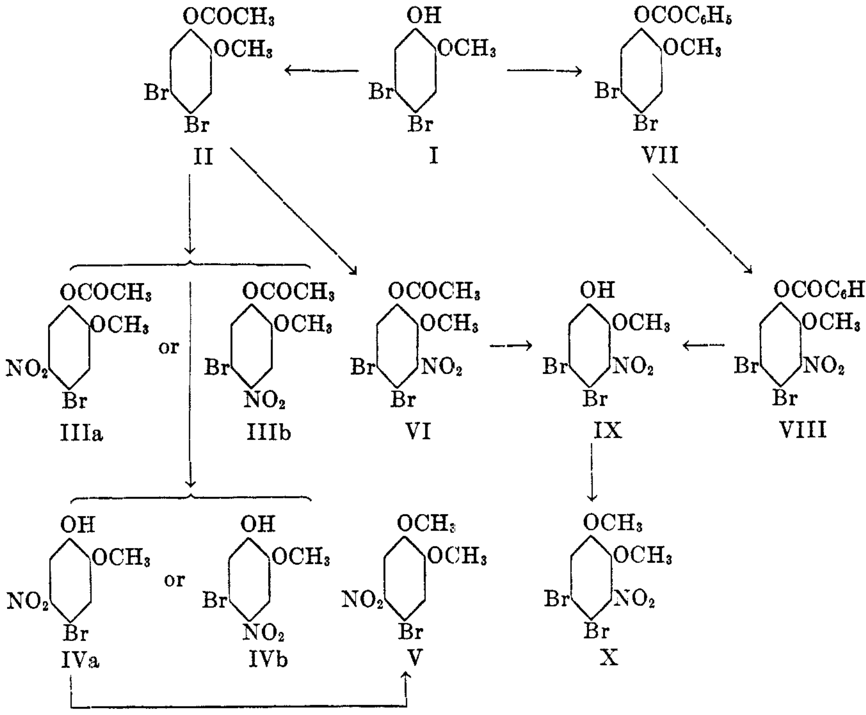
[20] Oxford, *J. Chem. Soc.*, **1926**, 2007.

[21] Pictet and Khotinsky, *Ber.*, **40**, 1165 (1907).

[22] Cardwell and Robinson, *J. Chem. Soc.*, **107**, 255 (1915).

group are in positions 4 and 5, the nitro group most probably in the latter, because the compound was obtained directly from 4,5-dibromoguaiacol, and was finally converted by methylation into 4-bromo-5-nitroveratrol (V) that melted at 122°. The structure of the latter has been established by nitration of 4-bromoveratrol[23], and also by nitration of the bromo compound obtained when the bromoamine prepared from 3-acetylamino-4-bromoveratrol was diazotized and the diazo complex was replaced by hydrogen.[24]

FIGURE 1



Examination of product (VI) showed that it was a nitrodibromo derivative of acetylguaiacol which on hydrolysis gave the corresponding guaiacol (IX). When the latter was methylated in the usual way it gave a nitrodibromoveratrol (X) that melted at 150–151° and which is probably identical with that obtained by Cousin[25] by bromination of 3-nitroveratrol

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[23] GASPARI [*Gazz. chim. ital.*, **26**, II, 231 (1896)] found 124.5–125°; JONES AND ROBINSON [*J. Chem. Soc.*, **111**, 916 (1917)] recorded 125° for this product.

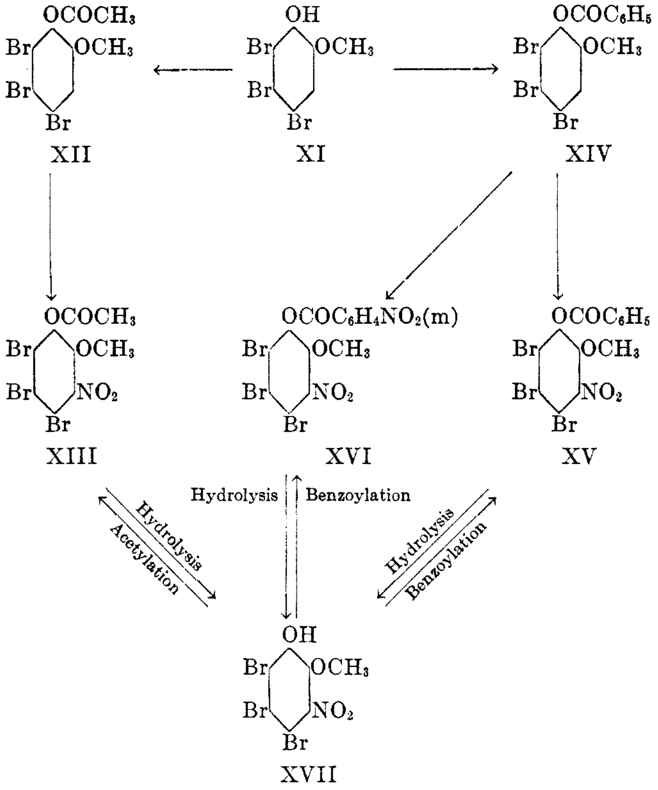
[24] SIMONSEN AND RAU [*J. Chem. Soc.*, **113**, 786 (1918)] found 123°.

[25] COUSIN, *Ann. chim. phys.*, [7], **13**, 505 (1898).

and also by nitration of that dibromoveratrol melting at 92–93°,[26] the latter of which has been proved by Jones and Robinson[27] to be the 4,5-derivative.

Treatment of the benzoyl derivative of 4,5-dibromoguaiacol (VII) with fuming nitric acid gave a nitro compound (VIII) without loss of bromine, and hydrolysis of the latter gave the nitrodibromoguaiacol (IX) mentioned above. These relations are shown in Fig. 1.

FIGURE 2



4,5,6-Tribromoguaiacol, (XI) prepared as described below was converted into the acetyl and benzoyl derivatives, respectively. Treatment of the acetyl derivative (XII) with fuming nitric acid at room temperature gave a nitro compound (XIII) without loss of halogen, which indicated that the entering group had taken position 3, and that the chief directive influence was probably exercised by alkoxyl. Nitration of the

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[26] Cousin [*Ann. chim. phys.*, [7], **13**, 490 (1898)] found 91°.

[27] Jones and Robinson, *J. Chem. Soc.* **111**, 913 (1917).

benzoyl derivative (XIV) in the same way gave a mononitro compound (XV) and a dinitro derivative (XVI) in which the nitro radicals occupy position 3 in each of the phenyl nuclei. This is in general agreement with the observations of Raiford and Wickert[28] who studied the nitration of the benzoyl derivative of *sym*-tribromoaniline. Hydrolysis of products XIII, XV, and XVI gave compound XVII, 2-methoxy-3-nitro-4,5,6-tribromophenol, which was further characterized by the preparation of several of its derivatives. These relations are shown in Fig. 2.

EXPERIMENTAL

4,5-Dibromoguaiacol.—One gram-molecular proportion of guaiacol mixed with about half its weight of chloroform was placed in a suitable vessel provided with a mechanical stirrer and cooled to about 5°. A solution of two molecular proportions of bromine in about twice its weight of chloroform was added from a dropping funnel at such a rate that only a small amount of free halogen was present at any time, while the mixture was stirred continuously and held between 5° and 10°. About half the bromine was added in thirty minutes, while the remainder required ninety. Next the mixture was transferred to a suitable flask and the chloroform was distilled on a steam bath. To avoid the formation of an oily mixture in crystallization it was necessary to remove the chloroform used as solvent as completely as possible and the last portion was distilled under reduced pressure. Crystallization from a mixture of 2 volumes of alcohol and 3 volumes of water gave nearly colorless needles that melted at 94–95°. By working up the mother liquor a total yield 88 per cent was obtained. Its properties agree with those on record.

2-Methoxy-4,5-dibromophenyl acetate was obtained in almost theoretical yield by heating the above guaiacol with excess of acetic anhydride on a steam bath for one and one-half hours. Crystallization of the product from ligroïn, (65–70°) gave colorless granules that melted at 101–102°.

Anal. Calc'd for $C_9H_8Br_2O_3$: Br., 49.38. Found: Br, 49.43.

Nitration of the acetyl derivative.—A portion of the dry powdered material was gradually added with stirring during one to one and one-half hours to twice its weight of fuming nitric acid at 25–28°; the mixture was stirred for two hours longer and then poured slowly into twice its volume of ice water. The average yield from several runs was 82 per cent. When a hot saturated methyl alcohol solution of this material was allowed to cool to room temperature it deposited fine nearly colorless needles that melted at 160–161°. Recrystallization did not change this. Analysis for halogen agrees with that required by 2-methoxy-4-bromo-5-nitrophenyl acetate.

Anal. Calc'd for $C_9H_8BrNO_5$: Br, 27.58. Found: Br, 27.63.

The alcohol from the filtrate left when the above compound had crystallized out was distilled off, and the residue was crystallized from ligroïn (65–70°) from which it separated in colorless square prisms that melted at 91.5–92.5°. The yield of purified product was 51 per cent. Analysis for halogen corresponds to 2-methoxy-3-nitro-4,5-dibromophenyl acetate.

Anal. Calc'd for $C_9H_7Br_2NO_5$: Br, 43.36. Found: Br, 43.37.

2-Methoxy-4-bromo-5-nitrophenol.—About 3 grams of the above nitrobromoacetyl derivative melting at 160–161° was hydrolyzed by warming with alcoholic solution of sodium hydroxide. The alcohol was evaporated, the residue was dissolved in water,

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[28] RAIFORD AND WICKERT, *J. Am. Chem. Soc.*, **53**, 3146 (1931).

and the liquid was acidified with hydrochloric acid. From dilute methyl alcohol the substance was deposited in canary-yellow masses that were not well crystallized, and that melted at 118–119°.

Anal. Calc'd for $C_7H_6BrNO_4$: Br, 32.25. Found: Br, 32.29.

The above phenol was further characterized by alkylation with dimethyl sulfate in the usual way. The product was crystallized from dilute alcohol from which it separated in pale yellow needles that melted at 122°, and is probably identical with the 4-bromo-5-nitroveratrol isolated by Simonsen and Rau,[24] and which melted at 123°.

2-Methoxy-3-nitro-4,5-dibromophenol.—A portion of the nitrodibromoacetyl derivative indicated above, mixed with aqueous-alcoholic sodium hydroxide, was heated on a steam bath under a return condenser until a red solution was obtained. Treatment of the latter with acid precipitated an almost quantitative yield of the phenol. By crystallization from methyl alcohol it was obtained in yellow microscopic needles that melted at 164–165°.

Anal. Calc'd for $C_7H_5Br_2NO_4$: Br, 48.93. Found: Br, 48.97.

3-Nitro-4,5-dibromoveratrol.—Three grams of the above guaiacol was dissolved in sodium hydroxide solution, and warmed to about 45°; the required amount of dimethyl sulfate was added, and the mixture was shaken frequently during an hour. The solid product separated in a yield of 93 per cent. Crystallization from alcohol gave colorless square prisms that melted at 150–151°. Cousin[29] found 149–150° for a compound of this composition which he prepared by bromination of 3-nitroveratrol and also by nitration of 4,5-dibromoveratrol, and for which he obtained satisfactory analytical data. The products are probably identical.

2-Methoxy-4,5-dibromophenyl benzoate.—Ten grams of the required guaiacol was dissolved in pyridine, cooled to 0° and shaken with slight excess of benzoyl chloride.[30] After standing for two hours the mixture was acidified, diluted with two volumes of water and allowed to stand overnight. The product was collected and extracted with dilute alkali. The yield was 98%. By crystallization from alcohol it was obtained in very small nearly colorless needles that melted at 110.5–111.5°.

Anal. Calc'd for $C_{14}H_{10}Br_2O_3$: Br, 41.45. Found: Br, 41.44.

2-Methoxy-3-nitro-4,5-dibromophenyl benzoate.—Twenty grams of the required benzoate, in finely powdered form, was slowly added with stirring, in about one hour, to 75 g.* of fuming nitric acid, the mixture was stirred for two hours longer and then poured into ice water. A yield of 80% was obtained. Crystallization from methyl alcohol gave colorless plates that melted at 116–117°.

Anal. Calc'd for $C_{14}H_9Br_2NO_5$: Br, 37.12. Found: Br, 37.16.

Five grams of the nitrobenzoate was warmed with an aqueous-alcoholic solution of sodium hydroxide until hydrolysis was complete, most of the alcohol was distilled off, the residue was cooled to 40–50° and a 25% excess of dimethyl sulfate was added dropwise with stirring which was continued for half an hour longer. The yield of product was 81%. Crystallization from alcohol gave colorless prisms that melted at 151°. The melting point of a mixture with an authentic sample of 3-nitro-4,5-dibromoveratrol (X) showed no depression.

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[29] Cousin, *Ann. chim. phys.*, [7], **13**, 505 (1898).

[30] Einhorn and Hollandt, *Ann.*, **301**, 101 (1898). The Schotten-Baumann method gave unsatisfactory results here.

* When smaller portions of acid were used the product separated as a sticky oil that could not be crystallized.

4,5,6-Tribromoguaiacol, the structure of which was established by Zangirolami,[31] was prepared as follows: One molecular proportion of guaiacol, dissolved in about half its weight of acetic acid was placed in a three-necked flask provided with a mechanical stirrer and an outlet tube connected with an absorption trap for hydrogen bromide. A solution of three molecular proportions of bromine in about an equal weight of acetic acid was dropped in at such a rate that only a small amount of free bromine was present at any time, while the mixture was stirred continuously. The first half of the bromine was added in an hour while the temperature was kept about 25°. Addition of the remainder required about two hours, and the temperature was maintained between 30° and 35° in order to keep the product in solution. The mixture was allowed to cool, the crystalline solid was filtered off and the filtrate concentrated under reduced pressure. Crystallization of the combined residues from 50% alcohol gave nearly colorless needles that melted at 115–116°.[32] The yield of purified material was 67%.

2-Methoxy-4,5,6-tribromophenyl acetate. Fifty grams of the required tribromo compound and an excess of acetic anhydride were heated on a steam bath for one and one-half hours. The yield was nearly quantitative. Crystallization from alcohol gave colorless blocks that melted at 119–120°.

Anal. Calc'd for $C_9H_7Br_3O_3$: Br, 59.55. Found: Br, 59.76.

2-Methoxy-3-nitro-4,5,6-tribromophenyl acetate.—A portion of the above dry powdered acetyl derivative was gradually added with stirring during a period of one to one and one-half hours to twice its weight of fuming nitric acid at 25–28°, the mixture was stirred for two hours longer, and then slowly poured into twice its volume of ice cold water. The average yield from several runs was 56%. Crystallization from ligroïn (65–70°) gave yellow needles that melted at 98–99°.

Anal. Calc'd for $C_9H_6Br_3NO_5$: Br, 53.57. Found: Br, 53.86.

3-Nitro-4,5,6-tribromoguaiacol.—Sixty grams of the required acetyl derivative was shaken at room temperature with slightly more than two molecular proportions of sodium hydroxide dissolved in 50% alcohol, and the resulting red liquid was acidified. The yellow oil that separated at this stage solidified when the mixture was poured into cold water and stirred. A yield of 60% was obtained. Crystallization from ligroïn (90–100°) gave nearly colorless needles that melted at 101–102°. When allowed to stand in the light this product becomes more deeply colored.

Anal. Calc'd for $C_7H_4Br_3NO_4$: Br, 59.11. Found: Br, 59.28.

2-Methoxy-3-nitro-4,5,6-tribromophenyl methyl carbonate.—Five grams of the above-described compound was dissolved in sodium hydroxide solution, shaken with 1.1 molecular proportions of methyl chlorocarbonate, and the resulting solid was collected, washed with dilute alkali, and then with water. Though the product was repeatedly crystallized from ligroïn (65–70°) from which it was deposited in colorless flakes, it showed a melting rage of 105–108°. The yield of purified material was 56%.

Anal. Calc'd for $C_9H_6Br_3NO_6$: Br, 51.72. Found: Br, 51.79.

The corresponding ethyl carbonate was prepared by the method given above. It was crystallized from petroleum ether from which it was obtained in irregular masses that melted at 93–94°. The yield of purified product was 29%.

Anal. Calc'd for $C_{10}H_8Br_3NO_6$: Br, 50.21. Found: Br, 50.28.

A third portion of the phenol was converted into the methyl ether in nearly quan-

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[31] ZANGIROLAMI, *Gazz. chim. ital.*, **62**, 570 (1932).

[32] TIEMANN AND KOPPE [*Ber.*, **14**, 2017 (1881)], who first obtained this compound, recorded 102° as the melting point; but HILL AND JENNINGS [*Am. Chem. J.*, **15**, 164 (1893)], who obtained it in a different way, found 115–116°.

titative yield by treatment with dimethyl sulfate in the usual maner. Crystallization from ligroïn (65–70°) gave fine colorless needles that melted at 122–123°.[33] Determination of halogen indicated that our product was nearly pure.

Anal. Calc'd for $C_8H_6Br_3NO_4$: Br, 57.14. Found: Br, 57.37.

2-Methoxy-4,5,6-tribromophenyl benzoate.—Thirty grams of the required tribromoguaiacol was dissolved in 50 cc. of pyridine, cooled to 0°, and shaken with excess of benzoyl chloride as previously indicated. After standing for two hours the mixture was acidified, diluted with two volumes of water, and allowed to stand overnight. The precipitate was washed with dilute alkali and then with dilute acid. A yield of 97% was obtained. Crystallization from alcohol gave hexagonal plates that melted at 148–149°.

Anal. Calc'd for $C_{14}H_9Br_3O_3$: Br, 51.61. Found: Br, 51.77.

Nitration of the benzoate.—Thirty-three grams of the required tribromo compound, in finely powdered form, was nitrated in the manner described above for the acetate, though the reaction went more slowly in this case. Preliminary examination of the product indicated that it was a mixture. Repeated extractions of it with small portions of boiling acetone made it possible to remove the more soluble compound which was obtained in a yield of 85%. This material separated in irregularly shaped crystals that melted at 140–141°. Analysis for halogen suggested a mononitro derivative. To fix its structure a portion of the 3-nitro-4,5,6-tribromoguaiacol described above, melting at 101–102°, was benzoylated. This product, after crystallization from acetone, melted at 140–141°, and a mixture melting point determination showed no depression. The product in question must be 2-methoxy-3-nitro-4,5,6-tribromophenyl benzoate.

Anal. Calc'd for $C_{14}H_8Br_3NO_5$: Br, 47.06. Found: Br, 47.22.

The residue left from the above extraction with acetone, which was obtained in yields of 3 to 4%, was crystallized from a larger portion of this solvent. It separated in the form of nearly colorless square prisms that melted 202–203°. Its structure was determined by preparing it from 3-nitro-4,5,6-tribromoguaiacol and m-nitrobenzoyl chloride. A mixture of the products melted without depression.

Anal. Calc'd for $C_{14}H_7Br_3N_2O_7$: Br, 43.24. Found: Br, 43.35.

The product in question was further identified by hydrolysis which gave 3-nitro-4,5,6-tribromoguaiacol that melts at 101–102°, as given above.

SUMMARY

1. When the 4,5-dibromo and 4,5,6-tribromo substitution products of guaiacol were treated with nitrous acid as directed by Zincke no nitro compound could be isolated. When nitric acid was used a reaction seemed to take place but again no product was obtained. Possibly complete degradation occurred.

2. Treatment of the acyl derivatives with fuming nitric acid gave nitro compounds in all instances. When the dibromo acetate was tested a mixture was obtained. In one portion the bromine atom in position 5

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[33] Cousin [*Compt. rend.*, **135**, 968 (1902)] reported 116–117° for a product which he states was obtained by nitration of 4,5,6-tribromoveratrol and also by bromination of 3-nitro-4,5-dibromoveratrol, and for which he later obtained satisfactory analytical data [*Ann. chim. phys.*, [7], **29**, 76 (1903)].

was replaced by the nitro radical, and in the other hydrogen in position 3 was substituted. In the benzoate a 3-nitro compound only was obtained. When the tribromo compounds were tested no bromine was replaced. The acetate gave the corresponding 3-nitro derivative, while the benzoate gave, in addition to the 3-nitro compound, a dinitro product in which the nitro radicals are in position 3 in each of the phenyl nuclei.

3. Additional data have been secured to support the view that acylation of hydroxyl in a benzene derivative suppresses its directive influence.

4. Further work is in progress.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

PHENANTHRENE DERIVATIVES. VIII. HEXAARYLETHANES CONTAINING THE PHENANTHRENE NUCLEUS*

W. E. BACHMANN AND M. C. KLOETZEL

Received September 17, 1937

Although attempts have been made to explain the spontaneous reversible dissociation of colorless hexaarylethanes into colored triarylmethyl radicals, no theory has as yet been entirely satisfactory. According to the conception of steric hindrance the aryl groups, in virtue of their size, prevent the aliphatic carbon atoms from approaching each other closely enough to form a normal carbon-carbon bond. Only roughly, however, does the parallelism between extent of dissociation and size of the aryl groups hold. The more recent resonance theory approaches the problem from the opposite point of view. According to this theory dissociation is attributed not to the weakness of the carbon-carbon bond but to the stability of the radicals produced on dissociation. On this assumption, Pauling and Wheland[1] have attempted to show that as the number of possible resonance structures for the radical increases so also does the extent of dissociation of the corresponding hexaarylethane increase. Although a considerable amount of experimental data has been correlated by them, the theory must still be considered qualitative in nature. A combination of steric hindrance and resonance appears to account for the dissociation in a more satisfactory manner.[2]

From the standpoint of both steric hindrance and resonance a study of the dissociation-promoting effect of the phenanthrene nucleus appeared particularly attractive. Indeed, Ingold[3] has recently predicted that the 9-phenanthryl group should possess a greater dissociating power than any group previously investigated. The phenanthrene nucleus provides the additional opportunity of studying the effect on dissociation of isomeric

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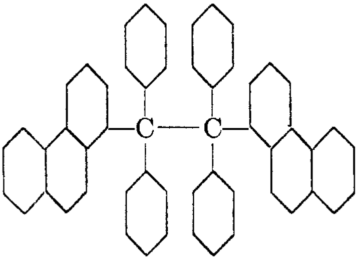
* From the Ph. D. dissertation of M. C. Kloetzel.

[1] PAULING AND WHELAND, *J. Chem. Phys.*, **1**, 362–374 (1933).

[2] BENT, CUTHBERTSON, DORFMAN, AND LEARY, *J. Am. Chem. Soc.*, **58**, 165–170 (1936); BENT AND CUTHBERTSON, *ibid.*, **58**, 170–173 (1936); BENT AND CLINE, *ibid.*, **58**, 1624–1627 (1936).

[3] INGOLD, *Trans. Faraday Soc.*, **30**, 52–57 (1934). From resonance considerations Ingold has predicted the order of decreasing effect of aryl groups in promotion of radical stability to be; 9-phenanthryl, α-anthryl, α-naphthyl, β-naphthyl, *p*-biphenyl, *m*-biphenyl, phenyl.

linkage to the aliphatic carbon atom. We have, accordingly, undertaken the synthesis and determination of the extent of dissociation of the following hexaarylethanes: *sym*-di-1-phenanthryltetraphenylethane (I), *sym*-di-2-phenanthryltetraphenylethane (II), *sym*-di-3-phenanthryltetraphenylethane (III), *sym*-di-9-phenanthryltetraphenylethane (IV) and *sym*-di-9-phenanthryldibiphenyleneethane (V).



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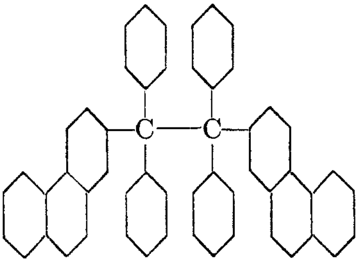

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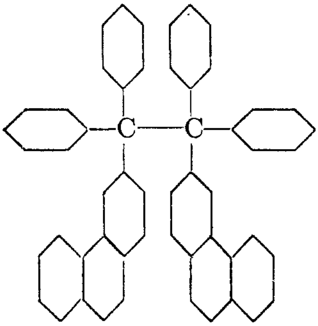

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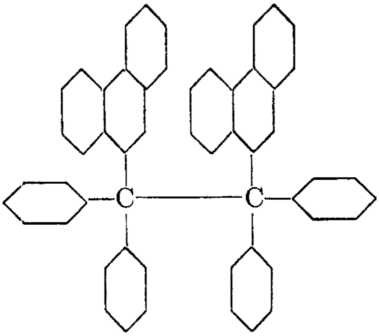

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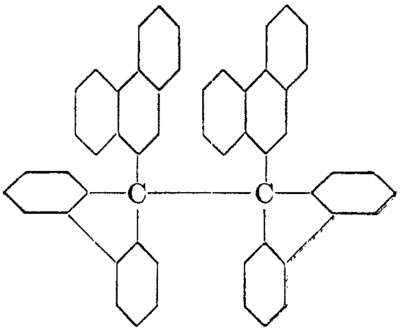
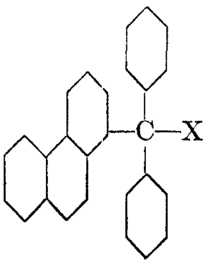


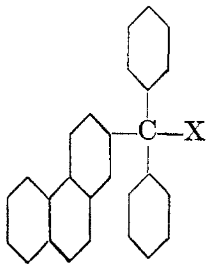
(V)

SYNTHESIS OF PHENANTHRYLDIARYLMETHANE DERIVATIVES

In formulas VI-X inclusive are represented the compounds that were prepared either as intermediates or for purposes of characterization.



(VI)



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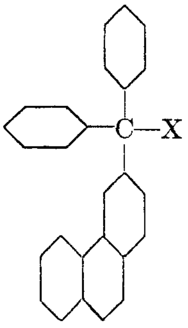

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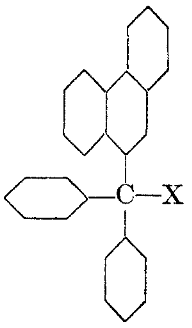

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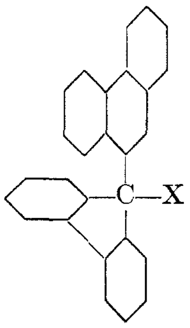

(X)

(*a*) X = OH
(*b*) X = Cl
(*c*) X = OCH_3
(*d*) X = OC_2H_5
(*e*) X = Na
(*f*) X = H
(*g*) X = COOH

The triarylcarbinols (X = OH) were obtained through the Grignard reaction. 1-Phenanthryldiphenylcarbinol (VI*a*) was prepared by interaction of phenylmagnesium bromide and 1-benzoylphenanthrene. The latter ketone is formed when phenanthrene is benzoylated according to the Perrier modification of the Friedel-Crafts reaction.[4] We have now found that 9-benzoylphenanthrene is formed at the same time in approximately equal amounts. 2-Phenanthryldiphenylcarbinol (VII*a*) and 3-phenanthryldiphenylcarbinol (VIII*a*) were obtained by interaction of phenylmagnesium bromide and the methyl esters of the corresponding phenanthroic acids. 9-Phenanthryldiphenylcarbinol (IX*a*) and 9-phen-

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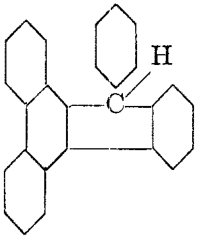
[4] Bachmann, *J. Am. Chem. Soc.*, **57**, 555-559 (1935).

anthrylbiphenylenecarbinol (X*a*) were most conveniently prepared from 9-phenanthrylmagnesium bromide and benzophenone and fluorenone respectively.

The triarylchloromethanes (X = Cl), with the exception of 9-phenanthryldiphenylchloromethane, were prepared from the carbinols by means of hot acetyl chloride. When heated with acetyl chloride, 9-phenanthryldiphenylcarbinol was converted by loss of a molecule of water into 1,2,3,4-dibenzo-9-phenylfluorene (XI); the triarylchloromethane was obtained by treating the powdered carbinol with cold acetyl chloride. For purposes of characterization the methyl ethers (X = OCH_3) and the ethyl ethers (X = OC_2H_5) of the carbinols were prepared, usually from the triarylchloromethane and sodium alcoholate, in a few instances also from the triarylchloromethane and the alcohol. By reaction with 45 per cent. sodium amalgam the methyl ethers of the carbinols yielded the intensely colored triarylmethylsodium compounds (X = Na), from which the triarylmethanes (X = H) were obtained by reaction with alcohol, and the triarylacetic acids (X = COOH) by reaction with carbon dioxide. The triarylmethanes were also prepared by reduction of the triarylcarbinols by hydriodic acid.



(XI)

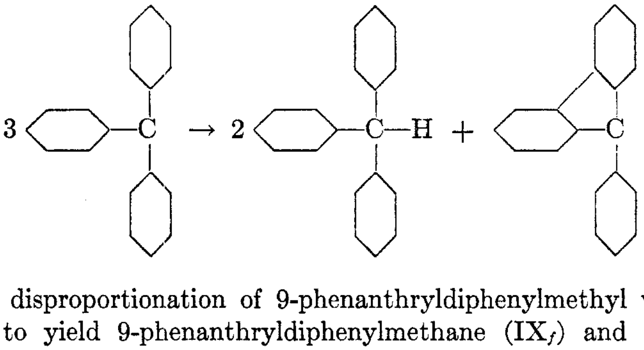
PREPARATION OF THE FREE RADICALS

By shaking a benzene solution of 1-, 2-, or 3-phenanthryldiphenylchloromethane with "molecular" silver a red solution of the equilibrium mixture of free radical and hexaarylethane was obtained. The radicals, 1-phenanthryldiphenylmethyl, 2-phenanthryldiphenylmethyl and 3-phenanthryldiphenylmethyl, rapidly absorbed oxygen of the air to give crystalline triarylmethyl peroxides. The 2-phenanthryldiphenylmethyl and 3-phenanthryldiphenylmethyl were also tested for their reaction toward iodine; it was found that in dilute solutions the radicals absorbed 63–69 per cent. of the theoretical amount of iodine necessary to form the triarylmethyl iodide, the reaction being reversible. Solutions of the radicals were found to be relatively stable; they could be kept a week or two without deterioration when protected from light. Of the three hexaarylethanes only *sym*-di-3-phenanthryltetraphenylethane (III) was isolated in a crystalline form.

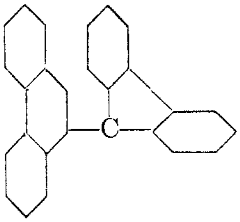
From the standpoint of testing Ingold's prediction in regard to the effectiveness of the 9-phenanthryl group in promoting dissociation, it was unfortunate that 9-phenanthryldiphenylmethyl proved to be an unstable radical. Silver abstracted the halogen quantitatively from 9-phenanthryldiphenylchloromethane (IX*b*) to give a deep-brown-red solution. On standing in the dark, at least half of the hexaarylethane decomposed in thirty minutes, undoubtedly through the radical stage, and after seventy-two hours the solution had lost its color. That all of the triarylchloromethane had been initially converted to the radical was shown by shaking a solution of 9-phenanthryldiphenylchloromethane with silver in the presence of oxygen. Under these conditions the theoretical volume of oxygen was absorbed and crystalline bis(9-phenanthryldiphenylmethyl) peroxide was isolated in excellent yield from the reaction mixture. The reaction between 9-phenanthryldiphenylchloromethane and silver follows the normal course to give the radical 9-phenanthryldiphenylmethyl, which then spontaneously decomposes. The same decomposition was observed to take place when the radical was prepared from 9-phenanthryldiphenylmethylsodium by means of tetramethylethylene bromide according to the following formulation.

$$2\ (C_{14}H_9)(C_6H_5)_2C{-}Na + (CH_3)_2BrC{-}CBr(CH_3)_2 \rightarrow 2\ (C_{14}H_9)(C_6H_5)_2C + (CH_3)_2C{=}C(CH_3)_2 + 2NaBr.$$

Attempts to determine the structure of the product formed in the decomposition reaction were unsuccessful. One of the characteristic reactions of triarylmethyls is disproportionation. With triphenylmethyl the following reaction takes place:



A similar disproportionation of 9-phenanthryldiphenylmethyl would be expected to yield 9-phenanthryldiphenylmethane (IX*f*) and either 9-phenanthrylbiphenylenemethyl (XII) or 1,2,3,4-dibenzo-9-phenylfluoryl (XIII). None of these compounds, however, was formed. Moreover,



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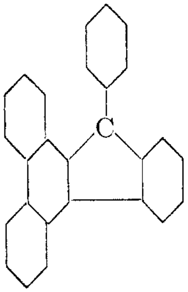

(XIII)

molecular weight determinations made on the product which was isolated to the extent of 96 per cent. showed it to be a dimer of the radical, and it appears likely that 9-phenanthryldiphenylmethyl dimerizes in the same way that triphenylmethyl condenses to give *p*-benzhydryltetraphenylmethane, $2(C_6H_5)_3C \rightarrow (C_6H_5)_2CH—C_6H_4—C(C_6H_5)_3$. Since a number of structures are possible for a dimer of this type from the radical containing the phenanthryl group, no further attempt was made to elucidate the structure. In an attempt to obtain a more stable radical containing the 9-phenanthryl group, *sym*-di-9-phenanthryldibiphenyleneethane (V) was prepared, but the 9-phenanthrylbiphenylenemethyl radical formed from it by dissociation likewise proved to be too unstable to allow a determination of the extent of dissociation of the hexaarylethane.

THE EXTENT OF DISSOCIATION OF THE HEXAARYLETHANES

The extent of dissociation was calculated from the apparent molecular weight of the hexaarylethane as determined by the cryoscopic method. Our first experiments were carried out with the crystalline *sym*-di-3-phenanthryltetraphenylethane (III). The results obtained on different samples of the hexaarylethane were extremely erratic; thus, in nitrobenzene the results indicated 82–134 per cent. dissociation of the hexaarylethane, although the original concentration of the latter was the same in all of the determinations. These results could only be caused by incomplete removal of the solvent from the crystalline hexaarylethane, although the compound was dried at 60° under reduced pressure. Hexaarylethanes are known to form additive compounds with a variety of solvents; among these benzene is noted for the great affinity with which it is held in combination. Addition of acetone to a concentrated benzene solution of hexaphenylethane results in the separation of crystalline hexaphenylethane containing benzene of crystallization,[5] and these are precisely the conditions which obtain in the crystallization of *sym*-di-3-phenanthryl-

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[5] Gomberg, *ibid.*, **24**, 601 (1902).

tetraphenylethane. Müller, Müller-Rodloff, and Bunge[6] found it necessary to heat solid tri-*p*-biphenylmethyl to 155–160° in order to free the compound of benzene, and the closely related pentaarylethanes containing the *p*-biphenyl group had to be fused under reduced pressure in order to

TABLE I

Dissociation of Hexaarylethanes

(Temperature, 5°C.; Concentration, 1.5-3.0%)

HEXAARYLETHANE	SOLVENT	DISSOC., %
sym-Di-1-phenanthryltetraphenylethane	Benzene	32–36
	Nitrobenzene	33–37
sym-Di-2-phenanthryltetraphenylethane	Benzene	16–17
	Nitrobenzene	30–37
sym-Di-3-phenanthryltetraphenylethane	Benzene	11–12
	Nitrobenzene	14
sym-Di-α-naphthyltetraphenylethane	Benzene	28–31[a]
	Nitrobenzene	28–36[b]
sym-Di-β-naphthyltetraphenylethane	Benzene	7–9[c]
sym-Di-*p*-biphenyltetraphenylethane	Benzene	16[d]

[a] Values of 57–62% were obtained by Schlenk and Renning, *Ann.*, **394**, 193 (1912), who isolated the hexaarylethane.

[b] Values of 66–79% were obtained by Gomberg and Schoepfle, *J. Am. Chem. Soc.*, **41**, 1655–76 (1919), using the crystalline hexaarylethane.

[c] Values of 27–34% were reported by Gomberg and Sullivan, *J. Am. Chem. Soc.*, **44**, 1810-33 (1922), who employed the crystalline hexaarylethane.

[d] Schlenk, Weickel, and Herzenstein, *Ann.*, **394**, 186 (1912), estimated that this hexaarylethane was approximately 15% dissociated at "ordinary temperatures", although they made no determination of its molecular weight. We also made some determinations of the molecular weight of hexa-*p*-biphenylethane by the indirect method. Schlenk and Weickel, *Ann.*, **372**, 5 (1910), reported that the hexaarylethane was completely dissociated in benzene solutions of 1.43%, 2.28% and 3.33% concentration. In benzene containing 0.93% of the hexaarylethane we found 74% dissociation; in nitrobenzene of 1.05% concentration the degree of dissociation was found to be 65%. The depressions in the freezing points of the solvents with these concentrations are, however, rather small (0.13° and 0.09°). When we attempted to employ concentrations of 2.28%, the concentration of Schlenk and Weickel, some of the hexaarylethane crystallized from the solution in the form of long needles. In the colored solution these crystals appeared to be colorless, but we were unable to obtain them colorless in the dry state.

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[6] Müller, Müller-Rodloff, and Bunge, *Ann* **520**, 251 (1935).

remove solvent of crystallization.[7] Unfortunately, hexaarylethanes are thermally unstable. They should not be heated above 60–70° during the drying process, and this temperature does not always suffice for complete removal of solvent of crystallization. In order to obviate this difficulty we have resorted to the indirect method of determining the apparent molecular weights which does not involve the crystallization of the hexaarylethanes.[8] We have also used the indirect method to determine the extent of dissociation of *sym*-di-α-naphthyltetraphenylethane, *sym*-di-β-naphthyltetraphenylethane and of *sym*-di-*p*-biphenyltetraphenylethane.

A solution containing a weighed amount of phenanthryldiphenylchloromethane in a known weight of solvent was shaken with silver in a nitrogen atmosphere until reaction was complete. A weighed portion of the filtered solution was transferred to the cryoscopic apparatus and the freezing point of the solution was determined. By comparison of this value with the freezing point of the solvent the apparent molecular weight of the hexaarylethane, and from it the extent of dissociation, were calculated. The results of the determinations are shown in Table I.

From the values in Table I it is apparent that the 1- and 2-phenanthryl groups are much more effective than the 3-phenanthryl group in promoting the dissociation of hexaarylethanes. Except for the low values obtained for *sym*-di-2-phenanthryltetraphenylethane in benzene, the substitution of nitrobenzene for benzene had little effect on the degree of dissociation. The 1-phenanthryl,2-phenanthryl and α-naphthyl groups possess a greater dissociating effect than the *p*-biphenyl and 3-phenanthryl groups, and the latter two groups are more effective than the β-naphthyl group. In comparison with other aromatic groups, the 1-phenanthryl, 2-phenanthryl, and α-naphthyl groups can be said to be most effective of all single groups so far investigated in promoting the dissociation of hexaarylethanes.

One of us (M. C. K.) is indebted to the Monsanto Chemical Works for the grant of a fellowship, and to Professor M. Gomberg for his interest and guidance in part of this investigation.

EXPERIMENTAL

1- and 9-Benzoylphenanthrene.—1-Benzoylphenanthrene was prepared from phenanthrene and benzoyl chloride according to the procedure of Bachmann.[4] The by-product gradually crystallized in large prisms. These were purified by recrystallization from ether, and proved to be 9-benzoylphenanthrene; yield, 6%; m.p. 79-81°. Mixed with 9-benzoylphenanthrene prepared from 9-cyanophenanthrene, the melting point was unchanged.

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[7] BACHMANN AND WISELOGLE, *J. Org. Chem.*, **1**, 373 (1936).

[8] GOMBERG AND CONE, *Ber.*, **37**, 2033–2051 (1904).

1-Phenanthryldiphenylcarbinol (*VI*a).—To a solution of the Grignard reagent prepared from 31.4 g. of bromobenzene in 100 cc. of anhydrous ether was added 28.1 g. of 1-benzoylphenanthrene dissolved in 75 cc. of anhydrous benzene. The mixture was refluxed for six hours, cooled and hydrolyzed with aqueous ammonium chloride. Recrystallization of the residue obtained by evaporation of the benzene-ether layer yielded the carbinol. 1-Phenanthryldiphenylcarbinol crystallizes from benzene-petroleum ether in colorless prisms; m.p. 163–164°; yield, 84%. The carbinol gives a blue-green color with concentrated sulfuric acid.

Anal. Calc'd for $C_{27}H_{20}O$: C, 90.0; H, 5.6.
Found: C, 90.6; H, 5.4.

1-Phenanthryldiphenylchloromethane.—A solution of 15 g. of 1-phenanthryldiphenylcarbinol in 40 cc. of acetyl chloride and 100 cc. of anhydrous benzene was refluxed for eighteen hours. After 50 cc. of solvent was distilled off, 100 cc. of petroleum ether (60–75°) was added. On cooling, 14.6 g. of the carbinol chloride crystallized; an additional quantity, making a total yield of 97%, was obtained by concentration. 1-Phenanthryldiphenylchloromethane crystallizes from benzene in colorless, rectangular prisms; m.p. 212° dec.

Anal. Calc'd for $C_{27}H_{19}Cl$:Cl, 9.4. Found: Cl, 9.2.

Although the chloride forms colored coördination compounds with stannic chloride, ferric chloride and zinc chloride, none of these was obtained in the crystalline form.

Methyl ether of 1-phenanthryldiphenylcarbinol.—To a solution of 4 g. of 1-phenanthryldiphenylchloromethane in 30 cc. of anhydrous benzene was added a solution of 0.8 g. of sodium in 20 cc. of methanol. A precipitate of sodium chloride was immediately produced on mixing. After being refluxed for thirty minutes the mixture was poured into water and the benzene layer was washed, dried and evaporated. The methyl ether crystallizes from acetone-methanol in colorless, hexagonal plates; m.p. 198–199°; yield, 88%.

Anal. Calc'd for $C_{28}H_{22}O$: C, 89.8; H, 5.9.
Found: C, 89.9; H, 5.9.

The *ethyl ether of 1-phenanthryldiphenylcarbinol*, prepared in the same manner as the methyl ether, crystallizes from acetone-ethanol in thin, colorless plates; m.p. 151–152°; yield, 87%.

Anal. Calc'd for $C_{29}H_{24}O$: C, 89.6; H, 6.2.
Found: C, 89.9; H, 6.3.

1-Phenanthryldiphenylmethane.—A mixture of 0.8 g. of the methyl ether of 1-phenanthryldiphenylcarbinol, 30 cc. of anhydrous benzene, 20 cc. of anhydrous ether and 3 g. of 45% sodium amalgam was shaken for eighteen hours in a glass-stoppered cylinder in a nitrogen atmosphere. After freezing the amalgam, 0.5 cc. of ethanol was added to the intense-green solution of 1-phenanthryldiphenylmethylsodium. The resulting decolorized solution was poured into water, the ether solution was dried and the solvent was evaporated. By recrystallization of the residue from benzene-ethanol the 1-phenanthryldiphenylmethane was obtained in 91% yield as colorless prisms; m.p. 175–176°.

Anal. Calc'd for $C_{27}H_{20}$: C, 94.1; H. 5.9.
Found: C, 94.4; H, 5.9.

1-Phenanthryldiphenylacetic acid.—Dry carbon dioxide was passed into a solution of 1-phenanthryldiphenylmethylsodium, prepared from 1.0 g. of the methyl ether, until the color of the organosodium derivative had completely disappeared. The solution was shaken with dilute hydrochloric acid and the benzene solution was separated, concentrated and treated with petroleum ether, whereupon the 1-phenanthryldiphenylacetic acid crystallized; yield, 87%. By another recrystallization from benzene-petroleum ether the acid was obtained as clusters of colorless needles; m.p. 230–232° dec.

Anal. Calc'd for $C_{28}H_{20}O_2$: C, 86.6; H, 5.2.
Found: C, 86.7; H, 5.2.

sym-*Di-1-phenanthryltetraphenylethane* (*I*).—A mixture of 3 g. of 1-phenanthryldiphenylchloromethane, 3 g. of "molecular" silver[9] (100 mesh) and 50 cc. of dry benzene was shaken for four days in a glass-stoppered cylinder protected from light. All operations involving the free radical were conducted in an atmosphere of carbon dioxide or nitrogen. The deep-red solution was transferred to a bulb and the benzene was distilled off at 43–48° under reduced pressure. The bulb was of the type previously described by Gomberg,[8] modified by the introduction of a ground-glass joint to facilitate removal of the crystalline hexaarylethane. Another small ground-glass joint, connected to a three-way stopcock through which the benzene was distilled off, was sealed onto the upper part of the bulb.

A solution of the residual red oil in 2 cc. of acetone did not deposit any crystals after standing at 0° for forty-eight hours, and addition of 1 cc. of hexane precipitated the hexaarylethane as a red oil which could not be induced to crystallize.

That the reaction of 1-phenanthryldiphenylchloromethane and silver quickly went to completion, resulting in a stable solution of *sym*-di-1-phenanthryltetraphenylethane, was shown by the following oxygen absorption experiments. A solution of 0.7 g. of the carbinol chloride in 12 cc. of bromobenzene was shaken with 0.7 g. of silver and the oxygen absorption was determined by means of the standard apparatus.[10] After being shaken for one hour, the solution absorbed the calculated volume of oxygen within two minutes. After shaking a sample for ninety-six hours, the solution still absorbed the calculated volume of oxygen.

Bis(1-phenanthryldiphenylmethyl) peroxide was obtained when a benzene solution of *sym*-di-1-phenanthryltetraphenylethane, prepared from 0.96 g. of the carbinol chloride, was filtered from silver and silver chloride and exposed to air. The red solution quickly became pale yellow and deposited colorless crystals of the peroxide. After evaporation of the solvent and removal of colored impurities with ether the peroxide weighed 0.65 g. (72% yield). After recrystallization from carbon disulfide the peroxide melted at 175–176° with decomposition. The peroxide is extremely insoluble in all ordinary solvents.

Anal. Calc'd for $C_{54}H_{38}O_2$: C, 90.2; H, 5.3.
Found: C, 89.9; H, 5.3.

2-Phenanthryldiphenylcarbinol (*VII*a).—To the Grignard reagent prepared from 32 g. of bromobenzene in 100 cc. of anhydrous ether was added a solution of 13.6 g. of methyl 2-phenanthroate[11] in 125 cc. of anhydrous benzene. After being refluxed for eight hours, the mixture, which contained a yellow addition product, was hydrolyzed with aqueous ammonium chloride. On addition of petroleum ether to the concentrated benzene extract, the 2-phenanthryldiphenylcarbinol crystallized. Recrystallization from benzene-petroleum ether gave colorless crystals of the carbinol; m.p. 174–175°; yield, 88%. This carbinol has been previously prepared by another method.[4]

2-Phenanthryldiphenylchloromethane was prepared in the same manner as its 1-isomer by warming for one hour a mixture of 15 g. of 2-phenanthryldiphenylcar-

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[9] GOMBERG AND CONE, *ibid.*, **39**, 3286 (1906).

[10] GOMBERG AND SCHOEPFLE, *J. Am. Chem. Soc.*, **39**, 1661 (1917).

[11] MOSETTIG AND VAN DE KAMP, *ibid.*, **52**, 3707 (1930).

binol, 15 cc. of acetyl chloride and 75 cc. of anhydrous benzene. 2-Phenanthryldiphenylchloromethane crystallizes from benzene-petroleum ether in clumps of colorless needles; m.p. 160–161°; yield, 96%.

Anal. Calc'd for $C_{27}H_{19}Cl$: Cl, 9.4.
Found: Cl, 9.1.

Coördination compounds of 2-phenanthryldiphenylchloromethane with metal halides.—When 0.01 g. of 2-phenanthryldiphenylchloromethane was dissolved in 5 cc. of a saturated benzene solution of mercuric chloride and the solution was allowed to stand in the cold for several days, the coördination compound crystallized as brown, iridescent needles. Similarly, the red stannic chloride addition compound was obtained in the crystalline form by adding a drop of 18% benzene solution of stannic chloride to the carbinol chloride in benzene. Intensely colored oils were obtained under similar conditions with ferric chloride and zinc chloride, but these could not be induced to crystallize.

The *methyl ether of 2-phenanthryldiphenylcarbinol* was prepared in 75% yield by exactly the same method as its 1-isomer. It was also prepared by refluxing for two hours a mixture of 1 g. of 2-phenanthryldiphenylcarbinol, 50 cc. of methanol and three drops of concentrated sulfuric acid. On cooling of the solution the methyl ether crystallized in 73% yield. The compound is dimorphic: on recrystallization from acetone-methanol it was obtained as long, colorless needles melting at 105–106°; recrystallized from acetone-petroleum ether (60–75°) it formed truncated octahedra melting at 111–112°.

Anal. Calc'd for $C_{28}H_{22}O$: C, 89.8; H, 5.9.
Found: C, 90.0; H, 6.1.

The *ethyl ether of 2-phenanthryldiphenylcarbinol* was prepared according to the procedure described for its 1-isomer, and crystallizes from petroleum ether in large, colorless prisms; m.p. 116–117° yield, 50%.

Anal. Calc'd for $C_{29}H_{24}O$: C, 89.6; H, 6.2.
Found: C, 89.7; H, 6.0.

2-Phenanthryldiphenylmethane was prepared in two ways. An intensely purple-red solution of 2-phenanthryldiphenylmethylsodium was formed by shaking a mixture of 0.75 g. of the methyl ether of 2-phenanthryldiphenylcarbinol and 2.5 g. of 45% sodium amalgam in 25 cc. of anhydrous ether and 25 cc. of anhydrous benzene. After twenty-four hours the amalgam was frozen and enough ethanol was added to decolorize the solution. 2-Phenanthryldiphenylmethane crystallizes from benzene-ethanol in long, colorless needles; m.p. 151–152°; yield, 91%.

The same hydrocarbon was obtained when 2-phenanthryldiphenylcarbinol was reduced with hydriodic acid. A solution of 1 g. of the carbinol in 20 cc. of acetic acid was refluxed for thirty minutes with 2 cc. of hydriodic acid (sp. g. 1.7). Sulfur dioxide was passed into the hot solution in order to remove the iodine which was liberated in the reaction. On being cooled, the solution deposited the 2-phenanthryldiphenylmethane; yield, 77%.

Anal. Calc'd for $C_{27}H_{20}$: C, 94.1; H, 5.9.
Found: C, 94.4; H, 5.9.

2-Phenanthryldiphenylacetic acid was prepared from 2-phenanthryldiphenylmethylsodium in the same manner as described for the 1-isomer. The acid crystallizes from acetic acid in colorless, columnar prisms containing solvent of crystallization; m.p. 232–233°; yield, 82%.

Anal. Calc'd for $C_{28}H_{20}O_2$: C, 86.6; H, 5.2.
Found: C, 86.8; H, 5.1.

sym-*Di-2-phenanthryltetraphenylethane* (*II*).—A cherry-red solution of the radical was obtained by shaking for four days a mixture of 3 g. of 2-phenanthryldiphenylchloromethane and 3 g. of "molecular" silver in 50 cc. of benzene. Oxygen absorption experiments indicated that reaction was complete after this period of time. When three times the amount of silver was used, two hours sufficed for complete reaction. Evaporation of the filtered solution as described for the 1-isomer left a red oil. All attempts to induce crystallization of the oil from acetone, benzene, ethyl acetate, or chloroform resulted in failure. Addition of hexane or methanol, in which the hexaarylethane is extremely insoluble, to solutions of the oil in any of the above solvents always caused deposition of a red oil. When the residual red oil was dissolved in 2 cc. of ether, gummy and poorly-defined crystals were obtained on standing at 0° for twelve hours. All of the solvent could not be removed from the crystals by heating to 60° under reduced pressure, and heating to 100° caused decomposition.

A solution of the radical prepared from 2.0 g. of the carbinol chloride in 50 cc. of benzene absorbed 21.0 cc. (62.7%) of a solution of iodine in benzene (0.02 g. per cc.).

Bis(2-phenanthryldiphenylmethyl) peroxide[4] was obtained in 79% yield by oxidation of the radical with air. A solution of the radical allowed to stand in the dark for six months gave only a 40% yield of the peroxide, an indication that approximately 50% of the radical had undergone decomposition in this period of time.

3-Phenanthryldiphenylcarbinol (*VIII*a).—To the Grignard reagent prepared from 53 g. of bromobenzene in 160 cc. of anhydrous ether was added a solution of 25 g. of methyl 3-phenanthroate[11] in 145 cc. of anhydrous benzene. After being refluxed for eight hours, the mixture was hydrolyzed with aqueous ammonium chloride. From acetone-petroleum ether the carbinol crystallizes in colorless, columnar needles containing solvent of crystallization; m.p. 92–93°; yield, 82%. When the carbinol is crystallized from petroleum ether alone the melting point is raised to 100–102°.

Anal. Calc'd for $C_{27}H_{20}O$: C, 90.0; H, 5.6.
Found: C, 90.3; H, 5.6.

This carbinol produces an intensely purple-blue color with concentrated sulfuric acid. The compound previously described[4] as 3-phenanthryldiphenylcarbinol was in reality the methyl ether of this carbinol, which was probably produced when the carbinol was crystallized in the presence of methanol.

3-Phenanthryldiphenylchloromethane, prepared in the same manner as described for the 2-isomer, crystallizes from benzene-petroleum ether in colorless, rectangular prisms; m.p. 132.5–133.5°; yield, 88%.

Anal. Calc'd for $C_{27}H_{19}Cl$: Cl, 9.4. Found: Cl, 9.3.

A sample of this 3-phenanthryldiphenylchloromethane gave on hydrolysis the carbinol melting at 92–93° after recrystallization from acetone-petroleum ether.

Treated with stannic chloride as described for the 2-isomer, 3-phenanthryldiphenylchloromethane produced a coördination compound in the form of small, deep-red plates having a purple iridescence. The ferric chloride compound was obtained as broad, red, iridescent needles by adding a saturated ethyl acetate solution of ferric chloride to the carbinol chloride in benzene, and the zinc chloride compound separated as small, brown crystals when a 6% ether solution of zinc chloride was added to the carbinol chloride in benzene.

The *methyl ether of 3-phenanthryldiphenylcarbinol*, prepared in 88% yield by the Williamson method as described for the 1-isomer, crystallizes from acetone-methanol in colorless, glistening plates; m.p. 147–148°. The same ether was prepared by refluxing for two hours a solution of 3 g. of 3-phenanthryldiphenylcarbinol in 125 cc.

of methanol containing nine drops of concentrated sulfuric acid. On cooling, the ether crystallized in 87% yield.

Anal. Calc'd for $C_{28}H_{22}O$: C, 89.8; H, 5.9.
Found: C, 90.1; H, 5.8.

The *ethyl ether of 3-phenanthryldiphenylcarbinol* was prepared by refluxing for two hours a solution of 1.8 g. of 3-phenanthryldiphenylcarbinol in 80 cc. of ethanol containing six drops of concentrated sulfuric acid. On cooling and concentrating the solution, a 90% yield of the ether was obtained. The ethyl ether crystallizes from acetone-ethanol in colorless needles; m.p. 155-156°.

Anal. Calc'd for $C_{29}H_{24}O$: C, 89.6; H, 6.2.
Found: C, 89.9; H, 6.3.

3-Phenanthryldiphenylmethane was prepared from the intensely purple-red 3-phenanthryldiphenylmethylsodium in the same manner as described for the 2-isomer. The hydrocarbon crystallizes from benzene-ethanol in long, flat, colorless needles; m.p. 122–123°; yield, 83%. 3-Phenanthryldiphenylmethane was also prepared by reduction of 3-phenanthryldiphenylcarbinol by hydriodic acid in the manner described for the 2-isomer.

Anal. Calc'd for $C_{27}H_{20}$: C, 94.1; H, 5.9.
Found: C, 94.3; H, 6.2.

3-Phenanthryldiphenylacetic acid was prepared by the method described for the 1-isomer. Crystallization of the acid from acetic acid produced clusters of colorless needles containing solvent of crystallization which was tenaciously held; yield, 63%. From benzene-petroleum ether the acid was obtained also as needles; m.p. 215-216°.

Anal. Calc'd for $C_{28}H_{20}O_2$: C, 86.6; H, 5.2.
Found: C. 87.0; H, 5.3.

sym-*Di-3-phenanthryltetraphenylethane* (*III*).—A deep-red benzene solution of the radical-ethane equilibrium mixture was prepared from 3 g. of 3-phenanthryldiphenylchloromethane as described for the 1-isomer. The viscous red oil remaining after removal of the benzene under reduced pressure was dissolved in 2 cc. of warm acetone and the hexaarylethane was allowed to crystallize at 0° for twelve hours. The crystalline material was washed several times with cold acetone and finally dried under reduced pressure in a stream of carbon dioxide; m.p. 150-152° dec. (in nitrogen); yield, 2.28 g. (85%). Although the crystalline material was practically colorless when freshly prepared, it rapidly became yellow when exposed to air.

The crystalline hexaarylethane, when dissolved in bromobenzene, absorbed the calculated volume of oxygen at room temperature within two minutes.

A solution of the hexaarylethane prepared from 1.0 g. of the carbinol chloride in 50 cc. of benzene decolorized 11.5 cc. of a benzene solution of iodine (0.02 g. per cc.). This corresponds to 68.6% absorption. When excess iodine was added, the solution became green and a dark oil, presumably a periodide[5] of 3-phenanthryldiphenyliodomethane, was deposited, which crystallized on standing.

Bis(3-phenanthryldiphenylmethyl) peroxide[4] was obtained in 85% yield by oxidation of a benzene solution of the hexaarylethane with air. A solution of the hexaarylethane which was allowed to stand in the dark for six months gave only a 69% yield of peroxide, an indication that approximately 19% of the hexaarylethane had undergone decomposition during this period of time. The peroxide was best recrystallized from amyl acetate; m.p. 197°.

9-Phenanthryldiphenylchloromethane (*IX*b).—When an attempt was made to prepare this chloride by heating the carbinol[12] with acetyl chloride, there was obtained

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[12] BACHMANN, *ibid.*, **56**, 1363-1367 (1934).

a good yield of 1,2,3,4-dibenzo-9-phenylfluorene. When the carbinol was treated with dry hydrogen chloride in ether there was also apparently some fluorenation, as the resulting product (m.p. 162–170°) did not contain the calculated amount of chlorine.

9-Phenanthryldiphenylchloromethane was finally successfully prepared by the following method. To 30 g. of the finely powdered 9-phenanthryldiphenylcarbinol was added 75 cc. of acetyl chloride. A reaction soon began and the mixture became warm. It was stirred for a few minutes and then allowed to stand at 0° for two hours. The chloride was filtered off, shaken with petroleum ether for two hours, and again filtered. When all traces of acetyl chloride had been removed in this manner the carbinol chloride could be recrystallized without decomposition from benzene-petroleum ether, and was obtained as colorless, columnar needles; m.p. 182–183° dec.; yield, 80%.

Anal. Calc'd for $C_{27}H_{19}Cl$: Cl, 9.4. Found: Cl, 9.0.

Coördination compounds of this halide could not be prepared, as in every instance fluorenation took place when a solution of the carbinol chloride was allowed to stand in contact with stannic chloride, ferric chloride or zinc chloride.

The *methyl ether of 9-phenanthryldiphenylcarbinol* was prepared in the usual manner from sodium methylate and 9-phenanthryldiphenylchloromethane; yield, 90%. The ether crystallizes from acetone-methanol in colorless, glistening prisms; m.p. 165°.

Anal. Calc'd for $C_{28}H_{22}O$: C, 89.8; H, 5.9.
Found: C, 89.8; H, 5.8.

The *ethyl ether of 9-phenanthryldiphenylcarbinol* was obtained from sodium ethylate and the carbinol chloride. Recrystallization from acetone-petroleum ether gave thin, colorless plates; m.p. 139–140°; yield, 42%.

Anal. Calc'd for $C_{29}H_{24}O$: C, 89.6; H, 6.2.
Found: C, 89.4; H, 6.1.

9-Phenanthryldiphenylmethane was prepared from the intensely green 9-phenanthryldiphenylmethylsodium in the same manner as described for the 2-isomer. The hydrocarbon crystallizes from benzene-ethanol in colorless needles; m.p. 174–175°; yield, 88%. 9-Phenanthryldiphenylmethane has been recently prepared from 9-bromophenanthrene and diphenylbromomethane.[12]

9-Phenanthryldiphenylacetic acid was prepared in the same manner as described for the preparation of the 1-isomer. Crystallization from acetic acid produced long, colorless needles which lost solvent of crystallization at approximately 130° and then melted at 257–259° dec.; yield, 96%.

Anal. Calc'd for $C_{28}H_{20}O_2$: C, 86.6; H, 5.2.
Found: C, 86.2; H, 5.0.

sym-*Di-9-phenanthryltetraphenylethane* (*IV*).—When a mixture of 0.8583 g. of 9-phenanthryldiphenylchloromethane, 1.0 g. of "molecular" silver (100 mesh) and 30 cc. of anhydrous benzene was shaken in a nitrogen atmosphere the solution became brown-red, but the intensity of the color soon began to decrease, and at the end of three days the solution was practically colorless and would absorb no oxygen. Estimation of the silver chloride indicated that the abstraction of the halogen from the carbinol halide had proceeded to the extent of 95–99%.

In each of the following experiments approximately 1 g. of the carbinol chloride in 12 cc. of bromobenzene was shaken with 1 g. of "molecular" silver (100 mesh) for the stated period of time. The oxygen absorption at the ends of these periods was: two minutes, 28%; five minutes, 30%; ten minutes, 26%; thirty minutes, 14%; three hours, 7%; three days, 0%.

When a bromobenzene solution (20 cc.) of the carbinol chloride (1.2 g.) was shaken with silver (5 g., 100 mesh) in the presence of oxygen, quantitative absorption of the latter was obtained within six minutes. From the reaction mixture was isolated a 78% yield of bis(9-phenanthryldiphenylmethyl) peroxide.

9-Phenanthryldiphenylmethyl was also prepared by a method involving the procedure of Ziegler and Schnell.[13] A mixture of 0.8 g. of the methyl ether of 9-phenanthryldiphenylcarbinol, 55 cc. of anhydrous ether and 3 g. of 45% sodium amalgam was shaken in an atmosphere of nitrogen for twenty-four hours. The solution was filtered into a nitrogen-filled bulb and a solution of 0.26 g. of tetramethylethylene bromide in 10 cc. of anhydrous ether was added. The green color of the sodium addition compound immediately gave way to the brown-red of the 9-phenanthryldiphenylmethyl radical. The color soon faded, however, and after standing in the dark for four hours the solution was practically colorless.

Bis(9-phenanthryldiphenylmethyl) peroxide.—The reaction mixture from the production of 9-phenanthryldiphenylmethyl in the presence of oxygen (as previously described) was filtered and the residue was washed with petroleum ether and dried. It was then treated with 3% nitric acid and finally with 28% ammonium hydroxide to remove silver and silver chloride. The remaining material was found to be nearly pure bis(9-phenanthryldiphenylmethyl) peroxide; m.p. 178–179° dec.; yield, 78%. This peroxide was found to be extremely insoluble in most solvents, and relatively unstable to heat, making its recrystallization difficult. A small amount was, however, recrystallized from chloroform-ethanol; m.p. 184–186° dec.

The identity of the peroxide was confirmed by synthesis from sodium peroxide and 9-phenanthryldiphenylchloromethane according to the method of Gomberg.[14] Air, freed from carbon dioxide, was passed through a mixture of 3 g. of 9-phenanthryldiphenylchloromethane, 10 g. of sodium peroxide, 90 cc. of ice water and 40 cc. of benzene until all the benzene was evaporated. The solid residue was boiled with 50 cc. of ether to dissolve the carbinol, and the small insoluble residue was extracted with 125 cc. of carbon disulfide for six hours. Approximately 100 cc. of the solvent was distilled off, and from the remaining solvent 0.05 g. of the colorless, crystalline peroxide separated; m.p. 184–186°; yield, 1.8%.

Anal. Calc'd for $C_{54}H_{38}O_2$: C, 90.2; H, 5.3.
Found: C, 90.1; H, 5.3.

The decomposition product of 9-phenanthryldiphenylmethyl.—Colorless solutions resulting from decomposition of the radical, prepared either from 9-phenanthryldiphenylchloromethane and silver or from 9-phenanthryldiphenylmethylsodium and tetramethylethylene dibromide, yielded the same decomposition products.

A solution of 5 g. of 9-phenanthryldiphenylchloromethane in 65 cc. of anhydrous benzene was shaken in a nitrogen atmosphere with 5 g. of "molecular" silver. After two days the colorless solution contained a colorless precipitate which was filtered off, freed from silver and silver chloride, washed with benzene and dried (3.34 g.). The filtrate on evaporation yielded 0.96 g. of the same product, making the total yield 95% (calculated on the basis of complete removal of chlorine from the carbinol chloride). By fractional crystallization from petroleum ether (60–75°), this product was separated into two fractions: the first crystallized from benzene-petroleum ether in irregular hexagonal plates, and constituted 96% of the total decomposition product. After four recrystallizations the product melted at 222–228° (dec.) in air, and at 275–280° (dec.) in nitrogen. Molecular-weight determination (Menzies

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[13] ZIEGLER AND SCHNELL, *Ann.*, **437**, 244 (1924).

[14] GOMBERG, *Ber.*, **33**, 3155 (1900).

boiling-point method in benzene) gave an average value of 646 (theoretical molecular weight of a dimer, 686). The second fraction (4%) crystallized from benzene-ethanol in colorless needles; m.p. 181° (dec.) with previous softening. An average molecular weight of 471 was obtained by the microebullioscopic method of Sucharda and Bobranski.[15]

9-Phenanthrylbiphenylenecarbinol (*X*a) was prepared in 70% yield according to the method of Bachmann.[12] In one instance, a sample crystallized from benzene-petroleum ether melted at 175-176°, solidified, and remelted at 191-192°, the melting point previously reported.

9-Phenanthrylbiphenylenemethyl acetate was obtained as colorless plates when five drops of concentrated sulfuric acid were added to a hot solution of 0.5 g. of 9-phenanthrylbiphenylenecarbinol in 10 cc. of acetic acid, and the vessel was scratched with a glass rod; m.p. 113-115°; yield, 66%.

Anal. Calc'd for $C_{29}H_{20}O_2$: CH_3COO, 14.6. Found: CH_3COO, 14.4.

9-Phenanthrylbiphenylenechloromethane.—A solution of 14.36 g. of 9-phenanthrylbiphenylenecarbinol in 30 cc. of anhydrous benzene was refluxed for three hours with 21 cc. of acetyl chloride. An equal volume of petroleum ether was added and on cooling the solution an 87% yield of the chloromethane crystallized in hexagonal prisms; m.p. 211-212° after recrystallization from benzene-petroleum ether.

Anal. Calc'd for $C_{27}H_{17}Cl$: Cl, 9.4. Found: Cl, 9.4.

Crystalline coördination compounds of 9-phenanthrylbiphenylenechloromethane with stannic chloride and with mercuric chloride were obtained. By repeatedly filtering off the brown, gelatinous precipitate formed when 0.8 g. of the carbinol chloride was dissolved in 20 cc. of a saturated benzene solution of mercuric chloride, a yield of 0.14 g. of the coördination compound was obtained; m.p. 237-240°.

Anal. Calc'd for $C_{14}H_9(C_6H_4)_2C\text{-}Cl \ldots 3HgCl_2$: Cl, 20.8. Found: Cl, 20.9.

Crystallization of the purple-iridescent coördination compound began almost immediately when a solution of 2 g. of stannic chloride in 2 cc. of anhydrous ethylene chloride was added to a solution of 1 g. of 9-phenanthrylbiphenylenechloromethane in 15 cc. of ethylene chloride; m.p. 230° dec.

Anal. Calc'd for $C_{14}H_9(C_6H_4)_2C\text{-}Cl \ldots SnCl_4$: Cl, 27.8. Found: Cl, 27.8.

9-Phenanthrylbiphenylenebromomethane.—After refluxing for one hour a mixture of 14.36 g. of 9-phenanthrylbiphenylenecarbinol, 34.5 g. of acetyl bromide and 30 cc. of anhydrous benzene, an equal volume of petroleum ether was added. The bromomethane crystallized on cooling of the solution; m.p. 230° dec.; yield, 78%.

Anal. Calc'd for $C_{27}H_{17}Br$: Br, 19.0. Found: Br, 18.9.

The *methyl ether of 9-phenanthrylbiphenylenecarbinol* was prepared from 9-phenanthrylbiphenylenechloromethane in the same manner as described for the preparation of the methyl ether of 1-phenanthryldiphenylcarbinol. Crystallization from acetone gave colorless, diamond-shaped plates; m.p. 231-232°; yield, 74%.

Anal. Calc'd for $C_{28}H_{20}O$: C, 90.3; H, 5.4.
Found: C, 90.3; H, 5.4.

The *ethyl ether of 9-phenanthrylbiphenylenecarbinol* was prepared in the usual manner from 2.25 g. of 9-phenanthrylbiphenylenebromomethane and sodium ethylate. The ether crystallizes from acetone-ethanol in colorless, diamond-shaped plates; m.p. 161-162°, solidifying, and remelting at 173-174°; yield, 40%.

Anal. Calc'd for $C_{29}H_{22}O$: C, 90.1; H, 5.7.
Found: C, 90.1; H, 5.6.

9-Phenanthrylbiphenylenemethane was prepared by refluxing for four hours a mix-

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[15] Sucharda and Bobranski, *Chem. Abstr.*, **23**, 2853 (1929).

ture of 1.79 g. of 9-phenanthrylbiphenylenecarbinol, 100 cc. of ethanol and 16 g. of zinc dust, during which time a total of 45 cc. of 36% hydrochloric acid was added in small portions. Some of the hydrocarbon separated during the addition of the hydrochloric acid. The mixture was filtered, and the filtrate was concentrated and cooled, whereupon the hydrocarbon crystallized. Extraction of the residue on the filter with benzene yielded more hydrocarbon. 9-Phenanthrylbiphenylenemethane crystallizes from benzene in colorless, diamond-shaped plates; m.p. 192–193°; yield, 90%. The hydrocarbon prepared in this manner was identical with that obtained from 9-bromofluorene and 9-phenanthrylmagnesium bromide.[12]

sym-*Di-9-phenanthryldibiphenyleneethane* (*V*).—On shaking the chloride in bromobenzene with silver, a brown-red solution of 9-phenanthrylbiphenylenemethyl was obtained. The following oxygen absorptions were obtained with such solutions shaken for varying periods of time: after one hour, 82%; after twenty hours, 20%; after seventy-two hours, 9%. When the carbinol bromide was shaken with silver and bromobenzene in the presence of oxygen, quantitative absorption of the latter was obtained within twenty minutes.

Bis(9-phenanthrylbiphenylenemethyl) peroxide was obtained when a brown-red solution of 9-phenanthrylbiphenylenemethyl, prepared by shaking a mixture of 1.42 g. of 9-phenanthrylbiphenylenebromomethane, 3 g. of "molecular" silver (80 mesh) and 40 cc. of anhydrous benzene for thirty-five minutes, was exposed to air. The solution became red and deposited 0.75 g. (62.5%) of the colorless, crystalline peroxide. After recrystallization from toluene the peroxide melted at 208–210° dec.

Anal. Calc'd for $C_{54}H_{34}O_2$: C, 90.7; H, 4.8.
Found: C, 90.6; H, 4.7.

1,2,3,4-Dibenzo-9-phenylfluoryl acetate.—Seven g. of lead dioxide was added to the boiling solution of 7 g. of 1,2,3,4-dibenzo-9-phenylfluorene[12] in 210 cc. of acetic acid over a period of one-half hour. After all the lead dioxide had been added the solution was refluxed for one hour more, enough water was added to the hot solution to start crystallization, and the solution was cooled. Recrystallization from acetone removed most of the colored impurities from the precipitated acetate. After sublimation *in vacuo* (250°/0.4 mm.) and recrystallization from acetic acid, the acetate melted at 254–255°; yield, 66.5%.

Anal. Calc'd for $C_{29}H_{20}O_2$: C, 87.0; H, 5.0.
Found: C, 86.9; H, 4.9.

A 0.5 g. sample of the acetate was reduced by heating for one hour with 0.5 g. of red phosphorus, 0.5 g. of iodine, 1 cc. of water and 15 cc. of acetic acid. The hot filtered solution was poured into water and the precipitated product was recrystallized from acetic acid; yield of 1,2,3,4-dibenzo-9-phenylfluorene, 90%; m.p. 210–212°.

1,2,3,4-Dibenzo-9-phenylfluorenol was obtained when an alcoholic solution of the acetate was heated for several minutes with potassium hydroxide and the solution was acidified with hydrochloric acid. The mixture was diluted with water and the carbinol extracted with benzene. The residue remaining when the solution was evaporated was sublimed *in vacuo* (250-260°/0.4 mm.) and the carbinol was obtained as square, colorless tablets on recrystallization from benzene-petroleum ether; m.p. 181°. The carbinol gives a deep-red color with concentrated sulfuric acid.

Anal. Calc'd for $C_{27}H_{18}O$: C, 90.5; H, 5.1.
Found: C, 90.8; H, 5.1.

1,2,3,4-Dibenzo-9-phenyl-9-chlorofluorene.—A mixture of 1.79 g. of 1,2,3,4-dibenzo-9-phenylfluoryl acetate, 3 cc. of acetyl chloride and 20 cc. of anhydrous benzene was refluxed for three hours, and an equal volume of petroleum ether (90–

TABLE II

MOLECULAR-WEIGHT DETERMINATIONS OF THE HEXAARYLETHANES
(Molecular Depression Constants: Nitrobenzene, 69.7; Benzene, 51.7)

WEIGHT SOLVENT (g.)	WEIGHT SOLUTE (g.)	CONC. (%)	F.P. DEPRESSION (degrees)	DISSOC. (%)
sym-Di-1-phenanthryltetraphenylethane in Benzene				
16.19	0.2791	1.69	0.176	36
17.43	0.2629	1.49	0.150	32
sym-Di-1-phenanthryltetraphenylethane in Nitrobenzene				
23.89	0.5319	2.18	0.310	37
20.66	0.4792	2.26	0.315	34
23.44	0.6043	2.51	0.347	33
sym-Di-2-phenanthryltetraphenylethane in Benzene				
19.80	0.3539	1.76	0.157	17
16.25	0.2790	1.69	0.150	16
sym-Di-2-phenanthryltetraphenylethane in Nitrobenzene				
19.77	0.4545	2.24	0.320	37
21.34	0.4476	2.05	0.284	33
23.32	0.5347	2.24	0.303	30
27.06	0.4951	1.80	0.241	30
sym-Di-3-phenanthryltetraphenylethane in Benzene				
15.78	0.4446	2.74	0.237	12
17.57	0.3181	1.78	0.151	11
17.51	0.5280	2.93	0.251	11
sym-Di-3-phenanthryltetraphenylethane in Nitrobenzene				
19.64	0.4625	2.30	0.273	14
23.02	0.6006	2.54	0.301	14
24.04	0.7837	3.16	0.377	14[a]
sym-Di-α-naphthyltetraphenylethane in Benzene				
18.99	0.4670	2.40	0.285	31
15.47	0.3419	2.16	0.250	28
sym-Di-α-naphthyltetraphenylethane in Nitrobenzene				
24.80	0.5446	2.14	0.356	36
18.23	0.4558	2.44	0.385	28
sym-Di-β-naphthyltetraphenylethane in Benzene				
17.54	0.4282	2.38	0.235	9
15.46	0.3773	2.38	0.231	7

[a] This determination was made employing the original indirect method of Gomberg and Cone[3], wherein the hexaarylethane solution was prepared directly in the freezing vessel by stirring the chloride with three times its weight of 100 mesh silver for three hours.

TABLE II—*Concluded*

WEIGHT SOLVENT (g.)	WEIGHT SOLUTE (g.)	CONC. (%)	F.P. DEPRESSION (degrees)	DISSOC. (%)
sym-Di-*p*-biphenyltetraphenylethane in Benzene				
17.00	0.4104	2.36	0.226	16
18.17	0.5771	3.08	0.298	16
Hexa-*p*-biphenylethane in Benzene				
18.44	0.1738	0.93	0.090	74
Hexa-*p*-biphenylethane in Nitrobenzene				
20.32	0.2160	1.05	0.130	65

100°) was added. Fifteen cc. of benzene was then distilled off, the solution was cooled to 0°, and crystallization was induced by scratching with a glass rod. Recrystallization from benzene-petroleum ether gave a 50% yield of the carbinol chloride; m.p. 172–174°.

Anal. Calc'd for $C_{27}H_{17}Cl$: Cl, 9.4. Found: Cl, 9.5.

A solution of 0.10 g. of 1,2,3,4-dibenzo-9-phenyl-9-chlorofluorene in 10 cc. of anhydrous benzene was shaken in a sealed tube with 0.2 g. of 100-mesh "molecular" silver. The red color of 1,2,3,4-dibenzo-9-phenylfluoryl quickly appeared, and the solution retained its color even after twelve hours. The red solution on exposure to air was quickly decolorized, and the colorless peroxide was deposited; m.p. 209–211° dec. The peroxide gives a red color with concentrated sulfuric acid.

Molecular-weight determinations of the hexaarylethanes.—Gomberg and Cone[8] were the first to determine the molecular weight of a hexaarylethane without previously isolating it. Subsequently the indirect method was used in a number of instances to determine the extent of dissociation of hexaarylethanes.[16]

We employed the Beckmann cryoscopic method for the molecular-weight determinations, modified for the use of an atmosphere of nitrogen.[17] One side-arm of the freezing vessel was fitted with a rubber stopper through which passed a stopcock which was used for evacuating the apparatus, and the second side arm was fitted with a rubber stopper through which passed a glass siphon of the same type as that used in connection with the bulb. A solution containing a carefully weighed sample of the halide in a known weight of solvent was shaken for twelve hours in a glass-stoppered cylinder in a nitrogen atmosphere, the cylinder being wrapped in a black cloth to prevent entrance of light. By means of oxygen absorption experiments on separate samples it was shown that in every instance the reaction had gone to completion and that there had been no decomposition of the radical during this period of time. The silver was allowed to settle, the stopper was removed from the cylinder, and the siphon connected to the cryoscopic apparatus was quickly inserted in its place. An aliquot portion of the radical solution was then transferred to the nitrogen-filled cryoscopic apparatus, the weight so transferred being determined by weighing the freezing vessel at the end of the run. Determination of the freezing point of this

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[16] GOMBERG AND FORRESTER, *J. Am. Chem. Soc.*, **47**, 2373–2391 (1925); GOMBERG AND McGILL, *ibid.*, **47**, 2400 (1925); LUND, *ibid.*, **49**, 1349 (1927).

[17] BECKMANN, *Z. physik. Chem.*, **44**, 170 (1903).

solution, together with a similar determination on a sample of pure solvent from which the solution had been made, then gave the requisite data for calculation of the molecular weight. From the molecular weight was calculated the dissociation of the hexaarylethane.

$$\text{Dissociation} = \frac{\text{M.W.}_c}{\text{M.W.}_f} - 1,$$

where M.W._c is the calculated molecular weight of the hexaarylethane and M.W._f is the molecular weight found.

Upon completion of each determination the radical solution was oxidized and, after evaporation of the solvent, the total oxidation products were weighed as peroxide. The weight of peroxide in every instance checked the theoretical weight to within 90%.

The results of the molecular weight determinations are shown in Table II.

SUMMARY

(1) *sym*-Di-1-phenanthryltetraphenylethane, *sym*-di-2-phenanthryltetraphenylethane and *sym*-di-3-phenanthryltetraphenylethane have been synthesized, the latter being obtained in the crystalline state.

(2) The dissociation of these hexaarylethanes has been determined in benzene and in nitrobenzene. The 1- and 2-phenanthryl groups have been found to rank with the α-naphthyl group in being more effective in promoting dissociation than any other aromatic group thus far investigated. The 3-phenanthryl group was found to be less than half as effective.

(3) 9-Phenanthryldiphenylmethyl and 9-phenanthrylbiphenylenemethyl were prepared, but were found to be too unstable to allow molecular weight determinations of the corresponding hexaarylethanes.

(4) A number of new phenanthryldiarylmethane derivatives containing the 1-, 2-, 3-, and 9-phenanthryl groups have been synthesized from phenanthrene, and their properties investigated.

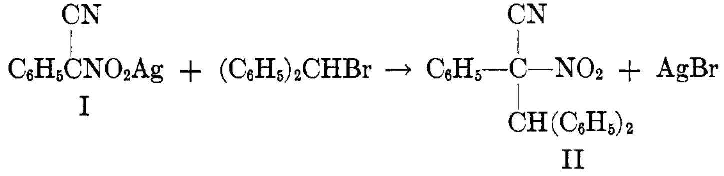
[Contribution from the Chemical Laboratory of the University of Illinois]

SALTS OF NITRO COMPOUNDS. II. THE REACTION OF THE SILVER SALT OF PHENYLNITROMETHANE WITH DIPHENYLBROMOMETHANE

G. B. BROWN and R. L. SHRINER

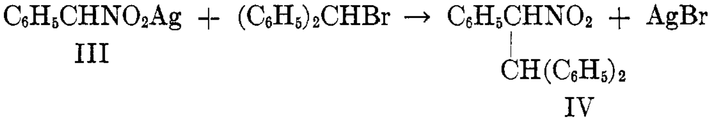
Received October 2, 1937

A previous study of the alkylation of the silver salt of phenylnitroacetonitrile (I) with methyl iodide or benzyl chloride showed that unstable nitronic esters were produced[1] indicating that oxygen-alkylation had occurred. However, Wieland and Hochtlen[2] obtained α-nitro-α,β,β-triphenylpropionitrile (II) by treatment of this same silver salt (I) with diphenylbromomethane. This reaction



$$\underset{\text{I}}{C_6H_5\overset{\displaystyle CN}{\overset{|}{C}}NO_2Ag} + (C_6H_5)_2CHBr \rightarrow \underset{\text{II}}{C_6H_5\text{—}\overset{\displaystyle CN}{\underset{\displaystyle CH(C_6H_5)_2}{\overset{|}{\underset{|}{C}}}}\text{—}NO_2} + AgBr$$

involved carbon-alkylation, and indicated that diphenylbromomethane behaved differently from methyl iodide or benzyl chloride. Since this seemed rather unusual, a study was made of the reaction between the silver salt of a primary nitro compound, phenylnitromethane (III), with diphenylbromomethane in order to determine whether carbon-alkylation would produce the compound IV by the following reaction:



$$\underset{\text{III}}{C_6H_5CHNO_2Ag} + (C_6H_5)_2CHBr \rightarrow \underset{\text{IV}}{C_6H_5\underset{\displaystyle CH(C_6H_5)_2}{\underset{|}{C}}HNO_2} + AgBr$$

A careful examination of the products of this reaction has shown that no compound corresponding to formula IV was produced. Instead, two compounds were isolated: *sym*-tetraphenylethane (V) and 1,2-dinitro-1,2-diphenylethane (VI).

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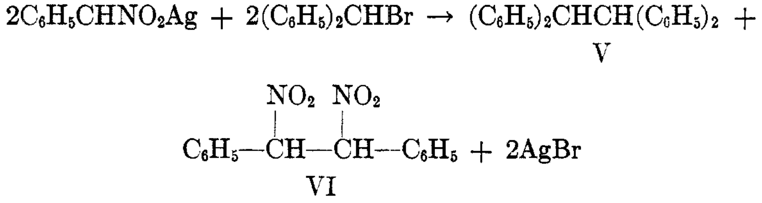
[1] Thurston and Shriner, J. Org. Chem. **2**, 183 (1937).

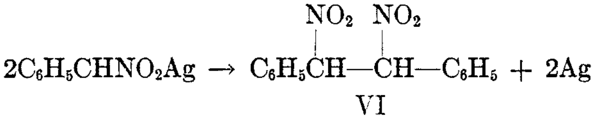
[2] Wieland and Hochtlen, *Ann.*, **505**, 237 (1933).



$$2C_6H_5CHNO_2Ag + 2(C_6H_5)_2CHBr \rightarrow \underset{\text{V}}{(C_6H_5)_2CHCH(C_6H_5)_2} +$$

$$\underset{\text{VI}}{C_6H_5-\overset{NO_2}{\overset{|}{C}}H-\overset{NO_2}{\overset{|}{C}}H-C_6H_5} + 2AgBr$$

These products were evidently formed by two simultaneous coupling reactions. The silver salt is very unstable and decomposes on standing or shaking in benzene solution, depositing metallic silver.

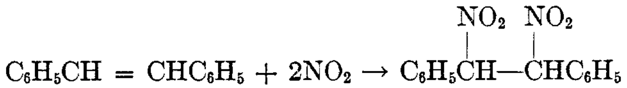


$$2C_6H_5CHNO_2Ag \rightarrow \underset{\text{VI}}{C_6H_5\overset{NO_2}{\overset{|}{C}}H-\overset{NO_2}{\overset{|}{C}}H-C_6H_5} + 2Ag$$

The free silver then caused coupling of two molecules of diphenylbromomethane to produce *sym*-tetraphenylethane (V).

$$2(C_6H_5)_2CHBr + 2Ag \rightarrow \underset{\text{V}}{(C_6H_5)_2CH-CH(C_6H_5)_2} + 2AgBr$$

The *sym*-tetraphenylethane (V) was readily characterized by comparison of the melting point with that of a mixture with an authentic specimen. The 1,2-dinitro-1,2-diphenylethane (VI) decomposed over a considerable range (224°–240°) when attempts were made to determine its melting point in a capillary tube. It melted with decomposition at 231–233° on the Maquenne block. This molecule also contains two similar asymmetric carbon atoms and hence may exist in *meso* and *racemic* modifications. Both of these forms had been prepared previously by Schmidt[3] and by Wieland[4] by treating stilbene with nitrogen dioxide.



$$C_6H_5CH = CHC_6H_5 + 2NO_2 \rightarrow C_6H_5\overset{NO_2}{\overset{|}{C}}H-\overset{NO_2}{\overset{|}{C}}HC_6H_5$$

This preparation was repeated and the two forms isolated. One form (α-isomer) melted with decomposition at 230–233° and the other form (β-isomer) melted at 154–155°. The β-form could be converted to the α-form by heating a sample just above the melting point for a minute and allowing it to resolidify. No data are available to indicate which of these forms is *meso* and which is *racemic.*

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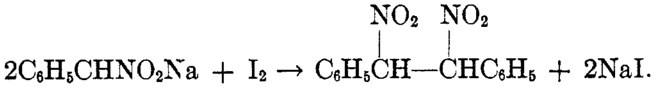
[3] SCHMIDT, *Ber.*, **34,** 623, 3537 (1901).

[4] WIELAND, *Ann.*, **424,** 105 (1921).

The β-form was also obtained by treating the sodium salt of phenylnitromethane with iodine.

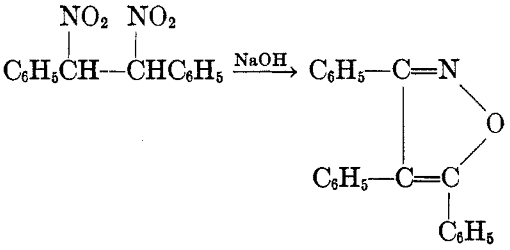


$$2C_6H_5CHNO_2Na + I_2 \rightarrow C_6H_5\overset{NO_2}{\overset{|}{C}}H{-}\overset{NO_2}{\overset{|}{C}}HC_6H_5 + 2NaI.$$

The compound from this reaction was shown to be identical with the β-form obtained by the nitrogen dioxide reaction with stilbene.

Mixtures of the α-form obtained synthetically with that produced by the action of diphenylbromomethane on the silver salt of phenylnitromethane decomposed at 230–233° on the Maquenne block thus indicating that they are identical.

The 1,2-dinitro-1,2-diphenylethane was further characterized by conversion to triphenylisoxazole (VII) by treatment with alkali.[5] The compound from the coupling reaction (α-form) and the synthetic α- and β-forms yielded the same triphenylisoxazole, melting at 214–215°. These results indicate that the second product of the action of diphenylbromomethane on the silver salt of phenylnitromethane is 1,2-dinitro-1,2-diphenylethane.



EXPERIMENTAL

Phenylnitromethane.—This compound was obtained as a yellow liquid boiling at 114–115° at 13 mm. according to the procedure described by Wislicenus and Enders.[6]

Sodium salt of phenylnitromethane.—Sodium (0.9 g.) was dissolved in a mixture of 10 cc. of absolute alcohol and 10 cc. of ether. One hundred cubic centimeters of ether was added, followed by 5 g. of phenylnitromethane in 25 cc. of ether, with stirring. The white, flocculent sodium salt precipitated, was collected on a filter, washed with absolute ether, and preserved in a vacuum desiccator. The yield was almost quantitative.

Anal. Calc'd for $C_7H_6NNaO_2$: Na, 14.46. Found: Na, 14.46, 14.40.

Silver salt of phenylnitromethane.—A solution of 5.35 g. of silver nitrate in 150 cc. of water was added to 5 g. of sodium aci-phenylnitromethane in 150 cc. of water, with

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[5] Nenitzescu, *Ber.*, **62B**, 2669 (1929); Heim, *ibid.*, **44**, 2016 (1911); Meisenheimer, *ibid.*, **54**, 3206 (1921). The mechanism of this reaction has not yet been established.

[6] Wislicenus and Enders, *ibid.*, **35**, 1755 (1902).

vigorous stirring. The silver aci-phenylnitromethane separated immediately as a white precipitate. It was filtered, washed with ether, and then with petroleum ether. The salt is very unstable and turns brownish-black quickly. The yield was 7.2 g., or 94 per cent of the theoretical. The salt explodes when heated.

Reaction between silver aci-phenylnitromethane and diphenylbromomethane.—To a suspension of 7 g. of the silver aci-phenylnitromethane in 200 cc. of dry benzene was added a solution of 7.5 g. of diphenylbromomethane[7] dissolved in 50 cc. of benzene, with stirring and cooling. This reaction mixture in various runs was stirred from 7.5 hours to four days. One run was allowed to stand for five weeks without stirring. The solution soon turned dark, and in the longer runs a silver mirror formed on the flask. The benzene solution was separated from the insoluble silver salt by filtration, and dried over magnesium sulfate; the benzene removed by distillation, and the residual oil was taken up in 250 cc. of warm absolute alcohol and allowed to crystallize. The first crop of crystals consisted chiefly of tetraphenylethane, which was purified by three recrystallizations from absolute alcohol. It melted at 210°, and the melting point of a mixture with a pure sample of tetraphenylethane showed no depression. Considerably larger amounts of tetraphenylethane were obtained in the experiments in which the reaction mixture was stirred a longer time.

Concentration of the alcohol filtrate yielded a mixture which was separated by three to five recrystallizations from xylene and a final recrystallization from alcohol. The 1,2-dinitro-1,2-diphenylethane obtained melted with decomposition at 231–233°, as determined by means of the Maquenne block. The melting point of a mixture with a sample of the α-form of 1,2-dinitro-1,2-diphenylethane, prepared from stilbene and nitrogen dioxide, was 230–234°, as determined by means of the Maquenne block. Melting points taken by the capillary tube method vary from 224–240°, depending on the rate of heating and the size of the capillary tube. Previous investigators[3,4] report melting points varying from 230–235° to 234–236°.

Anal. Calc'd for $C_{14}H_{12}N_2O_4$: C, 61.75; H, 4.42; N, 10.3.
Found: C 61.77, 61.83; H, 4.62, 4.45; N, 9.57, 9.49, 9.82, 9.98.

The nitrogen analyses carried out by the Dumas method were always low. A small sample of the 1,2-dinitro-1,2-diphenylethane was decomposed by heating slowly to 235° in a small test tube. The evolution of nitrogen dioxide was evident, and carbonization took place rapidly. The low analyses were evidently due to this faculty of evolving the oxides of nitrogen on heating, the unreduced oxides being caught by the potassium hydroxide. Attempts to determine the nitrogen by the Kjeldahl method, zinc or sodium thiosulfate being used as the reducing agent, were also unsuccessful.

1,2-Dinitro-1,2-diphenylethane. A. From stilbene.—The procedure described by Schmidt was followed. Nitrogen dioxide, generated by heating lead nitrate, was passed into a benzene solution of stilbene. Crystallization took place gradually. The crystals were filtered, washed with benzene and recrystallized from alcohol. The decomposition point, as determined by means of the Maquenne block, was 230–233°.

The filtrate and the wash benzene were shaken with 1 per cent sodium bicarbonate solution, and the benzene was removed by evaporation, leaving a yellow powder. On crystallization from ether, followed by recrystallization from acetic acid, broad, flat, needle clusters, melting point 154–155°, were obtained. This β-, or low-melting form, was converted to the α-, or high-melting form, by heating above its melting point for a few minutes and allowing to resolidify.

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[7] COURTOT, *Ann. chim.*, [9], **5**, 80 (1916),

B. From sodium aci-phenylnitromethane and iodine.—A solution of iodine in potassium iodide was slowly added to 2 g. of sodium aci-phenylnitromethane in 10 cc. of water until a slight excess was present. The solution was stirred for three hours, and a few cubic centimeters of dilute sodium thiosulfate was added to remove the last traces of iodine. The solution was extracted twice with 25 cc. of benzene, the extract was dried over calcium chloride, the benzene was distilled and the oily product was crystallized twice from alcohol, yielding the β-form of 1,2-dinitro-1,2-diphenylethane; melting point, 151–153°. The melting point of a mixture with a sample of the β-form, prepared by the reaction of nitrogen dioxide with stilbene, was 151–153°.

Triphenylisoxazole.—Approximately 50 mg. of the 1,2-dinitro-1,2-diphenylethane, prepared in the reaction of nitrogen dioxide and stilbene, was treated with 5 cc. of 30 per cent sodium hydroxide solution and heated on the steam bath for three hours. The crystals of triphenylisoxazole were filtered and recrystallized twice from acetic acid. It melted at 214–215° which checked the values in the literature.[5]

Anal. Calc'd for $C_{21}H_{15}NO$: C, 84.83; H, 5.05; N, 4.72.
Found: C, 84.28; H, 5.54; N, 4.60, 4.85.

Triphenylisoxazole was also prepared, according to the above procedure, from approximately 30 mg. of the 1,2-dinitro-1,2-diphenylethane prepared by the reaction of silver aci-phenylnitromethane and diphenylbromomethane. It also melted at 214–215°, and the melting point of a mixture showed no depression.

Decomposition of the silver salt of phenylnitromethane.—Five grams of the silver salt of phenylnitromethane was placed in 150 cc. of benzene and shaken for 17 days. The unchanged silver salt was removed by filtration and the colloidal silver was removed by passage through a layer of Norite on a sintered glass funnel. The solution was dried over calcium chloride, and the benzene was removed under reduced pressure. Two recrystallizations of the residue from ethyl alcohol yielded the β-form of 1,2-dinitro-1,2-diphenylethane melting at 153–154°.

The alcoholic filtrate from the recrystallizations was mixed with 10 cc. of 30 per cent. sodium hydroxide solution and heated on the steam bath for three hours. When this mixture cooled crystals of triphenylisoxazole melting at 213–214° were obtained.

SUMMARY

The reaction of the silver salt of phenylnitromethane and diphenylbromomethane resulted in a coupling of the nitro compound to give 1,2-dinitro-1,2-diphenylethane and of the diphenylbromomethane to yield *sym*-tetraphenylethane.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY AND ASHLAND COLLEGE]

THE PYROLYSIS OF ALKYLALLYL AND ALKYLCROTYL ETHERS OF PHENOL AND *o*-CRESOL

CHARLES D. HURD AND MILTON P. PUTERBAUGH

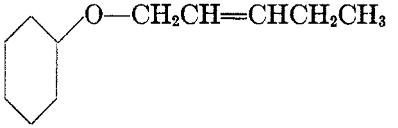
Received July 8, 1937; revised October 9, 1937

During the past five years study has been made of a variety of alkylallyl (pentenyl, hexenyl, heptenyl) ethers of phenol,[1] pyrogallol,[2] resorcinol,[3] and fluorescein.[4] In this work it was established that inversion of the alkylallyl group occurred during pyrolytic rearrangement of the ethers into isomeric phenols. Reports have also been made of similar studies with the α-methylcrotyl,[5] α-ethylcrotyl, and α-*n*-propylcrotyl phenyl ethers.[6]

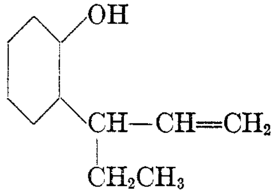
The present study was undertaken to obtain additional data in this field. The ethyl-, *n*-propyl- and *n*-butylallyl ethers of phenol and *o*-cresol were prepared, and a similar group of six ethers in the crotyl series was also synthesized. Some new data concerning the allyl ethers of catechol and resorcinol and various allylcatechols and resorcinols were obtained also.

Direct heating of the alkylallyl phenyl (and *o*-tolyl) ethers to 230–250° brought about rearrangement to the alkenylphenols or alkenylcresols. One important observation, hitherto unnoticed in similar experiments, was that of the concurrent production of phenol (or *o*-cresol) in significant amounts. The α-alkylcrotyl aryl ethers also yielded phenol and *o*-cresol as reaction products. It appears, therefore, that this finding is general.

Since this work was completed (in 1935) an article has appeared by Lauer and Filbert[7] on the rearrangement of γ-ethylallyl phenyl ether (I). Instead of obtaining the expected rearrangement product (II),



I



II

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[1] HURD AND MCNAMEE, *J. Am. Chem. Soc.*, **54**, 1648 (1932).

[2] HURD AND PARRISH, *ibid.*, **57**, 1731 (1935).

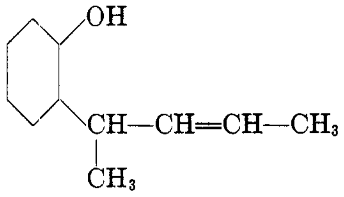
[3] HURD AND MCNAMEE, *ibid.*, **59**, 104 (1937).

[4] HURD AND SCHMERLING, *ibid.*, **59**, 112 (1937).

[5] HURD AND COHEN, *ibid.*, **53**, 1917 (1931).

[6] HURD AND WILLIAMS, *ibid.*, **58**, 2636 (1936).

[7] LAUER AND FILBERT, *ibid.*, **58**, 1388 (1936).



III

which would arise by simple inversion of the pentenyl group, these investigators showed that their product possessed structure III. That III was produced during this reaction was confirmed recently in this laboratory,[8] but it was shown that a considerable quantity of II was present also in the products. From this, it is evident that the *o*-pentenylphenol, obtained in the present work by pyrolysis of I, was a mixture of II and III. It is reasonable to assume also that the 6-pentenyl-2-methylphenol, obtained from pentenyl *o*-tolyl ether, was similar in structure. Likewise, the hexenyl- and heptenylphenols and cresols were undoubtedly mixtures of the same type.

EXPERIMENTAL

Allyl derivatives of catechol and resorcinol.—The directions given by Hurd, Greengard, and Pilgrim[9] were followed for the synthesis of these compounds. Physical constants, hitherto unreported for these compounds, are collected in Table I. The solubility in water at 26° for 4-allylcatechol was found to be 2.5 g. per 100 cc.; that for 3,6-diallylcatechol was 0.094 g. per 100 cc. Triallylcatechol and 4,6-diallylresorcinol were both analyzed by the Zerewitinoff method and both were shown to contain two available hydroxyls per molecule.

The 1-bromo-2-alkenes.—1-Pentene-3-ol, 1-hexene-3-ol and 1-heptene-3-ol were prepared by previously-described methods.[10] These alcohols (45–50 g.) were converted to bromides by refluxing for two hours with a mixture of 135 g. of 48% hydrobromic acid and 17 cc. of concentrated sulfuric acid. The yields were 52–70%. The products which were obtained and used had these constants: 1-bromo-2-pentene, b.p. 40° (25 mm.), n_D^{20} 1.4741; 1-bromo-2-hexene, b.p. 52–53° (17 mm.), n_D^{19} 1.4757, d_{27}^{27} 1.1780; 1-bromo-2-heptene, b.p. 45–47° (3 mm.), n_D^{23} 1.4720, d_{28}^{28} 1.1621.

The 4-chloro-2-alkenes.—Synthesis of 2-hexen-4-ol and 2-hepten-4-ol, and the reaction of these alcohols with phosphorus pentachloride was accomplished according to published directions.[11] The observed constants for 4-chloro-2-hexene were these: b.p. 38–43° (30 mm.), d_{20}^{20} 0.9148, n_D^{21} 1.4400. The 4-chloro-2-heptene was collected at 46–48° (12 mm.); n_D^{19} 1.4422. Unsuccessful attempts were made to convert 2-hexene-4-ol into its bromide by reaction with hydrobromic acid. Only a dark mass resulted.

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[8] Hurd and Pollack, Ph.D. dissertation of M. A. Pollack, Northwestern University, 1937.

[9] Hurd, Greengard, and Pilgrim, *J. Am. Chem. Soc.*, **52**, 1703 (1930).

[10] Delaby, *Ann. chim.*, [9], **19**, 275 (1923); Bouis, *ibid.*, [10], **9**, 409 (1928).

[11] Reif, *Ber.*, **39**, 1603 (1906); **41**, 2742 (1908); Hurd and Cohen, *J. Am. Chem. Soc.*, **53**, 1920 (1931).

2-Octen-4-ol.—*n*-Butylmagnesium bromide was made from 24 g. of magnesium, 147 g. of *n*-butyl bromide and 350 cc. of dry ether. It was chilled to −5°, stirred, and 78 g. of crotonaldehyde was added slowly. After reaction, the contents were poured on to 1.5 kg. of ice, and hydrolysis was completed by addition of 100 g. of ammonium chloride and 250 cc. of 6 *N* hydrochloric acid. The alcohol was separated, washed with sodium bicarbonate solution, dried over sodium sulfate and distilled. The yield was 70 g. (or 55%); b.p. 74° (8 mm.), d_4^{20} 0.8393, n_D^{20} 1.4395, mol. refraction 40.15 (calc'd, 40.04).

Anal. (by Loyal Stone): Calc'd for $C_8H_{16}O$: C, 74.8; H, 12.6.
Found: C, 74.1; H, 12.5.

TABLE I

DERIVATIVES OF CATECHOL AND RESORCINOL

DERIVATIVE	B.P.		n_D (t°)	
	°C.	mm.		
Catechol monoallyl ether	103–104.5	8	1.5467	9
			1.5408	21.5
Catechol diallyl ether	112–115	8	1.5385	15
			1.5308	21.5
Allylcatechol diallyl ether	140–155	12	—	
Resorcinol monoallyl ether	130–135	7	1.5510	15
3-Allylcatechol	132–138	9	1.5687	8
			1.5595	30
4-Allylcatechol	141–144	7	1.5689	7.5
			1.5600	29
3,6-Diallylcatechol	132–137	6	1.5587	8
			1.5498	30.5
Triallylcatechol	175–180	10	1.5558	11
			1.5518	20
4-Allylresorcinol	143–150	5–9	1.5753	15
4,6-Diallylresorcinol	178–183	12	1.5653	10
			1.5608	22

TABLE II

ALKYLALLYL ETHERS OF PHENOL AND *o*-CRESOL

ETHER	B.P.		d_{20}^{20}	n_D^{20}	ANALYSES, %			
					Calc'd		Found	
	°C.	mm.			C	H	C	H
γ-Ethylallyl phenyl ether......	91–95	4	0.9566[12]	1.5155	81.4	8.64	80.9	8.38
γ-*n*-Propylallyl phenyl ether...	105–107	4	0.9408	1.5109	81.8	9.09	82.3	9.05
γ-*n*-Butylallyl phenyl ether....	102–103	3	0.9340	1.5056 (30°)	82.1	9.47	82.0	9.49
γ-Ethylallyl *o*-tolyl ether......	106–108	3	0.9470	1.5140	81.7	9.14	81.7	8.96
γ-*n*-Propylallyl *o*-tolyl ether...	115–117	6	0.9370	1.5090	82.1	9.5	81.9	9.2
γ-*n*-Butylallyl *o*-tolyl ether....	105–108	3	0.9300	1.5059	82.3	9.8	82.1	9.5

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[12] LAUER AND FILBERT, *J. Am. Chem. Soc.*, **58**, 1389 (1936).

4-Chloro-2-octene.—One hundred ten grams of phosphorus pentachloride was added in small portions to a mixture of 65 g. of 2-octen-4-ol and 70 cc. of ether at 0°. The reaction was vigorous. After standing for ten hours the mixture was washed with water and sodium bicarbonate solution, and the insoluble layer was dried and distilled. Thirty-two grams (43% yield) was collected at 69–70° (9 mm.); d_4^{20} 0.8924; n_D^{20} 1.4452; mol. refraction 43.69 (calc'd 43.48).

Anal. Calc'd for $C_8H_{15}Cl$: Cl, 24.2. Found: Cl, 24.9.

Alkylallyl ethers of phenol and o-*cresol.*—Into 50 cc. of acetone which contained 40–45 g. of potassium carbonate and 20–30 g. of phenol or *o*-cresol (0.2–0.3 mole) there was dropped an equivalent amount of the 1-bromo-2-alkene. Stirring was maintained during the addition, after which the mixture was refluxed for four to five hours. About 200 cc. of water was then added to dissolve the salts, and the mixture was extracted with ether. The solution was dried, and the desired ether was distilled under diminished pressure. The yields of the ethers ranged from 52–57%.

TABLE III

ALKYLCROTYL ETHERS OF PHENOL AND *o*-CRESOL

ETHER	B.P.		d_{18}^{18}	n_D^{18}	ANALYSES, %			
					Calc'd		Found	
	°C.	mm.			C	H	C	H
α-Ethylcrotyl phenyl ether..	89–91	5	0.9290	1.5066	81.8	9.10	81.6	9.15
α-*n*-Propylcrotyl phenyl ether[13]....................	103–104	4	0.9282 (20°)	1.5000 (21°)	—	—	—	—
α-*n*-Butylcrotyl phenyl ether.....................	107–108	4	0.9208	1.4955	82.3	9.80	82.3	9.88
α-Ethylcrotyl *o*-tolyl ether..	100–102	6	0.9244	1.5032	82.1	9.47	82.3	9.52
α-*n*-Propylcrotyl *o*-tolyl ether.....................	96–98	4	0.9216	1.5000	82.3	9.80	82.5	10.3
α-*n*-Butylcrotyl *o*-tolyl ether	118–119	4	0.9143	1.4950	82.6	10.1	82.7	10.4

The significant data are collected in Table II. The combustion analyses were performed by Mr. Loyal Stone.

α-Alkylcrotyl ethers of phenol and o-*cresol.*—In general, these ethers were prepared like the alkylallyl ethers. Minor differences were the use of a refluxing period of 7 hours or longer and the use of an excess of phenol or cresol (about 1.3:1 instead of 1:1). Even with these modifications, the yields (20–30%) were much lower. This suggests the greater reactivity of bromide over chloride in this type of metathesis. The data concerning the ethers are grouped in Table III.

Pyrolysis of the Ethers

A quantity (13–20 g.) of the ether was placed in a small flask, fitted with an air condenser, heated by an oil bath or salt bath, to a temperature (usually 230–260°) so as to bring about refluxing of the contents of the flask. The temperature of the reaction liquid usually lagged behind that of the bath. No diluent (such as fluorene

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[13] Analyzed by HURD AND COHEN, *ibid.*, **53**, 1921 (1931).

or diethylaniline) was used during the heating, although such a procedure would have augmented[14] the yield of alkenylphenol. The duration of heating was from thirty to fifty minutes.

o-*Pentenylphenol.*—The products obtained from 14.5 g. of γ-ethylallyl phenyl ether were vacuum-distilled: 2.0 g. of phenol, 80–98° (5 mm.); 1.2 g. 98–110° (5 mm.); 5.0 g. of *o*-pentenylphenol 110–112° (7 mm.); 0.5 g., 112–116° (4 mm.); 2.1 g. of residue. The phenol was identified as phenoxyacetic acid, m.p. 98°. The yield of pentenylphenol, n_D^{20} 1.5322, was 34.5 per cent.

Anal. Calc'd for $C_{11}H_{14}O$: C, 81.5; H, 8.64; OH, 1.00.

Found: C, 81.8; H, 8.96; OH (Zerewitinoff), 0.98.

o-*Hexenylphenol.*—Twenty grams of the hexenyl phenyl ether yielded these products, when distilled at 6–7 mm.: 2.0 g. of phenol (which solidified in the receiver), 80–85°; 2.0 g., 85–120°; 8.0 g. (or 40% yield) of hexenylphenol, 120–122°; 4.0 g., 135–165°. The 85–120° fraction was largely phenol (bromination yielded tribromophenol, m.p. 96°). The hexenylphenol was soluble in alkali; n_D^{15} 1.5275, n_D^{20} 1.5255.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.8; H, 9.09; OH, 1.00.

Found: C, 81.8; H, 9.03; OH (Zerewitinoff), 1.02.

o-*Heptenylphenol.*—The alkali-soluble portion from 16 g. of the heptenyl phenyl ether which had been heated forty minutes was distilled at 6 mm. There was isolated 0.5 g. of solid phenol and 4.4 g. (28%) of *o*-heptenylphenol, b.p. 125–127° (6 mm.), d_{20}^{20} 1.1009, n_D^{20} 1.5215. There was 8 g. of alkali-insoluble material.

Anal. (Zerewitinoff). Calc'd for $C_{13}H_{17}OH$: OH, 1.00. Found: OH, 1.02.

6-Pentenyl-2-methylphenol.—The pentenyl *o*-tolyl ether (13.3 g.) was treated similarly. After heating, all but 1 g. of it was soluble in 120 cc. of 5% sodium hydroxide solution. After acidification, ether extraction, and drying it was distilled. A fraction weighing 5.8 g. (43.6% yield) was obtained which boiled at 107–110° (3 mm.); n_D^{20} 1.5322, d_{25}^{25} 0.9766. One gram of *o*-cresol was collected at 60° (4 mm.).

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.8; H, 9.09; OH, 1.00.

Found: C, 81.3; H, 9.13; OH, 1.01.

6-Hexenyl-2-methylphenol.—The hexenyl *o*-tolyl ether (13 g.) gave rise to 3 cc. of alkali-insoluble material and 3.4 g. (27% yield) of 6-hexenyl-2-methylphenol: b.p., 112–115° (3 mm.); d_{25}^{25} 0.9618; n_D^{20} 1.5255. *o*-Cresol was also collected in small quantity in this experiment.

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.1; H, 9.47.

Found: C, 82.2; H, 9.37.

6-Heptenyl-2-methylphenol.—From 13 g. of the heptenyl *o*-tolyl ether there was a large alkali-insoluble residue (9 g.). Only 2 g. of the desired phenol was collected: b.p. 120–121 (4 mm.), d_{20}^{20} 1.0930, n_D^{20} 1.5193. The yield of *o*-cresol [b.p., 60° (4 mm.)] was 0.5 g.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.3; H, 9.80.

Found: C, 82.0; H, 9.88.

Behavior of the α-alkylcrotyl ethers of phenol and o-*cresol towards heat.*—After being heated by an oil bath at 200–230° for thirty minutes all six of these ethers refluxed at 175–185°. Between one and two grams of phenol or *o*-cresol was isolated from each 10 g. of ether heated. The phenol and cresol were separated by alkali-solubility and then by distillation at 4 mm. Both were identified by their chloroacetic acid derivatives. A large amount of alkali-insoluble material was formed which has not yet been characterized.

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[14] HURD AND WEBB, *ibid.*, **58**, 2192 (1936).

SUMMARY

The γ-alkylallyl (alkyl being ethyl, *n*-propyl, or *n*-butyl) ethers of phenol and *o*-cresol were synthesized and pyrolyzed. Together with the *o*-alkenylphenol and 6-alkenyl-2-methylphenol which were formed as products of rearrangement, significant amounts of phenol and *o*-cresol were formed concurrently.

The α-alkylcrotyl (alkyl being ethyl, *n*-propyl, or *n*-butyl) ethers of phenol and *o*-cresol were prepared and heated also. Phenol and *o*-cresol were isolated as reaction products in these experiments also, but no other alkali-soluble material was identified.

New physical data on various allyl derivatives of catechol and resorcinol have been obtained.

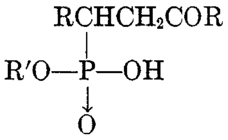
[Contribution from the Chemical Laboratory of the University of Illinois]

PHOSPHONIC ACIDS AND THEIR ALKYL ESTERS FROM α,β-UNSATURATED KETONES

LEWIS R. DRAKE AND C. S. MARVEL

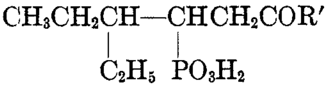
Received October 11, 1937

An interest in organic phosphorus compounds containing in the molecule a long aliphatic group has led us to investigate methods by which such compounds may be obtained. In the work reported here general methods for obtaining two types of such phosphorus compounds (I and II, where R′ is a long alkyl group) from α,β-unsaturated ketones have been developed.



$R'O{-}P(\rightarrow O)(OH){-}CH(R)CH_2COR$

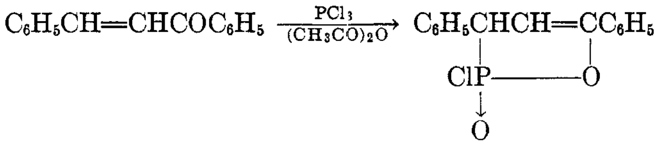
I



$CH_3CH_2CH(C_2H_5){-}CH(PO_3H_2)CH_2COR'$

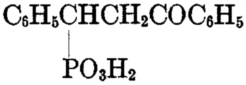
II

Previous work by Conant and his coworkers[1] has shown that phosphorus trichloride adds 1,4 to benzalacetophenone (III), or any closely related α,β-unsaturated ketone, to give an intermediate cyclic acid chloride (IV), which can be hydrolyzed to a ketophosphonic acid (V), or by the action of phenol converted to esters of type VI or VII.



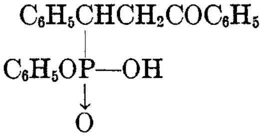
$C_6H_5CH{=}CHCOC_6H_5 \xrightarrow[(CH_3CO)_2O]{PCl_3} C_6H_5CHCH{=}CC_6H_5$ (with $ClP(\rightarrow O){-}O$ bridging)

III IV



$C_6H_5CH(PO_3H_2)CH_2COC_6H_5$

V



$C_6H_5O{-}P(\rightarrow O)(OH){-}CH(C_6H_5)CH_2COC_6H_5$

VI

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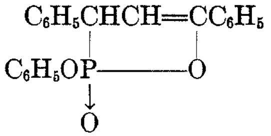
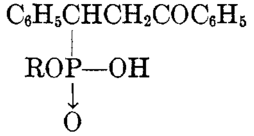
[1] (*a*) Conant, *J. Am. Chem. Soc.*, **39**, 2679 (1917); (*b*) Conant and Cook, *ibid.*, **42**, 830 (1920); (*c*) Conant and Pollack, *ibid.*, **43**, 1665 (1921); (*d*) Conant, Bump, and Holt, *ibid.*, **43**, 1677 (1921); (*e*) Conant, McDonald, and McB. Kinney, *ibid.*, **43**, 1928 (1921); (*f*) Conant and Coyne, *ibid.*, **44**, 2530 (1922); (*g*) Conant, Braverman and Hussey, *ibid.*, **45**, 165 (1923); (*h*) Conant, Wallingford, and Gandheker, *ibid.*, **45**, 762 (1923); (*i*) Conant and Wallingford, *ibid.*, **46**, 192 (1924); (*j*) Conant and Jackson, *ibid.*, **46**, 1003 (1924).



VII

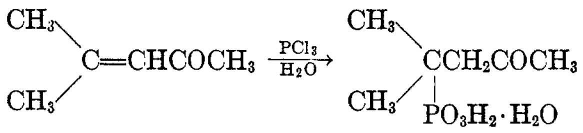
In the present work it was found that this cyclic acid chloride (IV) would react with the long-chain aliphatic alcohols—1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol, 1-octadecanol, and octadec-9-en-1-ol—to produce crystalline mono esters which are alkali-insoluble. This property indicated that the esters were of the cyclic type (VII). However, analysis showed that each ester contained two hydrogen atoms and one oxygen atom more than the cyclic molecule accounted for, and also, when treated with methylmagnesium iodide, each ester liberated one equivalent of methane and added one equivalent of methylmagnesium iodide. Hence, it is apparent that the presence of a long-chain alkyl group attached by an oxygen to the phosphorus atom masks some of the acidic properties of the hydroxyl group in compounds of the type illustrated by formula VIII.



$$\begin{array}{l} C_6H_5\underset{|}{C}HCH_2COC_6H_5 \\ ROP\text{—}OH \\ \quad\;\downarrow \\ \quad\;O \end{array}$$

VIII

Phosphorus trichloride combined readily with mesityl oxide (IX), and hydrolysis of the reaction mixture gave the ketophosphonic acid (X) in 33 per cent. yields. This acid proved to be identical with one previously



IX X

obtained by Michaelis[2] by the action of phosphorus trichloride and aluminum chloride on acetone. Michaelis assigned his compound the α-phosphonic acid structure (XI) but the present method of synthesis shows that the phosphonic acid group must be in the β-position with respect to the keto group.

$$(CH_3)_2CH\underset{\displaystyle PO_3H_2}{\underset{|}{C}}HCOCH_3$$

XI

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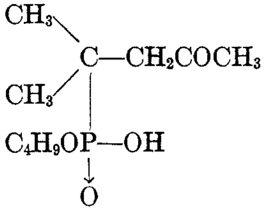
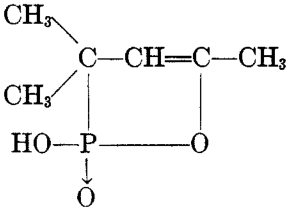
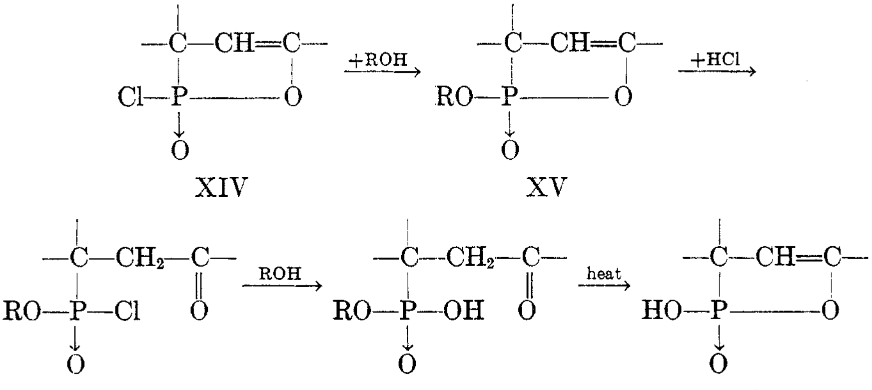
[2] MICHAELIS, *Ber.*, **17**, 1273 (1884); **18**, 898 (1885).

Mesityl oxide was treated with phosphorus trichloride in acetic anhydride solution and then alcohols were added as was done in the benzalacetophenone series. The esters did not crystallize but were obtained in liquid form. By distilling the reaction mixture at very low pressures (2 to 10 × 10^{-4} mm.) it was possible to isolate some of the expected esters. The *n*-butyl ester (XII) was obtained in fair yield. The *n*-decyl ester was isolated but the yield was very low. When either 1-tetradecanol or 1-hexadecanol was used, the product isolated appeared to be the cyclic compound XIII. *n*-Tetradecyl chloride was isolated in good yields from the experiment using the corresponding alcohol. This gives a hint as to the manner in which the various products are formed when one of the cyclic phosphonyl chlorides (XIV) is treated with an alcohol. The first step in the reaction is probably the formation of the cyclic ester (XV) and hydrogen chloride. These then combine to open the oxygen bridge, giving the ester acid chloride (XVI), which reacts again with the alcohol.


XII


XIII


XIV XV

XVI XVII XVIII

In this reaction the phosphonyl chloride acts on the alcohol to replace the hydroxyl group by chlorine. When the mono ester (XVII) is heated it may lose a molecule of alcohol to give a cyclic compound (XVIII). It must be recognized that the reactions may proceed in an entirely different sequence. Thus the first step may be the formation of an alkyl chloride and the cyclic compound (XVIII), which then may or may not open with a molecule of alcohol to give the mono ester (XVII).

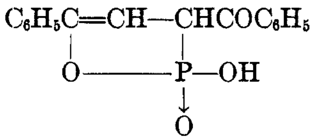
Dibenzoylethylene (XIX) was treated with phosphorus trichloride, and the intermediate addition product was rapidly hydrolyzed to the expected diketophosphonic acid (XX). When the intermediate addition product was treated with either 1-decanol or 1-tetradecanol it was converted into the cyclic compound (XXI) and some of the free acid (XX) was also formed. *n*-Tetradecyl chloride was isolated in good yields when 1-tetradecanol was used in this reaction.

$C_6H_5COCH{=}CHCOC_6H_5$

XIX

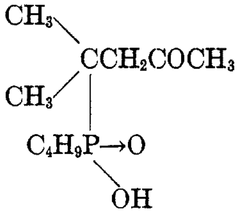
$C_6H_5COCH_2CH(PO_3H_2)COC_6H_5$

XX

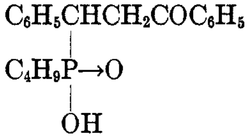


XXI

Conant, Bump, and Holt[1d] found that phenyldichlorophosphine ($C_6H_5PCl_2$) would add readily to benzalacetophenone, and that hydrolysis of the intermediate addition product with water gave a disubstituted phosphonic acid. We found that *n*-butyldichlorophosphine ($n\text{-}C_4H_9PCl_2$) added readily to mesityl oxide and to benzalacetophenone, and the expected products (XXII and XXIII) were obtained on hydrolysis.



XXII

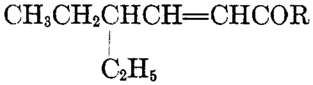


$C_6H_5CHCH_2COC_6H_5$ with $C_4H_9P(\rightarrow O)OH$ on the CH

XXIII

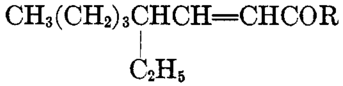
Diphenoxychlorophosphine $(C_6H_5O)_2PCl$, which had previously been shown to add to benzalacetophenone[1b] to give the mono (VI) and the diphenyl ester of the ketophosphonic acid (V), has now been found to add to mesityl oxide and methyl vinyl ketone. Methyl vinyl ketone also added phosphorus trichloride, and, while the corresponding phosphonic acid could not be isolated, a small yield of the didecyl ester was obtained.

The second type (II) of phosphorus compound, containing a long alkyl residue, was obtained from phosphorus trichloride and long chain aliphatic α,β-unsaturated ketones. A number of typical ketones were prepared by condensation of 2-ethylbutanal and 2-ethylhexanal with the methyl groups of acetone, 2-heptanone, and 2-octanone in the presence of methyl alcoholic potassium hydroxide solution,[3] followed by dehydration with



$$\underset{\displaystyle C_2H_5}{CH_3CH_2\underset{|}{C}HCH{=}CHCOR}$$

XXIV



$$\underset{\displaystyle C_2H_5}{CH_3(CH_2)_3\underset{|}{C}HCH{=}CHCOR}$$

XXV

$$R = CH_3, \quad n\text{-}C_5H_{11}, \quad \text{or} \quad n\text{-}C_6H_{13}$$

sulfuric acid. All except one (XXV, $R = n\text{-}C_6H_{13}$) of these α,β-unsaturated ketones (XXIV and XXV) combined with phosphorus trichloride to give a product which could be hydrolyzed to an alkali-soluble phosphonic acid. None of the addition products was obtained in a high state of purity because their physical properties were not such as to permit purification by crystallization or distillation. Some of the crude products analyzed high in phosphorus, indicating that water was apparently lost through anhydride formation and cyclization. There is, however, no question about the ready addition of phosphorus trichloride to these ketones.

This work shows (1) that the 1,4-addition of phosphorus trichloride and the closely related $RPCl_2$ and $(RO)_2PCl$ types to α,β-unsaturated ketones is a very general reaction and (2) that a phosphonyl acid chloride thus obtained may react with an alcohol to give either the alkyl phosphonyl ester and hydrogen chloride or the phosphonic acid and the alkyl chloride.

Under the conditions used with phosphorus trichloride and benzalacetophenone, no evidence of the addition of arsenic trichloride to benzalacetophenone or of phosphorus trichloride to phenyl cinnamate could be obtained.

EXPERIMENTAL

n-*Butyldichlorophosphine.*—Guichard's method[4] for preparing related alkyl dichlorophosphines was adapted to our needs. Fifty grams of di-*n*-butylmercury was placed in a large Pyrex bomb tube, and the tube was flushed out with nitrogen. Then 100 g. of phosphorus trichloride was run in slowly. A silky white precipitate came down almost immediately. The tube was sealed and heated in an electric

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[3] (*a*) POWELL AND BALDWIN, *J. Am. Chem. Soc.*, **58**, 1871 (1936); (*b*) WICKERT AND CARTER, Brit. Pat. 446,084; *Chem. Abstr.*, **30**, 6758 (1936); (*c*) Carbide and Carbon Chemicals Corporation, *Fr.* 799,037; *Chem. Abstr.*, **30**, 7581 (1936); (*d*) *Fr.* 798,967; *Chem. Abstr.*, **30**, 7583 (1936).

[4] GUICHARD, *Ber.*, **32**, 1572 (1899).

oven at 200° for nine hours. A considerable amount of carbonaceous material and free mercury were produced during the heating. The tube was cooled and opened and the contents of the tube were diluted with phosphorus trichloride to aid in transferring the material to a distilling flask. Fractional distillation gave 17 g. (61.4 per cent.) of a product boiling at 157–150° at 750 mm. The product fumed in air. Analysis indicated that the product was contaminated with some non-phosphorus derivative probably *n*-butylmercury chloride.

Anal. Calc'd for $C_4H_9Cl_2P$: P, 19.5. Found: P, 17.6, 17.24.

1,3-Diphenylpropan-1-one-3-phosphonic acid.—The hydrated acid was prepared by the method of Conant and Cook[1b] and melted at 117–118°. By recrystallization of a sample from anhydrous ethyl acetate, the anhydrous acid, m.p. 165–167°, was obtained. Recrystallization of the anhydrous acid from 45 per cent. alcohol gave the hydrated form.

Anal. Calc'd for $C_{15}H_{15}O_4P$: P, 10.7; neutr. equiv. 145.
Found: P, 10.67, 10.91; neutr. equiv. 144, 145.

Monoalkyl 1,3-diphenylpropan-1-one-3-phosphonates.—A mixture of 1 mole of benzalacetophenone, 1.5 moles of phosphorus trichloride and 1 mole of acetic anhydride was allowed to stand at 35° for three hours and then warmed under a pressure of 30 mm. to 70° for three hours. To the residue 2 moles of the alcohol was added, and the mixture was warmed to 125–135° on a hot plate for three hours. After standing overnight the solution was treated with 100 cc. of anhydrous ether, and the crystalline material which separated was collected by filtration, washed with ether, and recrystallized from ethyl acetate. The time required for the separation of the ester varied with the alcohol used. The *n*-decyl ester crystallized very soon after the addition of the ether but the *n*-octadecyl ester required almost a week to separate. None of these esters dissolved in sodium carbonate solution. The *n*-decyl, *n*-tetradecyl and *n*-hexadecyl esters were treated with methylmagnesium iodide in the Grignard machine.[5] These experiments are recorded in Table II.

TABLE I

MONOALKYL 1,3-DIPHENYLPROPAN-1-ONE-3-PHOSPHONATES

R GROUP	BENZAL-ACETO-PHENONE USED, g.	YIELD OF ESTER, g.	YIELD OF ESTER, PER CENT	M.P., °C.	EMPIRICAL FORMULA	ANAL., P PER CENT	
						Calc'd	Found
n-Decyl	104	172.5	80	107–108	$C_{25}H_{35}O_4P$	7.21	7.32, 7.22
n-Dodecyl	8	5.4	38.6	110–113	$C_{27}H_{39}O_4P$	6.77	6.60, 6.58
n-Tetradecyl	10	11.5	49	112–114	$C_{29}H_{43}O_4P$	6.37	6.40, 6.41
n-Hexadecyl	50	25	21	108–110	$C_{31}H_{47}O_4P$	6.04	6.11, 6.17
n-Octadecyl	50	15	9	105–109	$C_{33}H_{51}O_4P$	5.72	5.90, 5.95
n-Octadec-9-enyl	20.3	23.6	44	89–90	$C_{33}H_{49}O_4P$	5.75	5.76, 5.81

The *n*-decyl ester (1 g.) was hydrolyzed by boiling for one hour with 5 cc. of 10 per cent. aqueous sodium hydroxide. The decyl alcohol which separated was converted to the 3,5- dinitrobenzoyl ester which weighed 0.05 g. and melted at 53–55°.[6]

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[5] KOHLER, STONE, AND FUSON, *J. Am. Chem. Soc.*, **49**, 3181 (1927).

[6] The melting point given in the literature is 56–57°; REICHSTEIN, *Helv. Chim. Acta*, **9**, 802 (1926).

The alkaline residue was acidified, and the 1,3-diphenylpropan-1-one-3-phosphonic acid was filtered off and crystallized from ethyl acetate. The yield was 0.62 g. melting at 165–166°.

An attempt to reduce 10 g. of the *n*-decyl ester in 100 cc. of absolute alcohol containing a trace of hydrogen chloride[7] with hydrogen and a platinum oxide-platinum black[8] catalyst at 65° caused cleavage of the ester to give 2 g. of *n*-decyl alcohol, which was removed by distillation under a pressure of 1×10^{-4} mm. in a Hickman still.[9] The residue from this distillation was crystallized from cyclohexane. It melted at 168–171°. A mixture of this compound and anhydrous 1,3-diphenyl-propan-1-one-3-phosphonic acid melted at 142–144°. Analysis indicated that this new acid was formed by reduction of the ketone group to a methylene group.

Anal. Calc'd for $C_{15}H_{17}O_3P$: P, 11.22. Found: P, 11.11, 11.24.

4-Methylpentan-2-one-4-phosphonic acid.—A mixture of 19.6 g. of mesityl oxide, 30 g. of phosphorus trichloride and 20 g. of acetic anhydride was allowed to stand in a stoppered flask at 35° for twelve hours. The material was transferred to a Claisen flask and distilled under reduced pressure. A fraction of 12 g. boiling at 100–105° at 10 mm. was collected. This was not analyzed but was presumably the cyclic mono-acid chloride. It was poured into water, and the mixture became very warm and turned brown. Evaporation under reduced pressure left an oil which after the addition of about 1 cc. of water was allowed to stand. After about one week the material had crystallized. The crystals were collected on a filter and then dried on a clay plate. The melting point was 62–63° and was not changed when the acid was recrystallized from water.

TABLE II

MONOALKYL 1,3-DIPHENYLPROPAN-1-ONE-3-PHOSPHONATES AND METHYLMAGNESIUM IODIDE

R GROUP	SAMPLE, g.	SAMPLE IN MILLIEQUIVALENTS	CH_4, MILLIEQUIVALENTS	ADDED CH_3MgI, MILLIEQUIVALENTS
n-Decyl	0.200	0.465	0.530	0.457
n-Decyl	0.200	0.465	0.526	0.453
n-Tetradecyl	0.100	0.205	0.196	0.191
n-Tetradecyl	0.230	0.475	0.492	0.460
n-Hexadecyl	0.220	0.427	0.426	0.401
n-Hexadecyl	0.100	0.194	0.201	0.210

Anal. Calc'd for $C_6H_{13}PO_4H_2O$: P, 15.6. Found: P, 15.9, 15.7.

Alkyl esters of 4-methylpentan-2-one-4-phosphonic acid.—A mixture of 9.8 g. of mesityl oxide, 15 g. of phosphorus trichloride and 10 g. of acetic anhydride was allowed to stand for two hours and then the volatile material was removed by heating to 70° under 18 mm. pressure. The residue was treated with a solution of 2.3 g. of sodium in 20 cc. of *n*-butyl alcohol and excess ether. The ether was removed by

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[7] BROWN, DURAND, AND MARVEL, *J. Chem. Am. Soc.*, **58**, 1594 (1936).

[8] ADAMS, VORHEES, AND SHRINER, *Organic Syntheses*, Coll. Vol. I. John Wiley and Sons, Inc., New York, **1932**, p. 452.

[9] HICKMAN AND SANFORD, *J. Phys. Chem.*, **34**, 643 (1930).

distillation, and the remainder was warmed at 100° for three hours. The resulting oil was taken up in ether, washed with 10 per cent. sodium carbonate solution, 10 per cent. sulfuric acid solution, and water. After drying of the ether solution over anhydrous magnesium sulfate and filtering, the solvent was removed. Five grams of light yellow oil remained. This was distilled in the Hickman still.[9] There was thus obtained 4.7 g. (20 per cent.) of *n*-butyl 4-methylpentan-2-one-4-phosphonate; b.p., 82–100° at 2×10^{-4} mm.; n_D^{20}, 1.4590; d_4^{20}, 1.110.

Anal. Calc'd for $C_{10}H_{21}O_4P$: P, 13.15. Found: P, 13.15; 12.85.

In a similar manner from 49 g. of mesityl oxide, 69 g. of phosphorus trichloride, 51 g. of acetic anhydride and 158 g. of decyl alcohol there were obtained 43 g. of decyl alcohol; 4 g. (2.5 per cent.) of *n*-decyl 4-methylpentan-2-one-4-phosphonate; b.p., 104–145° at 1×10^{-4} mm.; n_D^{20}, 1.4580; d_4^{20}, 0.9800; and a residue which could not be distilled without decomposition.

Anal. Calc'd for $C_{16}H_{32}O_4P$: P, 9.7. Found: P, 9.50, 9.40.

When similar attempts were made to prepare *n*-tetradecyl and *n*-hexadecyl esters of this acid the products obtained on distillation were the corresponding alkyl chlorides, respectively, and the residue was apparently the cyclic compound (XV).

From 49 g. of mesityl oxide, 69 g. of phosphorus trichloride, 51 g. of acetic anhydride and 107 g. of 1-tetradecanol there was obtained 36.5 g. (31 per cent.) of *n*-tetradecyl chloride, b.p., 44–53° at 2×10^{-4} mm.; 139–142° at 4 mm.; n_D^{20}, 1.4450; d_4^{20}, 0.8589.

Anal. Calc'd for $C_{14}H_{29}Cl$; Cl, 15.15. Found: Cl, 14.82.

The residue from this distillation sublimed on heating to about 110° at 2×10^{-4} mm. pressure. The crystals thus obtained were washed with acetone, and they melted at 143–144°. The product could be recrystallized from dioxane without change of melting point. This solid rapidly decolorized a solution of bromine in carbon tetrachloride.

Anal. Calc'd for $C_6H_{11}O_3P$: P, 19.1; neutr. equiv. 162.
Found: P, 19.15, 19.24; neutr. equiv. 163, 161.

This compound was boiled for two days with less than the theoretical amount of aqueous alkali containing a little phenolphthalein but the color was not discharged indicating that the ring was not opened by this treatment.

From 68.7 g. of mesityl oxide, 70 g. of phosphorus trichloride, 51 g. of acetic anhydride and 121 g. of 1-hexadecanol there was obtained 80 g. (61.5 per cent.) of *n*-hexadecyl chloride; b.p., 73–90° at 1×10^{-4} mm.; n_D^{20}, 1.4458; d_4^{20}, 0.8520.

Anal. Calc'd for $C_{16}H_{33}Cl$: Cl, 13.64. Found: Cl, 13.52.

About 1 g. of the same solid, m.p., 141–143° which was obtained in the preceding experiment was isolated by heating the residue after removal of the *n*-hexadecyl chloride.

1,4-Diphenylbutan-1,4-dione-2-phosphonic acid.—A mixture of 23.6 g. of dibenzoylethylene, 9.8 g. of phosphorus trichloride and 10 g. of acetic anhydride was allowed to stand for three hours at 35°. The volatile material was then removed by heating to 70° under about 70 mm. pressure. The residual sticky material was dissolved in chloroform, and water was added slowly until a total of 15 g. was introduced. A greenish solid separated and was removed by filtration. After crystallization from ethyl acetate, the product weighed 18.5 g. (81.5 per cent. based on the phosphorus trichloride) and melted at 183–185° with some decomposition.

Anal. Calc'd for $C_{16}H_{13}O_5P$: P, 9.75; neutr. equiv. 159.
Found: P, 9.80, 10.05; neutr. equiv. 155, 159.

Cyclic compound (XXI) from above acid.—A reaction mixture of 11.8 g. of dibenzoylethylene, 9.4 g. of phosphorus trichloride and 5 g. of acetic anhydride was allowed to stand as above and then treated with 1-decanol in the hope of obtaining this ester. The mixture was heated for two hours at 100–120°, and the brown liquid was set aside for about two weeks. A light tan solid (0.7 g.) separated and after washing with ether, melted at 197–198°.

Anal. Calc'd for $C_{16}H_{13}O_4P$: P, 10.32. Found: P, 10.22, 10.50.

Addition of excess ether to the solution from which this compound separated caused the precipitation of a small amount of the free acid, m.p., 183–185°. Distillation of the mother liquor yielded about 4 g. of decene (b.p., 81–83° at 20 mm.; n_D^{20}, 1.4260; d_4^{20}, 0.7520) and 4 g. of 1-decanol (b.p., 130–125° at 20 mm.; n_D^{20}, 1.4355).

Another reaction mixture of the same size was treated with an equivalent amount of 1-tetradecanol. This gave 1 g. of the cyclic compound (m.p., 197–199°); 2.5 g. of the pure acid (m.p., 183–185°), 7 g. of *n*-tetradecyl chloride (b.p., 120–125° at 4 mm.; n_D^{20}, 1.4452; d_4^{20}, 0.8587), and 3 g. of 1-tetradecanol (b.p., 140° at 4 mm.; m.p., 36–38°).

n-Butyl 1,3-diphenylpropan-1-one-3-phosphonic acid (*XXIII*).—A mixture of 5 g. of *n*-butyldichlorophosphine, 6.5 g. of benzalacetophenone, and 3.2 g. of acetic anhydride was allowed to stand at 35° for six hours. The volatile material was evaporated under 18 mm. pressure at 70°, and the residue was dissolved in chloroform and treated with 10 cc. of water. The chloroform solution was extracted with 50 cc. of ten per cent. sodium hydroxide solution, and the alkaline solution was extracted with ether. Acidification of the solution precipitated a yellow oil which was collected in ether and treated twice with decolorizing carbon. Then the solution was dried over anhydrous magnesium sulfate. Evaporation left a yellow solid which was crystallized from dioxane after treatment with decolorizing carbon. The yield was 5 g. (50 per cent.) of a colorless product, m.p., 191–193°.

Anal. Calc'd for $C_{19}H_{23}O_3P$: P, 9.40; neutr. equiv., 330.
Found: P, 9.60, 9.20; neutr. equiv., 330, 328.

Potassium n-butyl 4-methylpentan-2-one-4-phosphonate (*XXII*).—A reaction mixture of 3 g. of mesityl oxide, 5 g. of *n*-butyldichlorophosphine and 3 g. of acetic anhydride was allowed to stand for twenty-four hours. Evaporation at 70° and 20 mm. left a sticky residue which was taken up in 25 cc. of 10 per cent. sodium hydroxide solution and extracted continuously with ether for about twenty-four hours. The free acid was liberated with dilute sulfuric acid, collected in ether, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed by heating on a steam cone. The residual sticky material weighed 5 g. after drying in a desiccator.

Anal. Calc'd for $C_{10}H_{21}O_3P$: P, 14.1. Found: P, 16.22, 15.90.

Since this analysis indicated that the free acid was not pure, the material was taken up in water and treated with 1.5 g. of potassium hydroxide to give a solution which was essentially neutral to litmus. Any free acid or anhydride was removed by extraction with ether. The water was removed by addition of benzene and slow distillation. The residual potassium salt was very hygroscopic.

Anal. Calc'd for $C_{10}H_{20}KO_3P$: P, 12.0. Found: P, 12.2, 12.3.

Diphenyl 4-methylpentan-2-one-4-phosphonate.—A mixture of 4 g. of mesityl oxide and 10 g. of diphenoxychlorophosphine was allowed to stand at 25° for one hour. Then 5 g. of glacial acetic acid was added, and the reaction mixture was set aside for two days. Since no crystals separated ether was added, and the ether solution was extracted twice with 10 per cent. sodium hydroxide solution. The ether solution was dried, the solvent was removed, and the residue was distilled. The yield was 5.4 g. (41 per cent.) of the diphenyl ester, b.p., 136–150° at 8×10^{-4} mm.; n_D^{20}, 1.5531. The ester was soluble in paraffin oil. It reacted with bromine in carbon tetrachloride to evolve hydrogen bromide.

Anal. Calc'd for $C_{18}H_{21}O_4P$: P, 9.34. Found: P, 9.53, 9.50.

Diphenyl butan-2-one-4-phosphonate.—In a similar manner 1.3 g. (13.6 per cent.) of this ester was prepared from 3.5 g. of methyl vinyl ketone and 8.2 g. of diphenoxychlorophosphine. B.p., 95–112° at 3×10^{-4} mm.; n_D^{20}, 1.5575; d_4^{20}, 1.222.

Anal. Calc'd for $C_{16}H_{17}O_4P$: P, 10.2. Found: P, 9.38, 10.1.

Didecyl butan-2-one-4-phosphonate.—An attempt to isolate the phosphonic acid by the addition of phosphorus trichloride to methyl vinyl ketone and hydrolysis of the addition product did not yield the desired product. However, by treatment of 3.5 g. of the ketone with 6.8 g. of phosphorus trichloride and 5 g. of acetic anhydride and addition after two days of 7.9 g. of 1-decanol in 25 cc. of chloroform, a product corresponding in analysis to the di-*n*-decyl ester was obtained on distillation. The yield was 0.4 g. (1.8 per cent) of product boiling at 120–170° at 1×10^{-4} mm.; n_D^{20}, 1.4528; d_4^{20}, 0.9287.

Anal. Calc'd for $C_{24}H_{49}O_4P$: P, 7.17. Found: P, 7.10, 6.95.

α, β-Unsaturated ketones from 2-ethylhexanal and 2-ethylbutanal.—The technical octyl aldehyde of Carbide and Carbon Chemicals Corporation was redistilled, and the 2-ethylhexanal boiling at 162–165° at 753 mm.; n_D^{20}, 1.4150; d_4^{20}, 0.8205 was collected. The 2,4-dinitrophenylhydrazone prepared by the method of Allen[10] was crystallized from dilute alcohol, and melted at 114–115°.

Anal. Calc'd for $C_{14}H_{20}N_4O_4$: N, 18.20. Found: N, 18.28.

The technical ethylbutyraldehyde of Carbide and Carbon Chemicals Corporation was redistilled and the 2-ethylbutanal boiling at 115–116° at 740 mm.; n_D^{20}, 1.4025; d_4^{20}, 0.811 was collected. Its 2,4-dinitrophenylhydrazone was obtained as light yellow plates which melted at 129–130° after recrystallization from ethyl acetate.

Anal. Calc'd for $C_{12}H_{16}N_4O_4$: N, 20.00. Found: N, 20.20.

These two aldehydes were each condensed with acetone, 2-heptanone and 2-octanone by heating the various reaction mixtures on the steam cone from eighteen to twenty-four hours in 25 to 50 cc. of methyl alcohol containing 1 g. of potassium hydroxide. After the alkaline tretament, the solution was treated with dilute sulfuric acid. The organic layer was separated and then boiled with 50 cc. of 10 per cent. sulfuric acid for about three hours. The sulfuric acid was removed, and the organic material was dried and distilled. Some of these products have been described previously in the patent literature.[3,b,c,d] The results of the experiments are collected in Table III.

5-Ethylnonan-2-one-4-phosphonic acid.—A mixture of 10 g. of 5-ethylnon-3-en-2-one, 8.5 g. of phosphorus trichloride and 6.2 g. of acetic anhydride was placed in an Erlenmeyer flask and held at 35° for three hours. The volatile material was then removed by evaporation at 70° under 18 mm. pressure. The residual heavy viscous mass was dissolved in ether and small amounts of water were added. The ether solution was then extracted with 10 per cent. sodium hydroxide solution; the alkaline solution was separated and acidified with 10 per cent. sulfuric acid. The free phosphonic acid was taken up in ether, and the ether solution was dried over anhydrous magnesium sulfate and treated twice with decolorizing carbon. On evaporation

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[10] ALLEN, *J. Am. Chem. Soc.*, **52**, 2955 (1930).

TABLE III

New α, β-Unsaturated Ketones

ALDEHYDE	AMT., g.	KETONE	AMT., g.	COMPOUND OBTAINED	AMT., g.	B.P., °C.	n_D^{20}	d_4^{20}	EMPIRICAL FORMULA	ANALYSIS Calc'd C	ANALYSIS Calc'd H	ANALYSIS Found C	ANALYSIS Found H
2-Ethylhexanal	64	Acetone	90	5-Ethylnon-3-en-2-one	22.5	163–167 at 2 mm.	1.4920	0.9059	$C_{11}H_{20}O$	78.60	11.90	78.40	11.67
2-Ethylhexanal	32	2-Heptanone	28	9-Ethyltri-dec-7-en-6-one[3c]	16	159–162 at 15–16 mm.	1.4540	0.8455	$C_{15}H_{28}O$	80.36	12.50	80.25	12.20
2-Ethylhexanal	40	2-Octanone	40	10-Ethyltetradec-8-en-7-one	30	130–134 at 3–4 mm.	1.4545	0.8479	$C_{16}H_{30}O$	80.67	12.60	80.70	13.01
2-Ethylhexanal				By-product	10	80–93 at 1 × 10^{-4} mm.	1.4800	0.8823	$C_{24}H_{44}O$	82.76	12.64	82.74	12.72
2-Ethylbutanal	50	Acetone	58	5-Ethylhept-3-ene-2-one[3b,d]	5	85–88 at 20 mm.	1.4470	0.8631	$C_9H_{16}O$	77.14	11.43	76.63	11.80
				3,9-diethylundec-4,7-dien-6-one[3d]	16	120–122 at 1–2 mm.	1.4940	0.9181	$C_{15}H_{26}O$	81.08	11.71	81.41	11.36
2-Ethylbutanal	50	2-Heptanone	57	3-Ethylundec-4-en-6-one[3d]	40	141–143 at 19 mm.	1.4530	0.8496	$C_{13}H_{24}O$	79.59	12.24	79.53	12.39
2-Ethylbutanal	28	2-Octanone	36	3-Ethyldodec-4-en-6-one	15	97–103 at 2 mm.	1.4550	0.8500	$C_{14}H_{26}O$	80.00	12.39	79.90	12.34

of the ether and drying for two days in a vacuum desiccator over sulfuric acid, a light brown spongy mass weighing 5 g. remained. Low phosphorus content showed that some impurities were still present. This residue was again taken up in ether and treated twice with decolorizing carbon. The residue after removal of ether was again dried under reduced pressure over sulfuric acid. The solid then melted at 66–69°.

Anal. Calc'd for $C_{11}H_{23}O_4P$: P, 12.4. Found: P, 11.26, 11.26.

Sodium 9-ethyltridecan-6-one-8-phosphonate.—In a similar manner the phosphonic acid was prepared from 5 g. of 9-ethyltridec-7-en-6-one, 3.42 g. of phosphorus trichloride, 2.5 g. of acetic anhydride and a few cc. of water. About 0.5 g. of a dark brown oil was obtained. This oil was exactly neutralized with 0.3 *N* sodium hydroxide solution, and this alkaline solution was mixed with benzene and distilled to remove all of the water. After removal of water and benzene, the residue was washed with acetone and dried on a clay plate in a vacuum desiccator over sulfuric acid.

Anal. Calc'd for $C_{15}H_{29}Na_2O_4P$: P, 8.85. Found: P, 8.5.

5-Ethylheptan-2-one-4-phosphonic acid.—From 4 g. of 5-ethylhept-3-en-2-one, 4 g. of phosphorus trichloride and 3 g. of acetic anhydride there was obtained 4 g. of a dark brown viscous material which would not solidify. It was soluble in alkali to give solutions which foamed readily.

Anal. Calc'd for $C_9H_{19}O_4P$: P, 13.95. Found: P, 13.5. 13.3.

Anhydride of 3,9-diethylundec-4-en-6-one-8-phosphonic acid.—From 10 g. of 3,9-diethylundec-4,7-dien-6-one, 7 g. of phosphorus trichloride and 5 g. of acetic anhydride a thick yellow oil resulted. After drying in a vacuum desiccator over sulfuric acid, this changed to a yellow solid which was very hygroscopic. Analysis indicated that this material was probably an anhydride of the expected phosphonic acid.

Anal. Calc'd for $C_{30}H_{52}O_5P_2$: P, 11.20. Found: P, 11.10, 11.70.

3-Ethylundecan-6-one-4-phosphonic acid.—From 10 g. of 3-ethylundec-4-en-6-one, 7.5 g. of phosphorus trichloride, and 5.6 g. of acetic anhydride there was obtained a thick yellow oil which seemed to be an anhydride of the expected acid.

Anal. Calc'd for $C_{20}H_{48}P_2O_5$: P, 12.32. Found: P, 12.54.

On redissolving this oil in ether and evaporating slowly, first in the air, and then in a vacuum desiccator, a spongy yellow mass weighing 5 g. and melting at 60–65° was obtained.

Anal. Calc'd for $C_{13}H_{27}O_4P$: P, 11.15. Found: P, 11.3, 11.48.

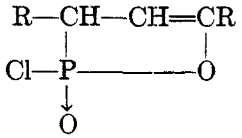
Anhydride of 3-ethyldodecan-6-one-4-phosphonic acid.—From 10 g. of 3 ethyldodec-4-en-6-one, 6.8 g. of phosphorus trichloride, and 5 g. of acetic anhydride by the usual procedure, 10 g. of a thick dark oily material was obtained. Analysis indicated the anhydride but evaporation with moist ether did not give a solid acid as it did in the preceding experiment.

Anal. Calc'd for $C_{28}H_{52}O_5P_2$: P, 11.70. Found: P, 11.70, 11.63.

SUMMARY

1. The addition of phosphorus trichloride to α,β-unsaturated ketones has been shown to be a general reaction for alkyl substituted as well as aryl substituted systems of the type RCH=CHCOR.

2. The intermediate addition products of the type

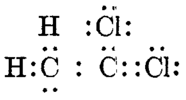


have been found to react with long-chain primary alcohols to yield mono esters of the open-chain ketophosphonic acids and alkyl halides. The monoesters have no marked tendency to form salts with alkalies.

3. Diphenoxychlorophosphine and *n*-butyldichlorophosphine also add readily to the aliphatic α,β-unsaturated ketones to give respectively diphenyl esters of the expected phosphonic acid and a disubstituted phosphonic acid.

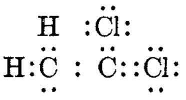
THE PEROXIDE EFFECT IN THE ADDITION OF REAGENTS TO UNSATURATED COMPOUNDS. XV. CORRECTION

In the recent paper under the above general title[1] formula II at the top of page 299 should be



$$\begin{array}{ccc} & \text{H} & :\ddot{\text{Cl}}: \\ \text{H}: & \underset{\cdot\cdot}{\ddot{\text{C}}} & :\ \ddot{\text{C}}::\ddot{\text{Cl}}: \end{array}$$

instead of



$$\begin{array}{ccc} & \text{H} & :\ddot{\text{Cl}}: \\ \text{H}: & \underset{\cdot\cdot}{\ddot{\text{C}}} & :\ \ddot{\text{C}}::\underset{\cdot\cdot}{\ddot{\text{Cl}}}: \end{array}$$

M. S. KHARASCH

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THE UNIVERSITY OF CHICAGO

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[1] KHARASCH, ENGELMANN, AND MAYO, J. ORG. CHEM., **2**, 288 (1937).

INDOLE FORMATION FROM PYRROLES. ADDENDUM AND CORRECTION

In a recent paper[1] all the dimethylindoles related to the dipyrroles were synthesized except the 2,4-isomer. It was concluded, by exclusion, that the latter was the one that resulted from dimethyldipyrrole. The availability of a specimen of 1,2,3-*o*-xylidine has made it possible to complete the series by synthesizing 2,4-dimethylindole from the acet-*o*-xylidide, using the sodium amide procedure. The physical properties of the indole and its picrate, and mixture melting points proved the identity of the substance and the product described in the previous paper. Thus, acid treatment of 2-methylpyrrole, and of the corresponding dipyrrole, give 2,4-dimethylindole.

On page 238, line 25, the word, "impossible," is wrong; it should read, "possible."

C. F. H. ALLEN.

RESEARCH LABORATORIES,
EASTMAN KODAK COMPANY.

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[1] ALLEN, YOUNG, AND GILBERT, J. ORG. CHEM., **2**, 235 (1937).

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

THE ACTION OF MERCURIC ACETATE ON PEPTIDES, DIKETOPIPERAZINES, AND PROTEINS

E. J. MATSON, W. O. TEETERS, AND R. L. SHRINER

Received October 2, 1937

Both peptides[1] and diketopiperazines[2] have been suggested as the structural units in proteins.[3] A reagent which would behave in a different manner with these structures would be valuable. In the present investigation it has been found that a solution of mercuric acetate in very dilute acetic acid does react differentially. Accordingly, a study was made of the action of mercuric acetate on glycylglycine, 2,5-diketopiperazine, 3,6-dimethyl-2,5-diketopiperazine, and three proteins, casein, gelatin, and silk fibroïn. The reagent in all the experiments consisted of an aqueous solution of mercuric acetate to which had been added a few drops of acetic acid in order to prevent the precipitation of mercuric oxide or basic mercuric salts. The concentration of the acetic acid was about 0.5 per cent. in most of the experiments.

Glycylglycine.—Refluxing glycylglycine with the mercuric acetate solution resulted in the complete reduction of the mercuric acetate to free mercury in thirty minutes. Reduction also occurred when the solution was allowed to stand three days at room temperature. The products of this reaction, other than mercury, have not yet been identified but this result parallels the observations of other workers[4] on the action of mercuric acetate with free amino acids. Hydrolysis and oxidation of the peptide evidently took place, resulting in the reduction of the mercuric ion to free mercury.

Diketopiperazines.—Treatment of 2,5-diketopiperazine or 3,6-dimethyl-2,5-diketopiperazine with the mercuric acetate solution produced in each case white insoluble precipitates containing mercury. No reduction to free mercury took place.

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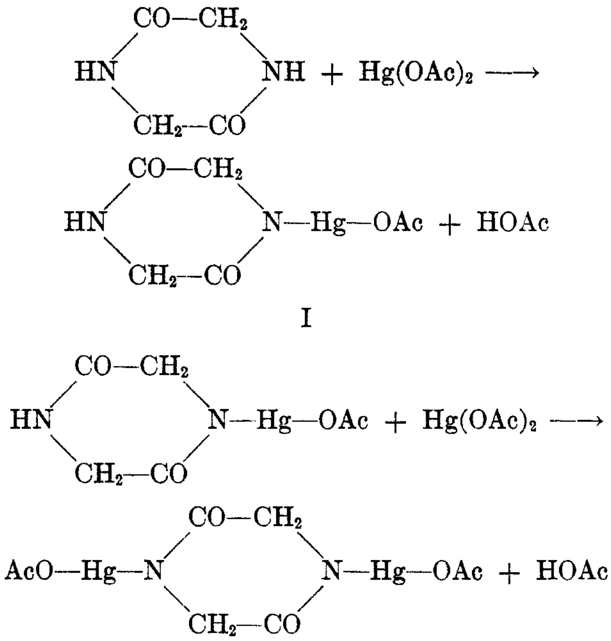
[1] HOFMEISTER, *Ergeb. Physiol.*, **1**, 759 (1902); FISCHER, *Ber.* **35**, 1095 (1902); *ibid.*, **36**, 2094, 2982 (1903); *ibid.*, **39**, 607 (1906).

[2] ABDERHALDEN, *Z. physiol. Chem.*, **128**, 119 (1923); *Naturwissenschaften*, **12**, 716 (1924); ABDERHALDEN AND SCHWAB, *Z. physiol. Chem.*, **139**, 169 (1924).

[3] VICKERY AND OSBORNE, *Physiol. Rev.*, **8**, 393 (1928).

[4] SANNIÉ AND TRUHART, *Compt. rend.*, **196**, 65 (1933); TRUHART, *ibid.*, **204**, 1348 (1937).

Examination of these mercury compounds showed that they were acetoxymercuri derivatives produced by the following reactions:

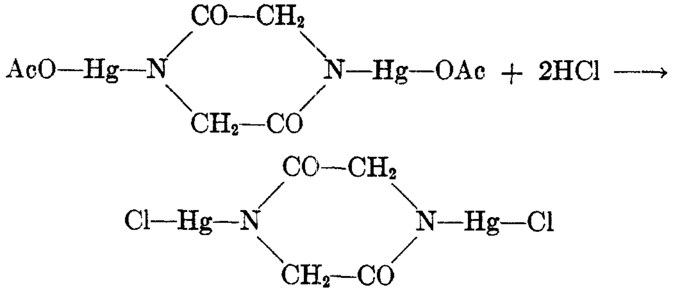


I

II

The monoacetoxymercuridiketopiperazine (I) could not be obtained pure. Even when less than the theoretical amount of mercuric acetate was used in the reaction, analysis of the precipitate showed a high percentage of mercury, indicating the presence of the diacetoxymercuri derivative (II). Upon addition of a solution of the diketopiperazine to an excess of mercuric acetate, compound (II) was obtained; the analysis for nitrogen, mercury, and acetyl group checked the theoretical closely. 3,6-Dimethyl-2,5-diketopiperazine gave an analogous product under similar conditions. These compounds are very stable and quite insoluble in all neutral solvents. Sodium hydroxide solution decomposes these mercuri compounds, forming yellow mercuric oxide, and ammonium sulfide produces mercuric sulfide.

These mercuri derivatives of diketopiperazine are soluble in mineral acids. Exact neutralization of a hydrochloric acid solution of II produced a white insoluble precipitate, which analysis indicates to be the dichloromercuridiketopiperazine (III).

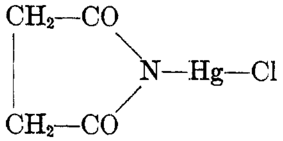


III

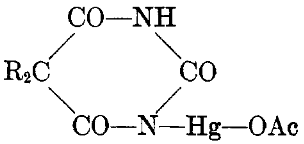
These mercuridiketopiperazines (I, II, III) are represented as $>$N—Hg—X rather than C—Hg—X or —O—Hg—X derivatives by analogy to mercury derivatives of other amides and imides. The chloro-mercuriformamide[5] and chloromercurisuccinimide[6] are assigned the $>$N—Hg—Cl structures IV and V, respectively.

$HCONHHgCl$

IV



V



VI

Rupp and Poggendorf[7] prepared the acetoxymercuri derivatives of substituted barbituric acids (VI), and assigned the $>$N—Hg—OAc structure. Levy and Schaefer[8] have pointed out that the —Hg—O— structure is much less stable than the Hg—N$<$ linkage. The compounds obtained in the present work were characterized by their extreme insolubility in all solvents, which recalls the characteristics of the insoluble, infusible aminomercuric chloride H_2NHgCl.

Proteins.—The action of mercuric acetate on the three proteins, casein, gelatin and silk fibroïn, resulted in the reduction of the mercuric acetate to free mercury. None of the characteristic insoluble acetoxymercuri derivatives of the diketopiperazines was produced.

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[5] Fischer and Grützner, *Arch. Pharm.*, **232**, 329 (1894).

[6] Menschutkin, *Ann.*, **162**, 171 (1872).

[7] Rupp and Poggendorf, *Arch. Pharm.*, **269**, 607 (1931).

[8] Levy and Schaefer, *Ber.*, **35**, 1309 (1902).

In the experiments with casein a small amount of a light-yellow material separated along with the finely divided globules of mercury. This material could not be purified but was separated as well as possible by washing with water and decantation from the mercury. Analysis showed 24.4 per cent. mercury, which is far too low for a mercury-substituted diketopiperazine. During the analysis a tar distilled onto the gold crucible, and after analysis the residue had a strong odor of burnt casein. From the mercury analysis and the observations made during analysis it is believed that the sample was chiefly casein which had occluded droplets of mercury. It is possible that the casein molecule itself may also have been mercurated to some extent,[9] or it may be that some of the cyclic structures present in some of the amino acids underwent mercuration. The product was very small in amount and its properties were totally different from those of the compounds I and II.

The first product of the action of mercuric acetate on gelatin was mercurous acetate. Continued refluxing yielded free mercury. Except for a trace of a flocculent precipitate, silk fibroïn yielded only free mercury as the product, and no acetoxymercuridiketopiperazine derivatives.

In order to obtain reactions with the proteins, three to four days of refluxing was necessary. During this time partial hydrolysis of the protein probably occurred, and the resulting peptides and amino acids reduced the mercuric acetate to free mercury.

For each of these three proteins various workers[2] have announced either the isolation or detection of appreciable amounts of diketopiperazines. The isolation of these rings has commonly involved hydrolysis procedures which are objectionable because they may lead to the secondary formation of diketopiperazines during the reaction. It is evident that no diketopiperazine units were detached by the treatment with mercuric acetate, since if they had been liberated by hydrolysis, the insoluble acetoxymercuri derivatives should have been formed.

The present investigation indicates either that the mercuric acetate solution is not able to detach diketopiperazine units or that no such units are present.

The polypeptide structure is generally accepted, since the physical and chemical properties of the proteins indicate that they are polyfunctional linear polymers; *i.e.* polyamides.[10] Studies of the action of enzymes on peptides, diketopiperazines and proteins, the X-ray diffraction patterns, and the orientation of protein molecules in films all point toward the polypeptide chain structure. In harmony with these investigations is the fact that amino acids, peptides, and proteins yield free mercury as the

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[9] VON RAD, *D. R. P.*, 100,874 (1897).

[10] CAROTHERS, *Chem. Rev.*, **8**, 353 (1931).

final product when refluxed with mercuric acetate solution, whereas diketopiperazines form insoluble acetoxymercuri derivatives.

EXPERIMENTAL

2,5-Diketopiperazine.[11]—In a 1-l. beaker 550 g. (4 moles) of ethyl glycinate hydrochloride[12] was made into a paste with 280 cc. of water. The mixture was kept at −5° in an ice-salt bath and was stirred while 320 cc. of 11.5 *N* sodium hydroxide was dropped in over a period of three hours. The ester hydrochloride gradually went into solution, and some sodium chloride precipitated. The quantity of sodium hydroxide was somewhat less than that necessary for combination with the hydrogen chloride present in the glycine ester. After the addition of the sodium hydroxide the solution was allowed to stand at room temperature for twenty-four hours. The mixture was cooled thoroughly, and the glycine anhydride which had separated was removed by filtration. The glycine anhydride was freed from sodium hydroxide by washing with the smallest amount of ice water possible. The crude product was recrystallized twice from six times its weight of boiling water; Norite was used to decolorize the solution. After the final recrystallization the glycine anhydride no longer gave a positive biuret reaction. The yield of the pure product, which decomposed at 275°, was 10 g., 49 per cent. of the theoretical.

3,6-Dimethyl-2,5-diketopiperazine.[13]—Ninety-six grams of *dl*-alanine was heated in 500 cc. of glycerol at 170–180° for three hours. At the end of that time the solution was clear. It was allowed to stand in the refrigerator for three days. Twice the volume of cold absolute alcohol was stirred into the mixture to make it less viscuous. The crystalline mass was removed by filtration, and was recrystallized twice from hot water. Norite was used in each recrystallization. The crystals were dried at 80° for twenty-four hours. The yield was 4.5 g. The mother liquors were combined and concentrated and allowed to stand again in the refrigerator. By repeated treatment of the mother liquors by the procedure described above, another 16 g. of the pure material was recovered, giving a total yield of 20.5 g., 14.5 per cent. of the theoretical. The pure product melted at 279° (corr.) with decomposition.

Glycylglycine.—The method used for preparing glycylglycine was exactly the procedure reported by Dunn.[14] Glycine was treated with chloroacetyl chloride and sodium hydroxide, to give *N*-chloroacetylglycine. This was then allowed to stand in concentrated ammonium hydroxide solution, forming the desired glycylglycine.

1,4-Diacetoxymercuri-2,5-diketopiperazine.—In 40 cc. of hot water, to which had been added a few drops of acetic acid, there was dissolved 12.72 g. (0.04 mole) of mercuric acetate. The solution was filtered and placed in a 200-cc., three-necked flask equipped with a paraffin oil-sealed stirrer. Another solution was prepared by dissolving 1.14 g. (0.01 mole) of 2,5-diketopiperazine in 35 cc. of hot water. This was added to the refluxing mercuric acetate solution over a period of forty-five minutes. Soon after the addition of the anhydride solution was begun a white precipitate started to form. The product was removed by filtration, washed first with cold

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[11] Fischer, *Ber.* **39B**, 2893 (1906).

[12] Adams and Marvel, Org. Chem. Reag. III, *Univ. Illinois Bull.*, **19**, No. 6, p. 19 (1921).

[13] Shibata and Asahina, *Bull. Chem. Soc. Japan*, **1**, 71 (1926); Maillard, *Compt. rend.*, **153**, 1078 (1911).

[14] Dunn, Butler, and Deakers, *J. Biol. Chem.*, **99**, 217 (1933).

glacial acetic acid, and then with boiling dilute acetic acid. The product was dried *in vacuo;* it weighed 6.3 g., a yield of 100 per cent. based on the analysis and on the glycine anhydride used. The decomposition point was 390–400° on the Maquenne block. It was insoluble in all common organic solvents. The test for acetate was positive. Yellow mercuric oxide was precipitated by the action of sodium hydroxide; black mercuric sulfide arose from the addition of ammonium sulfide. Dilute hydrochloric and sulfuric acids dissolved the substance.

Anal. Calc'd for $C_8H_{10}Hg_2N_2O_6$: Hg, 63.45; N, 4.43; CH_3CO, 13.6. Found: Hg, 62.07, 61.97; N, 4.50, 4.48; CH_3CO, 14.4, 14.1.

1,4-Diacetoxymercuri-3,6-dimethyl-2,5-diketopiperazine.—In 55 cc. of hot water there was dissolved 2.75 g. (0.02 mole) of 3,6-dimethyl-2,5-diketopiperazine. Another solution was prepared by dissolving 40.7 g. (0.13 mole) of mercuric acetate in 130 cc. of hot water, to which a few drops of acetic acid had been added. The two solutions were mixed and were kept warm on a hotplate. A white solid began to form immediately, and in ten minutes precipitation was complete. The solid was separated by filtration, and was washed with hot water, dioxane, and ether. Dried *in vacuo* it weighed 6.0 g., 46 per cent. of the theoretical yield, based on the amount of alanine anhydride used. It was insoluble in all common organic solvents. The decomposition point was 390–400° on the Maquenne block. The behavior of this product toward reagents was the same as that of the corresponding unmethylated compound.

Anal. Calc'd for $C_{10}H_{14}Hg_2N_2O_6$: Hg, 60.86; N, 4.25; CH_3CO, 13.1.

Found: Hg, 60.03, 59.92; N, 4.03, 4.00; CH_3CO, 13.2.

1,4-Dichloromercuri-2,5-diketopiperazine.—In 30 cc. of water was suspended 6.3 g. of 1,4-diacetoxymercuri-2,5-diketopiperazine. Solution was effected by addition of the minimum amount of concentrated hydrochloric acid. The solution was then made faintly alkaline to phenophthalein by addition of 1 *N* sodium hydroxide. The white precipitate which had formed was separated by filtration, and was washed with water, dioxane, and ether. The yield was 4.0 g., 69 per cent. of the theoretical. The material melted with decomposition at 385–395°. It gave a positive Beilstein test for halogen, but gave no evidence of the presence of acetyl groups. The behavior of the product toward various reagents was the same as that of the corresponding acetoxymercuri compound.

Anal. Calc'd for $C_4H_4Cl_2Hg_2N_2O_2$: Cl, 12.2; Hg, 68.6; N, 4.80.

Found: Cl, 11.5; Hg, 68.0; N, 4.83, 4.82.

Action of mercuric acetate on glycylglycine.—A 5-g. sample of glycylglycine was dissolved in 25 cc. of water, and to this was added a solution of 10 g. of mercuric acetate dissolved in 50 cc. of water to which several drops of acetic acid had been added. The solution was refluxed, and almost at once there was a yellow precipitate, which turned gray (probably free mercury). At the end of thirty minutes the solid had changed to a globule of free mercury. The supernatant liquid was decanted, and the mercury was washed first with alcohol and then with dry ether. The mercury weighed 7.4 g., indicating that all of the mercury in the mercuric acetate was reduced to free mercury. The supernatant solution gave a positive ninhydrin reaction. It was evaporated to dryness. The residue was dissolved in methyl alcohol, and two volumes of dry ether was added. The solution was put in the refrigerator; after two weeks white crystals appeared on the sides of the flask. This compound was water-soluble, gave a negative ninhydrin reaction, contained no nitrogen, and melted with decomposition at 220°. Admixture of glycylglycine with the white crystals lowered the decomposition point to 190°; the melting point of a mixture with glycine was 205–

206°. The melting point of the crystalline compound corresponds closely to that of polyglycollide,[8] which melts at 220–223°, and which has the formula $HO(CH_2.CO.O)_x H$. Pure glycylglycine is recrystallized by this procedure, but none was obtained from the reaction mixture. The amount of the compound was too small for analysis. This reaction is being studied further with larger amounts of materials. Truhart[4] obtained glycollic acid by the action of mercuric oxide on glycine.

The above reaction was also carried out at 25°. After three days free mercury was deposited.

Action of Mercuric Acetate on Proteins

A. Casein.—Fifty grams of casein was suspended in 750 cc. of hot water. To this was added a solution of 39.5 g. of mercuric acetate in 500 cc. of hot water to which 10 cc. of acetic acid had been added. Refluxing was continued for four days, during which time a flocculent brown precipitate had formed. A considerable quantity of free mercury in very small globules was mixed with light-colored particles in this precipitate. A small amount of the flocculent material was freed from mercury as completely as possible by repeated decantation of a dioxane suspension, although there was still an appreciable number of small globules visible under the microscope. This light-yellow material was washed with dioxane and ether, and was air-dried. The weight was 0.6 g. Analysis showed the presence of 24.4 per cent. of mercury. During the analysis a small amount of tar, removable with ether, distilled onto the gold. The residue in the crucible smelled strongly of burnt casein.

The substance was dispersed by dilute hydrochloric acid, sodium hydroxide, ammonium hydroxide, or ammonium polysulfide just as casein is. It evidently consisted of casein which had occluded droplets of mercury.

B. Gelatin.—Fifty grams of an especially purified gelatin was dissolved in 750 cc. of water. To this was added a solution of 39.5 g. of mercuric acetate dissolved in 500 cc. of hot water to which 10 cc. of acetic acid had been added. After the solution had been refluxed for nine hours it contained a quantity of balls of light crystals suspended in the boiling solution. They were collected on a filter, decanted as well as possible from free mercury present, washed with acetone and ether, and were dried in an Abderhalden drier for twenty-four hours at 56° under 8 mm. pressure. The weight was 1.3 g. The crystals were very small, thin needles, containing no nitrogen. Their grayish cast was probably due to a trace of free mercury. The material was undoubtedly mercurous acetate.

Anal. Calc'd for $C_2H_3HgO_2$: Hg, 77.26. Found: Hg, 78.63.

The gelatin solution was refluxed three days longer. It became darker as refluxing continued, and contained an increasing amount of free mercury and of a dark-brown gelatinous material. The latter was decanted as well as possible from the free mercury, was washed with water, acetone, and ether, and was dried in air for twelve hours. It weighed 8 g. The material was ground to 60-mesh size and analyzed for mercury, of which 62.3 per cent. was found. A nitrogen test was positive. Microscopic examination of the solid showed that the mercury was undoubtedly present entirely in the free state, since the dark mass was largely composed of minute globules of the free metal. The precipitate, then, must have contained 5 g. of mercury, giving with the 9 g. of mercury isolated directly from the reaction mixture a total of 14 g. (56 per cent. of the mercury present).

C. Silk fibroin.—In 500 cc. of hot water, to which 10 cc. of acetic acid had been added, there was dissolved 39.5 g. of mercuric acetate. This solution was added to a suspension in 750 cc. of hot water of 50 g. of silk winder waste which had been washed repeatedly with hot distilled water. The mixture was refluxed for four days. At the end of that time 11 g. of free mercury (44 per cent of the mercury present) had precipitated in small globules, largely on the fibers of silk. In the liquid only a few milligrams of brown flocculent precipitate was observed.

SUMMARY

Mercuric acetate is reduced by glycylglycine to free mercury. 2,5-Diketopiperazine reacts with an excess of mercuric acetate in aqueous solution to produce 1,4-diacetoxy-mercuri-2,5-diketopiperazine which is converted by hydrochloric acid to 1,4-dichloromercuri-2,5-diketopiperazine. 3,6-Dimethyl-2,5-diketopiperazine formed 1,4-diacetoxymercuri-3,6-dimethyl-2,5-diketopiperazine.

Casein, gelatin and silk fibroin were refluxed with aqueous mercuric acetate and were found to cause reduction of the mercuric acetate to free mercury, but did not produce any insoluble acetoxymercuridiketopiperazines.

[Contribution from the Chemical Laboratory of Stanford University]

THE DIRECT INTRODUCTION OF THE AMINO GROUP INTO THE AROMATIC AND HETEROCYCLIC NUCLEUS. III. FURTHER OBSERVATIONS CONCERNING THE ACTION OF THE ALKALI AMIDES ON QUINOLINE AND ISOQUINOLINE

F. W. BERGSTROM

Received October 15, 1937

It has previously been demonstrated[1] that the reaction of Chichibabin[2] in which the —CH=N— group of a heterocyclic compound is converted to $—C(NH_2)=N—$, can be carried out in liquid ammonia at room temperatures. Thus, it was found that quinoline reacts with barium amide to give hydrogen and 2-aminoquinoline in good yield, and that isoquinoline reacts with both barium amide and potassium amide (particularly if the latter is in excess of one equivalent) to give hydrogen and 1-aminoisoquinoline. Quinoline, on the contrary, is converted either by sodium amide or by potassium amide largely to resins, although six to eleven per cent. yields of 2-aminoquinoline may be obtained if the reaction mixture (with potassium amide) is treated with ammonium iodide to destroy potassium salts, or if it is shaken with mercury. A dilute potassium amalgam is formed in the latter case. The present paper is a continuation of this work.

THE FORMATION OF ADDITION COMPOUNDS BETWEEN THE ALKALI AMIDES AND QUINOLINE

Ziegler and Zeiser,[3] in discussing the action of sodium amide on pyridine under a heated hydrocarbon[2], suggested that there was first formed an addition compound,

$$\cdot CH=N\cdot + NaNH_2 = \cdot CH(NH_2)NNa\cdot \qquad (1)$$

which loses sodium hydride to give 2-aminopyridine. Subsequently, sodium 2-aminopyridine and hydrogen are formed in accordance with the equation,

$$\cdot C(NH_2)=N\cdot + NaH = \cdot C(NHNa)=N\cdot + H_2$$

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[1] (*a*) Bergstrom, *J. Am. Chem. Soc.*, **56**, 1748–51 (1934); (*b*) Bergstrom, *Ann.*, **515**, 34–42 (1934).

[2] Chichibabin and Seide, *J. Russ. Phys. Chem. Soc.*, **46**, 1216–36 (1914); *Chem. Abstr.*, **9**, 1901 (1915).

[3] Ziegler and Zeiser, *Ber.*, **63B**, 1848 (1930).

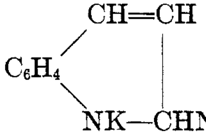
A related reaction was observed by Kirssanov and Ivastchenko,[4] who found that sodium amide converts benzalaniline in toluene to *N*-phenylbenzamidine, as expressed by the equation, $2C_6H_5CH{=}NC_6H_5 + NaNH_2 = C_6H_5C(NHNa){=}NC_6H_5 + C_6H_5CH_2NHC_6H_5$. Other substances are formed at the same time.

Since sodium salts of amidines, RC(NH)NHNa, result when nitriles are treated with sodium amide[5] it is suggested that in all reactions of the alkali amides with compounds containing carbon multiply linked to nitrogen, addition compounds are first formed.

Although no intermediates of the type assumed in equation (1) have been isolated in the reactions of pyridine or quinoline with sodium amide in a heated inert solvent, the author has obtained evidence for the formation of addition compounds of sodium amide and potassium amide with isoquinoline in liquid ammonia[1b]. Attempts to isolate these substances in a pure state failed because of their instability in the absence of solvent at room temperatures.

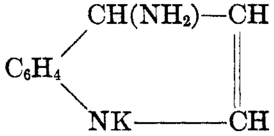
In the present work it was found that a liquid ammonia solution of quinoline readily dissolves the sparingly soluble sodium amide to form and opaque green solution which contains the reactants in approximately equimolar proportions, suggesting the formation of an addition compound, $C_9H_7N \cdot NaNH_2$. Its partial decomposition at room temperatures in the solid state is indicated by the fact that there is a small loss in weight during the reaction, whereas none would be expected on the basis of equation (1). Its decomposition in solution may be followed in a semiquantitative manner by adding ammonium chloride or ammonium bromide to quinoline-alkali amide mixtures of different ages. Quinoline is regenerated in amounts which are the smaller the longer the period of reaction, indicating a slow decomposition. This is accelerated by an excess of amide ions.

In the next section, it will be shown that 2- and 4-aminoquinolines are obtained by the action of potassium nitrate on aged potassium amide-quinoline reaction mixtures, which fail to give quinoline when treated with ammonium bromide. One way of viewing these results is to make the assumption that a molecular compound, $C_9H_7N \cdot KNH_2$, is first formed, and passes on standing into



(I)

and



(II)

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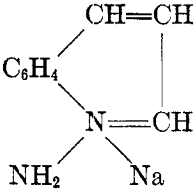
[4] Kirssanov and Ivastchenko, *Bull. soc. chim.*, [5], **2,** 1944–50, 2109–24 (1935).

[5] Cornell, *J. Am. Chem. Soc.*, **50,** 3311–8 (1928); Kirssanov and Poliakova, *Bull. soc. chim.* [5], **3,** 1600–6 (1936); Ziegler, *U. S. Patent*, 2,049,582; *Chem. Abstr.*, **30,** 6389 (1936).

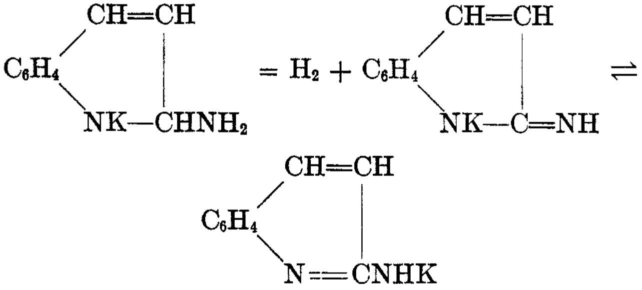
which do not give quinoline when treated with ammonium salts, but are converted by potassium nitrate and an excess of potassium amide to a mixture of 2- and 4-aminoquinolines. It is highly improbable that the primary addition compound has the structure,



because the heterocyclic nitrogen has a decet of electrons around it.

THE CONVERSION OF THE ADDITION COMPOUND INTO 2-AMINOQUINOLINE

2-Aminoquinoline, or its monopotassium salt, may be formed from the addition compound of potassium amide and quinoline, (*a*) by direct loss of gaseous hydrogen, giving potassium 2-aminoquinoline, in accordance with the equation,



(2)

(*b*) by the loss of potassium hydride, according to the mechanisms of Ziegler and Zeiser,[3] Kirssanov and Ivastchenko,[4] and Kabachnik,[6] or, (*c*), by some other mechanism which does not involve the actual separation of a metallic hydride, but rather the removal of a hydrogen atom and an electron (essentially the removal of H^-) by another molecule of quinoline, by its addition compound with potassium amide, by the solvent ammonia or by some added reagent. It will be seen that (*c*) is in many respects merely an extension of (*b*) to low-temperature reactions in which the actual splitting off of an alkali hydride is unlikely. It may of course be assumed that even at room temperatures the addition compound reversibly dissociates to form a very small amount of alkali hydride, or hydride ion, but there is no apparent method of telling whether or not

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[6] KABACHNIK, *Bull. Acad. Sci. U. R. S. S., Classe Sci. math. Nat.*, **1935**, 971–8; *Chem. Abstr.*, **30**, 3820 (1936).

this is the case. Mechanism (*c*) has been adopted in explaining the reactions described in the succeeding paragraphs.

THE ACTION OF THE ALKALI AMIDES ON QUINOLINE AND ISOQUINOLINE IN THE PRESENCE OF NITRATES

2-Aminoquinoline is formed in about 50 per cent. yields, accompanied by smaller amounts of 4-aminoquinoline (the quantity isolated does not exceed 10 per cent.) when an excess of potassium amide reacts with quinoline in the presence of potassium nitrate. The latter is reduced to potassium nitrite, and very little tar is obtained. The same reaction takes place if the addition compound, first formed by mixing an excess of potassium amide with quinoline in liquid ammonia at room temperatures, is allowed to stand for periods of a week or more, and then treated with potassium nitrate in the same solvent. The reaction follows the equation*

$$C_9H_7N + 2KNH_2 + KNO_3 = C_9H_6N\cdot NHK + KNO_2 + KOH + NH_3 \quad (3)$$

The yield of 2-aminoquinoline is at first roughly proportional to the amount of addition compound, $C_9H_7N\cdot KNH_2$, in solution, the latter having been determined by adding an ammonium salt to similarly prepared solutions of equal age, and recovering the quinoline. However, it was found that 25 per cent. yields of 2-aminoquinoline could be obtained by the action of potassium nitrate on potassium amide-quinoline reaction mixtures from which no quinoline could be regenerated by the action of ammonium bromide. Possibly the addition compounds from which quinoline and aminoquinoline are formed are not the same.

As an alternative, it could be assumed that the primary addition compound is (reversibly?) converted to another substance (a polymer?) or to a mixture of substances (products of a dismutation?) which react with potassium nitrate to form 2- and 4-aminoquinoline, but from which no quinoline is formed on treatment with ammonium bromide. It would be expected, in the latter case, that aminoquinolines would be present as such and in relatively large quantity in solution, but this is very improbable, in view of the fact that the decomposition of the addition compound by water gives them in almost negligible amount.

The conversion of quinoline to aminoquinoline by the methods just discussed occurs rapidly only in the presence of an excess of amide ions. Thus a very small quantity of 2-aminoquinoline is formed when an excess

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* Attempts are now being made to carry out reactions between solid sodium amide and organic substances under solvents other than ammonia, and in the presence of some added compound which will function as does the potassium nitrate here.

of the sparingly soluble sodium amide reacts with quinoline in the presence of sodium nitrate. An excess of potassium amide reacts with isoquinoline in liquid ammonia to give 1-aminoisoquinoline and hydrogen in good yields. In the presence of potassium nitrate, some nitrite is formed, together with a smaller quantity of hydrogen (about 55 per cent. as against 80 per cent. when no nitrate is used), though the yield of aminoisoquinoline is not greatly affected. A fairly good yield of the latter results from the long-time reaction between an excess of sodium amide, isoquinoline and sodium nitrate in liquid ammonia at room temperatures, while a small quantity is even obtained from an excess of isoquinoline, potassium amide, and potassium nitrate. In the two latter cases, very little hydrogen is formed.

Previously, the reaction between isoquinoline and excess potassium amide, in liquid ammonia, was given the ionic interpretation expressed by the equations,

$$\cdot\mathrm{CH{=}N}\cdot + \mathrm{NH_2^-} = \cdot\mathrm{CH(NH_2)N^-}\cdot \qquad (4)\quad (a)$$

$$\cdot\mathrm{CH(NH_2)N^-}\cdot + \mathrm{NH_2^-} = \cdot\mathrm{CH(NH^-)N^-}\cdot + \mathrm{NH_3} \qquad (b)$$

$$\cdot\mathrm{CH(NH^-)N^-}\cdot = \cdot\mathrm{C(NH^-){=}N}\cdot\ [\text{or}\cdot\mathrm{C({=}NH)N^-}\cdot\,] + (\mathrm{H} + e^-) \qquad (c)$$

In the above, only the reactive $\cdot\mathrm{CH} = \mathrm{N}\cdot$ group of isoquinoline has been written, and no account has been taken of the probable initial formation of $\mathrm{C_9H_7N\cdot KNH_2}$. In (*a*), potassium amide and isoquinoline form an addition compound, which reacts reversibly with amide ions in (*b*) to form the anion of the dipotassium salt of aminodihydroisoquinoline. This is unstable in the presence of a substance that can react with hydrogen and an electron and convert it to the ion of the monopotassium salt of 1-aminoisoquinoline. Thus, the reaction of equation (4*c*) takes place because hydrogen and an electron react irreversibly with the solvent in the sense of the equation,

$$\mathrm{NH_3} + (\mathrm{H} + e^-) = \mathrm{NH_2^-} + \mathrm{H_2} \qquad (5)$$

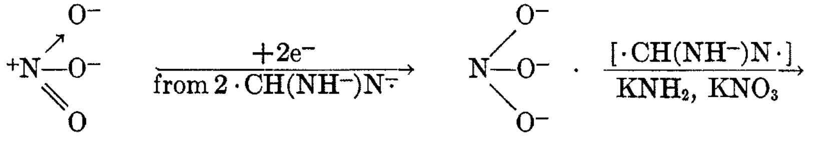
If potassium nitrate is present, some of it is reduced, but the solvent is also attacked, though to a lesser extent, with the formation of hydrogen.

The reactions involved in the preparation of 2-aminoquinoline from an excess of potassium amide, quinoline, and potassium nitrate in liquid ammonia follow the same course (see equations 4) but differ because liquid ammonia itself cannot decompose the addition compound (4*c*) into aminoquinoline and hydrogen. Some reducible substance, such as potassium nitrate, must be present. It is interesting that this compound, of many tested, is the only one really effective.

It therefore follows that $\mathrm{H^-}$ $(\mathrm{H} + e^-)$ is removed with much more difficulty from the doubly charged anion of equation (4*c*), if this is derived from quinoline.† If the viewpoint is adopted that the doubly charged anion is in equilibrium with a very low concentration of H^-, then, in the case of isoquinoline, this concentration is greater than is stable in liquid ammonia, while it is less in the case of quinoline.

That the concentration of H^- (or its ease of removal from 4*c*) is less the lower the concentration of NH_2^-, is also shown by the extremely slow reaction between isoquinoline and the sparingly soluble sodium amide in liquid ammonia. In the presence of sodium nitrate, the reaction is more rapid, although still much slower than with an excess of potassium amide.

There is no way at present of deciding whether the electron is removed at the same time as the hydrogen (that is, as hydride ion, H^-), or separately, as possibly is the case in the reaction between an excess of potassium amide, quinoline and mercury (equation 8). If an electron is first removed by the potassium nitrate, potassium nitrite and potassium aminoquinoline (E) should be formed in accordance with some such scheme as the following,[7]



(A) (B) (C) (D)

$$\cdot C(NH^-) = N\cdot + NO_2^- + OH^- \qquad (6)$$

(E)

(4-Aminoquinoline is similarly formed from II.)

If this mechanism is correct, and the intermediate ion, C, is liberated as such, the following ammonolytic reaction should occur,

$$NO_3^{3-} + NH_3 = NO_2^- + NH_2^- + OH^- \qquad (7)$$

since salts of orthonitrous acid (K_3NO_3) do not appear to exist in liquid ammonia[8]. This will leave the intermediate, D, in solution, to be con-

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† An excess of potassium amide reacts fairly rapidly with 2-phenylquinoline in the presence of potassium nitrate to give 4-amino-2-phenylquinoline in yields of 92 per cent. and above. The reaction still occurs with an excess of 2-phenylquinoline, but it is much slower, and also less complete.[13] It is therefore possible to remove H^- from addition compounds of the type of (4*a*).

[7] The structure of the nitrate ion is due to ELLIOTT, *J. Am. Chem. Soc.*, **59**, 1382 (1937).

[8] A liquid ammonia solution of sodium (which contains negative electrons) reduces sodium nitrate to sodium nitrite, in the probable manner of the equation, $NaNO_3 + 2Na + NH_3 = NaNH_2 + NaNH_2 + NaOH$ [BURGESS AND HOLDEN,

verted to the anion of aminoquinoline, E, by the action of potassium nitrate and potassium amide, in accordance with the equation,

$$2[\cdot \underset{(D)}{CH(NH^-)N}\cdot] + KNO_3 = 2[\cdot \underset{(E)}{C(NH^-) = N}\cdot] + KNO_2 + H_2O \quad (7a)$$

$$H_2O + KNH_2 = KOH + NH_3$$

This may have occurred in experiment 21 of Table III. The actual mechanism of the change is probably expressed by equations similar to 4*b* and 4*c*. It must be pointed out however that D, which is apparently formed when excess potassium amide and quinoline react in the presence of mercury, gives only a small amount of aminoquinoline with potassium amide alone.

If hydride ion is removed from (4*c*), potassium nitrate should be reduced in the following manner,

$$NO_3^- + H^- = NO_2^- + OH^-$$

The Ziegler mechanism[3] for the reaction of sodium amide and pyridine under a heated inert solvent is apparently in best accord with the fact. The assumption of a preliminary addition compound, $C_5H_5N \cdot NaNH_2$, would affect his theory in no essential manner. If the explanations of the present article are at all valid, an excess of sodium amide should accelerate the formation of 2-aminopyridine by increasing the tendency of sodium hydride to split off (*cf.* equations 4*a*–4*c*). Sodium hydride should be lost thermally even in the presence of an excess of pyridine. If the loss of sodium hydride is a reversible one, the equilibrium will be displaced because of removal of sodium hydride, either by a reaction with 2-aminopyridine to form its sodium salt, or by reaction with organic molecules present to form reduction products.

It will be noted that if an intermediate anion of the type in equation (4*c*) is produced in the sodium amide-pyridine reaction, the loss of H^- (*i.e.*, of NaH) from it will give the sodium salt of 2-aminopyridine directly.

THE REACTION OF THE ALKALI AMIDES WITH QUINOLINE AND ISOQUINOLINE IN THE PRESENCE OF MERCURY

It has previously been recorded that an excess of potassium amide reacts with quinoline in the presence of mercury to form a potassium amalgam and a mixture of organic products from which a small yield of 2-aminoquinoline can be obtained.[1a]

J. Am. Chem. Soc., **59**, 461 (1937); *cf.* Divers, *Proc. Roy. Soc.* (London), **21**, 110 (1873); *Phil. Trans. Roy. Soc.* (London), **163**, 368 (1873)]. The mechanism of the reduction is possibly that given above in equation (6).

In subsequent experiments, the maximum amount of potassium found in the mercury approached one atom per mole of quinoline used, the small amount of hydrogen formed simultaneously being about the same as would have been obtained in the absence of the mercury. The relative amount of potassium in the amalgam, as well as the yield of aminoquinoline, is increased by continuous mechanical shaking.[13] Furthermore, an excess of potassium amide reacts with 2-phenylquinoline and with 5,6-benzoquinoline in the presence of mercury to form the respective amino derivatives in good yield, together with an amalgam containing almost two atoms of potassium per mole of the phenyl- or benzoquinoline.[13]

If excess potassium amide and quinoline are allowed to react for about a week, and the solution is then treated with mercury, a potassium amalgam is formed, together with a small amount of 2-aminoquinoline. The results are about the same as if the three reactants were mixed at the beginning, though the yields of product are generally smaller, and indicate that the substance which reacts with the mercury is a secondary addition compound, such as that of equation (4*c*) (an alternative explanation is given in the preceding section).

Potassium amalgam is not formed in significant quantity when potassium amide reacts with an excess of quinoline, nor when isoquinoline reacts with an excess of the amide. However, hydrogen is formed in the latter reaction, just as if the mercury had not been present[1a]. If isoquinoline reacts with the sparingly soluble sodium amide, sodium amalgam is obtained, together with 1-aminoisoquinoline in yields generally not exceeding 20 per cent. of the theoretical, the rate of reaction being much greater than in the absence of mercury. It appears though that some of the aminoisoquinoline must be formed by the action of sodium amide alone on the isoquinoline, with only a slight evolution of hydrogen, and not in accordance with the scheme below. (*Cf.* Reference 1*b*, p. 35, fine print.)

Tentatively, the following equations are proposed as representing the course of the reactions. (*Cf.* equations 4*a*–4*c*, 6, 7*a*.)

$$2\ \cdot\mathrm{CH{=}N}\cdot \xrightarrow{2\mathrm{NH_2^-}} 2\ \cdot\mathrm{CH(NH_2)N}\cdot^- \overset{2\mathrm{NH_2^-}}{\rightleftharpoons} 2\ \cdot\mathrm{CH(NH^-)N}\cdot^- \qquad (8)$$

$$\underset{\text{(B)}}{2\ \cdot\mathrm{CH(NH^-)N}\cdot^-} + \mathrm{Hg} = \mathrm{Hg^{--}} + \underset{\text{(D)}}{2\ \cdot[\mathrm{CH(NH^-)N}\cdot]}$$

$$\mathrm{Hg^{--}} + 2\mathrm{K^+} + (x - 1)\ \mathrm{Hg} \rightarrow \mathrm{K_2Hg}_x$$

$$2\,\underset{\text{(B)}}{[\cdot\mathrm{CH(NH^-)N}\cdot]} + \mathrm{Hg} + 2\mathrm{NH_2^-} = \underset{\text{(E)}}{2\cdot\mathrm{C(NH^-){=}N}\cdot} + 2\mathrm{NH_3} + \mathrm{Hg^{--}}$$

$$\mathrm{Hg^{--}} + 2\mathrm{K^+} + (\mathrm{x} - 1)\mathrm{Hg} = \mathrm{K_2Hg}_x$$

It is possible that this stepwise mechanism will be necessary to explain the low yield of aminoquinoline in experiments where only one atom of potassium per mole of quinoline was found in the mercury. In view of the lack of definite proof that this is the course of the reaction, it is perhaps better at present to give the following overall equation as the most probable,

$$\cdot CH{=}N\cdot + 3NH_2^- + xHg = Hg_x^{--} + 2NH_3 + \underset{(E)}{\cdot C(NH^-){=}N\cdot}$$

(E is the anion of the potassium salt of 2-aminoquinoline)

The ease, and therefore the rate, of removal of e^- (the negative electron) is presumably proportional to the concentration of B, which is the greater the higher the concentration of NH_2^- ions. Furthermore, e^- is the more readily removed if the doubly charged anion, B, is derived from isoquinoline, since this reacts with sodium amide to give a sodium amalgam, while quinoline does not. The failure to get an amalgam when isoquinoline reacts with an excess of potassium amide and mercury is due to the greater ease with which $(H + e^-)$ react with the solvent to form hydrogen and NH_2^-.

The removal of an electron from the anion of an alkali metal salt by mercury is not a new reaction, since Bent and his coworkers[9] have found that the sodium salts of a number of free groups react reversibly with mercury in ether to form a dilute sodium amalgam and the corresponding free group.

THE ACTION OF BARIUM AMIDE ON QUINOLINE

Barium amide has previously been recorded as attacking quinoline to form hydrogen and 2-aminoquinoline[1a], in a reaction which is markedly catalyzed by soluble barium salts. This reaction has now been carried out on a larger scale in a steel apparatus designed to simulate the well-known manipulations in glass, with the result that no 4-aminoquinoline could be isolated. Apparently barium amide reacts preferably with the alpha position of a heterocyclic compound containing the —CH=N— group. When barium nitrate is used as a catalyst, an oxygenated compound of unknown structure is formed in small quantity, along with the 2-aminoquinoline.

EXPERIMENTAL

The Formation of Addition Compounds between the Alkali Amides and Quinoline

Expt. 1.—Quinoline (0.54 g. or 4.2 millimoles), dissolved in a small volume of liquid ammonia, reacted with the sodium amide from 0.36 g. sodium (16. milliatoms) for six days at room temperatures in a two-legged reaction tube.[10] Approximately half of the green solution was carefully decanted into the clean leg of the reaction

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[9] Bent and others, *J. Am. Chem. Soc.*, **52**, 1498 (1930); **53**, 1786 (1931); **54**, 1393, 3250 (1932); **57**, 1217, 1242, 1259, 1452, 1455 (1935).

[10] Bergstrom, *ibid.*, **53**, 4068-9 (1931).

tube, the whole tube then being immersed in ice water so that refluxing ammonia would wash down the solution adhering to the upper walls and the bend. Further treatment, leading to analysis, has already been described.[11] Found, Na 15.5% (tube evacuated at room temperatures) and Na 16.2% (tube evacuated at 115°, where there is some decomposition); calc'd. for $C_9H_7N \cdot NaNH_2$, Na 13.7%. The high sodium content is due in part to the transference of a small amount of sodium amide in solution (solubility about one gram per liter) or in fine suspension. The solid analyzed, although having approximately the composition of the above addition compound, is scarcely pure, in view of the results of experiment 3.

Expt. 2.—This was a repetition of experiment 1, except that the time of reaction was 40 minutes. The reaction is apparently complete in about five minutes. Found, specimen evacuated at 20°, Na 14.03%. The maximum amount of sodium amide has therefore been dissolved by the quinoline in a relatively short time.

Expt. 3.—This is a repetition of the two preceding, except that the time of reaction was one hour at room temperatures, and the change in weight during the reaction was determined in accordance with the method of a previous article.[10] After evaporation of solvent ammonia from the tube, the contents were evacuated at intervals for several days (Töpler pump). A loss in weight of 0.0365 gram was observed (2.14 millimoles, calculated as ammonia), 1.070 g. (8.29 millimoles) of quinoline and the sodium amide from 0.513 g. (22.3 milliatoms) of sodium having been used in the reaction. It is apparent that the addition compound is slowly decomposing with evolution of ammonia.

Expts. 4–6.—In view of the known approximate minimum time for a liquid ammonia solution of quinoline to take up one mol of sodium amide (experiment 2), it was certain that in the following experiments the addition compound between the two had formed completely, and that no free quinoline was present.

Quinoline was treated with an excess of sodium amide or potassium amide (prepared from a solution of the metal in liquid ammonia and iron oxide) in a reaction tube at room temperatures for varying periods of time.[10, 12] The volumes of solvent were about the same in all experiments. The solution of the reaction product, contained in the leg not underneath the addition tube, was cooled to −33° or below by a bath of liquid ammonia, and an excess of ammonium bromide was introduced into the empty leg against a current of ammonia gas. The addition tube was then sealed, the whole was warmed to room temperatures and a few cc. of solvent was distilled over to dissolve the ammonium bromide, the resulting solution being poured into the alkali amide-quinoline reaction mixture, causing it to become light yellow within a short while. The residue remaining after evaporation of solvent ammonia was steam-distilled, and the distillate was treated with an excess of dilute alcoholic picric acid to precipitate quinoline picrate. This was washed with alcohol, dried to constant weight, and identified by its melting point.

Expts. 7–8.—These differ from experiments 4–6 only in that at the end of the reaction period, half of the solution (as nearly as could be estimated) was decanted into the second leg of the reaction tube, which contained about 0.75–1.0 mole of potassium nitrate for each mole of quinoline initially used. All ammonia was evaporated into the leg not containing the potassium nitrate. An excess of ammonium bromide was introduced into this leg, after cooling to −33°, and the addition tube was resealed.

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[11] FRANKLIN, "The Nitrogen System of Compounds," The Reinhold Publishing Company, New York, **1935**, p. 319–325.

[12] SCHURMAN AND FERNELIUS, *J. Am. Chem. Soc.*, **52**, 2428 (1930).

After warming to room temperatures, solvent was distilled from the leg into which ammonium bromide was introduced into the leg containing the potassium nitrate, and reaction was allowed to continue for four to six days. After evaporation of ammonia, the legs of the tube were separated, quinoline being steam distilled from the contents of the leg containing the ammonium bromide, as in experiments 4–6, and aminoquinoline was obtained from the contents of the other leg by crystallization from water. (The hot aqueous solution was filtered to remove tar. See also Table II.)

The Conversion of the Primary Addition Compound into 2-Aminoquinoline

Expt. 10.—In one leg of a two-legged reaction tube[10] was placed 1.09 g. (8.45 millimoles) of redistilled synthetic quinoline and 1.14 g. (11.3 millimoles) of C. P. dry potassium nitrate. The other leg contained 1.05 g. (26.8 milliatoms) of potassium, in short lengths of glass tubing, together with some polished iron wire to serve as a catalyst for its conversion to amide. Since ammonia was distilled directly into the leg containing the potassium, it was necessary to vent hydrogen from time to time by shutting the valve on the supply tank, and opening a relief valve. This process was repeated as often as necessary. The resulting potassium amide was decanted, with shaking, into the leg containing the quinoline and potassium nitrate, a brownish-red solution being formed instead of the green solution observed when nitrate is not used. The colorless crystalline precipitate which slowly formed during the reaction was washed with solvent after twelve days and analyzed.

TABLE I

SUMMARY OF EXPERIMENTS 4–9

Expt.	4	5	6	7	8	9[d]
Amide, millimoles	$NaNH_2$ 31.3	KNH_2 38.4	KNH_2 36.5	KNH_2 50.4	KNH_2 54.5	KNH_2 12.98
Quinoline, millimoles	15.8	12.2	12.2	16.3	18.31	16.26
Time of Reaction at 20°–25°.	2.5 hrs.	30 min.[c]	16 hrs.	5 days	9 days	9 days
Quinoline recovered, per cent	62	76	38	0	0[a]	42.6[b]

[a] A little aminoquinoline was separated by steam distillation and recovered as picrate (6% yield).

[b] Quinoline recovered as picrate, 8.81 millimoles (m. p. 197–199.2°), and 0.41 millimole (m. p. 193–7°). Allowance for the 3.28 millimoles quinoline used in excess gives the percentage recovery recorded.

[c] Solution kept 15 minutes at −40° (orange-brown in color), then warmed to room temperature (becomes opaque, green). After 30 minutes at room temperature the solution was poured into the ammonium bromide.

[d] Same manipulation as in experiments 4–6.

Anal. Calc'd. for KOH: K, 69.6.
Found: K, 68.6; N (by alkaline distillation without previous digestion), None.

The washings of the precipitate were hydrolyzed, after evaporation of solvent ammonia, with a mixture of benzene and alcohol, water was added, and the two organic solvents were evaporated on a steam bath. The hot aqueous solution was filtered (if oily drops were present, more water was added), 2-aminoquinoline, (0.638 g., 4.43 millimoles, 52.5%) separating on cooling. A second crop, obtained by strongly concentrating the filtrate, was crystallized twice from benzene, and then melted at 151.5–153.0°, uncorr. The melting point of a mixture with 4-aminoquinoline, prepared by the pyrolysis of 4-aminoquinoline-2-carboxylic acid[13] (151.7–152.5°) showed their identity.

TABLE II

SUMMARY OF EXPERIMENTS 7–8 AND 11–15

NO.	AMIDE	MILLIMOLES	QUINOLINE, MILLIMOLES	KNO_3 MILLIMOLES	TIME OF REACTION,[i] DAYS		2-AMINO QUINOLINE[a]		NOTES
					A	B	Millimoles	%	
10	KNH_2	26.8	8.45	11.3	0	12	4.43	52.5	*c*
11	KNH_2	25.8	13.4	34.7	0	5	5.4	40	*b*
12	KNH_2	470	155	198	0	1.5 50–70°	82.6	53.3	*d*
13	$NaNH_2$	41	12.7	($NaNO_3$) 17.2	0	21	0.15	1.2	*g*
14	KNH_2	53.6	17.00	19.8	0.02	2.3	8.75	51.5	*h*
15	KNH_2	37.9	11.80	15.5	3	1	3.27	30.5	
7	KNH_2	50.4	16.3	10.0	5	4	2.08	25.5	*e*
8	KNH_2	54.5	18.31	15.0	9	6	2.04	22.3	*f*

[a] Melting points of yields reported varied within the range, 126.0–129.0° uncorr.

[b] Potassium from a calibrated tube, iron wire catalyst removed before the reaction, which took place in a straight tube[1a]. H_2, N.T.P., 2.0 cc.; N_2, 1.5 cc.; m. p. of product, 123–128°.

[c] A second crop, obtained by strongly concentrating the filtrate of the 2-aminoquinoline, weighed 0.160 g. (1.11 millimoles), m. p. 150–151.3°. The m. p., after recrystallization from benzene, was 151–152.3°; m. p. of mixture with authentic 4-aminoquinoline, 151–152° uncorr.

[d] In the rocking autoclave. See description.

[e, f] Same experiments as listed in Table I. One half of the reaction mixture only reacted with the potassium nitrate, for the times given in Table II.

[f] The filtrate of the 2-aminoquinoline was evaporated to dryness and extracted several times with boiling benzene, the latter being concentrated to crystallization; 0.379 g. of material, m. p. about 85–120°, was obtained, presumably a mixture of 2- and 4-aminoquinolines. It could not be resolved by crystallization from benzene. Total yield of aminoquinolines, about 50% of the theory.

[g] Much tar formed. The aminoquinoline was very impure.

[h] In addition to the 2-aminoquinoline, 0.82 g. of material, m. p. 90°–125°, was obtained. It could not be resolved by crystallization.

[i] A. Time of reaction of the amide and quinoline before adding the KNO_3.
B. Time of reaction after adding the KNO_3.

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[13] BERGSTROM, unpublished work.

In duplicate experiments, it often proved impossible to separate the mixture of 2- and 4-aminoquinolines by crystallization. (This generally melted below 100° and over a range. The hydrate of 4-aminoquinoline melts at 70°.)

Expts. 11–15.—These were duplicates of the preceding, except that the catalyst was 0.02–0.05 g. Fe_2O_3, and the precipitated alkali hydroxide was not washed prior to evaporation of solvent from the reaction tube. The extreme activity of ferric oxide as a catalyst makes it necessary to vent hydrogen from the tube at intervals of a few minutes, otherwise ammonia will not distill in.

Nitrite formed in the Reaction

In determining nitrite quantitatively it is necessary to avoid the presence of iron oxide, which catalyzes the following reaction between potassium amide and potassium nitrate.[13]

$$3KNH_2 + 3KNO_3 = 3KNO_2 + 3KOH + N_2 + NH_3.$$

In a blank test (8 days duration), it was found that this reaction does not occur to an appreciable extent in the absence of iron and iron oxide. The following procedure was therefore adopted.

Expt. 16.—Dry synthetic quinoline (0.6507 g., 5.041 millimoles) was weighed out in a small porcelain boat and placed, together with dry potassium nitrate (1.01 g., 10 millimoles), in one leg of a two-legged glass reaction tube. The other leg contained potassium (0.60 g., 15.4 milliatoms from a calibrated tube) and some polished iron wire. The potassium amide, quinoline, and potassium nitrate were allowed to react (in the leg not containing the iron), for eight days with occasional shaking, after which solvent was evaporated, the tube was evacuated, and the contents were hydrolyzed with water vapor. The tube was then broken open, and the solution was rapidly filtered into a 50-cc. volumetric flask, and made up to volume. Nitrite was determined on a tenth aliquot according to a slight modification of the Coade-Werner method.[14]

The aliquot was placed in the cup of a Lunge nitrometer, introduced into the burette and washed down with the minimum quantity of water. This was followed by a solution of 0.1 g. thiourea in 4 or 5 cc. of water, and then by 2 cc. of dilute acetic acid (1:3). The gas evolution was slower than in the experiments of Coade and Werner, and was accelerated by shaking the tube. To test for carbon dioxide, 5 cc. of 33% potassium hydroxide was run into the burette through the cup, the burette being shaken to facilitate absorption. The correction for the solubility of nitrogen in the aqueous solution was neglected. The gas volume was read with mercury surfaces level, the pressure upon the gas equalling the barometric reading less the mercury equivalent of the water column, the latter being calculated from the height of the column and its density (about 1.02–1.05) or determined directly by opening the burette to the atmosphere and reading the difference between the mercury levels.

Found, N_2 (0° and 760 mm.), 8.50 cc. = 0.380 millimoles or 75.5% of the theoretical, assuming one mole KNO_2 produced per mole of KNO_3. Azide, possibly a trace. Crude 2-aminoquinoline (m. p. 121–127°), 50% of the theoretical.

Expt. 17.—In a repetition, there was obtained a 79.2% yield of nitrite, and a 50.7% yield of 2-aminoquinoline, m. p. 127–128.5°, with a small amount of high-melting material, probably 4-aminoquinoline.

Larger scale preparation of 2-aminoquinoline.—The reaction between potassium

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[14] Coade and Werner, *J. Chem. Soc.*, **103**, 1221–8 (1913).

amide and quinoline, in the presence of potassium nitrate, was carried out in a steel autoclave, Figure 1. (The dimensions given are in inches.) This consists of a length of seamless steel tube, *GH*, into one end of which is screwed and welded a steel plug, machined so it may be clamped in a parallel-jaw vise. A large hexagonal nut, *F*, is screwed on the head against a metallic gasket to insure tightness.*

The interior of the autoclave is divided into two compartments by means of the removable vessel, *IJKM*, which is made in the following manner. A thin steel tube, 1 mm. or 1/32 inch in thickness and fitting snugly into the autoclave, is cut parallel to the axis so that a cross section has the appearance of *L* in Figure 1. A steel plate, *JM*, is welded to the edges of the cut cylinder, and a bottom is welded on at *M*, so as to give a container, open at one end, with a volume of 250 cc. Two small elliptical springs, *K*, holds the vessel in place in the autoclave. A heavy steel strap is welded on at *I* to aid in the removal of the inner compartment. The autoclave head is constructed in the manner shown, so that the whole apparatus can be rocked in a constant temperature bath with tube *C* vertical. The contents therefore will not come in contact with the valve.

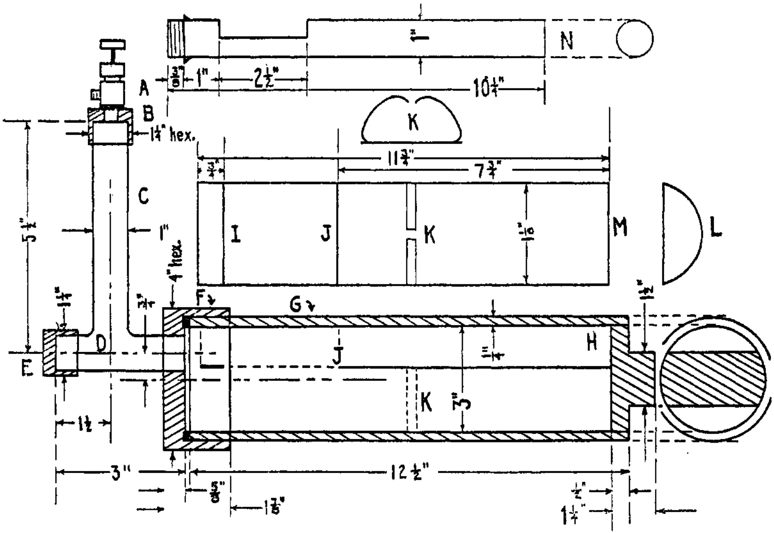

Fig. 1

Expt. 12.—(See Table II.) Twenty grams (155 millimoles) of quinoline was placed in the autoclave proper, together with 20 g. (198 millimoles) of dried c. p. potassium nitrate. The inner compartment contained 18.4 g. (470 millimoles) of

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* Aluminum is the most satisfactory material, but cannot be used if the autoclave contents contain salts of mercury. Tin is recommended for use wherever possible, because of ease of removal of the head, but it cannot be used with sodium amide or dilute potassium amide solutions because of attack [*J. Phys. Chem.*, **30**, 15–17 (1926)]. Strong potassium amide passivifies the tin, and barium amide is without chemical action. Lead gaskets are dissolved by the alkali amides. Copper gaskets are satisfactory, but make it difficult to remove the head.

potassium and 0.1 g. of ferric oxide to serve as a catalyst for its conversion to amide. The head, *F*, was screwed into place and tightened against the gasket, note being taken of the position of a mark on it with relation to stamped numbers around the top of the body of the autoclave. The head was then removed and the inner compartment adjusted so that the pouring lip, *J*, would be above the solution in the autoclave, and parallel with it, when the autoclave was horizontal and *C* projected vertically upward.

Most of the air in the autoclave was displaced with ammonia gas before the tightening of the head, and the rest was removed by alternately filling with ammonia at the tank pressure of about 8 atmospheres, and venting the mixture of ammonia and air to the atmosphere. The autoclave was now weighed on a "solution type" balance, and again after solvent had been distilled in (autoclave in a vertical position and cooled with ice). Generally, the formation of hydrogen in the reaction between potassium and ammonia seriously retards the introduction of further ammonia. The valve *A* must therefore occasionally be disconnected from the supply and the hydrogen vented. The conversion of potassium to potassium amide is complete when no more hydrogen is formed (gases released through valve are tested for inflammability, or bubbled into water). The autoclave should contain from 150 to 300 grams of ammonia (that is, about 250-500 cc. at room temperatures), the smaller quantity if it is to be heated.

The bomb was tipped to a horizontal position, with *C* pointing vertically upwards, to mix the contents of the two compartments, after which it was rocked in an oil bath for 18 hours at 50–70°. When thoroughly cool, the solvent was evaporated, the head, *F*, was removed, and the contents were hydrolyzed with benzene and alcohol, the solid being disintegrated with a steel rod. Water was added and the first two solvents were evaporated. If oily drops were present, enough boiling water was added to dissolve the major portion, the solution was filtered rapidly and cooled. The yield of 2-aminoquinoline, m. p. 127–128°, was 11.90 g. (two crops, 82.6 millimoles, 53.3%). Three grams of a solid was obtained by concentration of the last aqueous filtrate, m. p. under 100°. It proved to be a mixture that could not be resolved by crystallization. The presence of 4-aminoquinoline hydrate, m. p. 70°, was suspected.

The reaction of excess potassium amide with quinoline in the presence of other reducible compounds.—In an attempt to find other salts which could replace potassium nitrate in the aminoquinoline synthesis, quinoline was treated with 3 moles of potassium amide and a little over one mole of a salt in liquid ammonia for about three weeks at room temperatures. No aminoquinoline or other definite product was isolated if the salt was potassium chlorate, potassium perchlorate, or potassium cyanate. Very small and probably in most cases insignificant yields of 2-aminoquinoline were obtained with the following: diïsobutylene (3%, 8 day reaction); sodium azide (with 5 equivalents of potassium amide, 6% in 2.4 months, together with 1.7 cc. H_2 and 1.5 cc. N_2); potassium iodate (18.2%, m. p. 118–24°, or 9.9% m. p. 127–9°; potassium iodide was formed, as well as a very explosive caked precipitate).

The action of alkali amides on quinoline in the presence of mercury.—Expts. 22–23.—Potassium and a catalyst (Fe or Fe_2O_3) was introduced into one leg of a two-legged reaction tube,[10] the other leg, which is under the addition arm, being sealed in a current of ammonia. With both legs cool, the tube was placed in an upright position, and the desired amounts of quinoline (purified synthetic) and mercury (distilled *in vacuo*) were introduced through the addition arm, which was then sealed. The potassium amide, after formation, was decanted into the leg containing the quinoline and mercury, and the tube was shaken at irregular intervals for several days at room temperatures. The amalgam was thoroughly washed with ammonia, the solvent was evaporated, and the legs were separated. The mercury was boiled with water for some time, cooled and titrated with acid to determine potassium. The ammonia-soluble material was treated as in the experiments listed in Table II. The results are tabulated in Table III.

The Action of Barium Amide on Quinoline

Expt. 25.—Quinoline (25 grams, 0.194 mole) and anhydrous barium thiocyanate (75 g. or 0.296 mole, dried for several weeks *in vacuo* over concentrated sulfuric acid) were placed in the autoclave of Figure 1, the removable vessel containing 16.3 g. potassium (0.418 atom) and 0.1 g. ferric oxide. The larger compartment also contained a number of steel balls, whose rolling motion (as the autoclave was rocked) aided in breaking up the solid reaction product. Ammonia (340 g.) was run directly into the bomb from a supply cylinder of the commercial liquid, the apparatus being tilted so that approximately the proper amount flowed into each compartment (since it is imperative that the smaller compartment not be flooded, it is safer to distil the ammonia in).

TABLE III

SUMMARY OF EXPERIMENTS 19–24

NO.	POTASSIUM AMIDE, MILLIMOLES	MERCURY, CC.	QUINOLINE, MILLIMOLES	REACTION TIME, DAYS	POTASSIUM IN MERCURY M. ATOMS	YIELD OF 2-AMINOQUINOLINE, %	NOTES
19	28.0	2.0	9.77	20	Solid amalgam	Almost none	*a*
20	14.3	2.03	19.68	9	0.12		*b*
21	34.2	2	11.36	7	10.20	15.7	*c*
22	16.0[1a]	1.5	8.5	7	6.89	11.3	
23	15	2.5	8.4	4	6.24	5.5	
24	16.0	1.5	8.5	5	6.88	11.0	*d*

[a] In a straight reaction tube[1a], with a short side-arm near the top for the mercury. Gas was displaced from the large tube before the reaction in the usual manner, and from the short tube by swabbing externally with cotton dipped in liquid ammonia. Solvent condensed on the inner walls and on top of the mercury, displacing air and other gases on evaporation. Hydrogen (5.7 cc., N.T.P., 0.25 millimole) but no nitrogen, was obtained at the completion of the experiment.

[b] The amount of potassium is close to the blank.

[c] In a two-legged tube. The reaction took place in the absence of the iron wire catalyst. At the end of 7 days, the tube was cooled, the amalgam washed and removed by cutting off the end of the tube, and 16.1 millimoles of potassium nitrate was introduced, the tube being resealed. After four days at room temperatures the solvent was evaporated and the product crystallized from water. Yield of mixed aminoquinolines, 0.58 g., (4.0 millimoles) or 35% (m. p. 70–105°). Yield of pure 2-aminoquinoline, m. p. 127.6–128.3°, is 0.257 g. (15.7%).

[d] Potassium amide and quinoline reacted 7 days, after which the tube was cooled to −33°, and mercury was introduced. After five days at room temperatures, the amalgam was washed, the solvent evaporated, and the contents treated as already described.

TABLE IV

THE ACTION OF THE ALKALI AMIDES ON ISOQUINOLINE IN THE PRESENCE OF SALTS OR MERCURY

NO.	AMIDE[d]	MILLI-MOLES	ISOQUINOLINE, MILLI-MOLES	ADDED SUBST.	MILLI-MOLES	REACTION TIME, DAYS	1-AMINO-ISOQUINOLINE, M. MOLES[a]	PER CENT. OF THEORY	NOTES
27	KNH_2	480	233	KNO_3	148	1.1	146	62.6	*b*
28	KNH_2	404	194	KNO_3	208	1	124	64.0	*b*
29	KNH_2	31.2	9.87	KNO_3	11.5	26	6.95	70.5	*c*
30	KNH_2	24.0	7.83	KI	24.3	0.9	5.00	63.9	*m*
31	$NaNH_2$	46.5	10.98	$NaNO_3$	16.8	49	6.94	63.2	*d*
32	$NaNH_2$	35.6	12.07	$NaNO_3$	20.1	21	2.91	24.1	*i*
33	$NaNH_2$	18.3	17.00	$NaNO_3$	20.1	3	2.62	15.4	*j*
					cc.				
34	$NaNH_2$	30.0	10.53	Hg[g]	2.5	31	1.15	10.9	*e*
35	$NaNH_2$	23.0	10.47	Hg	2.0	10	5.12	49.0	*f*
36	$NaNH_2$	33.0	10.97	Hg	2.0	21	0.90	8.2	*h*
37	KNH_2	19.4	24.40	Hg	2.5	13	Very small amt.?		*k*
38	KNH_2	15.0	8.50	Hg	2.5	0.04	Not detd.		*n*
39	KNH_2	11.03	10.95	Hg	2.5	10	Trace?		*o*

[a] The yields of 1-aminoisoquinoline reported melted in the range 120–121.5°, uncorr.

[b] In the steel autoclave of Figure 1. The isoquinoline and potassium nitrate were in the autoclave proper, the potassium and iron oxide catalyst in the small compartment. After evaporation of solvent benzene was added to the contents, which were hydrolyzed with the minimum quantity of water. The hydrolysate was extracted several times with boiling benzene, and the extracts were concentrated to get aminoisoquinoline. (*Cf.* experiment 12.)

[c] In a straight reaction tube.[1a] Potassium metal and ferric oxide (0.02 g.) were sealed in the tube, and ammonia was distilled in until prevented by the pressure of the generated hydrogen, which was then vented (see experiment 10), the process being repeated as necessary. With the desired amount of solvent in the tube, the latter was cooled in a liquid ammonia bath, and the small tube at the top was broken open so that the isoquinoline and potassium nitrate could be introduced. (A current of ammonia passed out of the open end to prevent access of air.) After sealing, with the usual precautions (*cf.* ref. 1*a*), and warming to room temperatures, the solution was found to be an opaque brown or reddish brown, and not green, as when potassium nitrate is omitted. The reaction time was far longer than necessary; 104.7 cc. (4.67 millimoles) of hydrogen (N.T.P.), and 8.8 cc. nitrogen (N.T.P.) were obtained, the latter probably being formed by decomposition of potassium nitrate in the presence of ferric oxide. The yield of hydrogen (47.3 per cent.) was distinctly inferior to that obtained in comparable experiments where no nitrate was used (about 70 per cent.).

[d] Ferric oxide (0.02–0.12 g.) used as a catalyst for the conversion of the alkali metal to amide, unless otherwise mentioned. The smaller amount was sufficient to convert potassium to potassium amide. The reactions were carried out in two-legged tubes, unless otherwise mentioned.

TABLE IV—*Concluded*

[e] In a straight tube, note *c*; 6.4 cc. (0.28 millimole) of hydrogen formed.

[f] In a two-legged reaction tube (*cf.* experiments 22–3). The product melted at 117.7–120.8°, uncorr. The mercury contained 2.92 milliatoms of sodium, or 0.279 atoms per mole of quinoline. The mercury was washed with ammonia at the end of the reaction to remove as much soluble material as possible. Since it was too tedious to wash all of the sodium amide over, solvent was evaporated from the tube, and the latter was inverted to allow the dilute amalgam to run out through the open stopcock. Sodium amide remained in the reaction tube, together with a small amount of mercury. The latter was removed (in experiment 36) by washing out with pure mercury in the following manner. The reaction tube was evacuated with a water pump, the end of the stopcock capillary was dipped into mercury, and the stopcock was opened to draw some inside; finally air was allowed to enter to establish atmospheric pressure within. After shaking, with the stopcock closed, the latter was opened, and the tube was again inverted, whereupon the mercury ran out and was caught in an Erlenmeyer flask. The high yield of aminoisoquinoline reported was not duplicated. Thus, with the same relative amounts of materials, a 21.2 per cent. of aminoisoquinoline, m. p. 115–120°, was obtained. The mercury contained 0.338 atom of sodium per mole of isoquinoline used.

[g] The mercury used was prepared for electrode potential measurements and was of high purity (electrolyzed, and distilled *in vacuo*).

[h] In a two-legged tube (see experiments 22–23); 2.34 milliatoms of sodium in the mercury, or 0.214 atom per mole of isoquinoline. *Cf.* note *f*.

[i] In a straight tube. Yield of crude product, m. p. 115–8°, is 4.68 millimoles or 39 per cent.

[j] An iron wire catalyst was used for the conversion of sodium to sodium amide. The concentration of isoquinoline was somewhat higher than in related experiments.

[k] In a two-legged tube (see experiments 22–23); 0.950 milliatoms of potassium found in the mercury. The chief reaction product was thick liquid tar.

[m] It was thought that the potassium iodide might slow down the reaction because of the effect of potassium ion on the dissociation of potassium amide. The reaction appeared to be almost as rapid as when no potassium iodide was used. Yield of hydrogen 83.8 per cent. of the theoretical

[n] *Cf.* Reference 1*b*, p. 40. Hydrogen, 7.19 millimoles, or 85 per cent. of the theory. Milliatoms of potassium in the mercury, 0.15 (probably of no significance).

[o] In a two-legged tube; 11 cc. of hydrogen, N.T.P. (0.49 millimoles) was collected during the first day of the reaction; 1.180 milliatoms of potassium was found in the mercury, *i.e.* 0.108 atom per mole of isoquinoline used.

The bottom of the autoclave was heated for a while with a small flame to cause the liquid inside to boil and dissolve the barium thiocyanate. The contents of the compartments were mixed by tipping the autoclave to a horizontal position, after which it was rocked for about two days at room temperatures, though the reaction was apparently complete in a shorter time (no evolution of hydrogen). After evaporation of ammonia, water was cautiously added to the contents of the autoclave while stirring was effected with a metal rod. After addition of benzene (about 150 cc.), the bomb was heated, and the hot upper layer was decanted through a filter. The extraction with benzene was repeated twice. Concentration of the extracts gave several crops of slightly brownish crystals, m. p. 127–129° (22.5 g., 0.156 mole, or 80.4% of the theoretical). No 4-aminoquinoline was isolated.

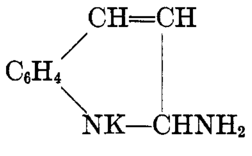
Expt. 26.—Potassium amide from 12.6 g. of potassium was added to 20.5 g. quinoline and 63 g. dry barium nitrate in liquid ammonia, according to the method of the previous experiment, the mixture being rocked for 32 hours at 60–70°, and allowed to stand for one day at room temperatures. The product was hydrolyzed directly with water, an excess of hydrochloric acid was added, and the precipitated hydrochloride was separated by filtration. This was treated with an excess of ammonia water, filtered, and crystallized from benzene. The yield of 2-aminoquinoline was 15.8 g. or 69%. An oxygen-containing by-product, 1.92 g., m. p. 197–198.5° uncorr., was isolated from the aqueous filtrate of the last crop of 2-aminoquinoline, and was crystallized from pyridine. Further discussion is reserved for a future paper.

The reaction of other bases with isoquinoline.—The failure of quinoline to react with bases other than the alkali and alkaline earth amides to give definite products has been recorded.[1a] In the present work, the behavior of isoquinoline has been found to be the same. The following compounds, in threefold excess, reacted with isoquinoline in liquid ammonia at room temperatures for the periods indicated (in days): potassium anilide (33) (no nitrogen or hydrogen formed); potassium anilide and potassium nitrate (7); barium anilide (27); potassium quinaldine (78); barium quinaldine (1); potassium quinaldine and potassium nitrate (46); potassium triphenylmethyl (124); potassium diphenylmethyl (8); and potassium indole (17). The very small quantities of 1-aminoisoquinoline obtained in some of these experiments probably were due to small amounts of potassium amide or barium amide formed in the partial ammonolysis of the salts. Otherwise, no definite substances were isolated.

Lithium diethylamide, $(C_2H_5)_2N\cdot Li$, reacts readily with isoquinoline in ether, apparently with the formation of tar alone.[15]

SUMMARY

(1) It has been shown that quinoline forms addition compounds with the alkali amides in liquid ammonia, although it has proven impossible to isolate them in a pure condition since they slowly decompose in solution, as well as in the solid state, into substances of an indefinite nature. There is some evidence that the addition compound first formed slowly changes into other ones, presumably



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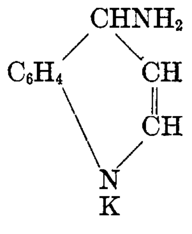

although the experimental results may be interpreted otherwise.

(2) An excess of potassium amide converts quinoline to a mixture of 2- and 4-aminoquinolines (with the former predominating) in the presence of potassium nitrate, which is reduced to potassium nitrite. The addition

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[15] GLENN WHITE, Thesis, Stanford University, **1936**.

compound of potassium amide and quinoline may be formed and kept for several days, then treated with potassium nitrate, with sensibly the same results as above (an excess of potassium amide should be used).

(3) The action of the alkali amides on quinoline and isoquinoline in liquid ammonia is explained by the following reactions (the $\cdot CH{=}N\cdot$ group alone will be written; NH_2^- will replace KNH_2 and $NaNH_2$):

(*a*) $\cdot CH{=}N\cdot + NH_2^- = \cdot CH(NH_2)N\cdot^-$

(*b*) $\cdot CH(NH_2)N\cdot^- + NH_2^- \rightleftharpoons \cdot CH(NH^-)N\cdot^- + NH_3$.

(*c*) $\cdot CH(NH^-)N\cdot^- = \cdot C(NH^-){=}N\cdot\ [\rightleftharpoons \cdot C({=}NH)N\cdot^-] + (H + e^-)$

The third step takes place in the presence of a substance that can react with $(H + e^-)$, or, what amounts almost to the same thing, with H^-. There is some evidence that the electron can be removed first, followed by the hydrogen, although it is by no means certain that this occurs in the reaction as usually carried out.

Solvent ammonia alone is sufficient to remove H^- when an excess of the soluble potassium amide reacts with isoquinoline, since $H^- + NH_3 = H_2 + NH_2^-$. The sparingly soluble sodium amide and isoquinoline react at an extremely slow rate unless sodium nitrate is present, the latter being reduced to nitrite. Potassium amide (in excess) reacts with quinoline to form 2- and 4-aminoquinoline in the presence of potassium nitrate, but not in pure ammonia. Therefore the ease of removal of H^- in step (*c*) above is greater with isoquinoline than with quinoline.

The mechanisms proposed constitute an extension of those of Ziegler and Zeiser, Kirssanov and Ivastechenko, and Kabachnik.

Unsuccessful attempts were made to replace nitrates in the above reactions with other salts.

(4) An excess of potassium amide reacts with quinoline in the presence of mercury to form a dilute potassium amalgam, together with a small quantity of 2-aminoquinoline. With continuous mechanical shaking, the yields of both are increased. The overall reaction is possibly the following:

$$\cdot CH{=}N\cdot + 3NH_2^- + xHg = Hg_x^{--} + 2NH_3 + \cdot C(NH^-){=}N\cdot$$

(5) Sodium amide reacts slowly with isoquinoline and mercury to form a dilute sodium amalgam and 1-aminoisoquinoline in poor yield.

(6) A rocking steel autoclave for carrying out reactions in liquid ammonia on a scale larger than is possible in glass has been described.

(7) Only 2-aminoquinoline could be isolated as a product of the reaction of barium amide with quinoline.

(8) No base other than NH_2^- (in the presence or absence of NO_3^-) has been found to react with isoquinoline in liquid ammonia to give products of the type of 1-aminoisoquinoline.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]*

AMINO ACID CATALYSIS OF THE MUTAROTATION OF GLUCOSE

F. H. WESTHEIMER

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Several authors[1] have noticed the catalytic effects due to amino acids, and have tried to correlate this catalysis with enzyme action. Before, however, the effects of amino acids can reasonably be considered, it is necessary to know the mechanism of the catalysis, and whether the results are really extraordinary.

It is a logical deduction from the work of Brønsted[2] and of Lowry[3] that amino acids will accelerate those reactions subject to general acid or general base catalysis. Thus it could be predicted that the dipolar ion, glycine ($H_3N^+CH_2COO^-$) would be a catalyst for the mutarotation of glucose, and that the rate constant would be of the same order of magnitude as the constant for glycolate ion.[4]

This investigation provides at once a properly controlled study of amino acid catalysis and an inquiry into the limits of validity of Brønsted's generalization. The catalytic effect on the mutarotation of glucose of a number of amino acids is recorded. An attempt has been made to include all the possible types: bases with net positive charge, with net negative charge, and with no net charge, bases with primary, secondary, tertiary, and quaternary nitrogen, etc. The rate constants are compared with the base strength of the catalyst, following Brønsted's method. The base strength of dimethylglycine, for which no reliable value was available, was measured electrometrically. Finally, the possible significance of the catalysis is discussed.

EXPERIMENTAL

The mutarotation of glucose was measured polarimetrically, in 200 mm. tubes, jacketed at 18.00° ± 0.05°. The light from a Pyrex mercury arc was filtered through

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* Preliminary research was done in the Chemical Laboratories of Columbia University.

[1] DAKIN, *J. Biol. Chem.*, **7**, 49 (1909); HAEHN, *Z. angew. Chem.*, **39**, 1148 (1926); BLANCHARD, KLEIN, AND MACDONALD, *J. Am. Chem. Soc.*, **53**, 2809 (1931); FISCHER AND MARSHALL, *Ber.*, **64B**, 2825 (1931); HERBST AND ENGEL, *J. Biol. Chem.*, **107**, 505 (1934); LANGENBECK, *Ber.*, **69**, 248 (1936).

[2] BRØNSTED, *Chem. Rev.*, **5**, 231 (1928).

[3] LOWRY, *J. Chem. Soc.*, **127**, 2883 (1925).

[4] BRØNSTED AND GUGGENHEIM, *J. Am. Chem. Soc.*, **49**, 2554 (1927).

neodymium glass and a nickelous nitrate solution to obtain the 4916 line.[5] The polarimeter was loaned to the author by the Sprague Institute, through the courtesy of Dr. Marburg.

The electrometric titrations were carried out in an air thermostat at 18.1° ± 0.1°. One hundred cubic centimeters of approximately 0.01 *M* dimethylglycinium chloride was titrated with standard sodium hydroxide introduced through a microburet. The solution was stirred at all times. Electrolytic hydrogen, freed from oxygen with alkaline pyrogallol, was bubbled over a lightly platinized platinum electrode. The E.M.F. between this half-cell and a saturated calomel cell was measured through an agar-potassium chloride bridge with a Leeds and Northrup Student-Type Potentiometer. The pH of 0.05 *M* potassium acid phthalate, measured with this apparatus, was correct within 0.01 pH unit.[6]

Materials.—Glucose was prepared according to Hudson and Dale,[7] and the rate of mutarotation in acidified water at pH 5 was the same as that reported by those authors and by Bronsted and Guggenheim.

Pure picoline was prepared from redistilled Eastman product, after conversion to the mercuric chloride complex of m.p. 154°.[8] Vacuum-distilled quinoline froze at −15°.[9] Ammonium chloride was recrystallized from water, methylammonium chloride from absolute alcohol.

Since the melting points of the amino acids depend markedly on the way in which the measurement is made, the method of preparation of the compounds used is given below.

Eastman's glycine and alanine were twice recrystallized from water-alcohol. Eastman's sarcosine was recrystallized several times from methanol. Dimethylglycinium chloride and dimethylglycine were prepared essentially according to Clarke,[10] but the hydrochloride was recrystallized from acetic acid, not water, and the free amino acid was recrystallized from isopropyl alcohol. Eastman's betaïne hydrochloride was washed with hot absolute alcohol, recrystallized from dilute alcohol.[11] From the hydrochloride, betaïne was prepared in the usual manner, and recrystallized from isopropyl alcohol.

p-Benzbetaïne was prepared according to Willstatter,[12] pyridyl betaïne according to Gerichten[13] and phenyl betaïne according to Reitzenstein.[14]

β-Alanine, prepared according to *Organic Syntheses*,[15] was recrystallized from methanol-ether. Glutamic acid, prepared from "Ajinomoto" by the method of *Organic Syntheses*[16] was recrystallized from water. Glycylglycine was prepared

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[5] Wood, "Physical Optics", The Macmillan Company, New York City, **1914**, p. 15.

[6] Clark, "Determination of Hydrogen Ions", 3rd Edition, The Williams and Wilkins Company, Baltimore, Maryland, **1928**, p. 485.

[7] Hudson and Dale, *J. Am. Chem. Soc.*, **39**, 320 (1917).

[8] Ladenberg, *Ann.*, **247**, 1 (1888).

[9] Beilstein's "Handbuch", 4th Edition, Springer, Berlin, **1935**, Vol. 20, p. 341.

[10] Clarke, Gillespie, and Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

[11] Stoltzenberg, *Ber.*, **45**, 2248 (1912).

[12] Willstätter and Kahn, *Ber.*, **37**, 401 (1904); Michael and Wing, *Am. Chem. J.*, **7**, 195 (1885).

[13] Gerichten, *Ber.*, **15**, 1251 (1882).

[14] Reitzenstenn, *Ann.*, **326**, 326 (1903).

[15] *Organic Syntheses*, John Wiley & Son, New York City, **1936**, Vol. 16, p. 1.

[16] Reference 15, Coll. Vol. I, p. 281.

according to Fischer.[17] Proline, aspartic acid, arginine monohydrochloride and lysine hydrochloride were obtained from Pfanstiehl Chemical Company; all were recrystallized before use. Histidine, from Hoffmann-LaRoche, was generously contributed by Dr. A. H. Corwin of Johns Hopkins University. Hippuric acid melted at 188°.

RESULTS

In order to correlate the results of this research with the work of Brønsted and Guggenheim,[4] some of the principles of general acid and base catalysis must be recalled. Brønsted and his co-workers[18] have shown that the catalytic constant of a base is related to the dissociation constant of that base by the relation $k_B = GK_B^x$, where k_B is the cataytlic constant of any particular base, K_B the corresponding dissociation constant, and G and x are constants for the series of bases under consideration.

The values of G and of x, however, may vary according to the charge type of the catalyst. In the case of nitramide catalysis, G varies from 2 to 780, x from 0.87 to 0.75 as the charge on the catalyst is changed from -2 to $+2$.[19] Not only may the values of G and x vary, but the relations between the members of the same charge type are not strictly accurate. Pflüger[20] studied the effects of *N*-disubstituted anilines in the catalysis of the decomposition of nitramide in *m*-cresol solution.[21] He found that variation in the catalyst molecule on or near the nitrogen affected the rate, and that deviations of several tenths of a logarithmic unit from Brønsted's equation occurred.

It was necessary, then, to measure the catalytic effects of a series of uncharged molecules and compare these rate constants with those of the amino acids. Since such primary amines as aniline cause side reactions to take place,[4] tertiary amines and betaïnes were chosen.

The rate of base catalysis was measured at pH values between 4 and 6, except in the case of histidine when the pH approached 6.5. In this entire region, the catalytic effect of hydrogen and hydroxyl ions is small compared with the catalytic effect of water and of the catalyst employed. To the uncharged amino acids was added enough hydrochloric acid to convert approximately one-hundredth of the compound into the conjugate acid, thus maintaining the pH within the appropriate region. The hydrolysis of the hydrochlorides of arginine and of lysine automatically maintained the correct acidity. That the catalysis of the amino acids is

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[17] FISCHER, *Ber.*, **34**, 2870 (1901).

[18] BRØNSTED AND PEDERSON, *Z. physik. Chem.*, **108**, 185 (1924); BRØNSTED AND DUUS, *ibid.*, **117**, 299 (1925); BRØNSTED AND VOLQUARTZ, *ibid.*, **155**, 211 (1931).

[19] PEDERSON, *J. Phys. Chem.*, **38**, 581 (1934).

[20] PFLUGER, Private communication.

[21] BRØNSTED, DELBANCO, AND TOVBORG-JENSEN, *Z. physik. Chem.*, **169**, 361 (1934); BRØNSTED, NICHOLSON, AND DELBANCO, *ibid.*, **169**, 379 (1934).

TABLE I

Base Catalysis of the Mutarotation of Glucose

COMPOUND	CONCENTRATION	CONCENTRATION OF THE CONJUGATE ACID	$k \times 10^3$, OBSERVED	$k \times 10^3$, CALCULATED	$k_B \times 10^3$
Picoline	0.0448	0.085	7.45	7.63	52.
	.0505	.080	8.15	7.93	
	.0640	.097	8.58	8.62	
Quinoline	0.0238	0.0238	5.82	6.01	30.
	.0335	.0335	6.39	6.31	
	.0509	.0204	6.94	6.83	
Betaïne	0.250	0.003	5.93	5.98	2.70
	.310	.003	6.19	6.14	
	.374	.004	6.20	6.31	
	.429	.004	6.55	6.48	
p-Benzbetaïne	0.168	0.002	6.21	6.31	6.00
	.197	.002	6.54	6.48	
	.228	.002	6.66	6.67	
Glycine	0.184	0.002	6.31	6.47	6.35
	.265	.003	6.75	6.97	
	.348	.003	7.31	7.51	
	.441	.004	8.25	8.10	
	.555	.006	8.94	8.83	
	.770	.008	10.88	10.20	
	.995	.010	12.40	11.62	
Alanine	0.228	0.002	6.95	6.75	6.35
	.333	.003	7.44	7.42	
	.412	.004	7.84	7.92	
	.514	.005	8.87	8.56	
Sarcosine	0.312	0.003	6.84	7.02	5.50
	.380	.004	7.41	7.39	
	.380	.004	7.55	7.39	
	.456	.005	7.71	7.81	
	.541	.005	8.07	8.28	
Dimethylglycine	0.275	0.003	6.14	6.26	3.50
	.336	.003	6.35	6.48	
	.421	.004	6.96	6.78	
	.546	.005	7.04	7.21	
β-Alanine	0.138	0.001	7.38	7.46	15.7
	.186	.002	8.20	8.22	
	.292	.003	9.95	9.89	

TABLE I—*Concluded*

COMPOUND	CONCENTRATION	CONCENTRATION OF THE CONJUGATE ACID	$k \times 10^3$, OBSERVED	$k \times 10^3$, CALCULATED	$k_B \times 10^3$
Glycylglycine	0.120	0.001	6.79	6.60	10.8
	.165	.002	7.11	7.08	
	.228	.002	7.72	7.76	
Proline	0.230	0.002	6.04	6.02	3.13
	.320	.003	6.23	6.20	
Asparagine	0.076	0.001	5.60	5.68	5.00
	.116	.001	5.95	5.88	
	.163	.002	6.09	6.12	
Histidine	0.0056	0.0001	6.47	6.45	206.
	.0084	.0001	6.87	7.03	
	.0122	.0001	8.15	7.81	
	.0140	.0001	8.20	8.18	
Glutamate ion	0.0380	0.0190	6.52	6.57	23.5
	.0600	.0190	7.09	7.09	
	.1022	.0190	8.11	8.09	
	.1290	.0190	8.64	8.74	
Aspartate ion	0.0690	0.0095	6.92	7.08	24.8
	.1072	.0095	7.78	7.71	
	.1255	.0095	8.55	8.49	
Arginine·HCl	0.068	0.001	5.66	5.67	5.45
	.095	.001	5.89	5.82	
	.137	.001	5.99	6.05	
Lysine·HCl	0.120	0.001	6.13	6.03	6.10
	.179	.002	6.41	6.39	
	.236	.002	6.71	6.74	
Hippurate ion	0.0508	0.0095	5.96	5.97	11.1
	.0828	.0095	6.41	6.23	
	.1271	.0095	6.74	6.83	
Pyridyl betaïne	0.393	0.004	5.74		1.1
Phenyl betaïne	0.22	0.002	5.54		1.1

not due primarily to the substituted ammonium ion is shown by the negligible effects of ammonium and methyl ammonium chlorides. The constant for water was determined as 5.17, 5.35, and 5.40 × 10^{-3}. Brønsted's value (5.30 × 10^{-3}) was chosen.

In Figure 1 the observed rate constants for a few compounds are plotted against the molarity of the catalyst; the slope is k_B. The numbering is that used in Table IV. The data, calculated with common rather than natural logarithms, are given in Table I. The constants are in min.$^{-1}$

It is to be noted that there is little evidence of curvature in the lines of Figure 1, even with those points representing solutions as concentrated as 0.5 molar. In the most concentrated glycine solutions, the curvature is in the direction opposite to that usually observed.

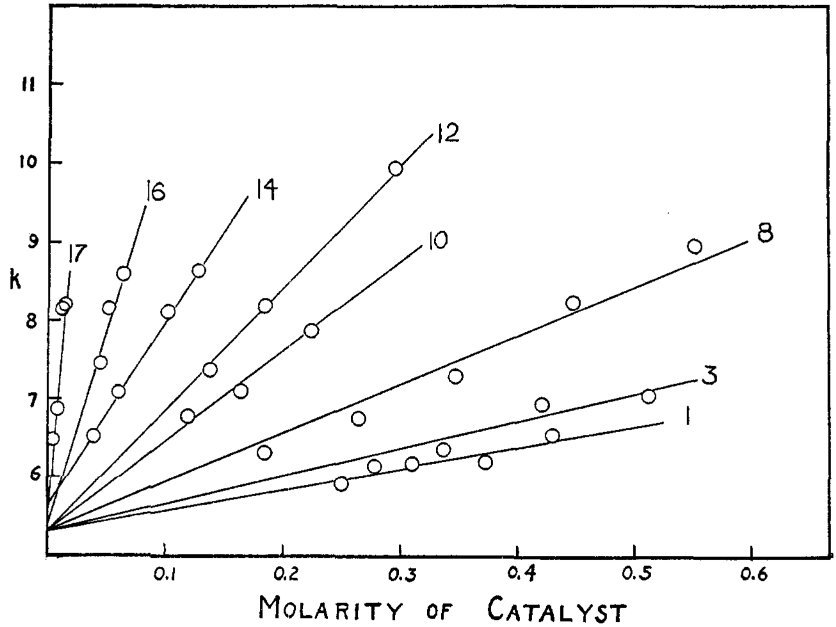

Figure 1.—Rate constants plotted against molality of catalyst. The data are those of Table I.

In Table II are recorded the results of an investigation of acid catalysis by amino acids. The pH of the solution was measured by a quinhydrone electrode, and hydrogen-ion catalysis was not neglected in computing the calculated values of k.

The observed constants were, in all cases here recorded, without drift; the average deviation was between 0.6 and 2 per cent, When aniline, *p*-aminobenzoate ion, and sulfanilate ion were tried, there were large drifts, and the final readings were far from those expected from the concentration of glucose used. To show that such was not the case with the amino acids, even when present in concentrated solution, the velocity constant determination for 7 per cent (0.995 M) glycine is presented in

Table III. In its freedom from drift, and in the size of the average deviation, this run is typical.

The electrometric titration of glycine gave a value for the pK of 2.25 ± 0.02, at 18°. Since Harned's value at 25° is 2.25, and the temperature coefficient of dissociation constants measured near 25° is in general low, the apparatus and method were judged satisfactory.

TABLE II

Acid Catalysis of the Mutarotation of Glucose

COMPOUND	CONCENTRATION	CONCENTRATION OF THE CONJUGATE BASE	$k \times 10^3$, OBSERVED	$k \times 10^3$, CALCULATED	$k_A \times 10^3$
Glycinium ion	0.000	0.517	8.60	8.57	11.0
	.000	.504	8.76	8.57	
	.0572	.515	9.25	9.25	
	.164	.521	10.35	10.61	
	.236	.504	11.64	11.56	
Glutamic Acid	0.0333	0.1085	8.51	8.53	19.5
	.0472	.0880	8.27	8.32	

TABLE III

A Typical Velocity Determination

TIME	ROTATION	$R_t - R_\infty$	$\log (R_t - R_\infty)$	D	$k \times 10^3$	DEV.
0	16.21	7.97	0.902	0.047	10.68	−0.20
4.40	15.42	7.18	.856	.094	11.09	+0.21
8.48	14.68	6.44	.809	.146	10.92	+0.04
13.37	13.96	5.72	.757	.209	10.73	−0.15
19.45	13.18	4.94	.694	.278	10.91	+0.03
25.50	12.46	4.22	.625	.338	10.90	+0.02
31.00	11.91	3.67	.565	.394	10.72	−0.16
36.67	11.47	3.23	.509	.465	10.75	−0.13
43.17	10.98	2.74	.438	.549	10.99	+0.11
49.90	10.50	2.26	.354	.638	11.08	+0.20
57.50	10.08	1.84	.265	.760	10.79	− .09
70.52	9.61	1.39	.143	.954	10.97	+ .09
86.83	9.11	0.89	1.949			
∞	8.24					
				Average	10.88	0.11 or 1.0%

Three titrations of dimethylglycinium chloride gave a pK for this acid of 1.85 ± 0.05. The titration carried out at a concentration of 0.01818 gave the value 1.85 ± 0.02, that at 0.01357 a value of 1.87 ± 0.06, and that at 0.00901 a value of 1.83 ± 0.06. The acid is so strong that, in the most dilute solution, some drift in the values of K could be expected.

DISCUSSION OF RESULTS

It is quite obvious from the data here given that amino acids are good catalysts for the mutarotation of glucose. Histidine, at pH 6, is a better catalyst than the same concentration of a strong acid. The logarithms of the catalytic rate constants of these compounds are plotted against the logarithm of the dissociation constant of the conjugate acid. In order that the comparison be made upon a fair basis, statistical factors must be taken into consideration.[2,19] For unsymmetrical bases such as aspartate and glutamate ions, the usual statistical correction does not hold. A derivation similar to Pedersen's shows that the correction, to be subtracted from log k_B is log $\frac{a^x + 1}{(a + 1)^x}$, where "$a$" is the true ratio between the dissociation constants of the two possible conjugate acids of the unsymmetrical base, and "x" the exponent in the Brønsted equation (about 0.34 in this case). A crude first approximation of the factor, "a" was obtained by comparing the ratio of the two dissociation constants of aspartic acid with those of succinic acid, and making a similar comparison

TABLE IV

COMPARISON OF RATE WITH DISSOCIATION CONSTANTS

COMPOUND	NUMBER	$3 + \log k_B$		pK. OF CONJUGATE ACID
		Uncorr.	Corr.	
Betaïne	1	0.43	0.23	1.82
Proline	2	.50	.30	1.88
Dimethylglycine	3	.54	.34	1.85
Arginine·HCl	4	.74	.54	1.92
Sarcosine	5	.74	.54	2.13
p-Benzbetaïne	6	.78	.58	3.41
Lysine·HCl	7	.79	.59	2.08
Glycine	8	.80	.60	2.25
Alanine	9	.80	.60	2.42
Glycylglycine	10	1.03	.83	2.88
Hippurate ion	11	1.05	.85	3.80
β-Alanine	12	1.20	1.00	3.49
Aspartate ion	13	1.37	0.99	3.82
Glutamate ion	14	1.39	1.03	4.22
Quinoline	15	1.48	1.48	4.85
α-Picoline	16	1.72	1.72	6.38
Histidine	17	2.31	2.31	6.21

with glutamic and glutaric acids. This method is not free from objection, and the values of 3 and 9 obtained for "*a*" may be in error. But since the logarithmic corrections must lie between zero and 0.2, the values employed, of 0.18 and 0.16 cannot be far from correct. In addition, there is a statistical correction of −0.20 logarithmic units for all carboxylate ion bases.

The results are given in Table IV with and without statistical correction. The dissociation constants are taken from Landholt-Bornstein.[22] The data of Table IV, with statistical correction, are plotted in Figure 2.*

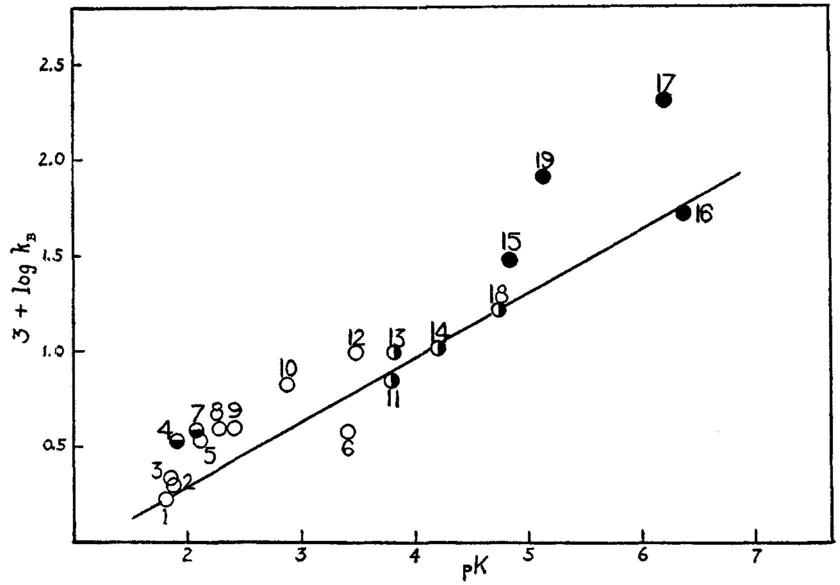

FIGURE 2.—Logarithm of the basic catalysis constant plotted against pK of the conjugate acid. The data are those of Table IV. Solid circles are for nitrogen bases, vertical half-circles for negatively charged bases, horizontal half-circles for positively charged bases, open circles for dipolar ions.

Included in the plot are the points for acetate ion (18) and pyridine (19) taken from the work of Brønsted and Guggenheim. Otherwise the numbering corresponds with Table IV.

Excluding the nitrogen bases, it is apparent that, although the points

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[22] *Lanholdt-Bornstein Tabellen,* Springer, Berlin, 5th Edition. 3rd Erganzungsband, 3rd Part, p. 2102 (1936); 2nd Erganzungsband, 2nd part, p. 1079 (1931).

* The straight line corresponds to the equation $k_B = 0.28 K_B^{0.34}$. It parallels that of Bronsted and Guggenheim, but differs from it due to the application here of statistical corrections.

do not lie precisely upon the line, there are no large deviations. For the mutarotation of glucose, then, there is little or no distinction between bases with a net negative charge, such as acetate ion, bases with a net negative charge but also containing a dipolar ion, such as aspartate ion, bases with no net charge, such as glycine, and bases with a net positive charge, such as lysine monohydrochloride. The deviations, about 0.2 logarithmic unit, are as great within any one group as among the different charge types. It is at once apparent, however, that this applies only to those bases which accept a proton in the transformation of a carboxylate ion into a carboxylic acid. It does not hold for nitrogen bases, nor the cobaltamines studied by Brønsted and Guggenheim. Furthermore, the agreement among the nitrogen bases, as a group, seems very poor.

A new line, with greater slope, might serve for all bases regardless of type, but then the deviations would be as great as 0.4 logarithmic units. Apparently the quantitative relationship put forward by Brønsted is valid only when the structure of the compounds used as catalysts is not markedly varied.

Finally, it may be noted that it is impossible to ascribe the irregularities of the results to catalysis by the undissociated, as contrasted with the dipolar ion form of the amino acids, for Edsall[23] has estimated the ratio of these forms for several amino acids, and has come to the conclusion that less than 0.01 per cent. of the amino acids is in the unionized condition. It is true that the undissociated form is a stronger base by a factor of about 10^5. However, in the case of the mutarotation of glucose the rate varies, approximately, as the cube root of the base strength of the catalyst ($k_B = 0.28\ K_B^{0.34}$). The contribution to the rate, then, of the undissociated form is well within the experimental error.

Langenbeck[1,24] has been searching for catalysts for ester hydrolysis and for other reactions, which would operate in neutral solution. In other words, he has been attempting model research in the enzyme field. Similarly, it was hoped that dipolar ions, which are at once acids and bases, would prove especially effective catalysts for the mutarotation of glucose. The present work shows that the catalysis by the various amino acids is approximately that which could be anticipated due to the groups involved. While it is not doubted that the acid and base groups play some rôle in enzyme reactions, it must certainly be in a different manner from that of the simple chemical analogues.

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[23] Edsall, *J. Am. Chem. Soc.*, **55**, 2337 (1933).

[24] Langenbeck and co-workers, *Ber.*, **67**, 387, 1204 (1934); *Ann.*, **485**, 53 (1931); **499**, 201 (1932); *Z. physik. Chem.*, **227**, 263 (1934); *cf.* Olivier, *Rec. trav. chim.*, **54**, 322, 599 (1935).

SUMMARY

(1) The catalytic constants for the mutarotation of glucose have been measured for many amino acids, a few betaïnes and tertiary amines.

(2) The pK of dimethylglycinium ion, determined electrometrically, is 1.85.

(3) All carboxylate ion bases, regardless of charge type, conform to the Brønsted equation, with deviations amounting to about 0.2 logarithmic units. Nitrogen bases must be classed separately.

(4) The implications of the amino acid catalysis are discussed.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, THE UNIVERSITY OF VERMONT]

GUANIDINE STRUCTURE AND HYPOGLYCEMIA: A BRANCHED-CHAIN ANALOGUE OF SYNTHALIN

CHARLES E. BRAUN* AND BERNARD J. LUDWIG†

Received October 27, 1937

The announcement in 1927 by Frank and his co-workers[1] of the synthesis of synthalin (1,10-diguanidodecane) with its hypoglycemic properties held out considerable possibility for its use as a therapeutic agent in the treatment of diabetes. However, its toxic effects soon destroyed the hope which followed its discovery, and even the subsequent report by Frank[2] of the preparation of synthalin B or neosynthalin (1,12-diguanidododecane), which was less toxic but also less effective than synthalin, failed to remove the serious doubt as to the utilization of guanidine derivatives as orally active substitutes for insulin.

Since both synthalin and neosynthalin were shown to be diguanido derivatives of normal hydrocarbons and therefore to possess straight-chain skeletons, it was considered of interest to prepare an isomer of neosynthalin in which the bridging carbon chain between the two guanidine residues not only would be shortened but also would have attached to it highly branched groups. Such a compound is highly desirable, as it would present the possibility of a substance with greater hypoglycemic activity and lower toxicity than neosynthalin, and also, would make available data bearing on the question of whether or not the hypoglycemia produced by certain guanidines and diguanidines is secondary to their toxic effects.

With these objectives in mind, the synthesis of 2,4-dimethyl-6,6-di(guanidomethyl)octane, in the form of the dihydrochloride, was undertaken. The structural relationships between these compounds may be seen from the following formulas of the free bases.

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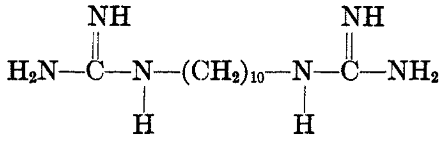
* On leave: now at Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.

† Eli Lilly Fellow in Organic Chemistry, 1935–1936.

[1] FRANK, NOTHMANN, AND WAGNER, *Klin. Wochschr.*, **5**, 2100 (1926); FRANK, *Naturwissenschaften*, **15**, 213 (1927).

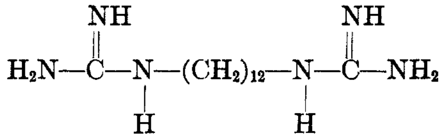
[2] FRANK, *Deut. med. Wochschr.*, **53**, 1845 (1927); FRANK, NOTHMANN, AND WAGNER, *Klin. Wochschr.*, **7**, 1996 (1928).



$$H_2N-\overset{\overset{\displaystyle NH}{\|}}{C}-\underset{\underset{\displaystyle H}{|}}{N}-(CH_2)_{10}-\underset{\underset{\displaystyle H}{|}}{N}-\overset{\overset{\displaystyle NH}{\|}}{C}-NH_2$$

Synthalin

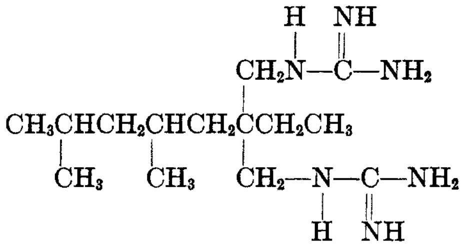
(1,10-diguanidodecane)



$$H_2N-\overset{\overset{\displaystyle NH}{\|}}{C}-\underset{\underset{\displaystyle H}{|}}{N}-(CH_2)_{12}-\underset{\underset{\displaystyle H}{|}}{N}-\overset{\overset{\displaystyle NH}{\|}}{C}-NH_2$$

Neosynthalin

(1,12-diguanidodecane)



$$CH_3\underset{\underset{\displaystyle CH_3}{|}}{C}HCH_2\underset{\underset{\displaystyle CH_3}{|}}{C}HCH_2\overset{\overset{\displaystyle CH_2\overset{\overset{\displaystyle H}{|}}{N}-\overset{\overset{\displaystyle NH}{\|}}{C}-NH_2}{|}}{\underset{\underset{\displaystyle CH_2-\underset{\underset{\displaystyle H}{|}}{N}-\underset{\underset{\displaystyle NH}{\|}}{C}-NH_2}{|}}{C}}CH_2CH_3$$

2,4-Dimethyl-6,6-di(guanidomethyl)octane

EXPERIMENTAL

Synthetic Part

Ethyl (2,4-dimethylpentyl)ethylcyanoacetate[3].—This compound was kindly supplied by The Lilly Research Laboratories, where it was prepared from ethyl cyanoacetate by condensation with ethyl bromide in the presence of sodium ethylate. After purification, the ethyl ethylcyanoacetate was condensed with 2,4-dimethylpentyl bromide in the presence of sodium ethylate. The ethyl (2,4-dimethylpentyl)-ethylcyanoacetate used in this work had the following constants: b.p. 99–105° (3–4 mm.); n_D^{25} 1.4349–1.4356.

(2,4-dimethylpentyl)ethylcyanoacetamide.—All attempts to convert ethyl (2,4-dimethylpentyl)ethylcyanoacetate directly into the corresponding amide through reaction with ammonia under varied conditions, or with ammonium carbonate, or ammonium acetate were unsuccessful.

The ester was converted into the acid by saponification after the method of Conrad and Zart.[4] Sodium, 1.15 g. (0.05 mole), was added gradually to 60 cc. of absolute ethyl alcohol. When the sodium had completely dissolved, the solution of sodium ethylate, after being diluted with 10 cc. of water, was added to 12 g. (0.05 mole) of the ester, and the resulting solution was evaporated to dryness on the steam

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[3] SHONLE, WALDO, KELTCH, AND COLES, *J. Am. Chem. Soc.*, **58**, 586 (1936).

[4] CONRAD, AND ZART, *Ann.*, **340**, 335 (1905).

bath. The solid residue was taken up in 100 cc. of water, and the solution was acidified with dilute hydrochloric acid, whereupon crude ethyl (2,4-dimethylpentyl)-cyanoacetic acid separated as a light-brown viscous oil which was extracted with ether, dried over anhydrous sodium sulfate, and freed from ether at room temperature under reduced pressure. No attempt was made to purify the acid, which was converted at once into the acid chloride.

The crude acid was heated for three hours on a steam bath with 10.4 cc. (0.15 mole) of thionyl chloride. The acid chloride remaining after evaporation of the excess of thionyl chloride was cooled in an ice bath, and was poured slowly with vigorous stirring into an excess of ice-cold concentrated ammonium hydroxide. The amide, which precipitated at once as a grayish-white powder, was purified by solution in methyl alcohol, treatment with Norite, and reprecipitation by the addition of a large volume of cold water. The purified product was a white powder, m.p. 74°. The conversion of the ester into the amide was repeated several times with an average overall yield of 50.3 per cent.

Anal. Calc'd for $C_{12}H_{22}N_2O$: N, 13.33. Found: 13.22 (by Kjeldahl).

Ethyl (2,4-dimethylpentyl)malononitrile.—Ethyl (2,4-dimethylpentyl)cyanoacetamide, 10.5 g. (0.05 mole), was thoroughly mixed in a 250-cc. distilling flask with three times its weight of phosphorus pentoxide. The reaction mixture, when dry-distilled under reduced pressure, produced a yellow liquid which boiled at 124–134° (18–20 mm.). Redistillation of the crude dinitrile gave 8.5 g. of a water-white product; b.p. 124–128° (15 mm.). A total of 195 g. of the amide was converted into 129.5 g. of the dinitrile with an average yield of 73 per cent.

Anal. Calc'd for $C_{12}H_{20}N_2$: N, 14.58. Found: 13.97 (by Kjeldahl).

2,4-Dimethyl-6,6-di(aminomethyl)octane dihydrochloride.—After many attempts to reduce the dinitrile to the corresponding diamine, the best conditions were found to be the following.

The dinitrile, 26.0 g. (0.135 mole), was added to 1270 cc. of absolute ethyl alcohol, and the solution was heated to boiling under reflux. Sodium, 130 g., was then added at such a rate that the solution continued to boil vigorously. When the sodium had completely disappeared, the solution was cooled, diluted with 825 cc. of water, and acidified with concentrated hydrochloric acid. After the alcohol had been distilled off, there remained an oily (nitrogen-free) layer which was extracted with ether. The remaining strongly acid aqueous solution was then made alkaline with concentrated sodium hydroxide solution, and the free diamine was extracted with ether. The diamine dihydrochloride was precipitated from the thoroughly dried ethereal extract with dry hydrogen chloride. Purification was effected by dissolving the crude dihydrochloride in a small volume of absolute ethyl alcohol and reprecipitating it by the addition of anhydrous ether. The purified product (0.617 g.; 1.67 per cent. yield) was a white powder, very soluble in water; m.p. 242° with decomposition. During the reduction a part of the nitrogen was split out as ammonia, which accounts in part at least for the low yield.

Anal. Calc'd for $C_{12}H_{30}Cl_2N_2$: Cl, 25.96; N, 10.26.
Found: Cl, 26.18; N, 10.83 (modified micro-Kjeldahl).

The diamine readily formed a light-yellow-colored monopicrate, which, after recrystallization from boiling dilute alcohol, melted at 129°.

2,4-Dimethyl-6,6-di(guanidomethyl)octane dihydrochloride.—The diamine dihydrochloride, 0.552 g. (0.002 mole), and cyanamide (Eastman Kodak Co.), 0.34 g. (0.008 mole), were added to 10 cc. of absolute ethyl alcohol, and the mixture was heated under reflux on a steam bath for eighteen hours, after which the alcohol was removed *in vacuo*. The residue was dissolved in a small volume of boiling absolute ethyl alcohol, the solution was treated with Norite, and the dihydrochloride of the diguanidine was precipitated by the addition of anhydrous ether. Purification was effected by repetition of the absolute alcohol—anhydrous ether procedure. The purified product (0.316 g.; 72.2 per cent. yield) was a white hygroscopic powder which decomposed at 112–113° with evolution of gas. It gave a positive Sakaguchi reaction for guanidine residues.

Anal. Calc'd for $C_{14}H_{34}Cl_2N_6$: Cl, 19.85; N, 23.53.

Found: Cl, 19.13; N, 23.19 (modified micro-Kjeldahl).

The picrate, after recrystallization from boiling water, was bright yellow, and melted at 214–215°.

Physiological Part

The physiological investigation of 2,4-dimethyl-6,6-di(guanidomethyl)octane dihydrochloride was carried out at The Lilly Research Laboratories. Due to the small amount of material available (about 160 mg.) an intensive study could not be made, and therefore, the results obtained should be considered only in a qualitative sense.

TABLE

PHYSIOLOGICAL TESTS OF 2,4-DIMETHYL-6,6-DI(GUANIDOMETHYL)OCTANE DIHYDROCHLORIDE

DOSE IN MG. FREE BASE PER KILO	BLOOD SUGAR IN MG. PER 100 CC. BLOOD				
	Initial	At Indicated Times After Administration			
		1.5 hr.	3 hr.	5 hr.	10 hr.
2.48	102	95	102	99	—
4.96	93	91	83	83	—
7.44	102	89	97	89	—
9.92	91	87	93	91	—
19.84	78	89	85	83	—
24.80	91	91	91	95	—
75.00	93	93	97	76	87

Rabbits were used as the experimental animals. The compound was administered subcutaneously, and the blood-sugar was determined by the micro method of Shaffer and Somogyi[5] at various intervals following injection. Twenty-five hundredths cc. of blood was diluted 1 to 15 with the zinc reagent, and 2 cc. of the filtrate was used for each determination. The results obtained are shown in the accompanying table.

The data show that no significant hypoglycemia followed the administration of 2,4-dimethyl-6,6-di(guanidomethyl)octane dihydrochloride even in doses as high as 75 mg. per kilo. No symptoms of toxemia were observed in any of the animals, all of which survived. This becomes important in view of the reported minimum lethal doses for synthalin[6] and neosynthalin[7] of 4 and 8 mg. per kilo respectively.

Therefore, in the synthalin type of diguanidine it appears that the loss of toxicity is accompanied by the disappearance of hypoglycemic properties, suggesting that

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[5] SHAFFER, AND SOMOGYI, *J. Biol. Chem.*, **100,** 695 (1933).

[6] Private communication from The Lilly Research Laboratories.

the hypoglycemia which follows administration of synthalin or neosynthalin is secondary to their toxic effects. This view is consistent with the observations of Bischoff, Sahyun and Long.[7]

Since Frank and his co-workers in their development of synthalin and neosynthalin have shown that the hypoglycemic activity increased with elongation of the carbon chain between the two guanidine residues, reaching a maximum in synthalin, and, since it has been demonstrated here that the hypoglycemic activity is lost when the guanidine residues are brought into close proximity as they are in 2,4-dimethyl-6,6-di(guanidomethyl)octane, it appears that hypoglycemic activity in the aliphatic diguanidines depends more upon the position of the guanidine residues than upon the structure of the remainder of the molecule. It would seem therefore of interest not only to prepare and study synthalin analogues in which the length of the carbon chain has been maintained but into which highly branched groups have been introduced at various positions, but also, to investigate the effect of introducing ethylenic linkages into the chain.

ACKNOWLEDGMENT

The authors wish to thank Dr. G. H. A. Clowes, Director of Research, The Lilly Research Laboratories, Indianapolis, Indiana, for suggesting the possibilities of this problem, Messrs. H. A. Shonle and W. J. Doran for supplying the starting compound for this work and Dr. E. D. Campbell for the physiological assays.

SUMMARY

1. The method of synthesis and general properties of 2,4-dimethyl-6,6-di(guanidomethyl)octane dihydrochloride, a branched-chain isomer of neosynthalin and an analogue of synthalin, have been described.

2. The physiological behavior of this diguanidine has been studied, and the observations are briefly discussed in connection with the general problem of guanidine structure and hypoglycemic activitv.

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[7] Bischoff, Sahyun, and Long, *J. Biol. Chem.*, **81**, 325 (1929).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

THE REACTION OF CYCLOPARAFFINS WITH AROMATIC HYDROCARBONS: DECYCLOALKYLATION*

ARISTID V. GROSSE AND VLADIMIR N. IPATIEFF

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We have recently described a number of new reactions between different classes of hydrocarbons[1] in the presence of suitable catalysts[2].

Previous to our investigations only the reaction between aromatic hydrocarbons and olefins in the presence of aluminum chloride was known. It was described by Balsohn[3] in 1879. This synthesis was the starting point of our research.

The main objective of our investigations is to effect all possible reactions between the different classes of hydrocarbons. Naturally suitable catalysts and conditions must be evolved so that the reactions will proceed smoothly in any desired direction and give only negligible quantities of by-products.

If we consider, for the present only the paraffins, olefins, aromatics, and cycloparaffins, the following combinations of hydrocarbons are possible:

(1) paraffins and olefins,
(2) aromatics and olefins,
(3) cycloparaffins and olefins,
(4) paraffins and aromatics,
(5) cycloparaffins and aromatics,
(6) paraffins and cycloparaffins.

With these six combinations the theory of structure will permit the following reactions.

In cases 1, 2, and 3 only the direct addition of an olefin to the respective hydrocarbons is possible in accordance with the following three general equations:

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* Presented in part before the Division of Organic Chemistry at the ninety-third meeting of the American Chemical Society, Pittsburgh, Pa., Sept. 7-10, 1936.

[1] See Ipatieff and Grosse, articles in *J. Am. Chem. Soc.* and J. ORG. CHEM., since 1935.

[2] GROSSE AND IPATIEFF, J. ORG. CHEM., **1**, 559 (1937).

[3] BALSOHN, *Bull. soc. chim.*, [2], **31**, 539 (1879).

$$(a)\quad \underset{\text{Paraffin}}{C_mH_{2m+2}} + \underset{\text{Olefin}}{C_nH_{2n}} \longrightarrow \underset{\text{Alkyl-paraffin}}{C_{m+n}H_{2(m+n)+2}}$$

$$(b)\quad \underset{\substack{\text{Aromatic}\\ \text{Hydrocarbon}}}{Ar\cdot H} + \underset{\text{Olefin}}{C_nH_{2n}} \longrightarrow \underset{\substack{\text{Alkyl aromatic}\\ \text{Hydrocarbon}}}{Ar\cdot C_nH_{2n+1}}$$

$$(c)\quad \underset{\substack{\text{Cyclo-}\\ \text{paraffin}}}{C_mH_{2m}} + \underset{\text{Olefin}}{C_nH_{2n}} \longrightarrow \underset{\text{Alkyl-cycloparaffin}}{C_mH_{2n-1}\cdot C_nH_{2n+1}}$$

In the last case another modification is also possible, namely the cleavage of the ring and formation of a straight chain olefin:

$$\underset{\text{Cycloparaffin}}{C_mH_{2m}} + \underset{\text{Olefin}}{C_nH_{2n}} \longrightarrow \underset{\text{Olefin}}{C_{m+n}H_{2(m+n)}}$$

All these cases may be considered as *alkylations.*

Case 4 may be considered as a *destructive alkylation*: the reaction consists in the cleavage of the paraffin into a paraffin of lower molecular weight and the alkylation of the aromatic hydrocarbon:

$$\underset{\text{Paraffin}}{C_{m+n}H_{2(m+n)+2}} + \underset{\substack{\text{Aromatic}\\ \text{Hydro-}\\ \text{carbon}}}{Ar\cdot H} \longrightarrow \underset{\substack{\text{Lower}\\ \text{Mol. Wt.}\\ \text{Paraffin}}}{C_mH_{2m+2}} + \underset{\substack{\text{Alkyl-aromatic}\\ \text{Hydrocarbon}}}{Ar\cdot C_nH_{2n+1}}$$

These reactions have been described previously[4]. The present paper will deal with the reaction of cycloparaffins and aromatic hydrocarbons (case 5). The reaction of paraffins and cycloparaffins (case 6) will be discussed in a future publication[5].

The reaction between cycloparaffins and aromatic hydrocarbons, which might be appropriately termed *decycloalkylation*, takes place in accordance with the following equation:

$$\underset{\substack{\text{Cyclo-}\\ \text{paraffin}}}{C_nH_{2n}} + \underset{\substack{\text{Aromatic}\\ \text{Hydrocarbon}}}{Ar\cdot H} \xrightarrow{\text{Catalyst}} \underset{\substack{\text{Alkyl-aromatic}\\ \text{Hydrocarbon}}}{Ar\cdot C_nH_{2n+1}}$$

The ease and smoothness of the reaction, as well as the definiteness of its direction, naturally depend to a very great extent on the nature of the hydrocarbons used and, in the case of the cycloparaffins, upon the stability of the ring.

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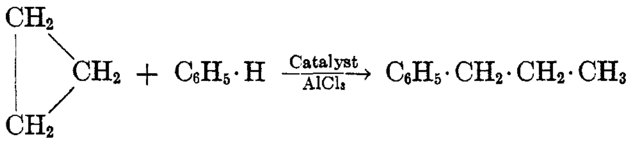
[4] (*a*) Ipatieff and Grosse, *J. Am. Chem. Soc.*, **57**, 1616 (1935); (*b*) Ipatieff, Komarewsky, and Grosse, *ibid.*, **57**, 1722 (1935); (*c*) Grosse and Ipatieff, *ibid.*, **57**, 2415 (1935); (*d*) Ipatieff and Grosse, *Ind. Eng. Chem.*, **28**, 461 (1936); (*e*) Ipatieff and Grosse, *J. Am. Chem. Soc.*, **58**, 915 2339 (1936); (*f*) Ipatieff, Grosse, Pines, and Komarewsky, *ibid.*, **58**, 913 (1936); (*g*) Ipatieff and Grosse, *J. Gen. Chem.* (U.S.S.R.), **68**, [6], 423 (1936); (*h*) Ipatieff, Komarewsky, and Grosse, *ibid.*, **68**, [6], 433 (1936); (*i*) Grosse and Ipatieff, *ibid.*, **68**, [6], 1514 (1936).

[5] See Grosse and Ipatieff, Abstracts of papers delivered at the ninety-third meeting of the American Chemical Society, Sept. 7-10, 1936, Organic Division.

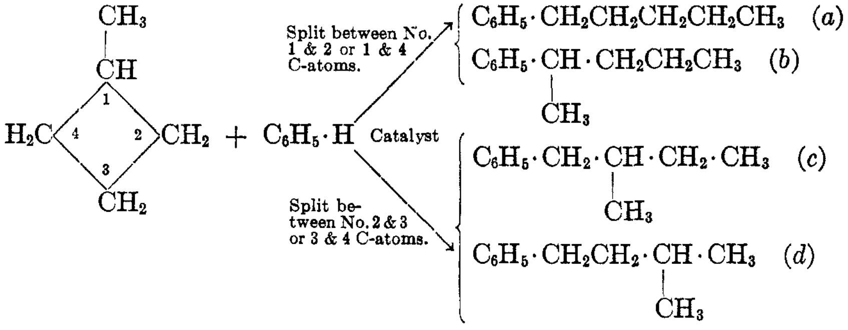
As an example one may cite the interaction of cyclopropane and benzene,



Due to the instability of the *cyclopropane ring,* this reaction proceeds readily at temperatures even below 0° and the only products are *n*-propylbenzenes. The higher propylbenzenes are, of course, formed by the stepwise alkylation of the primary product. It is of interest that the hitherto unknown hexa-*n*-propylbenzene may be prepared by this method.

It is worth mentioning that in our opinion the cyclopropane is not first isomerized to propylene, since the latter, under the same conditions, gives *only* isopropylbenzenes, and is not able to alkylate above the tetraisopropylbenzene stage[6].

The reaction between aromatic hydrocarbons and *cyclobutane* compounds also proceeds readily. In the presence of aluminum chloride, *methylcyclobutane* readily alkylates benzene at room temperature. Theoretically four monoamylbenzenes are possible, as shown below,



and we believe at least two of these are formed in the reaction. One of these products was identified as *isoamylbenzene(d).*

The monoamylbenzenes may be partly isomerized and further alkylated to di- and higher amylbenzenes.

As one might expect, *cyclopentane* reacts much less readily with benzene in the presence of aluminum chloride. Cyclopentane requires a temperature of about 150°, and the amylbenzenes formed are contaminated with products of dealkylation (ethylbenzene and toluene) and of a side reaction (see

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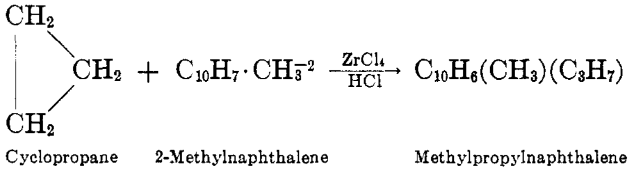
[6] See Berry and Reid, *J. Am. Chem. Soc.*, **49**, 3142 (1927).

experimental part). It is possible that alkylated cyclopentanes and cyclohexanes, which have not been investigated as yet[7], would react more readily and smoothly.

In all cases so-called "lower layers," consisting of addition compounds of aluminum chloride and the aromatic hydrocarbons, are formed.

Other catalytic agents may be used in place of aluminum chloride. Our other metal halides[8] have also proven useful. An example is the use of *zirconium chloride* in the alkylation of 2-methylnaphthalene with cyclopropane. The decycloalkylation proceeds in accordance with the general equation, *i.e.*,



Higher propylated naphthalenes are readily obtained in the presence of an excess of cyclopropane.

EXPERIMENTAL

1. Reaction between cyclopropane and benzene.—In one experiment the reaction was allowed to take place at 25–30° in a glass flask fitted with stirrer. About 1 mole of cyclopropane per mole of benzene was used. The cyclopropane* (40.0 g.) was passed through a potassium permanganate bubbler to oxidize any possible traces of propylene, and then through a calcium chloride drier. The pure dry gas was introduced at a fairly steady rate for 3.0 hours into the reaction mixture of benzene† (87.5 g.) and powdered aluminum chloride (8.9 g., Merck's C.P. grade). Small quantities (*ca.* 0.3 g.) of hydrogen chloride were introduced from time to time. The reaction was rapid, and the aluminum chloride became yellow, and gradually sticky, forming finally an orange-yellow lower layer. The cyclopropane reacted completely; no gas was given off during the reaction. The weights of the upper and lower layers were 116.0 and 18.4 g., respectively.

On fractionation of the washed clear, water-white *upper layer* the fractions recorded in Table I were obtained (see also Figure 1).

The fraction boiling at 153–161° is practically pure *n-propylbenzene.* Upon further fractionation this yielded a product boiling under 760 mm. pressure at 156–

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[7] In a preliminary experiment of V. N. Ipatieff and V. Komarewsky (see IPATIEFF "Catalytic Reactions at High Pressures and Temperatures," **1936**, page 727) cyclohexane itself did not react with benzene according to the decycloalkylation reaction, but gave mainly cyclohexylbenzene.

[8] See citation 2, page 1.

* From Malincrodt Chemical Works, St. Louis, fractionated at low temperatures; b.p. −32.9°/760 mm.; $n_D^{-42.5} = 1.3799$.

† Eastman's C.P. grade for molecular-weight determination was used throughout this investigation.

157°; d_4^{20}, 0.8622; n_D^{20} 1.4921. Analysis and molecular weight determination, C 89.72%, H 10.09%, mol. wt. 119, 121, agree with the calculated values for propylbenzene; C 89.99%, H 10.01%, mol. wt. 120. Oxidation of this fraction with potassium permanganate solution yielded benzoic acid (m.p. 122°). This proved the absence of isomeric methyl—or methylethylbenzenes. The hydrocarbon was further definitely identified by the preparation of its diacetamido derivative.[9] The melting

TABLE I

PRODUCTS OF REACTION BETWEEN CYCLOPROPANE AND BENZENE

B. P. AT 760 MM., °C.	VOL., %	REMARKS	n_D^{20}
78-80	38.3	Unchanged *benzene*; freezes completely in ice	1.5008
153-161	29.2	*n*-Propylbenzene	
210-218	12.8	Dipropylbenzenes	1.4906-1.4913
218-275	9.5	Tri- and higher propylbenzenes	1.4936
275-290	3.2	Higher propylbenzenes	1.4974
>290	6.0	Hexa-*n*-propylbenzene	

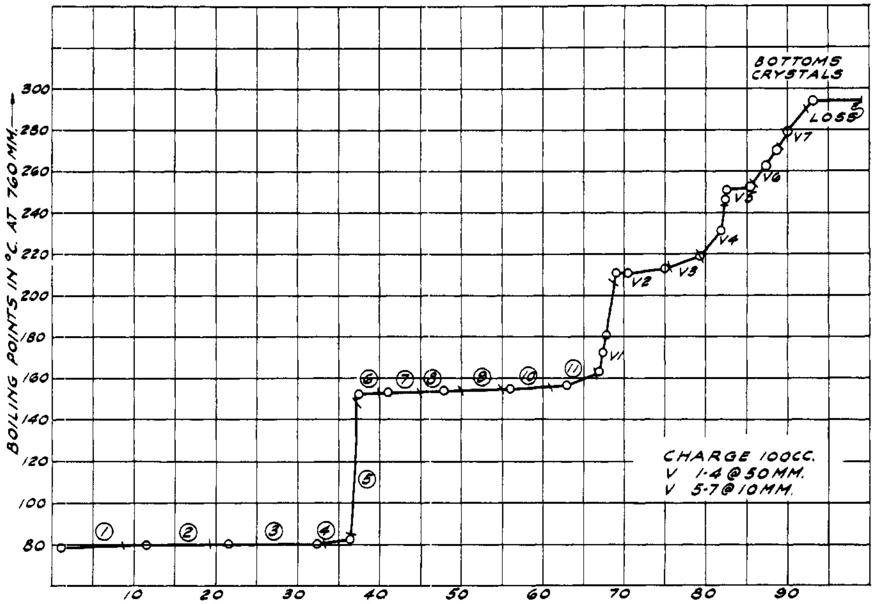

FIG. 1

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[9] Prepared by the method of V. N. Ipatieff and L. Schmerling, J. Am. Chem. Soc., **59**, 1056 (1937).

point (208°) was not depressed by admixture with a known sample of the same material (mixture melting point 208°). The melting point of a mixture with isopropyldiacetamidobenzene (m.p. 216°) showed a depression of 19–14°. None of the latter compound could be detected in other fractions of our product. In a synthetic mixture containing 10% of the iso compound the latter could be detected readily, so that a purity of at least 90% may be assumed for the *n*-propylbenzene.

Furthermore the *Raman spectra* of pure synthetic *n*-propyl and isopropylbenzenes were obtained by Dr. E. Rosenbaum and one of us (A. V. G.). These were compared with the spectrum of the fraction boiling at 153–161°, which was found to contain lines corresponding only to the normal compound. Thus the physical results completely support the conclusions drawn from our chemical experiments*.

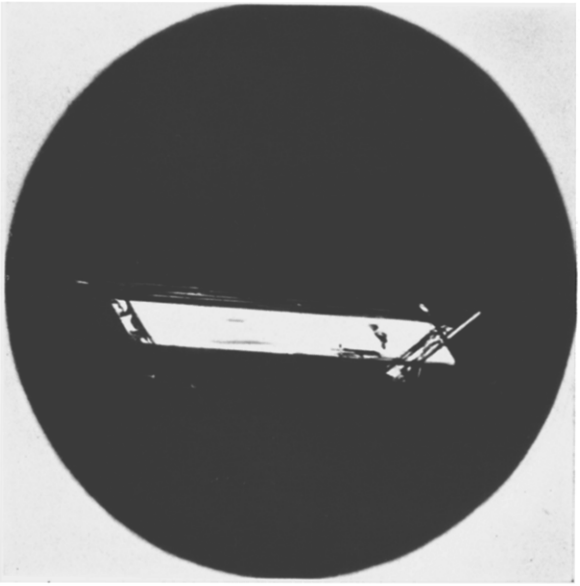

FIGURE 2.—HEXA-*n*-PROPYLBENZENE (CRYSTAL FROM ALCOHOL, *ca.* 24×)

The fraction boiling at 210-218° presumably contains the isomeric dipropylbenzenes. These, however, were not identified.

The solid residue (b.p. > 290°), upon crystallization from hot methyl or ethyl alcohol, yielded beautiful large flat white plates (see Figure 2) of *hexa-n-propylbenzene*. An analysis and molecular weight determination (C, 86.82%; H, 12.84%; mol. wt., 335, 329) agree with the calculated values for hexapropylbenzene (C, 87.19%; H, 12.81%; mol. wt., 330). The crystals melted sharply at 103.0°, and recrystallized upon solidification in long spear-shaped crystals. The melting point of a mixture with 1,2,4,5-tetra-*i*-propylbenzene, (m.p. 119.0°), the highest alkylation product of benzene ever obtained with propylene, showed a depression of 39–33°. Our com-

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* A description of the Raman spectroscopic work will be published separately by Dr. E. Rosenbaum and A. V. Grosse.

pound is probably identical with the hydrocarbon obtained by E. Wertyporoch and T. Firla.[10]

Our hydrocarbon boils without decomposition at atmospheric pressure. Its vapor pressure was determined by Mr. R. Wackher in the range of 10 to 600 mm.; the values lead to the following vapor-pressure equation:

$$\ln_{10} p_{(\text{mm. Hg})} = -0.05223\, A/T_{(^\circ\text{K})} + B;$$
$$A = 68352, \text{ and } B = 8.779.$$

The boiling points (T) for the corresponding pressures are:

p, mm. Hg	10	20	50	100	200	760
T, °C	185.8	204.3	231.1	253.5	278.0	332.2

The heat of vaporization is 16330 cal./mole, or 49 cal/g.; Trouton's constant = 24.

The density, d_4^T, corrected to vacuum, is:

at T°C	103°(m.p.)	110°	150°	200°	220°
d_4^T	0.8163	0.8112	0.7821	0.7457	0.7312

The change of density with temperature from the melting point to 230° can be represented by the equation:

$$d_4^T = 0.8163 - 0.000727\ (T - 103^\circ)$$

One might argue from the fact that since only *n*-propylbenzene, and no *i*-propylbenzene, is obtained as the initial alkylation product that the hexapropylbenzene, obtained by us, has six *normal* propyl groups. In our estimation, this conclusion is further substantiated by the fact that the 1,2,4,5-tetra-*i*-propylbenzene of melting point 119.0° could *not* be alkylated to a hexapropylbenzene with *i*-propyl chloride in the presence of aluminum chloride, either at room temperature or at about 100°.

The physical constants of our hydrocarbon are consistent with the trend exhibited by those of the other hexaalkyl benzenes, as the following comparison shows.

	MELTING POINT	BOILING POINT AT 760 MM.
$C_6(CH_3)_6$	166°	265°
$C_6(C_2H_5)_6$	129°	298°
$C_6(n\text{-}C_3H_7)_6$	103°	332°

The composition of the *lower layer*, after decomposition with water, is similar to that of the upper layer. It was found to contain aromatic hydrocarbons, in the following volume percentages: benzene, 20; *n*-propylbenzene, 20; dipropylbenzenes, 5; higher liquid propylbenzenes, 5; and hexa-*n*-propylbenzene, 50.

In another experiment 1 mole of cyclopropane (42.0 g.) was added to 2.25 moles of benzene (175.0 g.) containing 8.75 g. aluminum chloride and 0.8 g. hydrogen chloride, during 5 hours at +5 to 0°. Due to the large excess of benzene much larger quantities of *n*-propylbenzene (d_4^{20} 0.8621; n_D^{20} 1.4925) were obtained. The following products were isolated: *upper layer*, benzene 121.5 g., *n*-propylbenzene 70.0 g., dipropylbenzenes 9.5 g., higher liquid propylbenzenes 1.0 g., hexa-*n*-propylbenzene 2.0 g.; *lower layer*, benzene 4.3 g., *n*-propylbenzene 1.7 g., dipropylbenzenes 1.6 g.,

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[10] WERTYPOROCH AND FIRLA, *Ann.*, **500**, 287 (1933).

higher liquid propylbenzenes 1.1 g., hexa-*n*-propylbenzene 2.0 g. (Aluminum chloride + hydrogen chloride = 9.6 g.).

2. Reaction between methylcyclobutane and benzene.—A mixture of methylcyclobutane[11] (10.82 g.), benzene (25.60 g.), and aluminum chloride (1.35 g.) was saturated with hydrogen chloride (0.3 g.) and sealed in a Pyrex tube; the whole shaken for 22 hours at 25°. The white, powdery aluminum chloride changed rapidly to a yellow, sticky mass, and then to a yellow-red, mobile lower layer.

The weights of the *upper* and *lower* layers, including the aluminum chloride, were 30.1 and 7.2 g., respectively; no gas was evolved during the reaction.

The washed colorless *upper layer* (36.5 cc.) gave, on fractional distillation, the fractions described in Table II (see also Figure 3).

The fraction boiling at 193–197° was a mixture of *isoamylbenzene* and at least one other isomeric amylbenzene, probably 2-phenylpentane. This was indicated by the following facts: (1) analysis gave C, 89.17%; H, 10.82%; calc'd for $C_6H_5 \cdot C_5H_{11}$: C, 89.18%; H, 10.82%; (2) oxidation with potassium permanganate solution gave only benzoic acid; (3) diacetamido derivatives were isolated. On crystallization from hot water the *less soluble* fraction of the latter gave, on washing with *n*-heptane, followed by repeated recrystallizations from water, white feathery crystals, melting at 210°; these proved to be identical with *diacetamidoisoamylbenzene* in appearance, solubility and melting point (210°); there was no depression of melting point upon mixture with an authentic sample. The *more soluble* fraction yielded flat, spearlike, colorless needles (flat rectangular plates under the microscope) of a diacetamido derivative (N, 10.64%; calc'd, 10.69%), melting at about 180° but *not* identical with the diacetamido derivative of *tert.*-amylbenzene (m.p. 181°).

TABLE II

PRODUCTS OF REACTION BETWEEN METHYLCYCLOBUTANE AND BENZENE

BOILING RANGE AT 750 MM.	VOL., CC.	n_D^{20}	REMARKS
28–40°	7.2	1.3743	Stable to $KMnO_4$ solution; about 70% unreacted *methylcyclobutane* and about 30% i-*pentane*.
78–81.5°	22.0	1.5000–1.5022	Pure *benzene*, freezing in ice, except fractions 2 and 3 (see Figure 3).
193.5–197.5°	4.9	1.4930–1.4957	Absolutely stable to $KMnO_4$ solution; d_4^{20} = 0.8680.
260–265°	1.2	1.5267	Stable to $KMnO_4$ solution; pleasant geranium odor.
>265°	0.2	1.5648	

The fraction boiling at 260–265° probably consisted of diamylbenzenes, since on oxidation with potassium permanganate solution organic acids were obtained in form of white crystals sparingly soluble in water, and readily soluble in alkali. The melting point was 340°, with sintering. These phthalic acids were not identified further.

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[11] Synthesized by the method of Gustavson, *J. prakt. Chem.*, [2], **54**, 98 (1896), and Phillipov, *ibid.*, [2], **93**, 162 (1916), followed by hydrogenation with Raney nickel. The hydrocarbon was absolutely stable to potassium permanganate solution and to nitrating mixture; b.p. (760 mm.) 36.3 ± 0.2°; n_D^{20} 1.3850; d_4^0 0.7120.

The *lower layer*, after decomposition with ice, contained: 33 vol. %, benzene; 7 vol. % iso- (and isomeric) amylbenzenes; 20 vol.% of an aromatic hydrocarbon boiling at about 250°, n_D^{20} 1.5845, which gave an oil on nitration; and 30 vol. % of a yellow viscous oil boiling at 300–350°, n_D^{20} 1.5840.

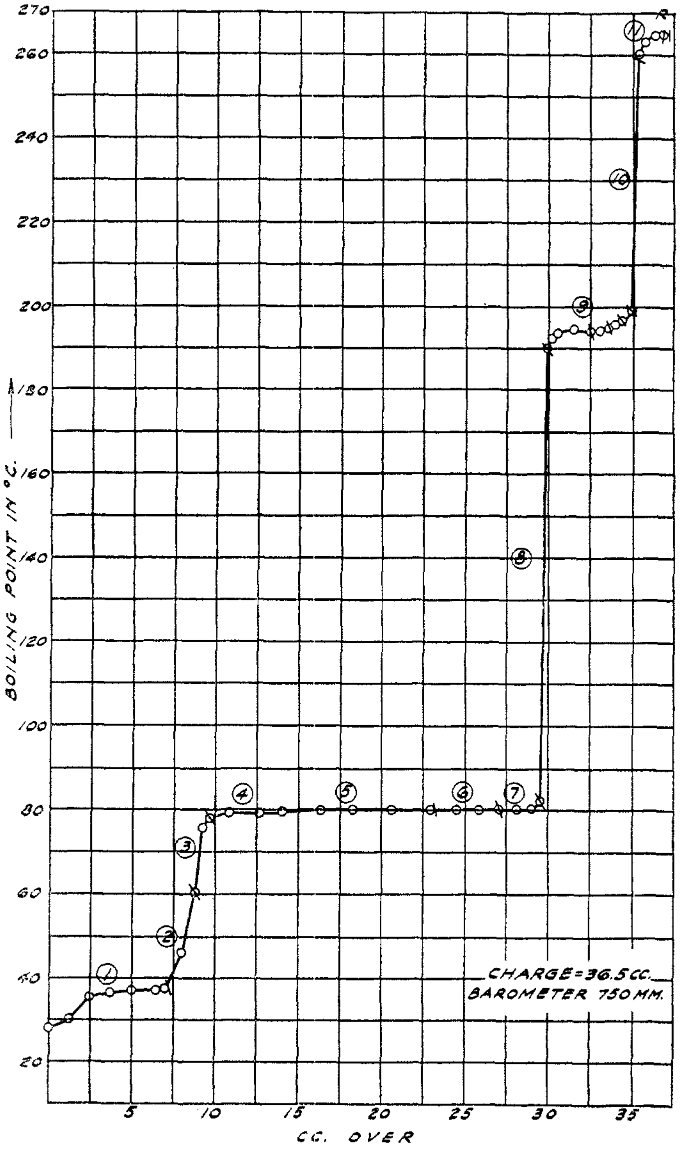

FIG. 3

The aromatic hydrocarbons boiling above 250° must be, in view of their particularly high indices of refraction, derivatives of dinuclear hydrocarbons, *e.g.* diphenyl, b.p. 255°, n_D^{77} 1.588. Their presence would account for the formation of *i*-pentane (found in fraction 28–40°) according to a dehydro-hydrogenation reaction, *e.g.*:

$$2\ C_6H_6 + CH_3\cdot C_4H_7 \rightarrow C_6H_5\cdot C_6H_5 + C_5H_{12}$$

3. Reaction Between Cyclopentane and Benzene.—Cyclopentane* (52.0 g.) and benzene (117.0 g.), after saturation with hydrogen chloride (*ca.* 0.80 g.), were heated with aluminum chloride (9.97 g.) in a sealed tube in a rotating Ipatieff autoclave at 150° for 8 hours.

The following reaction products were obtained: *upper layer,* 145.52 g., *lower layer* (containing aluminum chloride) 33.75 g., gas, none; 35.2 g. of unchanged cyclopentane and 84.7 g. of benzene were recovered from the upper layer. The latter contained furthermore: ≃ 0.5–1 g. of pentanes, boiling at 27–36°; 3.2 g. toluene (b.p. 113°, n_D^{20} 1.4860, identified as dinitro derivative); ≃ 3.4 g. ethylbenzene (b.p.

TABLE III

PRODUCTS OF REACTION BETWEEN CYCLOPENTANE AND BENZENE

FRACTION	BOILING RANGE AT 760 MM.	WEIGHT, G.	n_D^{20}	REMARKS
4	180–200	1.0	1.4912	Amylbenzenes or isomers
5a	200–208	4.2	1.4998	See Table IV
5b	208–215	4.6	1.5257	See Table IV
6	215–225	1.7	1.5291	Cyclopentylbenzene
Residue	>225	6.0	1.5488	Probably dialkyl- and higher benzenes

TABLE IV

COMPARISON OF FRACTIONS *5a* AND *5b* WITH AMYLBENZENES AND CYCLOPENTYLBENZENE

PROPERTIES	AMYLBENZENES[12] $C_{11}H_{16}$	*5a* ←	*5b* →	CYCLOPENTYLBENZENE[13] $C_{11}H_{14}$
C, %	89.18	89.27	90.11	90.12
H, %	10.82	10.71	9.89	9.88
Molecular weight	148	≃143	≃140	146
Boiling point at 760 mm., °C.	186–205	*200*–208	208–*215*	215
d_4^{20}	0.855–0.875	0.8991	0.9441	0.9577
n_D^{20}	1.485–1.497	1.4998	1.5257	1.5348

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* Obtained by depolymerization of dicyclopentadiene (from the Gesellschaft für Teerverwertung, Duisburg-Meiderich, Germany) and hydrogenation of cyclopentadiene with R. Adams' Pt-catalyst; b.p. (760 mm.) 48.5 ± 0.1°; n_D^{20} 1.4060; d_4^{20} 0.7531; absolutely stable to potassium permanganate solution and to nitrating mixture.

[12] See Table of physical constants of all amylbenzenes in a paper of IPATIEFF AND SCHMERLING (in print).

[13] VON BRAUN AND DEUTSCH, *Ber.*, **45,** 1271 (1912).

136°, n_D^{20} 1.4910, identified as diacetamido derivative); no *xylenes* and no material boiling between 136° and 180°.

The *main reaction product*, which consisted of aromatic hydrocarbons boiling above 190°, was separated into the fractions recorded in Table III.

Fractions 4 and 5*a* contained mainly amylbenzenes, while in 5*b* and 6 cyclopentylbenzene predominated. This follows from a comparison of their physical constants and analytical figures with the isomeric amylbenzenes and cyclopentylbenzene (see Table IV).

In view of the large number of isomeric amylbenzenes (eight) and small quantities of available material an identification of the particular isomers present was not possible.

The aromatic hydrocarbon in fractions 5*b* and 6 could, however, be definitely identified as cyclopentylbenzene. It dissolved completely in fuming (7% SO_3) sulfuric acid, forming a crystalline sulfonic acid. Its diacetamido derivative (colorless fine needles, moderately soluble in hot water; N 10.67%, calc'd 10.77%) melted at 228° and showed no depression of melting point when mixed with an authentic sample of diacetamidocyclopentylbenzene (m.p. 228°).

The residue probably contains di- and higher alkylbenzenes.

The *lower layer*, on decomposition with ice, gave 9.4 g. benzene and smaller quantities of aromatic hydrocarbons boiling from 225–375°, more or less contaminated with unsaturated hydrocarbons in the higher fractions.

Evidently a reaction analogous to that between cyclopropane or methylcyclobutane and benzene takes place, *i.e.* rupture of the ring and alkylation to *n*-amylbenzene, which, because of the more drastic conditions of the experiment, is partly or wholly isomerized and further dealkylated to ethylbenzene and toluene.

The formation of cyclopentylbenzene is due to a dehydrohydrogenation reaction (similar to that in the case of methylcyclobutane), some of the hydrogen being taken up by the formation of pentanes from cyclopentane.

4. Reaction between cyclopropane and 2-Methylnaphthalene in the presence of zirconium chloride (*$ZrCl_4$*).—The alkylation proceeded at 35–30° during 4.0 hours in the same apparatus and in the same way as in the case of benzene. The 2-methylnaphthalene began to turn a deep purple color as soon as the zirconium chloride was added. Towards the end of the reaction the opaque material assumed a lighter color; no lower layer formed and the zirconium-chloride-containing suspension remained powdery. After standing overnight at 25° the product solidified only to a small extent, showing that the original aromatic hydrocarbon had changed. The cyclopropane was completely absorbed by the liquid.

The quantities of reagents used were: 2-methylnaphthalene* 89.0 g.; cyclopropane 20.0 g.; zirconium tetrachloride† 4.25 g.; hydrogen chloride *ca.* 1.6 g. The following products were obtained: *brown suspension* 13.8 g.; *liquid product* 100.4 g.; gas none; loss 0.7 g.

The *brown suspension* was filtered off after the whole product had been warmed to 50–60°. It was decomposed with water and gave a colorless solution of zirconium oxychloride and white insoluble crystals of aromatic hydrocarbons (probably mostly 2-methylnaphthalene); they evidently formed (at least partly) an *addition compound* with zirconium tetrachloride.

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* Obtained from the Gesellschaft für Teerverwertung, Duisburg-Meiderich, Germany; m.p. 35.1°.

† C.P. powder from the Titanium Alloy Manufacturing Co., Niagara Falls, N. Y.

The water-white *liquid product* contained *ca.* 80 vol. % of unreacted pure 2-methylnaphthalene (b.p. 147° at 50 mm.; m.p. 35°), *ca.* 15 vol. % of a liquid boiling at 136–138° at 9.5 mm., and *ca.* 3 vol. % of a white crystalline residue, boiling above 260° at 5 mm.

The liquid of b.p. 136–138°/9.5 mm. represented an individual or a mixture of isomeric aromatic hydrocarbons of the composition of *methylpropylnaphthalene*, $C_{14}H_{16}$ (calc'd C 91.24%, H 8.76%; found C 91.34%, H 8.68%; n_D^{20} 1.5880). It became sticky at −78°, was stable to potassium permaganate solution, and was readily nitrated to a heavy oil.

The *white residue*, also stable to potassium permanganate solution, crystallized in flakes from alcohol, in spearlike prisms from benzene; m.p. 204°, and probably represents a polypropylated naphthalene.

SUMMARY AND CONCLUSIONS

1. A catalytic reaction between cycloparaffins and aromatic hydrocarbons is described. This reaction consists in the cleavage of the cycloparaffin ring and alkylation of the aromatic hydrocarbon, and has been named by us *decycloalkylation.*
2. *Cyclopropane* alkylates *benzene* in stages from *n*-propylbenzene up to the solid hexa-*n*-propylbenzene.
3. *Cyclopropane* alkylates 2-methylnaphthalene to mono- and higher propylated derivatives.
4. *Methylcyclobutane* condenses with *benzene* to isoamylbenzene, its isomers, and higher alkylated benzenes.
5. *Cyclopentane* alkylates *benzene* to amylbenzenes and other hydrocarbons.
6. Aluminum and zirconium chlorides are convenient catalysts for these decycloalkylations.

ACKNOWLEDGMENTS

Acknowledgment is made to Mr. R. W. Moehl for analytical data and to Drs. J. Mavity and L. Schmerling for their valuable assistance in identifying some of the reaction products.

[Contribution from the Department of Chemistry and Chemical Engineering of the University of Pennsylvania]

THE KINETICS OF THE FORMATION OF THE GRIGNARD REAGENT. I. PRELIMINARY EXPERIMENTS

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The general purpose of these investigations was the study of the kinetics of the Grignard reaction. More specifically, it was desired to measure the overall rate of reaction of organic halogen compounds with magnesium at the solid-liquid interface. It was believed that any substance possessing catalytic properties for this reaction would increase the velocity constant of the reaction provided the rate-controlling process was a chemical one. Likewise, the measurement of temperature coefficients, the effect of stirring and a comparison of the velocity constants for various alkyl and aryl halides might indicate whether the rate of reaction was controlled by a chemical process or one of diffusion. Some observations made in the preliminary stages of the investigation caused modification of the method generally used in studying the dissolution of metals. The general experimental technique was similar to that used by Kilpatrick and Rushton.[1]

EXPERIMENTAL

The preliminary experiments were carried out in a three-necked flask of 500 cc. capacity fitted with condenser, graduated dropping funnel, and mercury seal; the flask takes the place of the vessel, used in later experiments, which is labelled *F* in Figure 1. The flask was immersed in a water thermostat regulated at 25 ± .05°.

Cylinders of pure magnesium* were turned down on a lathe to a diameter of 1.5 cm., cut to 4.5 cm. lengths, drilled through the center and mounted on glass shafts with sodium silicate. The magnesium cylinders were treated in various ways, the purpose being to remove any oxide coating and obtain a uniform cylinder. In most cases the cylinders were polished with emery paper, cleaned with dilute acid, washed with water, alcohol, and ether, cemented on the glass shaft with sodium silicate and dried in the oven at 110°. The ends of the cylinders were also covered with sodium silicate. A cylinder was weighed, coupled to the motor shaft and rotated in an ether solution of ethyl bromide. With solutions 0.1 to 2.0 M no reaction was observed even after prolonged periods of stirring, while with higher concentrations (2.0 to 4.0 M) what little reaction took place was at the boundary of the silicate coating. Better but non-reproducible results were obtained when freshly turned-down cylinders were

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[1] Kilpatrick and Rushton, *J. Phys. Chem.*, **38**, 269 (1934).

* The authors acknowledge the gift of a supply of pure magnesium metal from the Aluminum Company of America.

used. From this it might be concluded that polishing in the presence of air increases the coating rather than reduces it.[2] It was also noted that when a cylinder accidentally fell to the bottom of the flask reaction took place at the point of contact with the glass. This is the usual case in the preparation of Grignard compounds and the necessity of such a contact will be shown in a series of experiments.

Magnesium ribbon suspended in a test-tube containing a dilute solution of ethyl bromide did not react until it was in contact with the wall of the vessel or wrapped around a rod of glass, steel, brass, bakelite, aluminum, or even a magnesium rod. A spiral of magnesium ribbon suspended in ethyl bromide did not react, but if two spirals were coiled together reaction began readily at the points of contact. Wrapping a cylinder of magnesium with string, glass wool, rubber bands, quartz fibers, bare platinum or copper wire, and paraffin-coated insulated copper wire, were all equally effective in starting the reaction at (or under) the contact. A glass vessel was not necessary, as was shown by the use of a quartz or hard-rubber vessel. It was also noticed that the reaction could be started by scoring the surface of the magnesium.

From the above observations it was apparent that we were dealing with a surface phenomenon involving the removal or rupture of a film in the magnesium surface, or with an adsorption and activation of the ethyl bromide. Examples of contact corrosion have been reported by Mears and Evans.[3] They observed that an intensive corrosion took place in aqueous solution at the point where metals were in contact with glass or a similar piece of metal. Durdin and Markevitch[4] studied the rate of dissolution of magnesium partially covered with paraffin in aqueous solutions of acids. They report that a more intensive evolution of hydrogen, and pitting, took place at the boundary of the paraffin coating.

Further experiments were carried out in an apparatus designed to secure greater flexibility of operation. This apparatus, shown in Figure 1, consisted of a reaction vessel *A*, connected by a ground-glass joint to a glass cup *B* with side-arms *C* and *D*, which terminated in ground-glass joints by means of which a graduated dropping funnel and coil condenser were attached. A drying tube was blown directly into the top of the condenser, and through this passed a tube whereby the air in the apparatus could be flushed out with a stream of dry nitrogen. Drying was brought about by bubbling the gas through concentrated sulfuric acid, and a gas trap was interposed between the drying vessel and the reaction vessel in order to prevent any of the acid from being carried over. The Monel metal cup *E*, forming the upper half of the mercury seal, was held in place by a pin passing through the collar and shaft. The glass shaft on which the magnesium cylinder was held was fastened to the steel shaft by means of the tubular phosphor-bronze spring clip *F*. Two of these sets were immersed side by side in a thermostat and stirred by the same motor, so arranged that the motor, the two Monel metal cups, and the shafts carrying the samples could be raised and lowered at will.

In the hope of obtaining a uniform reaction on the surface of the cylinder, various attempts were made to start the reaction with dissolved substances or substances suspended in ether. If high concentrations of alkyl halide were used and the reaction started locally, the temperature of the reacting layer rose and pitting resulted. At low concentrations, iodine, ethylmagnesium bromide, and bromine were ineffective in starting a uniform reaction. A small amount of absolute ethyl alcohol was effec-

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[2] Dobinski, *Phil. Mag.*, **23**, 397 (1937).

[3] Mears and Evans, *Trans. Faraday Soc.*, **30**, 417 (1930).

[4] Durdin and Markevitch, *J. Gen. Chem.* (USSR), **6**, 236 (1936).

tive in a few cases, especially if it contained lithium chloride.[5] Aluminum chloride started the reaction but was not dependable. Organic acids containing chlorine seemed to have some effect while other organic acids reacted with magnesium without starting the reaction with ethyl bromide.

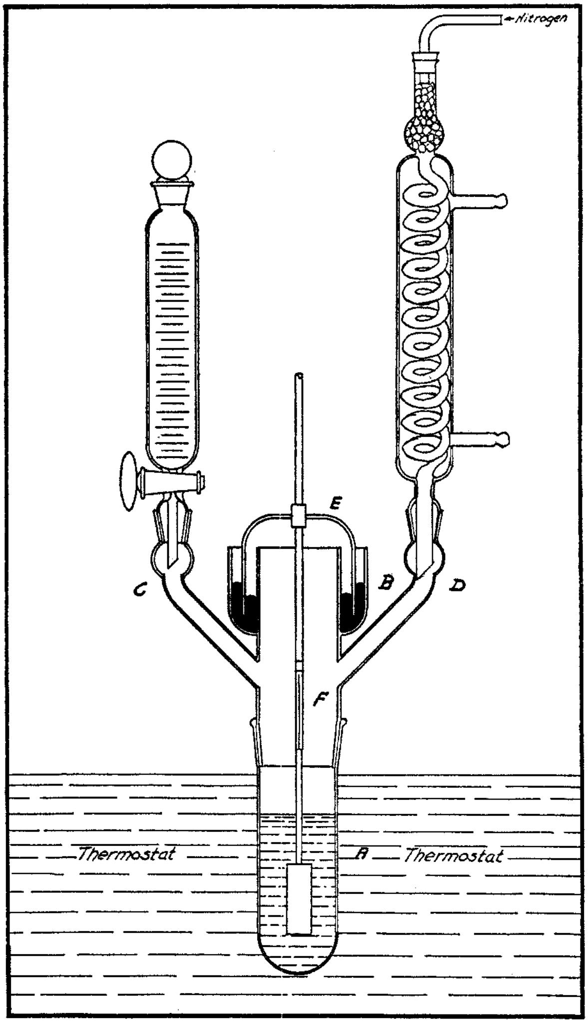

Fig. 1

Several electrolysis experiments were carried out. First, ethyl bromide was electrolyzed in ethereal solution with the magnesium cylinder as anode and a platinum wire as cathode. The reaction could be started in this manner, and continued after

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[5] Sclar and Kilpatrick, *J. Am. Chem. Soc.*, **59**, 584 (1937).

the circuit was broken. Next a similar solution was electrolyzed with two platinum electrodes. After the circuit was broken a cylinder of magnesium was introduced, and the reaction began almost immediately and continued until all the ethyl bromide had reacted. In all cases the solution became slightly yellow as if free bromine had been produced.

Amalgamation of the surface did not initiate reaction. Magnesium bromide dietherate, prepared by the method of Evans and Rowley,[6] and added to the reaction mixture, initiated the reaction, but uniform results were not obtained. After reaction with ethyl bromide, upon the addition of a second portion of ethyl bromide solution the reaction continued but the results were not uniform.

In view of the lack of success in initiating a uniform reaction by substances in solution, attention was again turned to a suitable contact agent. The reaction vessel was packed with finely powdered glass, the ether solution of ethyl bromide was added, and the magnesium cylinder was rotated slowly to minimize abrasion. This arrangement was effective, although there was always the possibility of mechanical abrasion and also the difficulty of separating the solution for analysis. Finely pulverized kaolin was also tried as a contact substance but appeared to be too fine.

It was finally decided that it would be necessary to supply some sort of contact which would be of the same character in each experiment in order that results might be obtained under the same conditions. It was also necessary that the contact substance be easily removable from the solution at the end of the reaction, and be of such material as would not contaminate the ethereal solution. It was impractical to arrange the apparatus so that the magnesium cylinder would be in contact with the walls of the vessel, and it was necessary that the cylinder should be able to rotate in the solution at various speeds in order that the effect of the rotational speed could be measured. With this in mind, a contact was designed in the following manner. Lengths of Pyrex tubing about 10 cm. in length and 15 mm. in diameter were ground longitudinally until the resulting pieces were in the shape of a curved trough, the edge describing an arc equal in length to about one-third the original circumference of the tube. This was attached to a phosphor-bronze clip so arranged that the upper end of the clip could be slipped over the inner edge of the mercury seal, the lower end supporting the top of the glass contact. The contact could then be made to bear lightly against the surface of the magnesium cylinder while it was rotating in the solution. The pressure of the spring holding the contact was so slight that no abrasion resulted and the design was such that no metal other than magnesium touched the solution.

Using this contact and an 0.130 molar solution of ethyl bromide, six magnesium cylinders lost in fifteen minutes 0.084, 0.094, 0.081, 0.088, 0.117, and 0.092 g. respectively. The average loss was 0.093 g. with an average deviation of approximately ten per cent. The use of polished or unpolished cylinders did not materially affect the reproducibility of the results. Occasionally the cylinder reacted on the upper part only and showed a small loss; this was due to the unevenness of the cylinder. In all cases a precipitate occurred from one to three minutes after the ethyl bromide was added. This was attributed to the presence of moisture. The ether was washed with salt solution, allowed to stand overnight over calcium chloride and distilled into a flask containing sodium chips. A second distillation was then made from this flask, through a distilling tube containing glass beads and sodium pellets, into a flask containing phosphorus pentoxide. From this flask it was finally distilled through

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[6] Evans and Rowley, *ibid.*, **52**, 3523 (1930).

another distilling tube into a receiver containing sodium pellets. The receiver was protected by drying towers containing phosphorus pentoxide and calcium chloride. The ethyl bromide was also dried by distillation over phosphorus pentoxide.

The magnesium cylinders were polished (to remove ridges) with fine emery paper, washed with alcohol and ether, then dried in the oven, and kept in a desiccator over anhydrite. The glass shoe and the reaction vessel were dried in the oven before use.

It was found that solutions which were made up and stored in glass-stoppered flasks absorbed moisture from the air quite rapidly, giving tests for water after a few hours. It was therefore decided to make up the solutions individually before each run. Since the error of pipetting 0.5 cc. of ethyl bromide by the ordinary method was too great, a hypodermic syringe was fitted with a brass stop so arranged that the capacity could be adjusted by regulating a screw. Upon calibration it was found that the amount of ethyl bromide delivered from the syringe was constant within 0.2 per cent. The water was removed from the thermostat and replaced by mineral oil. These precautions increased the time elapsing before the appearance of a precipitate in the solution.

The amount of Grignard reagent present was determined by acid titration of the reaction mixture, by the method of Gilman, Wilkinson, Fishel, and Meyers.[7] The total weight of magnesium reacting being known from the weighings, the amount of magnesium present as magnesium bromide was obtained by difference.

A summary of a complete experiment is given in Table I.

All quantities except time are expressed in grams of magnesium; ΔW is the loss in weight of the magnesium cylinder, and column four gives the amount of Grignard reagent formed. The final yield of Grignard reagent, based upon the ethyl bromide present initially, is eighty-six per cent., while that for the ten-minute runs, based upon the number of molecules of ethyl bromide reacting is only seventy-two per cent. Column five indicates that the greater part of the Wurtz reaction takes place at the beginning. It should be mentioned that in computing the reacting surface of the magnesium the top and bottom of the cylinder were omitted, as no reaction took place there.

If the rate-controlling process is the diffusion of ethyl bromide, after the maximum rate is reached the rate should be proportional to the ethyl bromide concentration, and the rate of disappearance of ethyl bromide should be given by the equation

$$\frac{-dC_{\mathrm{C_2H_5Br}}}{dt} = kSC_{\mathrm{C_2H_5Br}} \tag{1}$$

This would also be true if the process is chemically controlled, provided the rate is proportional to the ethyl bromide concentration and to the surface S.[1] The velocity constant can be calculated from the equation,

$$k = \frac{2.30\,V}{S(t_2 - t_1)} \log \frac{(a - x)_1}{(a - x)_2} \tag{2}$$

where $(a - x)_1$ and $(a - x)_2$ are the concentrations of ethyl bromide at the times t_1 and t_2. If this equation holds a plot of log $(a - x)$ versus time

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[7] GILMAN, WILKINSON, FISHEL, AND MEYERS, *ibid.*, **45**, 150 (1923).

should give a straight line of slope $-kS/2.3V$. Calculation of the velocity constant for the intervals 10–15, 15–20, and 20–25 gives k = 0.33, 0.71, and 0.40 respectively. This might be due to inaccurate analysis. However, it was found that if the assumption was made that any side-reactions (including the Wurtz) took place in the first period, the concentration of ethyl bromide could thereafter be computed on the basis of the Grignard reagent formed. In other words a graph of log $(a - x)$ versus time, where a and x are the concentrations of ethyl bromide corresponding to the amount of Grignard reagent formed at completion of

TABLE I

Summary of a Complete Experiment

Initial concentration $C_2H_5Br = 0.130M$.

Average dimensions of cylinders: Length, 2.56 cm.; Diameter, 1.00 cm.; Surface, 8.05 cm.²

$T = 25°$
RPM = 1100
V = 50 cc.

NO. OF RUNS	TIME, MIN.	ΔW, g.	C_2H_5MgBr (g. Mg)	$MgBr_2$ (g. Mg)	$\frac{MgBr_2}{C_2H_5MgBr}$	C_2H_5Br REACTING	C_2H_5Br REMAINING	YIELD GRIGNARD REAGENT (%)
	0					0.0	0.156	
6	10	0.068 a.d. = .007	0.057 a.d. = .013	0.011	0.19	0.079	0.077	72
6	15	0.093 a.d. = .009	0.089 a.d. = .007	0.004	0.045	0.097	0.059	92
6	20	0.115 a.d. = .004	0.109 a.d. = .002	0.007	0.064	0.123	0.033	89
6	25	0.131 a.d. = .008	0.120 a.d. = .007	0.011	0.092	0.142	0.014	85
6	30	0.139 a.d. = .002	0.127 a.d. = .002	0.012	0.095	0.151	0.005	84
6	40	0.145 a.d. = .001	0.134 a.d. = .001	0.011	0.082	0.156	—	86
6	50	0.145 a.d. = .001	0.134 a.d. = .001	0.011	0.082	0.156	—	86

a.d. = Average deviation.

the reaction and at time t, respectively, gives a straight line of slope $-kS/2.3V$. Using equation (2) for the intervals given above, k becomes 0.67, 0.71, and 0.73. Table II gives the data for these calculations, concentrations being expressed in millimoles per liter.

TABLE II

COMPUTATION OF THE VELOCITY CONSTANT FROM THE DATA OF TABLE I

TIME, MIN.	x	$a - x$	$\log (a - x)$	$kS/2.3V$	$kS/2.3V$	k, CM. MIN.$^{-1}$
10	46.3	62.9	1.799		0.0480	0.67_5
				0.0468		
15	72.5	36.7	1.565		0.0472	0.66_5
				0.0498		
20	88.5	20.7	1.316		0.0480	0.66_5
				0.0510		
25	97.7	11.5	1.061		0.0488	0.69
				0.0642		
30	103.7	5.5	0.740		0.0518	0.73
						Avge. 0.68

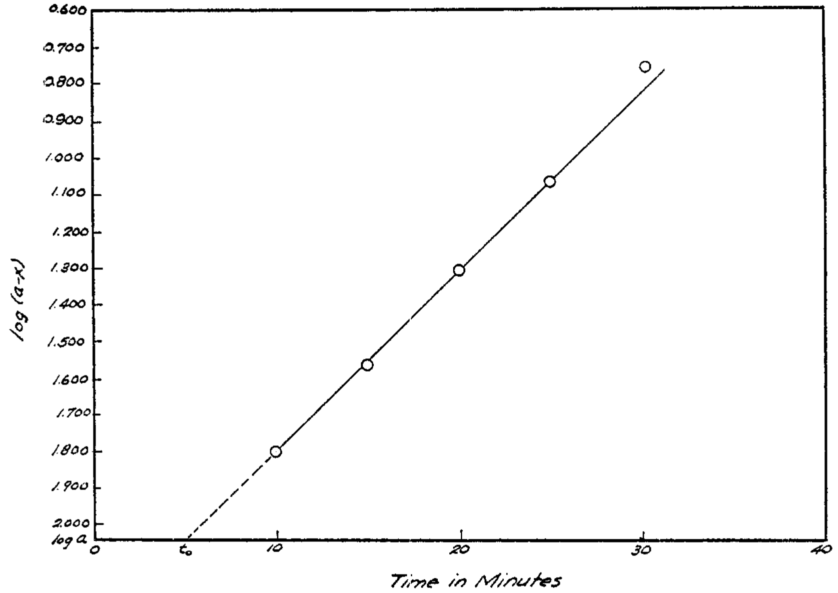

FIG. 2

Figure 2 shows a plot of $\log (a - x)$ versus time; the slope of the line corresponds to $k = 0.69$. It should be noted that the line cuts the horizontal line $\log (a - x) = \log a$ at five minutes. In column five are given the values of $kS/2.3V$ computed from equation (2). Those in column six are computed by subtracting the arbitrary induction period of five minutes, given by the intercept, from the recorded times. The values of the velocity constant given in the last column are obtained from the $kS/2.3V$ of the preceding column.

Table III summarizes the results of the effect of concentration on the velocity constant k. Each k represents 24, 30, or 36 individual runs, and k is computed from the slope of the line in graphs similar to Figure 2.

TABLE III

EXPERIMENTS WITH VARYING INITIAL CONCENTRATIONS OF ETHYL BROMIDE

$V = 50$ cc. RPM = 1100 $T = 25°$

AVERAGE LENGTH OF CYLINDERS, CM.	AVERAGE SURFACE CYLINDERS, CM.^{2}	INITIAL CONCENTRATION C_2H_5Br, MMOLES/L.	a, MMOLES/L.	FINAL YIELD GRIGNARD, %	t_0, MIN.	k, CM. MIN.$^{-1}$
2.55	8.05	130	109	84	5	0.69
2.55	8.00	195	164	84	4	0.65
2.54	8.00	260	215	82	2	0.69
$V = 25$ cc.						
2.58	8.08	260	216	83	2	0.65
$V = 75$ cc.						
2.58	8.08	97.5	73	75	5	0.64

TABLE IV

EFFECT OF LENGTH OF CYLINDER

$V = 50$ cc. RPM = 1100

AVERAGE LENGTH, CM.	AVERAGE SURFACE, CM.^{2}	INITIAL CONCENTRATION C_2H_5Br, MMOLES/L.	a, MMOLES/L.	FINAL YIELD GRIGNARD, %	t_0, MIN.	k, CM. MIN.$^{-1}$
1.26	3.88	130	109	84	6	0.81
2.55	8.05	130	109	84	5	0.69
5.09	16.0	130	105.5	81	5	0.57

The diameters of the cylinders used in these and subsequent experiments are between 0.98 and 1.00 cm.

The arbitrary induction period (t_0) is shorter the higher the initial concentration of the ethyl bromide. If the first step is a cleaning of the surface of the magnesium, a certain amount of ethyl bromide would be consumed in the process, and at higher concentrations this would take place in shorter time.[5] The contact may prevent contamination of the surface by reaction products. In some cases pitting was observed and ascribed to unevenness of surface and the coating on the surface. The velocity constant is independent of the initial concentration of the ethyl bromide, and within the reproducibility of the experiments the results are in accord with equation (2).

In an effort to study the effect of surface three lengths of bar were used; the results are summarized in Table IV.

The velocity constant decreases with increasing surface, while the induction period is not significantly changed. This increase in the velocity constant is probably related to the cylinder length rather than to the surface. For long bars the contact will not be as efficient as for short bars, as it is difficult to keep the shoe in intimate contact for the whole length of a long cylinder.

TABLE V

EFFECT OF IODINE

V = 50 cc. RPM = 1100 T = 25°

AVERAGE LENGTH, CM.	AVERAGE SURFACE, CM.^{2}	INITIAL CONCENTRATION IODINE, MMOLES/L.	INITIAL CONCENTRATION, C_2H_5Br, MMOLES/L.	a MMOLES/L.	FINAL YIELD GRIGNARD, %	t_0, MIN.	k, CM. MIN.$^{-1}$
2.57	8.05	7.88	130	111	85	3	0.65
2.56	8.03	11.8	130	116	89	2	0.65
2.55	8.00	15.7	130	120	92	0	0.65
2.57	8.05	23.6	130	116	89	—	—
2.54	8.00	39.4	130	96	74	—	—
2.58	8.14	63.0	130	71	54	—	—
2.55	8.03	78.8	130	55	42	—	—

TABLE VI

THE EFFECT OF TEMPERATURE

V = 50 cc. RPM = 1100

T, °C.	AVERAGE LENGTH, CM.	AVERAGE SURFACE, CM.^{2}	INITIAL CONCENTRATION C_2H_5Br MMOLES/L.	a, MMOLES/L.	t_0, MIN.	k, CM. MIN.$^{-1}$	$\frac{k_{30}}{k_{25}}$
30	2.56	8.00	130	109	4	0.79	1.14
25	2.56	8.05	130	109	5	0.69	

The effect of small amounts of iodine is to decrease the induction period without increasing the velocity constant. With higher concentrations of iodine the rate is no longer proportional to the ethyl bromide concentration. This is probably due to the reaction of iodine with the metal and with ethylmagnesium bromide. Ethyl iodide is formed during the reaction and will also react with the magnesium.[7]

Table V shows the decrease in yield of Grignard reagent at higher concentrations of iodine. The optimum concentration is approximately 0.015 molar. Iodine is not a catalyst in the sense that it increases the velocity constant as given by equation (2); it does, however, clean the surface.[5, 8]

Table VI shows the effect of temperature on the reaction. The temperature coefficient 1.3 for ten degrees is small, but cannot be taken as a final argument in favor of a diffusion-controlled process, as the temperature coefficient of the diffusion of ethyl bromide in ethyl ether may not be small.

DISCUSSION

Gilman and others[9, 10, 11, 12] have made extensive contributions to the literature on the preparation of the Grignard reagent. In most cases the effect of catalysts is interpreted in terms of increase of yield rather than of rate of reaction. In some cases, however, rate studies are carried out, and the catalyst is supposed to have increased the rate of the reaction. No kinetic law has been given in any of these cases, and a shortening of the induction period would be included in the increase in rate. Iodine, for example, cleans the surface, and the chemical rate of reaction of an alkyl halide with a cleaned magnesium surface may be much faster than the rate of transport of the alkyl halide to the surface. If this is the case there should be no great difference in the velocity constants for the various alkyl halides. However, the literature indicates considerable difference, and actual determinations of the velocity constants after the maximum rate of reaction has been reached should prove interesting. The rôle of iodine is not unlike that played by halogen compounds and halogens in the reaction of magnesium with alcohol.[5]

Quite apart from our attempts at a quantitative determination of the velocity constant, our observations on the effect of a contact require further attention and explanation. With the "shoe" employed, the possibility of a temperature effect at the surface of the metal suggests itself. It is possible for the outermost layer to be at a temperature considerably higher than the metal and the bulk of the solution, but in view of our qualitative experiments where the contact substance was not in motion with respect to the metal, the more likely explanation seems to be that the contact buckles or ruptures the coating and allows the reaction to begin. If the products are soluble and do not react further to form

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[8] Wohl, *Ber.*, **39**, 1952 (1906).

[9] Gilman and Meyers, *J. Am. Chem. Soc.*, **45**, 159 (1923).

[10] Gilman and Van der Wal, *Bull. soc. chim.*, **45**, 344 (1929).

[11] St. John and St. John, *Rec. trav. chim.*, **55**, 585 (1936).

[12] Gilman and Zoellner, *J. Am. Chem. Soc.*, **53**, 1583 (1931).

insoluble products, the reaction continues, and for high concentrations of reactants may spread over the surface from the point of contact. If the reaction is rapid enough there will be a temperature effect, and pitting will result. And if insoluble products which adhere to the metal are formed, pitting will result. The shoe may prevent products such as MgOHX from adhering, and give a more uniform reaction. If this view is correct, it should be possible to shorten the time required for the preparation of Grignard compounds which are difficult to prepare by mixing the magnesium turnings with ground glass and shaking rather than stirring. Of course, the effect of oxygen should not be neglected.[13]

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SUMMARY

1. After the induction period the reaction between ethyl bromide and magnesium is proportional to the ethyl bromide concentration.
2. A contact is necessary for uniform reaction.
3. Iodine reduces the interval before the maximum rate is reached.

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[13] GOEBEL AND MARVEL, *ibid.*, **55**, 1693 (1933).

[CONTRIBUTION NO. 161 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

EFFECT OF GROUPS ON REACTION RATE. REACTION OF α,β-DIBROMIDES WITH SODIUM IODIDE

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The reaction of α,β-dibromides with iodides is well suited for a quantitative study of the effect of substituents on reaction rate for the reasons that the dibromides can be prepared readily in a state of purity and the progress of the reaction can be followed easily by titration of the liberated iodine. The reaction was apparently first used by Perkin,[1] who obtained coumarine from its dibromide by the action of potassium iodide. Since that time it has come to supply one of the standard methods by which the organic chemist is accustomed to prepare ethylene derivatives. Further knowledge concerning the factors which influence its rate will be of immediate practical importance in the laboratory.

Slator[2] studied the rates of the decomposition of ethylene iodide and of ethylene iodobromide under the influence of the iodide ion, Biilmann[3] that of the reaction of α,β-dibromopropionic acid with potassium iodide; van Duin[4] established the generality of the reaction and measured the rate at 25° in a number of cases, and Dillon and his co-workers[5] the rates of reaction of ethylene, propylene, and butylene bromides with potassium iodide. Except for the experiments of Dillon, all the rate measurements were made at one temperature.

It is now generally recognized, particularly in the light of the discussions of Hinshelwood,[6] that the reaction rate constant is the resultant of the several factors which are indicated in the equation, $K = PZe^{-E/RT}$. The so-called critical increment, E, is calculated from the temperature coefficients of the velocity constant; Z, the collision factor, is calculated from kinetic theory; and P, the probability factor, is the value which must be inserted in the equation, after E and Z have been found, to give the correct value for K. The factor P has been interpreted as measuring the probability of successful collision, and as such is dependent upon the

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[1] PERKIN, *J. Chem. Soc.*, **24**, 437 (1871)

[2] SLATOR, *ibid.*, **85**, 1697 (1904).

[3] BIILMANN, *Rec. trav. chim.*, **36**, 319 (1917).

[4] VAN DUIN, *ibid.*, **45**, 345 (1926).

[5] DILLON, YOUNG, AND LUCAS, *J. Am. Chem. Soc.*, **52**, 1953 (1930).

[6] HINSHELWOOD, *J. Chem. Soc.*, **1935**, 1111.

shapes of the molecules, their orientation, the nature of the medium in which the reaction occurs, and various other factors. In the present work we have measured the rates of reaction of a number of α,β-dibromides with sodium iodide in absolute alcohol and in dry acetone at several temperatures for the purpose of determining the effect of substituent groups upon the constants, E and P, of the above equation.

The duration of the runs and the extent of the reactions in our several experiments are reported in Table I. In each case the initial concentrations in the reaction mixture, while known exactly, were approximately 0.015 molal of the dibromide and approximately 0.30 molal of sodium iodide. The longest runs were those with propylene dibromide and allyl alcohol dibromide in alcohol solution at 25.3° in which 14 per cent. and 7 per cent., respectively, of these materials were converted into ethylene derivatives during 458 hours; the shortest runs were those with the dibromides of *p*-nitro- and *m*-chlorobenzalacetophenone in acetone at 14.3° in which 27 per cent. and 24 per cent. conversion respectively was accom-

TABLE I

DURATION AND EXTENT OF THE REACTIONS

Experiments in Alcohol

Temperature	25.3°		37.2°		56.3°	
DIBROMIDE	DURATION (HOURS)	EXTENT (%)	DURATION (HOURS)	EXTENT (%)	DURATION (HOURS)	EXTENT (%)
Ethylene	178.	47	28.	41	1.2	12
Propylene	458.	14	164.	23	32.1	25
Amylene-1	417.	11	103.	19	32.4	31
Allyl alcohol	458.	7	103.	8	32.1	20
Acrylic acid	44.	24	32.	54	2.2	27
Ethyl acrylate	117.	81	7.5	36	1.5	38
Crotonic acid	—	—	28.	17	9.7	29
Maleic acid	80.	81	20.6	69	4.4	80

Experiments in Acetone

Temperature	0°		8.6°		14.3°		25.3°	
DIBROMIDE	DURATION (HOURS)	EXTENT (%)	DURATION (HOURS)	EXTENT (%)	DURATION (HOURS)	EXTENT (%)	DURATION (HOURS)	EXTENT (%)
Benzalacetophenone	0.17	18	0.025	14	0.025	23	—	—
p-Nitrobenzalacetophenone	0.19	27	0.021	18	0.017	27	—	—
m-Chlorobenzalacetophenone	—	—	—	—	0.017	24	—	—
Benzalacetone	—	—	—	—	—	—	0.037	58
Acrylic acid	20.8	18	—	—	—	—	7.7	23

plished in 61 seconds. Acetone was used as a solvent for the chalcone dibromides because of the slight solubility of these substances in alcohol. Acrylic acid dibromide (α,β-dibromopropionic acid) reacts with sodium iodide much faster in acetone than in alcohol—and acetone has been found in a number of cases in this laboratory to be a much better solvent than alcohol for use in the preparation of ethylene derivatives from α,β-dibromo compounds.

The experimental data from all of our runs, except those with the dibromides of propylene and amylene-1, gave good second-order reaction constants when calculated in accordance with the formula,

$$K_2 = \frac{1}{t(2a - b)} \ln \frac{b(a - x)}{a(b - 2x)},$$

where a is the initial concentration of the dibromide in moles per liter, b the initial concentration of sodium iodide, and x the number of moles per liter of the dibromide which have reacted at the end of the time t. The constancy of the reaction constants is illustrated by the data of the run with acrylic acid dibromide, which are reported in detail as a typical example in Table II, where the constants are calculated for the time, t, in minutes. The reaction was inconveniently slow when 0.03 M sodium iodide was used—and solutions approximately 0.3 M in sodium iodide were accordingly used in all other cases. The data of our experiment with acrylic acid dibromide are especially interesting because they supply an example of the kinetic salt effect which has been discussed by Dillon;[7] the constant was increased by about ten per cent. when the initial concentration of sodium iodide was increased to tenfold.

In Table III the rate constants are calculated for the time, t, in seconds, in order that they may be compared more conveniently with constants which have been reported by others in discussions of the critical increment and probability factors, E and P. The constants reported in the table are average values of the second-order reaction constants, except for the experiments with the dibromides of propylene and amylene-1, in which cases the constants were found to decrease steadily as the reactions progressed—and the reported constants are those which were obtained by extrapolating the pseudo-unimolecular constants to zero time. We do not place great confidence in the constants which we have listed for these two reactions, but believe that they may have some interest as a basis for comparison. Although second-order constants are reported in the table, we have found that our data correspond to good pseudo-unimolecular constants in all cases except these two.

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[7] DILLON, *J. Am. Chem. Soc.*, **54**, 952 (1932).

The chalcone dibromides have rates several thousand times as great as those of the aliphatic compounds with which we have worked. The evidence is not sufficient to enable us to judge whether this difference of rate is to be ascribed to the phenyl or to the carbonyl or benzoyl group, or to both, but some of the difference is undoubtedly to be attributed to the use of acetone as a solvent for the chalcone dibromides and of alcohol for the aliphatic compounds, for the reaction rate of acrylic acid dibromide at 25.3° in acetone is about 290 times as great as in alcohol. The *m*-chloro- and *p*-nitrochalcone dibromides react considerably faster than the unsubstituted compound. *p*-Methoxychalcone dibromide reacted so fast that its rate could not be measured. In the aliphatic series, in accordance with the views of Hughes and Ingold,[8] electron-attracting substituents like the carboxyl and carbethoxy groups increase the rate, while substituents which

TABLE II

DETAILS OF EXPERIMENT WITH ACRYLIC ACID DIBROMIDE IN ALCOHOL SOLUTION

a	b	THIOSULFATE		t (MIN.)	x	$a - x$	$K_2 \times 10^4$
		N	cc.				
Temperature = 25.3°							
.015	.030	.0200	0.35	2363	.00035	.01465	3.38
.015	.030	.0200	0.92	7143	.00092	.01408	3.05
.015	.030	.0200	0.76	5698	.00076	.01424	3.12
.015	.030	.0200	2.16	18420	.00216	.01284	3.04
.015	.300	.0186	1.42	883	.00132	.01363	3.51
.015	.300	.0186	1.90	1135	.00177	.01318	3.73
.015	.300	.0186	1.92	1160	.00179	.01316	3.68
.015	.300	.0186	1.89	1190	.00176	.01319	3.54
.015	.300	.0186	2.05	1298	.00191	.01304	3.53
.015	.300	.0186	3.92	2660	.00365	.01130	3.55
Temperature = 37.2°							$K_2 \times 10^3$
.01467	.298	.00183	6.90	200	.00126	.01341	1.52
.01467	.298	.00183	12.45	395	.00228	.01239	1.45
.01467	.298	.0186	1.37	455	.00255	.01212	1.42
.01467	.298	.0186	3.35	1360	.00623	.00844	1.40
.01467	.298	.0186	4.27	1915	.00793	.00674	1.41
Temperature = 56.3°							$K_2 \times 10^3$
.01458	.2916	.0186	1.98	50	.00188	.01270	8.08
.01458	.2916	.0186	2.54	75	.00241	.01217	8.33
.01458	.2916	.0186	3.48	110	.00331	.01127	8.11
.01458	.2916	.0186	4.10	133	.00390	.01068	8.13

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[8] HUGHES AND INGOLD, *J. Chem. Soc.*, **1935**, 244.

tend to supply electrons, either by an inductive effect like methyl or by a tautomeric effect like hydroxyl, diminish it.

The actual order of the influence of the substituents upon the rates depends upon the temperature which is chosen for the comparison. Thus, at 25.3° the rate is greater for propylene than for amylene-1 dibromide, but at 37.2° and at 56.3° the order is reversed. Similarly, maleic acid dibromide reacts more slowly than the dibromide of ethyl acrylate at 25.3° and at 37.2°, but more rapidly at 56.3°. These cases show that the numbers which represent the reaction constants are not alone a sufficient basis for an adequate discussion of the effects of substituent groups.

TABLE III

REACTION RATE CONSTANTS ($K = K_2 \times 10^6$ sec^{-1})

Experiments in Alcohol

Temperature	25.3°		37.2°		56.3°	
DIBROMIDE	K	AV. DEV. (%)	K	AV. DEV. (%)	K	AV. DEV. (%)
Ethylene	3.40	5	12.8	4	94.2	4
Propylene	0.422	—	2.12	—	20.0	—
Amylene-1	0.355	—	2.48	—	26.7	—
Allyl alcohol	0.155	4	0.91	2	8.52	4
Acrylic acid	5.98	3	24.0	2	136.0	1
Ethyl acrylate	19.2	5	68.8	6	343.0	3
Crotonic acid	—	—	6.75	3	32.7	4
Maleic acid	18.0	4	59.8	4	372.0	3

Experiments in Acetone

Temperature	0°		8.6°		14.3°		25.3°	
DIBROMIDE	K	AV. DEV. (%)	K	AV. DEV. (%)	K	AV. DEV. (%)	K	AV. DEV. (%)
Benzalacetophenone	195	2	532	1	990	2	—	—
p-Nitrobenzalacetophenone	291	2	852	6	1660	1	—	—
m-Chlorobenzalacetophenone	—	—	—	—	1520	4	—	—
Benzalacetone	—	—	—	—	—	—	2070	2
Acrylic acid	81	4	—	—	—	—	1730	2

From the reaction constants, K, at the several temperatures (Table III) the energies of activation listed in Table IV have been calculated. The averages of these values for each reaction (substantially and within the limits of precision the same as the average energies of activation over the temperature range of our experiments), have been substituted in the equation, $K = PZe^{-E/RT}$, Z being taken as equal to 2×10^{11}, and have given us the values for P, the probability factor, which are listed in

Table V. The value of Z has been calculated from kinetic theory for the concentrations and temperatures at which we have worked, and is in the neighborhood of 2×10^{11}, which is the value we have adopted for all our calculations. A difference of 25° in temperature does not change the sig-

TABLE IV

ENERGIES OF ACTIVATION: REACTIONS OF DIBROMIDES WITH SODIUM IODIDE

Reactions in Alcohol

DIBROMIDE	$E_{25.3°}^{37.2°}$ (kcal.)	$E_{37.2°}^{56.3°}$ (kcal.)
Ethylene	20.6	21.3
Propylene	23.6	28.8
Amylene-1	28.4	26.2
Allyl alcohol	25.8	24.8
Acrylic acid	20.3	19.2
Ethyl acrylate	18.6	17.8
Crotonic acid	—	17.9
Maleic acid	18.8	19.6

Reactions in Acetone

DIBROMIDE	$E_{0°}^{8.6°}$ (kcal.)	$E_{8.6°}^{14.3°}$ (kcal.)	$E_{0°}^{25.3°}$ (kcal.)
Benzalacetophenone	18.0	17.3	—
p-Nitrobenzalacetophenone	19.1	19.2	—
Acrylic acid	—	—	19.5

TABLE V

PROBABILITY FACTORS: REACTIONS OF DIBROMIDES WITH SODIUM IODIDE

Reactions in Alcohol

DIBROMIDE	P
Ethylene	0.04
Propylene	1.4
Amylene-1	240.
Allyl alcohol	27.
Acrylic acid	0.007
Ethyl acrylate	0.0015
Crotonic acid	0.00013
Maleic acid	0.022

Reactions in Acetone

DIBROMIDE	P
Benzalacetophenone	1.2
p-Nitrobenzalacetophenone	31.
Acrylic acid	1.4

nificant figures of this number. Z is the number of collisions per second. If all the collisions should result in reaction, then K would be equal to Z. The other factors in the equation are the factors which determine the success of the collisions in producing the reaction. The number, $e^{-E/RT}$, is the fraction of all of the molecules which possess sufficient energy to react, and P is the probability of this energy becoming effective through successful collision. $P = 1$ corresponds to 100 per cent. probability, or to the successful reaction of all of the molecules which have sufficient energy, and 1 is evidently the highest value of P which is theoretically possible. Uncertainties in the estimation of some of the other factors may possibly double the value of P, making it 2, but the values of 27 and 31 calculated from satisfactory data for the reactions respectively of the dibromides of allyl alcohol in alcohol and of *p*-nitrobenzalacetophenone in acetone make it clear that the notion of P as a probability factor must be interpreted liberally.

The probability factors for the reactions of the dibromides of propylene and amylene-1 with sodium iodide have been calculated, and are reported as a matter of interest, but are discounted for the reason that these reactions gave no really satisfactory constants. It is difficult to see why the probability of successful collision should be greater in the cases of the compounds with the longer chains. Our data however appear to warrant the conclusion that ethylene dibromide owes its greater rate of reaction to its smaller energy of activation. The effect of the —CH_2OH group in slowing the reaction, somewhat greater than the effect of the methyl and *n*-propyl groups, is definitely related to an increase in the energy of activation which overbalances the effect of an increase in the probability factor.

Of the groups which increase the rate, the carboxyl and carbethoxy groups apparently act by decreasing the energy of activation, for the probability of successful collision is less than for ethylene dibromide. Acrylic ester dibromide reacts more rapidly than acrylic acid dibromide, and has a smaller energy of activation and a smaller probability factor; the greater rate is attributable to the smaller energy of activation. Crotonic acid dibromide reacts more slowly than acrylic acid dibromide, and has a smaller energy of activation and a smaller probability factor; the effect of the smaller probability factor overbalances that of the smaller energy of activation.

Acrylic acid dibromide has about the same energy of activation in alcohol as in acetone, but in the latter solvent the probability factor is 200 times as great, and it reacts much faster. The effect of the acetone is to increase the probability factor, a result which may perhaps be related to the fact that acetone forms a molecular compound with sodium iodide and so increases the probability of its reaction.

The data give us the following conclusions as to the principal effects of the several groups.

The —CH_3, —C_3H_7, and —CH_2OH groups increase E.

The —$COOC_2H_5$ and —COOH groups decrease E, the former more than the latter.

The effect of two —COOH groups in decreasing E is greater than the effect of one.

The effect of a —COOH group in decreasing E is more than sufficient to counteract the effect of a —CH_3 group tending to increase it.

One —COOH group reduces P; a second —COOH group increases P again, but not however to the value which it would possess if no —COOH group were present.

EXPERIMENTS

The temperatures of the reactions were controlled by immersing the vessels at 0° in a mixture of ice and distilled water in a Dewar flask, at 8.6° and 14.3° in a water bath cooled by a regulated flow of tap water, at 25.3° and 37.2° in electrically regulated thermostats, and at 56.3° in an electrically heated and regulated glycerine bath.

For the slower reactions it was found that satisfactory results could be obtained by mixing the solutions of the dibromide and the sodium iodide in the reaction vessel, and pipetting out from time to time samples for titration of the free iodine with sodium thiosulfate. For the fast reactions it was found necessary to make up the solutions in separate test-tubes, mix rapidly, and then to stop the reaction by diluting the mixture with water.

Preparation of Materials

The *alcohol* which was used for solvent was commercial absolute alcohol.

The *acetone* was purified from the bisulfite compound, dried over anhydrous magnesium perchlorate, and fractionated. It boiled at 56.3° with a boiling-point range of 0.09° (Beckmann thermometer). The *International Critical Tables* report b.p. 56.1°; Heilbron,[9] 56.5°. All the temperatures reported in the present paper are corrected temperatures unless otherwise noted.

Ethylene dibromide was fractionated twice through a Davis column, and finally distilled twice at room temperature in a Hickman still; b.p. 131.5–132.0°. Heilbron reports b.p. 131.7°.

Propylene dibromide was fractionated twice and then distilled five times in the Hickman still. The index of refraction for the sodium D line at 28° was determined on each fraction, and found to be: 1st, 1.5160; 2nd, 1.5167; 3rd, 1.5164; 4th, 1.5164; 5th (principal fraction), 1.5163 (b.p. 139–140°); and 6th (residue), 1.5158. The value given in the *International Critical Tables* for n_D^{20} is 1.5203; b.p. 140°.

Amylene-1 dibromide was prepared by combining bromine at 0° with pure pentene-1 obtained by fractionating commercial amylene five times through a Davis column. It was distilled once at atmospheric pressure, (b.p. 183–185°), and twice in the Hickman still. Brochet[10] reports b.p. 190–191°; Dykstra, Lewis, and Boord,[11] 184°.

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[9] HEILBRON, "Dictionary of Organic Compounds," New York, **1934**.

[10] BROCHET, *Bull. soc. chim.*, [3], **7**, 567 (1896).

[11] DYKSTRA, LEWIS, AND BOORD, *J. Am. Chem. Soc.*, **52**, 3400 (1930).

Dibromohydrine (allyl alcohol dibromide).—Kahlbaum's material was distilled twice in the Hickman still. The product boiled at atmospheric pressure at 219° with decomposition, in agreement with the reports of Heilbron and of Read and Hurst.[12]

α, β-Dibromopropionic acid (acrylic acid dibromide).—Kahlbaum's material was used directly. It was found to melt at 59–64° and to titrate as 100% dibromopropionic acid. As this substance exists in two forms, melting at 51° and at 64° respectively, the latter being transformed slowly into the former when the substance is melted, the reverse change occurring on standing, the melting point of our sample is not significant.

Ethyl α, β-dibromopropionate (ethyl acrylate dibromide).—Kahlbaum's material was used after three distillations in the Hickman still. The product boiled at atmospheric pressure at 214–215° as reported by Heilbron.

α, β-Dibromobutyric acid (crotonic acid dibromide) was prepared from crotonic acid. Eastman Kodak Company pure crotonic acid was recrystallized twice from water, combined with bromine in carbon disulfide solution, and the dibromide was recrystallized to constancy of melting point; m.p. 87° as reported by Heilbron.

Dibromosuccinic acid (maleic acid dibromide).—Kahlbaum's material was recrystallized once; it melted in a sealed tube at 255–256° with decomposition, in agreement with Heilbron.

Benzalacetophenone dibromide was prepared by adding the theoretical amount of bromine to benzalacetophenone dissolved in chloroform, and recrystallizing from that solvent; m.p. 156–157° as reported by Allen.[13]

p-*Nitrobenzalacetophenone dibromide* was prepared by titrating recrystallzed *p*-nitrobenzalacetophenone, m.p. 163–164°, with bromine in chloroform at room temperature. The material, recrystallized from alcohol and carbon disulfide, melted at 152°. Sorge[14] reports m.p. 148°, and Wieland,[15] 151°.

m-*Chlorobenzalacetophenone dibromide,* prepared by adding the calculated quantity of bromine to *m*-chlorobenzalacetophenone in chloroform solution, melted at 187°, as reported by Sorge and by Bodforss.[16]

Benzalacetone dibromide, prepared from benzalacetone by a similar procedure, melted at 124–125° as reported by Claisen and Claparede[17] and by Auwers and Brink.[18]

SUMMARY

The rates of reaction at several temperatures of sodium iodide in alcohol with the dibromides of ethylene, propylene, amylene-1, allyl alcohol, acrylic acid, ethyl acrylate, crotonic acid and maleic acid, and of sodium iodide in acetone with the dibromides of benzalacetophenone, *p*-nitro- and *m*-chlorobenzalacetophenones, benzalacetone, and acrylic acid have been measured.

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[12] READ AND HURST, *J. Chem. Soc.* **121,** 995 (1914).

[13] ALLEN, in "Organic Syntheses," Vol. 8, p. 61, New York, **1928.**

[14] SORGE, *Ber.*, **35,** 1068 (1902).

[15] WIELAND, *ibid.*, **37,** 1149 (1904).

[16] BODFORSS, *ibid.*, **49,** 2801 (1916).

[17] CLAISEN AND CLAPAREDE, *ibid.*, **14,** 2462 (1881).

[18] AUWERS AND BRINK, *J. prakt. Chem.*, [2], **133,** 154 (1932).

Good second-order constants have been obtained in all cases except those of the reactions of the dibromides of propylene and amylene-1. For these two neither first-order nor second-order constants appear to be satisfactory.

Acrylic acid dibromide reacts with sodium iodide much faster in acetone than in alcohol.

The effects of the substituent groups upon the reaction rates have been discussed briefly.

Energies of activation, E, have been calculated for the several reactions; the probability factors, P, have been calculated from the equation $K = PZe^{-E/RT}$; and conclusions have been drawn as to the effects of the substituent groups upon E and P.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL, BOSTON]

A SYNTHESIS OF HOMOARGININE

JESSE P. GREENSTEIN

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The only amino acid containing the guanidine group that has been isolated from the proteins is arginine or δ-guanidoornithine. The possibility that other homologues of arginine may exist was suggested at one time by Kossel[1] and also by Winterstein and Küng.[2] The supposition largely rested on the anomalous behavior of nitrate protamine and on the presence of non-crystallizable syrups in the arginine fraction of several protein hydrolysates. It seems highly probable at this time, however, that the syrups may have been composed of breakdown as well as racemic products of arginine.

Many attempts have nevertheless been made to prepare homologues of arginine, notably by Winterstein and Küng[2], Heckel[3], and Steib[4]. The early methods simply employed the cyanamide reaction with lysine or with α-β-diaminopropionic acid, whereby non-crystallizable mixtures of mono- and diguanido acids resulted.

The action of *O*-methylisourea on the peptide lysylglutamic acid has been studied and a monoguanidine-substituted derivative has been obtained.[5] Examination of the product indicated that it was predominantly an ϵ derivative but its properties were such that some α substitution was suspected. The problem resolved itself therefore into the finding of a method whereby the α amino group could be masked, leaving the ω amino group free for the preparation of the guanido derivative. The first successful attempt in this direction had been accomplished by Steib[4] who prepared the α-toluolsulfonyl derivative of ϵ-benzoyllysine. Treatment of this molecule with baryta removed the ϵ benzoyl radical; in the following step the ϵ guanido group was prepared, and finally the α toluolsulfonyl group was removed by means of hot hydriodic acid. A very low yield of the hygroscopic nitrate of ϵ-guanidolysine was obtained in this manner.

In view of the improved procedures now available for the masking of

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[1] KOSSEL, *Z. physiol. Chem.*, **84**, 1–10 (1913).

[2] WINTERSTEIN AND KÜNG, *ibid.*, **59**, 141–164 (1909).

[3] HECKEL, *Monatsh.*, **29**, 779–785 (1908).

[4] STEIB, *Z. physiol. Chem.*, **155**, 292–305 (1926).

[5] GREENSTEIN, *J. Biol. Chem.*, **109**, 529–540, 541–544 (1935).

groups, it was thought of interest to prepare the ε-guanidolysine (homoarginine) in amounts sufficient to be of use in further studies. The method of Bergmann, Zervas, and Ross[6] for the preparation of ε-carbobenzoxy-*l*-lysine provided the starting point for the synthesis. A satisfactory yield of the crystalline nonhygroscopic sulfate of *dl*-homoarginine was obtained by the following series of reactions:

dl-Lysine → Dicarbobenzoxylysine → Dicarbobenzoxylysyl chloride → ε-Carbobenzoxy-α-Carboxylysine anhydride → ε-Carbobenzoxylysine → ε-Carbobenzoxy-α-benzoyllysine → α-Benzoyllysine → ε-Guanido-α-benzoyllysine → *dl*-Homoarginine

The homoarginine was treated with arginase but no action whatever of the enzyme on this substrate was detectable under conditions by which sixty to seventy per cent. of arginine was split. This confirms the observation by Steib[4]. The great specificity of arginase is thus revealed, the action of the enzyme evidently requiring a specific distance between the guanidine group which it attacks and the α amino (or α hydroxyl) and carboxyl groups which it needs as probable points of attachment.

EXPERIMENTAL

*ε-Carbobenzoxy-*dl*-lysine.*—The preparation of this substance followed substantially the methods used by Bergmann, Zervas, and Ross for the *l*-lysine derivative.[6] *dl*-Lysine was synthesized from cyclohexanone oxime along the lines recommended by Eck and Marvel.[7] The racemic dicarbobenzoxylysine crystallized in tiny square prisms from ethyl acetate-petroleum ether, and melted at 104°. It was converted to the acid chloride in dry, chilled, chloroform solution with phosphorous pentachloride. Evaporation *in vacuo* at 50° converted the substance into the carboxylic anhydride (m.p. 92°). Treatment with acetone-hydrogen chloride yielded carbobenzoxy-*dl*-lysine hydrochloride, which after neutralization with ammonia gave the free acid (m. p. 263°).*

Anal. Calc'd for $C_{14}H_{20}N_2O_4$: N, 10.0. Found: N, 10.0.

*α Benzoyl-*dl*-lysine.*—Twenty-four grams of ε-carbobenzoxy-*dl*-lysine was dissolved in 160 cc. 1*N* sodium hydroxide solution and treated at 10° with 18 g. of benzoyl chloride and 150 cc. of 1*N* sodium hydroxide solution. On acidification with 5*N* hydrochloric acid an oil separated, and rapidly hardened on cooling. This product, ε-carbobenzoxy-α-benzoyllysine, was dried, pulverized, and extracted several times with ligroïn to remove adhering benzoic acid. It was then dissolved in a methyl alcohol-water mixture; the solution was treated with 60 cc. of 5*N* hydrochloric acid and catalytically hydrogenated in the presence of palladium. When the reaction was at an end, the filtrate from the catalyst was evaporated *in vacuo*, and the aqueous solution was shaken with ether to remove some benzoic acid. After neutralization with ammonia, scratching of the sides of the flask induced the appearance of a white

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[6] BERGMAN, ZERVAS, AND ROSS, *ibid.*, **111**, 245–260 (1935).

[7] ECK AND MARVEL, *ibid.*, **106**, 387–391 (1934).

* During evaporation of the acetone-hydrogen chloride mixture, an oil separates which can be removed by ether extraction and subsequently discarded.

precipitate of α-benzoyl-*dl*-lysine. The substance was filtered off, washed well with ice-water, and dried; yield 17 g.; m.p. 211°.

Anal. Calc'd for $C_{13}H_{18}N_2O_3$: N, 11.2. Found: N, 11.1.

*ε-Guanido-α-benzoyl-*dl*-lysine.*—The hydrochloride of 0-methyl isourea[5, 8] (40.32 g.) was dissolved in 200 cc. of methanol, and the solution was treated at 0° with 86.9 cc. 4.2*N* sodium methylate solution. The sodium chloride was separated by filtration through infusorial earth, and to the clear filtrate 17 g. of α-benzoyllysine was added, together with enough water to bring the substance into solution. A slight amount of warming was also necessary. The solution was filtered, and allowed to stand at room temperature. Crystallization of long needles began after fifteen minutes. After twenty-four hours the crystalline mass was collected by filtration, washed with ice-water, and recrystallized from hot water. This time the guanidine derivative crystallized in long prisms. It was collected by filtration, washed, and dried. The yield was 12.8 g.; m.p. 273°.

Anal. Calc'd for $C_{14}H_{20}N_4O_3$: N, 19.2. Found: N, 19.1.

*ε-Guanido *dl*-lysine (homoarginine) sulfate.*—Twelve grams of the benzoyl derivative was dissolved in 120 ccm. of 5*N* hydrochloric acid, and the solution was boiled under reflux for three hours. After cooling, the benzoic acid was extracted with ether, and the aqueous solution was evaporated to a syrup *in vacuo.* Inasmuch as the syrup failed to crystallize it was taken up in water and shaken with a slight excess of silver sulfate. The silver chloride was removed by filtration, and the filtrate was treated with hydrogen sulfide. On evaporation *in vacuo* a syrup again was obtained. It was dissolved in a little water, and treated with a large volume of absolute alcohol. A white oil separated; this solidified on standing in the ice chest for a week. The procedure of dissolving in water and precipitating with alcohol was repeated twice more, after which a crystalline solid in the form of prisms was finally obtained. The crystalline sulfate was non-hygroscopic and amounted to 7.1 gm. The substance decomposed with foaming at 127° after preliminary softening at 112°. It crystallized with 1½ molecules of water.

Anal. Calc'd for $(C_7H_{16}N_4O_2)_2 \cdot H_2SO_4 + 1\frac{1}{2}\,H_2O$: N, 22.3; SO_4, 19.1.
Found: N, 22.0; SO_4, 19.0.

Homoarginine sulfate, on drying for four hours at 56° under 4 mm. pressure, lost 5.2 per cent. in weight; calculated for 1.5 moles of crystal water, 5.3 per cent. The substance gives a positive Sakaguchi reaction. It was further characterized by the formation of its benzilidene derivative.

Benzilidene homoarginine.—Six-tenths gram of homoargine sulfate was dissolved in 10 cc. of water, was treated with enough 1*N* sodium hydroxide solution to bring the pH of the solution to about 9, and then shaken with 0.5 cc. of benzaldehyde. Scratching induced crystallization of the benzilidene derivative in the form of small prisms. After chilling, the product was collected by filtration, washed twice with ice-water, then with a methanol-ether mixture, and finally with dry ether. The yield was 0.4 gm.; m.p. 248° with decomposition.

Anal. Calc'd for $C_{14}H_{20}N_4O_2$: N, 20.3. Found: N, 19.9.

Behavior of homoarginine with arginase.—One-fourth gram of neutralized homoarginine sulfate was incubated at 40° and at pH 8 with an arginase solution prepared from fresh rat liver. A few drops of Manganese chloride solution was added. Simultaneously, a solution containing 0.1 g. of arginine base with an equivalent amount of sulfuric acid was similarly treated. After one hour the solutions were boiled,

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[8] KAPFHAMMER AND MÜLLER, *Z. physiol. Chem.*, **225**, 1–12 (1934).

filtered, and treated with urease. After a half-hour's incubation at 40°, the solutions were made up to volume, and aliquots of each were directly Nesslerized. A splitting of 60 to 70 per cent. of arginine was revealed in this way. No trace of any attack by arginase on the homoarginine was evident.

SUMMARY

1. *dl*-Homoarginine (ϵ-guanidolysine) has been synthesized from *dl*-lysine.

2. The substance is not attacked by arginase.

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

CONSTITUENTS OF PYRETHRUM FLOWERS.
XI. CHRYSANTHIN*

W. GORDON ROSE AND H. L. HALLER

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When pyrethrum flowers are extracted with a suitable organic solvent and the solvent is removed, an oleoresin is obtained which contains, besides the active insecticidal principles pyrethrin I and pyrethrin II, comparatively large quantities of extraneous substances consisting of fats, waxes, free fatty acids, and other compounds.

The separation of the pyrethrins from the accompanying inert material has been the subject of numerous investigations. The preliminary steps in the purification of the oleoresin, developed by Staudinger and Ruzicka,[1] had not been improved, however, until the procedure now in use in the laboratory of the Division of Insecticide Investigations, Bureau of Entomology and Plant Quarantine, was described.[2] The oleoresin employed for these studies is obtained by extracting pyrethrum flowers with a low-boiling petroleum ether and removing the solvent by distillation. In the removal of the solvent from the petroleum-ether extracts, a crystalline product occasionally separates.†

Preliminary examination showed the compound to be different from pyrethrol,[3] a crystalline product frequently encountered in the operations incidental to the purification of the pyrethrins.

It is proposed to designate the compound "chrysanthin," for reasons which will be stated below.

Chrysanthin is a colorless, crystalline compound and is optically active. It melts at 201° when it is crystallized from ethyl acetate and at 177–178° when it is crystallized from ethanol. It does not contain nitrogen or sul-

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* For article X of this series see J. ORG. CHEM., **2**, 308 (1937).

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

[2] LAFORGE AND HALLER, *J. Am. Chem. Soc.*, **57**, 1893 (1935).

† The deposition of crystalline material does not always take place, and in no instance is the quantity of crude product greater than 0.1 per cent of the total extractive. The crystalline product used in this investigation was isolated from a lot of crude material obtained from McCormick & Co., Baltimore, Md., through the courtesy of Dr. A. Edison Badertscher.

[3] FUJITANI, *Arch. expt. Path. Pharmakol.*, **61**, 47 (1909).

fur, nor does it yield methyl iodide by the Zeisel method. Determination of carbon, hydrogen, and molecular weight show it to possess the molecular formula $C_{17}H_{22}O_5$.

On catalytic hydrogenation with platinum oxide catalyst, chrysanthin absorbs two atoms of hydrogen per molecule. When it is oxidized with chromic acid in aqueous acetic acid solution, it loses two atoms of hydrogen, and a neutral compound having the formula $C_{17}H_{20}O_5$ is obtained. Acetic anhydride-pyridine reagent shows that free hydroxyl groups are not present in chrysanthin, and attempts to prepare an oxime or semicarbazone were not successful.

Fusion of chrysanthin with potassium hydroxide yields a very small quantity of a substance having a strong phenol-like odor, which with ferric chloride gives a violet-red color that is stable for several hours.

Perhaps the most characteristic reaction of chrysanthin is its behavior with dilute aqueous alkali. When it is gently heated with 5 per cent. aqueous sodium hydroxide, it readily goes into solution. On acidification of the alkaline solution with dilute hydrochloric acid, water-soluble products only are obtained. One of these has been identified as acetic acid. The other is an acid possessing the empirical formula $C_{15}H_{26}O_7$. This acid is very soluble in water and in ethanol and only slightly soluble in ether and in chloroform. It melts at 190–192°, and when dried at 110° it loses one molecule of water and yields an acid that melts at 210–211°. With acetic anhydride-pyridine reagent the presence of one hydroxyl group can be demonstrated.

In a recent article Chou and Chu[4] have described the isolation of a crystalline compound from the benzene extracts of pyrethrum flowers and have given it the name "chrysanthine." When crystallized from a mixture of chloroform and alcohol, chrysanthine melts at 200°, and has a specific rotation of $-30°$ in chloroform. On the basis of carbon and hydrogen determinations but no reported molecular-weight determination, the empirical formula $C_{10}H_{13}O_3$ was assigned, a formula that is obviously not possible.

A direct comparison between the compound isolated by Chou and Chu and the one isolated by us has not been possible, but the facts that the melting point and the optical rotation are approximately the same for both compounds and that the values for carbon and hydrogen differ only slightly seem to indicate that the two compounds are identical. It is for this reason that the name "chrysanthin" is also used for the compound isolated by us. We have dropped the final "e" because such nomenclature is more in keeping with present standards.

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[4] CHOU AND CHU, *Chinese J. Physiol.*, **8**, 167 (1934).

Preliminary insecticidal tests of chrysanthin with mosquito larvae and codling moth larvae‡ as test insects have shown it to be relatively nontoxic.

EXPERIMENTAL

Purification and analysis of chrysanthin.—The crude material† was washed with warm petroleum ether (b.p. 30–60°), in which chrysanthin is insoluble, and then extracted with hot ethyl acetate. When the extract, which had been decolorized with active carbon, had cooled, the chrysanthin separated. It was recrystallized from ethyl acetate and from ethanol. After recrystallization from hot ethyl acetate it melted at 201°, when the rate of heating was 8 to 10° per minute; when the rate of heating was slower (3 to 4° per minute), the substance sintered at 190° but did not flow to a clear liquid even at 300°. After recrystallization from ethanol the melting point, with rapid heating, was 177–178°; heated more slowly, its behavior was similar to that described for the higher-melting modification. Both modifications have the same composition.

Chrysanthin is optically active: 0.1563 g. dissolved in 3.03 ml. of chloroform at 20° rotated the plane of polarized light in a 1-dm. tube 4.55° to the left; therefore, $[\alpha]^{20}_{D}$ − 30.5°.

The saponification equivalent was determined by a slight modification of the method of Chargaff.[5] From 20 to 30 mg. of substance was refluxed for 30 minutes with 5 ml. 0.06 *N* sodium *n*-propylate in *n*-propyl alcohol, protected from atmospheric carbon dioxide by means of a soda lime tube. The condenser was washed with 10 ml. of carbon dioxide-free water, and the aqueous alcoholic solution was cooled and titrated. The quantity of acid required was substracted from that required to neutralize the same volume of sodium propylate solution when refluxed for 30 minutes without the substance. The saponification equivalents so obtained were 155, 155, 156, 155.

The molecular-weight determination was made by the Rast method. The melting point of camphor was depressed 11.5° when 0.453 mg. of chrysanthin was dissolved in 4.549 mg. of the former; 0.208 mg. chrysanthin in 3.661 mg. of camphor depressed the melting point 6.7°. The specimen of camphor used had a molar freezing point depression of 36.5°. These data indicate molecular weights of 315 and 307, respectively.

Anal. Calc'd for $C_{17}H_{22}O_5$: C, 66.62; H, 7.25; mol. wt., 306.2.
Found: C, 66.80, 66.65; H, 7.37, 7.13.

The acids from chrysanthin.—Four grams of chrysanthin was suspended in 22 ml. of 1.5 *N* sodium hydroxide, and the solution was heated to 90°. The chrysanthin dissolved readily in the warm alkali, with the formation of a light yellow solution. Neutral or acid solutions are colorless. The solution was acidified to congo and steam-distilled. The distillate was made alkaline, evaporated to dryness, the residue dissolved in water, and an equal volume of ethanol added to the solution. Half of the resulting solution was refluxed with 1.2 grams of *p*-phenylphenacyl bromide for an hour. Recrystallization of the product from ethanol gave 0.65 g. of *p*-phenylphenacyl acetate, m.p. 111–112°. The melting point was not depressed

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‡ The tests against mosquito larvae were carried out by Dr. D. E. Fink of the Division of Control Investigations and those with the coddling moth larvae by Dr. E. H. Siegler of the Division of Fruit Insect Investigations of this Bureau.

[5] CHARGAFF, *Z. physiol. Chem.*, **199**, 221 (1931).

on mixing with an equal quantity of an authentic sample of *p*-phenylphenacyl acetate.[6]

Preliminary attempts to extract the other acidic product with ether or chloroform in a continuous extractor had shown that this acid cannot be isolated readily by extraction, owing to its limited solubility in solvents immiscible with water. The solution remaining in the steam-distillation flask was therefore concentrated by allowing it to stand under an evacuated bell jar. When the volume had been reduced to 5-6 ml., the solution was filtered and carefully washed with 4-5 ml. of water. Some difficulty was experienced in recrystallizing this acid; recrystallization was finally effected by suspending the substance in hot dibutyl ether, adding alcohol sufficient to dissolve the acid, and allowing it to stand until crystallization was complete. The product so obtained, when dried *in vacuo* at 60°, melted at 190-192° when heated at the rate of 8-10° per minute. When mixed with chrysanthin, the mixture melted at 165-180°. This cleavage product is acidic and has a neutralization equivalent of 320.

Anal. Calc'd for $C_{15}H_{26}O_7$: C, 56.56; H, 8.23; mol. wt., 318.2.
Found: C, 56.77, 56.86; H, 8.20, 8.11.

On drying at 112° or at 137° *in vacuo*, the loss in weight was 6.5 per cent. The resulting substance melts at 210-211°, and has the empirical formula $C_{15}H_{24}O_6$.

Anal. Calc'd: C, 59.95; H, 8.06.
Found: C, 59.59, 59.74; H, 8.09, 7.83.

The presence of a hydroxyl group was demonstrated by heating the acid with acetic anhydride-pyridine reagent, decomposing the excess acetic anhydride with water, and titrating the acetic acid so formed. Control titrations on the reagent required 9.72 ml. of 0.0180 *N* sodium hydroxide solution to neutralize the acetic acid formed. When 16.5 mg. of the acidic cleavage product was heated with the same quantity of the reagent, 9.57 ml. of alkali was required. Since the cleavage product has a neutral equivalent of 320, 12.60 ml. of alkali would be required if the cleavage product contained no hydroxyl group. The results indicate 1.05 hydroxyl groups per molecule. Attempts to isolate an acetylation product were not successful. Attempts to prepare derivatives in which the carboxyl group was esterified were also unsuccessful.

The presence of acetic acid having been demonstrated to be one of the saponification products of chrysanthin, acetyl determinations were made by the method of Clark[7] and also by the method described by Elek and Harte.[8] The former gave results that were too high, while the latter yielded low values.

Anal. Calc'd for $C_{17}H_{22}O_5$: 1 CH_3CO, 14.05.
Found: CH_3CO, Clark's method, 14.95, 14.95, 15.15; Elek and Harte's method, 10.95, 11.32, 11.03.

Dihydrochrysanthin.—Chrysanthin (0.95 gram) dissolved in 50 ml. of ethanol was reduced at atmospheric pressure and temperature with hydrogen and Adams' platinum catalyst. One mole of hydrogen was absorbed. The product after three recrystallizations from ethanol weighed 0.30 g.; it melted at 205-208° when heated rapidly. A mixture of this product, which has been designated "dihydrochrysanthin," with an equal quantity of chrysanthin melted at 165-185°. Dihydrochrysan-

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

[7] CLARK, *Ind. Eng. Chem., Anal. Ed.*, **8**, 487 (1936).

[8] ELEK AND HARTE, *ibid.*, **8**, 267 (1936).

thin is also cleaved by refluxing with sodium propylate solution. The saponification equivalent obtained was 156. When 0.334 mg. of dihydrochrysanthin was dissolved in 9.296 mg. of camphor, the freezing point of the latter was depressed 4.0°. This indicates a molecular weight of 328.

Anal. Calc'd for $C_{17}H_{24}O_5$: C, 66.19; H, 7.85; mol. wt., 308.2.
Found: C, 66.42, 66.16; H, 7.68, 7.88.

Oxidation of chrysanthin.—Two grams of chrysanthin in 20 ml. of 50 per cent acetic acid was oxidized by adding 10 ml. of a 10 per cent aqueous solution of chromic anhydride to the well-stirred solution heated to 85–90°. The reaction mixture was poured into 100 g. of cracked ice and the product that separated was removed by filtration. After three recrystallizations from alcohol the product, designated "dehydrochrysanthin," melted at 175–177°. The yield was 0.045 g. When mixed with an equal quantity of chrysanthin the melting point was 148–152°. Determination of the equivalent weight by saponification with sodium propylate gave a value of 154.

Anal. Calc'd for $C_{17}H_{20}O_5$: C, 67.05; H, 6.64; mol. wt., 304.2.
Found: C, 66.97, 67.00; H, 6.69, 6.60.

SUMMARY

A colorless, crystalline, optically active compound, designated "chrysanthin," has been isolated from pyrethrum flowers.

Chrysanthin possesses the empirical formula $C_{17}H_{22}O_5$.

On catalytic hydrogenation it yields a dihydro compound; on mild oxidation a dehydro compound is formed.

When chrysanthin is heated in dilute aqueous alkali, acetic acid and a water-soluble acid having the empirical formula $C_{15}H_{26}O_7$ are formed.

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

THE ADDITION OF HYDROGEN CHLORIDE TO BUTADIENE

M. S. KHARASCH, J. KRITCHEVSKY, AND F. R. MAYO

Received December 15, 1937

It was established by Kharasch, Margolis and Mayo[1] that the addition of hydrogen bromide to butadiene at low temperature and in the presence of antioxidants yields about 80 per cent. of 3-bromo-1-butene and 20 per cent. of 1-bromo-2-butene. It was shown also that larger proportions of the latter are obtained as the reaction temperature is increased or as oxygen or peroxides are substituted for antioxidants. Since hydrogen bromide and peroxides cause rapid rearrangement of the addition product to an equilibrium mixture of its components, there remained the question whether the effect of peroxides is to cause primary 1,4 instead of 1,2 addition, or to rearrange the first-formed 1,2 addition product. None of the third structurally possible addition product, 4-bromo-1-butene, was found.

Since oxygen and peroxides are known not to influence the addition of hydrogen chloride to ethylene derivatives,[2] it was anticipated that the study of the addition of hydrogen chloride to butadiene would elucidate the addition of halogen acids to conjugated systems in the absence of any peroxide effect.

Only one previous study of the addition of hydrogen chloride to butadiene has been reported. Ganguly[3] obtained both 1-chloro-2-butene and 3-chloro-1-butene as addition products but he did not report their proportions, nor does he record more than one experiment. His work on the addition of hydrogen bromide to butadiene ignored the rapid isomerization of the addition products and hence need not be considered here.*

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[1] Kharasch, Margolis, and Mayo, *J. Org. Chem.*, **1**, 393 (1936).

[2] Kharasch and Mayo, unpublished work; Abraham and Smith, *J. Chem. Soc.*, **1936**, 1605.

[3] Ganguly, *J. Indian Chem. Soc.*, **13**, 580 (1936).

* Ganguly offers the following interpretation of his findings:

"The difference between the behaviour of hydrogen chloride and hydrogen bromide on butadiene is probably due to the difference in their (*i*) dipole moment and thereby the permanent inductive electronic drift and more so (*ii*) the molecular volume—it being an established fact that there is a connection between the bulk of the new entrant and its orienting power."

THE ADDITION OF HYDROGEN CHLORIDE TO BUTADIENE

The following structural isomers are possible as a result of the addition of hydrogen chloride to butadiene:

$$\begin{array}{lll} & \nearrow & H_2C{=}CH{-}CHCl{-}CH_3 \quad (I) \\ H_2C{=}CH{-}CH{=}CH_2 + HCl & \rightarrow & H_3C{-}CH{=}CH{-}CH_2Cl \quad (II) \\ & \searrow & H_2C{=}CH{-}CH_2{-}CH_2Cl \quad (III) \end{array}$$

Table I shows that the addition of hydrogen chloride to butadiene yields 75 to 80 per cent. of 3-chloro-1-butene (I, hereafter called secondary chloride) and 20 to 25 per cent. of 1-chloro-2-butene (II, hereafter called crotyl chloride). Careful distillation (described in the experimental part) of several of the addition mixtures failed to give any indication of the presence of the third possible addition product, 4-chloro-1-butene (III). Within the limits of experimental error, the composition of the addition product is independent of temperature (−80° to 25°) in the absence or presence of a solvent (glacial acetic acid). Although no experiments were performed in the absence of air, the addition of an antioxidant in one experiment had no effect.

TABLE I

ADDITION OF HYDROGEN CHLORIDE TO BUTADIENE

MOLES HCl[a]	SOLVENT OR ANTIOXIDANT, MOLES[a]	REACTION		YIELD		BUTADIENE RECOVERED, %	ADDITION PRODUCT	
		Time in hours	Temperature, °C.	Addition Products, %	Polymer, %		3-Cl-1-Butene, %	1-Cl-2-Butene, %
1.0	None	1	−80	31	29	37	78	22[b]
1.0	None	1	−80	34	33	24	77	23[b]
1.0	None	1	−80	36	30	27	80	20[b]
1.5	None	24	−80	32	32	28	80	20[b]
1.5	None	72	−80	33	30	30	75	25[c]
1.0	None	1	Room	31	29	31	78	22[b]
1.0	None	1	Room	35	44	15	80	20[b]
1.0	Thiophenol, .02	1	Room	28	28	32	82	18[b]
1.5	Ether, 4.0	24	−80	—	—	85	—	—
1.5	Ether, 2.0	24	Room	—	—	95	—	—
1.5	Glacial acetic acid, 1.8	24	Room	50	1	40	78	22[b]
1.5	Glacial acetic acid, 1.7	24	Room	79	None	15	78	22[c]
1.5	Glacial acetic acid, 1.5	48	Room	61	None	30	78	22[b]
							75	25[c]

[a] Per mole butadiene used.

[b] Analysis by index of refraction.

[c] Analysis by Podbielniak distillation.

In the absence of a solvent, the yield of chlorobutenes was about 35 per cent., nearly independent of reaction time and temperature. In glacial acetic acid at room temperature, yields varied from 50 to 80 per cent. No addition took place in ether as a solvent.

The fact that the addition of hydrogen chloride to butadiene, under a variety of conditions, results in a mixture of 75–80 per cent. of the secondary chloride and 25–20 per cent. of crotyl chloride is of interest. However, before any conclusions may be drawn from these data it is essential to establish whether these substances undergo any appreciable isomerization under the experimental conditions.

TABLE II

REARRANGEMENT OF THE CHLOROBUTENES[a]

1-Chloro-2-butene							3-Chloro-1-butene		
MOLES[b]		REARRANGEMENT[c] (%)	EXPT. NO.	CATALYST	REACTION		REARRANGEMENT[c] (%)	MOLES[b]	
HCl	Catalyst				Temp.	Time (Days)		Catalyst	HCl
0.99		3	1		−80°	0.042	1		0.99
	0.003	33	2	$FeCl_3$	−80°	1	26	0.003	
0.02	$.0_36$	48	3	$FeCl_3$	0°	1	47	$.0_36$	0.02
	$.0_53$	16	4	$FeCl_3$	Room	1	22	$.0_56$	
	$.0_36$	47	5	$FeCl_3$	Room	1	47	$.0_36$	
	.02	46	6	$FeCl_3$	Room	1	50	.02	
	.003	46	7	$FeCl_3$	Room	2	47	.004	
0.09	.01	28	8	Cu_2Cl_2	Room	1	37	.01	0.08
1.00		6	9		Room	1	20		1.00
0.99		6	10		Room	1	23		0.99
0.99	.03	7	11	H_2O	Room	1	22	.03	1.00
			12	H_2O, Benzoyl peroxide	Room	1	5	.01, .003	0.47
			13	Ascaridole	Room	1	14	.05	0.50
1.00		18	14		Room	7	25		1.00
1.00		20	15		Room	21	50		1.00
1.00		22	16		Room	49	74		1.00
0.99	$.0_37$	27	17	$FeCl_3$	Room	1	68	.0011	0.99
0.10	.03	67	18	$FeCl_3 \cdot 6H_2O$	100°	0.25	24	.03	0.10
1.00	.90	25	19	Acetic acid	100°	0.25	1	.90	1.00

[a] The pure chlorobutene indicated was the starting material in each case.

[b] Expressed in moles per mole of chlorobutene used.

[c] Indicates the proportion of the other chlorobutene in the rearrangement product, the remainder being the original chlorobutene.

ISOMERIZATION OF 1-CHLORO-2-BUTENE AND 3-CHLORO-1-BUTENE

The results of our isomerization experiments with the chlorobutenes are given in Table II and Figure 1. It should be noted that in most cases, equilibrium was approached from both sides.

Our experience with many samples of both of the chlorobutenes indicates that in the absence of catalysts the materials are quite stable. No change in their respective indices of refraction has been noted, even at the end of two or three weeks at room temperature.

Anhydrous ferric chloride, cuprous chloride in the presence of hydrogen chloride, and even hydrogen chloride alone are catalysts for the rearrangement of either compound to an equilibrium mixture of the two. Of these catalysts ferric chloride is the most effective. Even a small quantity of ferric chloride brings about the establishment of equilibrium in a day at room temperature. Our experiments indicate also that cuprous chloride in the presence of hydrogen chloride is a more effective rearranging agent than hydrogen chloride itself. With hydrogen chloride as the only catalyst, several weeks at room temperature are required to attain equi-

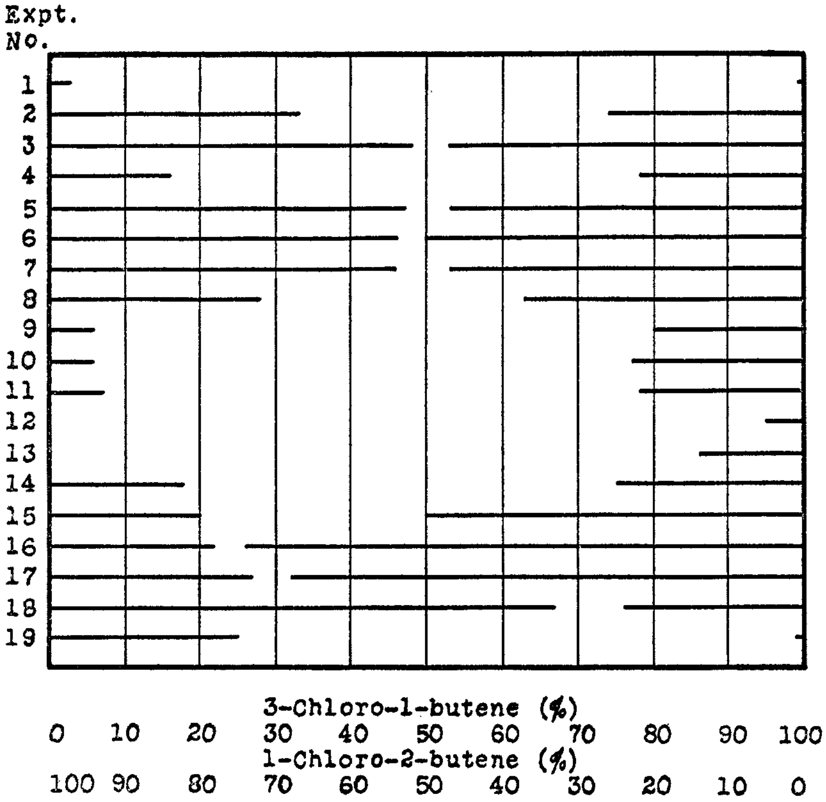

FIGURE 1.—REARRANGEMENT OF THE CHLOROBUTENES

The length of each line represents the percentage of pure chlorobutene isomerized under conditions given in Table II.

librium. Other experiments recorded in Table II and Figure 1 indicate that neither water nor peroxides have any notable effect on the rate of rearrangement. The anticipated effect of temperature on the rates of isomerization of the two isomers has been found.

A study of the equilibrium of the two isomeric chlorides in the presence of added materials revealed a number of facts of considerable interest. Thus, several experiments show that the equilibrium at room temperature in the presence of a trace of ferric chloride is a mixture containing 50 per cent. of each of the chlorides. It is equally clear that in the presence of one mole of hydrogen chloride, the equilibrium mixture contains 70–75 per cent. of crotyl and 25–30 per cent. of secondary chloride, irrespective of the presence or absence of a trace of ferric chloride (although the ferric chloride has a great influence on the rate of isomerization). We believe these data show unequivocally that *the composition of the equilibrium mixture depends upon the proportion of hydrogen chloride present and not upon the presence of a trace of ferric chloride.* Low-temperature experiments indicate that the equilibrium in the absence of hydrogen chloride is about the same at −80° as at room temperature. Experiments at 100° indicate that the equilibrium mixture at that temperature is richer in secondary chloride.

DISCUSSION

From the isomerization experiments described in the preceding section we conclude that the composition of the mixture obtained by the addition of hydrogen chloride to butadiene under the conditions employed by us is not appreciably affected by isomerization. In support of this conclusion the following facts are cited. (1) The addition product, under a variety of conditions, contains 75–80 per cent. of secondary chloride. Under the experimental conditions, this mixture could not have been formed by isomerization of crotyl chloride. (2) The improbability that the 20–25 per cent. of crotyl chloride found in the addition mixture was formed by rearrangement of secondary chloride is indicated by the results of experiments in which hydrogen chloride was allowed to react with butadiene for one hour at −80°. At that temperature rearrangement of either chloride is negligible when hydrogen chloride is used as a catalyst. The addition product obtained was the same as in experiments conducted over longer periods up to three days. (3) It is significant that the same addition mixture as that observed at −80° (20–25 per cent crotyl chloride) is obtained irrespective of whether the addition is allowed to proceed for one hour or two days at room temperature.

These facts effectively dispose of the hypothesis that either isomer is formed from the other in any appreciable quantities during the course of our addition reaction. Hence, we must conclude that the composition of the mixture of addition products obtained by us is independent of the solvent, and of the presence of unchanged butadiene or its polymers.

The negligible rearrangement of the products during the addition of hydrogen chloride to butadiene does not seem at all anomalous when the isomerization experiments are carefully scrutinized. First, it is to be noted that the concentration of hydrogen chloride in the addition experiments is less than in the rearrangement experiments. Second, it is apparent that the rate of attainment of the isomerization equilibrium decreases with time and that, in the absence of metallic catalysts about as much change in composition takes place during the first day as during the succeeding week. The addition mixture obtained by us corresponds in composition to an isomerization system in which the rate of change is relatively low.

The foregoing evidence indicates that the addition of hydrogen chloride to butadiene gives as the primary product a mixture of 75 to 80 per cent. of secondary chloride by 1,2 addition and 20 to 25 per cent. of crotyl chloride by 1,4 addition, irrespective of temperature (−80° to 25°), and of the presence or absence of acetic acid as solvent.

TABLE III

PHYSICAL PROPERTIES OF THE CHLOROBUTENES

CHLOROBUTENE	K., K., & M.			LITERATURE			REFERENCE
	B. p., °C.	Pressure	n_D^{20}	B. p., °C.	Pressure	n_D^{20}	
3-Chloro-1-butene	64	750 mm.	1.4150	64	Atm.	1.41503	*6*
1-Chloro-2-butene	84	750 mm.	1.4350	84	Atm.	1.43503	*6*
4-Chloro-1-butene				75.0	773 mm.	1.42330	*7*

It is now of interest to point out that, within the limits of experimental error, Kharasch, Margolis, and Mayo[1] obtained practically the same result for the addition of hydrogen bromide to butadiene at −80° in the absence of air and in the presence of an antioxidant. Under those conditions, which minimize rearrangement, the proportion of secondary bromide was 80 to 90 per cent. Therefore it seems probable that the peroxide effect observed can be ascribed to the effect of peroxides and hydrogen bromide on the rearrangement of the mixture first formed rather than to a primary directive effect of peroxides on the addition reaction. From the results of both papers, we conclude that the addition of halogen acids to butadiene results in both 1,2 and 1,4 addition, but that the amount of 1,2 product formed in the primary reaction is three to five times that of the 1,4 product.

EXPERIMENTAL

Preparation of butadiene.—Butadiene was prepared and purified as described by Kharasch, Margolis and Mayo.[1]

Method of addition.—Addition mixtures were prepared by passing butadiene into hydrogen chloride or its solution in the hope of inhibiting polymerization. Anhydrous hydrogen chloride was condensed in a glass tube in a cooling mixture. The necessary low temperature (about −100°) was attained by passing a stream of air through an acetone-solid carbon dioxide bath. Butadiene (usually about one-tenth mole, although up to a full mole was used in some experiments) was condensed in the tube, which was then stoppered or sealed, depending on the conditions of the experiment. No precautions were taken to exclude air or water except that the container was open only through a calcium chloride tube. When ether was used as solvent, the hydrogen chloride was first dissolved in the ether, and temperatures below −80° were unnecessary. When glacial acetic acid was used as solvent, the required amount of hydrogen chloride was dissolved with slow cooling. The solution was then frozen; the butadiene was condensed as an upper layer; the tube was sealed and allowed to reach room temperature. All reaction mixtures were homogeneous.

Isolation of the addition product.—In experiments made without a solvent, the reaction product was distilled at atmospheric pressure up to a vapor temperature of 90°. The residue did not volatilize, and its weight is recorded in the table as "yield of butadiene polymer." It was not tested for chlorine. During the distillation, the hydrogen chloride escaped and the unchanged butadiene was recovered in a cooled trap. In a few cases, the addition mixture was first distilled *in vacuo*. This procedure permitted collection of the butadiene and addition product at −80° and their isolation from the polymer (which did not distill) and from the hydrogen chloride (which did not condense) without heating the addition product. Since this procedure yielded the same result as the distillation in air, it was subsequently abandoned. When a solvent was employed, the addition mixture was distilled first through a small column to isolate the chlorobutene fraction. This fraction was washed several times with water to remove acetic acid.

All products were dried over anhydrous potassium carbonate and distilled. They were analyzed by index of refraction or by fractional distillation through a Podbielniak column. In one instance recorded in Table I the product was analyzed by both methods, with a difference of only 3%. We estimate the precision of our results to be ±5%. Numerous Podbielniak distillations showed the absence of 4-chloro-1-butene (*cf.* second paragraph below).

Preparation of the pure chlorobutenes.—Crotyl alcohol was prepared from crotonaldehyde and aluminum isopropoxide by the method of Young, Hartung, and Crossley.[4]

When pure crotyl alcohol was treated with 1% cuprous chloride,[5] saturated with anhydrous hydrogen chloride at −20°, and allowed to stand at this temperature over night, an 85% yield of a mixture of the chlorobutenes was obtained. The chlorobutene mixture contained 75–85% of crotyl chloride and 15–25% of secondary chlo-

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[4] Young, Hartung, and Crossley, *J. Am. Chem. Soc.*, **58**, 100 (1936).

[5] Dewael, *Bull. soc. chim. Belg.*, **39**, 40 (1930), suggests such a method for the preparation of allyl chloride.

[6] Baudrenghien, *ibid.*, **31**, 166 (1922).

[7] Juvala, *Ber.*, **63**, 1993 (1930).

ride. These were separated by distillation through a Podbielniak column. There was no evidence of rearrangement of either of the chlorobutenes during distillation. Furthermore, the pure products prepared at different times uniformly had the constants recorded. In all Podbielniak distillations the boiling point always rose very sharply between 66° and 80°.

Physical properties of the chlorobutenes.—Table 3 lists the values recorded in the literature and those obtained by us for the boiling point and index of refraction of the three possible addition products of hydrogen chloride to butadiene. Studies of mixtures of pure 3-chloro-1-butene and pure 1-chloro-2-butene indicate that the indices of refraction are a linear function of composition ($\pm 1\%$).

Isomerization experiments with pure chlorobutenes.—Anhydrous hydrogen chloride was condensed on the chlorobutene (0.05 to 0.5 mole) at about $-100°$; the reaction tubes were then sealed off. At the end of the stated time interval, the hydrogen chloride was removed and the chlorobutene mixture was isolated and analyzed as in the addition experiments. In about one-third of the isomerization experiments the hydrogen chloride was removed, and the product was first distilled at reduced pressure. In the remaining experiments both distillations were at atmospheric pressure. In about one-fourth of the isomerization experiments, analysis was made by both index of refraction and Polbielniak distillation. It is to be noted that at no time did the discrepancy between the two methods exceed 3%. In the remaining experiments, analysis was by index of refraction only.

SUMMARY

1. The addition of hydrogen chloride to butadiene has been investigated in the absence of a solvent at $-80°$ and room temperatures, and in glacial acetic acid at room temperatures.

2. The product is uniformly 75 to 80 per cent. of 3-chloro-1-butene by 1,2 addition and 20 to 25 per cent. of 1-chloro-2-butene by 1,4 addition.

3. The effects of hydrogen chloride and ferric chloride on the rate of rearrangement of the addition products, and on the composition of the equilibrium mixture, have been determined, and have been shown not to invalidate the conclusion drawn above.

4. The treatment of crotyl alcohol with cuprous chloride and anhydrous hydrogen chloride at $-20°$ gives a mixture containing 75 to 85 per cent. of 1-chloro-2-butene and 15 to 25 per cent. of 3-chloro-1-butene.

RECENT BOOKS

DIE CHEMIE DER METALL-ORGANISCHEN VERBINDUNGEN. *Erich Krause and Aristid von Grosse.* Gebrüder Borntraeger, Berlin, Germany, 1937, xvi + 926 pp., 38 figs., 16 x 25 cm. Price, RM. 55.20; bound, RM. 58.50

Several splendid books [Schmidt (Runge); Courtot; Goddard and Goddard] on the general subject of organometallic compounds have appeared in recent years.

The book by Krause and von Grosse is most welcome particularly because of the extensive personal investigations by these authors in several branches of the field of organometallic chemistry. Although the book was started long years ago, its completion was delayed by the untimely death of Krause and other interruptions. The literature has been surveyed up to January 1936.

The authors make no claim to completeness, and have touched lightly on some fields, particularly those concerned with organic compounds of magnesium, mercury and antimony, because of the availability of special treatises in those branches. The inordinate expanse of work in organometallic chemistry compels any author to pick and choose material to be crowded into one volume. Others would probably have preferred to see relatively greater space devoted to the more reactive organometallic compounds and less space to organic compounds of metalloids like arsenic. For example, it will come as a surprise to organic chemists to find not a single mention of the classical studies on the reactions of organomagnesium compounds with conjugated systems.

Some of the sections with the number of pages devoted to them are: organomagnesium halides, 47; organozinc compounds, 8; organoalkali compounds, 41; organomercury compounds, 64; Group III metals, 58; Group IV metals, 81; Group V elements, 224 (of which 143 pages are devoted to arsenicals); Group VI elements, 46; Group VII elements, 23 (practically all of which is concerned with the preparation and properties of alkyl and aryl halides); general properties of organometallic or organo-element compounds, 43; organometallic compounds of transitional elements, 23; sub-Group I elements, 13; experimental manipulation of sensitive organometallic compounds, 10.

When one considers the wealth of material compressed into a single volume, it is not surprising to find occasional and varied errors as well as some inconsistencies. For example, the President-elect of the American Chemical Society is variously referred to as C. A. Kraus, C. H. Kraus, Ch. Kraus, Ch. A. Kraus, C. Kraus and Kraus. The reviewer having just emerged from an onerous task of editing finds himself ready and anxious to waive consideration of what after all are essentially minor errors.

We heartily recommend the volume as the best general survey of organometallic compounds.

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[CONTRIBUTION FROM THE ESSO LABORATORIES OF THE STANDARD OIL DEVELOPMENT CO.]

HIGH-MOLECULAR-WEIGHT HYDROCARBONS AND HYDROCARBON INTERMEDIATES

L. A. MIKESKA, C. F. SMITH, AND E. LIEBER

Received September 20, 1937; revised January 3, 1938

In a previous publication from this laboratory on "Chemical Structure of Lubricating Oils"[1] several series of synthetic hydrocarbons of high molecular weight were described and characterized as to their viscosities, viscosity indices, aniline points and other physical properties of interest to oil chemists and petroleum technologists.

By comparing the physical properties of one hydrocarbon with those of another, the two differing from each other in only one structural factor, as for instance, straight versus branched chain, saturated versus unsaturated side chains, or aromatic versus hydroaromatic nuclei, it was possible to draw certain definite conclusions with respect to the effect of various structural factors on the physical properties of the hydrocarbons involved. It was further concluded on the basis of the physical properties of these synthetic products, that it is possible, in a general way, to deduce the probable structure of the hydrocarbons constituting the various types of widely differing lubricating oils.

For the sake of brevity, the scope of the paper referred to above was limited to the consideration of the physical properties of the hydrocarbons in question. Description of the methods of preparation of the final products as well as of the intermediates was, therefore, postponed.

It is the purpose of this paper and of others to follow to give a concise description of the synthetic methods employed, as well as a complete description and characterization of not only the ultimate materials sought but of the intermediates as well.

This paper covers monosubstituted derivatives of benzene, diphenyl and naphthalene.

The numbers in brackets appearing after the names of the hydrocarbons described in this paper refer to the numbers connoting the individual hydrocarbons in Table I in the original article.[1]

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[1] MIKESKA, *Ind. Eng. Chem.*, **28**, 970 (1936).

EXPERIMENTAL

General method of procedure.—All the aromatic hydrocarbons were prepared by reduction of the appropriate ketones or else by the action of Grignard reagents on the ketones with subsequent dehydration of the resulting alcohols. The ketones were in turn prepared by condensing, in the presence of aluminum chloride, acid chlorides of the required structure and molecular weight with carefully chosen aromatic groups.

Reduction of the ketones to the corresponding hydrocarbons by Clemmensen's method was found unsatisfactory, probably because of their insolubility in aqueous hydrochloric acid. Modification of Clemmensen's method, however, yielded the desired hydrocarbons in a state of high purity in a relatively short time.

Naphthenes, insofar as they were studied, were obtained by exhaustive hydrogenation of the corresponding aromatics in the presence of platinum oxide.[2]

Inasmuch as the general method of preparation of the intermediate ketones was essentially the same in all cases, the preparation of only one ketone, stearophenone, is given in full detail. In the case of other ketones, only deviations from the standard procedure are recorded.

Stearophenone.—Stearophenone was prepared by the method of Claus and Häfelin.[3]

Three hundred grams of pure molten stearic acid (m.p. 69°C.) was poured with stirring into 75 g. of phosphorus trichloride. The mixture was heated to 70° for half an hour, during which time the phosphorous acid formed settled to the bottom of the flask as a viscous colorless liquid. The stearyl chloride was carefully decanted into 800 cc. of benzene contained in a two-liter Erlenmeyer flask.

The flask was then immersed in an ice bath, and cooled to 0°, whereupon 150 g. of aluminum chloride was added slowly with occasional shaking of the flask. When all the aluminum chloride had been added, which took about an hour, the flask was removed from the ice bath and allowed to stand overnight at room temperature. The next day the reaction product was poured into a mixture of ice and 200 cc. of concentrated hydrochloric acid.

The ketone was thus precipitated in snow-white crystalline form. The mixture was transferred into a separatory funnel, and extracted with ether. The extract was washed free of hydrochloric acid and dried over sodium sulfate. When dry, the filtered solution was saturated with ammonia gas to precipitate the small amount of unchanged stearic acid carried over. On removal of the ammonium stearate by filtration, the filtrate was treated with an equal volume of methyl alcohol and cooled to 0°. The ketone crystallized immediately. The first crop consisted of 236 g. of snow-white product melting at 63.5–64.5°. An additional 15 g., melting at 59–63°, was obtained from the mother liquors. In another experiment 887 g. of the pure ketone was obtained from 900 g. of stearic acid. Claus and Häfelin[3] give the melting point as 59°, while N. K. Adam[4] gives the melting point as 63–63.5°.

Anal. Calc'd for $C_{24}H_{40}O$: C, 83.64; H, 11.70.
Found: C, 83.67; H, 11.66.

In some cases, especially if the starting products are not quite pure, the original ketone may be obtained in various shades of darkness. In that case, it is better to distill the raw material before the recrystallization as outlined above.

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[2] Voorhies and Adams, *J. Am. Chem. Soc.*, **44**, 1397 (1922).

[3] Claus and Häfelin, *J. prakt. Chem.*, [2], **54**, 399 (1896).

[4] Adam, *Proc. Roy. Soc.* (London), **A103**, 684 (1923).

Octadecylbenzene [*I*].—Octadecylbenzene was originally prepared by F. Krafft[5] by the action of sodium on a mixture of bromobenzene and octadecyl iodide. Our product was obtained by reduction of stearophenone to the corresponding hydrocarbon.

Early attempts to reduce the ketone to hydrocarbon by Clemmensen's[6] method were abandoned because of the long time required to bring the reaction to completion. A modification of Clemmensen's method which worked satisfactorily for all the ketones used was finally adopted.

About a three-inch layer of mossy zinc amalgamated according to Clemmensen's directions with 5% mercuric chloride, was placed in a two-liter Erlenmeyer flask, provided with an inlet tube for hydrogen chloride, and a return condenser. Two hundred fifty grams of stearophenone dissolved in 750 cc. of xylol was then added, followed by just enough concentrated hydrochloric acid to cover only about half of the zinc amalgam. This left the xylol solution of the stearophenone in direct contact with the other half of the zinc amalgam.

The mixture was then heated to boiling. During refluxing, hydrogen chloride was passed into the reaction mixture to replace the hydrochloric acid consumed. After a contact time of seven hours, the product was isolated, and was distilled under 5 mm. pressure. The product distilled at 220–235° and weighed 228 g. The residue consisted of 30 g. of heavy oil. The distillate was redissolved in xylol and placed in contact with zinc-mercury amalgam as before for 7 hours. On isolation and distillation under 4 mm. pressure, 190 g. of a product boiling at 195–205° and melting at 33° was obtained.

Anal. Calc'd for $C_{24}H_{42}$: C, 87.19; H, 12.81.
Found: C, 87.27; H, 12.73.

Krafft reported the melting point of octadecylbenzene as 36°. The product described above was, therefore, recrystallized twice from ether. In this state of purity it melted at 35–36°.

Octadecylcyclohexane [*II*].—Ninety grams of octadecylbenzene dissolved in 200 cc. of glacial acetic was placed in a bottle securely attached to a shaker. A half-gram of platinum oxide catalyst[2] was then added. The bottle was evacuated, and filled with hydrogen from an attached reservoir of the latter. Shaking was continued until the calculated amount of hydrogen had been absorbed. The product was then poured into water, extracted with ether, washed free of acetic acid and dried over sodium sulfate. The residue obtained on removal of the ether was distilled under 4 mm. pressure. The entire product passed over between 204 and 210°. Without any further purification it melted at 40°.

Anal. Calc'd for $C_{24}H_{48}$: C, 85.61; H, 14.39.
Found: C, 85.59; H, 14.46.

*Heptadecyl-*n*-butylphenylcarbinol.*—One and a half grams of dry activated magnesium was suspended in 15 cc. of dry ether. To this was then added 4 g. of *n*-butyl chloride. When the reaction had gone to completion, the Grignard reagent was added slowly to 15 g. of stearophenone in 60 cc. of dry ether. The solution was refluxed under a return condenser for about two hours, whereupon it was poured into ice and hydrochloric acid. The carbinol was extracted with ether, washed free of hydrochloric acid, and dried over sodium sulfate. On removal of the ether, the

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[5] KRAFFT, *Ber.*, **19**, 2982 (1886).

[6] CLEMMENSEN, *ibid.*, **46**, 1837 (1913).

residue was distilled under 2 mm. pressure. The entire product distilled between 235 and 240°.

The carbinol has a tendency to dehydrate on distillation. If a pure product is desired, only a small quantity must be distilled at a time. The yields obtained are practically quantitative.

Anal. Calc'd for $C_{28}H_{50}O$: C, 83.49; H, 12.52.
Found: C, 83.46; H, 12.49.

(1-Butyloctadecen-1-yl)benzene [*5*].—A mixture of 336 g. of heptadecyl-*n*-butylphenylcarbinol, prepared as described in the preceding experiment was dehydrated by heating with 100 g. of oxalic acid for 1.5 hours at 180° to 200° in an atmosphere of carbon dioxide. The product was then dissolved in ether and washed free of oxalic acid. On removal of the solvent, 275 g. of a product distilling at 210–220° under 1 mm. pressure was obtained. Analysis showed that the product still contained some oxygen. The product was, therefore, redissolved in dry ether and treated as before with a Grignard solution prepared from 15 g. of magnesium and 45 g. of *n*-butyl chloride. The carbinol was isolated, and was treated once more with oxalic acid at 180° to 200°. On distillation, 241 g. of a colorless oil boiling between 205° and 210° under 1 mm. pressure was obtained.

Anal. Calc'd for $C_{28}H_{48}$: C, 87.41; H, 12.59.
Found: C, 87.73; H, 12.61.

(1-Butyloctadecyl)benzene [*4*].—One hundred sixty grams of (1-butyloctadecen-1-yl)benzene and 100 cc. of glacial acetic acid contained in a thick glass bottle was treated with 0.2 g. of platinum oxide catalyst. The air in the bottle was replaced with a measured amount of hydrogen. Absorption of the hydrogen began immediately on shaking. The volume of hydrogen consumed was measured as the absorption continued. When one molecule (3200 cc. at 26° and 257 mm.) had been absorbed, the hydrogenation was discontinued.

A little alcohol was added to coagulate the platinum catalyst, which was then filtered off. The filtrate was poured into water, extracted with ether, washed, and dried over sodium sulfate. On removal of the solvent, 193 g. of product boiling at 200–201° under 1 mm. pressure was obtained. On recrystallizing twice from ether, the product melted at 38°.

Anal. Calc'd for $C_{28}H_{50}$: C, 86.95; H, 13.05.
Found: C, 86.90; H, 13.05.

Heptadecyl biphenyl ketone.—One hundred grams of stearic acid was converted into stearyl chloride as described in the preparation of stearophenone. The chloride was then added to a solution of 55 g. of biphenyl in 200 cc. of carbon bisulfide. The solution was cooled to 0°, whereupon 50 g. of aluminum chloride was added little by little. The reaction mixture was then allowed to stand at room temperature overnight.

The next day the reaction solution was poured into ice and hydrochloric acid, whereupon a voluminous snow-white precipitate was obtained. The product was thoroughly washed with water to remove hydrochloric acid and inorganic salts, and finally dried in the air. The product was then washed several times with ether, in which it is insoluble, in order to remove unchanged stearic acid, and was finally recrystallized from chloroform. When pure, the ketone melted at 106–107°.

Anal. Calc'd for $C_{30}H_{44}O$: C, 85.63; H, 10.56.
Found: C, 85.55; H, 10.60.

Octadecylbiphenyl [*40*].—Two hundred fifty grams of heptadecyl biphenyl ketone was reduced with zinc-mercury amalgam exactly as described for octadecylbenzene.

After the second reduction the product was isolated, and was distilled under 5 mm. pressure, under which conditions it boiled at 270–275°. A yield of 178 g. was obtained. On recrystallization from chloroform, the hydrocarbon melted at 79–81°.

Anal. Calc'd for $C_{30}H_{46}$: C, 88.60; H, 11.40.
Found: C, 88.40; H, 11.38.

(1-Butyloctadecen-1-yl)biphenyl [*41*].—*n*-Butylmagnesium chloride solution was prepared in the usual manner from 40.7 g. of dry magnesium, 122 g. of *n*-butyl chloride and 400 cc. of dry ether. This was added slowly to a suspension of 326 g. of heptadecyl biphenyl ketone in 1200 cc. of dry ether. The product, which was isolated in the usual way, consisted of 464 g. of semi-crystalline material. Without any further purification, the product was dehydrated with oxalic acid as described in previous experiments. On distillation under 7 mm. pressure, 312 g. of distillate boiling at 300–310° was obtained.

The distillate was re-treated with *n*-butylmagnesium chloride, with subsequent dehydration by means of oxalic acid. The product was isolated as usual, and was finally heated to 150° under 7 mm. pressure to insure the removal of the last traces of solvents. The residue, of which 297 g. was obtained, consisted of a practically colorless viscous oil which solidified partially on prolonged standing at room temperature.

Anal. Calc'd for $C_{34}H_{52}$: C, 88.62; H, 11.38.
Found: C, 88.49; H, 11.31.

(1-Butyloctadecyl)biphenyl [*42*].—The reduction of (1-butyloctadecen-1-yl)-biphenyl was carried out in every respect as described for the reduction of (1-butyloctadecen-1-yl)benzene. After distillation, the product was recrystallized from ether. When pure, it melted at 41.5–43°C.

Anal. Calc'd for $C_{34}H_{54}$: C, 88.24; H, 11.76.
Found: C, 88.45; H, 11.82.

(1-Butyloctadecyl)bicyclohexyl [*46*].— The procedure employed in the preparation of the bicyclohexyl derivative was in every respect similar to the procedure used in the preparation of octadecylcyclohexane. The product, consisting of a colorless oil, distilled at 255–260° under a pressure of 1 mm.

Anal. Calc'd for $C_{34}H_{66}$: C, 85.97; H, 14.03.
Found: C, 86.38; H, 13.97.

Heptadecyl naphthyl ketone.—Heptadecyl α-naphthyl ketone was first prepared by Ryan and Nolan[7] by the action of α-naphthylmagnesium bromide on the nitrile of stearic acid. Our product was prepared by the action of stearyl chloride on naphthalene in the presence of aluminum chloride, in carbon bisulfide solution.

Our method of procedure was essentially the same as that recently reported by Seidel and Engelfried[8] except in so far as the final stages of purification are concerned.

Six hundred grams of pure stearic acid was converted into stearyl chloride by treatment with 150 g. of phosphorus trichloride. The stearyl chloride was decanted from the phosphorous acid formed into a solution of 290 g. of naphthalene in 800 cc. of carbon bisulfide. The mixture was cooled to 0°, whereupon 300 g. of aluminum chloride was added with cooling and occasional shaking. When all the chloride had been added, the flask was taken out of the ice bath and the mixture was allowed to stand at room temperature overnight. The next day the solution was decomposed with ice and hydrochloric acid. The ketone was extracted with ether, washed, dried, and the solvent was removed. The residue was taken up with fresh ether and

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[7] RYAN AND NOLAN, *Proc. Roy. Irish Acad.*, **B30**, 1 (1912).

[8] SEIDEL AND ENGELFRIED, *Ber.*, **69**, 2584 (1936).

saturated with ammonia to remove unchanged stearic acid. Ammonium stearate was then removed by filtration, the ether was removed by evaporation and the residue was distilled under 3 mm. pressure. The entire product, 690 g., distilled at 240–260°.

The product was then dissolved in 1200 cc. of ether. On addition of 1200 cc. of methyl alcohol the product crystallized in a snow-white form, and melted at 54.5–56°. No attempt was made to separate the two isomers.

Anal. Calc'd for $C_{28}H_{42}O$: C, 85.21; H, 10.73.
Found: C, 85.46; H, 10.58.

(1-Butyloctadecen-1-yl)naphthalene [*18*].—Two hundred eighty-six grams of heptadecyl naphthyl ketone was dissolved in 900 cc. of dry ether. This was then heated for four hours with *n*-butylmagnesium chloride prepared from 20 g. of magnesium and 70 g. of *n*-butyl chloride.

The carbinol was then isolated in the usual way by decomposition with dilute hydrochloric acid. On removal of the solvent, 295 g. of crystalline material was obtained.

No attempt was made to purify the carbinol. The product was dehydrated by heating with 50 g. of oxalic acid for 1.5 hours at 180–200° in an atmosphere of carbon dioxide. On recovery of the olefin the product was retreated with *n*-butylmagnesium chloride and finally with oxalic acid as before. The olefin was finally distilled under 3 mm. pressure; 215 g. of the product boiling between 232° and 240° was obtained. It consisted of a practically colorless viscous oil.

Anal. Calc'd for $C_{32}H_{50}$: C, 88.39; H, 11.61.
Found: C, 88.41; H, 11.52.

(1-Butyloctadecyl)naphthalene [*19*].—Fifty grams of (1-butyloctadecen-1-yl)-naphthalene was treated with hydrogen in glacial acetic acid in the presence of platinum oxide catalyst[2] until one mole of hydrogen had been absorbed. The catalyst was then removed by filtration, the product was dissolved in ether, washed free of acetic acid, and dried over sodium sulfate. On removal of the solvent, the residue distilled at 200–201° under 2 mm. pressure. On recrystallization from ether, the product melted at 38°.

Anal. Calc'd for $C_{32}H_{52}$: C, 86.95; H, 13.05.
Found: C, 86.90; H, 13.03.

Heptadecyl tetrahydronaphthyl ketone.—The ketone was prepared by the action of molecular proportions of stearyl chloride on tetralin in carbon bisulfide solution in the presence of aluminum chloride exactly as described for the corresponding naphthalene derivative. On removal of the unchanged stearic acid the product was distilled under 2 mm. pressure; 333 g. of ketone boiling between 255–263° was obtained from 300 g. of stearic acid and 145 g. tetralin.

On crystallization from acetone, the ketone melted at 49.5–50°.

Anal. Calc'd for $C_{28}H_{46}O$: C, 84.38; H, 11.62.
Found: C, 84.41; H, 11.64.

Octadecyltetrahydronaphthalene [*31*].—One hundred grams of heptadecyl tetrahydronaphthyl ketone was reduced with zinc-mercury amalgam exactly as described for octadecylbenzene. After the reduction, the product was isolated and distilled under 4 mm. pressure; 66 g. of product distilling at 237–275° was obtained. The product was analyzed without any further purification.

Anal. Calc'd for $C_{28}H_{48}$: C, 87.41; H, 12.59.
Found: C, 87.41; H, 12.58.

Octadecyldecahydronaphthalene [*37*].—Fifty grams of octadecyltetrahydronaphthalene was treated with hydrogen at room temperature in glacial acetic acid in the presence of platinum oxide. When three moles of hydrogen had been absorbed the reaction was interrupted, and the catalyst was removed by filtration. The filtrate was dissolved in ether, washed free of acetic acid, and dried over sodium sulfate. On addition of methyl alcohol to the filtrate the product crystallized. It was recrystallized from a mixture of methyl alcohol and ether. A colorless crystalline product which melted at 43–47° was obtained.

Anal. Calc'd for $C_{28}H_{54}$: C, 86.07; H, 13.93.
Found: C, 85.94; G, 13.94.

(1-Butyloctadecen-1-yl)tetrahydronaphthalene [34].—Four hundred grams of heptadecyl tetrahydronaphthyl ketone was converted into the ethylene derivative in a manner in every respect analogous to the preparation of (1-butyloctadecen-1-yl)-naphthalene. After the second treatment with *n*-butylmagnesium chloride and oxalic acid, the product was isolated in the usual way, and was distilled under 4 mm. pressure; 405 g. of the olefin, a viscous colorless oil boiling at 263–264°, was obtained.

Anal. Calc'd for $C_{32}H_{54}$: C, 87.59; H, 12.41.
Found: C, 87.63; H, 12.39.

(1-Butyloctadecyl)tetrahydronaphthalene [33].—The saturation of the ethylenic product was carried out exactly as described in the preparation of (1-butyloctadecyl)naphthalene. When the required volume of hydrogen had been absorbed, the catalyst was removed by filtration, the filtrate was dissolved in ether, washed free of acetic acid and dried over sodium sulfate. On removal of the sodium sulfate and ether, the residual oil was distilled under 2 mm. pressure. The entire product distilled at 235–245°.

Anal. Calc'd for $C_{32}H_{56}$: C, 87.19; H, 12.81.
Found: C, 87.22; H, 12.72.

(1-Butyloctadecyl)decahydronaphthalene [39].—The procedure employed in the preparation of (1-butyloctadecyl)decahydronaphthalene was in every respect analogous to the procedure used in the preparation of octadecyldecahydronaphthalene. When the required amount of hydrogen had been absorbed, the product was isolated and distilled under 3 mm. pressure. The entire product, consisting of a viscous colorless oil, distilled at 240–245°.

Anal. Calc'd for $C_{32}H_{62}$: C, 86.00; H, 14.00.
Found: C, 85.88; H, 14.18.

SUMMARY

The preparation of fifteen hydrocarbons of high molecular weight, and of their intermediates is described. Inasmuch as the physical properties usually given for hydrocarbons have been recorded in a previous publication, they are not included in this paper. The melting points of products melting above room temperature as well as the approximate boiling points of most of the compounds described are given.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, PURDUE UNIVERSITY]

THE PREPARATION AND PROPERTIES OF SOME ESTERS OF 2-METHYL-2-METHOXYPROPANOL*

LEWIS E. THOMAS WITH R. E. NELSON

Received January 12, 1938

2-Methyl-2-methoxypropanol was recently made available in this laboratory.[1] A search of the literature revealed that the lower fatty acid esters of 2-methyl-2-methoxypropanol had never been prepared. Inasmuch as their structural formulas indicate a possible use as selective solvents, it seemed desirable to undertake their preparation and the determination of their physical properties. The three compounds prepared were 2-methyl-2-methoxypropyl acetate, 2-methyl-2-methoxypropyl propanoate, 2-methyl-2-methoxyproprpyl butanoate.

EXPERIMENTAL

2-Methyl-2-methoxypropyl acetate.—One-tenth mole of 2-methyl-2-methoxypropanol was added drop-wise connected to one-tenth mole of acetic anhydride containing a few drops of sulfuric acid. Stirring was effected by means of a mercury-sealed mechanical stirrer, and temperature was maintained at 55–60° by immersion of the flask in an oil bath heated by a Bunsen burner. Stirring was continued for 3.5 hours after complete addition of the 2-methyl-2-methoxypropanol.

The reaction mixture was allowed to stand 144 hours before rectification on a modified Podbielniak column. The desired product boiled at 58–58.5° under 15 mm. pressure. A 73.7% yield was obtained.

In a second preparation the acetic anhydride (0.4 mole) and sulfuric acid mixture was added drop-wise to the 2-methyl-2-methoxypropanol (0.4 mole), and the temperature was maintained at 65°–70°. Stirring was continued for 3 hours after complete addition of the acetic anhydride and sulfuric acid. The reaction mixture stood for 45 hours before rectification. The product boiled at 58°–58.5° C. under 15 mm. pressure. A 65.8% yield was obtained.

The lower yield in the second run is probably attributable to the shorter reaction time.

Two carbon determinations on the product, 2-methyl-2-methoxypropyl acetate, by the wet method[2] gave 57.4 ± 0.1%, as compared with a theoretical value of 57.49%. The boiling point, refractive index, and density are tabulated.

2-Methyl-2-methoxypropyl propanoate.—The reaction between 0.5 mole of 2-

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* Abstract of a Master's Thesis presented to the Faculty of the Graduate School of Purdue University by Lewis E. Thomas.

[1] SPARKS AND NELSON, *J. Am. Chem. Soc.*, **58**, 671 (1936).

[2] POLLARD AND FORSEE, *Ind. Eng. Chem.*, *Anal. Ed.*, **7**, 77 (1935).

methyl-2-methoxypropanol and 0.5 mole of propanoic anhydride was carried out in the manner already described. Stirring was continued for 2.5 hours after complete addition of the anhydride. The temperature was maintained at 85–90°. The reaction mixture was allowed to stand for 162 hours before rectification. The product boiled at 78–78.5° under a pressure of 20 mm. A 90% yield was obtained.

Two carbon determinations on this product by the wet method[2] gave 60.1 ± 0.1%, as compared with a theoretical value of 59.97%. The boiling point, refractive index, and density are tabulated.

2-Methyl-2-methoxypropyl butanoate.—A mixture of 1.0 mole of butanoic acid and a few drops of concentrated sulfuric acid was added drop-wise to 0.5 mole of 2-methyl-2-methoxypropanol. Stirring was continued for 2.5 hours after complete addition of the sulfuric and butanoic acids. The temperature was maintained at 85–90°. After 160 hours the mixture was rectified by means of a modified Podbielniak column; the product boiled at 87.5–88° under 20 mm. pressure. A 72.4% yield was obtained.

TABLE

PHYSICAL CONSTANTS OF 2-METHYL-2-METHOXYPROPANOL ESTERS

ESTER	n_D^{20}	B. P. (733.69 mm.)	d_4^{25}
Acetate	1.4113	162.7–162.8°	0.9327
Propanoate	1.4150	176.1–176.2°	0.9463
Butanoate	1.4187	193.4–193.5°	0.9602

Two carbon determinations on this product by the wet method[2] gave 62.1 ± 0.1%, as compared with a theoretical value of 62.07%. The boiling point, refractive index, and density are tabulated.

SUMMARY

1. A method is described for the preparation of 2-methyl-2-methoxypropyl ethanoate, 2-methyl-2-methoxypropyl propanoate, and 2-methyl-2-methoxypropyl butanoate.

2. Conditions for carrying out the reactions and yields of products are given.

3. Some physical properties of the products have been determined.

[CONTRIBUTION NO. 128 FROM THE DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF TEXAS]

KETO ETHERS. III. β-HALOGENOETHOXYETHYL ALKYL KETONES DERIVED FROM ETHYLENE BROMOHYDRIN

JOE HALLER CLARK* WITH HENRY R. HENZE

Received January 20, 1938

There has been in progress in this laboratory in recent years a series of investigations concerning the synthesis and properties of simple aliphatic compounds, chiefly of the bifunctional type. Thus, there have been studied the preparation of α-chloro ethers by the method of Henry[1], the conversion of such ethers into alkoxy nitriles according to Gauthier's[2] procedure, and the utilization of these nitriles in the synthesis of the corresponding keto ethers by the method of Blaise[3] as modified by Behal and Sommelet.[4] Although many α-chloro ethers[5] have been obtained, according to the method mentioned above, from unsubstituted alcohols, few compounds of this type have been procured from chlorine-substituted alcohols.[6,7] Likewise, even fewer unsubstituted alcohols have been converted into α-bromo ethers,[8] and a survey of the literature reveals that bromine-substituted alcohols have never been utilized in this manner.

It was the purpose of this investigation to attempt the utilization of ethylene bromohydrin in the synthesis of an α-chloro ether by the method of Henry.[1] Should this synthesis prove successful, it was planned next to convert the chloro ether so obtained into the corresponding nitrile by action of cuprous chloride.[2] This reaction was of particular interest since, although Lingo,[6] and Allen and Henze[7], with similarly constituted β-chloro compounds, had observed no formation of dinitriles, Henry[9] had reported

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* From a thesis presented by Joe Haller Clark to the Graduate School of the University of Texas in partial fulfillment of the requirements for the degree of Master of Arts, June, 1937.

[1] HENRY, *Bull. l'acad. roy. méd. Belg.*, [3], **25**, 439–440 (1893).

[2] GAUTHIER, *Compt. rend.*, **143**, 831–832 (1906).

[3] BLAISE, *ibid.*, **132**, 38 (1901).

[4] BÉHAL AND SOMMELET, *ibid.*, **138**, 89 (1904).

[5] LINGO, "A Bibliography of the Preparations, Properties and Uses of Chloroalkyl Ethers," Library, Dept. of Chemistry, University of Texas, **1935**.

[6] LINGO, Thesis, University of Texas, **1936**.

[7] ALLEN WITH HENZE, *J. Amer. Chem. Soc.*, **59**, 540–542 (1937).

[8] BLAIR AND HENZE, *ibid.*, **54**, 399–401 (1932).

[9] HENRY, *Bull. soc. chim.*, [2], **44**, 458 (1885).

replacement of the β bromine atom in an otherwise unsubstituted ether by the action of potassium cyanide. Moreover, although repeated attempts have been made in this laboratory to bring about interaction between α-chloro ethers and either potassium or sodium cyanide, absolutely no evidence of reaction has been observed. Finally, should the brominated ether nitrile result, it was hoped to utilize it in preparing a new series of brominated ether ketones.

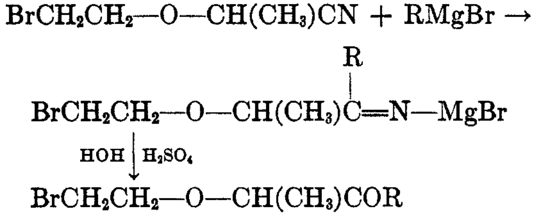
The preparation of α-chloroethyl β-bromoethyl ether was successful, as

$$3\ \mathrm{BrCH_2CH_2OH + (CH_3CHO)_3 + 3\ HCl = 3\ H_2O +}\ 3\ \mathrm{CH_3CHCl{-}O{-}CH_2CH_2Br}$$

was its conversion into α-(β-bromoethyoxy)propionitrile. From the latter,

$$\mathrm{CH_3CHCl{-}O{-}CH_2CH_2Br + CuCN = CuCl + CH_3CH(CN){-}O{-}CH_2CH_2Br}$$

by means of the Grignard reaction, there have been obtained nine α-(β-bromoethoxy)ethyl alkyl ketones. In an attempt to prepare α-(β-bromoethoxy)ethyl methyl ketone from methylmagnesium iodide and the nitrile, replacement of the bromine atom was observed, in a type of reaction previously reported from this laboratory,[7] and the α-(β-iodoethoxy)-ethyl methyl ketone isolated represents the first iodo alkoxy ketone prepared in an essentially pure state. The desired bromo alkoxy ketone was produced smoothly by the interaction of the nitrile with methylmagnesium bromide.



$$\mathrm{BrCH_2CH_2{-}O{-}CH(CH_3)CN + RMgBr} \rightarrow \mathrm{BrCH_2CH_2{-}O{-}CH(CH_3)\overset{R}{\overset{|}{C}}{=}N{-}MgBr} \xrightarrow[\mathrm{H_2SO_4}]{\mathrm{HOH}} \mathrm{BrCH_2CH_2{-}O{-}CH(CH_3)COR}$$

EXPERIMENTAL

Preparation of α-chloroethyl β-bromoethyl ether.—Two hundred fifty grams (2 moles) of ethylene bromohydrin and 88 g. of paraldehyde (2 moles calculated as acetaldehyde) were brought together in a flask of 500 cc. capacity. Immediately after the alcohol and aldehyde were mixed a rise in temperature of about one degree was noted, and the mixture assumed a brilliant yellow color. After two or three minutes, however, the yellow color faded and the temperature of the mixture dropped about three degrees. The heat effect is probably due to hemiacetal formation.[10] The flask was fitted with a mechanical stirrer, and was immersed in an ice-bath while its

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[10] **Leslie**, Thesis, University of Texas, **1934**.

contents were being saturated with dry hydrogen chloride. Three and one-half hours were required for saturation, continued passage of the gas beyond this time always resulted in a decrease in the yield of chloro ether obtained.

The lower etherial layer was separated from the acidic, aqueous layer formed and dried for two hours over anhydrous calcium chloride. Aëration of the crude halogenated ether under diminished pressure caused the colorless liquid to assume a bright yellow color. Fractionation at reduced pressure resulted in the collection of 260 g. of colorless material distilling between 65° and 72° at a pressure of 10 mm., representing a yield of 69% of the theoretical. Repeated fractionation yielded α-chloroethyl β-bromoethyl ether as a colorless, mobile liquid of rather pungent, but not unpleasant odor when freshly distilled. This ether is extremely susceptible to hydrolysis. B.p. 84.2° (corr.)/37 mm.; n_D^{20} 1.4770; d_4^{20} 1.5095; γ_4^{20} 34.87 dynes/cm.; $[R]$ calc'd 34.95; $[R]$ found 35.09; P calc'd 298.3; P found 301.8; Molal free surface energy $[\gamma(M/d)^{2/3}]$ 868.0 ergs.

Anal. Calc'd for total halogen content; substance, 0.1940 g., 0.2066 g.
Calc'd for C_4H_8BrClO: AgBr + AgCl, 0.3427 g., 0.3649 g.
Found: 0.3408 g., 0.3624 g.

α-(β-Bromoethoxy)propionitrile.—To 130 g. of dry cuprous cyanide, a 10% excess over the amount theoretically required, was added slowly with vigorous stirring 230 g. of α-chloroethyl β-bromoethyl ether diluted with 150 cc. of anhydrous benzene. (Anhydrous ether was also tried as a diluent but the yield was less satisfactory.) A considerable amount of heat was evolved, resulting in the rapid refluxing of the solvent. The mixture was stirred without heating for one hour, then filtered from the cuprous salts, and the benzene was removed at very low pressure. Distillation of the residual liquid produced 121.3 g. of nitrile, equivalent to a yield of 56%, which distilled between 76°/4 mm. and 85°/6 mm. After the sixth redistillation: b.p. 69° (corr.)/3 mm.; n_D^{20} 1.4618; d_4^{20} 1.4182; γ_4^{20} 37.89 dynes/cm.; $[R]$ calc'd 34.52; $[R]$ found 34.49; P calc'd 307.9; P found 311.5; Molal free surface energy 950.0 ergs.

Anal. Calc'd for C_5H_8BrNO: Br, 44.89; N, 7.87.
Found: Br, 44.85, 45.01; N, 7.70.

Although the mixture of cuprous salts, produced in the preparation of this nitrile, was carefully examined for the presence of bromide, the latter was not identified. Likewise, no evidence of the formation of a dinitrile was obtained. Hence, the β-substituted bromine atom did not react with cuprous cyanide.

Preparation of the keto ethers.—The method of Béhal and Sommelet[4] for preparing alkoxy ketones from alkoxy nitriles was applied successfully to the synthesis of the β-halogenoethoxyethyl alkyl ketones. In general, and with the exception of the methyl ketone member of the series, the appropriate alkylmagnesium bromide was prepared under anhydrous conditions and treated with α-(β-bromoethoxy)propionitrile diluted with 4 to 5 volumes of absolute ether. The reaction product was stirred for 30 minutes and, after standing from 6 to 8 hours, was decomposed by addition of 200 to 250 cc. of ice-cold, 10% sulfuric acid; the brilliant, yellow-colored ether solution was separated, washed with sodium carbonate solution, dried over anhydrous sodium sulfate, and fractionated under a pressure of 2 to 6 mm. until the product was sufficiently pure. The bromo keto ethers were obtained as limpid oils having a faintly rancid odor. All keto ethers were colorless when freshly and carefully fractionated, but usually turned yellow to yellow-green in color after relatively short standing. None of the ketones was appreciably soluble in water, but all were readily soluble in the usual organic solvents such as ethyl alcohol, acetone, ether, benzene and chloroform.

In an attempt to prepare the simplest member of this series by the interaction of α-(β-bromethoxy)propionitrile and methylmagnesium iodide, there resulted an oily, yellow-colored liquid which contained iodine, but not bromine. In view of the experience of one of us[7] with the replacement of chlorine by iodine as a result of the action of methylmagnesium iodide on α-1,3-dichloroisopropoxypropionitrile, it seemed probable that an analogous reaction, resulting in the substitution of iodine for bromine, had occurred. All the physical properties of, and analytical data for, the purified keto ether substantiate its identity as being α-(β-iodoethoxy)ethyl methyl ketone. This ketone is relatively stable and was obtained in 61% yield. B.p. 82° (corr.)/2 mm.; n_D^{20} 1.5022; d_4^{20} 1.6042; γ^{20} 37.13 dynes/cm.; [*R*] calc'd 44.36; [*R*] found 44.55; *P* calc'd 371.1; *P* found 372.5; Molal free surface energy 1052.4 ergs.

Anal. Calc'd for $C_6H_{11}IO_2$: I, 52.43. Found: I, 52.73, 52.74.

TABLE I

BROMO KETO ETHERS DERIVED FROM ETHYLENE BROMOHYDRIN

$BrCH_2CH_2-O-CH(CH_3)COR$

−R	B.P.		n_D^{20}	d_4^{20}	γ^{20} (DYNES /CM.)	FREE SUR-FACE ENERGY (ERGS)	YIELD, %
	°C. (Corr.)	Mm.					
$-CH_3$	63.5	2.0	1.4625	1.3551	34.75	954.4	57
$-CH_2CH_3$	91.0	6.5	1.4615	1.3099	34.13	1004.3	71
$-CH_2CH_2CH_3$	82.5–83.0	2.5	1.4615	1.2603	33.02	1041.1	55
$-CH(CH_3)_2$	80.0–81.0	2.5	1.4589	1.2544	32.55	1029.5	46
$-CH_2CH_2CH_2CH_3$	102.0–102.5	4.0	1.4611	1.2198	32.26	1082.6	62
$-CH_2CH(CH_3)_2$	91.0–92.0	2.0	1.4589	1.2180	31.33	1052.4	48
$-CH(CH_3)CH_2CH_3$	89.5	2.5	1.4611	1.2234	32.47	1087.6	44
$-CH_2CH_2CH_2CH_2CH_3$	119.5–120.0	5.5	1.4619	1.1916	32.26	1142.6	71
$-CH_2CH_2CH(CH_3)_2$	100.5–101.0	2.5	1.4600	1.1868	31.07	1103.4	43

TABLE II

BROMO KETO ETHERS DERIVED FROM ETHYLENE BROMOHYDRIN

$BrCH_2CH_2-O-CH(CH_3)COR$

−R	BROMINE, %		MOLECULAR REFRACTION		Δ[*R*]	PARACHOR		Δ*P*
	Calc'd	Found	Calc'd	Found		Calc'd	Found	
$-CH_3$	40.97	40.75	39.33	39.61	+0.28	348.1	349.4	+1.4
$-CH_2CH_3$	38.22	38.27	43.94	43.84	−0.10	387.1	385.8	−1.3
$-CH_2CH_2CH_3$	35.82	35.99	48.56	48.62	+0.06	426.1	424.4	−1.7
$-CH(CH_3)_2$	35.82	35.93	48.56	48.61	+0.05	426.1	424.8	−1.3
$-CH_2CH_2CH_2CH_3$	33.70	33.81	53.18	53.35	+0.17	465.1	463.3	−1.8
$-CH_2CH(CH_3)_2$	33.70	33.68	53.18	53.22	+0.04	465.1	460.6	−4.5
$-CH(CH_3)CH_2CH_3$	33.70	33.55	53.18	53.20	+0.02	465.1	462.7	−2.4
$-CH_2CH_2CH_2CH_2CH_3$	31.82	31.82	57.80	57.93	+0.13	504.1	502.3	−1.8
$-CH_2CH_2CH(CH_3)_2$	31.82	31.67	57.80	57.96	+0.16	504.1	499.7	−4.4

The semicarbazone of the above-mentioned iodo ketone separated in the form of large, prismatic crystals, and was precipitated from benzene solution by addition of petroleum benzine; m.p. 121.2° (corr.) decomp.

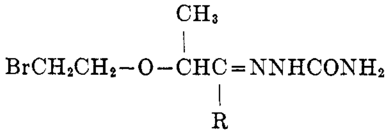
Anal. Calc'd for $C_7H_4IN_3O_2$: I, 42.43; N, 14.05.
Found: I, 42.22, 42.20; N, 13.99.

The synthesis of the desired α-(β-bromoethoxy)ethyl methyl ketone was accomplished by using methylmagnesium bromide as the Grignard reagent. All attempts to prepare a bromo keto ether derived from *tert.*-butyl bromide yielded oily material decomposing upon distillation under pressure of less than 2 mm.

Semicarbazones were readily formed from all the bromo keto ethers containing *n*-alkyl substituents and, also, from the isoamyl member of the series. It proved impossible to prepare semicarbazones, or other derivatives of the carbonyl group, from the isobutyl, *sec.*-butyl and isopropyl derivatives; this behavior is in strict agreement with similar experience in the instance of the corresponding α-1,3-dichloroisopropoxyethyl ketones.[7]

TABLE III

SEMICARBAZONES OF α-(β-BROMOETHOXY)ETHYL ALKYL KETONES



$$BrCH_2CH_2{-}O{-}\underset{\displaystyle R}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}HC{=}NNHCONH_2$$

–R	M.P. °C. (CORR.)	NITROGEN, %	
		Calc'd	Found
$-CH_3$	124.5(dec.)	16.67	16.67
$-CH_2CH_3$	99.5	15.79	15.70
$-CH_2CH_2CH_3$	112.5	15.00	15.20
$-CH_2CH_2CH_2CH_3$	117.7	14.28	14.15
$-CH_2CH_2CH_2CH_2CH_3$	106.3	13.63	13.72
$-CH_2CH_2CH(CH_3)_2$	83.0	13.63	13.73

Boiling points were taken with short, accurately calibrated Anschütz thermometers, and the properly corrected values are reported for the bromo keto ethers. The melting points of the semicarbazones, too, are reported as corrected values. Surface tensions of the liquids were measured by means of Cassel's[11] precision capillarimeter at 20°. Densities were determined by means of a modified U-shaped tube weighing 1.3862 grams and having a volume of 1.8332 cc. The data resulting from the determination of physical constants, the values derived from the latter by calculation, and such information as was obtained through analysis of the bromo keto ethers have been tabulated in Tables I and II. The data resulting from a study of the semicarbazones of the bromoethoxyethyl alkyl ketones are recorded in Table III.

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[11] CASSEL, *Chem.-Ztg.*, **53**, 479 (1929).

SUMMARY

1. The preparation of α-chlorethyl β-bromoethyl ether represents the initial utilization of a bromine-substituted alcohol in the chloro ether synthesis according to Henry's method.

2. In the conversion of the dihalogenated ether into α-(β-bromoethoxy)propionitrile no evidence of the formation of a dinitrile was observed.

3. Nine examples of a new type of brominated keto ether have been obtained. Whereas normal, iso- and secondary alkyl groups are represented in this series, the simplest example of the tertiary alkyl type could not be synthesized from the corresponding nitrile by means of the Grignard reaction.

In an attempted preparation of α-(β-bromoethoxy)ethyl methyl ketone from methylmagnesium iodide, replacement of bromine by iodine was observed and the corresponding β-iodo ketone was isolated and identified.

4. Although semicarbazones, useful in the identification of keto ethers, were prepared from each of the normal alkyl homologs and, as well, from the isoamyl member of the series, none was obtained from the isopropyl, *sec*-butyl and isobutyl ketones.

5. For the series of compounds included in this investigation, as for those of analogous compounds previously synthesized in this laboratory, the molecular refraction was found to be far more sensitive than the parachor as an index of purity.

[Contribution from the Department of Pharmacology, Vanderbilt University School of Medicine]

DIACYLUREAS. I. PREPARATION AND PROPERTIES OF DIACYLUREAS DERIVED FROM NORMAL ALIPHATIC ACIDS*

ROGER W. STOUGHTON

Received December 16, 1937; revised February 18, 1938

A survey of the literature on the simple open-chain diacylureas revealed only a few scattered references, many of which were in the patent literature and gave only meager details as to the chemistry and hypnotic action of these compounds. In view of their structural position, intermediate between the monoacylureas and the barbiturates, it was believed that the preparation and study of these diacylureas would be of interest. The present communication deals with compounds derived from normal aliphatic acids and the correlation of their properties with the existing data. The preparation of compounds derived from other acids is already under way and will form the basis of later communications.

$$2\,RCONH_2 + COCl_2 \rightarrow RCONHCONHCOR + 2\,HCl \qquad (1)$$

$$RCONCO + R'CONH_2 \rightarrow RCONHCONHCOR' \qquad (2)$$

$$RCONHCONH_2 + R'COCl \xrightarrow{(H_2SO_4)} RCONHCONHCOR' + HCl \qquad (3)$$

$$2\,RCOOC_2H_5 + NH_2CONH_2 \xrightarrow{(NaOC_2H_5)} \qquad (4)$$

$$RCONHCONHCOR + 2\,C_2H_5OH$$

$$2\,R_2C(OH)CONHCN + 3\,H_2O \rightarrow \qquad (5)$$

$$R_2C(OH)CONHCONHCOC(OH)R_2 + 2\,NH_3 + CO_2$$

The synthetic methods that have been reported parallel those employed in the preparation of the barbiturates. Schmidt[1] first prepared diacetylurea in 1872 by the condensation of two molecules of acetamide with one molecule of phosgene (equation 1). Later Bornwater[2] substituted oxalyl chloride for phosgene, but this modification probably is applicable to only

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* Presented before the Division of Medicinal Chemistry at the Ninety-fourth Meeting of the American Chemical Society, Rochester, N. Y., September 10, 1937.

[1] Schmidt, *J. prakt. Chem.*, **5**, 63 (1872).

[2] Bornwater, *Rec. trav. chim.*, **31**, 118 (1912).

a few amides.[3] A second method, consisting of the reaction of an acylisocyanate with an amide (equation 2), was suggested by Scholl,[4] and has received some recognition in the patent literature.[5] Another method[6,7] consists in the reaction of an acid halide or anhydride with a monoureide in the presence of a catalyst (equation 3). This procedure was found to be the most convenient laboratory method for the preparation of the normal aliphatic diureides and was the one employed in this investigation. It also makes possible the preparation of compounds with two different acyl groups attached to the urea nucleus.

The only successful attempt to prepare a diacylurea by the condensation of an ester with urea in the presence of sodium ethylate (equation 4) was reported by Clemmensen and Heitman.[8] They prepared a series of diureides derived from α-hydroxy acids. Several monoureides[9] have been synthesized by this method, but no unsubstituted diacylureas; yet it is the most common procedure for the preparation of barbiturates. When the ethyl esters of the normal aliphatic acids were condensed with urea by means of sodium ethylate, the only products ever isolated were the corresponding monoureide, amide, and sodium cyanate. Furthermore, it was found that the diacylureas derived from the normal aliphatic acids reacted in the cold with sodium ethylate to form an ethyl ester and the monoacylurea, which was further decomposed on heating to sodium cyanate and the amide. Thus it appears that the normal aliphatic esters, unlike hydroxy acid esters, condense with urea to form only a monoureide under the conditions ordinarily employed. Clemmensen and Heitman[8] also reported the preparation of the hydroxy acylureas by the hydrolysis of the corresponding acylcyanamides (equation 5).

In the present investigation eighteen new diureides, with both similar and dissimilar acyl groups attached to the urea part of the molecule, have been prepared in good yields by the reaction of an acid chloride with a monoacylurea in benzene solution with a little sulfuric acid as catalyst. It has been assumed that each of the two acyl groups is always attached to a different nitrogen atom in the urea to form a symmetrical compound, and no evidence indicating that this is not true has been obtained. Diacetylurea obtained from acetamide and phosgene or oxalyl chloride was found to be identical with that obtained from the acetylation of mono-

[3] Figee, *ibid.*, **34**, 289 (1915).

[4] Scholl, *Ber.*, **23**, 3515 (1890).

[5] Bayer & Co., *German Patent* 286,760, Dec. 6, 1913.

[6] Werner, *J. Chem. Soc.*, **109**, 1120 (1916).

[7] Bayer & Co., *British Patent* 132,795, Sept. 16, 1919.

[8] Clemmensen and Heitman, *Am. Chem. J.*, **40**, 280 (1908); **42**, 319 (1909).

[9] (*a*) Stendal, *Compt. rend.*, **196**, 1810 (1933); (*b*) Jerzmanowska-Sienkiewiczowa, *Roczniki Chem.*, **15**, 510 (1935).

acetylurea. Werner[6] has suggested that the second acyl group is attached to the oxygen atom to form a pseudo-ureido ester. Several of the compounds with different acyl groups in the same molecule have been prepared by treating the two different monoureides with the proper acyl chloride, and identical compounds were always obtained; for instance, the compound obtained by treating acetylurea with butyryl chloride was the same as the one obtained from butyrylurea and acetyl chloride. Consequently, such a pseudo-structure is very unlikely.

These compounds are soluble in alkali, as would be expected in view of the presence of enolizable hydrogen, but are almost immediately hydrolyzed to a monoureide and a fatty acid salt. Clemmensen and Heitmann[8] claimed that the di(α-hydroxyacyl)ureas were stable to cold alkali and acted only as dibasic acids. The *N*,*N*′-diacylureas appeared to go into solution on the addition of one equivalent of alkali, but it was difficult to obtain quantitative data on this point because of the rapidity of hydrolysis. Acids promoted hydrolysis at a slower rate than alkalies, but even boiling water hydrolyzed these compounds slowly.

Unlike the barbituric acids, these simple diacylureas decompose readily on heating and could not be satisfactorily distilled. Werner[6] decomposed diacetylurea and, from the products isolated, he postulated decomposition as occurring simultaneously in two different ways (equations 6 and 7).

$$\mathrm{RCONHCONHCOR \rightarrow RCONH_2 + RCN + CO_2} \qquad (6)$$

$$\mathrm{3\ RCONHCONHCOR \rightarrow 3\ RCONHCOR + (HCNO)_3} \qquad (7)$$

This result has been confirmed by a quantitative study of the decomposition of *sym*-dienanthylurea. Carbon dioxide was evolved, enanthonitrile distilled off, and from the residue enanthamide, dienanthamide, and cyanuric acid were obtained. The amounts of these various products were in excellent stoichiometrical agreement with the above equations and indicated that in this case approximately two-thirds of the original material had decomposed according to equation 6 and the remaining third according to equation 7.

These nineteen diacylureas form a series of compounds which it is interesting to compare with the barbituric acids. The most striking difference is the instability of the former towards alkali and heat. However, this is a difference in degree only, as the barbituric acids are themselves hydrolyzed more or less rapidly to form monoureides. This instability towards alkali made it impossible to prepare the simple diacylureas by using a basic condensing agent, as is the common procedure with the malonylureas. It should be pointed out that the diureides of other types of acids would be expected to have properties somewhat different from those of the ones described here. This has already been demonstrated in the case of compounds derived from the α-hydroxy acids. It is also interesting to note that these N,N'-diacylureas were found to give no color test with the cobaltous acetate reagent of Koppanyi[10] as do the barbituric acids.

Because of the similarity of these compounds to the barbiturates, their pharmacological properties are of interest. No study of the hypnotic properties of the previously known diacylureas was found in the literature, but the patents[5,7] on the bromine-substituted derivatives contain the statement that such compounds possess hypnotic and sedative properties. Consequently, preliminary studies of these new substances as hypnotics have been made and are reported briefly here. When administered intravenously to white mice, the most active compounds (those containing eight to ten carbon atoms) had a minimum effective dose of from eighty to one hundred and fifty milligrams per kilogram of body weight. As a group they had an activity comparable with that of the common barbiturates, but the anesthesia produced was very short, averaging only one or two minutes. They were, however, inactive when administered intraperitoneally or orally except after large doses. Even though these compounds appear *in vitro* to be stable at the pH of blood, they must be destroyed very rapidly in the body to be such very short-acting hypnotics. On oral administration, large doses must be given in order that the drug may be absorbed more rapidly than it is destroyed. The anesthesia produced, in contradistinction to that of many of the barbituric acids, is characterized by marked analgesia and absence of excitement. More complete pharmacological studies will be reported elsewhere at a later date.

EXPERIMENTAL

Propionylurea.—In a large test-tube, stoppered with a cork loosely fitted with a thermometer, were placed 6 g. of urea, 15 cc. of propionic anhydride, 5 cc. of propionic acid and 0.4 cc. of concentrated sulfuric acid. This was placed in a beaker of boiling water and stirred occasionally with the thermometer. Soon after the urea dissolved, the temperature rose to 105–110°, and in five minutes crystals began to appear in the solution. Fifteen minutes after the appearance of the first crystal, the temperature had dropped to 98°; the test-tube was cooled, and 20 cc. of water was added. After standing one hour in the ice-box, the crystals were collected, washed with saturated sodium bicarbonate solution and finally with water. This gave 8.5 g. (78%) of a pure product.

n-*Butyrylurea.*—In a 200-cc. 3-necked flask, fitted with mechanical stirrer, reflux condenser, and dropping funnel, were placed 10 g. (0.17 mole) of urea, 25 cc. of benzene and two drops of concentrated sulfuric acid. This was warmed on a steam bath and to the boiling solution 15 g. (0.15 mole) of *n*-butyryl chloride was added

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[10] Koppanyi, Dille, Murphy, and Krop, *J. Am. Pharm. Assoc.*, **23**, 1074 (1934).

drop-wise over a period of fifteen minutes. After four hours of refluxing the mixture was cooled, and the solid that had formed was collected and washed with a little petroleum ether. The product was transferred to a beaker, and washed, first with sodium bicarbonate solution, and then with water.

The other monoacylureas were prepared exactly as described above by substituting a proportionate amount of the proper acyl chloride. In all cases the product obtained after washing with sodium bicarbonate was pure enough to be used in the synthesis of diacylureas. The analytical samples were recrystallized from *n*-butyl alcohol. The yields varied from 75 to 85 per cent., based on the amount of acyl chloride used. The physical properties of these compounds are recorded in Table I.

Preparation of sym-*diacylureas.*—This procedure is illustrated by the preparation of *N*-acetyl-*N'*-propionylurea.

In a 200-cc. flask fitted with a reflux condenser were placed 12 g. (0.1 mole) of propionylurea, 30 cc. of dry benzene, 10 g. (0.13 mole) of acetyl chloride, and three drops of concentrated sulfuric acid, and the mixture was refluxed on a steam bath. Hydrogen chloride was evolved and the ureide slowly dissolved. After four to six hours' heating, the evolution of hydrogen chloride ceased and a clear, straw-colored solution was obtained. This was cooled, diluted with 100 to 200 cc. of petroleum ether, and allowed to stand in the ice-box over night. The white solid that separated was collected, washed with a 10 per cent. sodium bicarbonate solution, and recrystallized.

TABLE I

PROPERTIES OF THE MONOACYLUREAS

UREA	M. P., °C., CORRECTED	FORMULA	PER CENT. NITROGEN	
			Calc'd	Found
Acetyl-[6]	216–217	$C_3H_6N_2O_2$	27.44	27.33
Propionyl-	210–211	$C_4H_8N_2O_2$	24.13	24.21
n-Butyryl-[11]	173–174	$C_5H_{10}N_2O_2$	21.53	21.32
n-Valeryl-	182–183	$C_6H_{12}N_2O_2$	19.43	19.45
n-Caproyl-	192–193	$C_7H_{14}N_2O_2$	17.71	17.76
n-Enanthyl-	191–192	$C_8H_{16}N_2O_2$	16.27	16.12
n-Caprylyl-[9a]	191–192	$C_9H_{18}N_2O_2$	15.04	14.97

[11] MOLDENHAUER, *Ann.*, **94**, 101 (1855).

All the diacylureas with the exception of the diacetylurea were prepared as above by substituting proportionate amounts of the proper acylurea and acyl chloride. Slightly better over-all yields were obtained in the case of those diureides with different acyl groups when the monoureide of the acid with the higher molecular weight was prepared first and then treated with the acyl halide of the lower molecular weight. Even with compounds in which both acyl groups were the same, satisfactory yields could be obtained only by isolating the intermediate monoacylurea rather than by trying to force the reaction through in one step. Yields of between 75 and 85 per cent. were obtained. When available, the acid anhydride could be substituted for the acid chloride, but the latter seemed preferable in most cases. The physical properties of these compounds are recorded in Table II.

They were all white crystalline substances, soluble in the common organic solvents but only slightly soluble in petroleum ether. Diacetylurea was soluble in water to the extent of 7 per cent. at 25°, and the aqueous solubility of the others decreased regularly as the molecular weight increased. The diacylureas were much more soluble, both in water and organic solvents, than the corresponding monoacylureas; for instance, monoacetylurea dissolved in water to the extent of only 2 per cent., and was only slightly soluble in hot alcohol. This difference was less noticeable in the compounds of higher molecular weight. These substances were soluble in dilute alkali but were almost immediately hydrolyzed by it to monoureides and salts of fatty acids. The acyl group with the smaller molecular weight was always hydrolyzed off more rapidly, and, therefore, compounds with larger acyl groups were slightly more stable than those with smaller. In cold water or dilute acids they appeared to be perfectly stable for several days but were hydrolyzed slowly on boiling. They were also slightly soluble in strong acids.

TABLE II

PROPERTIES OF THE DIACYLUREAS

UREA	M. P., °C., CORRECTED	SOLVENT FOR RECRYSTALLIZATION	FORMULA	PER CENT. NITROGEN	
				Calc'd	Found
sym-Diacetyl-[6]	154–155	50% Acetic acid	$C_5H_8N_2O_3$	19.44	19.29
N-Acetyl-*N*′-propionyl-	112–113	Benzene	$C_6H_{10}N_2O_3$	17.72	17.65
sym-Dipropionyl-	105–106	CCl_4	$C_7H_{12}N_2O_3$	16.27	16.18
N-Acetyl-*N*′-butyryl-	80–81	Bz.–pet. ether	$C_7H_{12}N_2O_3$	16.27	16.43
N-Butyryl-*N*′-propionyl-	96–97	Dil. methanol	$C_8H_{14}N_2O_3$	15.05	14.90
N-Acetyl-*N*′-valeryl-	66–67	Bz.–pet. ether	$C_8H_{14}N_2O_3$	15.05	15.10
sym-Dibutyryl-	86–87	Bz.-pet. ether	$C_9H_{16}N_2O_3$	13.99	14.01
N-Propionyl-*N*′-valeryl-	82–83	Dil. methanol	$C_9H_{16}N_2O_3$	13.99	14.03
N-Acetyl-*N*′-caproyl-	85–86	Bz.-pet. ether	$C_9H_{16}N_2O_3$	13.99	13.93
N-Butyryl-*N*′-valeryl-	75–76	Dil. methanol	$C_{10}H_{18}N_2O_3$	13.08	13.08
N-Caproyl-*N*′-propionyl-	92–93	Dil. methanol	$C_{10}H_{18}N_2O_3$	13.08	13.09
N-Acetyl-*N*′-enanthyl-	80–81	Bz.–pet. ether	$C_{10}H_{18}N_2O_3$	13.08	13.20
sym-Divaleryl-	83–84	Bz.–pet. ether	$C_{11}H_{20}N_2O_3$	12.27	12.21
N-Butyryl-*N*′-caprylyl-	66–67	Pet. ether	$C_{11}H_{20}N_2O_3$	12.27	12.30
N-Enanthyl-*N*′-propionyl-	82–83	Bz.–pet. ether	$C_{11}H_{20}N_2O_3$	12.27	12.37
N-Acetyl-*N*′-caproyl-	92–93	50% Acetic acid	$C_{11}H_{20}N_2O_3$	12.27	12.26
N-Caproyl-*N*′-valeryl-	80–81	Bz.–pet. ether	$C_{12}H_{22}N_2O_3$	11.56	11.65
sym-Dicaproyl-	87–88	Bz.–pet. ether	$C_{13}H_{24}N_2O_3$	10.93	10.98
sym-Dienanthyl-	89–90	Bz.–pet. ether	$C_{15}H_{28}N_2O_3$	9.85	9.94

Decomposition of dibutyrylurea with sodium ethylate.—To a solution of 0.4 g. of sodium in 25 cc. of absolute alcohol was added 3.5 g. of dibutyrylurea, and the mixture was allowed to stand over night at room temperature. An equal volume of anhydrous ether was added and the solution poured into an ice-hydrochloric acid mixture. The ether layer was separated, dried with calcium chloride, and distilled. After the ether had been removed, 1.5 g. of a liquid boiling at 118–121° was collected and identified as ethyl butyrate. The aqueous layer was concentrated under a vacuum and 0.4 g. of dibutyrylurea was isolated from it.

In a second experiment the solution was heated for two hours, and a white precipitate of sodium cyanate was obtained. On evaporation of the alcoholic mother liquors, a small amount of butyramide separated. The same products were also obtained when monobutyryl urea was refluxed with sodium ethylate. These experiments were repeated with dicaproylurea with similar results.

Pyrolysis of sym-*dienanthylurea.*—Five grams of *sym*-dienanthylurea was placed in a small distilling flask fitted with a thermometer, so placed that the bulb was below the surface of the liquid, and a side-arm test-tube that served as a receiver. This was connected with two U-tubes filled with soda lime. The flask was heated in a mineral-oil bath at such a rate that the inside temperature reached 230° in two hours. At 80° the compound melted to a clear colorless liquid; at 160–170° small bubbles of carbon dioxide were evolved, the liquid became cloudy, and a grayish precipitate deposited; and at 200° a colorless liquid began to collect in the receiver. At the end of two hours the mixture was cooled slightly and the last traces of volatile material were swept over by the application of a vacuum to the system.

TABLE III

HYPNOTIC ACTIVITY

UREA	NO. OF CARBON ATOMS	MINIMUM EFFECTIVE DOSE		
		Intravenously g./kg.	Intraperitoneally g./kg.	Orally g./kg.
sym-Diacetyl-	5	2.3	>3.0	—
N-Acetyl-*N*′-propionyl-	6	1.5	2.3	—
sym-Dipropionyl-	7	0.35	1.5	—
N-Acetyl-*N*′-butyryl-	7	0.23	1.2	—
N-Butyryl-*N*′-propionyl-	8	0.17	1.1	—
N-Acetyl-*N*′-valeryl-	8	0.15	1.0	—
sym-Dibutyryl-	9	0.11	0.8	3.5
N-Propionyl-*N*′-valeryl-	9	0.14	0.9	—
N-Acetyl-*N*′-caproyl-	9	0.09	0.7	—
N-Butyryl-*N*′-valeryl-	10	0.10	0.9	4.5
N-Caproyl-*N*′-propionyl	10	—	1.2	—
N-Acetyl-*N*′-enanthyl-	10	0.08	0.6	3.0
sym-Divaleryl-	11	—	1.1	6.0
N-Butyryl-*N*′-caproyl-	11	—	1.2	—
N-Enanthyl-*N*′-propionyl-	11	—	2.5	—
N-Acetyl-*N*′-caprylyl-	11	—	>3.0	—
N-Caproyl-*N*′-valeryl-	12	—	>3.0	—
sym-Dicaproyl-	13	—	>3.0	—
sym-Dienanthyl-	15	—	>3.0	—

The soda lime tubes were weighed, and it was found that 0.5 g. of carbon dioxide had been absorbed. The volatile liquid was redistilled, and 1.3 g. of material boiling at 181–184° was obtained. This proved to be enanthonitrile, and was characterized by the formation of α-iminoheptylmercaptoacetic acid hydrochloride.[12] The nonvolatile residue within the flask, which had solidified on cooling, was treated with

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[12] CONDO, HINKEL, FASSERO, AND SHRINER, *J. Am. Chem. Soc.*, **59**, 231 (1937).

20 cc. of warm benzene. The grayish solid did not dissolve. It was recrystallized from water and 0.25 g. of a white solid, which was identified as cyanuric acid, was obtained. The benzene solution was diluted with petroleum ether and allowed to stand in the ice-box. A yield of 1.4 g. of a white solid, which proved to be crude enanthamide, was obtained. After recrystallization from benzene—petroleum ether mixture, it was obtained pure and melted at 95–96°. The original benzene-petroleum ether mother liquors were evaporated to dryness under a vacuum, and 1.5 g. of a cream-colored solid remained. After recrystallization from dilute methanol, fine colorless needles, which had a melting point of 92–93°, were obtained. This compound proved identical with the product obtained by refluxing enanthamide with enanthyl chloride, and was dienanthamide.

Anal. Calc'd for $C_{14}H_{27}NO_2$: N, 5.80. Found: N, 5.85.

These results indicate that approximately two-thirds of the original material decomposed as indicated by equation 6 and one-third as indicated by equation 7.

Pharmacological experiments.—Preliminary studies of these compounds as hypnotics have been made on male albino mice. Those members of this series which were soluble enough in water to allow a saline solution to be injected into the tail vein without using excessive quantities of fluid were administered intravenously. Secondly, all substances were tested intraperitoneally by injection of a 4 per cent. acacia emulsion. Finally, a 5 per cent. acacia emulsion of a few of the most active compounds was given orally by means of a stomach tube. Five or more mice were used at each dose level, and three or four levels close to the minimum effective dose were studied. The minimum effective dose was taken as that dose which would cause 50 per cent. of the animals to lose the ability to right themselves. Because of the small number of animals used, the results, as recorded in Table III, are approximate only, but accurate enough to give a general idea of the relative activity of these compounds.

The length of anesthesia varied greatly with the route of administration: On intravenous injection of a minimum effective dose of the more active compounds, anesthesia was induced at once but lasted only about one minute; on intraperitoneal injection, anesthesia was produced in three to five minutes and maintained for ten to fifteen minutes; while on oral administration the animals remained anesthetized for approximately one hour after an induction period of from five to fifteen minutes.

While no thorough study of the toxicity of these substances has been made, preliminary experiments with a few of the most active compounds indicated that the minimum lethal dose on intraperitoneal injection was two or three times greater than the minimum effective dose.

SUMMARY

(*1*) The available data on aliphatic diacylureas has been summarized.

(*2*) A series of nineteen diacylureas derived from normal aliphatic acids has been prepared by the reaction of acid chlorides with monoacylureas, and their physical and chemical properties have been studied. These compounds resemble the barbituric acids with the exception that they are hydrolyzed very rapidly by alkali and are unstable to heat.

(*3*) Compounds with eight to ten carbon atoms in the molecule are active hypnotics when administered intravenously, but are relatively inactive on oral administration.

[Contribution from the Chemical Laboratory of the University of California, Berkeley, California]

THE DISSOCIATION OF HYDROGEN IONS FROM THE SULFATES OF AMINOPHENYLBORIC ACIDS

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INTRODUCTION

The nomenclature of some derivatives of boric acid is anomalous. Phenylboric acid is $C_6H_5B(OH)_2$, not $C_6H_5OB(OH)_2$. After this anomaly normal nomenclature is used, and aminophenylboric acid is $NH_2C_6H_4B(OH)_2$. We shall call $B(OH)_2$ the boric acid group.

The relationships between the dissociation constants of the aminophenylboric acids have sufficient theoretical interest to warrant a comparison of their values amongst themselves and with the dissociation constants of phenylboric acid and aniline. Since all the factors that govern acidic and basic strength are not known, these comparisons must be made with considerable caution. We shall restrict our comparisons to those between acids and bases of similar types, in the same solvent, and at one temperature, and our discussion to what we believe to be the more important factors.

We measured the dissociation constants by a method equivalent to electrometric titration of the sulfate, which we shall treat as a dibasic acid. The pH numbers of solutions containing weighed quantities of the sulfates, neutralized to varying degrees with sodium hydroxide, were measured. The concentrations of the solutions varied between 0.02 N and 0.005 N.

From these measurements the first and second dissociation constants of the positive ions were calculated from the equations,

$$K_1 = \frac{(\mathrm{H}^+)\left[(\mathrm{Na}^+) + (\mathrm{H}^+) - \frac{k_w}{(\mathrm{H}^+)}\right]}{\mathrm{M} - \left[(\mathrm{Na}^+) + (\mathrm{H}^+) - \frac{k_w}{(\mathrm{H}^+)}\right]}$$

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* From a thesis in partial fulfillment of requirements for the degree of doctor of philosophy.

and

$$K_2 = \frac{(\mathrm{H}^+)\left[(\mathrm{Na}^+) + (\mathrm{H}^+) - \frac{k_w}{(\mathrm{H}^+)} - M\right]}{2\mathrm{M} - \left[(\mathrm{Na}^+) + (\mathrm{H}^+) - \frac{k_w}{(\mathrm{H}^+)}\right]}.$$

M is the molality of aminophenylboric acid in all its forms. It was obtained from the weight concentration and equivalent weight of the sulfate, the latter being determined from the titration curve of the first acidic hydrogen atom. As the first and second dissociation constants of aminophenylboric acid sulfates are widely separated the above equations and method of determining the equivalent weights are justifiable. When necessary the equation for K_1 was corrected for the concentration of bisulfate ion, using 1.2×10^{-2} for the second dissociation constant of sulfuric acid. Only measurements near the half neutralization points of the first and second dissociations were used for calculating K_1 and K_2.

The K's obtained in this way involve the activity of hydrogen ion and the concentrations of the other substances. They are, therefore, neither classical nor thermodynamic dissociation constants. But when determined for identical conditions they measure the relative acid strengths. In the range of concentrations and degrees of neutralization used, the values for aniline, phenylboric acid, and aminophenylboric acids show no trend great enough to be apparent above the erratic errors, so the values of K measure the relative strengths of the acids under practically identical conditions, *viz.* in aqueous solution about 0.01 N with respect to sodium sulfate.

To check accuracy, a determination of the dissociation constant of anilinium ion was made, starting with aniline sulfate. The value of 2.1×10^{-5} was obtained, which agrees well with the accepted value $k_w/k_b = 2.2 \times 10^{-5}$.

As acid solutions of the aminophenylboric acids are reduced by hydrogen in the presence of platinum, a hydrogen electrode could not be used in the acid range. Measurements in this range were made with a glass electrode, the hydrogen electrode being used for alkaline solutions. Over the short alkaline range in which both electrodes could be used, the two gave concordant results.

The benzoylaminophenylboric acids are too insoluble in water for aqueous solutions to be used for determinations of acidic strength.

The dissociation constants for these compounds in an alcohol-water mixture containing 25 per cent. alcohol by volume were determined, with a hydrogen electrode. This solvent was used for the determination of the dissociation constants of many boric acid derivatives by Branch, Yabroff and Bettman.[1] The equivalent weights were taken as those determined by titration to the phenolphthalein end-point in the presence of large amounts of mannitol.

The equivalent weights of the sulfates of ortho and meta aminophenylboric acids agreed well with the formula, $[C_6H_4B(OH)_2NH_3]^+{}_2 SO_4^{--}$, that of the para isomer with $[C_6H_4B(OH)_2NH_3]^+{}_2SO_4^{--} + 2H_2O$, those of ortho and meta benzoylaminophenylboric acids with $[C_6H_5CONHC_6H_4B(OH)_2]_2 - H_2O$, and that of the para with $C_6H_5CONHC_6H_4B(OH)_2$.[2]

RESULTS AND DISCUSSION

The results are summarized in Tables I and II. For the amine sulfates, the products of the two dissociation constants are listed in column 4. $\Delta P_k = (\log_{10}K_o - \log_{10}K)$ is a useful quantity for comparing the effect of groups on acid strength. An acid strengthening or negative group gives a negative ΔP_k value. For the ΔP_k of a first dissociation constant, K_o is taken as that of aniline sulfate, for a second dissociation constant $K_o = K_a$ of phenylboric acid in water,[1] and K_o for the products is the product of the dissociation constants of aniline sulfate and phenylboric acid. For the benzoyl derivatives K_o is taken as the dissociation constant of phenylboric acid in 25 per cent. alcohol.[1] These ΔP_k's are included in the tables.

Zwitter ions. For an amino acid the relationships between the various equilibria are given by the series of equations:

$$K_E = \frac{K_1 - K_{1A}}{K_{1A}} = \frac{K_{2A} - K_2}{K_2} = \frac{K_{1Z}}{K_1 - K_{1Z}} = \frac{K_2}{K_{2Z} - K_2} = \frac{K_{1Z}}{K_{1A}} = \frac{K_{2A}}{K_{2Z}},$$

in which K_E is the equilibrium constant of the reaction, true amino acid to zwitter ion, K_1 and K_2 are the measured dissociation constants, K_{1A} and K_{1Z} are the two dissociation constants of the positive ion forming the true amino acid and the zwitter ion respectively, K_{2A} is the dissociation constant of the true amino acid and K_{2Z} that of the zwitter ion.

These constants can be obtained by assuming K_{1A} to be equal to the hydrolysis constant of the ester of the positive ion[3] or K_{1Z} to the hydrolysis constant of the positive ion of the betaïne.[4]

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[1] BRANCH, YABROFF, AND BETTMAN, *J. Chem. Soc.*, **56**, 937 (1934).

[2] The formulas for the ortho and meta compounds agree with those found by SEAMAN AND JOHNSON, *J. Am. Chem. Soc.*, **53**, 711 (1931), who did not prepare the para isomers.

[3] EBERT, *Z. physik. Chem.*, **121**, 385 (1926).

[4] MIYAMOTO AND SCHMIDT, *Univ. California Pub. Physiol.*, **8**, 1 (1932).

Log $K_{2A[m-NH_2C_6H_4B(OH)_2]}$ approximately equals log $K_{a[C_6H_5B(OH)_2]}$, as the introduction of a meta amino group does not greatly change the strength of an acid.

$$\text{Log } K_{2Z[m-\overset{+}{N}H_3C_6H_4B(\overset{-}{O_2}H)]} = P + \log K_{a(C_6N_5\overset{+}{N}H_3)},$$

P being the effect of the borate ion group. As the negativity of the boric acid group is practically zero, *P* is approximately the effect of the work of

TABLE I

DISSOCIATION CONSTANTS OF THE SULFATES OF AMINOPHENYLBORIC ACID IN WATER AT 25°

SUBSTANCE	$K_1 \times 10^5$	$K_2 \times 10^{10}$	$K_1K_2 \times 10^{14}$	ΔP_{k_1}	ΔP_{k_2}	$\Delta P_{k_1k_2}$
Aniline sulfate	2.1	—	2.9	0	—	0
Phenylboric acid	—	13.7			0	
Sulfate of *o*-aminophenylboric acid	2.7	5.9	1.6	−0.11	0.37	0.26
Sulfate of *m*-aminophenylboric acid	3.5	15.4	5.3	−0.22	−0.05	−0.27
Sulfate of *p*-aminophenylboric acid	19.5	6.7	13.1	−0.97	0.31	−0.66

TABLE II

DISSOCIATION CONSTANTS OF THE BENZOYLAMINOPHENYLBORIC ACIDS IN 25 PER CENT· ALCOHOL AT 25°

SUBSTANCE	$K \times 10^{10}$	ΔP_{k_a}
Phenylboric acid	1.97	0
o-Benzoylaminophenylboric acid	4.47	−0.36
m-Benzoylaminophenylboric acid	5.84	−0.47
p-Benzoylaminophenylboric acid	2.9	−0.17

completely separating opposite charges situated with respect to each other as in $m - \overset{+}{N}H_3C_6H_4B(\overset{-}{O_2}H)$. Hence

$$\log K_E = \log K_{2A} - \log K_{2Z}$$

and approximately equals

$$P + \log \frac{K_{aC_6H_5B(OH)_2} \times K_{b(C_6H_5NH_2)}}{k_w}.$$

Similarly log $K_{E(m-NH_2C_6H_4COOH)}$ approximately equals

$$P' + \log \frac{K_{a(C_6H_5COOH)} \times K_{b(m-NH_2C_6H_4CO_2CH_3)}}{k_w},$$

P' being the effect on log $K_{A(m-\overset{+}{N}H_3C_6H_4CO_2CH_3)}$ of changing the group CO_2CH_3 to CO_2^-. P' is approximately the effect of the work of completely separating opposite charges situated with respect to each other as in $m - \overset{+}{N}H_3C_6H_4CO_2^-$. Obviously, P and P' are approximately equal, and within at least a factor of ten

$$K_{E[m-NH_2C_6H_4B(OH)_2]} = \frac{K_{E(m-NH_2C_6H_4COOH)} \times K_{aC_6H_5B(OH)_2} \times K_{b(C_6H_5NH_2)}}{K_{a(C_6H_5COOH)} \times K_{b(m-NH_2C_6H_4CO_2CH_3)}}.$$

$K_{E(m-NH_2C_6H_4COOH)}$ can be calculated from the dissociation constants of *m*-aminobenzoic acid and methyl *m*-aminobenzoate,[5] assuming $K_{1A} = K_{a(m-\overset{+}{N}H_3C_6H_4CO_2CH_3)}$.

Then

$$K_{E(m-NH_2C_6H_4COOH)} = \frac{(9 \times 10^{-4}) - (2.8 \times 10^{-4})}{2.8 \times 10^{-4}} = 2.2,$$

and

$$K_{E(m-NH_2C_6H_4B(OH)_2} = \frac{2.2 \times 1.4 \times 10^{-9} \times 4.6 \times 10^{-10}}{6.6 \times 10^{-5} \times 3.6 \times 10^{-11}} = 6 \times 10^{-}.$$

Similarly for *o*- and *p*-aminophenylboric acids K_E must be much smaller than the small values of K_E for *o*- and *p*-aminobenzoic acids. The true amino acids must be in great preponderance over the zwitter ions in aqueous solutions of the three aminophenylboric acids. The measured values K_1 and K_2 may be taken as, within experimental error, equal to K_{1A} and K_{2A} respectively.

In an amino acid the product $K_1 \cdot K_2 = K_{1A} \cdot K_{2A} = K_{1Z} \cdot K_{2Z}$. The difference between $K_1 \cdot K_2$ and the product of the hydrolysis constant of the parent amine and the dissociation constant of the parent acid ($\Delta P_{k_1k_2}$) is independent of zwitter-ion formation, and of any interaction of the groups in the neutral molecule. It measures the combined effects of the dipole of the acidic group on the charge in the positive ion, of the dipole of the amino group on the charge of the negative ion, of the interaction of the acidic group with the aminium-ion group in the positive ion, and of the interaction of the amino group with the ionized acidic group in the negative ion.

The $\Delta P_{k_1k_2}$ of an aminocarboxylic acid should have a much more negative value than that of the corresponding aminoboric acid, as the carboxyl group is much more negative than the boric acid group ($-B(OH)_2$). Thus for *m*-aminobenzoic acid, if Cummings'[5] values for its dissociation

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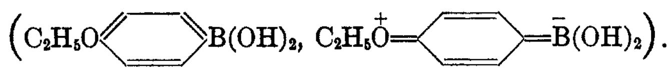
[5] Cummings, *Proc. Roy. Soc.*, **79**, 82 (1906).

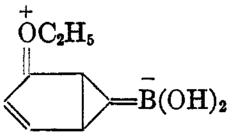
constants and the generally accepted values for those of benzoic acid and aniline are used, $\Delta P_{k_1k_2} = -1.01$, while for *m*-aminophenylboric acid, $\Delta P_{k_1k_2} = -0.27$.

The $\Delta P_{k_1k_2}$ values for the aminophenylboric acids are peculiar, in that the sign for the ortho compound is opposite to that for the other two isomers, and the numerical value of $\Delta P_{k_1k_2}$ for the para compound is greater than that for the meta isomer in spite of the greater separation of the groups. The significance of these facts is discussed later.

Resonance.—Branch, Yabroff, and Bettman[1] found that ortho and para ethoxyphenylboric acids are weaker than phenylboric acid while the meta isomer is stronger. They attributed these results to the opposing actions of the negativity of the ethoxy group and its resonance interaction with the boric acid group. The resonance involved is indicated by the formulas:



From the separation of charges in the quinoidal form it is obvious that this resonance is stronger in the undissociated acid than in its ion, and therefore it tends to reduce the strengths of the acids. This type of resonance is weak in the meta acid for the quinoidal form



has a high energy level, one of the bonds being between somewhat widely separated atoms. The meta acid is therefore stronger than either its ortho or para isomer. Owing to the weakness of the resonance and the negativity of the ethoxy group the meta acid is stronger than phenylboric acid.

This type of resonance is also possible in aminophenylboric acid, and similarly must be greatly reduced in the negative ions and the meta isomer. It cannot occur in the positive ions, the four bonds of the nitrogen atom being already satisfied. It therefore tends to make the first dissociation constants greater than that of anilinium ion, the second dissociation constants less than that of phenylboric acid, the first dissociation constant of the sulfates of *o*- and *p*-aminophenylboric acids greater than, and their second dissociation constants less than, the corresponding constants of the meta isomer.

These expected resonance effects are very apparent in both dissociation constants of the sulfate of *p*-aminophenylboric acid. Its first dissociation constant is much greater than that of its meta isomer, and than the K_a of anilinium ion, while its second dissociation is much smaller than that of its meta isomer and than the K_a of phenylboric acid. Similarly K_2 of the sulfate of *o*-aminophenylboric acid is less than K_2 of the meta isomer and than the K_a of phenylboric acid. On the other hand, hand, K_1 of the sulfate of *o*-aminophenylboric acid is anomalous in being smaller than that of its meta isomer.

Since this type of resonance is reduced rather than absent in the negative ion, but is impossible in the positive ion, it favors the negative ion over the positive ion. Hence it tends to make K_1K_2 for the ortho and para compounds greater than K_1K_2 for the meta compound and than $K_{a(\text{anilinium})} \times K_{a(\text{phenylboric acid})}$. This effect is observable in the para compound, but again the ortho isomer is anomalous, its $\Delta P_{k_1k_2}$ being positive.

Chelation.—The low values of K_1 and K_1K_2 for the sulfate of *o*-aminophenylboric acid show that there is some factor that stabilizes the positive ion with respect to the neutral molecule and the negative ion.

Many anomalies have been observed in the properties of ortho derivatives of benzene. Some of these have been attributed to the formation of chelate rings by an atom bridging the narrow gap between ortho groups. For example lack of hydroxyl infra-red bands in *o*-hydroxycarbonylbenzenes;[6] the anomalously high dissociation of salicylic acid;[7] and the anomalously low dissociation of *o*-nitrophenylboric acid.[8]

Chelation in the positive ion of *o*-aminophenylboric acid is a probable reason for its stability. In the only chelation possible the proton of the aminium ion binds the nitrogen to an oxygen atom. This implies the resonance, $(\overset{+}{H_3N}C_6H_4BO_2H_2,\ H_2NC_6H_4\overset{+}{B}O_2H_3)$. To both this theory and that of chelation of *o*-hydroxycarbonylbenzenes, the objection may be raised that the groups accepting the proton, $-B(OH)_2$ and $-COR$, respectively, are not sufficiently basic. However, the ability of the boric acid group to function in this way is greatly enhanced by the resonance that arises from the existence of a quinoidal form $\overset{+}{H_2N} = C_6H_4 = \overset{-+}{BO_2}H_3$, as the corresponding form is impossible in $\overset{+}{H_3N}C_6H_4BO_2H_2$. Similarly the ability of the carbonyl group to accept the proton from an *o*-hydroxyl group is enhanced by the resonance arising from the quinoidal form $O = C_6H_4 = C(OH)R$, as this is much more stable than the corresponding form $\overset{+}{HO} = C_6H_4 = \overset{-}{C}(O)R$, in which the proton is on the hydroxyl group.

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[6] HILBERT, WULF, HENDRICKS, AND LIDDEL, *Nature*, **135**, 147 (1935); *J. Am. Chem. Soc.*, **58**, 548 (1936).

[7] BRANCH AND YABROFF, *J. Am. Chem. Soc.*, **56**, 2568 (1934).

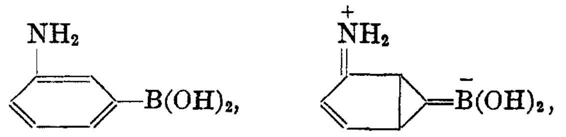
[8] BETTMAN, BRANCH, AND YABROFF, *ibid.*, **56**, 1865 (1934).

If this chelation is the correct explanation of the low value of K_1 in the ortho compound, it must be more energetic than the chelation of the neutral molecule which would result from the resonance between amino acid and zwitter ion forms. In an *o*-amino acid, such as this, the distance between the groups is such that one would expect the equilibrium between amino acid and zwitter ion to degenerate to resonance, and a chelate ring to form. This type of chelation should be stronger in *o*-aminobenzoic acid than in *o*-aminophenylboric acid, as benzoic acid is stronger than phenylboric acid. Consequently it is not surprising to find that K_1 for *o*-aminobenzoic acid is not anomalously low like that for *o*-aminophenylboric acid, the chelation of the positive ion being compensated by that of the neutral molecule.

Negativity.—We shall define the negativity of a substituent group as the property of the group whereby it affects the dissociation of a proton from another part of the molecule, when the arrangement of the charges in the group are not displaced by resonance interactions with other parts of the molecule. It is evident that this proviso is an idealization that is never rigorously achieved, and hence evidence concerning the negativity is always to some extent incomplete. The negativity of a group arises from the charges and electric dipoles inherent to the group. Since there is always some interaction between a group and the solvent, the negativity of a group strictly refers to the group in a particular solvent. The hydrogen atom is a convenient arbitrary zero of negativity.

The effect of a group on the strength of an aromatic acid most nearly measures negativity of the group, when it is in the meta position, for this position is the least favorable to resonance.

For the sulfate of *m*-aminophenylboric acid, $\Delta P_{k_1} = -0.22$. The boric acid group is acting as if it were a definitely negative group. But Bettman, Branch and Yabroff found ΔP_k for the boric acid group in *m*-carboxyphenylboric acid $= +0.01$. This discrepancy is too great for experimental error. As the resonance interaction of a boric acid with a carboxyl group is much less than with an amino group, the true negativity of the boric acid group is more accurately obtained from the dissociation of the *m*-carboxyphenylboric acid than from that of the sulfate of *m*-aminophenylboric acid, and is probably very nearly zero. The apparent negativity shown by the group in *m*-aminophenylboric acid is presumably due to the resonance,



which makes the boric acid group appear to be negative.

The ΔP_{k_2} of *m*-aminophenylboric acid is -0.05. The amino group is acting as a negative one. The resonance described above tends to make it act as a positive group. The conjugation of the amino group with the benzene ring charges the ring negatively, and so gives a pseudopositivity to the group. Zwitter ion formation has a similar effect. The result therefore shows a definite inherent negativity for the amino group. This agrees with the fact that hydrazine is a weaker base than ammonia, and the expected order of negativities, CH_3, NH_2, OH, F. However, Ebert[3] obtained 5.6×10^{-6} for K_{2A} of glycine, and Miyamoto and Schmidt[4] 4.4×10^{-6}. Both of these results make the amino group positive, and more so than the methyl and other alkyl groups. Miyamoto and Schmidt used 4.54×10^{-3}, 2.5×10^{-10}, and 1.85×10^{-8} for K_1, K_2, and the hydrolysis constant of the methyl ester ion, respectively. Had they not introduced the basic constant of betaine, but had been content with the assumption that K_{2A} = the hydrolysis constant of the methyl ester ion, and the equation $K_1 \cdot K_2 = K_{1A} \cdot K_{2A}$, they would have obtained $K_{2A} = 6.1 \times 10^{-5}$. This value is greater than K_a of acetic acid, and makes the amino group negative. Edsall[9] has calculated the values of K_{2A} for several amino fatty acids, and finds that they are greater than the dissociation constants of the corresponding unsubstituted acids, and hence that the amino group acts as a negative group in amino fatty acids. His value for glycine is 5×10^{-5}.

The aminobenzoic acids are like the aminophenylboric acids in that they have very similar resonances. Cummings[5] has measured the constants necessary to determine K_{2A} for *m*-aminobenzoic acid. It is doubtful whether he fully corrected for the nearness of the values of K_1 and K_2. We redetermined the necessary constants, finding significant variation only in K_2.

Our method was the electrometric titration of the sulfates of *m*-aminobenzoic acid and methyl *m*-aminobenzoate using a hydrogen electrode. For K_1 and K_2 values of the amino acid we solved by means of successive approximations the simultaneous equations

$$K_1 = \frac{(\mathrm{H}^+)^2[(\mathrm{H}^+) + (\mathrm{Na}^+) + (\mathrm{HSO}_4^-)]}{M[(\mathrm{H}^+) + 2\mathrm{K}_2] - [(\mathrm{H}^+) + \mathrm{K}_2][(\mathrm{H}^+) + (\mathrm{Na}^+) + (\mathrm{HSO}_4^-])}$$

and

$$K_2 = \frac{(\mathrm{H}^+)\{[\mathrm{K}_1 + (\mathrm{H}^+)](\mathrm{H}^+) + (\mathrm{Na}^+) + (\mathrm{HSO}_4^-)] - \mathrm{K}_1 M\}}{K_1\{2\mathrm{M} - [(\mathrm{H}^+) + (\mathrm{Na}^+) + (\mathrm{HSO}_4^-)]\}}$$

The bisulfate ion concentration equals

$$\frac{0.5M(\mathrm{H}^+)}{1.2 \times 10^{-2} + \mathrm{H}^+},$$

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[9] Edsall, *ibid.*, **55**, 2337 (1933).

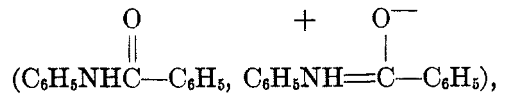
1.2×10^{-2} being the second dissociation constant of sulfuric acid. The equations were set up from points near half neutralization of the first and second acidic hydrogen atoms.

Cummings' values are $K_1 = 9 \times 10^{-4}$, $K_2 = 1.63 \times 10^{-5}$ and the hydrolysis constant of the ester, assumed equal to $K_{1A} = 2.8 \times 10^{-4}$. Our values are $K_1 = 8.85 \times 10^{-4}$, $K_A = 2.5 \times 10^{-5}$, and $K_{1A} = 2.8 \times 10^{-4}$. Cummings' values give $K_{2A} = 5.2 \times 10^{-5}$, and $\Delta P_{k_2} = +0.10$, and ours $K_{2A} = 7.9 \times 10^{-5}$ and $\Delta P_{k_2} = -0.08$. The positivity obtained from Cummings' values could easily be accounted for by the resonance interactions of the amino with the carboxyl group and with the benzene ring, both of which produce a pseudo-positivity. Our values show a negativity more than sufficient to counterbalance the effects of these resonances.

Our conclusion is that the amino group is inherently a negative one.

Benzoylaminophenylboric acids.—The ΔP_k values for the three benzoylaminophenylboric acids are negative. The benzoylamino group is negative, as might be expected from the high negativities of acyl groups.

That the order of strengths is meta > ortho > para > unsubstituted acid, while negative groups produce greater effects in the ortho than in the meta position, indicates that the conjugation between the boric acid and amino groups is not entirely removed by the resonance of the type



$$(C_6H_5NH\overset{\overset{O}{\|}}{C}{-}C_6H_5,\ C_6H_5\overset{+}{N}H{=}\overset{\overset{O^-}{|}}{C}{-}C_6H_5),$$

which is introduced with benzoylation.

Hydroxyphenylboric acids.—The hydroxyphenylboric acids have possibilities of resonance and chelation very similar to those of the aminophenylboric acids. The resonance enhances dissociation from the phenolic group, and hinders that from the boric acid group. Chelation has the reverse effect. Unfortunately the yield of the ortho isomer was so small that it was impossible to make sure that it was the required compound and to measure its dissociation constant. The amount of *p*-aminophenylboric acid was so small that it seemed hopeless to attempt to get sufficient of the phenol. However, the meta compound was prepared by the method of Bean and Johnson,[10] and both of its dissociation constants were measured. The results were $K_1 = 2.8 \times 10^{-9}$ and $K_2 = 1.4 \times 10^{-11}$ (uncorrected for salt effect, which should be appreciable for the divalent ion).

The value of K_1 indicates that the proton dissociates from the boric acid group, and the negativity of the hydroxyl group is the predominant factor. The value of K_2 shows that the group BO_2H^- is positive, a fact

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[10] Bean and Johnson, *ibid.*, **54**, 4415 (1932).

that in view of the negative charge hardly needs experimental corroboration.

EXPERIMENTAL

The aminophenylboric acids were prepared by the catalytic reduction of the nitro compounds with hydrogen, described by Bean and Johnson,[10] except that an equivalent of sulfuric acid was added before reduction in each case. The sulfates were crystallized from the reaction mixture by vacuum concentration. The reduction in acid solution is just as efficient as it is in neutral solution, if the hydrogenation is stopped as soon as the theoretical amount of hydrogen has been absorbed. If this is not done, the reduction in acid solution proceeds past the amine stage, and ammonia and an unstable boric acid derivative are formed.

The ortho and meta benzoylaminophenylboric acids were obtained from the mother liquors from the crystallizations of the aminophenylboric acid sulfates by shaking with benzoyl chloride and sodium carbonate. They crystallize as semianhydrides as reported by Seaman and Johnson.[2] It was found necessary to use the pure sulfate of *p*-aminophenylboric acid, and an exact equivalent of benzoyl chloride to obtain the *p*-benzoylaminophenylboric acid. The equivalent weight of this compound agreed with the formula, $C_6H_5CONHC_6H_4B(OH)_2$.

The *m*-hydroxyphenylboric acid was prepared from the corresponding amine sulfate according to the method of Bean and Johnson.[10]

The hydrogen electrode was used in junction with a saturated calomel cell, connection being made through a saturated solution of potassium chloride. The electromotive forces were measured by balancing with a Leeds and Northrup potentiometer using a lamp-scale type of galvanometer. The cells were enclosed in an air thermostat at 25°. The solutions were brought to this temperature in a water thermostat. Fresh liquid junctions were provided for all measurements.

The glass electrodes were tubes sealed with a thin diaphram of 0.15 Corning glass. They were partially filled with a saturated solution of quinhydrone, into which platinum leads dipped. They are similar to those described by MacInnes and Dole.[11]

The glass and hydrogen electrodes were used in conjunction with the same calomel cell and saturated solution of potassium chloride. The current from the glass electrodes was amplified by a De Eds[12] amplifier. By means of a multi-pole high resistance switch the same potentiometer and galvanometer could be used for both glass and hydrogen electrodes.

The glass electrodes were checked before and after each measurement by observing the pH value of a standard buffer solution.

Measurements with the glass electrodes were reproducible within 0.5 millivolts, and those with the hydrogen electrodes within 0.1 millivolts. The two types of electrodes agreed within these limits in solutions varying from pH = 2 to pH = 7. The glass electrodes were not used in more alkaline solutions.

Table III includes the solvent, the type of electrode, and the molality or range of molalities used; the number of approximately half-neutralized solutions for which pH numbers were determined; the range of dissociation constants calculated from each of these solutions; and the mean of these constants.

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[11] MACINNES AND DOLE, *ibid.*, **52**, 29 (1930).

[12] DE EDS, *Science*, **78**, 556 (1933).

TABLE III
Dissociation Constants at 25°C.

ACID		SOLVENT	ELECTRODE	MOLALITY	NUMBER OF HALF-NEUTRALIZED SOLUTIONS	RANGE OF K_a	K_a
Aniline sulfate		Water	Hydrogen	0.015-0.08	9	1.91-2.36 × 10^{-5}	2.12 × 10^{-5}
Sulfate of *o*-aminophenylboric acid	K_1	Water	Glass	0.005-0.01	6	1.70-3.95 × 10^{-5}	2.65 × 10^{-5}
	K_2	Water	Hydrogen	0.01 -0.02	6	5.68-6.65 × 10^{-10}	5.94 × 10^{-10}
Sulfate of *m*-aminophenylboric acid	K_1	Water	Glass	0.005-0.01	8	2.89-4.06 × 10^{-5}	3.46 × 10^{-5}
	K_2	Water	Hydrogen	0.01 -0.02	8	1.41-1.63 × 10^{-9}	1.54 × 10^{-9}
Sulfate of *p*-aminophenylboric acid	K_1	Water	Glass	0.004	3	1.93-1.96 × 10^{-4}	1.95 × 10^{-4}
	K_2	Water	Hydrogen	0.008	3	6.63-6.75 × 10^{-10}	6.70 × 10^{-10}
o-Benzoylaminophenylboric acid		25% C_2H_5OH	Hydrogen	0.005-0.01	6	4.22-4.75 × 10^{-10}	4.47 × 10^{-10}
m-Benzoylaminophenylboric acid		25% C_2H_5OH	Hydrogen	0.005-0.01	5	5.78-5.96 × 10^{-10}	5.84 × 10^{-10}
p-Benzoylaminophenylboric acid		25% C_2H_5OH	Hydrogen	0.005	2	2.85-2.90 × 10^{-10}	2.88 × 10^{-10}
m-Hydroxyphenylboric acid	K_1	Water	Hydrogen	0.01	5	2.45-3.14 × 10^{-9}	2.79 × 10^{-9}
	K_2	Water	Hydrogen	0.01	5	0.88-2.32 × 10^{-11}	1.44 × 10^{-11}
Sulfate of *m*-aminobenzoic acid	K_1	Water	Hydrogen	0.03	3	8.67-9.25 × 10^{-4}	8.85 × 10^{-4}
	K_2	Water	Hydrogen	0.03	3	2.48-2.58 × 10^{-5}	2.52 × 10^{-5}
Sulfate of methyl *m*-amino benzoate		Water	Hydrogen	0.03	3	2.75-2.85 × 10^{-4}	2.80 × 10^{-4}

SUMMARY

The acid strengths of the positive ions of the three aminophenylboric acids have been compared with each other and with that of anilinium ion. The acid strengths of the three aminophenylboric acids have been compared with each other and with that of phenylboric acid.

It has been shown that zwitter ion formation has little to do with these relative strengths.

The relative strengths have been explained on the assumption that there is a strong resonance in *o*- and *p*-aminophenylboric acid, that this resonance, though reduced, persists in the negative ions and the meta amino acid, that the positive ion of the ortho acid has a hydrogen bridge connecting the substituent groups, that the boric acid group has practically zero negativity, but that the amino group is negative.

It has been shown that the amino group is negative in the amino fatty acids, and in *m*-aminobenzoic acid.

The dissociation constants of the benzoylaminophenylboric acids and both constants of *m*-hydroxyphenylboric acid have been measured. The first hydrogen lost by the last-named substance appears to be from the boric acid group.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ETHYL GASOLINE CORPORATION]

STUDIES OF ALKYL LEAD COMPOUNDS

GEORGE CALINGAERT AND HAROLD SOROOS

Received March 9, 1938

Although the field of alkyl compounds of lead is fairly well known,[1,2] recent studies undertaken in this laboratory have shown that some compounds not previously reported in the literature exhibit behaviors somewhat at variance from what one might expect from the properties of known related compounds. The present article covers the description and properties of some of these new compounds in this group.

METHYLBUTYLLEAD COMPOUNDS

Only two of the four possible trimethylbutyllead compounds have been reported.[3] From the statements found in the literature[4,5,6] one might expect that the *sec.*-butyl isomer would be somewhat unstable, and the *tert.*-butyl so unstable as to make it doubtful that it could be prepared in a sufficient degree of purity for a study of its characteristics. Actually, it was found that the *sec.*-butyl isomer could be prepared by the standard method of interaction of a *sec.*-butyl Grignard reagent and trimethyllead halide. When the preparation of trimetyl-*tert.*-butyllead was attempted by the same method, with the use, as is customary, of the bromide, a large amount of metallic lead was precipitated, and the only product obtained was tetramethyllead. A systematic study of the preparation resulted in a method using the unstable and seldom used trimethyllead iodide, which gave comparatively high yields (88 per cent.). Contrary to expectations, the material proved to be more stable than any other alkyl lead compound with branched chains, and indeed, in some respects even more stable than a compound containing no branched chain. This is

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[1] For a comprehensive survey, see KRAUSE AND VON GROSSE, "Die Chemie der metall-organischen Verbindungen," Borntraeger, Berlin, **1937**.

[2] CALINGAERT, *Chem. Rev.*, **2**, 43–85 (1925).

[3] Ref. *1*, p. 384; ref. *2*, p. 58.

[4] Ref. *1*, p. 388; GRÜTTNER AND KRAUSE, *Ber.*, **50**, 574 (1917).

[5] GRÜTTNER AND KRAUSE, *Ann.*, **415**, 338 (1918).

[6] Present authors.

probably related to its similarity in structure with the very symmetrical hexamethylethane.*

In the preparation of trimethyl-*sec.*-butyllead a fair yield of dimethyl-di-*sec.*-butyllead was obtained simultaneously. This is probably to be attributed to the relative instability of the trimethyllead iodide and bromide used in the preparation.

The properties of all four trimethylbutyllead compounds are given in Table I. The boiling points decrease regularly from the normal to the tertiary isomer. The secondary shows the exaltation of the refractive index, which has been reported previously for similar compounds.[5] No further exaltation, however, is evident in the case of the tertiary isomer; indeed, the index of refraction is almost that of the normal isomer. This unexpected result is probably related to the peculiar structure of this compound, a point which will be further discussed.

TABLE I

TRIMETHYLBUTYLLEAD COMPOUNDS

COMPOUND	B.P., °C. (13 MM.)	d_4^{20}	n_D^{20}	F.P., °C.
Trimethyl-*n*-butyllead[3]	65	1.6777	1.5046	
Trimethyl-*sec.*-butyllead[6]	59	1.7011	1.5133	
Trimethyl-*iso*-butyllead[3]	57	1.6716	1.5026	
Trimethyl-*iso*-butyllead[6]	57	1.6822	1.5050	
Trimethyl-*tert.* butyllead[6]	47	1.6615	1.5089	5.7

HEXAMETHYLDILEAD

Hexaethyldilead is the only member of the hexaalkyldilead series which has been previously isolated.[7] According to the literature, the stability of the hexaalkyldilead compounds increases with the length of the chain, and the product of reaction of Grignard reagents with lead halides contains more and more hexaalkyldilead and less tetraalkyllead as the alkyl groups increase in size.[8] It is further stated that in the case of methyl halides the product is pure tetramethyllead, and that no hexamethyldilead is formed.[8] In the course of the preparation of tetramethyllead by various methods in this laboratory, it was observed that when the compound was made from methylmagnesium iodide, a residue was present after the distillation of the tetramethyllead. A systematic investiga-

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* Dr. Henry Gilman has suggested that the compound might prove useful in the preparation of free tertiary butyl radicals, using the Paneth technique.

[7] MIDGLEY, HOCHWALT, AND CALINGAERT, *J. Am. Chem. Soc.*, **45**, 1821 (1923).

[8] GRÜTTNER AND KRAUSE, *Ber.*, **49**, 1415 (1916).

tion disclosed that the material was hexamethyldilead, and following this, attempts were made to synthesize the compound by the known methods. The reduction of trialkyl lead halide with sodium in liquid ammonia* gave only low yields, the product being mostly tetramethyllead and metallic lead. It was finally found that by suitable control of the Grignard reaction, using trimethyllead iodide, yields as high as 61 per cent. could be obtained.

Hexamethyldilead is a solid, m.p. 38°, *d* 2.38, crystallizing in large hexagonal plates, fairly unstable, decomposing slowly in the dark and more rapidly in diffused daylight, and leaving a residue of metallic lead. This compound and also the trimethyl-*tert.*-butyllead mentioned above are closely related structurally to hexamethylethane. Indeed, this relation becomes at once apparent if the three compounds are named, in accordance with the latest international convention: tetramethylbutane, $Me_3C \cdot CMe_3$; 2-plumbatetramethylbutane, $Me_3Pb \cdot CMe_3$; and 2,3-diplumbatetramethylbutane, $Me_3Pb \cdot PbMe_3$. All three show the typical properties of compounds of such structure, among which the camphor-like odor and the relatively high melting point are most familiar. Observations were made with a petrographic microscope of the crystalline structure of all three compounds, and it was found that hexamethylethane and trimethyl-*tert.*-butyllead crystallize in the cubic system, while hexamethyldilead crystallizes in the hexagonal system. It is somewhat surprising that the comparatively less symmetrical trimethyl-*tert.*-butyllead shows a greater degree of crystalline symmetry than the seemingly more symmetrical hexamethyldilead. Thus, in its physical characteristics at least, trimethyl-*tert.*-butyllead behaves more like a molecule of hexamethylethane in which one quarternary carbon atom has been replaced by lead.

EXPERIMENTAL

Trimethyllead iodide.—To 134 g. (0.5 mole) of tetramethyllead in 200 ml. of ether contained in a 2-liter beaker and cooled to below −60° by the addition of solid carbon dioxide, was added through a dropping funnel with mechanical stirring, 127 g. (1.0 atom) of iodine in 800 ml. of ether. The mixture of trimethyllead iodide, methyl iodide, and ether was allowed to warm to room temperature, and the methyl iodide and ether distilled. The crude trimethyllead iodide, contaminated with some lead iodide was extracted with hot ether. The ether was again distilled and the light cream-colored trimethyllead iodide was dried on a porous clay plate. Yield 114 g. (60%).

Anal. Calc'd for C_3H_9PbI: Pb, 54.6. Found: Pb, 54.4, 54.6

*Trimethyl-*sec.*-butyllead.*—To 120 g. (0.3 mole) of trimethyllead iodide suspended in 200 ml. of dry ether and contained in a 3-necked round-bottomed flask, fitted with

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* This method has been used successfully in this laboratory for the preparation of Et_6Pb_2 from Et_3PbBr (68 per cent yield).

a reflux condenser, vapor-proof mechanical stirrer, and dropping funnel, was added a solution of *sec.*-butylmagnesium bromide prepared from 66 g. (0.5 mole) of *sec*-butylbromide, 12 g. (0.5 atom) magnesium, and 200 ml. of ether. Reaction took place with the lead salt going into solution and the formation of two layers. After refluxing for one hour and allowing to stand overnight, the reaction mixture was decomposed with ice and dilute hydrochloric acid. The ether layer was separated, and after drying and removing the solvent, the residue was distilled from a small Claisen flask. The distillate was fractionated in an atmosphere of nitrogen. The fraction, b.p. 55–56° 11 mm., d_4^{20} 1.6962, upon refractionation gave 39 g. (yield 50%) of trimethyl-*sec.*-butyllead, b.p. 59° 13 mm., d_4^{20} 1.7011, n_D^{20} 1.5133.

Anal. Calc'd for $C_7H_{18}Pb$: Pb, 67.0, Found: Pb, 67.2. Tetramethyllead (16%) and dimethyl-di-*sec.*-butyllead (22%) were obtained as by-products in the above reaction. When trimethyllead bromide was used instead of the iodide, the yield of trimethyl-*sec.*-butyllead was only 28%, together with tetramethyllead (23%), and dimethyl-di-*sec.*-butyllead (26%).

*Trimethyl-*tert.*-butyllead.*—Attempts to prepare trimethyl-*tert.*-butyllead by the action of *tert.*-butylmagnesium chloride and trimethyllead bromide resulted in the formation of tetramethyllead and metallic lead. The tetramethyllead was contaminated with hydrocarbons, including hexamethylethane and probably 2,2,4-trimethylpentane. The use of trimethyllead iodide in place of the bromide resulted in a high yield of the desired compound.

To 107 g. (0.28 mole) of trimethyllead iodide suspended in 250 ml. of dry ether, and contained in a 3-necked round-bottomed flask, fitted with a reflux condenser, vapor-proof mechanical stirrer, and dropping funnel, was added a solution of *tert.*-butylmagnesium chloride prepared from 93 g. (1 mole) *tert.*-butyl chloride, 24 g. (1 atom) magnesium and 250 ml. of dry ether. After decomposition of the reaction mixture with ice and dilute hydrochloric acid, the ether layer was separated and dried over anhydrous sodium carbonate. After removal of the solvent, distillation of the residue from a small Claisen flask gave 83 g. of material, d_4 1.5981, which upon fractionation in an atmosphere of nitrogen, gave 96 g. of trimethyl-*tert.*-butyllead, b.p., 47–48° 13 mm., d_4 1.6570, yield 88%. Upon refractionation all but a small amount of the material boiled at 47.0–47.2° 13 mm., and gave the following physical constants: d_4^{20} 1.6615, n_D^{20} 1.5089, m.p. 5.7°. The material has a camphor-like odor.

Anal. Calc'd for $C_7H_{18}Pb$: Pb, 67.0, Found: Pb, 67.6, 67.25.

Hexamethyldilead.—(*a*) *Trimethyllead iodide and sodium in liquid ammonia.*—Two and three-tenths grams (0.1 atom) of freshly cut sodium in small pieces was added slowly to a solution of 38 g. (0.1 mole) of trimethyllead iodide in about 150 ml. of liquid ammonia contained in a 500-ml. Pyrex cylinder. After the ammonia had distilled off at room temperature, the organic lead was extracted with several portions of ether. The solvent was removed by distillation, and the volatile tetramethyllead was distilled under reduced pressure with the bath temperature below 35° to prevent decomposition of any hexamethyldilead, leaving 3.5 g (yield 7%) of a yellow oil, which upon standing a short time, crystallized in large yellow plates.

Anal. Calc'd for $C_6H_{18}Pb_2$: Pb, 82.1, Found: Pb, 81.3.

(*b*) *Methylmagnesium bromide and lead chloride.*—To a solution of methylmagnesium bromide prepared from 13 g. (0.5 atom) magnesium, 60 g. (0.6 mole) methyl bromide and 250 ml. of ether, contained in a 3-necked round-bottomed flask, fitted with a reflux condenser, vapor-proof mechanical stirrer, and cooled in an ice-salt-water freezing mixture maintained at −5 to −8° was added in small portions, 139 g. (0.5 mole) of freshly dried lead chloride. Reaction took place with the momentary formation of a reddish coloration, which changed to a yellow-green, and finally black, caused by the deposition of metallic lead. After stirring for 30 minutes, the reaction mixture was decomposed with ice and water, the yellow-green ether layer was separated and the residue extracted with 2 100-ml. portions of ether. The combined ether solutions were shaken with anhydrous sodium carbonate and filtered. Most of the ether was removed by distillation at atmospheric pressure and the last traces at 100 mm. The pressure was then reduced to 2 mm., and the distillation was continued with the bath temperature below 35°. Three grams of distillate were collected, and a residue 25.5 g. of large greenish-yellow crystals of hexamethyldilead remained in the distilling flask. Yield of crude hexamethyldilead 25.5 g. (61%). The crystalline residue was dissolved in 25 ml. of ether and filtered from a small amount of black solid. After distillation of the ether under reduced pressure, a residue of light cream-colored soft crystals remained, m.p. 37-8°C., *d* 2.38.

Anal. Calc'd for $C_6H_{18}Pb_2$: Pb, 82.1, Found: Pb 82.0, 82.6

SUMMARY

Three of the four trimethylbutyllead isomers have been prepared and the properties of the four isomers are compared. Hexamethyldilead was prepared, and its properties are compared with those of the structurally related hexamethylethane and trimethyl-*tert.*-butyllead.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE SYNTHESIS OF CONDENSED POLYNUCLEAR HYDROCARBONS BY THE CYCLODEHYDRATION OF AROMATIC ALCOHOLS. VII. CYCLODEHYDRATION INVOLVING THE WAGNER REARRANGEMENT*

DONALD PRICE†, DAVID DAVIDSON, AND MARSTON TAYLOR BOGERT

Received March 24, 1938

The continued and increasing activity in the study of polynuclear hydrocarbons because of their tremendous biological significance, renders any investigation which throws light upon the structure or mechanism of formation of polycylic hydroaromatic compounds of considerable importance. The preceding papers of this series[1] have yielded the following rules for the cyclodehydration of phenylated alcohols or olefins[2]. Benzene derivatives with unbranched side-chains of five to seven carbon atoms carrying an hydroxyl group or an olefinic bond will give tetralin or indan derivatives when treated with sulfuric acid except when the hydroxyl group is adjacent to the phenyl nucleus, in which case polymerization takes place. Larger rings than six-membered are not formed. In certain instances tetralins and indans are formed simultaneously. With few exceptions the reaction mechanism involves the intermediate formation of olefins.

The present contribution deals with a study of the case of a phenylated alcohol in which a quaternary carbon atom ajoins the carbinol group. Previous references to the possibility of cyclo dehydration of compounds of this type have been made by Bogert and Davidson[3], and by Linstead[2], but no clear-cut case has so far been reported. In this investigation it has been found that 1-phenyl-4,4-dimethyl-pentanol-3 (I) when treated

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* The authors wish to acknowledge their indebtedness to Dr. David Perlman for much advice and assistance during the course of this work.

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[1] BOGERT AND DAVIDSON, *J. Am. Chem. Soc.*, **56**, 185 (1934); BOGERT, DAVIDSON, AND APFELBAUM, *ibid.*, **56**, 959 (1934); ROBLIN, DAVIDSON, AND BOGERT, *ibid.*, **57**, 151 (1935); PERLMAN, DAVIDSON, AND BOGERT, *J. Org. Chem.*, **1**, 288, 300 (1936); PERLMAN AND BOGERT, *J. Am. Chem. Soc.*, **59**, 2534 (1937).

[2] LINSTEAD, "Annual Reports on the Progress of Chemistry," Chemical Society (London), **1936**, p. 320.

[3] BOGERT AND DAVIDSON, *loc. cit.*[1], p. 188.

with 90 per cent. sulfuric acid undergoes the Wagner rearrangement[4], followed by cyclization as shown in Chart I. The structure of the resulting hydrocarbon was confirmed by oxidation to dimethylhomophthalic acid and dehydrogenation to 1,2-dimethylnaphthalene as well as by its synthesis from 1-phenyl-3,4-dimethyl-pentanol-3 (II).

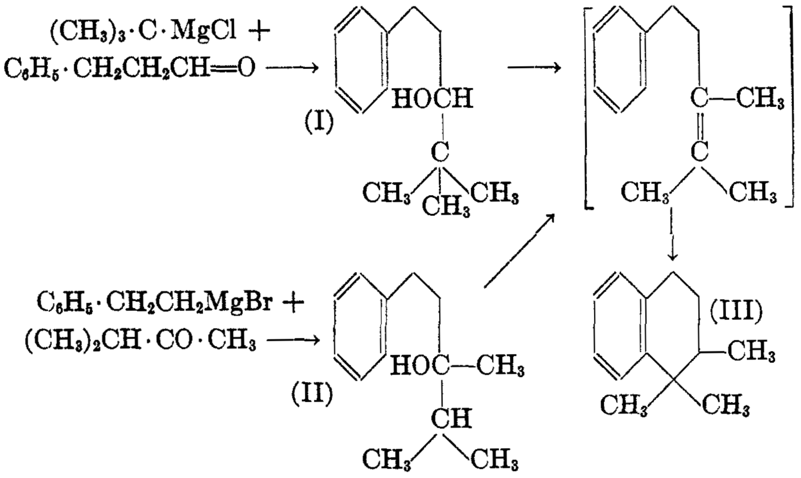
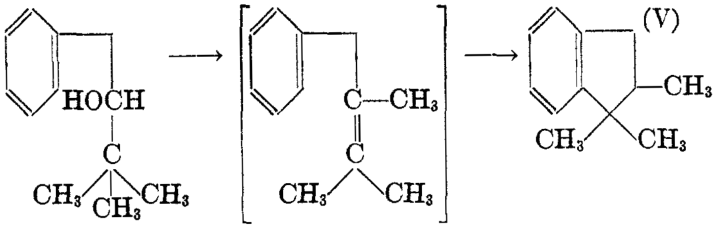


CHART I

A similar rearrangement was also found to take place in the case of the lower homologue, 1-phenyl-3,3-dimethyl-butanol-2 (IV), which yielded 1,1,2-trimethylindan (V), a cycle which had previously been obtained by Bogert and Davidson (paper I of this series[1]) from 1-phenyl-2,3-dimethylbutanol-2.

$$(CH_3)_3\cdot C\cdot MgCl + C_6H_5\cdot CH_2CH{=}O \rightarrow$$



(IV)

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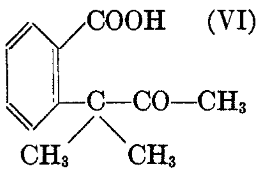
[4] *Cf.* WALLIS, "Molecular Rearrangements," in GILMAN'S "Organic Chemistry," John Wiley & Sons, Inc., New York, **1938**, Vol. I, pp. 720 *ff*.

The structure of V was confirmed by oxidation with chromic acid, which yielded VI.


(VI)

This substance was also obtained in the same manner by oxidation of a sample of the 1,1,2-trimethylindan prepared by Bogert and Davidson[1]. The melting points of the oxidation products from both sources agreed within half a degree, and the melting point of a mixture showed no depression.

EXPERIMENTAL

1-Phenyl-4,4-dimethylpentanol-3, (I).—*tert.*-Butylmagnesium chloride was prepared according to "Organic Syntheses," Coll. Vol. I, p. 510, from 227 g. (2.5 moles) *tert.*-butyl chloride. The reaction mixture was cooled to 2° in an ice-salt bath, and 100.6 g. (0.75 mole) of β-phenylpropionic aldehyde, dissolved in an equal volume of ether, was added over a period of 2.5 hours with stirring, the temperature being kept below 10°. The addition compound was decomposed by the addition of ice and 25–30% sulfuric acid in slight excess; the ether layer was shaken out with a solution of sodium bisulfite, washed with sodium carbonate solution, then with water, and finally was dried over sodium sulfate.

The residue, after removal of the ether on the steam bath, was distilled under reduced pressure, and yielded 100.1 g. (70% theoretical) of crude alcohol boiling at 116–126°/6–7 mm. Repeated fractionation failed to yield a product which gave entirely satisfactory analyses. A sample boiling at 90–91°/2 mm. (bath temperature 130–135°) gave the following results.

Anal. Calc'd for $C_{13}H_{20}O$: C, 81.17; H, 10.49.
Found C, 80.73; H, 9.54.

The *phenylurethane* was prepared by allowing equimolecular proportions of the alcohol and phenyl isocyanate to stand several days at room temperature in a well-stoppered bottle, and then recrystallizing the product repeatedly from Skelly Solvent "D." (petroleum fraction, b.p. 77–115°); microscopic white needles; m.p. 91°.

Anal. Calc'd for $C_{20}H_{25}O_2N$: C, 77.12; H, 8.10.
Found C, 77.20; H, 8.33.

Cyclodehydration of 1-phenyl-4,4-dimethyl-pentanol-3.—Seventy cc. (64.7 g.) of 1-phenyl-4,4-dimethyl-pentanol-3 was run into 210 cc. of 90% sulfuric acid cooled to 2° in a 500-cc. beaker-flask, with rapid stirring over a period of 2 hours, stirring being continued for 2 hours longer, while the reaction mixture was allowed to warm to room temperature. It was then diluted with ice water, and extracted with 400 cc. of light petroleum ether in three portions; the combined extracts were shaken in a separatory funnel with 30 cc. portions of 90% sulfuric acid until the last was almost colorless.

The solution was washed with water, with dilute sodium carbonate solution, again with water, and was then dried over anhydrous potassium carbonate. Filtration, and removal of the petroleum ether on the steam bath yielded a water-white product which was carefully distilled through a Widmer column; more than 90% of it passed over at 77–81°/1.5 mm. (bath temperature 135–139°) without change in refractive index. The yield was 55% of the theoretical. Samples redistilled for analysis boiled at 77–77.5°/1 mm. and 242° (uncorr.) at 760 mm.; n_D^{25}, 1.5269.

Anal. Calc'd for $C_{13}H_{18}$: C, 89.58; H, 10.42.

Found: (77–77.5°/1 mm.) C, 89.49; H, 10.59: (242°/760 mm.) C, 89.75; H, 10.66.

Oxidation of 1,1,2-trimethyltetralin.—Two grams of 1,1,2-trimethyltetralin was oxidized by refluxing with 20 g. of potassium permanganate in 500 cc. of water for 10 to 12 hours with good stirring, after which the permanganate color was discharged by the addition of about 25 cc. of ethyl alcohol. The solution was filtered hot, and the manganese dioxide precipitate was washed well with boiling water, the washings being added to the main filtrate which was then evaporated to about 100 cc. and made acid to Congo red with hydrochloric acid.

The white precipitate which separated was dried *in vacuo*, and was found to melt at 123°, the melting-point reported for dimethylhomophthalic acid. Its identity was further established by mixture melting-point determinations with the anhydride of known dimethylhomophthalic acid run in two ways. (*1*) A sample was mixed with the known anhydride, and the temperature of the mixture was raised above the melting point of the free acid; the sample was then allowed to resolidify; m.p. 82° (m.p. of known anhydride, 82.5–83°) (2). The anhydride was formed by heating a sample to 150° for a short time. A mixture of the product with the known anhydride was found to melt at 82° (corr.).

Dehydrogenation of 1,1,2-trimethyl-tetralin.—One mole equivalent (2.3 g.) of the tetralin and 0.85 g. flowers of sulfur (2 atomic equivalents) were placed in a 10-cc. distilling flask with side-tube set at right angles to the neck. The side-tube was stoppered, the neck was provided with a short reflux condenser, and the reaction mixture was heated over a small flame. When the initial, somewhat vigorous, evolution of hydrogen sulfide had abated, the mixture was refluxed gently for 2.5 hours. The flask was then arranged for downward distillation, and one gram of a fluorescent liquid smelling strongly of hydrogen sulfide was distilled over.

The product was converted to the *picrate* by dissolving it in 10 cc. of boiling alcohol and adding 1.3 g. of picric acid in an equal volume of the same boiling solvent. Upon cooling, the picrate crystallized in orange-red needles and was dried *in vacuuo*; yield, 0.9 g., m.p. 129.8° (corr.). The melting-point of the picrate of 1,2-dimethylnaphthalene is reported in Beilstein as 129.5–130.5°C. A further crop of crystals was obtained from the mother liquor.

1-Phenyl-3,3-dimethylbutanol-2 (IV).—This compound was prepared in the same manner as 1-phenyl-4,4-dimethylpentanol-3, from 186.0 g. (2 moles) *tert.*-butyl chloride and 120.1 g. (1 mole) phenylacetaldehyde (b.p. 91–92°/20 mm.), the temperature being kept below 5°. The yield in several experiments amounted to 65% of the theoretical (calculated on the basis of the phenylacetaldehyde used); b.p. 78.5°/2 mm. (bath temperature 125°); n_D^{25}, 1.1566.

Anal. Calc'd for $C_{12}H_{18}O$: C, 80.85; H, 10.19.

Found: C, 81.02; H, 10.14.

Cyclization of 1-phenyl-3,3-dimethylbutanol-2.—In this procedure, which was the same as for 1-phenyl-4,4-dimethylpentanol-3, except that the reaction mixture was extracted with petroleum ether without dilution, 55 cc. of the alcohol was added to 73 cc. of 90% sulfuric acid at such a rate as to keep the temperature below 5° (3.5

hours). On distillation through a Widmer column, nearly all of the product but a small forerun came over at 55–56°/2 mm. (bath temperature 135°); yield of distilled product, 41% of the theoretical. No further purification for analysis was necessary; n_D^{25}, 1.5101. A sample of product distilled at atmospheric pressure, boiled at 208°.

Anal. Calc'd for $C_{12}H_{16}$: C, 89.94; H, 10.08.
Found: C, 89.97; H, 10.16.

An additional quantity of the cyclic compound was obtained by diluting the extracted reaction mixture with ice and treating the oily layer as above.

Oxidation of 1,1,2-trimethylindan.—One g. of 1,1,2-trimethyl-indan was dissolved in 20 cc. glacial acetic acid, heated to boiling under reflux, and 5 g. of chromium trioxide in 10 cc. of glacial acetic acid and 10 cc. of water was added, little by little, through the top of the condenser, the rather vigorous reaction being allowed to subside before the addition of each fresh portion. The mixture was refluxed for one hour, after which 20 cc. of acetic acid was distilled off, and 100 cc. of water was added. When cool the solution was extracted with four 50-cc. portions of ether; the combined ether extracts were washed several times with water, and dried over anhydrous sodium sulfate. Upon evaporation of the ether, a residue of acetic acid remained, from which the compound was separated by taking up in alcohol and adding water. The product obtained in this manner was quite pure but was further purified for analysis by recrystallization from a mixture of chloroform and heptane; m.p. 157.5° (corr.); yield about 60% of the theoretical.

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.87; H, 6.85.
Found: C, 69.70; H, 6.93.

A second oxidation using chromium trioxide in glacial acetic acid, without the addition of water, gave the same product. A sample of the 1,1,2-trimethylindan prepared by Bogert and Davidson[1] was oxidized by the same procedure, and the product was shown to be identical with the above oxidation product by its melting-point and by a mixture melting-point of the two substances.

1-Phenyl-3,4-dimethylpentanol-3 (II).—The Grignard reagent was prepared in the usual way from 231 g. (1.25 moles) of phenethyl bromide (prepared for us in 84% yield by Mr. Harry G. Steinman, according to the procedure of Roblin[5]), and 30.4 g. (1.25 moles) of magnesium turnings, without external cooling. One hundred grams of methyl isopropyl ketone in an equal volume of ether was added dropwise, the temperature being kept below 7°, and the condensation product worked up as described for the other alcohols.

On distillation under reduced pressure, several low-boiling fractions came over, one of which consisted of styrene. A 50% yield of the crude product was obtained, which on further purification for analysis boiled at 118–119°/3 mm.; n_D^{25}, 1.5083.

Anal. Calc'd for $C_{13}H_{20}O$: C, 81.18; H, 10.49.
Found: C, 81.37; H, 10.73.

Cyclodehydration of 1-phenyl-3,4-dimethylpentanol-3—The cyclization was carried out exactly as described for 1-phenyl-3,3-dimethylbutanol-3, using 38 g. (40 cc.) of the alcohol and 60 cc. of 90% sulfuric acid. The yield of the product, almost all of which distilled at 94.5°/2 mm., amounted to 86% of the theoretical; b.p., 241–242°/760.7 mm.; n_D^{25}, 1.5270. Analysis, refractive index, and boiling-point showed this

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[5] Roblin, Dissertation, Columbia University, **1934.**

compound to be identical with the 1,1,2-trimethyltetralin prepared from 1-phenyl-4,4-dimethylpentanol-3.

Anal. Calc'd for $C_{13}H_{18}$: C, 89.58; H, 10.42.
Found: C, 89.28; H, 10.51.

SUMMARY

In several cases, cyclodehydration of aromatic alcohols having a quaternary carbon atom adjacent to the carbinol group has been found to involve the Wagner rearrangement.

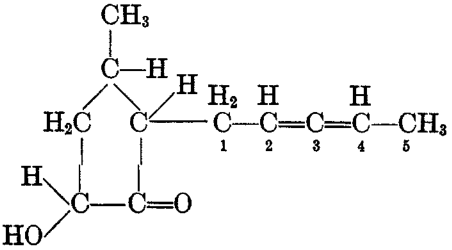
[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, U. S. DEPARTMENT OF AGRICULTURE, WASHINGTON, D. C.]

CONSTITUENTS OF PYRETHRUM FLOWERS. XII. THE NATURE OF THE SIDE-CHAIN OF PYRETHROLONE*

F. B. LAFORGE AND H. L. HALLER†

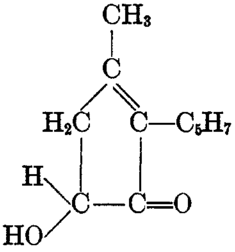
Received March 31, 1938

As a result of previous investigations[1] the structure of pyrethrolone originally proposed by Staudinger and Ruzicka,[2] represented by formula I,



I

has been revised with respect to the cyclopentanolone nucleus to one derived from a cyclopentenolone nucleus represented by formula II.



II

The original formula I, with the cumulated system of double bonds in the side chain, has met with general skepticism on the grounds that this system has never been encountered in nature. The evidence for the cumulated system was based on the formation of acetaldehyde on ozonization

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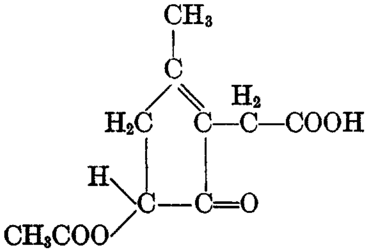
* For article XI of this series see ROSE AND HALLER, J. ORG. CHEM., **2**, 484 (1937).

† We are indebted to W. G. Rose and F. Acree, Jr., for technical assistance and the microcombustions, and to E. L. Gooden for the optical data.

[1] LAFORGE AND HALLER, *J. Am. Chem. Soc.*, **58**, 1061 (1936); **58**, 1777 (1936).

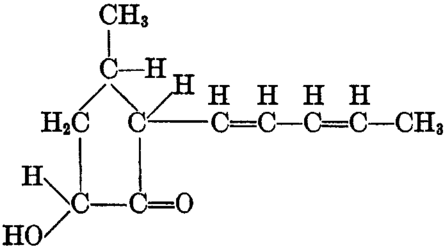
[2] STAUDINGER AND RUZICKA, *Helv. Chim. Acta*, **7**, 212 (1924).

of pyrethrolone, which establishes the position of one double bond in the 3,4 position, and the isolation of malonic acid when the products of ozonization had been further oxidized with hydrogen peroxide. In only one instance an acid of the probable formula III‡ was isolated in very small yield from the products of ozonization of acetyl pyrethrolone.



III

In a later article Ruzicka[3] without giving any reasons, proposed formula IV, with a conjugated system, for pyrethrolone.



IV

In several abstracts and reviews of our article on this subject,[1] the erroneous assumption is made that we had substantiated this later view of Ruzicka.

To obtain further evidence on the positions of the two double bonds in the side-chain of pyrethrolone, we have since made a large number of experiments, the results of which, although still inconclusive, do not favor conjugation, but rather point to some other system.

From our previous experience it was evident that pyrethrolone, owing to its relative instability, was not well suited for chemical manipulation,

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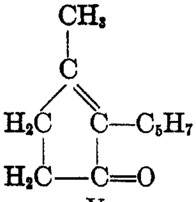
‡ The original formula has been revised by us by changing the location of the nuclear double bond. See reference *1* and also Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 232 (1924).

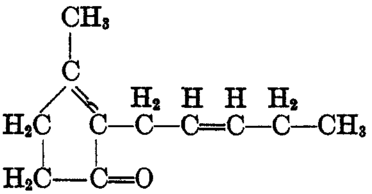
[3] Ruzicka and Pfeiffer, *ibid.*, **16**, 1208 (1933).

and in most of the experiments described herein pyrethrone of formula V was employed as the starting material.



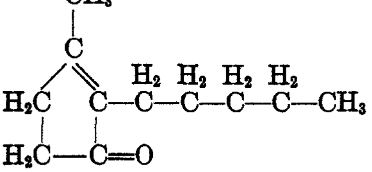
V

Pyrethrone was obtained in the earlier stages of our investigations rather unexpectedly in an attempt to reduce the side-chain of pyrethrolone with aluminum amalgam. With the assumption of the presence of a conjugated system, as in formula IV, a 1,4 addition of hydrogen might be expected with the formation of a compound having a chain containing a single double bond. Subsequent reduction of the hydroxyl group would have furnished jasmone of the known structure VI.[3,4]



VI

The reduction of pyrethrolone with aluminum amalgam, however, took another course and resulted in the formation, in fairly good yield, of a low-boiling compound of formula $C_{11}H_{14}O$, which still contained the two double bonds in the side-chain and which on hydrogenation furnished a tetrahydro derivative identical with dihydrojasmone of formula VII. (The nuclear double bond is very resistant to hydrogenation.)



VII

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[4] Treff and Werner, *Ber.*, **66**, 1521 (1933); **68**, 640 (1935).

The double-bond system was hence unaffected by this treatment, while the hydroxyl group was eliminated. The same experiment is reported by Staudinger and Ruzicka, who obtained no low-boiling reaction product. We attribute our favorable result to the quality of the metal employed and the manner of preparing the amalgam.

Owing to the importance of pyrethrone, its preparation and properties are described in special detail in the experimental part. Pyrethrone is a colorless liquid with a pleasant flowery odor resembling dihydrojasmone. It is optically inactive. It was characterized by its refractive index and by the properties of its semicarbazone, *p*-nitrophenylhydrazone, and oxime.

The observed molecular refraction showed a marked exaltation over the calculated value. The compound is very unstable toward acids that cause polymerization.

Because of its established relation to dihydrojasmone, the only uncertainty in the formula of pyrethrone is the position of one of the two double bonds in the side-chain. That one of the two occupies the 3,4 position, as in pyrethrolone, follows from the formation of acetaldehyde on ozonization. Only the 1,2 and 2,3 positions remain open for the remaining double bond corresponding to the conjugated and the cumulated systems, respectively, and between which systems the choice must be made. The foregoing considerations are predicated on the assumption of an open chain in pyrethrone and pyrethrolone. The possibility of the presence of a second ring system that is easily cleaved by hydrogenation, with the formation of a saturated five-membered straight chain, cannot be excluded from consideration.

It is not possible to hydrogenate one of the double bonds in the side-chain without hydrogenating the other, and when only half the calculated volume of hydrogen is allowed to react, mixtures of fully hydrogenated material and the original substance result. It is possible, however, to eliminate one of the double bonds of pyrethrone by the addition of 1 mole of hydrobromic acid in acetic acid solution followed by zinc reduction. By these reactions a dihydropyrethrone was obtained, the semicarbazone of which melted at 202°, and which absorbed 1 mole of hydrogen to give the known tetrahydropyrethrone semicarbazone. The semicarbazone of the dihydro derivative was distinctly different from that of jasmone, which melts at 215°, and with which it is isomeric. Hence, it must be concluded that the double bond eliminated in this process was in the 2,3 position if the side-chain of pyrethrone contains the cumulative system, and in the 1,2 position if the conjugated system is present.

The reaction of pyrethrone with hydrobromic acid does not proceed smoothly and is accompanied by polymerization. An oxidation or ozonization experiment, which might have decided the position of the remaining double bond, was not made owing to the difficult accessibility of the material.

Reduction of a conjugated system with aluminum amalgam usually results in a 1,4 addition of hydrogen. Since this method was used in the preparation of pyrethrone and the double-bond system was not affected, the result is against the assumption of the presence of a conjugated system in pyrethrone, and hence in pyrethrolone.

Pyrethrolone and pyrethrone do not form characteristic reaction products with maleic anhydride, and they definitely do not react with α-naphthoquinone, since the two components may be recovered for the most part unchanged after they have been heated together.

The most characteristic property of both pyrethrone and pyrethrolone is their behavior toward bromine. This reaction had been studied by Staudinger and Ruzicka, who reached the conclusion that 1 mole of bromine is added to pyrethrolone in organic solvents. They supposed the bromine addition product to be unstable. A conjugated system is known to add bromine in either the 1,2 or the 1,4 position.

When 1 mole of bromine is added to pyrethrone in an organic solvent and the solution is concentrated, there is an evolution of hydrobromic acid, and complete evaporation of the solvent results in decomposition of the product.

In our earlier experiments no attempt was made to isolate the bromine addition product, but the reaction was carried out in acetic acid and, to determine if a 1,4 addition had occurred, the solution was reduced directly with zinc dust, and the debrominated material was isolated. If a conjugated system were present and a 1,4 addition had occurred, the product would be the known compound jasmone of formula VI. The experiments resulted, however, in the regeneration of the original pyrethrone. It was concluded that the addition of bromine had occurred on adjacent carbon atoms; therefore, a choice could not be made between the two systems. Attempts were made to substitute acetyl for the added bromine by reactions with potassium or silver acetate. Contrary to expectations, half of the added bromine was removed with the greatest ease whereas the other half seemed to be very firmly bound.

We were led by this observation to carry out the addition of bromine in ethanol solution. We noted that, after the addition of 1 mole of bromine, treatment of the reaction product with alcoholic potassium hydroxide solution caused the separation of potassium bromide, and the neutralized solution yielded, on evaporation of the solvent, a stable compound containing 1 bromide atom. The monobromo compound yielded the original pyrethrone on zinc reduction in acetic acid. In subsequent experiments it was found that, after addition of 1 mole of bromine in ethanol, the solution was acid and could be directly titrated with standard alcoholic alkali, indicating that nearly half the added bromine is present as free hydrobromic acid in the solution.

It must be concluded that the reaction of pyrethrone with 1 mole of bromine is one of substitution, or is at least an addition with subsequent elimination of hydrobromic acid that takes place so easily that it amounts to substitution. Reduction of the product by zinc dust in ethanol gave the original pyrethrone.

Further experiments were made by adding 2 moles of bromine to pyrethrone in ethanol solution. It was observed that the 2 moles were absorbed, although a few minutes was required for complete decolorization of the solution. Titration of the reaction product indicated the presence of 2 moles of free hydrobromic acid. The neutralized solution yielded a stable sirup, and the quantity indicated that the product was a dibromide. Reduction of the dibromo compound with zinc gave the original pyrethrone, which was identified by its properties and constants, and by the preparation of its semicarbazone, *p*-nitrophenylhydrazone, and oxime.

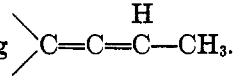
The reaction with the second mole of bromine therefore proceeds in a manner analogous to the reaction with the first, and is equivalent to a substitution. Pyrethrolone presents the same picture as pyrethrone with respect to its behavior on addition of bromine. When 2 moles were added to pyrethrolone followed by reduction with zinc, pyrethrolone was regenerated. Only the unsaturated side-chain is involved in the reaction with bromine, for tetrahydropyrethrone and tetrahydropyrethrolone do not decolorize bromine.

There is no obvious interpretation of these reactions, but such a course has not been observed with compounds containing the conjugated system.

Allene is stated to add 4 atoms of bromine, forming an unstable tetrabromide, but a search of the literature has furnished very little additional information as to the behavior of other compounds with the cumulated system towards halogen. It is our intention to investigate this matter, and a comparison of facts may permit a conclusion as to the nature of the double-bond system in pyrethrone, and hence in the pyrethrins.

Pyrethrone reacts with 2 moles of perbenzoic acid to give an unstable product that could not be characterized, whereas the monobromo compound does not seem to react with this reagent.

It is evident that the double-bond system present in pyrethrone is of remarkable stability and that no shift takes place when the compound is subjected to the reactions with bromine described above.

Some other observations, which are not recorded in the experimental part because the results are not clear-cut, point to the presence of a cumulated system in pyrethrone. When pyrethrone is heated in a sealed tube with sodium metal in ether solution, a sodium compound is formed as a brown powder. When this is treated with carbon dioxide, an amorphous acid is obtained. This is an indication of the formation of a compound with an acetylene grouping that yields an acid on treatment with carbon dioxide, a reaction that is characteristic of the grouping  $>C=C=\overset{H}{C}-CH_3$.

EXPERIMENTAL

Reduction of pyrethrolone with aluminum amalgam.—Pyrethrone was prepared by treatment of pyrethrolone with aluminum amalgam in ether solution. The preparation has been repeated many times in the course of this investigation and always with uniform results.

The amalgam was prepared from specially purified aluminum[§] by the use of Nessler's reagent, a procedure in common use. The sheet metal was cut into strips, folded loosely in a zigzag manner, placed in an Erlenmeyer flask, and treated for a few minutes with 10 per cent. aqueous potassium hydroxide. It was then washed with water and covered with the Nessler's reagent. After about three or four minutes the solution was poured off, and the amalgamated aluminum was thoroughly washed with water until the washings were no longer alkaline. It was then immediately washed with alcohol followed by ether. The pyrethrolone dissolved in ether was added at once, and the reaction was allowed to proceed for about 15 hours (usually overnight). The proportions employed were 5 grams of freshly distilled pyrethrolone, 15 grams of amalgamated aluminum, and 300 cc. of ordinary ether. As a rule several portions were set up, and after completion of the reaction the ether solution was filtered from the separated gray precipitate, and the solvent was removed. The residue was then distilled. About one-third passed over below 100° at 0.35 mm. pressure, but the distillation was continued until the temperature reached 130°, as considerable pyrethrone is present in the higher-boiling fraction. The total quantity of distillate was always about half the quantity of pyrethrolone employed. In a typical instance 21 grams of pyrethrolone gave 10.35 grams of distillate. The residue is not distillable, and suddenly polymerizes to a stiff resin on further heating. It may consist of the pinacol corresponding to pyrethrone. For purification, the distillate was converted into the semicarbazone.

Pyrethrone semicarbazone.—The 10.35 grams of distillate was dissolved in 90 cc. of 95 per cent. ethanol, and 14 cc. of pyridine and a solution of 14 grams of semicarbazide hydrochloride in 18 cc. of water were added. In about 30 minutes crystallization began and was complete after standing overnight. After filtration and washing with a little ethanol, the semicarbazone was suspended in water and again filtered, and finally was washed with a little ethanol. After drying, the semicarbazone was equal in weight to the distillate employed. It melted with decomposition at about 210° and was sufficiently pure for most purposes. After recrystallization from methanol, in which it is difficultly soluble at the boiling temperature, the melting point was raised to 216–218°.

Anal. Calc'd for $C_{12}H_{17}N_3O$: C, 65.75; H, 7.76.

Found: C, 65.39, 65.57, 64.95; H, 7.88, 8.26, 8.09.

[§] The aluminum sheets had a thickness of 0.203 mm. (0.008 in.) and a minimum aluminum content of 99.8 per cent.

Hydrogenation of pyrethrone semicarbazone.—As a control 0.219 gram of pure pyrethrone semicarbazone was suspended in 30 cc. of ethanol containing 0.15 gram of previously reduced platinum oxide catalyst, and the consumed hydrogen was measured. Absorption practically ceased after 7 minutes when 45.0 cc. had been taken up by the sample (calc'd 44 cc.). The filtered and concentrated solution yielded 0.18 gram of crystalline product, which melted at 176° and which was identified as tetrahydropyrethrone (dihydrojasmone) semicarbazone by a mixture melting-point determination.

Pyrethrone.—Hydrolysis of the semicarbazone to the free ketone at first presented difficulties. Boiling with aqueous mineral acids or with oxalic acid or phthalic anhydride caused complete polymerization, and no volatile product could be isolated. The desired result was obtained, however, by the following procedure:

Portions of about 0.5 gram of the semicarbazone were placed in a 200-cc. round-bottomed flask equipped for steam distillation, and after addition of 1.2 grams of oxalic acid in 12 cc. of water a rapid current of steam was passed through the liquid to remove the ketone as rapidly as it was liberated. Toward the end of the process any crystals adhering to the upper part of the flask were shaken down, and the distillation was continued. The operation required about 7 to 8 minutes, during which time about 100 cc. of distillate was collected. A number of separate distillations were made, and, after cooling, the distilled liquid was collected with ether. After drying and evaporation of the solvent the residue was distilled at 0.35 mm. Practically all passed over from 85 to 90°. From 6.5 grams of semicarbazone 4.1 grams of pyrethrone was obtained; from 5.5 grams, 3.35 grams; from 5 grams, 3 grams. The yield was hence 81 to 85 per cent. of the theoretical.

Pyrethrone is a colorless liquid boiling at 85–87° and 0.35 mm., and at 122–124° and 11 mm. It has a pleasant odor resembling that of dihydrojasmone. n_D^{29} 1.5224, n_D^{27} 1.5250, n_D^{21} 1.5268. $n_F^{29} - n_C^{29}$ 0.018, d_4^{21} 0.965; $[M]_D$ found, 51.63; calc'd, 49.30; $[\alpha]_D$ 0. Owing to its volatility it is difficult to obtain sharp analytical figures.

Anal. Calc'd for $C_{11}H_{14}O$: C, 81.48; H, 8.64.
Found: C, 80.35, 80.02; H, 9.02, 8.63.

Pyrethrone oxime.—This derivative was prepared by heating 0.1 gram of pyrethrone, 0.1 gram of hydroxylamine hydrochloride, and 2 drops of pyridine in 1 cc. of ethanol for 3 hours in a sealed tube at 100°. Water was added to the solution, causing the separation of an oil that crystallized on cooling. The 0.12 gram of crude product was recrystallized by dissolving in a little methanol and slowly adding about 3 volumes of 75 per cent. aqueous methanol to the cold solution. It formed needles melting at 63°. By dissolving it in a small quantity of petroleum ether, filtering, and concentrating the solution, the compound separated in needles melting at 67°.

Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.57; H, 8.47; N, 7.90.
Found: C, 74.42, 74.08; H, 8.45, 8.30; N, 8.17.

Pyrethrone benzoyl oxime.—Two cubic centimeters of a benzene solution containing 0.03 gram of pyrethrone oxime, 0.03 gram of benzoyl chloride, and 1 drop of pyridine were heated for three hours on the steam bath. Petroleum ether was added, and the solution washed with water, dilute acid, and sodium carbonate, and then dried. On evaporation of the solvents the reaction product was obtained in good yield as an oil that crystallized at once. It was recrystallized from petroleum ether and melted at 94°.

Anal. Calc'd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76.
Found: C. 76.39. 76.51; H, 6.59, 6.73.

p-*Nitrophenylhydrazone of pyrethrone.*—An aqueous solution of 0.23 gram of *p*-nitrophenylhydrazine hydrochloride was added to a solution of 0.2 gram of pyrethrone in 1 cc. of ethanol. Crystallization began in a few minutes, and after several hours the separated compound was removed by filtration. It melted at 132°, and after recrystallization from benzene it melted at 139°. It can also be crystallized from acetic acid, forming red prisms which melt at 139°.

Anal. Calc'd for $C_{17}H_{19}N_3O_2$: C, 68.68; H, 6.40; N, 14.14.
Found: C, 68.80, 69.00; H, 6.61, 6.69; N, 14.46, 14.46.

Dihydropyrethrone.—One gram of pyrethrone was dissolved in 5 cc. of acetic acid, and 0.5 gram of hydrobromic acid was passed into the solution, the quantity being gaged by the gain in weight of the solution. After standing overnight, the mixture was diluted with an equal quantity of acetic acid, and, with warming and agitation, the solution was treated with about 3 grams of zinc dust, which was slowly added over a period of 2 hours. The solution was diluted with water, and the suspended oil was taken up in petroleum ether. After the petroleum ether solution had been washed with water and with sodium carbonate solution and dried, the solvent was removed, and the residue was distilled. The yield of distilled product boiling at 115–118° and 11 mm. was 0.5 gram.

The semicarbazone was prepared by dissolving 0.35 gram of the distillate in 10 cc. of ethanol and adding 0.5 cc. of pyridine and a solution of 0.45 gram of semicarbazide hydrochloride in 0.5 cc. of water. The crystalline product that separated on standing was removed and washed with ethanol and water. It melted at 198°, and, after one recrystallization from methanol, at 202°. The yield was 0.36 gram.

Anal. Calc'd for $C_{12}H_{19}N_3O$: C, 65.15; H, 8.60.
Found: C, 65.08, 65.16; H, 8.25, 8.54.

Tetrahydropyrethrone semicarbazone from dihydropyrethrone semicarbazone.—When 0.103 gram of the semicarbazone was hydrogenated with platinum oxide catalyst in ethanol, 11.0 cc. of hydrogen was absorbed in 3 minutes (calc'd for H_2, 10.4 cc.). The solution was filtered, and concentrated to a small volume, from which the product separated. The compound was pure tetrahydropyrethrone (dihydrojasmone) semicarbazone melting at 176°, and its identity was established by the melting point (176°) of a mixture of it with authentic material.

Anal. Calc'd for $C_{12}H_{21}N_3O$: C, 64.57; H, 9.42.
Found: C, 64.90, 64.32; H, 9.21, 9.11.

Addition of 1 mole of bromine to pyrethrone in acetic acid followed by reduction.—Nine-tenths of a gram of pyrethrone was dissolved in 5 cc. of acetic acid, and 0.9 gram of bromine in 9 cc. of the same solvent was added. It was decolorized instantly. The solution was treated with 3 grams of zinc dust, with agitation and heating on the steam bath for 2 hours. About 50 cc. of water was added, and the suspension was decanted from the zinc and extracted with petroleum ether. After being washed with water and sodium carbonate solution and dried, the solvent was removed, and the residue was distilled. It boiled at about 90° and 0.35 mm. The yield of distilled substance was 0.45 gram; n_D^{30} 1.5238. The semicarbazone was prepared from 0.1 gram in the manner already described with use of 1 cc. of ethanol, 0.3 cc. of pyridine, and 0.2 gram of semicarbazide hydrochloride in 0.3 cc. of water. The crude product melted at 209°, and, after recrystallization from methanol, at 212–213°. When mixed with authentic pyrethrone semicarbazone, no depression in the melting point was observed.

Anal. Calc'd for $C_{12}H_{17}N_3O$: C, 65.75; H, 7.76.
Found: C, 65.56; H, 7.95.

Addition of 1 mole of bromine to pyrethrone in ethanol.—Two and four-tenths grams of pyrethrone was dissolved in 20 cc. of ethanol, and a solution of 2.4 grams of bromine in 20 cc. of the same solvent was slowly added, both solutions having been cooled in a freezing mixture. The bromine was decolorized almost instantly. Twenty-three cubic centimeters of a 5 per cent. solution of potassium hydroxide in 90 per cent. ethanol was then gradually added. After standing one-half hour, the potassium bromide that had separated was removed by filtration. Upon drying, it weighed 1.8 grams.

The solution was neutralized with acetic acid and concentrated to a sirup under reduced pressure. The product was dissolved in 16 cc. of acetic acid and reduced by the gradual addition of 11 grams of zinc dust, with mechanical agitation at 100° for 2 hours. The solution was diluted with water, extracted with petroleum ether, washed with water and sodium carbonate solution, and dried. The solvent was then removed, and the residue was distilled. It yielded 0.9 gram of a fraction boiling at 85–100° and 0.35 mm. and 0.35 gram of a fraction boiling at 100–130° and the same pressure. The higher-boiling fraction contained bromine and, when treated with zinc in acetic acid as before, it yielded 0.15 gram of the low-boiling fraction. This was combined with the first fraction, and the semicarbazone was prepared in the manner already described. The yield of semicarbazone melting at 210° was 1.2 grams. The free ketone was prepared from the semicarbazone by decomposition with oxalic acid in a current of steam, and the product was isolated by extraction with ether. The ether residue was distilled, and all passed over from 85 to 90° at 0.35 mm.; n_{D}^{20} 1.5185.

This material was used for experiments to test its reactivity with maleic anhydride and α-naphthoquinone to be described later. The experiment just described demonstrated that when pyrethrone is treated with 1 mole of bromine 1 mole of hydrobromic acid is liberated.

In another experiment the bromination of pyrethrone was repeated under the same conditions. The quantities employed were 1.6 grams of pyrethrone and 1.6 grams of bromine, each dissolved in 20 cc. of ethanol. In this case the liberated hydrobromic acid was titrated with a 5.08 per cent. potassium hydroxide-ethanol solution, phenolphthalein being used as indicator. There was a temporary appearance of the pink color after addition of 9 cc., but it remained permanently after addition of 11 cc., which is the quantity corresponding to 0.81 gram of hydrobromic acid. The potassium bromide that separated was removed by filtration and dried. It weighed 1.1 grams, whereas the theoretical yield is 1.19 grams. The ethanolic solution was then placed in a flask fitted with a condenser and a mechanical stirring device, and was boiled for 6 hours with the gradual addition of 6 grams of zinc dust. After filtration the solution was evaporated to a very small volume under reduced pressure, water was added, and the reaction product was extracted with petroleum ether. The residue after removal of the solvent was distilled, and boiled at 90–95° and 0.35 mm. The distillate weighed 1.1 grams.

The semicarbazone prepared from 0.15 gram of the distillate yielded 0.17 gram melting at 216–218°.

The *p*-nitrophenylhydrazone was prepared by mixing a solution of 0.2 gram of the distillate in 1 cc. of ethanol with a solution of 0.234 gram of *p*-nitrophenylhydrazine hydrochoride in 1 cc. of water. Crystallization began in a few minutes, and after standing overnight the material was separated and washed with 50 per cent. ethanol. It was recrystallized from acetic acid, and melted at 139°. The compound was identified as the *p*-nitrophenylhydrazone of pyrethrone by the mixture melting point, which was also 139°.

The oxime was prepared from 0.2 gram of the distillate, with the substances in the same proportion as in the preparation of pyrethrone oxime. The first product was contaminated with a small quantity of oily material, which was removed by pressing between filter paper. Upon recrystallization from dilute methanol it melted at 62°. When dissolved in a little petroleum ether, filtered, and evaporated to a small volume, it separated as needles melting at 67°. A mixture melting-point determination showed it to be identical with pyrethrone oxime.

Reaction of pyrethrone with 2 moles of bromine.—Three and seventy-five hundredths grams of pyrethrone was dissolved in 20 cc. of ethanol, cooled in a freezing mixture, and a cold solution of 7.5 grams of bromine in 40 cc. of ethanol was gradually added. The bromine was absorbed instantly until about three-fourths of the solution had been added, then more slowly. The solution was colorless in about 10 minutes after all the bromine had been added. It was then titrated to a permanent alkaline reaction with 1.1 N sodium ethylate solution. This required 42 cc., or about the theoretical quantity corresponding to 3.75 grams of bromine. The solution was evaporated to a small volume under reduced pressure with separation of sodium bromide. Water was added, and the reaction product was extracted with ether. The solution was dried, and the solvent was removed, leaving 8.0 grams of yellow oil. The yield indicates that the product retains 2 atoms of bromine.

The oil was dissolved in 100 cc. of 90 per cent. ethanol and treated on the steam bath, with mechanical agitation, with 15 grams of zinc dust added gradually over a period of several hours. The reaction was then allowed to proceed overnight. The solution was separated from the zinc, and the reduction was continued for three hours longer with the addition of 10 grams more of zinc dust. The ethanolic solution was then concentrated to a sirup, which was dissolved in ether. The solution was then washed with water, dried, and the solvent was evaporated. The remaining oil weighed 3.1 grams. Upon distillation 2.1 grams of distillate boiling between 80° and 120° at 0.35 mm. was obtained. It was converted into the semicarbazone. The yield was 2.35 grams; m.p. 210°. A small quantity was recrystallized, and melted at 216°. The low yield is probably due to the formation of water-soluble pinacol, as was observed when pyrethrolone was subjected to the same treatment.

Two grams was hydrolyzed in four portions with oxalic acid in a current of steam. The yield was 1.2 grams, or 88 per cent. of the theoretical of distillate boiling at 85–90° at 0.35 mm.; n_D^{20} 1.5195, $n_F^{26} - n_C^{26}$ 0.017. The semicarbazone was prepared from 0.2 gram of the distillate, the yield being 0.25 gram. It was recrystallized from methanol, and melted at 216°. The melting point of a mixture with authentic material was 216°.

Anal. Calc'd for $C_{12}H_{17}N_3O$: C, 65.75; H, 7.76.
Found: C, 65.18, 64.98; H, 7.75, 8.10.

The p-nitrophenylhydrazone was prepared by mixing 0.2 gram of the distillate in 1 cc. of ethanol with a solution of 0.234 gram of p-nitrophenylhydrazine hydrochloride in 1 cc. of water. The crystalline mass that separated on standing was washed with 50 per cent. alcohol, and recrystallized from 90 per cent. acetic acid. It melted at 126°. After two additional crystallizations, however, the melting point was raised to 139°, and the melting point was not depressed when the material was mixed with authentic pyrethrone p-nitrophenylhydrazone. The oxime was prepared by heating 0.2 gram of distillate, 0.2 gram of hydroxylamine hydrochloride, 0.15 cc. of pyridine, and 2 cc. of ethanol in a sealed tube on the water bath overnight. Water was added to cause the separation of an oil that crystallized on cooling. The material was removed by filtration and recrystallized by dissolving it in very little methanol and adding cold 75 per cent. aqueous methanol. It formed needles that melted at 45-50°. It was evidently not pure, and was therefore dissolved in petroleum ether, filtered, and the solution was concentrated to a small volume. On cooling, needles separated, which were filtered and washed with a little of the same solvent. The process involved considerable loss, and the recrystallized substance still melted at 47-51°. Owing to lack of material further purification was not attempted.

Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.57; H, 8.47.
Found: C, 74.44, 74.18, 74.34; H, 8.56, 8.76, 8.85.

The benzoyl compound was prepared from 0.2 gram of the oxime by the method described for the preparation of pyrethrone benzoyl oxime. After two recrystallizations from petroleum ether it melted at 89°. A mixture of the product with an equal quantity of pyrethrone benzoyl oxime melted at 90-91°.

Since the derivatives obtained require more purification than the corresponding derivatives obtained from pure pyrethrone or from the product recovered after addition of 1 mole of bromine, it is apparent that a small quantity of some other substance is present in the crude material.

Reaction of pyrethrolone with 2 moles of bromine.—A solution of 4.5 grams of pyrethrolone in 40 cc. of ethanol was treated with 8.0 grams of bromine in 50 cc. of ethanol at a temperature below 0°. Decolorization took place in about 10 minutes. After addition of 50 cc. of 1 *N* sodium ethylate the solution was neutral to litmus. The solvent was removed under reduced pressure, and after addition of water the residue was extracted with ether. The dried ether solution was evaporated, and the orange-colored oil was dissolved in 50 cc. of 90 per cent. alcohol and reduced with 15 grams of zinc dust on the steam bath with mechanical stirring for six hours. After filtration and addition of 15 grams of fresh zinc dust the reduction was continued for 15 hours longer. On evaporation under reduced pressure the alcoholic solution yielded a light-yellow oil, which was taken up in ether. After washing and drying the ether solution yielded 2.8 grams of residue. It was distilled at 0.35 mm. and yielded 2.1 grams of distillate boiling at 130-140°. The semicarbazone was prepared from 0.28 gram, the yield being 0.3 gram. After recrystallization by dissolving in ethyl acetate containing a little methanol and concentration of the solution, the product melted at 208°. The melting point was not depressed when the material was mixed with pyrethrolone semicarbazone.

The aqueous washings of the product obtained on zinc reduction were extracted with ether for 15 hours on a continuous extractor. The ether solution on evaporation yielded 1.6 grams of colorless viscous oil, which was completely soluble in water. It was probably a pinacol. It decomposed on attempted distillation. The main portion of the distilled first-reaction product, assumed to be pyrethrolone, was employed for an oxidation experiment described below.

Behavior of pyrethrone with α-naphthoquinone.—Six-tenths of a gram of pyrethrone and 0.5 gram of α-naphthoquinone were dissolved in 2 cc. of ethanol and heated in a sealed tube at 100° for three hours. On cooling, crystals separated, which were filtered off and washed with cold ethanol. The product was unchanged α-naphthoquinone, of which 0.35 gram was recovered. It melted at 126°. The ethanol solution was diluted with water, and was extracted with petroleum ether. On removal of the solvent 0.5 gram of dark liquid was obtained, which yielded on distillation 0.35 gram of distillate. The semicarbazone prepared from this material melted at 214-215° and was identified as pyrethrone semicarbazone. The yield was 0.3 gram. Hence no reaction had occurred.

A similar experiment was made with the pyrethrone distillate recovered in the second experiment described, where 1 mole of bromine had been added to pyrethrone followed by zinc-alcohol reduction. One-tenth gram of the distillate was heated with 0.14 gram of α-naphthoquinone in 1 cc. of ethanol to 100° for two hours. The cooled solution deposited crystals, which were filtered off and washed with ethanol. The recovered product (0.045 gram) melted at 126° and was identified as α-naphthoquinone.

Sixteen-hundredths gram of the same distillate heated with 0.1 gram of maleic anhydride in 0.5 cc. of acetone in a sealed tube for two hours on the steam bath yielded an insoluble amorphous resin.

Pyrethrone and maleic anhydride.—When molecular proportions of pyrethrone, with or without solvent, were heated to 100°, an amorphous resin was obtained that was insoluble in all solvents. The fact that pyrethrone is very sensitive to traces of acids at this temperature indicates polymerization.

Quantitative diene-number experiments by the method of Kaufmann and Baltes[5] gave values of 17 and 12 instead of the calculated 156.5. The results can therefore be regarded as negative.

Action of perbenzoic acid on pyrethrone.—A chloroform solution of perbenzoic acid was prepared,[6] and its oxygen value was determined by titration.

One and three-tenths grams of pyrethrone was added to 33 cc. of the perbenzoic acid-chloroform solution that contained 2.2 equivalents of active oxygen. After 24 hours, titration of an aliquot of the solution indicated that 2 atoms of oxygen had been consumed. After extraction with potassium carbonate solution, the dried solution was concentrated under reduced pressure and yielded 1.8 grams of viscous, colorless sirup, which did not crystallize, and which decomposed on heating. It yielded no crystalline semicarbazone.

Eight-tenths gram of pyrethrone in 2.5 cc. of chloroform was treated with 0.8 gram of bromine in 2.5 cc. of the same solvent. The solution was extracted with 5 per cent. aqueous potassium hydroxide, followed by water, and then mixed with 15 cc. of a chloroform solution containing 0.679 gram of perbenzoic acid. After 24 hours titration indicated that practically no reaction had taken place. After 72 hours scarcely any further change had occurred, as was shown by the final titration.

Permanganate oxidation of pyrethrone.—One hundred cubic centimeters of acetone that had been treated with permanganate was placed in a flask and cooled in an ice-salt mixture. One gram of potassium permanganate and a solution of 0.4 gram of pyrethrone in 4 cc. of acetone were added, and the solution was stirred with a mechanical stirrer. After the purple color had disappeared, another gram of potassium permanganate was added, followed by 0.4 gram of pyrethrone dissolved in 4 cc. of acetone. The reaction was continued until 2.4 grams of pyrethrone had been added. The acetone solution was filtered to remove the manganese dioxide and then evaporated, and the residue was taken up in petroleum ether. After the solution had been dried and the solvent had been removed, the remaining liquid was distilled at 0.35 mm. It yielded 0.9 gram of pyrethrone, which was identified by conversion to the semicarbazone, which melted at 215°. The manganese dioxide was extracted with hot water, filtered, and the filtrate was acidified with sulfuric acid. It was extracted with ether on a continuous extractor for 24 hours. The ether extract yielded, on evaporation, a small quantity of brown residue from which crystals

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[5] KAUFMANN AND BALTES, *Fette und Seifen.*, **43**, 93 (1936).

[6] CAROTHERS (Editor-in-Chief), "Organic Syntheses," New York, **1933**, Vol. XIII, p. 86.

separated. These were removed and purified. The substance was identified as oxalic acid.

Ozonization of pyrethrolone.—One gram of pyrethrolone was dissolved in 10 cc. of carbon tetrachloride, and ozonized oxygen was passed through the solution at 0° for 7 hours. The amorphous ozonide separated during the process. Ice was added, and the vesel was shaken for 2 hours. The ozonide was not completely decomposed. After standing overnight, the aqueous solution was separated, and the organic solvent was washed with water. One-third of the total aqueous washings was added to an aqueous solution of 1.2 grams of dimethone[7] in 300 cc. of water. After 24 hours the separated addition product was removed and dried; m.p. 139°. The yield was 0.135 gram, corresponding to 0.405 gram that would have been obtained from the total aqueous washings. The theoretical yield corresponding to 1 equivalent of acetaldehyde from 1 gram of pyrethrolone is 1.73 grams. Therefore, about 23 per cent. of the acetaldehyde was recovered.

Ozonization of tetrahydropyrethrolone.—One and one-half grams of tetrahydropyrethrolone in 10 cc. of carbon tetrachloride was ozonized for 7 hours at 0°. There was no separation of ozonide. The reaction product was treated in the same manner as described in the foregoing experiment. All the aqueous washings were added to 300 cc. of an aqueous solution containing 1.2 grams of dimethone. The separated crystals melted at 128°. The yield was 0.207 gram, or 11.9 per cent. of the theory. Since the material was not pure, it may have contained some formaldehyde-dimethone addition product.

In another experiment 1 gram of tetrahydropyrethrolone was ozonized for 7 hours in 10 cc. of carbon tetrachloride. The carbon tetrachloride solution was shaken for 1 hour with 1 cc. of 30 per cent. hydrogen peroxide, washed with water, dried, and evaporated, leaving 0.65 gram of oil. It was distilled at 20 mm. and boiled at about 115°. The yield was 0.4 gram. It was identified as caproic acid.

Anal. Calc'd for $C_6H_{12}O_2$: m.w. 116.0.
Found: m.w. (titration) 116.2.

Ozonization of pyrethrone.—One gram of pyrethrone was dissolved in 10 cc. of carbon tetrachloride and cooled to 0°, and ozonized oxygen was passed through the solution for about 7 hours, or until ozone appeared at the exit tube. Some ozonide separated from the solution. The reaction product was shaken with ice and water for one hour. The aqueous solution was separated from the carbon tetrachloride and distilled into a solution of 1.6 grams of dimethone in 400 cc. of water. After standing overnight the separated crystalline deposit was removed and dried. It weighed 0.44 gram. The crude product melted over a wide range and was evidently a mixture. It was treated with dilute sulfuric acid according to the method of Vorländer,[7] and the reaction product was separated into two fractions. The yield of the part that was soluble in sodium carbonate solution was 0.22 gram. It melted at 190°. About the same quantity of material insoluble in sodium carbonate solution was obtained which, after recrystallization from 50 per cent. acetic acid, melted at 174° and was identified as the anhydride of ethylidenedimethone. The quantity obtained corresponds to 15 per cent. of the theoretical for 1 mole of acetaldehyde recovered. The material soluble in sodium carbonate was the dimethone reaction product of formaldehyde.

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[7] VORLÄNDER, *Z. anal. Chem.*, **77**, 241 (1929).

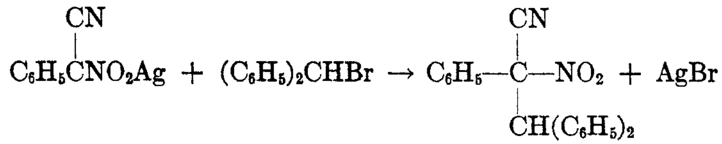
[Contribution from the Chemical Laboratory of the University of Illinois]

SALTS OF NITRO COMPOUNDS. III. THE REACTION OF THE SILVER SALT OF PHENYLNITROACETONITRILE WITH DIPHENYLBROMOMETHANE

R. L. SHRINER and G. B. BROWN

Received April 7, 1938

The alkylation of the silver salt of phenylnitroacetonitrile (I) with methyl iodide or benzyl chloride was found[1] to produce unstable nitronic esters, which showed that oxygen-alkylation had occurred. However, Wieland and Höchtlen[2] treated this same silver salt (I) with diphenylbromomethane and obtained α-nitro-α,β,β-triphenylpropionitrile (II), which involved carbon-alkylation. An examination of the literature on the alkylation of the silver salts of other nitro compounds showed that both carbon-[3] and oxygen-[4] alkylation have been reported, but that oxygen-alkylation seems to be more common. Since the course of the alkylation involving diphenylbromomethane seemed somewhat unusual, a careful study was made of this reaction in order to determine whether carbon-alkylation was the only reaction which occurred.



$$\mathrm{C_6H_5\overset{\displaystyle CN}{\overset{|}{C}}NO_2Ag} + \mathrm{(C_6H_5)_2CHBr} \rightarrow \mathrm{C_6H_5{-}\underset{\displaystyle CH(C_6H_5)_2}{\underset{|}{\overset{\displaystyle CN}{\overset{|}{C}}}}{-}NO_2} + \mathrm{AgBr}$$

I II

Treatment of the silver salt of phenylnitroacetonitrile with diphenylbromomethane did produce the carbon-alkylated compound (II) in agreement with the observations of Wieland and Höchtlen[2] but the yield of this product amounted to only 10 to 18 per cent. The major part of the reac-

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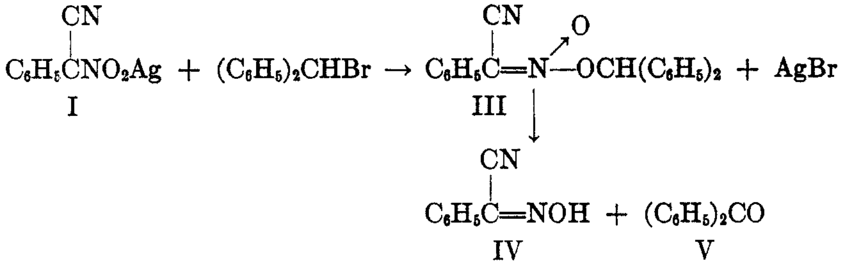
[1] Thurston and Shriner, *J. Org. Chem.*, **2**, 183 (1937).

[2] Wieland and Höchtlen, *Ann.* **505**, 237 (1933).

[3] Nef, *Ann.*, **280**, 263 (1894); Duden, *Ber.*, **26**, 3008 (1893); Ulpiani, *Atti. acad. Lincei*, [5], **12**, I, 439 (1903): *Chem. Zentr.*, **74**, II, 346 (1903); Hantzsch, *Ber.*,**39**, 2472 (1906); Steinkopf, *Ann.*, **434**, 21 (1923).

[4] Ratz, *Monatsh.*, **25**, 55 (1904); Kohler and Stone, *J. Am. Chem. Soc.*, **52**, 761 (1930); Nenitzescu and Isacescu, *Ber.*, **63**, 2484 (1930), *Bull. soc. chim. Rom.*, **14**, 53 (1932); Thurston and Shriner, *J. Am. Chem. Soc.*, **57**, 2163 (1935); Wislicenus and Elvert, *Ber.*, **41**, 4121 (1908).

tion mixture was composed of benzoylcyanide oxime (IV) and benzophenone (V) which would be the decomposition products expected if the nitronic ester (III) had been produced and then disproportionated.



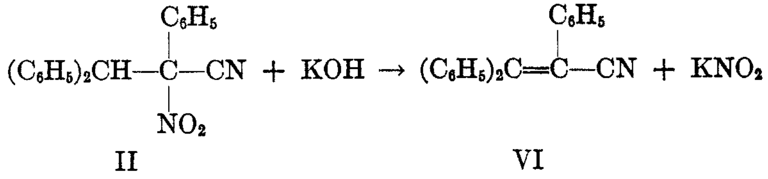
$$\underset{\text{I}}{C_6H_5\overset{CN}{\overset{|}{C}}NO_2Ag} + (C_6H_5)_2CHBr \rightarrow \underset{\text{III}}{C_6H_5\overset{CN}{\overset{|}{C}}{=}\overset{\nearrow O}{N}{-}OCH(C_6H_5)_2} + AgBr$$

$$\downarrow$$

$$\underset{\text{IV}}{C_6H_5\overset{CN}{\overset{|}{C}}{=}NOH} + \underset{\text{V}}{(C_6H_5)_2CO}$$

This decomposition of a nitronic ester into an oxime and a ketone or aldehyde has been shown to be characteristic of such structures.[5] The quantities of these two products which were isolated amounted to about 50 per cent. of the theoretical yield, and indicated that oxygen-alkylation predominates over carbon-alkylation. The balance of the reaction mixture was composed of a mixture of the reactants and their decomposition products.

The second part of the present study was concerned with the proof of structure of the carbon-alkylation product, α-nitro-α,β,β-triphenylpropionitrile (II). No independent synthesis of this compound has ever been carried out. Its structure was based upon an analysis and the fact that alcoholic potassium hydroxide converted it into triphenylacrylonitrile (VI).[2]



$$\underset{\text{II}}{(C_6H_5)_2CH{-}\underset{NO_2}{\underset{|}{\overset{C_6H_5}{\overset{|}{C}}}}{-}CN} + KOH \rightarrow \underset{\text{VI}}{(C_6H_5)_2C{=}\overset{C_6H_5}{\overset{|}{C}}{-}CN} + KNO_2$$

In the course of the present work, triphenylacrylonitrile was obtained, not only by the action of alkali, but also by the action of phosphorus and hydriodic acid, on II. The triphenylacrylonitrile (VI) was characterized

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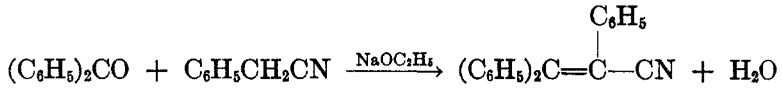
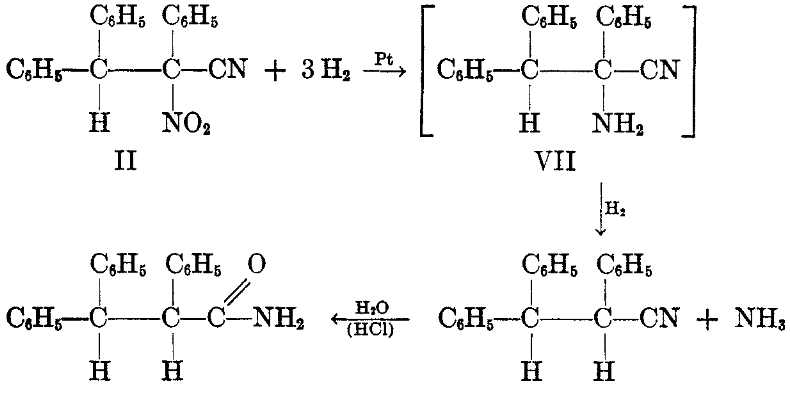
[5] Ratz, *Monatsh.*, **26**, 1487 (1905); Kohler and Stone, *J. Am. Chem. Soc.*, **52**, 761 (1930); Nenitzescu and Isacescu, *Ber.*, **63**, 2484 (1930); *Bull. soc. chim. Rom.*, **14**, 53 (1932); *ibid.*, **18**, 63 (1936); Arndt and Rose, *J. Chem. Soc.*, **1935**, 1; Thurston and Shriner, *J. Am. Chem. Soc.*, **57**, 2163 (1935); *J. Org. Chem.*, **2**, 183 (1937); Arndt, Loewe, and Isik, *Rev. fac. sci. Univ. Istanbol*, **2**, 1 (1937).

by comparison with an authentic sample synthesized by the following reaction according to the method of Bodroux.[6]



$$(C_6H_5)_2CO + C_6H_5CH_2CN \xrightarrow{NaOC_2H_5} (C_6H_5)_2C{=}\overset{C_6H_5}{\overset{|}{C}}{-}CN + H_2O$$

The most conclusive evidence supporting the structure assigned to the carbon-alkylation product (II) was obtained by characterizing the products obtained by catalytic reduction. Treatment of an alcohol solution of the compound II with platinum and hydrogen at room temperature produced ammonia and a 93 per cent. yield of α,β,β-triphenylpropionitrile (VIII).



$$\underset{\text{II}}{C_6H_5{-}\underset{H}{\overset{C_6H_5}{C}}{-}\underset{NO_2}{\overset{C_6H_5}{C}}{-}CN} + 3\,H_2 \xrightarrow{Pt} \underset{\text{VII}}{\left[C_6H_5{-}\underset{H}{\overset{C_6H_5}{C}}{-}\underset{NH_2}{\overset{C_6H_5}{C}}{-}CN\right]}$$

$$\text{VII} \xrightarrow{H_2} \underset{\text{VIII}}{C_6H_5{-}\underset{H}{\overset{C_6H_5}{C}}{-}\underset{H}{\overset{C_6H_5}{C}}{-}CN} + NH_3$$

$$\underset{\text{IX}}{C_6H_5{-}\underset{H}{\overset{C_6H_5}{C}}{-}\underset{H}{\overset{C_6H_5}{C}}{-}\overset{O}{\overset{\|}{C}}{-}NH_2} \xleftarrow[(HCl)]{H_2O} \text{VIII}$$

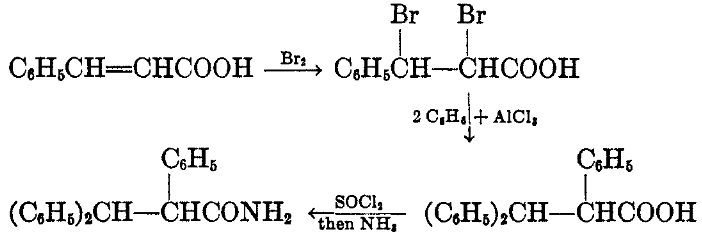
II

VII

IX

VIII

The reduction of the nitro group in II would produce the substituted α-amino nitrile (VII) which readily undergoes hydrogenolysis[7] to the nitrile (VIII). The latter was characterized by heating it in a sealed tube with concentrated hydrochloric acid at 170°; under these conditions it was hydrolyzed to the amide (IX) which was identical with a sample synthesized by the following reactions:



$$C_6H_5CH{=}CHCOOH \xrightarrow{Br_2} C_6H_5\overset{Br}{\overset{|}{C}}H{-}\overset{Br}{\overset{|}{C}}HCOOH$$

$$\xrightarrow{2\,C_6H_6 + AlCl_3} (C_6H_5)_2CH{-}\overset{C_6H_5}{\overset{|}{C}}HCOOH \xrightarrow[\text{then } NH_3]{SOCl_2} \underset{\text{IX}}{(C_6H_5)_2CH{-}\overset{C_6H_5}{\overset{|}{C}}HCONH_2}$$

IX

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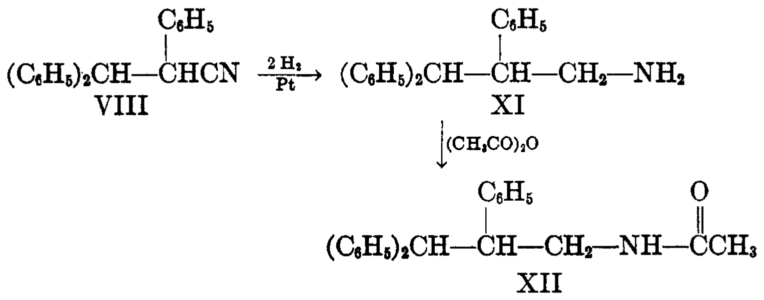
[6] Bodroux, *Compt. rend.*, **152**, 1596 (1911).

[7] See Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, **1937**, pp. 88, 139, for a discussion of hydrogenolysis of this type of molecule.

If the reduction of II was carried out in acetic anhydride solution, two products were obtained. One of these was the triphenylpropionitrile (VIII) and the other proved to be *N*-(2,3,3-triphenyl-*n*-propyl)acetamide (XII). The latter was evidently formed by further reduction of the nitrile (VIII).



$$\underset{\text{VIII}}{(C_6H_5)_2CH{-}\overset{\overset{\displaystyle C_6H_5}{|}}{C}HCN} \xrightarrow[Pt]{2\,H_2} \underset{\text{XI}}{(C_6H_5)_2CH{-}\overset{\overset{\displaystyle C_6H_5}{|}}{C}H{-}CH_2{-}NH_2}$$

$$\Big\downarrow (CH_3CO)_2O$$

$$\underset{\text{XII}}{(C_6H_5)_2CH{-}\overset{\overset{\displaystyle C_6H_5}{|}}{C}H{-}CH_2{-}NH{-}\overset{\overset{\displaystyle O}{\|}}{C}CH_3}$$

In order to prepare a sample of the amide (XII), it was found more convenient to reduce the nitrile (VIII) by means of Raney nickel catalyst at a temperature of 120° and a hydrogen pressure of 2500 pounds. Subsequent acetylation of the amine (XI) gave the amide (XII), which was identical with the amide obtained from II by reduction with platinum and hydrogen.

The formation of these compounds (VIII and XII) leaves no doubt that the carbon-alkylation product is α-nitro-α,β,β-triphenylpropionitrile.

It is of interest to point out that this α-nitro-α,β,β-triphenylpropionitrile (II) is an example of a highly substituted ethane which might conceivably undergo dissociation in a manner analogous to that exhibited by pentaphenylethane.[8] However, the above-mentioned action of hydriodic acid produced no diphenylmethane and a boiling benzene solution of the compound was not affected by air. Pyrolysis did not yield tetraphenylethane, which might be expected if a diphenylmethyl radical had been produced by dissociation. The thermal decomposition products were triphenylacrylonitrile, tetraphenylethylene, benzoic acid, benzophenone and oxides of nitrogen.

EXPERIMENTAL

Silver aci-*phenylnitroacetonitrile*.—A solution of 46.0 g. of silver nitrate in 200 cc. of water was added, with vigorous stirring, to 300 cc. of water containing 50.0 g. of sodium *aci*-phenylnitroacetonitrile, prepared according to the method of Wislicenus and Enders.[9] The silver salt separated immediately as a yellow precipitate. It was collected on a filter, washed by suspending it in 500 cc. of absolute alcohol,

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[8] Bachman, *J. Am. Chem. Soc.*, **55**, 3005 (1933).

[9] Wislicenus and Enders, *Ber.*, **35**, 1755 (1902).

and again collected on a filter. After removing most of the liquid it was dried in a vacuum desiccator over calcium chloride, or used immediately. The yield was almost theoretical, and the salt is stable.

Anal. Calc'd for $C_8H_5N_2O_2Ag$: Ag, 40.10. Found: Ag, 40.18, 39.80.

Reaction of diphenylbromomethane with silver aci-*phenylnitroacetonitrile.*—Seventy grams of the silver salt (0.260 mole) was suspended in 200 cc. of benzene, and 67.0 g. of diphenylbromomethane (0.271 mole), prepared according to the method of Courtot,[10] was added, with stirring, over a period of one-half hour, the temperature being kept below 20° by means of a water bath. The stirring was continued for twenty-one hours at room temperature. At the end of this time the insoluble salts were removed by filtration, washed with benzene and dried in a vacuum desiccator; their total weight was 50.1 g. An analysis of this precipitate showed that it contained 5.3 per cent. of the original silver salt and 94.7 per cent. silver bromide.

The red benzene solution and the wash benzene from the silver salts was evaporated under reduced pressure, 100 cc. of 70 per cent. aqueous alcohol was added, and the solution was placed in the refrigerator overnight. Seven and one-half grams of crude α-nitro-α,β,β-triphenylpropionitrile, melting at 141–142°, crystallized. Recrystallization from alcohol, with the use of Norite to decolorize the solution, followed by two recrystallizations from acetic acid and two more from alcohol, raised the melting point to 144.5 to 145° (decomp.) which is the melting point previously recorded.[2] An analysis was made on the purified material in order to check its composition since the previously reported analyses differed somewhat from the calculated.

Anal. Calc'd for $C_{21}H_{16}N_2O_2$: C, 76.82; H, 4.88; N, 8.53; mol. wt., 328.3.
Found: C, 76.68; H, 4.77; N, 8.60; mol. wt., 316.

This represented a yield of 8.78 per cent. In other runs in which the time of stirring varied from two to forty-eight hours the yields were 9.9, 7.2, 9.7 and 10.6 per cent. When the benzene was removed at reduced pressure without heating, and the recrystallizations carried out at temperatures not exceeding 40–50° the yields were 15.0 and 18.5 per cent.

The solution from the above crystallization was evaporated in a current of air, the residue was dissolved in 150 cc. of chloroform and extracted with five 60-cc. portions of 10 per cent. aqueous sodium hydroxide. The sodium hydroxide solution was washed twice with chloroform and acidified with dilute acetic acid. The dark oil which separated was dissolved in a large volume of water, and the solution was cooled. Benzoyl cyanide oxime (10.3 g.) melting at 126–127° crystallized. This represented 28.1 per cent. of the original silver salt.

The chloroform solution from the above extraction was dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue of 67 g. was dissolved in 150 cc. of alcohol and to the solution were added 17.5 g. of hydroxylamine hydrochloride in 60 cc. of water and 25 g. of potassium hydroxide. The solution was refluxed for seven and one-half hours, during which time the evolution of ammonia was noted. The solution was cooled, 50 cc. of 25 per cent, sodium hydroxide was added, and the whole was extracted five times with ether. The alkaline solution was then poured into 500 cc. of water and acidified with acetic acid. Seven and six-tenths grams of light yellow leaflets separated, and was dried in a vacuum desiccator over calcium chloride. Without further recrystallization this benzophenone oxime melted at 139–140°. This represented 14.8 per cent. of the theoretical yield.

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[10] COURTOT, *Ann. chim.*, [9], **5**, 80 (1916).

The acidified solution was extracted with ether, and the ether was removed under reduced pressure, leaving approximately 5 g. of oily residue. It was recrystallized from alcohol and a compound was obtained which charred at 238° and melted at 245–249°, with decomposition. This is probably a polymerization product of benzoylcyanide similar to that reported by Diels and Stein.[11]

The ether extract from the benzophenone oxime preparation was concentrated, and the 52 g. of red-brown oil which remained was taken up in methyl alcohol; no crystallization occurred. The solvent was removed, and the oil was distilled at 105–138°/3 mm. All fractions of the distillate showed the presence of a ketone and were combined and heated with 200 cc. of an alcoholic solution of 2,4-dinitrophenylhydrazine. A total of 31.0 g. of benzophenone 2,4-dinitrophenylhydrazone, melting at 234.5°, was obtained. This represents 16 g. of benzophenone or 33.8 per cent. of the theoretical yield. The total quantity of benzophenone recovered as the oxime and 2,4-dinitrophenylhydrazone was 48.6 per cent.

The filtrates from this hydrazone preparation, which were ketone-free, were concentrated under reduced pressure and washed with 5 per cent. hydrochloric acid, to remove any unchanged 2,4-dinitrophenylhydrazine. Twenty grams of a yellow-orange oil remaining deposited crystals after standing several weeks. These crystals were identified as benzohydryl ether melting at 107–108°. The remainder of the oil was a mixture of benzohydrol, benzohydryl ether, and diphenylbromomethane.

The 10 cc. of residue left from the distillation was sublimed at 3 mm. against a tube cooled by acetone-dry ice. The fractions up to 160° were liquid at room temperature and those from 160–240° were semi-solid. The higher fractions were crystallized from alcohol, yielding 1.0 g. of a product melting at 107–108°. A mixture with a sample of benzohydryl ether, synthesized by the method of Schenk,[12] showed no depression of the melting point. The benzohydrol and benzohydryl ether have been shown to be produced by the hydrolysis of diphenylbromomethane.[12]

Action of alcoholic potassium hydroxide on α-nitro-α,β,β-triphenylpropionitrile.—One gram of the nitrile (0.00342 mole) was suspended in 17 cc. of 1.0 per cent. methyl alcoholic potassium hydroxide (0.0034 mole) and refluxed for fourteen hours. Concentration and cooling of the solution yielded 0.7 g. of crystals which melted at 165–166° after recrystallization from methanol. A mixture of this product with synthetic triphenylacrylonitrile prepared as described below showed no depression of the melting point. It gave a violet color with concentrated sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}N$: N, 4.99. Found: N, 5.08.

The filtrate was evaporated to dryness and extracted with ether. The presence of nitrites in the ether-insoluble residue was demonstrated by treatment with potassium iodide solution and hydrochloric acid.

Action of hydrogen iodide on α-nitro-α,β,β-triphenylpropionitrile.—Under an atmosphere of nitrogen in an all glass apparatus 2.4 g. of red phosphorus and 0.2 g. of iodine in 60 cc. of glacial acetic acid were allowed to react for twenty minutes. Four grams of the nitrile and 2.0 cc. of water were added, and the solution was refluxed for fifty minutes. The acetic acid solution was filtered and concentrated, yielding 1.0 g. of a substance, which, after two recrystallizations from alcohol, melted at 164.5–165.5°. A mixture with synthetic triphenylacrylonitrile showed no depression of the melting point.

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[11] Diels and Stein, *Ber.*, **40**, 1655 (1907).

[12] Schenk, *Pharm. Ztg.*, **54**, 725 (1909).

Synthesis of triphenylacrylonitrile.—The method of Bodroux[6] was used in the preparation of this compound. To 125 cc. of dry ether in a three-necked flask fitted with a mercury-sealed stirrer and a condenser were added 11 g. of sodamide and 30 g. of benzyl cyanide. The mixture was refluxed for three hours to insure complete formation of the sodium salt. At the end of this time 44 g. of benzophenone, dissolved in 60 cc. of dry ether, was added. A reaction took place immediately, and the mass became quite thick. Stirring was continued for two hours. Fifty cubic centimeters of water, followed by 50 cc. of concentrated hydrochloric acid, was added. The insoluble product was filtered and recrystallized from 400 cc. of alcohol. The yield of the product, melting at 166–166.5°, was 17.2 g. or 25 per cent. of the theoretical.

Reduction of α-nitro-α,β,β-triphenylpropionitrile.—

1. To 50 cc. of acetic anhydride was added 5 g. of the nitrile (0.0152 mole) and 0.2 g. of platinum oxide. In fourteen hours, with the addition of another 0.2 g. of platinum oxide after the sixth hour, 0.057 mole of hydrogen was absorbed. The platinum was removed by filtration, and the acetic anhydride was decomposed with water and evaporated at reduced pressure. The sticky substance which remained was repeatedly crystallized from aqueous alcohol, yielding a small quantity of a white compound melting at 100–101°, a large amount of a mixture melting between 95 and 105°, and a small amount of a compound melting at 143–144°.

2. The above procedure was repeated but the solution was poured into 40 per cent. sodium hydroxide to decompose the acetic anhydride. After dilution this was extracted three times with chloroform; the chloroform solution was dried over magnesium sulfate and evaporated at reduced pressure. The viscous oil remaining was dissolved in 10 cc. of hot ethyl acetate, and 50 cc. of high-boiling petroleum ether was added. After standing twelve hours crystals separated from the light-brown solution. After two recrystallizations from ethyl acetate and high-boiling petroleum ether 1.7 g. of product melting at 140–142° was obtained. Further recrystallizations from 70 per cent. aqueous alcohol yielded fine needles melting at 143.5–144.0°. A mixture with *N*-(2,3,3-triphenyl-*n*-propyl)acetamide, prepared as described below, showed no depression of the melting point.

Anal. Calc'd for $C_{23}H_{23}NO$: C, 83.97; H, 6.99; N, 4.25; mol. wt., 329.
Found: C, 84.14; H, 7.07; N, 4.25; mol. wt., 304.

3. To 140 cc. of absolute alcohol was added 5.0 g. of the nitrile (0.0152 mole) and 0.24 g. of platinum oxide. After twenty-five minutes 0.0529 mole of hydrogen was absorbed, and no further absorption took place during the next hour. The solution, which was strongly ammoniacal, was concentrated under reduced pressure, yielding a total of 4.0 g. of α,β,β-triphenylpropionitrile which melted at 101.5–102° after two recrystallizations from alcohol. A mixture with the low-melting compound obtained in the first reduction above showed no depression of the melting point. The yield was 93 per cent. of the theoretical.

Anal. Calc'd for $C_{21}H_{17}N$: N, 4.96. Found: N, 5.17.

Hydrolysis of α,β,β-triphenylpropionitrile.—Five-tenths of a gram of the compound melting at 101.5–102° in 12 cc. of concentrated hydrochloric acid was heated in a sealed tube at 170° for four hours.[13] The long needles which were present after the tube cooled were removed by filtration, washed by heating with sodium bicarbonate solution, and twice recrystallized from alcohol. They melted at 209°. If placed in the melting point bath at 200° the crystals melted at 210.3°. A mixture

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[13] Kohler, *Am. Chem. J.*, **35**, 401 (1906).

of this compound with a synthetic sample prepared as described below showed no depression of the melting point.

α,β,β-Triphenylpropionamide.—The necessary α,β,β-triphenylpropionic acid was synthesized by the following method.[14] In a 1-l. three-necked flask fitted with a dropping funnel, mercury-sealed stirrer, and a thermometer, were placed 50 g. of cinnamic acid and 100 cc. of dry ether. The solution was cooled to 10–15° with an ice-water bath, and 54 g. of bromine was added with stirring at such a rate that the temperature did not rise above 20°. The flask was then fitted for downward distillation, and the ether was removed, care being taken to remove the last traces of ether by heating on a water bath at reduced pressure. The cake was broken into small lumps and covered with 400 cc. of thiophene-free benzene. Stirring was started, and 70 g. of aluminum chloride was added, in small portions, to the suspension heated to 60°. After all the aluminum chloride was added the content of the flask was refluxed for about fifteen minutes. The mixture was cooled and poured on 1 kg. of cracked ice and 25 cc. of hydrochloric acid. The whole was transferred to a flask and distilled until water-clear. The solid residue was filtered from the hot aqueous solution and washed with two 1-l. portions of warm water. The dried solid was then boiled with 500 cc. of 5 per cent. sodium carbonate until most of the organic matter dissolved. The solution was filtered, and, while still hot, was decomposed with dilute hydrochloric acid. The precipitated acid was washed well with warm water and dried. It was recrystallized from hot alcohol with the aid of Norite. Colorless crystals of the α,β,β-triphenylpropionic acid which melted at 208° were obtained. Eighty grams of this acid was refluxed with 270 g. of thionyl chloride for one hour. The excess thionyl chloride was removed by distillation under reduced pressure.

To insure complete removal of the thionyl chloride 200 cc. of benzene was added to the residue and distilled. The residue was dissolved in 300 cc. of high-boiling petroleum ether and saturated with ammonia. After removal of the precipitated amide by filtration, the solution was again saturated with ammonia, and a second crop of crystals was obtained. The combined portions of the amide were dried on a suction funnel, and then boiled with two 500-cc. portions of 5 per cent. sodium carbonate solution, and then with two 300-cc. portions of water. After drying, the crude product was recrystallized three times from 500-cc. portions of alcohol. Further recrystallization did not change the melting point. A 62 per cent. yield of colorless crystals was obtained. The amide melted at 208–209°. If placed in a hot bath it melted at 210° which is 3° lower than the melting point reported by Kohler.[13]

Anal. Calc'd for $C_{21}H_{19}NO$: N, 4.65. Found: N, 4.71.

Reduction of α,β,β-triphenylpropionitrile.—To 1.3 g. of the nitrile in 100 cc. of dioxane was added 0.5 g. of Raney nickel, and this was treated with hydrogen for thirty minutes at 120° and 2500 pounds pressure.[15] The Raney nickel was removed by filtration, and the dioxane was distilled at reduced pressure. To the sticky residue was added 10 cc. of acetic anhydride and the solution refluxed for ten minutes. The acetic anhydride was decomposed by the addition of water and removed by allowing it to stand overnight in a vacuum desiccator with soda-lime. The solid residue was recrystallized once from a mixture of ethyl acetate and high-boiling petroleum ether and three times from aqueous alcohol, yielding 0.3 g. of fine needles melting at 143–144°. A mixture with *N*-(2,3,3-triphenyl-*n*-propyl)acetamide, described above, showed no depression of the melting point.

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[14] Private communication, C. F. Koelsch, University of Minnesota.

[15] Ref. 7, page 53.

Pyrolysis of α-nitro-α,β,β-triphenylpropionitrile.—One gram of the nitrile was heated to 160°, the compound melting and decomposition taking place with evolution of nitrogen dioxide and darkening of the liquid. Crystallization of the product from alcohol yielded approximately 0.25 g. of a solid melting at 210–213°, the separation of which was accomplished by sublimation against a tube cooled by acetone-dry ice. The first fraction, about 15 mg., was collected to 205°/18 mm. After recrystallization from alcohol this melted at 165°, and gave a violet color when dissolved in sulfuric acid; a mixture with triphenylacrylonitrile showed no depression of the melting point. The second fraction of the sublimate was collected from 205–270°/18 mm. and melted at 200–205°.

The unsublimed residue, after two recrystallizations from 100-cc. portions of alcohol, melted at 222–223° and a mixture with a sample of tetraphenyl ethylene, prepared according to the method of Lohse,[16] showed no depression of the melting point.

The original alcohol filtrate was treated with 2,4-dinitrophenylhydrazone, yielding benzophenone 2,4-dinitrophenylhydrazone melting at 237–238°.

Anal. Calc'd for $C_{19}H_{14}N_4O_4$: N, 15.46. Found: N, 15.27.

The remaining solution was concentrated and added to 50 cc. of 5 per cent. sodium hydroxide, the alkaline solution was extracted with ether, acidified and again extracted with ether. The ether extract of the acidified solution was evaporated, and the residue was recrystallized from water, melting at 120°. This acid, upon treatment with thionyl chloride and then with aniline yielded benzanilide melting at 160°.

ACKNOWLEDGMENT

The authors are indebted to J. T. Thurston for the syntheses of triphenylacrylonitrile and α,β,β-triphenylpropionamide.

SUMMARY

The mixture of compounds formed in the reaction between silver phenylnitroacetonitrile and diphenylbromomethane has been examined and shown to consist of:

(*a*) α-nitro-α,β,β-triphenylpropionitrile,
(*b*) benzophenone,
(*c*) benzoylcyanide oxime,
(*d*) unchanged silver salt,
(*e*) decomposition products of the above; a *tris*-benzoylcyanide, benzohydrol and benzohydryl ether

The amounts of these products isolated indicated that carbon alkylation had taken place to the extent of 10 to 18 per cent., and that oxygen alkylation amounted to about 48 per cent.

Further proof of the structure assigned to α-nitro-α,β,β-triphenylpropionitrile has been obtained by showing that catalytic reduction produces α,β,β-triphenylpropionitrile and 2,3,3-triphenyl-*n*-propylamine which was isolated as its acetyl derivative.

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[16] Lohse, *Ber.*, **29**, 1789 (1896).

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

OXYGEN EXCHANGE REACTIONS OF BENZALDEHYDE AND SOME OTHER SUBSTANCES

MURRAY SENKUS and WELDON G. BROWN

Received April 13, 1938

Through the courtesy of Professor H. C. Urey in making available to us some water in which the 0^{18} content had been reduced below normal by fractional distillation, we have been enabled to examine the exchange of oxygen between water and a number of organic substances. Experiments of this type have been reported recently by Cohn and Urey[1] who have found that in general the oxygen in carboxyl groups and in carbonyl groups is exchangeable while the oxygen in hydroxyl groups is not. They found further that the exchange reaction of acetone is subject to catalysis by both acids and bases, and, by a kinetic study, were able to show that the exchange does not proceed through the enolic form of acetone. Our results parallel those of Cohn and Urey to the extent that they deal with similar substances; thus we have found that the exchange reaction of benzaldehyde with water is very sensitive to catalysis by both acids and bases. We have also found in the exchange reaction of a tertiary alcohol trianisylcarbinol, a reaction which is subject to acid catalysis.

Our experimental method involved the use of the temperature-float method on a semi-micro scale to determine the density of water samples of about 0.5 cc. As Cohn and Urey have pointed out, the study of exchange reactions by means of density determinations is subject to certain disadvantages, as compared with the mass-spectrograph method which they used, chief among which is the necessity for very careful purification of the water samples. The difficulty is still further enhanced when it is necessary to work with very small quantities of liquid. Certainly our procedure leaves something to be desired, as it is not ordinarily possible with it to obtain results which are consistent to better than 7 or 8 p.p.m. in density. The isotopic water with which the experiments were carried out was 190 p.p.m. less dense than normal water, and thus the precision was of such an order that the occurrence of an exchange reaction could only be established with certainty if it produced a change in this density difference of at least 7 per cent.

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[1] Cohn and Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).

The reaction mixtures were contained in sealed tubes, and, where the mixture was not homogeneous, the tubes were mounted in a shaker producing violent agitation. The water was removed from the aqueous solutions by distillation, and purified by heating in sealed tubes with weighed quantities of potassium permanganate and sodium hydroxide.

TABLE I

EXPERIMENTAL DATA

	COMPOSITION OF REACTION MIXTURE				TEMP., °C.	TIME OF REACTION (HOURS)	FLOATING TEMP.*	EXTENT OF EXCHANGE
	Substance	Grams	Water	Catalyst				
1	Urea	0.554	0.721	None	25	2.5	2.535	None
2	Urea	0.858	0.512	None	25	24	2.555	None
3	Citric acid	1.710	0.730	None	25	24	2.550	None
4	Citric acid	1.747	0.823	None	75	24	2.855	91%
5	Citric acid	1.795	0.875	5 mg. H_2SO_4	25	28	2.600	19%
6	Citric acid	2.354	1.281	50 mg. H_2SO_4	25	24	2.632	30%
7	Citric acid	2.000	0.863	190 mg. H_2SO_4	25	24	2.705	41%
8	Sod. acetate	1.394	1.458	None	25	24	2.555	None
9	Benzaldehyde	2.650	1.707	None	25	100	2.685	Complete
10	Benzaldehyde	6.083	1.482	None	25	20	2.735	85%
11	Benzaldehyde	8.634	1.591	None	25	1	2.630	31%
12	Benzaldehyde	25.31	3.207	None	25	4	2.745	62%
13	Benzaldehyde	10.69	1.443	23 mg. H_2SO_4	25	3.5	2.875	Complete
14	Benzaldehyde	12.49	1.653	9 mg. H_2SO_4	25	1	2.850	Complete
15	Benzaldehyde	14.26	1.821	4 mg. KOH	25	3.5	2.865	Complete
16	Benzaldehyde	12.93	1.689	10 mg. KOH	25	1	2.875	Complete
17	Alloxan hydrate	3.560	2.252	None	25	16	2.665	48%
18	Alloxan hydrate	1.633	1.057	None	25	110	2.704	61%
19	Alloxan hydrate	2.717	1.154	None	25	430	2.825	87%
20	Diphenylmethylcarbinol	11.31	1.806	None	95	10.5	2.560	None
21	Diphenylmethylcarbinol	12.05	2.286	6 mg. KOH	95	22	2.560	None
22	Trianisyl carbinol	9.159	0.608	None	95	43	2.560	None
23	Trianisyl carbinol	7.755	0.739	8 mg. H_2SO_4	95	24	2.730	Complete
24	Trianisyl carbinol	5.826	0.796	6 mg. H_2SO_4	95	1	2.680	86%
25	Trimethylcarbinol	11.34	2.022	None	25	10	2.555	None
26	Trimethylcarbinol	11.36	2.010	20 mg. H_2SO_4	25	10	2.565	None
27	Trimethylcarbinol	5.687	1.953	23 mg. H_2SO_4	95	2	2.550	None
28	Trimethylcarbinol	5.522	2.008	None	95	20	2.550	None

* The floating temperatures given are readings on a Beckmann thermometer. On the same scale the floating temperature for normal water is 3.105°, for the light water used in these experiments 2.545°.

The samples were then distilled twice *in vacuo*, the final receiver being that in which the floating temperature was determined. In all cases blank experiments, using normal water, were conducted as a check on the method of purification; these indicated the necessity for minor modifications of the procedure in certain instances.

The experimental results are summarized in Table I. In confirmation of the result of Cohn and Urey, urea was found to exhibit no exchange at room temperature. The behavior of citric acid is of interest in that it shows definite acid catalysis, as might be expected in view of the acid catalysis of esterification reactions. Cohn and Urey observed a correlation between the ease of exchange and the acid strength of carboxylic acids; the effect would therefore seem to be primarily one of self-catalysis.

The discovery that benzaldehyde undergoes a rapid exchange of oxygen with water came as a distinct surprise, especially in view of the limited solubility of this substance in water (0.3 parts per 100). It is known, of course, that acetaldehyde shows a rapid exchange reaction, both from the work of Cohn and Urey and from the work of Herbert and Lauder,[2] and it is to be expected that all aldehydes which are sufficiently soluble in water would exchange oxygen readily. Comparing our results on benzaldehyde in neutral solution with those of Herbert and Lauder on acetaldehyde it will be seen that the benzaldehyde reaction proceeds nearly, but not quite, as fast as the acetaldehyde reaction, and allowing for the enormous difference in concentrations of the aldehydes, it would appear that the specific rate constant for benzaldehyde must be very much greater than for acetaldehyde. This is certainly at variance with what is known of the relative reactivities of these aldehydes in the majority of their reactions. In view of the sensitivity of benzaldehyde to autoöxidation, the acidic character of the oxidation product, benzoic acid, and the high sensitivity of the exchange reaction to acid catalysis, it may be mentioned that the benzaldehyde used in these experiments was carefully purified with respect to the elimination of benzoic acid and oxygen. It was first extracted with dilute sodium hydroxide solution, washed rapidly with water, dried, and distilled twice at 1 mm. pressure, and collected finally in the reaction tube. The isotopic water was also introduced by vacuum distillation, and air was not admitted to the system until the reaction tube had been sealed off.

The occurrence of catalysis by both sulfuric acid and by potassium hydroxide is of interest in that it provides further evidence of the amphoteric character of the carbonyl group. In the case of acetone, Cohn and Urey reached the conclusion that the enolic form is not involved in the exchange

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[2] Herbert and Lauder, *Trans. Faraday Soc.*, **34**, 433 (1938).

reaction only after a detailed kinetic analysis. The experiments with benzaldehyde, which is not capable of enolization, are perhaps even more convincing.

Cohn and Urey, having found no exchange to occur with methyl alcohol, glycerol, and phenol, concluded that the oxygen of hydroxyl groups is not exchangeable, and insofar as non-catalyzed exchange reactions are concerned, we have confirmed this conclusion with respect to dextrose, tertiary butyl alcohol, diphenylmethylcarbinol, and trianisylcarbinol. The experiments with dextrose were undertaken with particular reference to the exchange of the carbonyl oxygen and its relationship to the process of mutarotation, and are not reported herein as we have not yet obtained conclusive results in this connection. However, with regard to the remaining oxygen atoms in this molecule, no exchange was observed either at 25° for 24 hours or at 75° for 2 hours.

The non-occurrence of an exchange reaction with hydroxyl groups as in primary and secondary alcohols, and in the simple phenols, is not suprising, but it seemed not altogether improbable that we should find among the tertiary alcohols some cases in which exchange would occur readily. The particular cases would be those in which the hydroxyl group is attached to a radical which is very weakly electronegative in the sense of the electronegativity theory of Kharasch, Reinmuth, and Mayo.[3] This involves the use of alcohols of high molecular weight and of low solubility in water, but we were encouraged by our success with benzaldehyde to proceed. The experiments were limited, however, to alcohols of low melting point and the reactions were carried out at temperatures above the melting points. No exchange was observed in neutral solution with diphenylmethylcarbinol, nor with trianisylcarbinol. The latter represents, in the ease of substitution of the hydroxyl group, about as favorable a case as we could secure.

It is to be expected, in view of the circumstances under which alcoholic hydroxyl groups may be substituted or eliminated, that exchange reactions involving such groups would be acid-catalyzed, and, in the absence of exchange in neutral solution, it was anticipated that the predicted labilization of hydroxyl groups by very weakly electronegative groups could be demonstrated by examining the acid-catalyzed reaction. It was found that the exchange reaction of trianisylcarbinol is catalyzed to an extraordinary degree by sulfuric acid. With 6 milligrams of sulfuric acid in 0.8 gram of water the exchange was practically complete in 1 hour at 95°, whereas in the absence of acid no exchange had occurred in 43 hours at the same temperature. For comparison, the results with tertiary butyl

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[3] KHARASCH, REINMUTH, AND MAYO, *J. Chem. Educ.*, **13**, 7 (1936), and preceding papers cited therein.

alcohol are given, showing that with four times as much acid and twice the time of reaction no exchange took place. The acid is actually more dilute in this case, since teritary butyl alcohol is miscible with water, but on the other hand the solubility of trianisylcarbinol in water is very low, even at 95°, and, although it is not known exactly, it is certainly very much less than that of benzaldehyde. These experiments constitute, in our opinion, a very striking demonstration of the effect of certain substituents in labilizing hydroxyl groups.

The oxygen exchange of alloxan appears to take place in a step-wise fashion, and although our experiments on this substance do not reveal the sequence of events, it is evident that, given sufficient time, all of the oxygen atoms in this molecule are exchangeable at room temperature.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

FACTORS AFFECTING THE ADDITION OF BROMINE TO PHENANTHRENE

M. S. KHARASCH, P. C. WHITE, AND F. R. MAYO

Received April 11, 1938

A preliminary study of the side-chain and nuclear bromination of toluene in this laboratory has been reported.[1] The effects of light and of peroxides were found to be similar in that both accelerated side-chain bromination. It was further shown that the use of bromine-toluene ratios greater than 1:10 materially counteracts the effects of light and/or oxygen on side-chain bromination. The working hypothesis proposed is that: (*a*) the side-chain bromination of toluene is a chain reaction in which bromine atoms play the major rôle; (*b*) light and oxygen are both effective in the production of bromine atoms; (*c*) an excess of molecular bromine has a chain-breaking effect. Study of the bromination of other hydrocarbons, as yet unreported, has yielded data consistent with this hypothesis. It seemed desirable, therefore, to re-investigate the addition of bromine to phenanthrene with special attention to the effects of light and oxygen.

The addition of bromine to phenanthrene has been studied previously by Price,[2] and the (presumably) essentially similar addition of bromine to several phenanthrene derivatives by Fieser and Price.[3] Price concluded that the addition of bromine to phenanthrene takes place through a chain mechanism involving bromine atoms, but his observations as to the effects of light and oxygen on the reaction were not in all details those that past experience has led the present authors to regard as characteristic of such reactions.

According to Price the addition of bromine to phenanthrene is somewhat accelerated by light, but proceeds at a measurable rate in the dark. In our own experiments, when oxygen and other catalytic impurities were rigidly excluded, no detectable bromine addition took place in the dark in 24 hours. We believe that the discrepancy is attributable to Price's colorimetric method of determination, which necessitated repeated brief periods of intense illumination. Our own experiments (1 and 2, recorded

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[1] KHARASCH, MARGOLIS, WHITE, AND MAYO, *J. Am. Chem. Soc.*, **59**, 1405 (1937).

[2] PRICE, *ibid.*, **58**, 1834, 2101 (1936).

[3] FIESER AND PRICE, *ibid.*, **58**, 1838 (1936).

in Table I) indicate that intermittent illumination, particularly in the presence of air, is almost as effective in promoting the reaction as is steady illumination.

The difference between the rates of the air-exposed and the vacuum reactions recorded in Table I is also notable. Price's statement that the removal of oxygen from the solvent by boiling at diminished pressure had no demonstrable effect on the rate of the reaction is interpretable as indicative that mere traces of oxygen, especially in conjunction with intermittent illumination, may be highly effective. In harmony with this is the observation that in the presence of diphenylamine the bromination of phenanthrene is much slower when oxygen is excluded (experiment 5).

TABLE I

EFFECT OF AIR ON THE PHOTOBROMINATION OF PHENANTHRENE

EXPT. NO.	TIME (MINUTES)	CONDITIONS OF ILLUMINATION		EXTENT OF REACTION (%)[c]	
		Lamp Wattage	Distance (Inches)	Air-Exposed	Vacuum
1	24	400	15	66	53
2	5[a]	400	15	59	20
3	30	100	12	62	41
4	40	100	24	54	39
5[b]	73	100	12	59	24

[a] The light was turned on 30 seconds every 5 minutes for a total period of 50 minutes (aggregate time of illumination, 5 minutes).

[b] One mole per cent. of diphenylamine was present in both reaction systems.

[c] All analyses were by titration of unreacted bromine. The experiments were carried out in carbon tetrachloride solution, the concentrations of both bromine and phenanthrene being 0.05 mole per liter.

TABLE II

EFFECT OF PEROXIDES ON THE BROMINATION OF PHENANTHRENE IN CARBON TETRACHLORIDE SOLUTION IN THE DARK

BROMINE CONCENTRATION[a] (MOLES/LITER)	PEROXIDE	PEROXIDE CONCENTRATION (MOLE %)	TIME (HOURS)	EXTENT OF REACTION (%)
0.5	None	—	1	0
0.5	Ascaridole	3	1	17
0.5	Ascaridole	10	1	92
0.05	None	—	24	0
0.05	Ascaridole	3	1	40, 40, 45
0.05	Triacetone perox.	3	24	18
0.05	Benzoyl perox.	3	24	45
0.05	Perbenzoic acid	3	24	29

[a] Equimolecular proportions of bromine and phenanthrene were used in all cases.

We believe, therefore, that in Price's experiments the reaction was accelerated by intermittent illumination, and catalyzed to some extent by atmospheric oxygen. These factors would account for his observation that the presence of benzoyl peroxide did not materially affect the rate. In our own experiments (Table II) benzoyl peroxide did facilitate bromination in the dark, although not to the same extent as did ascaridole—a less stable peroxide.

The experiments recorded in Table II also show that ascaridole, at least, is relatively more effective as a catalyst in the presence of low concentrations of bromine than in the presence of higher concentrations.

On the basis of these observations we conclude that the measurements of Price (and, by inference, those of Fieser and Price) apply to a photochemical, oxygen-catalyzed reaction, rather than to a dark, uncatalyzed reaction, as they have assumed.

MECHANISM OF THE DIAZOAMINOBENZENE CONVERSION: ADDENDUM

In connection with a paper published by myself in This Journal [**2**, 198, (1937)] dealing with the mechanism of the diazoaminobenzene conversion, and its analogy with the mobility and fission of keto-enol systems, my attention has been directed recently to the following item from a paper by K. H. Meyer [*Ber.*, **54B**, 2272, (1921)]. Although reference was made to this publication in relation to the general question of the diazoaminobenzene conversion in the author's original paper, mention of this reported direct combination of benzenediazonium chloride with aniline hydrochloride was unintentionally overlooked.

"5 g festes Benzoldiazoniumchlorid wurden in 20 ccm Wasser gelöst und mit einer konzentrierten wässrigen Lösung von 4 g festem Anilin-Chlorhydrat versetzt. Es trat sehr schnell die blaustichig rote Farbe des salzsauren Amino-azobenzols auf, die bei Zusatz von 2.5 ccm 70-proz. Ameisensaure und 5 ccm einer konzentrierten wässrigen Lösung von Natrium-formiat rasch viel intensiver wurde. Der bald sich Umkrystallisieren aus Ligroin als Amino-azobenzol, Schmp. 125°."

Since nothing is stated regarding the purity of the precipitated material in the above report, the following comments from a paper by Friswell and Green [*J. Chem. Soc.*, **47**, 919, (1885)] also cited in the author's original paper) should be added. "Diazoaminobenzene is invariably produced first—when sodium nitrite is added to aniline in solution in excess of strong or dilute acetic acid; when sodium nitrite is added to excess aniline hydrochloride or of any mixture of aniline and aniline hydrochloride, no matter how great the mass—although under such conditions a second reaction slowly takes place with the production of the isomeric compound."

H. Vincent Kidd

THE PEROXIDE EFFECT IN THE ADDITION OF REAGENTS TO UNSATURATED COMPOUNDS. XV. CORRECTION

In the last line of Table III (p. 293) of the paper of the above title [J. Org. Chem., **2**, 288–302 (1937)] the entry in the column headed "% 1,2-ADDITION PRODUCT" should read "0–10" instead of "90–100."

F. R. Mayo