[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL ENGINEERING OF THE UNIVERSITY OF WASHINGTON]

SIMULTANEOUS NITRATION AND PARTIAL DEALKYLATION OF *p*-CYMENE[1]

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In previous work (1) on the mononitration of *p*-cymene, it was found that approximately eight per cent of *p*-nitrotoluene was formed with the 2-nitro-*p*-cymene, even when the temperature of nitration was as low as −20°. The literature shows that dealkylation during nitration has been observed with certain aromatic compounds, and in general, the alkyl group is only partially eliminated with the formation of the corresponding nitro compound. Sometimes, however, the dealkylated nitro compound is obtained almost exclusively.

Several mechanisms have been advanced for the removal of alkyl groups when nitrating aromatic compounds. The best known one consists of the oxidation of the alkyl group to the carboxyl group, which in turn is replaced by the nitro group with the evolution of carbon dioxide (2, 3). This mechanism can be applicable only when it has been proved that the alkyl group is oxidized to the carboxyl group under the conditions of nitration, and that under these same conditions the aromatic acid will form the nitro compound with elimination of carbon dioxide (4).

A different mechanism has been applied to the polymethylbenzenes. When these are treated with nitric acid, a methyl group attached to the nucleus is attacked, giving a polymethylbenzyl nitrate, or a nitropolymethylbenzyl nitrate. The nitrate is decomposed by sulfuric acid to form a true nitro compound. Smith, Taylor, and Webster (5) subjected bromodurene to the action of nitric acid, forming 2,4,5-trimethyl-3-bromo-6-nitrobenzyl nitrate, which upon treatment with sulfuric acid formed 2-bromo-5,6-dinitropseudocumene. Smith and Guss (6) found similar results with dibromotetraethylbenzene. The transformation of the substituted benzyl nitrates into true nitro compounds by the action of sulfuric acid seems to be quite general for the polymethylbenzenes and their derivatives. Smith and Horner (7) suggest this as a possible course of other aromatic nitrations in which alkyl groups are replaced by nitro groups.

[1] *p*-Cymene Studies VII. For VI see *J. Am. Chem. Soc.*, **63**, 3251 (1941).

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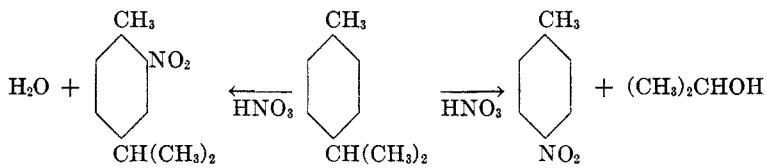
A POSSIBLE MECHANISM FOR SIMULTANEOUS NITRATION AND DEALKYLATION

In this work, we have considered the fate of the isopropyl group of the *p*-cymene in an attempt to explain the formation of *p*-nitrotoluene and 2,4-dinitrotoluene when *p*-cymene is mono- or di-nitrated. Although it was found that oxidation of *p*-cymene could occur at $-20°$, as evidenced by the evolution of nitrogen oxides and the darkening of the reaction mixture, if a good emulsion was maintained throughout the nitration, no nitrogen oxides could be observed. This rendered it unlikely that an oxidation product of *p*-cymene would be found as an intermediate in the formation of *p*-nitrotoluene.

Isopropanol has now been isolated in considerable amounts from the diluted, spent mixed acids after this nitration, always associated with some acetone, apparently formed by oxidation of a portion of the isopropanol by the nitric acid of the mixed acids. No attempt was made to account quantitatively for all of the removed side chains as isopropanol and acetone, based on the amount of *p*-nitrotoluene found, as a portion of the isopropanol reacts with the sulfuric acid of the mixed acids to form hydrocarbons. The amount of these hydrocarbons actually formed during nitration cannot be determined, as they are diluted with the much larger amount of nitro compounds from which quantitative separation is impossible.

The mononitration of *p*-cymene can now be regarded as involving two simultaneous reactions:



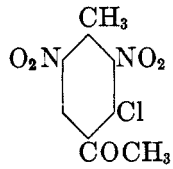
This mechanism involving the replacement of the alkyl group by the nitro group, without oxidation by the nitric acid, is perhaps the most general mode of formation of these dealkylated aromatic nitro compounds.

DISCUSSION

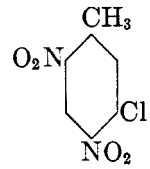
The replacement of the acetyl group by the nitro group, as observed by Barbier (8) who obtained some 2,4-dinitro-5-butyl-*m*-xylene, may possibly occur by direct reaction. Undoubtedly, many nitrations have resulted in the partial elimination of the side chain, which has not been observed due to the frequent difficulty of separating the dealkylated nitrated compound from the nitration products. It is advisable to test for the alkyl scission products in the dilute, spent mixed acids and to identify the alcohol, or nitric acid oxidation product thereof, formed from the alkyl group removed. Furthermore, the nitro group replaces the

eliminated group, simplifying the subsequent identification of the dealkylated nitro compound.

This direct replacement process may explain the structure of an unknown compound prepared by Lubs and Young (9) by nitrating the mixture of chloro compounds produced by direct chlorination of *p*-cymene. The compound of empirical formula $C_7H_5ClN_2O_4$, melting point 88–89°, was discussed extensively by Ganguly and LeFevre (10), who assigned structure I. This structure is untenable, for it requires a compound of empirical formula $C_9H_7ClN_2O_5$. It is very likely that this unknown compound was an impure chlorodinitrotoluene of structure II.



I



II

This latter compound, having the correct empirical formula, is known. It melts at 91° and can be converted into a diamine melting at 120–121°, which compares favorably with the (impure) diamine (m.p. 115–116°) derived from the compound of Ganguly and LeFevre. Compound II could have been formed from 3-chloro-*p*-cymene, which is a product of the direct chlorination of *p*-cymene, by replacement of the isopropyl by the nitro group.

The replacement of alkyl groups when halogenating is observed frequently, especially with *p*-cymene, or cumene derivatives as reported by Qvist (3, 11, 12, 13). Gustavson (14) obtained an almost quantitative yield of pentabromotoluene and isopropyl bromide by brominating *p*-cymene at 0° in the presence of aluminum bromide. The similarity to the nitration process is noteworthy.

EXPERIMENTAL

Mononitration of p-*cymene.* *p*-Cymene (500 g.) of b.p. 174.0–178.0° obtained from sulfite turpentine was nitrated according to our recommended conditions (1, 15).

Isolation of isopropanol and acetone from the spent acids. The nitro compounds were first removed and freed from dissolved isopropanol by repeatedly washing with water. The wash water was combined with the diluted spent acids and then was neutralized with aqueous potassium hydroxide solution (30–50%) below 25°. Potassium sulfate crystallized and was filtered off. The filtrate was fractionated four times through a 1.5-ft. rod and disk column for the lowest-boiling fraction, which was then distilled twice through a 150-ml. Vigreux flask of 8-inch column length. The final distillate (15 ml.) had a strong ammoniacal odor which was readily removed by distilling the material from dilute sulfuric acid. This final distillate (11 ml.) of boiling range 60–85° was found by analysis (16) to be isopropanol with but small

amounts of acetone and water. The presence of the isopropanol was proved by its characteristic odor, and by oxidation with chromic acid mixture to acetone, which was identified as its condensation product with benzaldehyde (17). Since it is shown that partial oxidation of the isopropanol occurs when *p*-cymene is nitrated, it was found expedient in subsequent fractionations of the dilution water from nitrations to eliminate the neutralization of the diluted spent acids and simply subject them directly to fractionation. This gives a mixture of isopropanol and acetone which is relatively richer in acetone.

Reaction of isopropanol with nitric and sulfuric acids. Isopropanol (2 ml.) was added dropwise with vigorous stirring at −10° to a solution containing 40 g. (21.7 ml.) of sulfuric acid (sp. gr. 1.84), 6 ml. of glacial acetic acid, and 7.4 g. (5.2 ml.) of nitric acid (sp. gr. 1.42) corresponding to the same proportions of the acids used in the nitration, but with one-fiftieth of their quantities. Some nitrogen oxides were evolved during the 15 minutes addition of the isopropanol; the resulting mixture was stirred for one hour, after which it was diluted with ice and water to a final volume of 150 ml. A small amount of an oily liquid less dense than the aqueous acids separated from the solution. When nitrating *p*-cymene, this oily liquid is not found, for it is dissolved in the greater amount of nitration products.

Isopropanol (50 ml.) was added dropwise with stirring to 500 g. (272 ml.) of sulfuric acid at −10° and the resulting mixture stirred for four hours. Upon dilution with ice and water, considerable amounts of a light yellow, water-insoluble oil of hydrocarbon nature, less dense than the aqueous acid, separated. The reaction of isopropanol with sulfuric acid has been reported by Ormandy and Craven (18), and more recently by Gutyra (19). The olefins produced by dehydration are principally polymerized at 0° by contact with sulfuric acid. At room temperature, besides polymerization, dehydrogenation and hydrogenation occur with the formation of both saturated and unsaturated hydrocarbons.

SUMMARY

The *p*-nitrotoluene obtained with the 2-nitro-*p*-cymene when *p*-cymene is mononitrated, is formed by substitution of the nitro group for the isopropyl group. Both isopropanol and acetone are found in the spent mixed acids; the acetone arises from oxidation of a portion of the isopropanol. It is believed that the mechanism involving substitution of the alkyl group without its being attacked by nitric acid is applicable to other compounds. Owing to the frequent difficulty of separating the dealkylated nitrated compounds from the nitration products, it is recommended that the diluted, spent mixed acids be tested for the alcohol, or nitric acid oxidation products thereof, formed from the alkyl group removed.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, UNIVERSITY OF MISSOURI]

THE PREPARATION AND REACTIONS OF THE 1,3-DIMETHYL-4-AMYLBENZENES

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In a previous paper (1) it was shown that the *s*- and *t*-butyl radicals in the 1,3-dimethyl-4-butylbenzenes reacted with decahydronaphthalene in the presence of aluminum chloride to form butanes in 24% and 41% yields respectively, and that the corresponding *n*-butyl and isobutyl hydrocarbons did not yield any paraffin.

To study further the effect of the branching of the chain on the yield of paraffin in this reaction, the eight 1,3-dimethyl-4-amylbenzenes were prepared and heated with decahydronaphthalene according to the directions of Ipatieff and Pines (2).

The effect of the branching of the pentane chain is striking. The 4-*n*-amyl and 4-isoamyl hydrocarbons did not yield any paraffin, but the 4-neopentyl isomer yielded some isopentane. The formation of a paraffin from this latter hydrocarbon was somewhat unexpected since no paraffin had been obtained previously from an alkyl group attached to the benzene ring through a primary carbon, and neopentyl derivatives are usually very stable. The formation of isopentane rather than neopentane is not surprising in view of the fact that neopentyl chloride and benzene in the presence of aluminum chloride yields only 2-methyl-3-phenylbutane (3). The paraffin did not react with a dilute solution of potassium permanganate or with bromine in carbon tetrachloride, indicating the absence of olefins such as isopropylethylene.

Of the three *s*-amyl radicals, (I) $CH_3CHC_3H_7$, (II) $C_2H_5CHC_2H_5$, and (III) $CH_3CHCH(CH_3)CH_3$, the one with the branched chain, III, gave a better yield of paraffin than the straight-chain radicals, I and II, and in less than half the time (Table III). The paraffins are mostly mixtures of *n*-pentane and isopentane, with the latter as the principal product from the highly branched radicals.

The best yield of paraffin was obtained from 1,3-dimethyl-5-*t*-amylbenzene. Since it is not certain that the 1,3-dimethyl-4-*t*-amylbenzene

[1] Abstract of a dissertation submitted by Orville Glenn Shanholtzer in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1941.

[2] Presented in part before the Organic Division of the American Chemical Society, St. Louis, Missouri, April 10, 1941.

was entirely pure, any definite conclusions as to the relative ease of cleavage of the amyl radical in the 5 position as compared with the 4 position are not justified. The *t*-amyl radical and the *t*-butyl radical are both cleaved to the same extent from the 5 position.

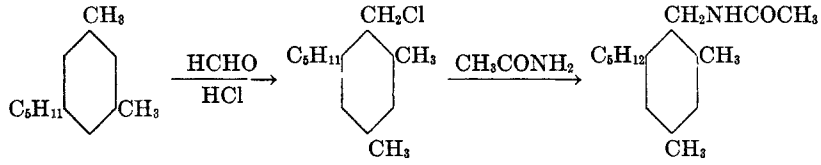
These data definitely confirm the observations of Ipatieff and Pines (2) that the more highly branched the chain in an alkylbenzene, the more readily the radical is cleaved by aluminum chloride.

No effort was made to study the effect of aluminum chloride on the 1,3-dimethyl-4-amylbenzenes due in part to the probable formation of complicated mixtures through the extensive isomerization possible with the various amyl radicals. Even *n*-amyl chloride and benzene in the presence of aluminum chloride did not yield pure 2-phenylpentane. Furthermore, the necessary 1,3-dimethyl-5-amylbenzenes are not readily available for reference compounds.

It should be possible to synthesize some of the 1,3-dimethyl-5-amylbenzenes through the reaction of 3,5-dimethylbenzyl-potassium or -sodium with the butyl halides (4), but this method was practical only with *n*-butyl chloride. With the other butyl halides, reactions other than the expected coupling must have occurred for the small trialkyl fraction boiled over a range, and relatively large amounts of high-boiling products were formed. The effect of the structure of the butyl chloride on the yield of crude trialkyl fraction was apparent. The primary halides gave better yields than either the secondary or tertiary halides. The 3,5-dimethylbenzylsodium gave a better yield of alkylbenzene than did 3,5-dimethylbenzylpotassium.

The reaction between *m*-xylene and *t*-amyl alcohol in the presence of 85% sulfuric acid (5) at temperatures below 20° led to a product which contains some other hydrocarbon along with the expected 1,3-dimethyl-4-*t*-amylbenzene. The reaction product boils over a wide range and analyses for carbon and hydrogen of the fraction which should be the 4-*t*-amyl hydrocarbon did not agree with the theoretical values even after the hydrocarbon had been fractionated repeatedly and carefully. A pure diacetamino derivative could not be obtained from this fraction, but analyses of the dibenzamino derivative corresponded to that of a dimethylamylbenzene.

The reaction between the 2,4-dimethyl-6-amylbenzyl chlorides and acetamide at around 200° forms the corresponding acetyl benzylamine:



This reaction appeared promising for the preparation of derivatives of these hydrocarbons, but mixtures of isomers did not show a very large depression

of their melting points and some of the acetylated amines could not readily be obtained pure.

All of the hydrocarbons in this series other than the 1,3-dimethyl-4-*t*-amylbenzene and 1,3-dimethyl-5-*t*-amylbenzene were prepared from ketones, either through the Clemmensen reduction, or by the addition of the appropriate Grignard reagent to a ketone followed by dehydration of the resulting carbinol and hydrogenation of the olefin at pressures up to 3300 pounds (225 atm.) with Raney nickel as the catalyst. The use of platinum at low pressures was unsatisfactory, probably due to traces of sulfur from the carbon disulfide used as a solvent for the preparation of the ketones. It was desirable to distill the olefin from Raney nickel before hydrogenation to ensure smooth reduction.

In the Grignard reactions, the effect of the branching of the chain in either the Grignard reagent or the ketone is clearly shown in the yield of hydrocarbon from 2,4-dimethylacetophenone and isopropylmagnesium bromide (32%) as compared with 2,4-dimethylisobutyrophenone and methylmagnesium iodide (64%), and 2,4-dimethyl-*n*-butyrophenone and methylmagnesium iodide (72%). These yields correspond to those obtained by Conant and Blatt (6) in their study of the effect of the branching of the chain in aliphatic ketones and Grignard reagents on the yield of tertiary carbinol.

In spite of the fact that products other than saturated hydrocarbons are formed during the reduction of alkyl aryl ketones by the Clemmensen method, this procedure was more satisfactory than high-pressure reduction of the ketones with hydrogen and Raney nickel. Prolonged refluxing was necessary to secure good yields. The formation of bimolecular reduction products lowered the yield of hydrocarbon.

Trimethylacetyl chloride and *m*-xylene formed not only some of the desired ketone but also a pale yellow solid, m.p. 165°, the identity of which has not yet been established. On the basis of Boeseken's observation that this acid chloride decomposes in the presence of aluminum chloride to form carbon monoxide, hydrogen chloride, isobutene, and a polymer of isobutene (7), a polybutylxylene might be formed, but analyses do not correspond to any of the polybutylxylenes. A methyl group from the radical of the acid chloride does not alkylate the nucleus as in the case of diamylacetyl chloride (8) for the yellow compound is not a ketone. Mesitylene and trimethylacetyl chloride also yielded the expected ketone and a solid by-product, while benzene formed a high-boiling liquid but no ketone. The structure and properties of these products are under investigation.

Acknowledgments. The authors wish to thank E. I. duPont de Nemours and Company for their generous gift of *m*-xylene, and the University Re-

search Council, University of Missouri, for a grant for the purchase of other chemicals for this investigation.

EXPERIMENTAL[3]

All fractionations were carried out with columns packed with single turn glass helices. The physical constants and analyses of the hydrocarbons have been summarized in Table I.

1,3-Dimethyl-5-t-amylbenzene was obtained from 53 g. of *m*-xylene, 15 g. of aluminum chloride, and 26 g. of *t*-amyl chloride at room temperature by the usual Friedel-Crafts procedure. The yield was 30 g. (64%), b.p. 102–103° (14 mm.). DeCapeller (9) states that he prepared this hydrocarbon from these reagents but mentions no physical constants.

TABLE I

ALKYL BENZENES[a]

ALKYL BENZENE	B.P. °C.	$n^{20}D$	ANALYSES[b]	
			Found % C	Found % H
1,3-Dimethyl-				
5-*t*-amyl	102–103 (14 mm.)	1.4982	88.43	11.37
4-*t*-amyl	93–95 (14 mm.)		87.93	11.37
4-*n*-amyl	123–124 (16 mm.)	1.4972	88.50	11.57
4-isoamyl	116–117 (15 mm.)	1.4966	88.42	11.40
4-neopentyl	97–98 (10 mm.)	1.5081	88.66	11.03
4-$CH_3CHCH_2CH_2CH_3$	102–103 (11 mm.)	1.4959	88.48	11.56
4-$CH_3C{=}CHCH_2CH_3$	104 (13 mm.)			
4-$CH_3CHCH(CH_3)CH_3$	100–102 (13 mm.)	1.5022	88.48	11.17
4-$CH_3C{=}C(CH_3)CH_3$	106–110 (16 mm.)			
4-$C_2H_5CHC_2H_5$	105–106 (13 mm.)	1.4973	88.40	11.49
4-$C_2H_5C{=}CHCH_3$	103–105 (16 mm.)			
4-$CH_2CH(CH_3)C_2H_5$	108–111 (13 mm.)	1.4942	88.35	11.67
4-$CH{=}C(CH_3)C_2H_5$	107 (10 mm.)			

[a] The position of the double bond in the olefin was not determined and the olefins were not analyzed.

[b] Calc'd for $C_{13}H_{20}$: C, 88.63; H, 11.37.

1,3-Dimethyl-4-t-amylbenzene. The procedure of Kirrmann and Graves (5) was adapted for the preparation of this hydrocarbon. The *t*-amyl alcohol (63 cc.) and *m*-xylene (375 cc.) were placed in a 2-liter round-bottom flask fitted with a mechanical stirrer and cooled with ice. A mixture of concentrated sulfuric acid (525 cc.) and water (110 cc.) was added over a period of one hour. Stirring was continued for an additional five hours. The acid layer was separated, the hydrocarbon washed repeatedly, dried, and fractionated. The following fractions were obtained at 16 mm.

[3] Most of the semimicro analyses are by O. G. Shanholtzer. The remainder are by D. R. Smith and E. Milberger in the micro laboratory at the University of Missouri.

after removal of excess *m*-xylene: (I) 19 g. up to 93°; (II) 4.5 g. 93–98°; (III) 22 g. 98–103°; (IV) 9.5 g. 103–104°; (V) 28 g. 85–94° (5 mm.).

The trialkyl fractions (III) from several runs were combined and carefully refractionated. The hydrocarbon boiled at 93–95° (14 mm.).

Preparation of 1,3-dimethyl-4-amylbenzenes from ketones. The ketones other than 2,4-dimethylisovalerophenone and 2,4-dimethylpivalophenone are already described in the literature.

The 2,4-dimethylisovalerophenone was prepared by the usual Friedel-Crafts procedure from *m*-xylene (54 g.), isovaleryl chloride (50 g.) and aluminum chloride (67 g.) with carbon disulfide (200 cc.) as the solvent; yield, 67 g. (85%), b.p. 131–132° (12 mm.); n_D^{20} 1.5113.

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.11; H, 9.47.
Found: C, 82.21; H, 9.51.

The semicarbazone of this ketone, prepared by the usual procedure, melted at 196°.

Anal. Calc'd for $C_{14}H_{21}N_3O$: C, 68.02; H, 8.50.
Found: C, 67.83; H, 8.50.

The 2,4-dimethylpivalophenone was prepared in the same manner from *m*-xylene (124 cc.), aluminum chloride (134 g.), and trimethylacetyl chloride (102 g.). The yield of ketone was 62 g. (38%), b.p. 107–109° (6 mm.); n_D^{20} 1.5058. This ketone did not form a semicarbazone.

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.11; H, 9.47.
Found: C, 82.09; H, 9.28.

The pale yellow crystalline solid, m.p. 165°, isolated from the residue analyzed C, 91.14%, H, 7.94%.

The preparation of *2-(2,4-dimethylphenyl)pentane* is typical of the hydrocarbons prepared through the Grignard reaction and is described in detail. Quantities are listed in Table II. 1,3-Dimethyl-4-*n*-butyrylbenzene (66 g.) was added to the Grignard reagent prepared from methyl iodide (71 g.) and magnesium (12 g.). The product was decomposed, washed, and dried in the usual manner. The crude carbinol was added to acetic anhydride (100 cc.) and sulfuric acid (4 drops). The acetic anhydride was distilled from the mixture at 65 mm., and the residue distilled at 14 mm. Two fractions were obtained: (I) 5 g. up to 107°; (II) 55 g. 107–109°; residue 4 g.

Fraction II was redistilled, washed and dried, distilled from sodium, and finally from Raney nickel. The olefin was reduced in methyl alcohol solution with Raney nickel at a pressure range of 2200 to 3300 pounds per square inch (150–225 atm.) over a temperature range of 25° to 210°. After removal of the solvent, the hydrocarbon was washed, dried, and heated with sodium to remove impurities formed from the solvent, and fractionated from sodium; yield 48 g. (78%), b.p. 102–103° (11 mm.).

The three valeryl ketones were reduced by the method of Clemmensen (10). The best yields were obtained when the solution was refluxed eighty to ninety hours. The hydrocarbon was heated with sodium and finally distilled from sodium to remove impurities.

After long standing, 10–15 g. of white crystalline solids separated from the high-boiling residues from these reductions. Analyses corresponded to the expected pinacols.

The solid from the 4-*n*-valeryl ketone melted at 146°.

Anal. Calc'd for $C_{26}H_{38}O_2$: C, 81.61; H, 10.02.
Found: C, 81.57; H, 10.46.

The solid from the 4-isovaleryl ketone melted at 139–140°.

Anal. Calc'd for $C_{26}H_{38}O_2$: C, 81.61; H, 10.02.
Found: C, 81.84; H, 10.02.

Reactions of the hydrocarbons with decahydronaphthalene. The procedure was that of Ipatieff and Pines (2). The paraffin was collected in a receiver immersed in liquid air. The same amounts of reagents were used in all the reactions: 11.5 g. of hydrocarbon, 8 g. of aluminum chloride, and 25 g. of decahydronaphthalene. The data

TABLE II

PREPARATION OF 1,3-DIMETHYL-4-AMYLBENZENES FROM KETONES

ACYL GROUP	KETONE, G.	HALIDE	G.	ALKYL BENZENE, G.	YIELD %
$CH_3C{=}O$	106	iso-C_3H_7Br	100	40	32
$C_2H_5C{=}O$	48	C_2H_5Br	30	30	56.5
n-$C_3H_7C{=}O$	66	CH_3I	71	48	72
i-$C_3H_7C{=}O$	101	CH_3I	99.4	65	64
$CH_3C(=O)-C_2H_5$	31.6	2,4-Dimethyl-benzylchloride	70	35	41
n-$C_4H_9C{=}O$	67	reduce[a]		40	64
i-$C_4H_9C{=}O$	40	reduce[a]		18	47
t-$C_4H_9C{=}O$	102	reduce[a]		62	38

[a] Reduced by method of Clemmensen.

TABLE III

FORMATION OF PARAFFINS FROM DECAHYDRONAPHTHALENE[a]

ALKYLBENZENE	TIME, HRS.	TEMP., °C.	PARAFFIN	G.	%
1,3-Dimethyl-					
4-*n*-amyl	1.25	60–75	Trace	—	—
4-isoamyl	1.5	59–79	Trace	—	—
4-$CH_2CH(CH)_3C_2H_5$	1.5	60–80	Trace	—	—
4-neopentyl	3.5	62–80	Isopentane	1	20
4-*t*-amyl	2.0	60–76	Mixture	2.7	—
5-*t*-amyl	1.5	63–80	Isopentane	2.7	80
4-$CH_3CHCH(CH_3)_2$	1.5	65–71	Isopentane	2.2	48
4-$C_2H_5CHC_2H_5$	4.0	60–80	Isopentane and pentane	1.7	37
4-$CH_3CHC_3H_7$	1.5	60–80	Trace	0.2	—
4-$CH_3CHC_3H_7$	4.0	75	Isopentane and pentane	1.9	41
5-*t*-butyl	1.5	65–75	Isobutane	3.5	81

[a] 11.5 g. of hydrocarbon, 8 g. of aluminum chloride, 25 g. decalin.

are summarized in Table III. The reactants were heated to 60–65° initially. If no paraffin distilled, the temperature was increased until liquid appeared in the trap, and held approximately constant until no more paraffin distilled. Prolonged heating did not increase the yield.

Chloromethylations. Preparation of 2,4-dimethylbenzyl chloride. *m*-Xylene (52.6 g.) was chloromethylated with formalin (40 g.), concentrated hydrochloric acid (200 g.), and gaseous hydrogen chloride according to the procedure of v. Braun and Nelles (11). The yield of 2,4-dimethylbenzyl chloride was 51 g. (66%), b.p. 92–94° (8 mm.). When zinc chloride (20 g.) was added to the above reagents, the yield was reduced to 30%.

The chloromethylation of *1,3-dimethyl-5-t-amylbenzene* (30 g.) was carried out in the same manner with 29 g. of formalin and 150 g. of concentrated hydrochloric acid at 70° for eight hours; yield, 16.5 g., b.p. 120–128° (3 mm.).

The *4-t-amyl* hydrocarbon was chloromethylated under the same conditions; yield, 13.5 g., b.p. 115–123° (4 mm.).

The *4-n-amyl* hydrocarbon (30 g.) yielded 14.5 g. of chloromethyl derivative, b.p. 125–135° (3 mm.).

Reaction of chloromethyl compounds with acetamide. A sample (3.5 g.) of each of the above chloromethyl compounds was heated with excess acetamide at 190–220° for one and one-half to two hours. The reaction product was poured into hot water to dissolve excess acetamide. The solid was recrystallized from petroleum ether. Yields were about 1.2 g. Their melting points and analyses are listed in Table IV.

TABLE IV

SUBSTITUTED BENZYLAMINE DERIVATIVES

ALKYL BENZENE	M.P., °C.	ANALYSES—% NITROGEN	
		Calc'd	Found
1,3-Dimethyl-benzene	109[a]		
4-*n*-amyl	105	5.66	5.88
5-*t*-amyl	150	5.66	5.63

[a] *Anal.* Calc'd for $C_{11}H_{15}NO$: C, 74.58; H, 8.48. Found: C, 74.52; H, 8.61.

Preparation of 1,3-dimethyl-5-n-amyl benzene. 3,5-Dimethylbenzylsodium was prepared by the method of Morton and Fallwell (4). Sodium sand (18 g.) and benzene (70 cc.) were placed in a flask fitted with a sealed stirrer, separatory funnel, and a reflux condenser. To this was added a mixture of benzene (37.5 cc.) and *n*-amyl chloride (37.5 cc.) over a period of two and one-half hours at 15–20°. The mixture was stirred for an additional one and one-half hours. Mesitylene (37.5 cc.) was added and the temperature raised to 75°. Stirring was continued for four and one-half hours.

A mixture of *n*-butyl chloride (23 g.) and benzene (23 g.) was added to the 3,5-dimethylbenzylsodium over a period of thirty minutes. The mixture was stirred an additional ten minutes, then decomposed with water, washed, dried, and distilled; yield, 10 g. (15%) b.p. 105–106° (10 mm.).

Anal. Calc'd for $C_{13}H_{20}$: C, 88.63; H, 11.37.
Found: C, 88.25; H, 11.43.

From *s*-butyl chloride and 3,5-dimethylbenzylsodium, the yield of trialkyl fraction b.p. 105–111° (15 mm.) was 3 g., and from isobutyl chloride 7 g., b.p. 105–110° (15 mm.). These trialkyl fractions were not purified or analyzed.

3,5-Dimethylbenzylpotassium was prepared according to the directions of Gilman,

Pacevitz, and Baine (12), from 100 cc. of mesitylene and 8.5 g. of potassium. The mixture was cooled to 80–90° and 12 cc. of *n*-butyl chloride added during twenty minutes. The mixture was refluxed for five minutes. The product was decomposed with alcohol, washed, dried, and distilled. The trialkyl fraction distilled at 85–105° (4 mm.); yield 4.5 g.

t-Butyl chloride (15 cc.) was added to the same amount of 3,5-dimethylbenzylpotassium. The trialkyl fraction distilled at 85–105° (4 mm.); yield 2.2 g.

Diacetamino and dibenzamino derivatives. These derivatives were prepared by an adaptation of the procedure of Ipatieff and Schmerling (13).

The nitrating mixture (10 cc. of concentrated sulfuric acid and 5 cc. of concentrated nitric acid) was stirred mechanically in a test tube at −10° to −15°. The low temperature is essential. The hydrocarbon (3 cc.) was added dropwise during five to fifteen minutes. The stirring was continued for an additional five minutes. The solution was allowed to come to room temperature, poured on ice, and the nitro compound extracted with ether. The ether solution was washed repeatedly with

TABLE V

DIACETAMINO AND DIBENZAMINO DERIVATIVES

ALKYL BENZENE	DIACETAMINO		DIBENZAMINO	
	M.p. °C.	% Nitrogen[a] found	M.p. °C.	% Nitrogen[b] found
1,3-Dimethyl-				
4-*n*-amyl	234	9.41	220	6.74
4-isoamyl	—	—	208	6.52
4-*t*-amyl	—	—	308	6.94
5-*t*-amyl	304	9.57	302	6.49
4-$CH_3CHCH(CH_3)CH_3$	264	9.55	234–235	6.85
4-$C_2H_5CHC_2H_5$	279–280	9.49	252–253	6.73
4-$CH_3CHC_3H_7$	234	9.88	241	6.65

[a] Calc'd. for $C_{17}H_{26}N_2O_2$: N, 9.65.

[b] Calc'd. for $C_{27}H_{30}N_2O_2$: N, 6.76.

5% sodium bicarbonate solution and with water. The ether was removed and the nitro compound dissolved in alcohol. Tin (15 g.) and concentrated hydrochloric acid (15 cc.) were added to the alcohol solution. The reaction was usually vigorous, and cooling was sometimes necessary. The mixture was stirred mechanically for one hour.

The acid solution was diluted with water to 100 cc. and extracted twice with 20-cc. portions of ether. This ether extract was discarded. The water layer was made strongly basic and extracted twice with 35-cc. portions of ether. These ether extracts of the basic solution were combined, washed repeatedly with water, and divided into two equal portions.

(a) Acetic anhydride (5 cc.) was added directly to one portion and the flask stoppered tightly. After some time (from a few minutes to several hours) the diacetamino derivative separated in fairly pure form. The solid was washed repeatedly with ether and recrystallized from dilute alcohol (an excess of alcohol should be avoided) or from pyridine.

(b) The ether was evaporated from the second portion and the amine benzoylated

by the usual Schotten-Baumann method. The dibenzamino derivatives were washed with ether and recrystallized from dilute alcohol or pyridine.

It was not possible to obtain derivatives of all the hydrocarbons in pure form. The melting points and analytical data are summarized in Table V.

SUMMARY

Seven of the eight 1,3-dimethyl-4-amylbenzenes have been synthesized by methods which leave no doubt as to the structure and position of the amyl radical.

The reaction between 3,5-dimethylbenzyl-sodium or -potassium leads mainly to products other than the desired 1,3-dimethyl-5-amylbenzenes.

In the reaction between decahydronaphthalene, 1,3-dimethyl-4-neopentylbenzene and aluminum chloride the neopentyl radical is cleaved to form isopentane in 20% yield. This is the first primary alkyl radical to react in this manner. The branched *s*-amyl radical gives a larger yield of mixed pentanes in this reaction than do the two straight-chain *s*-amyl radicals. The 1,3-dimethyl-5-*t*-amylbenzene gives the highest yield of isopentane.

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[COMMUNICATION NO. 815 FROM THE KODAK RESEARCH LABORATORIES]

THE IDENTIFICATION OF AROMATIC SULFONIC ACIDS CONTAINING AN AMINO GROUP

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Aromatic sulfonic acids are readily identified in most schemes of qualitative organic analysis (1) by formation of the sulfonamide. A less familiar method is the production of salts between the acids and amines, or amine derivatives (2–11). Where applicable, this latter procedure gives results in a much shorter time. Neither of these means of identification is applicable to sulfonic acids when there is an amino group present.[1] Inner salt formation prevents the use of the second procedure, and the sensitivity of the amino group to phosphorus pentachloride makes impossible the application of the first method.

However, it has been found that when many aromatic sulfonic acids containing one amino group are diazotized and the NH_2 replaced by Cl by means of the Sandmeyer reaction, the resulting chlorosulfonic acid is readily converted into a crystalline sulfonamide with a good melting point. Though several steps are involved, the yields are good in each, and one gram of the amino sulfonic acid gives sufficient chlorosulfonamide for identification.

In Table I are collected the melting points of the chlorosulfonamides derived from the common amino sulfonic acids.

The method is applicable to amino mono- and di-sulfonic acids in the benzene series and to monosulfonic acids in the naphthalene series. In the case of disulfonic acids in the latter series, the steps are satisfactory only to the formation of the disulfonyl chloride, owing to the very high melting points (350°) of the disulfonamides. While the disulfonchlorides are all solids with convenient melting points, in general they do not crystallize well, and are unsuited for qualitative organic analysis. Fortunately, the disulfonanilides have good melting points and are easily secured; in Table II are recorded the properties of the derivatives of the common amino polysulfonic acids.

[1] Substances of uncertain constitution resulting from the use of S-benzylthiuronium chloride together with their decomposition points have been described recently (11).

2-Naphthylamine-3,6-disulfonic acid yields a chloronaphthalene disulfonchloride (m.p. 165°) that crystallizes readily, so this derivative also serves for purposes of identification.

TABLE I

MELTING POINTS OF AROMATIC CHLOROSULFONAMIDES

AMINOSULFONIC ACID USED	M.P. (°C)[a]
Orthanilic (12)	188
Metanilic (13)	148
Sulfanilic (14)	144
4-Aminotoluene-2-sulfonic (15)	145
4-Aminotoluene-3-sulfonic (16)	156
2-Aminotoluene-4-sulfonic (17)	135
2-Aminotoluene-5-sulfonic	128 (18), 131 (19)
4-Nitroaniline-2-sulfonic (20)	185
4-Nitroaniline-3-sulfonic (21)	158
Aniline-2,4-disulfonic (22)	217
Aniline-2,5-disulfonic (19)	229
1-Aminonaphthalene-4-sulfonic (23)[b]	187
1-Aminonaphthalene-5-sulfonic (25)	226
1-Aminonaphthalene-6-sulfonic (25)	216
1-Aminonaphthalene-7-sulfonic (26, 27)	181
1-Aminonaphthalene-8-sulfonic (28)	197
2-Aminonaphthalene-1-sulfonic (29)	153
2-Aminonaphthalene-5-sulfonic (26)	214
2-Aminonaphthalene-6-sulfonic (30)	184
2-Aminonaphthalene-7-sulfonic (30)	176
2-Aminonaphthalene-8-sulfonic (31)	235

[a] Melting points are uncorrected.

[b] The 1-aminonaphthalene-2-sulfonic acid forms a 1-chloronaphthalene-2-sulfonamide which is reported as having no melting point up to 250° (24).

TABLE II

PROPERTIES OF CHLORONAPHTHALENE POLYSULFONANILIDES

NAPHTHYLAMINE SULFONIC ACID USED	SOLVENT	M.P. (°C)	ANALYSES; FOUND: N, %
1-Naphthylamine-4,8-disulfonic acid[a]	Benzene	233	5.8
2-Naphthylamine-3,6-disulfonic acid	Benzene-ligroin	185	5.9
2-Naphthylamine-4,8-disulfonic acid	Chlorobenzene	235	5.9
2-Naphthylamine-5,7-disulfonic acid	Dil. acetic acid	206	6.1, 5.8
2-Naphthylamine-6,8-disulfonic acid	Chlorobenzene	192	5.8
1-Naphthylamine-3,6,8-trisulfonic acid[b]	Chlorobenzene	249	6.5, 6.8

[a] Calc'd for $C_{22}H_{17}ClN_2O_4S_2$: C, 68.2; H, 4.5; N, 5.9.
Found: C, 68.1; H, 4.6.

[b] Calc'd for $C_{28}H_{22}ClN_3O_6S_3$: N, 6.7.

EXPERIMENTAL

Most of the aromatic amino sulfonic acids are encountered in varying degrees of purity as intermediates for the manufacture of commercial dyes, and require more or less purification as a preliminary operation to their identification. Usually, recrystallization from water in the presence of decolorizing carbon is sufficient; the addition of a little mineral acid is often advantageous. For example, 50 g. of a technical grade of 2-naphthylamine-4,8-disulfonic acid was dissolved in 250 cc. of boiling water containing 2 g. of Norit and filtered. On cooling, 25.8 g. of the amino acid separated in the form of white needles.

Qualitative procedure; A, for sulfonamides. It is advisable to start with 1.5–2 g. of recrystallized amino sulfonic acid in order to have an ample amount of derivative. Usually it is advantageous first to dissolve the acid in sodium carbonate solution, and then to acidify and diazotize. The indirect procedure does not seem to give as good results. Details for the preparation of 4-chlorotoluene-3-sulfonamide will serve as an illustration.

One and four-tenths grams of 4-aminotoluene-3-sulfonic acid (previously recrystallized from water) is dissolved in 10 cc. of water containing 0.41 g. of sodium carbonate. The solution is diazotized by adding 1.9 cc. of concentrated hydrochloric acid and then, quickly, 4.4 cc. of sodium nitrite solution (containing 120 g. of sodium nitrite per l.), the temperature being maintained at 10–15° by the addition of ice.

Meanwhile, a cuprous chloride solution is prepared (32) from 2.16 g. of copper sulfate, 0.56 g. of sodium chloride, 0.46 g. of sodium bisulfite, and 0.33 g. of sodium hydroxide; this requires about ten minutes. The cuprous chloride is dissolved in 10 cc. of concentrated hydrochloric acid and cooled in ice to 5°. At this temperature the diazonium solution is added fairly rapidly while stirring. The temperature is allowed to rise slowly to room temperature and stirring is continued for one hour, after which the solution is heated to 60–70° for thirty minutes on the steam-bath. The copper is then precipitated by hydrogen sulfide, the resulting copper sulfide is filtered, and the crude 4-chlorotoluene-3-sulfonic acid is obtained by evaporating the filtrate to dryness on the steam-bath.

The crude acid is then mixed with double its weight of phosphorus pentachloride in a small beaker. When the vigorous reaction has ended, the beaker is heated in an oil-bath to 130–140° for a short time to expel the phosphorus oxychloride. After cooling, the chloride is washed by decantation with cold water, the resulting oil added to 45 cc. of concentrated ammonium hydroxide, and the solution evaporated to dryness on the steam-bath. The crude sulfonamide remains as a residue and weighs 1.8 g. For purification it is recrystallized, with the addition of Norit, from 85 cc. of boiling water. The 4-chlorotoluene-3-sulfonamide is obtained in the form of slender white needles which melt at 155–156°.

Chlorobenzene-2,5-disulfonamide (I) and 2-chlorotoluene-5-sulfonamide (II) are new. Both crystallize as needles from water.

Anal. I. (m.p. 229°). Calc'd for $C_6H_7ClN_2O_4S_2$: N, 10.4 Found: N, 10.4.
II. (m.p. 131°). Calc'd for $C_7H_8ClNO_2S$: N, 6.8. Found: N, 7.0.

B, for sulfonanilides. The crude sulfonchloride (about 2 g.) secured as described is dissolved in 10 cc. of benzene, 2.5 g. of aniline is added, and the solution is refluxed for one hour. The solution is concentrated to half its volume and chilled. The resulting solid is filtered, washed with warm water, and recrystallized three times from chlorobenzene.

The chloronaphthalene polysulfonanilides, the properties of which are given in Table II, were secured by this procedure. They retain traces of the solvent used

for crystallization rather tenaciously, but this does not interfere with the determination of the melting point when done in the ordinary manner.

When used for qualitative analysis of unknowns, the solubility in benzene is first determined; if too soluble, ligroin (b.p. 90–120°) is added. The insoluble derivatives are then handled with chlorobenzene and ligroin in a similar manner.

SUMMARY

A convenient method for the identification of amino sulfonic acids in the benzene and naphthalene series has been devised. It consists of replacement of the amino group by chlorine through the Sandmeyer reaction followed by a conversion of the sulfonic acid group to a sulfonamide or sulfonanilide.

The procedure can be used in small quantities (1.5–2 g.) in qualitative organic analysis.

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[FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF VERMONT]

THE STRUCTURE OF N^4-*d*-GLUCOSIDOSULFANILAMIDE[1]

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In most of the work involving sugar derivatives of sulfanilamide, it has been assumed that these derivatives were glycosides without presentation of any experimental evidence to establish the structures (1). Some workers, however, have considered condensation products of sulfanilamide with sugars to be anils (2).

Kuhn and Birkofer (3) prepared the glucoside of sulfanilamide by directly condensing glucose with sulfanilamide in 95% ethyl alcohol using ammonium chloride as a catalyst. Their claim that this glucose derivative was a true N-glycoside and not an anil was based upon the fact that acetylation of their compound yielded a tetraacetyl derivative and not a pentaacetylated product as would have been expected if the original compound had been the anil. They assumed logically that the glucose residue was attached to the sulfanilamide molecule through the N^4- or primary amino nitrogen atom rather than through the N^1- or amide nitrogen, but submitted no experimental evidence in support of this assumption.

The confusion as to whether sugar derivatives of sulfanilamide are N-glycosides or anils is suggested in the comprehensive review of sulfanilamide derivates by Northey (4) in which such derivatives are listed as acyclic anils with the following notation appended: "Sugar derivatives are classified here, although they are probably not anils but glucosides." For support of the above statement Northey cites the work of Kuhn and Birkofer (3) and Meyer and Schreiber (1).

It is the purpose of this paper to support the claim of Kuhn and Birkofer (3) that their glucose derivative of sulfanilamide is an N-glucoside and also to present experimental evidence to show that the compound is an N^4-glucoside.

Our approach, a direct synthesis of the N^4-glucoside, was directly the opposite of that of Kuhn and Birkofer. Using a modification of the Koenigs and Knorr synthesis (5) we synthesized N^4-tetraacetyl-*d*-glucosido sulfanilamide from β-acetobromo-*d*-glucose and sulfanilamide. Upon

[1] The nomenclature used in this paper is that proposed by Crossley, Northey, and Hultquist, *J. Am. Chem. Soc.*, **60**, 2217 (1938).

[2] Eli Lilly Fellow in Organic Chemistry 1939–40, 1940–41.

deacetylation of this compound we obtained N^4-*d*-glucosidosulfanilamide which was identical with the "sulfanilamide-*d*-glucoside" prepared by Kuhn and Birkofer from glucose and sulfanilamide. Our conclusion that the glucose residue in this glucoside probably is on the N^4-nitrogen atom rests upon the fact that the glucoside, when compared directly with sulfanilamide and N^1-acetylsulfanilamide (6), failed to yield a picrate, a picramide, a substituted thiourea with α-naphthyl isothiocyanate, and failed to give a positive reaction with Ehrlich's reagent (7).

The conclusion that N^4-*d*-glucosidosulfanilamide is a *beta* glucoside appears to be justified by its method of synthesis from β-acetobromo-*d*-glucose.

The physiological assay of N^4-*d*-glucosidosulfanilamide showed that on an equal weight basis it is only about one-half as active against streptococci as sulfanilamide and is not less toxic. Even if the difference in molecular weights is considered (N^4-*d*-glucosidosulfanilamide contains 51.5% of sulfanilamide per mole), the glucoside is still slightly less active than sulfanilamide. However, the greater water solubility of the glucoside as compared to that of sulfanilamide might be of advantage in certain cases.

EXPERIMENTAL

N^4-Tetraacetyl-d-*glucosidosulfanilamide.* Sulfanilamide (15.0 g. or 0.087 mole), silver oxide (20.0 g. or 0.086 mole), and "Drierite" (15.0 g.) were stirred for one hour in 150 cc. of freshly distilled anhydrous dioxane in a reaction flask equipped with a mercury seal stirrer, a condenser, and a dropping-funnel. A solution of 30.0 g. (0.073 mole) of β-acetobromo-*d*-glucose (m.p. 87–88°) (8) in 150 cc. of anhydrous chloroform was then added slowly through the dropping-funnel. The reaction mixture was held at 40° for four hours and then at room temperature with constant stirring for twenty hours. The reaction had then gone to completion, as evidenced by the failure to detect any bromide ion after boiling a sample of the reaction mixture with water. The mixture was then filtered and the solvent removed *in vacuo* at room temperature. The residual gum was dissolved in boiling 95% ethyl alcohol, treated with "Norit" and the filtrate thrown into a large volume of cold water. After the solution had stood in the ice-chest, a white precipitate which had formed was filtered off, washed with ice-water and air dried. The crude yield was 20.5 g. or 56%. After purification by recrystallization from 95% alcohol, the N^4-tetraacetyl-*d*-glucosidosulfanilamide was obtained as white needle-like crystals; m.p. 191°; $[\alpha]_D^{19}$ − 62.6° (alcohol-free chloroform, c = 1.4056; $[\alpha]_D^{19}$ − 78.4° (anhydrous pyridine (c = 1.4484).

Anal. Calc'd for $C_{20}H_{26}N_2O_{11}S$: N, 5.57. Found: N, 5.50, 5.71.

Kuhn and Birkofer (3) reported the m.p. 189° and $[\alpha]_D^{22.5}$ −86° (pyridine) for this compound.

N^4-d-*Glucosidosulfanilamide.* Ten grams of the acetylated glucoside was dissolved in 50 cc. of anhydrous methyl alcohol containing 3 cc. of 1 *N* sodium methoxide in absolute methyl alcohol. The solution was then warmed slightly and placed in the ice-chest for forty-eight hours. The white material which had precipitated was filtered off and purified by recrystallization from 95% ethyl alcohol. The purified N^4-*d*-glucosidosulfanilamide melted at 197°. Kuhn and Birkhofer reported that

their glucoside melted at 195° after recrystallization from 90% alcohol, but with slow heating the melting point rose to 204°. Our glucoside also melted at 204° if the temperature was raised very slowly. A mixed melting point with the glucoside prepared directly from glucose and sulfanilamide by the procedure of Kuhn and Birkofer showed 197.5°. The yield of the purified glucoside was 3.75 g. or 58%. $[\alpha]_D^{23}$ − 119.6° (water, c = 0.418, t = 105 min.); $[\alpha]_D^{24}$ + 29.7° (0.1 N HCl, c = 0.4212, t = 390 min.).

Anal. Calc'd for $C_{12}H_{18}N_2O_7S$: N, 8.38. Found: N, 8.10, 8.35.

These data are in good agreement with those of Kuhn and Birkofer who reported $[\alpha]_D^{22}$ − 123° (water, t = 0 min.) and $[\alpha]_D^{22}$ + 32° (0.1 N HCl, t = ∞).

Position of the glucosido residue. The glucose residue in *d*-glucosidosulfanilamide can be on either the N^1- or the N^4-nitrogen atoms with the probability favoring the basic amino nitrogen atom or N^4-. If this is true, then the glucose residue blocks the free primary amino group at N^4- and no reactions characteristic of free primary amino groups should be obtained with N^4-*d*-glucosidosulfanilamide. When compared directly with sulfanilamide and N^1-acetylsulfanilamide, which have free amino groups at N^4-, our glucosidosulfanilamide failed to yield a picrate, a picramide, or a substituted α-naphthylthiourea with α-naphthyl isothiocyanate. Like N^4-acetylsulfanilamide (9), which has the amino group at N^4- blocked, our glucosidosulfanilamide failed to give a positive test (formation of an orange precipitate) with Ehrlich's reagent (7). These results, tabulated below, indicate that the glucosido residue must be on the N^4-nitrogen atom, since the glucoside failed to give a single positive reaction for a free primary amino group. This is supported by the observation that the glucoside of sulfanilamide is less active physiologically than sulfanilamide, a fact in accord with the general deduction that the introduction of substituents on the N^4-nitrogen atom of sulfanilamide will either destroy completely or greatly lower its activity against streptococci.

Since Kuhn and Birkofer showed that the glucosido residue of *d*-glucosidosulfanilamide is hydrolyzed off in dilute acid solutions, diazotization and coupling could not be used here as a test for the presence of a free amino group at the N^4-nitrogen atom.

COMPOUND	PICRATE	PICRAMIDE	α-NAPHTHYLTHIOUREA DERIVATIVE	EHRLICH'S REAGENT (7)
sulfanilamide	176–176.5° (from water)	discolored at 240° decomp. at 265° (from 95% ethyl alcohol)	180–181° (from 80% ethyl alcohol)	orange ppt.
N^1-acetylsulfanilamide	169° (from dilute ethyl alcohol)	—	—	orange ppt.
N^4-*d*-glucosidosulfanilamide	none	none	none	no ppt.
N^4-acetylsulfanilamide	none	—	—	no ppt.

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SUMMARY

1. The structures of N^4-tetraacetyl-*d*-glucosidosulfanilamide and N^4-*d*-glucosidosulfanilamide have been confirmed by direct synthesis, and experimental evidence has been presented to show that the glucosido residue in the glucoside is on the N^4-nitrogen atom.

2. The chemotherapeutic activity of N^4-*d*-glucosidosulfanilamide against streptococci has been briefly compared with that of sulfanilamide.

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ALIPHATIC SULFINIC ACIDS. I. ANALYSIS AND IDENTIFICATION

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A large amount of work has been done on aromatic sulfinic acids but little is known of the aliphatic acids and their derivatives except for several methods of preparation and a few observations on their spontaneous decomposition and structure (1). This paper deals with the preparation, properties, analysis, and identification of the magnesium and sodium salts of the straight-chain aliphatic sulfinic acids from the propane through the hexadecane.

The magnesium sulfinates were made by the simplest method, addition of sulfur dioxide to the Grignard reagent (1c, f, g). The sodium salts were prepared from the magnesium salts in two ways: 1. Reaction between magnesium sulfinate and sodium carbonate or hydroxide. 2. Reaction between magnesium salt in water suspension and mineral acid to form the free sulfinic acid, extraction of the latter with ether, and neutralization of the ether solution with sodium carbonate.

The magnesium sulfinates are white powders with the general formula $(RSO_2)_2Mg \cdot 2H_2O$. They are insoluble in alcohol; the lower members of the series are sparingly soluble in hot water but the octane and higher are quite insoluble. Although hydrated, they are water repellent and are wet with difficulty. The butane salt was obtained once from water as small, glistening, colorless plates, but not the other members, which always separated as powders. As shown in Table I, the octane to dodecane salts were 100% pure as originally prepared, even without recrystallization, but the tridecane to hexadecane were less pure. They all have the peculiar property of being extremely easy to electrify by friction. Grinding or even brushing the powder on paper causes the material to scatter; this could be avoided by crushing or rubbing on a grounded sheet of copper. Frequently, powder weighed out on a watch glass scattered when the glass was picked up in the fingers; this difficulty was eliminated by grounding the operator.

On standing in water at room temperature, the magnesium salts are stable for several days, but lose in reducing power quickly when heated, due to oxidation. During heating in water there may be some alkyl sulfide formed (indicated by a slight odor and a faint yellow color), as happens with solutions of sodium salts (2). Alkaline solutions are much less susceptible to oxidation.

All the sodium salts are colorless and dissolve readily in water to give solutions which foam on shaking. Their general formula is $RSO_2Na \cdot H_2O$. The lower

members may be recrystallized from absolute alcohol (1g), the octane and higher ones from hot 95% alcohol, as clusters of needles; the butane may be thrown out of solution in 95% alcohol by addition of ether. It was not possible to obtain any sodium salt that was 100% pure. Apparently oxidation takes place during handling in solution, *e.g.*, sodium decane sulfinate, 94.1% pure, when twice dissolved in alcohol and allowed to evaporate spontaneously showed 82.5% purity by analysis.

The dry sodium and magnesium salts are quite stable in air, losing about 3% in purity on standing three and a half months on a watch glass in the laboratory. A sample of magnesium butane sulfinate kept in a stoppered bottle, opened occasionally, lost none of its purity in two years (99.6% in 1938 and 99.4% in 1940, identical within the error of the analysis).

Many attempts were made to analyze the sodium and magnesium sulfinates by titration with oxidizing agents in acid solution. Although various reagents were tried and the acidity of the solutions varied from strong to weak in sulfuric or acetic acid, all attempts failed, only 80–90% of the theoretical values being obtained. This may be due to oxidation of some of the material to disulfone, as occurs when benzene sulfinic acid is oxidized in glacial acetic acid by powdered potassium permanganate (3).

In alkaline solution, however, the salts can be titrated potentiometrically with permanganate or calcium hypochlorite, and theoretical values obtained. Another convenient method is to add an excess of permanganate to the alkaline solution, then more than enough arsenious oxide to react with the manganese dioxide and extra permanganate, acidify, and, after the dioxide has disappeared, run to a colorimetric or potentiometric end-point with permanganate. The two methods check each other, and it is possible and advisable to get checks on a single sample by carrying out the direct alkaline potentiometric titration first and then continuing with excess permanganate, arsenious oxide, etc., to the acid end-point.

In neutral solution, potentiometric titration gives results which are almost, but not quite, as good as those obtained in alkaline solution.

Difficulties are encountered in analyzing the higher magnesium salts which do not dissolve in water. Erratic and high results are obtained if a suspension of salt is first digested with an excess of permanganate in either neutral or alkaline medium and the analysis then continued by the second method above. However, consistent figures result if the suspension is digested forty to sixty minutes with dilute sodium hydroxide (without permanganate) and then titrated hot to the potentiometric end-point. An improvement on this method is to digest the magnesium salt with dilute alkali plus insufficient permanganate (80–95% of the calculated amount) and then complete the titration with more permanganate. If desired, titration can be continued as described above to the acid end-point.

Sodium and magnesium sulfinates can be reduced by shaking the solution or

suspension in water with zinc and hydrochloric acid (1b, c, 8). A bad smell, like mercaptan, results on reduction of the salts containing a chain of five or fewer carbon atoms but as the number of carbon atoms increases from six, the smell becomes more like that of an alkyl thiocyanate and progressively fainter. The eleven carbon and higher members give only a very faint odor.

Sodium sulfinates react readily with alkyl halides to form sulfones and in this way a sulfinic acid may be identified. A series of disulfones, the 1,2-di-*n*-alkylsulfonylethanes, was made by the reaction of ethylene bromide with the sodium alkane sulfinates from the propane through the hexadecane. A few ethyl sulfones were made.

EXPERIMENTAL

Preparation of magnesium salts. The alkyl bromides were redistilled Eastman products or were made by treating the alcohol[1] with hydrobromic acid (4). The Grignard reagent was prepared in the usual way from 0.25 mole of alkyl bromide in 200 ml. of ether. Dried sulfur dioxide was passed into the cooled and rapidly stirred solution. The mixture was poured onto ice or ice plus ammonium chloride. Usually a large amount of solid, white or yellowish, separated during the addition of sulfur dioxide but occasionally no solid appeared until the solution was decomposed by ice. The crude magnesium compound was filtered from the aqueous solution and air dried; it was light gray or cream colored. It was extracted with hot carbon tetrachloride or chloroform to remove wax; any magnesium hydroxide was removed by shaking the solid with ammonium chloride solution.

Purification of magnesium salts. As the length of the carbon chain increases the solubility of the magnesium sulfinates decreases to such an extent that the octane and higher salts are practically insoluble in water. For this reason these members of the series were used and analyzed as made, without treatment other than removal of wax and magnesium hydroxide. The heptane and lower members were dissolved in a large volume of hot water; when the solution was boiled down, the magnesium sulfinate separated out as a white powder, practically dry, on the surface. A large proportion of the solid taken for purification was not recovered, due probably to oxidation to the more soluble magnesium sulfonate.

Preparation of sodium salts. The more soluble magnesium sulfinates, the propane to hexane, were dissolved in hot water and treated with 50–100% excess sodium carbonate. After filtration (which may be omitted) the solution was evaporated to dryness on a steam-bath and the sodium sulfinate extracted from the residue with boiling alcohol. As the length of the carbon chain increases, conversion is more difficult. The heptane to undecane magnesium salts were refluxed one to two hours with 3 *N* sodium carbonate, the mixture, without filtration, evaporated to dryness, and the residue extracted with alcohol. The dodecane salt required long refluxing with sodium carbonate (ten hours for 65% yield of sodium salt) or hydroxide (four hours for 78% yield). Since only a trace of magnesium tridecane sulfinate was converted by refluxing for seven hours with 25% sodium hydroxide, this and the higher sulfinates were changed to the free sulfinic acids, which were then neutralized. Finely powdered magnesium salt was shaken with ether and dilute hydrochloric

[1] *n*-Octyl alcohol was kindly furnished by the Carbide and Carbon Chemicals Corp., Charleston, W. Va.; the ten, twelve, fourteen, and sixteen carbon alcohols through the kindness of the du Pont Co., Wilmington, Del. The nine, eleven, thirteen, and fifteen carbon alcohols were prepared by addition of formaldehyde to the lower alkyl magnesium bromides.

or sulfuric acid. The aqueous layer was removed, made stronger in mineral acid, and extracted several times more with small portions of ether. The ether layers were neutralized as soon as possible with sodium carbonate. The carbonate layer was evaporated to dryness, etc.; the sodium sulfinate crystallized readily as the alcohol cooled.

Heating dry salts. Heating to drive off water of hydration gave erratic results, both sodium and magnesium salts undergoing some decomposition. After 24 hours at 70–75° a sample of magnesium butane sulfinate had not lost either in purity or weight, but six hours at 100° caused a loss in purity of 3–4%; another sample came to constant weight after 48 hours at 100–105° but had lost 27% of its reducing power.

Stability of salts in water. The following tests were carried out with magnesium butane sulfinate of 100% purity:

TABLE I

MAGNESIUM ALKANE SULFINATES, $(n\text{-}RSO_2)_2Mg\cdot 2H_2O$

CARBON ATOMS IN R	PREVIOUS PREP'N REF.	YIELD, CRUDE, %	MAGNESIUM, %		PURITY BY TITRATION WITH $KMnO_4$, %
			Calc'd	Found	
1	1a				
2	1a, e, g				
3	1d, e, g		8.86	8.54	
4	1e, f, g, h	69.0	8.04	8.09	100.0
			(%S 21.19	21.22)	
5	1g		7.36	7.39	100.7
6			6.78	6.72	
7			6.29	6.21	
8	1e	41.6	5.86	5.85	
9		37.6	5.49	5.47	100.1
10		34.5	5.17	5.16	99.0
11		49.8	4.88	4.83	101.1
12		56.5	4.62	4.65	99.8
13		38.7	4.38	4.29	96.4
14		39.2	4.17	4.24	95.0
15		43.0	3.98	3.90	95.5
16		57.2	3.81	3.77	94.5

Other known aliphatic sulfinic acids are: $CHCl_2SO_2H$ (5); CCl_3SO_2H (6); $C_2H_4(SO_2H)_2$ (1b); $i\text{-}C_3H_7SO_2H$ (7); $(CH_3)_2CHCH_2SO_2H$ (8); $(CH_3)_3CSO_2H$ (9); $i\text{-}C_5H_{11}SO_2H$ (1b); cyclo-$C_5H_9SO_2H$ (10); cyclo-$C_6H_{11}SO_2H$ (1f); 3-$CH_3C_6H_{10}SO_2H$ (10).

1. A sample stood in water five days at room temperature; the solution then reduced the calculated amount of permanganate.

2. A sample in water in an open beaker was heated six hours on a steam-bath, the water being replaced as it evaporated until the last hour, during which the beaker became dry. The residue reduced only 42% of the calculated permanganate; in another run, without evaporation to dryness, the residual solution had 63% of its original reducing power.

3. A water solution of sulfinate was freed of air by boiling twice under a vacuum. The evacuated flask was heated six hours at 100°; at the end of this time the solution reduced 98% of the calculated permanganate. These experiments show that oxidation takes place when magnesium sulfinate is heated in water exposed to air.

Alkaline solutions are less susceptible to oxidation, as shown by the following:

1. A solution of pure butane magnesium salt, made alkaline with sodium hydroxide, after standing 64 hours at room temperature exposed to air, had lost only 2% in purity. This loss may have been caused by sulfide formation (2).

2. A similar solution, containing 10 ml. of 0.5 *N* sodium hydroxide was heated six hours on a steam-bath, the water being replaced as it evaporated until the last hour during which the beaker became dry. The residue reduced 87.1% of the calculated permanganate; in another run, without evaporation to dryness, the residual solution had 95.3% of its original reducing power.

3. A solution of sodium butane sulfinate was made by adding the correct amount of sodium hydroxide to a solution of butane magnesium salt. Immediately after preparation, 1 ml. of this solution reacted with 7.92 ml. of permanganate. Samples were tested as follows:

a. One milliliter of solution and 75 ml. of water, but no excess sodium hydroxide, after standing 48 hours at room temperature, reduced 7.85 ml. of permanganate.

TABLE II

SODIUM ALKANE SULFINATES, n-$RSO_2Na \cdot H_2O$

NO. OF CARBON ATOMS IN R	YIELD, %	SULFUR, %	
		Calc'd	Found
4	58	19.77	19.10
8	86	14.69	15.03
9	80	13.81	14.39
10	36	13.02	13.09
11	85	12.32	11.90
12	65	11.69	11.52
13	70	11.12	11.50
14	67	10.60	10.93
15	87	10.13	10.18
16	72	9.71	9.57

b. The same quantities were heated six hours on a steam-bath. The solution remaining reduced 3.65 ml. of permanganate.

c. One milliliter of solution, 65 ml. of water, and 10 ml. of 0.5 *N* sodium hydroxide were heated six hours on a steam-bath. The residual solution reduced 6.71 ml. of permanganate.

Fenton and Ingold prepared sulfinic acids by heating sulfones to 200° with sodium ethoxide or with solid potassium hydroxide plus a little water (1e, 7). Although gas and other products were formed, the 40–70% yields indicate the great stability of sulfinates to alkalies.

Volumetric analysis of salts by oxidation with permanganate

Oxidation to colorimetric end-point in solution alkaline at start and later acidified. To a solution of 0.0536 g. of magnesium butane sulfinate in water were added 10 ml. of 0.5 *N* sodium hydroxide and an excess of permanganate. The mixture was allowed to stand about five minutes, and then an excess of arsenious oxide was run in, followed by two drops of 0.002 *M* potassium iodate as catalyst and 5–10 ml. of 6 *N* hydrochloric acid. Stirring was continued until all the manganese dioxide was dissolved and a colorless solution obtained. Permanganate was then added to the end-point; net volume used, 13.28 ml., calculated, 13.24 ml.; normality of the permanganate 0.0535 in acid solution, 0.0321 in basic.

On addition of permanganate, the basic solution first becomes green and then turns brown; sodium carbonate may be used in place of hydroxide. Titration may be slow or fast and the solution hot or cold.

Potentiometric analysis. One electrode was a platinum wire or foil and the other a saturated calomel electrode connected through a salt bridge. The solution was mechanically stirred. Approximately 0.05 g. of magnesium sulfinate was dissolved in 50–100 ml. of water, with or without 10 ml. of 0.5 *N* alkali, and permanganate run in from a burette to a break on the volume-potential curve. It is not necessary to plot the curve, for the end-point can be recognized by the sudden jump in potential; the first drop after the jump was taken as the end-point. Apparently, too large an ionic concentration interferes, for there is no sharp potentiometric end-point if the solution is as much as 0.2 *N* in sodium chloride in addition

TABLE III

1,2-DIALKYLSULFONYL ETHANES, (n-RSO_2CH_2-)$_2$

NO. OF CARBON ATOMS IN R	PREVIOUS PREP'N REF.	SULFUR, %		M.P., °C.
		Calc'd	Found	
1	1b			190
2	1b			136–137
3	1b	26.47	26.75	159.3–160.3
4	11	23.72	23.88	179.2–180.2
5		21.46	21.41	183.7–184.2
6		19.65	19.71	177.5–178.5
7		18.09	17.58	176–177.5
8		16.77	16.72	172.8–173.5
9		15.62	15.89	172.5–173.5
10		14.51	14.67	169.9–170.9
11		13.75	13.98	168.3–169.3
12		12.97	12.75	165.8–166.8
13		12.27	12.50	163.4–164.1
14		11.64	12.14	160.9–161.9
15		11.08	10.88	158.7–159.9
16		10.57	10.99	154.6–155.8

to the usual alkali, or if it is 0.15 *N* in alkali; in these cases titration to a colorimetric end-point is accurate.

Potentiometric analysis in basic solution. A sample of magnesium butane sulfinate weighing 0.0502 g. was dissolved in water and a little sodium hydroxide added. The permanganate used in the titration was 0.04001 *N* in basic solution, 0.06669 *N* in acid; calculated volume 16.59 ml., volume actually used 16.51 ml., which corresponds to 99.6% purity of salt. The titration was continued, using an excess of permanganate, arsenious oxide, hydrochloric acid, and more permanganate to the colorimetric end-point; calculated volume of permanganate 9.95 ml., net used 9.93 ml.

Analysis after digestion with alkali and insufficient permanganate. A sample of magnesium dodecane sulfinate weighing 0.02085 g. was heated just below the boiling point for 30 minutes with 95% of the calculated permanganate in 20 ml. of water and 10 ml. of 0.5 *N* sodium hydroxide. More permanganate was then added to the potentiometric end-point; volume used 5.77 ml., calculated 5.77 ml. The titration was continued to the colorimetric

end-point in acid; net permanganate used 3.45 ml., calculated 3.46 ml. The permanganate was 0.02743 *N* in basic solution, 0.04571 *N* in acid.

Analysis of sodium sulfinates. These salts were dissolved in water with or without alkali and titrated to either a potentiometric or colorimetric end-point, without difficulty.

Formation of disulfones. One gram of sodium sulfinate and 1–1.5 ml. of ethylene bromide were refluxed in 15–20 ml. of an alcohol. Sodium bromide may form in an hour or less, but the yield of disulfone increases with time of refluxing and boiling point of solvent. Sodium decane sulfinate gave 40% of disulfone after five hours refluxing in ethyl alcohol but 66% after the same length of time in normal propyl alcohol; normal butyl alcohol was frequently used. After refluxing, the mixture was poured into water and the insoluble disulfone filtered off and recrystallized from ethyl or propyl alcohol. The pure sodium salts of the sulfinic acids with three, five, six, and seven carbon atoms were not used, but the disulfones were made by refluxing ethylene bromide either with the impure salt or with the residue left after the mixture of sodium carbonate and magnesium sulfinate solution was evaporated to dryness.

Properties of disulfones. Colorless needles, soluble in hot and insoluble in cold alcohols; with increasing molecular weight the solubility in alcohol decreases; insoluble in water; sparingly soluble or insoluble in cold, but readily soluble in hot benzene, ethyl or amyl acetate, and ethylene chloride.

TABLE IV

ALKYLSULFONYL ETHANES, $RSO_2C_2H_5$

NO. OF CARBON ATOMS IN R	SULFUR, %		M.P., °C.
	Calc'd	Found	
11	12.91	12.96	76.5–77.5
12	12.22	12.47	75.0–76.0
16	10.07	9.99	77.0–79.0

Ethyl sulfones. These were made by refluxing sodium sulfinate and ethyl iodide in alcohol. The mixture was poured into water, the insoluble sulfone filtered off, and recrystallized from alcohol. The sulfones are colorless needles, soluble in hot alcohol, insoluble in cold.

The investigation of the aliphatic sulfinic acids and their derivatives is being continued.

SUMMARY

1. Sodium and magnesium salts of the normal aliphatic sulfinic acids have been prepared.

2. A method of analyzing these volumetrically is described.

3. The disulfones, $RSO_2CH_2CH_2SO_2R$, have been prepared to complete the series from the methyl through the hexadecyl radicals.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

SOME REACTIONS OF METHYLENE-BIS-AMINES AS AMMONO-ALDEHYDES

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The structural analogies between methylene-bis-amines,[2] considered as ammono-aldehydes or ammono-acetals, and the hydrate and acetals of formaldehyde, appear upon comparison of the formulas:

Ammonia System		Water System	
$NH_2 \cdot CH_2 \cdot NH_2$	Diaminomethane (1), known in form of derivatives:	$HO \cdot CH_2 \cdot OH$	Formaldehyde hydrate
$RNH \cdot CH_2 \cdot NHR$	Methylene diamines from primary amines		
$R_2N \cdot CH_2 \cdot NR_2$	Methylene diamines from secondary amines including those from cyclic secondary amines, *e.g.*, piperidine.	$RO \cdot CH_2 \cdot OR$	Formaldehyde acetals

Examples of reactions which validate this structural analogy are probably numerous, though this rationalization is generally not pointed out and may be unrecognized. Methylene imines may probably be considered as functionally equivalent to methylene diamines since Schiff bases of this type, even when trimeric, may be used interchangeably with methylene diamines in certain reactions (2), the two being related as are formaldehyde and formaldehyde hydrate:

$$HO \cdot CH_2 \cdot OH \rightleftharpoons CH_2O + H_2O$$

$$RNH \cdot CH_2 \cdot NHR \rightleftharpoons CH_2{:}NR + RNH_2 \quad (3).$$

The use of hexamethylenetetramine in the preparation of phenol-formaldehyde resins (4) involves $-\overset{|}{N} \cdot CH_2 \cdot \overset{|}{N}-$ units and may be considered to be a methylene diamine reaction. The condensation of succinimide and formaldehyde (5) to yield methylene-bis-N,N′-succinimide and tris-(methylenesuccinimido)amine

[1] This paper is constructed from the thesis submitted by J. R. Feldman to the Graduate School of the University of Pennsylvania in partial satisfaction of the requirements for the degree of Doctor of Philosophy, June 1941.

[2] Throughout this paper the more convenient general term methylene diamine will be used. These compounds have been designated previously as "diimines."

has been duplicated by use of hexamethylenetetramine (6). Methylene diamines can be used instead of formaldehyde in the Knoevenagel reaction (7). Ullmann (8) prepared 10-methyl-7,12-dihydro-1,2-benzacridine (9) from naphthol-2 by interaction with either trioxymethylene and *p*-toluidine or with methylene-bis-*p*-toluidine, and obtained other acridines similarly.

In the experimental demonstration that methylene diamines and formaldehyde (formalin) react in ways essentially identical, the method employed was to use methylene diamines and formalin interchangeably in certain reactions known to be characteristic of formaldehyde. In each group of comparable reactions the main product was the same whether the methylene diamine or formaldehyde was used. The manner of reaction of the methylene diamine was further revealed by the fact that the by-product (corresponding to the water split out in formaldehyde reactions) was the amine represented by the methylene diamine used. In many experiments the liberated amine was recovered and identified, and its amount found to correspond with that of the main product, making it possible to indicate the reaction by equation without assumptions.

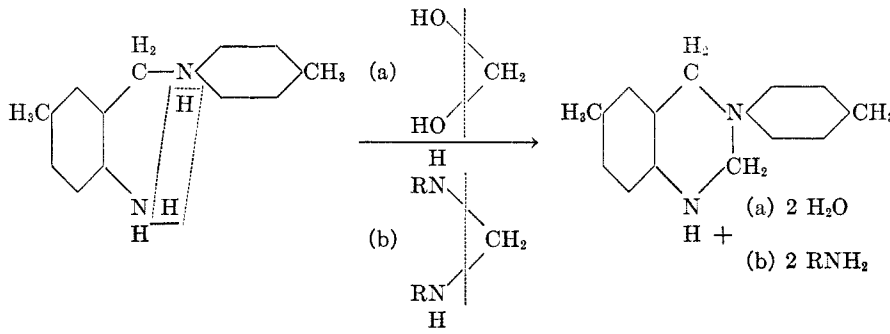
The susceptibility to acid hydrolysis which is characteristic of methylene diamines made necessary some precautionary experiments under anhydrous conditions. Though in most cases the products were isolated by direct methods, this did not exclude the possibility that small amounts of water (present for example in the alcohol used as solvent, or even as traces present in chemicals or on apparatus) might operate cyclically to yield formaldehyde as the actual reactant, as well as the amine obtained as by-product. Failure to exclude this possibility would make uncertain any conclusions drawn from the results of the methylene diamine reactions, and the analogy involved would be entirely invalid if it were shown that the methylene diamine reactions could occur only in presence of at least traces of water. Several of the reactions were therefore attempted using materials and apparatus which had been scrupulously dried. It was found that under these conditions the reactions occurred smoothly, and it is concluded that the observed aldehydic behavior of the methylene diamines studied was indicative of an inherent aldehydic character based upon structure.

The methylene diamines used were derived from both primary and secondary amines, *viz.*, methylene-bis-*p*-toluidine (I), methylene-bis-*p*-chloroaniline (II), methylene-bis-*p*-bromoaniline (III), methylene-bis-*p*-anisidine (IV), methylene-bis-ethylaniline (V), methylene-bis-piperidine (VI), and methylene-bis-morpholine (VII). The last three compounds, with no amino hydrogen, are ammonia-system analogs of formaldehyde acetals. Since acetals can be used instead of aldehydes in some reactions (10), it was expected that methylene diamines of these types would show a functional analogy with formaldehyde, and this was found to be the case. In some experiments the trimeric Schiff base methylene-*p*-toluidine (VIII) was used, and yielded in each case the same products as did the corresponding methylene diamine.

The reactions studied, and the results obtained, are outlined below. The reactions, whether in the water system or the ammonia system, are of types which are known to be, or which may be assumed to be, reversible, though

reversal may be inconsiderable in reactions leading to ring closures. No effort was made to disclose a reversible character in any of the ammonia-system reactions, and accordingly the reaction diagrams are given without indications of reversibility.

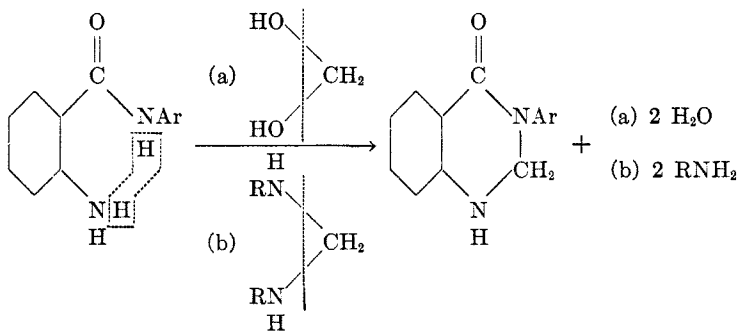
1. *Formation of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline from* o*-amino-*m*-xylyl-*p*-toluidine by action of methylene diamines.*



IX X

This ring closure, previously effected by means of formaldehyde (11) and also methylene-bis-*p*-toluidine (12), was found to occur when the other methylene diamines named above were used. The reaction took place when the methylene diamine and the aminobenzylamine were heated together in alcohol solution. It was unfavorably affected by presence of sodium ethoxide (*cf.* 2).

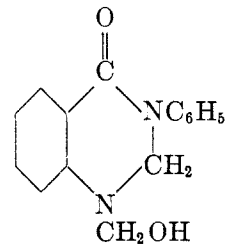
2. *Formation of 3-substituted-1,2,3,4-tetrahydroquinazolones from anthranilanilides by action of formaldehyde and of methylene diamines:*



Reaction (a), not previously reported, was found to occur upon treating the anthranilanilide, dissolved in alcohol containing alkali, with excess formalin at temperatures up to about 60°. The resulting tetrahydroquinazolones were identified as such by analysis and by oxidation to the corresponding dihydroquinazolones (13), which had been reported (14) or were synthesized from anthranilic acid and suitable formylamines (15). The anthranilanilides used were N-phenylanthranilamide (XI), N-(*p*-bromophenyl)anthramilamide (XII), and N-(*p*-anisyl)anthranilamide (XIII), and the resulting quinazolones were

respectively 3-phenyl-1,2,3,4-tetrahydroquinazolone-4 (XIV), 3-*p*-bromophenyl-1,2,3,4-tetrahydroquinazolone-4 (XV), and 3-*p*-anisyl-1,2,3,4-tetrahydroquinazolone-4 (XVI).

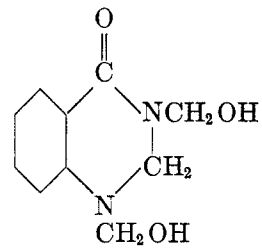
By interaction of anthranilanilide (XI) and formalin at lower temperatures and with the latter in larger excess the tetrahydroquinazolone (XIV, m.p. 175° obs.) was not obtained, but instead a compound of m.p. 109–110°obs. This product, with empirical formula $C_{15}H_{14}N_2O_2$, was identified (see Experimental Part) as 1-methylol-3-phenyl-1,2,3,4-tetrahydroquinazolone-4.



XVII

This compound is similar to certain methylol compounds previously reported (4a), and closely resembles the more stable bases prepared by Miller (16). The cleavage of formaldehyde from methylol compounds is familiar in the depolymerization of linear "polymers" of formaldehyde. Other examples include the condensation of 1-methylolpyrroles to yield dipyrrylmethanes (17), and the elimination of formaldehyde from methylol derivatives of methylene-N,N′-bisbenzamide reported by Einhorn (18).

Interaction of anthranilamide and formaldehyde failed to yield the expected tetrahydroquinazolone, but gave a product (m.p. 141°) found by analysis to have the empirical formula $C_{10}H_{12}N_2O_3$. Evidence given in the experimental section indicates this compound to be 1,3-bis-methylol-1,2,3,4-tetrahydroquinazolone-4:

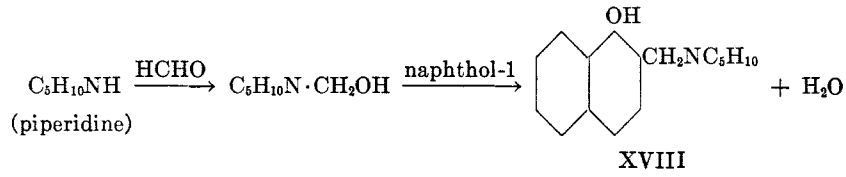


As this reaction could not be paralleled in experiments with anthranilamide and several methylene diamines it was not studied further.

Reaction (b) was caused to occur by heating anthranilanilides and methylene diamines together in absolute alcohol, and was assisted by the presence of sodium ethoxide. This fact, and the favorable effect of alkali in the corresponding formaldehyde reaction (a) are comprehensible if it is noted that in each case the ring closure involves removal of an amino hydrogen and an amido hydrogen,

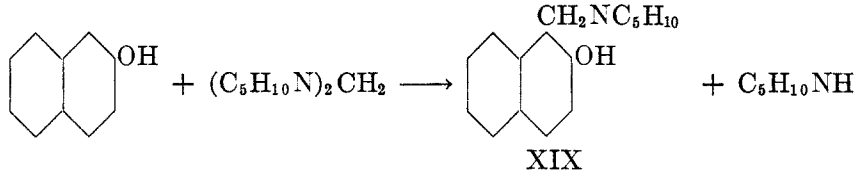
and with respect to the latter change resembles the alkylation of an amide and is promoted by presence of alkali. In the ring closures by methylene diamines this effect must be attributed to the influence of the alkaline agent upon the amide hydrogen rather than upon the methylene diamines, which are relatively quite stable in alkaline environment (4a).[3] The absence of added alkali does not by any means exclude reaction (b), from which it appears that the methylene diamine itself, or the by-product amine, may serve as alkaline promotor.

3. *Formation of aminomethylphenols by interaction of methylene diamines and phenols.* The related water-system reaction is illustrated by the condensation of phenol and formaldehyde as applied in the preparation of resins. Aminomethylphenols have been obtained by interaction of phenols, formaldehyde, and secondary amines by Auwers and Dombrowski (19), Caldwell and Thompson (20), and Bruson and MacMullen (21). The reaction is believed to involve intermediate formation of the methylolamine, and condensation of this with the phenol, *e.g.*,



XVIII

The same final result might be expected if the reactive intermediate were the methylene diamine, the possibility of whose formation cannot well be excluded. Experiments showed that interaction of methylene diamines (or of VIII) with phenols, upon heating in absolute alcohol, yielded compounds identical with those obtainable from formaldehyde, phenols, and amines, the reaction in each case occurring with liberation of half the amine, *e.g.*,



XIX

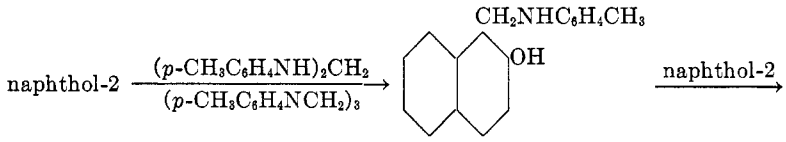
Reactions of this type were realized with naphthol-1, naphthol-2, and carvacrol. The methylene diamines used were I, II, and VI. The aminomethylphenols obtained were 2-piperidinomethylnaphthol-1 (XVIII), 1-piperidinomethylnaphthol-2 (XIX), 1-*p*-toluidinomethylnaphthol-2 (XX), 1-*p*-chloroanilinomethylnaphthol-2 (XXI), and piperidinomethylcarvacrol (XXII). The reaction occurred also (naphthol-2 and VI) under anhydrous conditions.

The aminomethylphenols prepared were found to exhibit a partially cryptophenolic character. They were insoluble in cold aqueous alkali, but dissolved

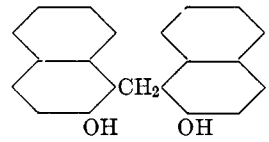
[3] Methylene-bis-piperidine can be distilled over sodium under reduced pressure without noticeable decomposition. Distillation of some methylene diamines leads to partial conversion to the trimeric Schiff bases (3).

on heating: 1-*p*-toluidinomethylnaphthol-2 thus dissolved was recovered with small loss upon acidification of the alkaline solution.

In the presence of alkali (compare the conditions above) the condensation of phenols, formaldehyde, and secondary amines was found by Auwers and Dombrowski (19) to go farther, yielding the bis-(hydroxyaryl)methane compounds. The same final result was obtained in the present study by interaction of naphthol-2 with I and with VIII.



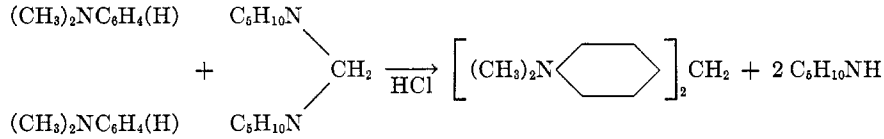
XX



XXIII

In the absence of added alkali, the same reactants yielded a mixture of XX and XXIII, indicating that the amine liberated in formation of the former can function as the alkaline agent needed to promote the second stage of the reaction. In the presence of sodium ethoxide, only the dinaphthylmethane compound (XXIII) was obtained. The over-all reaction is actually of the type considered in the following section, *viz.*, formation of diarylmethane bases from amines and formaldehyde, shown by v. Braun and Kruber (22) to involve an intermediate hydroxymethyl compound. The influence of alkali may perhaps be interpretable in a manner similar to that suggested by Hauser and Breslaw (23) for the coupling of phenols and diazonium compounds.

4. *Formation of 4,4'-dimethylaminodiphenylmethane (XXIV) from dimethylaniline by the action of methylene-bis-piperidine (VI).* The preparation of XXIV from dimethylaniline and either formaldehyde (24) or methylal (10a) is familiar. When dimethylaniline was heated with VI in absolute alcohol no reaction occurred. In the presence of hydrogen chloride the diphenylmethane base formed, with liberation of an equivalent amount of piperidine:

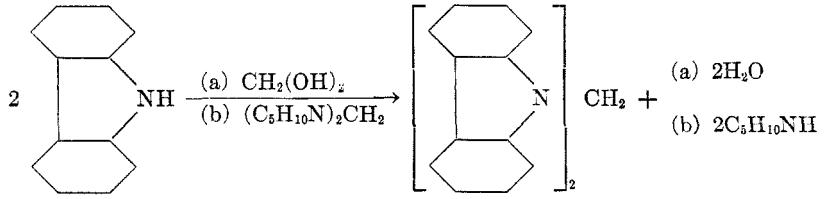


XXIV

5. *Interaction of carbazole with formaldehyde and with methylene-bis-piperidine.* The formation of methylene-bis-carbazole (XXV) by interaction of carbazole and formaldehyde or compounds containing methylene groups attached to oxygen or nitrogen was shown by Votoček and Veselý (25) to occur in acid solution.

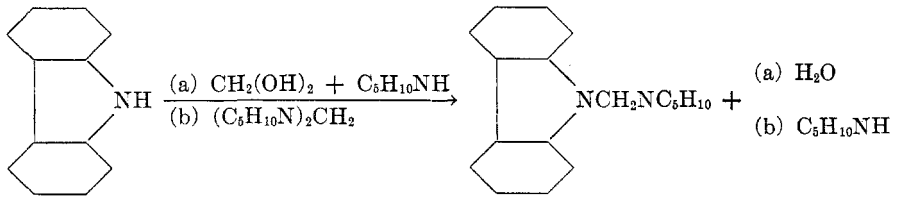
Trials using either formaldehyde or VI in glacial acetic acid yielded the expected methylene-bis-carbazole (XXV). When carbazole, piperidine, and formalin were heated in aqueous alcohol solution, in the absence of acid, the product (99%) was not XXV but 9-piperidinomethylcarbazole (XXVI). The same compound was obtained by heating together carbazole and VI in the absence of solvent or acid. The reactions involved in these experiments may be represented:

In acid solution:



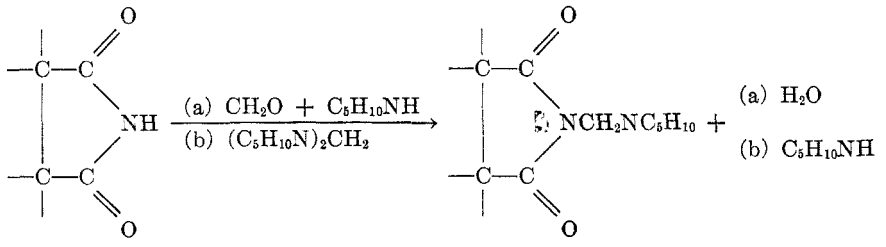
XXV

In absence of acid:



XXVI

6. *Formation of aminomethylimides by interaction of acid imides and methylene diamines.* The water-system equivalent of this reaction is illustrated by the formation of hydroxymethylamides (18) or hydroxymethylimides (26) by action of formaldehyde on amides or imides. Cherbuliez and Sulzer (27) obtained N-piperidinomethylsuccinimide (XXVIII) by interaction of N-hydroxymethylsuccinimide and piperidine, and Sachs (26) found that succinimide, formaldehyde, and piperidine reacted to yield the same compound. The corresponding ammonia-system reaction occurred readily when succinimide or phthalimide was warmed with methylene-bis-piperidine (VI) in absolute alcohol.



phthalimide or succinimide

XXVII or XXVIII

In these reactions succinimide and phthalimide (and also carbazole, section 5) may be regarded as weak acids, the acid character of which is increased in basic media (28).

7. *Interaction of methylene diamines and dimethyldihydroresorcinol.* Dimethyldihydroresorcinol ("methone", etc.), used as a reagent for aldehydes (29), was found to react with methylene diamines I, II, III, and IV to give high yields of methylene-bis-4,4-dimethylcyclohexadione-2,6 (methylene-bis-methone: XXIX) identical with the compound obtained from methone and formaldehyde.

EXPERIMENTAL

Analyses. Carbon and hydrogen were determined by a semimicro procedure, nitrogen by semimicro Kjeldahl (37), and halogen by a semimicro adaptation of Robertson's procedure (40a), using alkaline arsenite solution in the receiver (40b).

Starting Compounds. Methylene-bis-amines from *p*-substituted aromatic primary amines were prepared by the method of Bischoff and Reinfeld (3). The products were purified by crystallization from ethanol containing a small amount of potassium hydroxide, excepting methylene-bis-*p*-anisidine, which is extensively converted into the trimeric Schiff base by attempted crystallization from alcohol or ether (31, 2). The first fraction generally contained some trimeric Schiff base, but by diluting and chilling the mother liquor several fractions of pure methylene diamine were obtained. The compounds so prepared were methylene-bis-*p*-toluidine (I, m.p. 93.5–95° obs.), methylene-bis-*p*-chloroaniline (II, m.p. 64–66° obs.), methylene-bis-*p*-anisidine (IV, m.p. 63–65° obs.), and methylene-bis-*p*-bromoaniline (III, m.p. 90–92° obs.).

Methylene-bis-amines from secondary amines. Methylene-bis-ethylaniline (V, m.p. 74–75° obs.) was prepared by the method of v. Braun (32, 33). Methylene-bis-piperidine (VI, b.p. 69–72° at 2 mm.) was obtained in 90% yield by the method of Ehrenberg (34, 7). Methylene-bis-morpholine (VII, b.p. 99–107° at 2 mm.) was obtained similarly and in a yield of 69%. As this compound was not fully characterized by Mason and Zief (35) its identity was confirmed by analysis for nitrogen (calc'd for $C_9H_{18}N_2O_2$: N, 15.03; found: N, 14.99, 14.97).

Anthranilanilides were made by interaction of amines and isatoic anhydride (36). After evolution of carbon dioxide ceased, the mass was extracted with several portions of hot benzene, the solution was decolorized with charcoal, and the pure product obtained by chilling the filtered solution. The compounds so prepared were N-phenylanthranilamide (XI, m.p. 128.5–129°, obs.), N-*p*-bromophenylanthranilamide (XII, m.p. 154–155° obs.), and N-*p*-anisylanthranilamide (XIII, m.p. 123–123.7° obs.). The last-named compound has not been reported previously.

Anal. Calc'd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56.
Found: C, 69.67, 69.52; H, 5.86, 5.72; N, 11.51, 11.49.

REACTIONS

1. Formation of 3-p-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline (X) from o-amino-m-xylyl-p-toluidine (IX) by action of methylene-bis-amines. General procedure. About 0.01 mole (2.26 g.) of IX made by the procedure of Miller and Wagner (38), and an equivalent amount of the methylene diamine, were dissolved in 50–90 cc. of absolute ethanol, and the solution was boiled under reflux for an hour or longer. The volume was reduced to 10–15 cc. by removal of alcohol under reduced pressure. The concentrated solution was chilled, and the crude X was separated by filtration. To separate the rest of the X and the amine set free in the reaction (39), the mother liquor was diluted, acidified with dilute hydrochloric acid (1:20), and extracted with ether. The ether extract was evaporated to dryness and the residue of X combined with the main portion for crystallization from ligroin (90–120°). The purified tetrahydroquinazoline was identified by its m.p. (139° to 141°) and by mixed

m.p. test using a specimen prepared by action of formaldehyde on IX (11). The acid extract was evaporated to dryness, and the residue of amine hydrochloride weighed. When the amine was relatively volatile (piperidine, morpholine) it was isolated from the first filtrate: amine and alcohol were distilled, the last traces being removed by codistillation with two 25-cc. portions of toluene, and the distillate was acidified with hydrochloric acid and evaporated to dryness. The essential results of individual reactions are collected into Table I.

Reaction under anhydrous conditions. A mixture of 0.01 mole of IX (previously dried for several weeks over phosphorus pentoxide) and 0.011 mole of VI (distilled *in vacuo* over sodium) in 15 cc. of toluene (distilled through a 3-ball Snyder column and stored over sodium), in an all-glass apparatus which had been dried at 130–135° for forty-eight hours, was refluxed for two hours, with the open end of the condenser protected by calcium chloride and Ascarite tubes. The reaction products were isolated as outlined above; X was purified

TABLE I

FORMATION OF 3-*p*-TOLYL-6-METHYL-1,2,3,4-TETRAHYDROQUINAZOLINE (X) FROM *o*-AMINO-*m*-XYLYL-*p*-TOLUIDINE (IX) BY RING CLOSURE WITH METHYLENE DIAMINES

METHYLENE DIAMINE	TETRAHYDROQUINAZOLINE (X) % YIELD	AMINE	AMINE %	IDENT.
I	79 (86)[a]	*p*-toluidine	86	Bz-deriv. m.p. 152–153° obs.
II	76 (95)[a]	*p*-chloroaniline	86	Bz-deriv. m.p. 188°
III	77	*p*-bromoaniline	84	Bz-deriv. m.p. 201°
IV	70	*p*-anisidine	99[b]	Bz-deriv. m.p. 154.5–155°
VI	95	piperidine	99	B·HCl, m.p. 242.5–244°
VII	88	morpholine	73	B·HCl, m.p. 168–172°
VII	25[c]	morpholine	—	—
V	95	ethylaniline	—	—

[a] Crude yields in parentheses.

[b] The methylene diamine which escaped reaction with IX was probably decomposed during the isolation procedure, since the instability of this methylene diamine is exceptional (3, 31).

[c] Reaction in the presence of sodium ethoxide.

by crystallization from a mixture of dry toluene and ligroin. The yield of X was 92%; piperidine was recovered quantitatively as hydrochloride.

2. *Formation of 3-substituted tetrahydroquinazolones from anthranilanilides by action of formaldehyde and of methylene diamines. A. Ring closure with formaldehyde. General procedure.* The anthranilanilide (0.005–0.01 mole) was dissolved in 10–20 cc. of ethanol alkaline with sodium hydroxide, 2–5 cc. of 37% formalin (five times the theoretical formaldehyde) was added, and the solution was warmed to about 60° and then chilled. The separated product was crystallized from alcohol.

3-*p*-Bromophenyl-1,2,3,4-tetrahydroquinazolone-4 (XV) was obtained in 82% yield (0.85 g. from 1.00 g. of XII); the m.p. was 194–195° obs., or 199–200° corr.

Anal. Calc'd. for $C_{14}H_{11}BrN_2O$: C, 55.46; H, 3.66; N, 9.24; Br, 26.36; mol. wt., 303.
Found: C, 55.67, 55.85; H, 3.67, 3.63; N, 9.27, 8.98; Br, 26.12, 26.38; mol. wt. (Rast method), 296, 310.

3-*p*-Methoxy-1,2,3,4-tetrahydroquinazolone-4 (XVI) was obtained in 91% yield (1.15 g. from 1.20 g. of XIII). After crystallization from ethanol the compound melted at 185–185.5° obs.

Anal. Calc'd. for $C_{15}H_{14}N_2O_2$: C, 70.84; H, 5.56; N, 11.01.
Found: C, 71.00, 70.91; H, 5.76, 5.66; N, 10.83, 10.86.

3-Phenyl-1,2,3,4-tetrahydroquinazolone-4 (XIV) was obtained in 96% yield (2.15 g. from 2.11 g. of XI). The purified compound melted at 176° obs., or 180° corr.

Anal. Calc'd. for $C_{14}H_{12}N_2O$: C, 74.90; H, 5.38; N, 12.49.

Found: C, 75.07, 74.92; H, 5.65, 5.55; N, 12.27, 12.22.

1-Methylol-3-phenyl-1,2,3,4-tetrahydroquinazolone-4 (XVII). When preparation of XIV was attempted at lower temperature and with relatively more formaldehyde, the product was a lower-melting compound eventually identified as XVII. A warm solution of 1.2 g. of XI in 30 cc. of ethanol previously made alkaline to litmus with sodium hydroxide was treated with 5 cc. of 37% formalin, and was then chilled. The crystalline product weighed 0.80 g., and melted at 109–110° obs., or 110–111° corr., in a capillary tube. Dilution of the filtrate with water yielded a second crop (0.35 g.) of m.p. 108° obs., with effervescence. Mixed melting point tests showed that the compound was not impure XIV nor XI. When it was heated slowly on a Fisher-Johns melting point block or in a micro melting point apparatus the compound melted at 105–110° with gas evolution. The mass was then seen to resolidify, and showed no further change until it melted at 172–175° obs., the m.p. of XIV. The following experiment established that the new compound is converted by heat into 3-phenyltetrahydroquinazolone-4 with elimination of formaldehyde.

The compound of m.p. 110° (0.40 g.) was dissolved in 10 cc. of absolute ethanol in a distilling flask, and the alcohol was distilled into a solution of dimethyldihydroresorcinol. Distillation was repeated after addition of more absolute alcohol to the residue, and then twice with 20-cc. portions of water. The combined distillates yielded 0.25 g. of methylene-bis-methone (XXIX) of m.p. 190–191° obs. The residue in the distillation flask (0.25 g.) was XIV, m.p. 176–178° obs., and was identified by mixed m.p. tests.

Anal. Found: C, 71.01, 70.82; H, 5.24, 5.51; N, 11.01, 10.95.

These results are consistent with the molecular formula $C_{15}H_{14}N_2O_2$; Calc'd.: C, 70.85; H, 5.55; N, 11.02.

Interaction of anthranilamide and formaldehyde.[4] Treatment of 12.0 g. of anthranilamide (41) with formaldehyde by the general procedure (150 cc. of 95% ethanol made alkaline with sodium hydroxide; 30 cc. of 37% formalin) yielded 11.0 g. of a colorless crystalline product which melted at 139–141°, with gas evolution. Crystallization from alcohol yielded material of m.p. 141° obs., but was not uniformly satisfactory, as in solution the compound was decomposed by even gentle warming.

In absence of alkali, the interaction of anthranilamide and formaldehyde in ethanol at 70–75° yielded a colorless, viscous product which solidified when the mixture was chilled in ice. The separated substance softened at 65–70° and evolved a gas with the odor of formaldehyde, after which the mass resolidified, and on further heating sublimed around 170°. This product was not examined further.

The compound of m.p. 141° was found to yield formaldehyde on heating or by action of water or of aqueous ammonia. The cold water extract gave a strong test with Schiff's reagent. After concentrating the formaldehyde by distillation of the extract, it was precipitated as the dimethyldihydroresorcinol derivative (m.p. 190–192°) and identified by mixed m.p. test. A similar result was obtained when the compound was dissolved in alcohol and the alcohol distilled: the distillate contained formaldehyde, identified as the methone derivative. Aqueous ammonia dissolved the compound, and after acidification of the mixture with acetic acid and removal of solid material by filtration, the filtrate was treated with Thatcher's reagent (44). The red-orange crystalline product darkened at 110–115°, shrank at 165–170°, and at 210° melted to a dark red liquid, indicating it to be urotropin tetraiodide.

The essential structure of the compound of m.p. 141° was indicated by its conversion to

[4] The preliminary experiments and analysis are the work of the junior author. For preparative details, and for tests to determine the structure of the product, credit is due S. N. Hall.

3,4-dihydroquinazolone-4 by mild oxidation with potassium permanganate in acetone (see section D below). The product (1.7 g. from 2.5 g. of compound) melted at 210–214°, and at 210–212° obs. after crystallization from water. A mixture with a specimen of 3,4-dihydroquinazolone-4 made by Niementowski synthesis from anthranilic acid and formanilide melted at 209–211°. The picrates (m.p. 206–208°) of the two specimens were likewise identical.

Anal. Found: C, 57.35, 57.72; H, 5.61, 5.81; N, 13.28, 13.33.

These analytical values are consistent with the molecular formula $C_{10}H_{12}N_2O_3$ (Calc'd: C, 57.68; H, 5.81; N, 13.46).

All the foregoing evidence supports the conclusion that the compound is 1,3-bis-methylol-1,2,3,4-tetrahydroquinazolone-4.

B. Ring closure with methylene diamines. General procedure. A solution of the anthranilanilide (0.005–0.01 mole) and an equivalent amount of the methylene diamine in absolute alcohol was heated under reflux for periods of several hours up to twenty-four hours. In some experiments 0.1 g. of sodium was previously dissolved in the alcohol, in order to effect the reaction in presence of sodium ethoxide. The crystalline quinazolone separated when the solution was chilled. The mother liquor generally yielded one or more additional crops of product. The filtrate was evaporated and the residue was subjected to steam distillation. The residue in the flask was crystallized from ethanol in fractions, and the crude tetrahydroquinazolone was recrystallized from alcohol. The steam distillate was filtered to remove unchanged methylene diamine (in part present as trimeric Schiff base), and the filtrate was acidified slightly with 1:20 hydrochloric acid. Evaporation of the acid liquid left the amine as hydrochloride. This was weighed, and the amine was identified. In experiments with VI and VII the liberated piperidine and morpholine were isolated by the procedure outlined under 1. The essential results of individual reactions are collected into Table II.

C. Interaction of anthranilamide and methylene diamines. As shown in section A, the interaction of anthranilamide and formaldehyde yielded a compound other than the expected tetrahydroquinazolone-4. Experiments in which I, IV, and V were used instead of formaldehyde failed to yield any isolable or recognizable products other than unchanged amide, methylene diamine (or Schiff base formed from it), and free amine.

D. Proof of structure of tetrahydroquinazolones. General procedure (13). A solution of 0.003–0.01 mole of the tetrahydroquinazolone in 150–300 cc. of dry acetone was cooled to 0° and treated with 10% more than the calculated amount of potassium permanganate dissolved in acetone, added during two or three hours while stirring and chilling the mixture. Excess of sodium bisulfite was added, and the mixture was kept in a refrigerator for two days, after which it was filtered. The filtrate was freed of acetone by distillation, and the residue was crystallized from ethanol. The essential results of these experiments, and the evidence as to identities of XIV, XV, and XVI, are as follows:

Compound XIV yielded 48% [including tailings recovered as picrate, m.p. 177–178° (42)] of 3-phenyl-3,4-dihydroquinazolone-4, m.p. 138–139° obs. A mixture with a specimen (m.p. 139–140°) made from anthranilic acid and formanilide (15) melted at 138.5–139.5°.

Compound XV yielded 36% of 3-*p*-bromophenyl-3,4-dihydroquinazolone-4, m.p. 189–190° obs. A mixture with a specimen (m.p. 190–191°) made synthetically (15) from anthranilic acid and formyl-*p*-bromoaniline melted at 190–190.5°. As Paal and Koch reported the m.p. to be 174° (14b), the compound was analyzed for bromine. Calc'd for $C_{14}H_9BrN_2O$: Br, 26.54. Found: Br, 26.43, 26.24, 26.59, 26.32.

Compound XVI yielded 87% of 3-*p*-anisyl-3,4-dihydroquinazolone-4, m.p. 193.5–194° obs. A mixture with a specimen made by synthesis (m.p. 193–194°; see below) melted at 193–194°.

3-*p*-Methoxyphenyl-3,4-dihydroquinazolone-4, not previously reported, was prepared (15) by heating anthranilic acid and formyl-*p*-anisidine for ninety minutes at 150°. The

product was crystallized successively from alcohol, benzene, and light ligroin. The yield of pure material, m.p. 193–194°, was 28%.

Anal. Calc'd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.80; N, 11.10.

Found: C, 71.12, 71.32; H, 4.73, 4.59; N, 11.28, 11.14.

3-*p*-Bromophenyl-3,4-dihydroquinazolone-4 picrate, prepared from the base and an equivalent amount of picric acid in alcohol, melted at 171–173°. Analysis for bromine gave the values 14.71 and 15.07; calc'd for $C_{20}H_{14}BrN_3O_8$: Br, 15.02.

TABLE II

FORMATION OF 3-ARYL-1,2,3,4-TETRAHYDROQUINAZOLONES FROM ANTHRANILANILIDES BY RING CLOSURE WITH METHYLENE DIAMINES

METHYLENE DIAMINE	PRODUCT								
	3-phenyltetrahydroquinazolone (XIV)			3-*p*-bromophenyltetrahydroquinazolone (XV)			3-*p*-anisyltetrahydroquinazolone (XVI)		
	Conditions[a]	Yield %	Amine %	Conditions[a]	Yield %	Amine %	Conditions[a]	Yield %	Amine %
I	n.s. 115° 5 hrs.	26	30[b]		56			53	63[c]
II					14	—		49	46[d]
III				3.5 hrs.	73	ident.		55	66[e]
IV					70	84		86	92
V	NaOEt	47	—	NaOEt	40	—	NaOEt	22[f]	—
VI	8 hrs.	65	58	5 hrs.	40	—[g]	24 hrs.	52	39[h]
VI	NaOEt	87	78	NaOEt 9 hrs.	71	58	NaOEt	87	ident.
VII	n.s. 145° 2 hrs.	26	33	n.s. 145° 10 hrs.	33[i]	45	n.s. 145° 10 hrs.	39[i]	40
VII				NaOEt	36	38[j]			
VII				18 hrs.	12	10[k]			

[a] Reaction in boiling alcohol, 2 hours, unless other time stated; n.s. = no solvent (fusion); no NaOEt unless stated.

[b] Recovered considerable unchanged XI, and 72% of I.

[c] Recovered unchanged 39% of XIII and 40% of I.

[d] " " 31% of XIII and 53% of II.

[e] " " 33% of III.

[f] " " 31% of XIII.

[g] " " 53% of XII.

[h] " " 29% of XIII.

[i] Nearly half of this yield was obtained by evaporation of the first filtrate and by heating the residue *in vacuo* at 235°.

[j] Recovered unchanged 43% of XII.

[k] " " 29% of XII.

3. Formation of aminomethylphenols and methylene-bis-(hydroxyaryl) compounds by interaction of methylene diamines and phenols. A. Aminomethylphenols. General procedure. A mixture of about 0.02 mole of the phenol (naphthol-1, naphthol-2, or carvacrol), an equivalent amount of the methylene diamine (I, II, or VI) and 20 cc. of absolute ethanol was heated under reflux for fifteen to sixty minutes. The crystalline product separated when the solution was chilled; in some experiments the mother liquor was worked up to obtain additional crops of product, or unchanged methylene diamine. To recover the

amine liberated in the reaction, the filtrate was distilled under reduced pressure (to avoid formation of colored resins which otherwise appeared at about 130°), and the uncondensed vapors passed through a trap charged with hydrochloric acid. The distillate and the liquid from the trap were combined and evaporated to dryness. The residue of amine hydrochloride was weighed and the amine identified. The residue from the distillation was recrystallized from alcohol to obtain an additional crop of the aminomethylphenol. Essential results of the experiments are given in Table III.

TABLE III

FORMATION OF AMINOMETHYLPHENOLS FROM PHENOLS BY ACTION OF METHYLENE-BIS-AMINES

PHENOL	METHYLENE DIAMINE	AMINOMETHYLPHENOL			AMINE	
		Name	M.p. °C.	Yield %	%	Ident.
Naphthol-1	VI	2-Piperidinomethyl-naphthol-1 (19)	133.5–134.5	77[a]	97	B·HCl, m.p. 242.4°
Naphthol-2	VI	1-Piperidinomethyl-naphthol-2 (19)	95– 96.5	97	97	B·HCl, m.p. 239–241°
Naphthol-2	VI	1-Piperidinomethyl-naphthol-2	95– 96.5	61[b]	62	
Naphthol-2	I	1-*p*-Toluidinomethyl-naphthol-2	136.5–137	80[c]	84	
Naphthol-2	II	1-*p*-Chloroanilino-methylnaphthol-2	139–141.5	81	95	
Carvacrol	VI	Piperidinomethyl-carvacrol (20)	182–183	24	29	B·HCl, m.p. 235–239°

[a] Reaction at room temperature gave an almost identical result: yield 78%.
[b] Reaction under anhydrous conditions; solvent was dry 90–120° ligroin.
[c] Recovered 15.5% of I, m.p. 88–91°.

*1-(N-*p*-toluidinomethyl)naphthol-2* (*XX*). The composition of this compound, not previously reported, was determined by analysis.

Anal. Calc'd for $C_{18}H_{17}NO$: C, 81.9; H, 6.51; N, 5.32.
Found: C, 81.9; 81.6; H, 6.47, 6.27; N, 5.19, 5.25.

Compound XX was not dissolved by 10% sodium hydroxide solution cold, but it dissolved on heating. Acidification of the solution produced a gummy precipitate from which, after washings with ether and 10% alkali, most of XX (m.p. 136–137°) was recovered. An ether solution of XX was not affected by shaking with cold aqueous sodium hydroxide solution; the starting material was recovered quantitatively from the ether layer. These results indicate that the *p*-toluidinomethyl group is not attached to oxygen, and that the phenolic character of XX is relatively weak.

1-(N-*p*-chloroanilino)naphthol-2 (XXI), not previously reported, was characterized by analysis.

Anal. Calc'd for $C_{17}H_{14}ClNO$: C, 71.95; H, 4.97; N, 4.94.
Found: C, 72.03, 71.85; H, 5.03, 4.99; N, 4.88, 4.87.

B. 1,1'-Methylene-bis-naphthol-2 (*XXIII*). This compound (43) was obtained as the sole product when naphthol-2 and VIII (trimeric methylene-*p*-toluidine) were heated in the presence of sodium ethoxide in alcohol solution. A mixture of 2.88 g. (0.02 mole) of naphthol-2, 2.38 g. (0.0067 mole) of VIII, 25 cc. of absolute ethanol and 0.3 g. of sodium ethoxide (0.1 g. of sodium previously dissolved in the alcohol) was heated under reflux for several hours. The solution was saturated with carbon dioxide, and the precipitated

sodium carbonate was removed by filtration. Dilution of the filtrate caused the separation of 0.25 g. of XXIII (m.p. 194–195°; identified by mixed m.p. test), after removal of which the filtrate was made acid to litmus by addition of acetic acid and was chilled, yielding 1.3 g. of XXIII (total yield 52%), and a small amount of tarry material.

In the absence of added alkali, the interaction of naphthol-2 and I or VIII formed toluidinomethylnaphthol (XX) as the main product, but smaller amounts of methylene-bis-naphthol (XXIII) were isolated in several experiments, as illustrated by the following. A mixture of 2.20 g. (0.01 mole) of I, 1.58 g. (0.011 mole) of naphthol-2 and 20 cc. of absolute ethanol was heated under reflux for ninety minutes. The reaction mixture yielded 1.55 g. (59%) of XX (toluidinomethylnaphthol, m.p. 136–136.5°; identified by mixed m.p. test), 0.20 g. (22%) of XXIII (methylene-bis-naphthol, m.p. 197–198°), 0.1 g. of unchanged naphthol-2, and 2.3 g. (80%) of *p*-toluidine hydrochloride. To separate these compounds the reaction mixture was chilled, and the crystalline precipitate of XX was removed. The filtrate was diluted with 10% sodium hydroxide solution, the mixture was extracted with ether, and the ether extract was washed with 10% sodium hydroxide and with several portions of water (extract A). The ether solution was then extracted with 1:20 hydrochloric acid (extract B). The extract A was acidified with hydrochloric acid and the mixture was extracted with ether (extract C). Aqueous extract A contained 0.15 g. of XX, and extract C yielded 0.5 g. more, and also the naphthol. Extract B contained the *p*-toluidine as hydrochloride.

4. Formation of 4,4'-dimethylaminodiphenylmethane (XXIV) from dimethylaniline by action of methylene-bis-piperidine. A mixture of 3.63 g. (0.03 mole) of dimethylaniline and 1.82 g. (0.01 mole) of VI was saturated with hydrogen chloride. The resulting solid mass was dissolved in 10 cc. of hot absolute alcohol, and the solution was heated under reflux for several hours. The liquid was made alkaline by addition of an alcohol solution of sodium ethoxide. Piperidine and ethanol were removed by distillation and the removal was completed by codistillation with toluene. The piperidine hydrochloride recovered from the distillate weighed 0.7 g. (29%). The residue in the distillation flask was transferred to a filter and there washed several times with ethanol. The alcohol was removed by distillation, and the residue was submitted to steam distillation to remove remaining dimethylaniline. The residue of crude XXV in the flask was crystallized from dilute alcohol. The yield was 0.55 g. (22%), and the m.p. 88–90° obs. A mixture of the product and a specimen of XXIV made from dimethylaniline and formaldehyde had the same m.p.

When dimethylaniline and I were heated together in the absence of acid there was no evidence that reaction occurred.

5. Interaction of carbazole with formaldehyde and with methylene-bis-piperidine (VI). A. Formation of methylene-bis-carbazole (XXV). I. Carbazole and formaldehyde. A mixture of 1.5 cc. of 37% formalin and 2–3 cc. of glacial acetic acid was added to a hot solution of 3.34 g. (0.02 mole) of carbazole in 50 cc. of glacial acetic acid. The solution was chilled and diluted with water. The colorless needles of XXV were removed (1.15 g., m.p. 301–303° obs.), and a second crop was obtained from the filtrate by further dilution and chilling (0.65 g.; m.p. 296–301°); the total yield was 52%. A third crop melted between 220° and 240° and was probably mostly unchanged carbazole (m.p. 244.8°).

When the same reactants were brought together in the presence of a small amount of conc'd hydrochloric acid, the product was a dense bluish-white solid with no definite m.p. Recrystallization from aniline gave a product which melted at about 255°. Votoček and Veselý (25) obtained a bluish-white compound whether the reaction occurred in presence of acetic or mineral acid, and reported its m.p. to be 280°. It seems probable that their colored product was impure, and that the colorless compound of m.p. 301–303° is XXV.

Anal. Calc'd for $C_{25}H_{18}N_2$: C, 86.68; H, 5.24; N, 8.09.
Found: C, 86.26, 86.25; H, 5.09, 5.16; N, 7.95, 7.98.

II. Formation of XXV from carbazole and methylene-bis-piperidine (VI). In a mixture of 50 cc. of glacial acetic acid and 1.5 cc. of acetic anhydride (to establish anhydrous conditions), 3.34 g. (0.02 mole) of carbazole was dissolved. The solution was heated and 1.82 g. (0.01 mole) of VI was introduced. Reaction occurred at once, and a precipitate of

colorless needles appeared. The mixture was saturated with hydrogen chloride, which colored the precipitate pale blue. The product weighed 2.7 g. (77%), and melted at about 258°. After recrystallization from aniline and then from ether the compound weighed 0.7 g. (20%) and melted at 300–305° obs. A mixture with the compound made with formaldehyde melted at 304–305° obs.

B. Formation of 9-(N-piperidinomethyl)carbazole (XXVI). This compound, not previously reported, was obtained by interaction of carbazole and VI, or of carbazole, piperidine, and formaldehyde, in the absence of acid; *cf.* A, above.

I. Formation of XXVI from carbazole, piperidine, and formaldehyde. A mixture of 3.34 g. (0.02 mole) of carbazole, 40 cc. of 85% alcohol, 1.8 cc. of 37% formalin (0.022 mole of formaldehyde), and 1.7 g. (0.02 mole) of piperidine was heated under reflux for thirty minutes on a water-bath. The solution was chilled and the crystalline precipitate was removed (4.45 g.; melted at 95–96° to an opalescent liquid). Progressive dilution of the mother liquor caused separation of two additional crops (0.65 g., m.p. 97–98°; 0.15 g., m.p. 92–95°). The total yield (5.25 g.) was 99%. The first fraction, recrystallized from alcohol, melted at 99–99.5°.

Anal. Calc'd for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.59.
Found: C, 81.68, 81.45; H, 7.43, 7.45; N, 10.61, 10.50.

II. Formation of XXVI from carbazole and methylene-bis-piperidine (VI). A mixture of 3.34 g. (0.02 mole) of carbazole and 1.82 g. (0.01 mole) of VI was heated for an hour at 180–185°. These proportions were used because it was expected that this experiment would yield XXV. As the product was XXVI, twice the needed carbazole was present. The isolation procedure gave two crops of XXVI (1.05 g., m.p. 91–93°; 1.2 g., m.p. 95–96°; total yield 43%), 1.55 g. (46%) of unchanged carbazole, and 1.12 g. (47%) of piperidine hydrochloride, m.p. 234–235° obs.

6. Formation of aminomethylimides by interaction of acid imides and methylene-bis-amines. A. N-(N'-piperidinomethyl)phthalimide (XVII). I. Formation from phthalimide, piperidine, and formaldehyde (26). A mixture of 1.7 g. (0.02 mole) of piperidine, 10 cc. of 80% alcohol, 1.7 cc. of 37% formalin (0.022 mole of formaldehyde), and 2.94 g. (0.02 mole) of phthalimide was warmed on a water-bath just long enough to obtain a clear solution, which was immediately chilled. The product XXVII was isolated in two fractions: 4.5 g., m.p. 119–119.5°, and 0.15 g., m.p. 117–118°; total 4.65 g., or 95%. Sachs (26) reported for XXVII the m.p. 117–118°. The yield was decreased to 21% in an experiment in which the reactants were refluxed for fifteen minutes in 50% alcohol (26).

II. Formation of XXVII from phthalimide and VI. A mixture of 2.92 g. (0.02 mole) of phthalimide, 3.64 g. (0.02 mole) of VI, and 20 cc. of absolute ethanol was heated for two hours on a steam-bath. The solution was chilled, and 0.85 g. of XXVII (m.p. 119–119.5°) was removed. The filtrate yielded two additional crops of crystals by progressive dilution with water (3.2 g., m.p. 115–116°; 0.45 g., m.p. 118–119°). The yield of XXVII was 92%. The piperidine hydrochloride weighed 1.9 g. (79%), and melted at 243–244° obs.

B. N-(N'-piperidinomethyl)succinimide (XXVIII). I. Formation from succinimide, piperidine and formaldehyde. A mixture of 1.7 g. (0.02 mole) of piperidine, 10 cc. of 95% alcohol, 1.8 cc. of 37% formalin, and 1.98 g. (0.02 mole) of succinimide was warmed until a clear solution resulted, when 30 cc. of water was added. After several hours the crystalline precipitate was removed. The yield was 1.8 g. (46%) of XXVIII. The m.p. (107–107.5°) duplicates that reported for XXVIII by Cherbuliez and Sulzer, who prepared it (m.p. 106–107°) from N-hydroxymethylsuccinimide (27).

II. Formation of XXVIII from succinimide and VI. A mixture of 1.98 g. (0.02 mole) of succinimide, 3.64 g. (0.02 mole) of VI, and 10 cc. of absolute alcohol was refluxed for fifteen minutes. The isolation procedure, similar to that in A, II above, yielded in several fractions 3.8 g. (97%) of impure XXVIII (melted 98° to 107°). After recrystallization the product weighed 3.5 g. (89%) and melted at 106–107° obs. A mixed m.p. test showed it to be identical with XXVIII made by use of formaldehyde and piperidine. The piperidine liberated in the reaction was recovered as hydrochloride (2.25 g., or 93%).

7. Formation of methylene-bis-methone (XXIX) by interaction of methylene diamines with

dimethyldihydroresorcinol (methone). General procedure. Methone (1.4 g.; 0.01 mole) and methylene diamine (0.005 mole) were dissolved in 10–15 cc. of absolute alcohol or di-*n*-butyl ether with minimal warming. [By continued heating the yields of XXIX were decreased, with formation of a higher-melting substance, probably the "anhydride" (29a, 30), formation of which is favored in anhydrous solvents.] The solution was chilled, and the product was removed by filtration. The filtrate was diluted with ether (and water, when the reaction solvent was alcohol), and the liquid was extracted with dilute hydrochloric acid. This acid extract was evaporated to recover the amine as hydrochloride. The ether layer was heated under reduced pressure to remove solvents, yielding a second crop of XXIV. In each experiment the product was identified by mixed m.p. test using a specimen made from methone and formaldehyde. In the following summarized results are given in sequence the number of the methylene diamine, the solvent, the yield of XXIX, its m.p., and the yield of amine liberated in the reaction.

I, alcohol, 93%, 187°, —. I, butyl ether, 96%, 188–189°, 97%.

II, alcohol, 99%, 189–190°, 100%. II, butyl ether, 96%, 188–189°, 100%.

III, butyl ether, 96%, 187–188°, —.

IV, butyl ether, 58%, 188–189°, 78%.

In the last experiment the product first isolated was impure (two crops melted 160° to 176°). Purification decreased the indicated initial yield of 99% to 58%.

SUMMARY

The structural analogy between hydrated formaldehyde and methylene-bis-amines, considered as ammonia-system aldehydes, was validated by experimental demonstrations of a clear functional analogy, established by realizing with methylene-bis-amines or formaldehyde, used interchangeably, reactions characteristic of the latter. In each reaction studied both reagents led to the formation of the same principal product; the by-product of the ammonia-system reaction was the liberated amine, corresponding to the water split out when formaldehyde was used.

Methylene diamines of several types (from aromatic primary amines, ethylaniline, piperidine, morpholine) were used, in order to show that the reactions may be attributed to the essentially aldehydic character of the grouping —NCH$_2$N—.

Several reactions were effected under anhydrous conditions, to exclude the possibility that small amounts of water, operating cyclically, caused hydrolysis of the methylene diamine and liberation of formaldehyde as the actual reactant.

Reactions of formaldehyde and methylene diamines were compared using the following compounds: (a) *o*-amino-*m*-xylyl-*p*-toluidine, (b) N-arylanthranilamides (phenyl, *p*-bromophenyl-, *p*-anisyl), (c) phenols (naphthol-1, naphthol-2, carvacrol), (d) dimethylaniline, (e) carbazole, (f) phthalimide and succinimide, (g) dimethyldihydroresorcinol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

CATALYTIC HYDROGENATION OF COTTON HULL FIBER

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In view of the fact that cellulose has been made the subject of a very large amount of research, it may be surprising to some to learn that such investigation has devoted very little attention to study of reduction of cotton, and even less to the effect of molecular hydrogen in the presence of catalysts. Most of the earlier experiments involving the reduction of cellulose have been associated either with attempted production of liquid fuels by hydrogenation or with the destructive distillation of wood or cotton cellulose in the presence of hydrogen in attempts to obtain improved yields of methanol.

Although in most cases molecular hydrogen has been the reducing agent, a certain amount of research has been accomplished using other substances. Thus, in connection with the hydrogenation of coal to oils, Fischer and Schrader (1), in 1921, heated cellulose with sodium formate and water at 400° in an autoclave for three hours and obtained, in 12.9% yield, an ether extract which was a mobile, brown oil with an ethereal odor. In 1922, Willstätter and Kalb (2) reduced cellulose with hydriodic acid and red phosphorus at 250°; the yields of the products formed were: ether-insoluble residue, 9%; liquid hydrocarbons, 8%; solid hydrocarbons, 12%. Waterman and Kortlandt (3) attempted to reduce cellulose, in a liquid dispersing medium of melted paraffin wax, with a mixture of steam and carbon monoxide at a temperature of 423° and a maximum pressure of 115.9 atmospheres. There was substantial carbonization of the cotton fiber, but no evidence of any hydrogenation. Berl and Biebesheimer (4) treated cotton with 1 *N* sodium hydroxide solution at 310–330° and 180–200 atmospheres and hydrogenated the material thus obtained with *ferrum reductum* and iodine at 420–460°. The reduction product was a liquid resembling petroleum physically, and contained aliphatic, olefinic, naphthenic, and aromatic hydrocarbons, the distribution of which in the various fractions was similar to that in natural petroleum.

In 1913, Bergius (5) hydrogenated a coal-like residue obtained by the thermal decomposition of cellulose and produced a small amount of liquid resembling crude petroleum. The work of Bergius led Bowen and associates (6) to a study of the action of molecular hydrogen on cellulose. These workers found that cotton yarn did not undergo any appreciable reduction when heated with hydrogen at 440° and under pressures of the order of 120–130 atmospheres.

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Under similar conditions of pressure and temperature, after the cellulose had been impregnated with nickel salts, practically the whole of the material was converted to liquid and gas when hydrogenated, "the percentage weight of hydrogen adsorbed by the ash-free cellulose being 4.00 and 2.99" in two experiments. The liquid product consisted of an opaque, viscous tar containing carboxylic acids, phenols, and neutral oil, the material as a whole resembling the crude tar products obtained by the hydrogenation of coal. Vanadium oxide and ferric vanadate were found to have only a slight catalytic effect.

After noting that the dry distillation of cellulose was not influenced appreciably by hydrogen in the absence of catalysts even under pressures up to 300 atmospheres, Fierz-David (7), and Fierz-David and Hannig (8) attempted to prepare a liquid fuel by treating cotton cellulose with nickel hydroxide and distilling at 450–470° under hydrogen pressure of 150–220 atmospheres. The distillate was a yellow liquid, d_{20} 1.017, containing aldehydes, ketones, phenols, alkylfurans, a cyclic glycol, and fatty acids. Copper was found to have much less effect than nickel, and iron almost no effect. Fierz-David suggested that the practically complete volatilization of the cellulose was not due to hydrogenation but that the hydrogen merely acted as an inert gas improving the mechanism of the process. Frolich, Spalding, and Bacon (9), in an effort to determine the applicability of Fierz-David's suggestion, found that 86% of sulfite-pulp cellulose was converted to volatile products and 14% to coke in the presence of nitrogen and nickel at 400–500° and under a pressure of 200 atmospheres. The use of hydrogen in the presence of nickel brought about almost complete conversion of the sulfite-pulp cellulose to liquids and gases. Waterman and Perquin (10) have confirmed previous observations that cellulose is not hydrogenated to oils in the absence of a catalyst.

Boomer, Argue, and Edwards (11) subjected absorbent cotton to the action of hydrogen at 350° and 185–275 atmospheres pressure in a tetralin suspension medium without any catalyst, the tetralin apparently acting as a hydrogen carrier in fulfilling the function of a catalyst. A high conversion of the cotton to liquids and gases was reported, acidic material and a light oil having an aldehyde-like odor being present in the liquid portion.

A patent (12), issued in 1927, claims the conversion of cellulose in aqueous suspension to dihydroxypropane and glycerol by the action of hydrogen at 250–260° and 70–110 atmospheres in the presence of a nickel catalyst. Dihydroxypropane was the chief product using a copper catalyst and also with a copper-cobalt catalyst, but in the latter instance "isosorbid" appeared in the products. Similar experiments are claimed in which dimethylcellulose and diethylcellulose on hydrogenation gave dimethoxytrihydroxyhexane and diethoxytrihydroxyhexane, respectively.

The expenses of this investigation of the high-temperature—high-pressure catalytic hydrogenation-hydrogenolysis of cotton hull fiber were shared by the Cotton Research Foundation of Memphis, Tennessee, as administered through the Mellon Institute of Industrial Research and by the University of Texas.

We are particularly indebted to Dr. L. W. Bass and Dean A. P. Brogan for this support.

EXPERIMENTAL

Two hydrogenation units were used in this investigation. Both were purchased from the American Instrument Company (Washington, D. C.) and consist of hydrogenation bombs, constructed of chrome vanadium steel, electrically heated, the jacket being controlled by micromax indicating controllers (Leeds and Northrup). One bomb has a capacity of 310 cc., the other 4535 cc. In use, either bomb was filled half full, and hydrogen was introduced at 23–25° to a pressure of 2500 lbs./sq. in. and heated to 250°. Usually, 150 cc. of 4–15% aqueous sodium hydroxide solution was used in the smaller bomb and the pressure developed at 250° was about 4850 lbs./sq. in., whereas in the larger bomb, 2300 cc. of 7% aqueous sodium hydroxide solution was used and, at 250° the pressure rose to about 5425 lbs./sq. in.

In preparing the Raney (13) nickel catalyst according to the procedure described by Covert and Adkins (14), the nickel was washed by decantation until the wash water was neutral to litmus and then stored under water in glass-stoppered bottles.

Orientation experiments were carried out on cotton batting suspended in 4% sodium hydroxide solution to show that very little or no drop in pressure occurred when the fiber was heated for four hours at 225° in the presence of Raney nickel catalyst and hydrogen at 4175 lbs./sq. in. Upon cooling and opening the bomb, the cotton fiber appeared little changed except for slight embrittlement. However, when cotton batting or cotton hull fiber received preliminary digestion with alkali solutions under 75–85 lbs./sq. in. steam pressure and was transferred to the hydrogenation unit and exposed at 250° to hydrogen at 4800–5400 lbs./sq. in., a definite and extensive pressure drop was observed. In such experiments, upon cooling and opening the bomb, the cotton fiber had disappeared completely and a colorless, homogeneous solution was obtained.

Further exploratory experiments substantiated (15) that the solubility of cellulose in hot alkaline solutions increases with increasing concentration of alkali, and served to indicate the maximum concentration of alkali at which substantial hydrogenation took place in the presence of Raney nickel. Hydrogenation proceeded to a much greater extent in the presence of 7% alkali than with 10% or 15% alkali. Since the various preliminary experiments indicated also that variations in the treatment of the cellulose previous to hydrogenation occasioned considerable differences in the products formed, such as the amount of acids volatile with water and amount of alcohol-soluble material, definite conditions under which this study was to be made were established.

A typical experiment involved removal from cotton hull fiber of proteins, fats, waxes, and portions of hull by extraction with 0.5% caustic solution followed by a dilute acid wash and drying at 110°. A fairly constant loss of 16% of weight was noted during the preliminary treatment of the fiber. Twenty grams of such material was suspended in a solution of 10 g. of sodium hydroxide in 150 cc. of water. This mixture was digested two hours in an iron autoclave under 80–90 lbs./sq. in. steam pressure. After cooling to room temperature, the material was transferred to the small hydrogenation unit and hydrogenated in the presence of 8–10 g. of Raney nickel at 250°. In eleven hydrogenations, the pressure-drops varied from 860 lbs./sq. in. to 980 lbs./sq. in., with an average of 920 lbs./sq. in.

The resulting colorless solution was filtered from the catalyst into an amount of 1:3 sulfuric acid solution equivalent to the sodium hydroxide employed in hydrogenation. Some effervescence was noted; therefore, in another experiment, the amount of carbon dioxide present was determined, and found to represent 0.05 mole per 100 g. of purified hull fiber.

The neutral solution was extracted with three 50-cc. portions of ether. The ether extracts from eleven such hydrogenations were combined and dried over anhydrous sodium

sulfate. Removal of the ether under 20 mm. pressure left a residue of 37.6 g. of liquid material which was quite acidic. This liquid was fractionally distilled:

FRACTION	B.P. RANGE	d_4^{20}	n_D^{20}	VOL., CC.
1	up to 150° (754 mm.)			18.3
2	76–96° (33 mm.)	0.9734	1.4118	2.0
3	75–105° (5 mm.)	0.9825	1.4358	2.0
4	110–114° (5 mm.)	1.0746	1.4442	2.7
5	114–146° (3.5 mm.)	1.0819	1.4499	2.6

Neutralization and saponification data were obtained on fraction 4: free acid, 84.2%; ester, 15.8%; neutral equivalent, 137.1.

Anal. Calc'd for a mixture of 84.2% of $C_6H_{12}O_3$ and 15.8% of $C_6H_{10}O_2$: C, 55.88; H, 9.10; M_R (mixture of hydroxycaproic acid and lactone in molar ratio of 84.2:15.8), 32.40.

Found: C, 55.1; H, 8.99; M_R, 31.97.

Fraction 1 was subjected to further fractionation in an unsuccessful attempt to separate the acidic components for characterization by formation of solid derivatives. Qualitative tests, using the method of Dyer (16), suggested the presence of acetic acid and either propionic acid or one of the butyric acids in these sub-fractions. No evidence of the presence of formic acid was obtained.

After being extracted with ether, the reaction solution was concentrated under diminished pressure. The combined aqueous distillates from the eleven hydrogenations contained 0.270 equivalent of acids volatile with water and not extracted with ether. Evaporation to obtain the dry salts yielded an amount of material indicating the average equivalent weight of the acids to be 88.3.

Each of the eleven residues was boiled with absolute methanol to extract the organic material present. After removal of alcohol from the combined extracts, 83.5 g. of a viscous, brown syrup remained. This material could not be crystallized. It was leached with absolute ether and placed in a vacuum desiccator for seventy-two hours, then warmed at 100° under a pressure of 0.001 mm. for thirty hours. The residual material was of a lanolin-like consistency. With ferric chloride-amyl alcohol, there was produced a yellow-brown solution identical in color with that produced by known lactic acid. Neutralization and saponification data indicated the presence of 38.43% free acid and 61.57% ester or lactone.

Anal. Calc'd for mixture (38.43% of $C_5H_{10}O_4$ and 61.57% of $C_5H_8O_3$): C, 49.05; H, 7.17.

Found: 48.51; H, 6.78.

The semi-solid mixture was acetylated, the excess acid chloride was decomposed by reaction with ethanol, the mixture was ether-extracted and distilled under 0.01 mm. pressure. A fraction boiling at 95–120° was collected; d_4^{20} 1.1376; n_D^{20} 1.4458; apparent mol. wt. 85.1. Distillation of the saponification solution yielded material in which ethyl alcohol was definitely present. The analytical and other data are indicative of the presence of the ethyl ester of the diacetylated derivative of a dihydroxyvaleric acid; $C_4H_7O_2(CH_3CO)_2COOC_2H_5$.

Anal. Calc'd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37; mol. wt., 246.27; M_R, 57.96.

Found: C, 54.23; H, 7.30; mol. wt., 255.3 (3 × 85.1); M_R, 57.72.

A typical experiment of hydrogenation and hydrogenolysis using the larger unit: One hundred grams of purified hull fiber was suspended in a solution of 50 g. of sodium hydroxide in 700 cc. of water. The mixture was digested two hours in an autoclave under 80–90 lbs./sq. in. steam pressure. The materials resulting from three such experiments were combined and placed in the large hydrogenation bomb and hydrogenated in the presence of 100 g. of Raney nickel. Seventy-two minutes after heating was begun, the maximum pressure of 5600 lbs./sq. in. at 250° was recorded. Reaction began within five to ten minutes after this temperature and pressure were reached and, the temperature remaining constant, the

pressure decreased rapidly during the first three hours to 4350 lbs./sq. in.; no further decrease in pressure was noted after continued heating for an additional two hours. The $p^{23°}$ was 955 lbs./sq. in., and dp was calculated to be 195 lbs./sq. in.; thus the apparent moles of hydrogen used equalled 4.80. Gas samples were collected and the residual gases after hydrogenation were found to contain 42.8% gaseous hydrocarbon (most likely, methane). Since there were 7.73 moles of gas remaining in the bomb after hydrogenation, 3.31 moles of hydrocarbon were formed. The actual number of moles of hydrogen used, therefore, was 8.11.

Titration of the filtered, alkaline reaction solution, which was clear and colorless immediately after filtering but became yellow upon standing exposed to the air, indicated that 2.39 moles of the alkali present was bound by acidic products of the hydrogenation. An amount of sulfuric acid equivalent to that of the alkali used initially was added, the solution was extracted with four 150-cc. portions of ether, thus extracting all suspended water-insoluble material and color. After drying over sodium sulfate, the ether extract was distilled at 50–70° (20 mm.). The distillate, weighing 43.9 g., was acidic. When fractionated, it yielded: Fraction 1, (15.9 g.) b.p. range 40–73° (33–35 mm.); Fraction 2, (20 g.) b.p. range 59–103° (5–7 mm.); an appreciable residue could not be distilled under 4–5 mm. pressure.

Fraction 2 was redistilled: Portion 1, b.p. 93–94° (5 mm.); n_D^{20} 1.4440; d_4^{20} 1.0958; neutralization and saponification data indicated 78.8% acid and 21.2% ester or lactone. *Anal.* Found: C, 52.57; H, 8.30.

Portion 2, b.p. 94–95° (5 mm.); n_D^{20} 1.4436; d_4^{20} 1.1117; 81% acid; 19% ester or lactone.

The aqueous distillate, obtained when the ether-extracted hydrogenation solution was evaporated, was found to be acidic and required 262 cc. of 1 *N* sodium hydroxide solution for neutralization to phenolphthalein. The salt which precipitated (41.3 g.) when the neutralized solution was concentrated, gave a positive test for acetate. The mixed inorganic and organic material, which remained upon complete evaporation, was extracted with four 500-cc. portions of hot absolute ethanol. When the alcohol was removed under reduced pressure, there remained a viscous, light brown syrup; from the hydrogenation of 300 g. of hull fiber 126.6 g. of this syrup was obtained.

A portion, 42 g., of this syrupy material was acetylated, filtered from a small amount of insoluble, gummy solid, diluted with absolute ethanol, saturated with hydrogen chloride, and heated for two hours, diluted with absolute ether, and filtered from a small amount of ether-insoluble gum. After removal of ether, 34.6 g. of liquid remained and was fractionated. A fraction, weighing about 11 g., was taken boiling between 74–80° (38–39 mm.); n_D^{20} 1.4140; d_4^{20} 1.0264. The fraction was saponified (mol. wt. 118.3), and distilled. In the distillate, ethyl alcohol was positively identified. The residue in the flask, upon heating with concentrated sulfuric acid, yielded acetaldehyde.

Anal. Calc'd for $C_5H_{10}O_3$: Mol. wt. 118.13; C, 50.88; H, 8.54.
Found: Mol. wt. 118.3; C, 51.49; H, 8.65.

The identification of ethyl lactate establishes the production of lactic acid in the products of the hydrogenation-hydrogenolysis of cotton hull fiber.

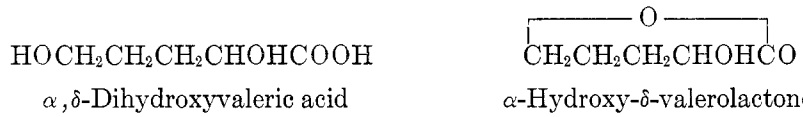
DISCUSSION OF RESULTS

The solubility of cellulose in hot alkaline solutions increases with increasing concentration of alkali (15) and the preliminary experiments of this investigation served to indicate the maximum concentration of alkali at which substantial hydrogenation took place in the presence of Raney nickel. Hydrogenation proceeded to a much greater degree in the presence of 7% alkali than in either 10% or 15% alkali. Since these experiments indicated also that variation in the treatment of cellulose previous to hydrogenation occasioned considerable differences in the products formed, such as acids volatile with water and amount of

alcohol-soluble material, definite conditions under which this study was to be made were established.

High-pressure—high-temperature hydrogenation, termed destructive hydrogenation or hydrogenolysis, involves two principal reactions: thermal decomposition and hydrogenation (11). From the fact that essentially no hydrogenation was found to take place until a temperature of 250° was reached, it appears probable that thermal decomposition of the cellulose at this temperature is followed by stabilization of the unsaturated fragments by hydrogenation.

Indications that hydroxy acids were among the products from cotton cellulose necessitated attempts to hydrogenate some of the more common hydroxy acids in alkaline solution. From this study (17) it was found that "at temperatures below 250° and hydrogen pressures not exceeding 330 atmospheres, alpha- and gamma-hydroxy acids are not affected, whereas beta-hydroxy acids are converted into the corresponding unsubstituted acids. . . . Of particular importance was the conversion, in alkaline solution at 250° and under a hydrogen pressure of 330 atmospheres, of formic acid into methane and carbon dioxide". From a consideration of these results, the dihydroxyvaleric acid and corresponding lactone found in the products from hull fiber may be given the following probable formulations:



α,δ-Dihydroxyvaleric acid — α-Hydroxy-δ-valerolactone

The following reasoning was employed in arriving at the formulations pictured: the pyranose ring was accepted as being present in the structural unit of cellulose, namely, cellobiose. Hydrogenolysis of the CH_2OH— grouping, which must necessarily be attached to the pyranose ring, might well result in the production of methane. (The very small amount of carbon dioxide in the residual gases of the hydrogenation obviates the possibility that the methane arose as the result of the hydrogenation of an intermediately-formed formic acid molecule.) The five carbon residue remaining after such cleavage would then possess the carbon chain represented in the formulas presented. Cleavage at the ether linkage between the units would give rise to the —COO— grouping, producing a tetrahydroxyvaleric acid or the corresponding delta-lactone. The replacement of the beta- and gamma-hydroxyl groups by hydrogen is made probable by the fact that the former is in itself unstable under hydrogenation conditions, while the latter would bear a 1,3 structural relationship to the alpha-hydroxyl group (the presence of which in the product was demonstrated). Connor and Adkins (18) have shown that hydroxyl groups in 1,3 relationship to each other are unstable towards hydrogenation, and one is almost invariably replaced by hydrogen, or else there is hydrogenolysis of carbon-to-carbon bonds.

Since the hydroxycaproic acid found in the products of hydrogenation was in equilibrium with a lactone form, the hydroxyl group in this acid must be in either the gamma or delta position. But the gamma position, as pointed out, is

improbable after hydrogenation, hence the acid is formulated as being the δ-hydroxycaproic.

Lactic acid was found to be stable in alkaline solution towards hydrogenation (17); it thus was to be expected as a product from hydrogenation of cotton in alkaline solution, and especially so in view of the fact that Heuser (19) has found that cellulose is converted largely into lactic acid when heated with strong alkali under high pressure and at high temperature.

The claim made in a patent (12), that cellulose in aqueous suspension and in the presence of a nickel catalyst is converted into dihydroxypropane and glycerol by action of hydrogen at 250–260° and 70–110 atmospheres, caused us to search for such materials in the products of our experiments. No evidence of these materials was to be found. In fact, in other experiments (20), it has been possible to show that when glycerol is heated with Raney nickel in the presence of alkali, hydrogen is *evolved* in the region 150–180°, and above this temperature continues to be evolved along with carbon dioxide. Hence, our failure to find glycerol among the products of hydrogenation-hydrogenolysis of cotton hull fiber is wholly explainable, in fact, is to be anticipated.

SUMMARY

1. Cotton cellulose in an aqueous medium containing 7% of sodium hydroxide has been converted to semi-solid, liquid, and gaseous products by the action of hydrogen at 250° and under pressures of 325–380 atmospheres in the presence of Raney nickel.

2. From three hundred grams of cotton hull fiber, there was formed by the action of 8.11 moles of hydrogen: 3.31 moles of gaseous hydrocarbon (chiefly methane); 0.15 mole of carbon dioxide; and 2.39 moles of acidic material.

3. The acidic material has been found to contain: lower fatty acids, including acetic and possibly propionic and one of the butyrics or both; lactic acid; gamma- or delta-hydroxycaproic acid and the corresponding lactone; and a dihydroxy-valeric acid and the corresponding lactone, with one hydroxyl of the acid in the alpha-position and the other probably in the delta-position.

4. Under the conditions employed in this investigation, cotton cellulose does not undergo hydrogenation at 225°.

5. A larger hydrogen pressure drop was observed when 7% aqueous solution of sodium hydroxide was used as the suspension medium than when 10% or 15% solutions of this alkali were used.

AUSTIN, TEX.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

THE REDUCTION OF BENZOXAZOLES AND BENZOTHIAZOLES IN LIQUID AMMONIA[1]

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The available information relative to the behavior of oxazoles, thiazoles, and related compounds towards reducing agents is quite limited. The only conclusive studies recorded are those of the reduction of 2-phenyloxazoline (1), 2,5-diphenyloxazole (2), and 2,4-dimethylthiazole (3), all of which were reduced with rupture of the heterocyclic rings by the use of sodium and alcohol. In the present paper there is described the reduction of benzoxazole, 2-phenylbenzoxazole, benzothiazole, and 2-chlorobenzothiazole. Reduction was effected through the use of sodium in liquid ammonia (method 1), and nascent hydrogen generated by the interaction of ammonium bromide and sodium in liquid ammonia (method 2). The effectiveness of these unusually strong reducing agents in the reduction of a variety of organic substances has been demonstrated previously (4–7).

EXPERIMENTAL

Methods and materials. All reduction reactions were carried out under strictly anhydrous conditions in liquid ammonia at −33.5° in an apparatus similar to that described by Johnson and Fernelius (8). Benzoxazole was prepared by the method of Niementowski (9) and 2-chlorobenzothiazole was prepared as described by Scott and Watt (10).

Preparation of 2-phenylbenzoxazole. This compound was prepared by a method which was suggested by Wheeler (11) but which has not been described. Benzamide (187 g.) and *o*-aminophenol (168 g.) were refluxed for six hours, during which ammonia and water were eliminated. Distillation of the reaction mixture followed by treatment with "Norit", recrystallization from alcohol, and final recrystallization from concentrated hydrochloric acid yielded 280 g. (80% yield) of colorless crystalline 2-phenylbenzoxazole, m.p. 103°.[2] This melting point is in agreement with that reported by Ladenberg (12) for 2-phenylbenzoxazole prepared by the condensation of *o*-aminophenol and phthalic anhydride.

Preparation of benzothiazole. The method of Hofmann (13) as modified by Kiprianov and co-workers (14) was found to be impractical for the preparation of appreciable quantities of benzothiazole. Consequently, this material was prepared by an adaptation of the method of Möhlau and Krohn (15) as modified by Mills (16). Dimethylaniline and sulfur were refluxed for eighteen hours, the resulting mixture was distilled and the fraction distilling over the range 200–260° was collected and dissolved in an equal volume of concentrated hydrochloric acid. The by-product "benzothiazolemethenesulfide" (17), $C_8H_7NS_2$, was precipitated by dilution with water and removed by filtration. Addition of an excess of aqueous ammonium nitrate solution to the filtrate resulted in the precipitation of benzothiazole nitrate, which was separated by filtration, washed with a small quantity of ammo-

[1] This work was supported in part by a grant from the University Research Institute (Project No. 25).

[2] All melting points reported in this paper are corrected.

nium nitrate solution, and thereafter dissolved in water. Benzothiazole was liberated by addition of aqueous ammonia, dried, and distilled; b.p. 131°/34 mm.; n_D^{20} 1.6379; d_4^{20} 1.246. The following physical constants have been recorded for benzothiazole: b.p. 227–228°/765 mm. (18); $n_D^{24.6}$ 1.6370 (19); d_4^{14} 1.244(18). Yield data together with information concerning the influence of variation in the dimethylaniline/sulfur ratio are shown in Table I.

Determination of reaction ratios. The ratio of moles of the oxazole or thiazole to gram-atoms of sodium was determined by dissolving a weighed quantity of oxazole or thiazole in liquid ammonia and adding sodium in small pieces until a permanent blue coloration was

TABLE I

PREPARATION OF BENZOTHIAZOLE

DIMETHYLANILINE (G.)	SULFUR (G.)	$C_8H_7NS_2$ (G.)	BENZOTHIAZOLE YIELD	
			(g.)	(%)
500	650	60	50	9
500	750	50	75	13.5
500	800	0	113	20

TABLE II

REACTION RATIOS (METHOD 1)

SUBSTANCE	WT. OF SUBSTANCE (G.)	WT. SODIUM REQUIRED (G.)	GRAM-ATOMS Na/GRAM-MOLE OF SUBSTANCE
Benzoxazole	5.69	2.15	1.95
2-Phenylbenzoxazole	10.00	2.20	1.86
Benzothiazole	7.02	2.39	2.00
2-Chlorobenzothiazole	1.08	0.54	3.70

TABLE III

REACTION RATIOS (METHOD 2)

SUBSTANCE	WT. OF SUBSTANCE (G.)	WT. Na (G.)	VOL. H_2 (CC.)	G.-ATOMS Na (AND/OR H)/MOLE OF SUBSTANCE
Benzoxazole	2.59	1.69	224	2.46
2-Phenylbenzoxazole	1.76	1.06	156	3.55
Benzothiazole	1.52	0.97	147	2.56
2-Chlorobenzothiazole	1.08	0.89	106	4.57

produced (method 1). Although the detection of the "end-point" was in some cases rendered difficult by the formation of colored reduction products, reproducible values could be obtained. These data are given in Table II.

A second procedure involved the addition of an excess of sodium, followed by addition of ammonium bromide and collection of the hydrogen thereby liberated (method 2). From the weights of materials involved and the weight of hydrogen liberated, the quantity of sodium utilized in the reduction of the oxazole or thiazole was calculated. The values listed in Table III were obtained by method 2 and represent the average of two closely agreeing results in each case.

IDENTIFICATION OF REDUCTION PRODUCTS

The only difference between the reactions carried out for the purpose of determining reaction ratios and those described in this section lies in the fact that for purposes of purification and identification of products, it was frequently necessary to effect reactions on a relatively larger scale. Without exception, the primary reduction products were unstable under ordinary atmospheric conditions. Hydrolysis or neutralization of the primary products resulted in the formation of substances which, in general, showed a pronounced tendency towards oxidation and decomposition leading to the production of dark-colored, tarry, resinous materials.

Reduction of benzoxazole by sodium. After evaporation of the solvent ammonia following the reduction of 8.01 g. of benzoxazole by 3.29 g. of sodium, the crude product was extracted with 10% sodium hydroxide solution. The resulting solution was treated with an excess of benzoyl chloride and cooled. The white crystals of dibenzoyl-*o*-aminophenol which separated were recrystallized once from alcohol and once from a mixture of benzene and petroleum ether, m.p. 180–182°.

Anal. Calc'd for $C_{20}H_{15}NO_3$: N, 4.42. Found: N, 4.29.

A mixture with an authentic sample of dibenzoyl-*o*-aminophenol (20) showed no depression in melting point. The material which was insoluble in sodium hydroxide consisted of a black tar which oxidized readily and which could not be identified.

In another experiment, the primary reduction product (a brick-red precipitate) obtained by addition of 8.18 g. of sodium to 21.10 g. of benzoxazole dissolved in 300 cc. of liquid ammonia was treated with a large excess (65 g.) of ethyl bromide. The solvent was evaporated and the residue extracted with anhydrous ether. Distillation of this extract yielded 25.1 g. of a colorless viscous oil which darkened upon exposure to air, and which had the following physical constants: B.p. 79–85°/1 mm., 200–205°/754 mm.; n_D^{20} 1.5380; d_4^{20} 1.015. M_r [assuming the product to be N-(*o*-ethoxyphenyl)propylideneimine], Calc'd, 53.86; Found, 54.52.

Anal. Calc'd for $C_{11}H_{14}NO$: C, 74.50; H, 8.47; N, 7.92. Found: C,[3] 72.33; H, 8.68; N, 7.84.

Molecular weight determinations (ebullioscopic in acetone) were inconclusive. The weight of product obtained corresponds to an 80% yield of N-(*o*-ethoxyphenyl)propylideneimine. The synthesis of this compound (which has not been described previously) from propanal and *o*-phenetidine by a method similar to that of Knoevenagle (21) was attempted but without success.

Reduction of benzoxazole by hydrogen. Benzoxazole (2.14 g.) was dissolved in liquid ammonia containing an excess of dissolved ammonium bromide. To this solution was added in small pieces 1.90 g. of sodium. Of the 0.0833 g. of hydrogen produced by the interaction of sodium and ammonium bromide, 0.0203 g. was collected as molecular hydrogen. From these data it was calculated that 0.0630 g. of hydrogen was utilized in the reduction of the oxazole and that the ratio of gram-atoms of hydrogen/gram-moles of oxazole was 3.47.

In a similar reaction involving 6.34 g. of benzoxazole, 20.91 g. of ammonium bromide, and 4.30 g. of sodium, the crude product was extracted with boiling benzene. From this solution, by concentrating and cooling, 5.2 g. (79% yield) of *o*-methylaminophenol, m.p. 86–87° (22) was obtained. The monobenzoyl derivative was prepared in benzene and recrystallized from a mixture of alcohol and water, m.p. 157–159° (23).

Anal. Calc'd for $C_{14}H_{13}NO_2$: N, 6.19. Found: N, 6.02.

Reduction of 2-phenylbenzoxazole by sodium. The reduction of this compound by means of either sodium or hydrogen yields tarry resinous products which are very susceptible to atmospheric oxidation. Despite repeated and varied methods of attack, no success at-

[3] Duplicate analyses for carbon were made on independently prepared samples. These analyses led to results which were in close agreement but which were uniformly low.

tended efforts at isolation and identification of the reduction products. 2-Phenylbenzoxazole is only slightly soluble in liquid ammonia at −33.5°.

Reduction of benzothiazole by sodium. Benzothiazole (13.5 g.) was reduced by addition of 2.37 g. of sodium. The solvent was evaporated from the resulting red solution and the reduction product was hydrolyzed by water. The red alkaline aqueous solution was subjected to distillation with steam. No benzothiazole (which is readily volatile with steam) was found to be present. The solution was acidified with acetic acid, buffered with sodium acetate solution, and treated with an excess of aqueous lead acetate solution. A tan colored solid separated, which was insoluble in all common organic solvents and which was purified by extraction with acetone, alcohol, and ether, m.p. > 275°.

Anal. Calc'd for $C_6H_7NS \cdot Pb(C_2H_3O_2)_2$ (a 1:1 double salt of *o*-aminothiophenol and lead acetate): N, 3.11; S, 7.11.

Found: N, 3.14; S, 7.18.

This compound has not been reported previously.

In a similar experiment, 5.87 g. of benzothiazole was reduced by 2.00 g. of sodium, and the primary reduction product was neutralized by ammonium bromide. After evaporation of the ammonia, the residue was extracted with alcohol. To this solution was added

TABLE IV

REDUCTION OF BENZOTHIAZOLE BY SODIUM

BENZOTHIAZOLE (G.)	SODIUM (EQUIVALENTS)	BENZOTHIAZOLE RECOVERED (%)	Hg SALT (G.)	BENZOTHIAZOLE ACCOUNTED FOR (%)
5.10	1	46.4	3.97	91.0
5.87	2	0	8.58	83.5
5.26	3	0	7.87	85.5

an alcoholic solution of mercuric cyanide, resulting in the precipitation of the golden-yellow mercuric salt of N-(*o*-mercaptophenyl)methylideneimine. The salt was purified by recrystallization from a mixture of carbon disulfide and ether, m.p. > 120° (decomp.).

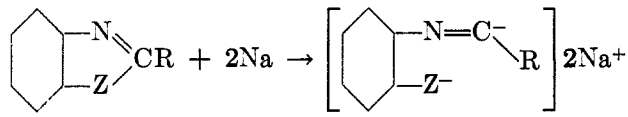
Anal. Calc'd for $C_{14}H_{12}HgN_2S_2$: N, 5.92. Found: N, 5.90.

A series of reactions was effected in order to determine the influence of variation in the sodium/benzothiazole ratio. Two reactions corresponding to each ratio were carried out. The product of one reaction was subjected to steam distillation to separate unchanged benzothiazole, which was identified as the picrate (24), m.p. 167°. The product of the other reaction was used in the formation of the mercuric salt of N-(*o*-mercaptophenyl)methylideneimine, the weight of which serves as a measure of the quantity of benzothiazole reduced. The results of these experiments are given in Table IV.

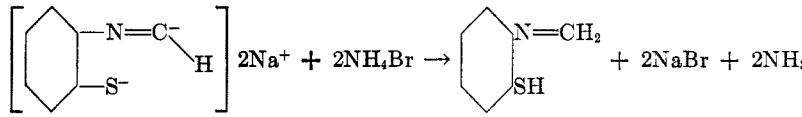
Reduction of 2-chlorobenzothiazole by sodium. The reduction of this compound was carried out primarily to secure essential information concerning reaction ratios. Although not investigated extensively, the ultimate products of these reactions appeared to be essentially the same as those obtained by the reduction of benzothiazole.

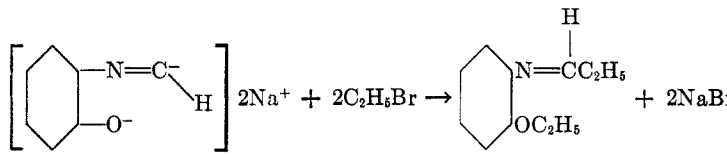
DISCUSSION OF RESULTS

The data of Tables II and IV indicate that benzoxazoles and benzothiazoles are reduced by sodium in liquid ammonia as shown by the equation,



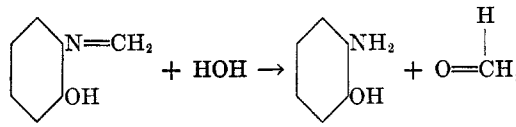
where R may be H or C_6H_5, and Z may be O or S. When R is Cl, the sodium / thiazole ratio is increased from two to four. Since the sodium salts are unstable, the character of the products ultimately isolated and identified depends upon the treatment of the primary products. When the sodium salts are neutralized by ammonium bromide or are treated with ethyl bromide, the corresponding Schiff bases are formed,

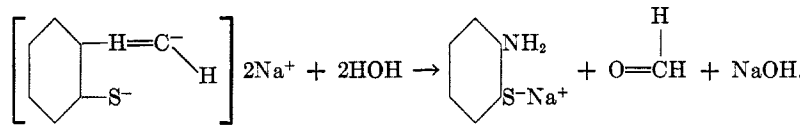




This view is supported by the isolation of the mercuric salt of N-(*o*-mercaptophenyl)methylideneimine and N-(*o*-ethoxyphenyl)propylideneimine, although the identity of this latter compound cannot presently be said to be finally established.

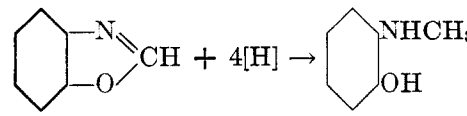
If, on the other hand, either the sodium salts or the Schiff bases are subjected to conditions favoring hydrolysis, the corresponding aminophenols or thiophenols are produced.





This has been shown by the isolation of dibenzoyl-*o*-aminophenol and the lead acetate double salt of *o*-aminothiophenol. In this connection it is significant that neither the sodium salts nor the Schiff bases showed any tendency towards ammonolysis (25).

That reduction by hydrogen is more extensive than reduction by sodium is shown by the isolation of a high yield of *o*-methylaminophenol from the products of the reduction of benzoxazole by hydrogen.



This conclusion is also indicated by the reaction ratio data obtained by method 2. An inspection of the data of Table III shows that the reaction ratios are uniformly low, but approach integral values greater than those obtained by method 1; the quantity of hydrogen collected was always less than that anticipated. This discrepancy is undoubtedly due in part to the solubility of hydrogen in the water over which the gases were collected, but probably due in larger measure to participation of the liberated hydrogen in a more extensive reduction. This situation is analogous to that encountered by Cappel and Fernelius (5) in their study of the reduction of 1,2,3-benzotriazole. In contrast with their results, however, the present study provided no indication of hydrogenation of the atomatic ring.

As has already been suggested, a major source of difficulty encountered throughout this investigation involved the marked instability and ease of oxidation and polymerization of the reduction products. That this behavior is generally characteristic of aminophenols and aminothiophenols has been demonstrated by earlier workers (26–29).

SUMMARY

1. A method for the preparation of 2-phenylbenzoxazole and an improved procedure for the preparation of appreciable quantities of benzothiazole in a high state of purity have been described.

2. Certain experiments on the reduction of benzoxazole, 2-phenylbenzoxazole, benzothiazole, and 2-chlorobenzothiazole by means of sodium and hydrogen (Na+ NH_4Br) in liquid ammonia have been described and a possible interpretation of the results of these experiments has been suggested.

3. Evidence that reduction by hydrogen is more extensive than reduction by sodium has been presented.

AUSTIN, TEX.

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[COMMUNICATION NO. 825 FROM THE KODAK RESEARCH LABORATORIES]

SOME DYES RELATED TO TOLUIDINE GREEN

C. F. H. ALLEN, G. F. FRAME, AND C. V. WILSON

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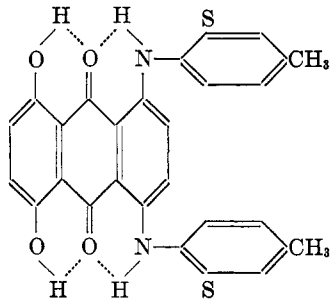
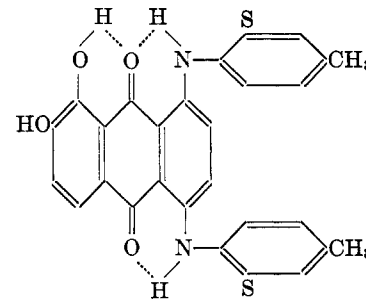
In previous papers (1, 2) certain homologs, isologs, and isomers of Toluidine Blue have been described. This communication deals with derivatives of Toluidine Green—in particular, with those containing substituents in the anthraquinone ring system, thus belonging to the second type of substitution products. An isomeric sulfonic acid belonging to the third type is also described.

Toluidine Green (I) and Alizarin Viridine (II) are isomers, differing only in the location of the hydroxyl groups; since the absorption curves are considerably different, the position of these groups must be important. In Toluidine Green, both hydroxyl groups are in a position such that hydrogen bonding is possible, whereas but one is available in Alizarin Viridine.



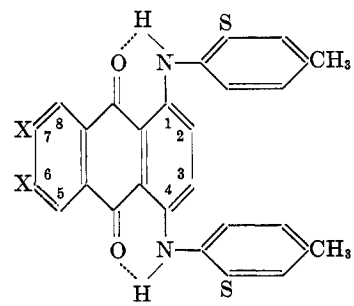
I



II

(S = SO_3Na)

If the location of the hydroxyls is important, the 6,7-dihydroxy isomer (III, X = OH), should resemble II rather than I. A comparison of the curves, Fig. 1, shows that this is indeed the case. Further, the spectral absorption character-



III

(S = SO_3Na)

istics are very similar to those of the parent, unsubstituted dye, Alizarin Cyanine Green, (III, X = H) (3); that is, the introduction of two hydroxyl groups into the latter structure has relatively little effect, except when they are in the 5- and 8-positions.

That this is not an isolated instance is evident by an inspection of the corresponding dichloro (III, X = Cl) and dibromo (III, X = Br) derivatives. The

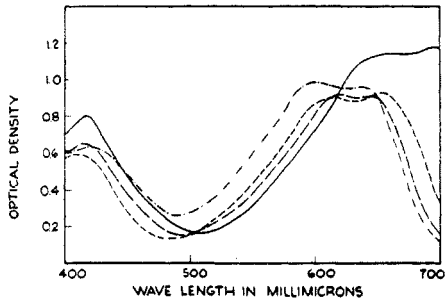


FIG. 1

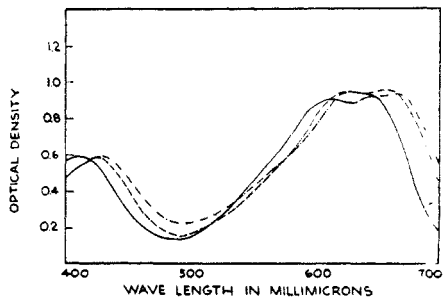


FIG. 2

FIG. 1. ALIZARIN CYANINE GREEN AND THREE DIHYDROXY DERIVATIVES

——, Toluidine Green; -----, Alizarin Viridine; — — —, Alizarin Cyanine Green; —·—·— 6,7-Dihydroxy Isomer of Toluidine Green.

FIG. 2. ALIZARIN CYANINE GREEN AND ITS 6,7-DIHALO DERIVATIVES

——, Alizarin Cyanine Green; — — —, 6,7-Dichloro Derivatives; —·—·—, 6,7-Dibromo Derivatives.

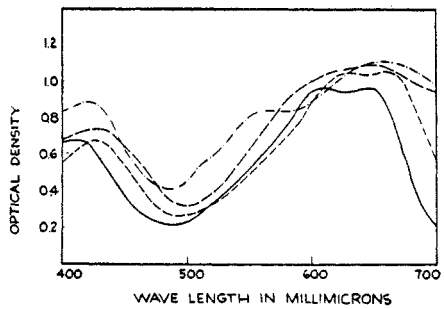


FIG. 3. ALIZARIN CYANINE GREEN AND ITS DICHLORO DERIVATIVES

——, Alizarin Cyanine Green; -----, 6,7-Dichloro derivatives; —·—·—, 5,8-Dichloro derivatives in basic solution; — — —, 5,8-Dichloro derivatives in acid solution.

shape of the curves, Fig. 2, is similar, although they are moved slightly towards the right.

For purposes of comparison the 5,8-dichloro- and 5,6,7,8-tetrachloro-1,4-ditoluidinoanthraquinones were prepared. Their absorption curves are practically identical (only the dichloro is shown in Fig. 3); that is, the effect of the chlorine atoms in the β-position is almost negligible.[1] The effect of chlorine

[1] An unexpected result was observed in the two 5,8-dichloro dyes; they are sensitive to hydrogen ion, giving green solutions. The curves are shown in Fig. 3.

atoms in the 5,8-positions of the anthraquinone nucleus is considerable on the large absorption band in the red end, the two peaks being displaced and farther separated. The left-hand peak of the large band is moved in the opposite direction to what it was by the OH of Toluidine Green (Fig. 4). The conclusions to be drawn from these examples are that (a) the effect of halogen atoms is much greater if they are in the alpha-positions, (b) the principal result is displacement of the left-hand peak of the main absorption band towards the shorter wavelength (bathochromic effect), and (c) the latter is of the same magnitude as that of the α-OH group but in the opposite direction.

As discussed in the previous paper, isomeric sulfonic acids are readily obtainable, the 2′-isomer being secured when the last step is sulfonation (3), and the 3′-isomer resulting by the use of 4-aminotoluene-2-sulfonic acid (4). The curves show variations in the red (Fig. 4) similar to those in the blue series.

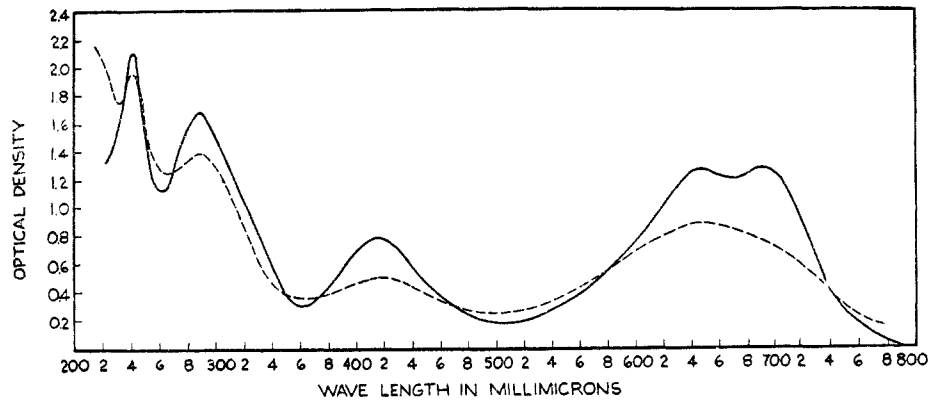


FIG. 4. TOLUIDINE GREEN AND ITS ISOMER SULFONIC ACID

——, Toluidine Green; 2′-SO_3Na; -----, Isomer; 3′-SO_3Na.

EXPERIMENTAL

I. INTERMEDIATES

(a) *1,4,6,7-Tetrachloroanthraquinone.* 3,6-Dichloro-2-(3′,4′-dichlorobenzoyl)benzoic acid is easily prepared from 3,6-dichlorophthalic anhydride and *o*-dichlorobenzene following Phillips's procedure (5).

A mixture of 10.8 g. of 3,6-dichlorophthalic anhydride, 37 g. of *o*-dichlorobenzene and 20 g. of anhydrous aluminum chloride was heated on the steam-bath (95–98°) for sixty hours. It was then poured upon iced hydrochloric acid, and the mixture steam distilled to remove the excess *o*-dichlorobenzene. The gummy product was separated from the cooled liquid, taken up in warm benzene, filtered, and the filtrate evaporated to dryness. This residue was redissolved in benzene; the acid crystallized on cooling. The yield was 8.0 g. It melts at 170–171° with preliminary softening at about 164°.

Anal. Calc'd for $C_{14}H_6Cl_4O_3$: Cl, 39.0. Found: Cl, 39.0.

For ring closure, a mixture of 68 g. of 20% oleum and 81 g. of sulfuric acid (sp. gr. 1.84) was heated to 160° and 6.8 g. of the above tetrachlorobenzoylbenzoic acid was then added in portions over a five-minute period. The mixture was maintained at 160° for a further five-minute period and then cooled to 70–80°. Chipped ice was added slowly; the temperature rose to 120° and a precipitate formed. After pouring into water, the 1,4,6,7-tetra-

chloroanthraquinone was filtered and washed thoroughly, first with water and then with methyl alcohol. The product was recrystallized from chloroform; the yield was 3 g. (47%). It melted at 259–260°.

Anal. Calc'd for $C_{14}H_4Cl_4O_2$: Cl, 41.0. Found: Cl, 41.1.

Ring closure of the tetrachlorobenzoylbenzoic acid can give either 1,4,5,6- or 1,4,6,7-tetrachloroanthraquinone. No proof of structure is offered for the compound actually isolated other than its subsequent treatment with *p*-toluidine. The reactivity of α-chlorine atoms is such that all would be replaced by *p*-toluidine. Hence in one case a tri-*p*-toluidino monochloroanthraquinone should result, while in the other a di-*p*-toluidino dichloroanthraquinone (the compound actually obtained) would be formed. This conclusion was confirmed by the nature of the absorption curves, those having halogen in the alpha-position being entirely different.

(b) *1,4,6,7-Tetrahydroxyanthraquinone* was prepared from *m*-hemipinic acid and hydroquinone by the procedure previously described (1) for the 1,4,5,8 isomer. The *m*-hemipinic acid (hemipic acid) was secured by Perkin's procedure (6).

Anal. Calc'd for $C_{14}H_8O_6$: C, 61.8; H, 2.9.
Found: C, 62.2; H, 3.0.

The tetraacetate was prepared in the usual manner using acetic anhydride and sodium acetate. It was purified by crystallizing from a small volume of methyl alcohol; it melted at 192–193°. On admixture with quinalizarin tetraacetate (m.p. 197–198°) the melting point was depressed to 170–175°.

Anal. Calc'd for $C_{22}H_{16}O_{10}$: C, 60.0; H, 3.6.
Found: C, 59.8; H, 3.6.

(c) *6,7-Dibromoquinizarin.* An intimate mixture of 5 g. each of 4,5-dibromophthalic anhydride (1) and hydroquinone was added, portionwise, to a melt made up from 32 g. of aluminum chloride and 5.5 g. of salt at 200–220°, over a ten-minute period. The temperature was maintained at 210° for one-half hour, after which the mass was removed from the container and allowed to cool. The solid was then powdered and decomposed with hot dilute hydrochloric acid. The red product that separated was filtered, washed thoroughly with warm water, then alcohol, and ether in order. It separated from xylene in red needles, m.p. 296–298°. The yield of pure dibromoquinizarin was 57%.

Anal. Calc'd for $C_{14}H_6Br_2O_4$: Br, 40.2. Found: Br, 40.0.

II. THE TOLUIDINOQUINONES

(a) *1,4-Di-*p*-toluidino-6,7-dihydroxyanthraquinone.* 1,4,6,7-Tetrahydroxyanthraquinone (1 g.) was dissolved in 150 cc. of acetic acid, 1 g. of tin added, and dry hydrogen chloride bubbled into the mixture at the boiling point for four hours. The 2,3-dihydro-1,4,6,7-tetrahydroxyanthraquinone was collected after filtering and cooling. A mixture of this substance, 1 g. of finely powdered boric acid, and 10 g. of *p*-toluidine was heated at 100° for fifteen hours. After aerial oxidation the dye base was isolated in the usual way. The crude product was recrystallized from xylene. It is greenish-blue in dioxane and dull blue in concentrated sulfuric acid.

Anal. Calc'd for $C_{28}H_{22}N_2O_4$: C, 74.7; H, 4.9.
Found: C, 73.6; H, 5.2.

(b) *1,4-Di-*p*-toluidino-6,7-dibromoanthraquinone* was secured in a similar manner from 6,7-dibromoquinizarin; the dihydro derivative melted at 287–289°. The toluidinoanthraquinone dissolved in xylene with a bluish-green color; it gave a violet solution in concentrated sulfuric acid.

Anal. Calc'd for $C_{28}H_{20}Br_2N_2O_2$: Br, 27.8; N, 4.9.
Found: Br, 27.5; N, 4.9.

(c) *The polychloroditoluidino anthraquinones.* 1,4-Di-*p*-toluidino-6,7-dichloroanthraquinone: A mixture of 3 g. of 1,4,6,7-tetrachloroanthraquinone and 35 g. of *p*-toluidine was heated for twenty-two hours at 165–175°. The mixture was cooled to 60–70° and poured into an excess of dilute hydrochloric acid. The crude product that separated was filtered,

washed with a little dilute hydrochloric acid, water, 70% methyl alcohol, methyl alcohol, and ether in that order. The methyl alcohol wash removed a violet-colored contaminant. The residue of 2.6 g. was recrystallized from xylene, from which it separated in fine blue needles, soluble in dioxane and in acetic acid with a bluish-green color. It dissolved in sulfuric acid with a violet color.

Anal. Calc'd for $C_{28}H_{20}Cl_2N_2O_2$: Cl, 14.6. Found: Cl, 14.6.

5,8-Dichloro-1,4-di-*p*-toluidinoanthraquinone and 5,6,7,8-tetrachloro-1,4-di-*p*-toluidinoanthraquinone were prepared by methods already described in the literature (7, 8, 9).

The dyes were obtained by sulfonation of the various ditoluidinoanthraquinones with concentrated sulfuric acid on the steam-bath exactly as has been previously described (1, 2).

The Toluidine Green isomer (3′-SO_3Na) was prepared from dibromoquinizarin, sodium 4-aminotoluene-2-sulfonate, boric acid, and aqueous sodium acetate, essentially as directed in the patent literature (10, 11).

SUMMARY

Several homologs of Toluidine Green have been prepared in order to compare their absorption characteristics with those of the parent substance. The absorption curves of the dyes having substituents in the 6,7-positions resemble the unsubstituted Alizarin Cyanine Green rather than Toluidine Green.

Halogen atoms and hydroxyl groups in the alpha-position have a much greater effect on the absorption curves of this type of dye than the same element or group in a beta-position.

The 3′-sulfonic acid is like the corresponding isomer in the 1,5-(blue) series, the curve falling off in the far red.

ROCHESTER, N. Y.

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[COMMUNICATION NO. 824 FROM THE KODAK RESEARCH LABORATORIES]

SOME DYES RELATED TO TOLUIDINE BLUE

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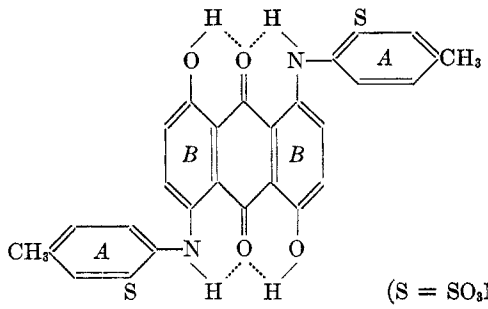
It was pointed out in a previous paper (1) that the dye Toluidine Blue has uncommon spectral absorption characteristics, and it seemed worth while to examine a few similar dyes.

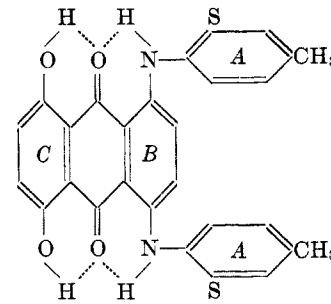
The relation between the color and constitution of anthraquinone dyes is well summarized in Houben (2); there are a large number of examples illustrating the effect of different groups by themselves or in combination. However, there are comparatively few instances in which simple homologs or isomers are concerned. The most noticeable effect among the acid anthraquinone dyes is found in the difference between the 1,4- and the 1,5-series; when arylamino groups are present the former are green and the latter are bluish.

Toluidine Blue (I) is a sulfonated 1,5-ditoluidino-4,8-dihydroxyanthraquinone, and its isomer (II), 1,4-ditoluidino-5,8-dihydroxyanthraquinone, is Toluidine Green (1); these colors thus fit into the series mentioned above. In these structures the rings *A* are aromatic nuclei of the benzene series; ring *B* is that portion of the anthraquinone residue to which the aromatic groups are attached; and *C* the portion without such groups.



(S = SO_3Na)

I



II

Isomers, homologs, and isologs can be secured by (a) varying the nature of the aromatic nuclei *A*, (b) introducing different substituents into *B* or *C*, and (c) changing the position or number of the sulfonic acid groups. Since rings *A* are always introduced into the molecule by the use of an aromatic amine, it is possible to determine the effect of substituents by using substituted anilines.

In this paper are described several dyes in the blue series obtained by the first and third variations; the second type is more easily secured in the green series, and will be described in the following paper.

The new dyes have been obtained, using *ortho*- and *meta*-toluidine, *p*-anisidine, *p*-t-amylaniline, *ortho*- and *para*-chloroaniline, *p*-xenylamine, and β-naphthylamine. The second, third, and last two of these are much more soluble in water than Toluidine Blue; from the sulfur-nitrogen ratio, determined on the second and third, it was concluded that there were two sulfonic acid groups to each

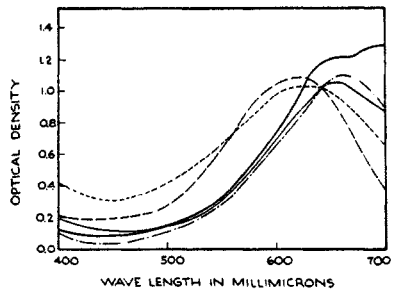


FIG. 1

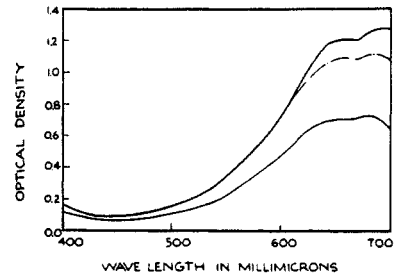


FIG. 2

FIG. 1. DYES RELATED TO TOLUIDINE BLUE, HAVING DIFFERENT TYPE OF ABSORPTION CURVE

———, Toluidine Blue (4′—CH_3); ——, 3′—CH_3; — · — ·, 2′—CH_3; ------, OCH_3; — — —, Effect of oleum on Toluidine Blue.

FIG. 2. 4′-*t*-AMYL HOMOLOG OF TOLUIDINE BLUE

———, Toluidine Blue, 1:20,000; — · — ·, 4′-*t*-amyl homolog, 1:13,000; ——, 4′-*t*-amyl homolog, 1:20,000.

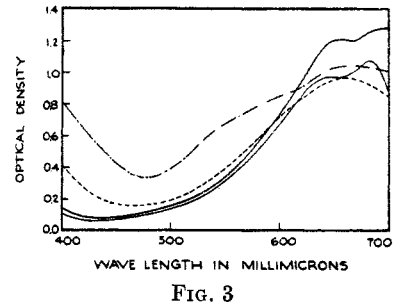


FIG. 3

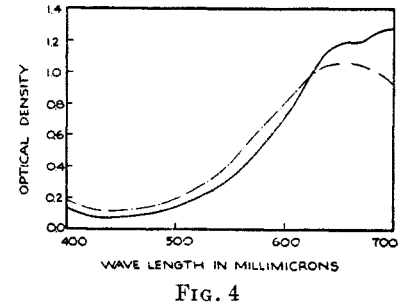


FIG. 4

FIG. 3. DYES RELATED TO TOLUIDINE BLUE, HAVING SAME TYPE OF ABSORPTION CURVE

———, Toluidine Blue (4′—CH_3); — · — ·, β-naphthyl isolog; ——, 4′-chloro isolog; ------, 4′-phenyl isolog.

FIG. 4. EFFECT OF POSITION OF SULFONIC ACID GROUPS

———, Toluidine Blue (2′—SO_3Na); — · — ·, isomer (3′—SO_3Na).

nitrogen in the more soluble dyes. The absorption curves of these dyes (Fig. 1) resemble that of the blue dye that results when Toluidine Blue is treated with fuming sulfuric acid; the latter has a sulfur-nitrogen ratio greater than 1, but a pure sample has never been secured. *p*-t-Amylaniline gives a dye which resembles Toluidine Blue but does not seem to be as strong (Fig. 2). The dyes from *p*-xenylamine and β-naphthylamine absorb in the violet and are greenish (Fig. 3),

while the one from *p*-chloroaniline does not have as high absorption in the far red. From these results it may be concluded that only *para*-alkylated amines can be expected to produce dyes closely resembling Toluidine Blue.

The third type of variation concerns the location of the sulfonic acid group. Direct sulfonation always introduces this group into the 2′-position, *ortho* to the NH, when the 4′-position is blocked; the position of the sulfonic acid group has been determined by reductive hydrolysis (1). Since 1,5-substitution is unsymmetrical, the usual procedures (3, 4) for securing 3′-sulfonic acids cannot be employed. Adapting a method of preparation useful for certain monoarylated anthraquinones (5, 6), the desired dye was obtained. This reaction consisted in heating a mixture of 4,8-dichloroanthrarufin and sodium 4-aminotoluene-2-sulfonate under pressure. The absorption curve of the isomer of Toluidine Blue, furnished by this procedure, falls off in the far red (Fig. 4).

EXPERIMENTAL

The anthraquinone derivatives were mostly prepared by a general procedure as described under the *m*-toluidino derivative. Under these conditions, however, the *ortho* amines did not react, and the addition of boric acid (second procedure) was employed. Two other isologs needed further modifications and are treated separately. The analyses of the anthraquinones are given in Table I. In general the melting points are accompanied by decomposition and/or sublimation, so that an accurate determination is not possible.

I. THE ANTHRAQUINONES

(a) *4,8-Di*-m-*toluidino-1,5-dihydroxyanthraquinone.* A mixture of 8 g. of 4,8-dichloroanthrarufin (m.p. *ca.* 337°) and 100 g. of *m*-toluidine was heated for sixteen hours at 160–175°. After cooling slowly to 50°, the mixture was poured into a large excess of dilute hydrochloric acid. The precipitated dye was filtered and washed thoroughly with warm water, followed by 70% alcohol. The yield of crude product was 11 g. For analysis and for subsequent sulfonation, the product was recrystallized first from chlorobenzene and then from xylene.

The 4,8-di-*p*-toluidino, 4,8-di-*p*-tertiary-amylanilino, 4,8-di-*p*-anisidino, and 4,8-di-*p*-chloroanilino derivatives were prepared in exactly the same manner. In all cases recrystallization was from chlorobenzene or xylene. If very insoluble, a digestion with chlorobenzene was found sufficient for purification.

(b) *4,8-Di*-o-*chloroanilino-1,5-dihydroxyanthraquinone.* *o*-Chloroaniline and *o*-toluidine failed to react with dichloroanthrarufin under the conditions used in the above experiment. It was found necessary to add boric acid, equivalent to about 2/3 the weight of the dichloroanthrarufin. The dyes were isolated as above and were recrystallized from a large volume of xylene for analysis.

(c) *4,8-Di*-p-*xenylamino-1,5-dihydroxyanthraquinone.* A mixture of 50 g. of *p*-xenylamine and 5 g. of dichloroanthrarufin was heated for eighteen hours at 170°. On pouring the partially cooled product into dilute hydrochloric acid everything precipitated, as the hydrochloride of the amine is not water-soluble. The product was collected, dried, ground to a powder, suspended in 10% sodium hydroxide solution, and stirred for three hours. It was filtered and the precipitate extracted thoroughly with ether to remove the amine. The residue was digested with chlorobenzene for purification, as its low solubility made crystallization impractical.

(d) *4,8-Di-β-naphthylamino-1,5-dihydroxyanthraquinone.* A mixture of 50 g. of β-naphthylamine and 5 g. of dichloroanthrarufin was heated for twenty-four hours at 170–180°. After cooling partially, the reaction mass was treated with about 15 times its volume of 70% ethyl alcohol and the insoluble portion filtered. This material was then transferred to a

beaker and stirred for a short time with ether in order to remove the unused β-naphthylamine. Finally, it was collected on a Büchner funnel and washed with ether. The light violet product is only slightly soluble in chlorobenzene, xylene, etc., but can be crystallized from a rather large volume of the former.

All the substances dissolve in concentrated sulfuric acid with production of a green color and give brilliant blue solutions when poured into water, except the naphthyl isolog, which gives a dull green. The solutions in xylene are all a brilliant blue.

TABLE I

ANALYSES OF SUBSTITUTED ANTHRAQUINONES

AMINE USED	CALC'D, %				FOUND, %			
	C	H	N	Cl	C	H	N	Cl
o-Toluidine	74.7	4.9	6.2		74.9	4.8	6.2	
m-Toluidine	74.7	4.9	6.2		74.7	5.0	6.4	
o-Chloroaniline			5.7	14.5			5.8	14.5
p-Chloroaniline				14.5				14.0
p-t-Amylaniline			5.3				5.0	
p-Xenylamine			5.0				5.2	
β-Naphthylamine			5.4				5.4	

II. SULFONATION

The substituted anthraquinones were sulfonated by the use of concentrated sulfuric acid on the steam-bath; this required two and one-half hours with all except the derivative formed from *o*-toluidine, in which the time had to be greatly increased. The dye-salt mixtures were extracted by boiling methanol—the only method of purification at all satisfactory. The procedure is illustrated by sulfonation of the isomer derived from *m*-toluidine.

(a) m-*Toluidine isomer*. A solution of 10 g. of 4,8-di-*m*-toluidinoanthrarufin in 75 cc. of concentrated sulfuric acid was stirred on the steam-bath for two hours. After cooling and pouring on ice, there was no separation of dye acid, so the entire solution was neutralized by sodium hydroxide. After several hours, much of the sodium sulfate had crystallized and was removed; the filtrate was evaporated to dryness. The pulverized residue was extracted in a Soxhlet apparatus with 500 cc. of methanol for fifty hours; 3 g. of dye was thus secured. From the analysis, it was estimated to be about 65% dye; Found: N, 2.3; S, 9.3, 9.5. This gives a 1:1.8 ratio of nitrogen to sulfur, indicating that it is essentially a tetrasulfonic acid, (two SO_3Na groups to each toluidine residue).

In a similar manner, the other isologs, except the one from *o*-toluidine, were secured. The one from *p*-anisidine, on analysis, showed 1.5% nitrogen and 6.5, 6.6, 6.5% sulfur, which gives a 1:1.9 nitrogen:sulfur ratio. The dye from *o*-chloroaniline has a 1:1 ratio.

Anal. Calc'd for $C_{26}H_{14}Cl_2N_2Na_2O_{10}S_2$: N, 4.0; S, 9.2.
Found: N, 4.0; S, 9.0, 8.9.

(b) For the *ortho* toluidino isomer, a mixture of 3 g. of the anthraquinone and 23 cc. of concentrated sulfuric acid was heated on the steam-bath for seven hours; the dye acid precipitated after icing. The methanol extraction required sixteen days, and 2.1 g. of dye resulted; in this, the sulfur:nitrogen ratio is 1:1.

Anal. Calc'd for $C_{28}H_{20}N_2Na_2O_{10}S_2$: S, 9.8. Found: S, 9.7, 9.8.

(c) *Fuming sulfuric acid on Toluidine Blue*. A solution of 5 g. of the dye and 25 cc. of 20% oleum was stirred at 35–40° for one hour, the solution poured upon ice, the dye acid filtered

and dissolved in hot sodium hydroxide. After again filtering, the dye was salted out; 4.75 g. of dye-salt mixture resulted. Upon analysis, 1.7% of nitrogen and 4.8, 4.8, 4.9% of sulfur were found; this indicated that the dye was of about 35% purity. The nitrogen:sulfur ratio is 1:1.3.

III. 4,8-DI-(3′-SULFO-*p*-TOLUIDINO)-1,5-DIHYDROXYANTHRAQUINONE (DISODIUM SALT)

A mixture of 3 g. each of dichloroanthrarufin, sodium acetate, and boric acid, and 8 g. of 4-aminotoluene-2-sulfonic acid in 20 cc. of water and 20 cc. of acetic acid in a sealed tube was heated at 225° for thirty hours. The tube contents were extracted by water and the blue solution filtered from the considerable insoluble material. The filtrate was evaporated to dryness and the residue was extracted with absolute methyl alcohol until all the blue color was removed. On standing, the methyl alcohol deposited a blue solid; this dissolved in water to give a brilliant blue solution comparable in strength and general appearance to the Toluidine Blue.

SUMMARY

Several homologs of Toluidine Blue have been prepared in order to compare their absorption characteristics with those of the parent substance. The closest resemblance is found with the *p*-t-amyl homolog.

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(5) German patent 201,904; [*Frdl.*, **9**, 736 (1908–10)].
(6) German patent 206,645; [*Frdl.*, **9**, 720 (1908–10)].

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

THE AMMONOLYSIS OF BENZIL BY LIQUID AMMONIA[1]

WILLIAM B. LESLIE AND GEORGE W. WATT

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The first observations relative to the interaction of benzil and ammonia were recorded by Zinin (1) more than one hundred years ago. In the intervening years, a considerable body of information on the reactions between benzil and ammoniacal media consisting of aqueous ammonia, alcoholic ammonia, ammonium formate, and ammonium acetate has become available and has led to rather marked divergence of opinion, particularly with regard to the mechanism of these reactions.[2]

Staudinger and Binkert (3) attempted to prepare a metal salt of benzil by the reaction between the diketone and potassium in liquid ammonia at and below −33.5°, and observed that reaction between benzil and ammonia precluded the possibility of formation of a metal ketyl. Strain (4) heated benzil with ammonia for two hours at 200° (*i.e.*, considerably above the critical temperature of ammonia) and obtained a forty per cent yield of lophine (2,4,5-triphenylglyoxaline). Strain also reported that benzamide and "imabenzil" result from the reaction between benzil and liquid ammonia at room temperature, but gave no experimental data in support of this statement.

The present paper describes the action of liquid ammonia and liquid ammonia solutions of ammonium chloride (an acid) and potassium amide (a base) upon benzil at 103° and 35°. These studies represent an effort to determine the identity of the products and the quantity of each with a degree of accuracy not approached in earlier investigations, as a step preliminary to the study of a series of reactions designed to shed further light upon the mechanism of the reactions concerned.

EXPERIMENTAL

Materials. Benzil was prepared by the method of Adams and Marvel (5). Scholl's (6) color test for the detection of benzoin in the presence of benzil was used as a criterion of purity and only that material (m.p. 95°)[3] which failed to give a positive test for benzoin was employed. All other chemicals used were reagent grade materials.

Reaction with liquid ammonia at 103°. Benzil (10.5 g.) was placed in a Pyrex tube (55 x 2.5 cm.) together with approximately 100 cc. of anhydrous liquid ammonia and the tube was sealed. The tube and about 300 cc. of commercial liquid ammonia were placed in an auto-

[1] This work was supported in part by a grant from the University Research Institute (Project No. 25).

[2] For primary references, review, and discussion of possible reaction mechanisms see reference (2).

[3] All melting points reported in this paper are corrected.

clave of the type described by Bergstrom (7) and the autoclave was heated by steam at 103° for forty-six hours. The tube was cooled, opened, and 10.05 g. of crude product was removed from the tube, dried, and ground to 60-mesh in an agate mortar. This material was extracted successively with 50-, 30-, and 20-cc. portions of hot water. The aqueous extracts were combined and boiled for one hour with an excess of aqueous potassium hydroxide.[4] The resulting solution was acidified with hydrochloric acid and cooled. The benzoic acid which separated was removed by filtration, and that remaining in the aqueous solution was removed by extraction with ether. The two crops of acid were combined, dried, and weighed; m.p. 122°. Neutralization equivalent, 123 (calculated, 122).

The water-insoluble material was dried, powdered (60-mesh), and extracted for ten minutes with carbon disulfide in a Soxhlet apparatus. The material insoluble in carbon disulfide was identified as lophine, m.p. 276.5°.

Anal. Calc'd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45.
Found: C, 84.97; H, 5.52; N, 9.51.

The melting point of this product was not depressed by mixing with lophine (m.p. 276.5°) prepared as described by Davidson and co-workers (2). Upon cooling the carbon disulfide solution, a small quantity of lophine separated.[5] This was removed by filtration and combined with the main body of this product.

The solvent was evaporated from the carbon disulfide solution and the resulting gummy material was boiled with 95% alcohol. A small quantity of pale yellow crystalline material failed to dissolve.[6] This product melted at 249–250° and the melting point was not raised by recrystallization from glacial acetic acid. A very small quantity of this product imparted an intense red coloration[7] to concentrated sulfuric acid. A mixture of this product and tetraphenylpyrazine (m.p. 251.5°) prepared as described by Davidson, Weiss, and Jelling (8) melted at 250.5°.

The alcoholic solution was concentrated and cooled. Thus were obtained orange-colored needle-like crystals which, after recrystallization from petroleum ether, melted at 112–113°. This product was shown to consist of 2,4,5-triphenyloxazole by a mixed melting point determination using 2,4,5-triphenyloxazole (m.p. 112–113°) prepared by the method of Schönberg (9).

The yield data relating to products separated by the foregoing procedure as well as those to be described in the following paragraphs are summarized in Table I.

In the foregoing procedure, the ketone was initially in contact with liquid ammonia at −50° (the temperature at which the ammonia was condensed in the tube) and could therefore react with ammonia before the temperature of 103° was reached. To eliminate the possibility of reaction below 103°, the following experiment was conducted. Benzil (32.5 g.) was placed in a Pyrex test tube. The tube was then placed in an inclined position (with the mouth of the tube above the level of the liquid) in a bomb (made of Monel metal and similar

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[4] In a preliminary experiment, the aqueous extracts were cooled, whereupon benzamide, m.p. 127.5°, separated from the solution. The melting point was not depressed when the substance was mixed with an authentic specimen of pure benzamide, m.p. 128°. Thereafter, benzamide was converted to and weighed as benzoic acid by the procedure described above.

[5] An estimation of the solubility of lophine in carbon disulfide resulted in a value of 0.03 g. of lophine/100 cc. of carbon disulfide at 25°.

[6] The solubility of tetraphenylpyrazine in 95% alcohol was found to be 0.014 g./100 cc. of solvent, at 25°.

[7] Laurent [*Ann.*, **52**, 357 (1844)] observed that tetraphenylpyrazine imparts a red coloration to concentrated sulfuric acid and Leuckart [*J. prakt. Chem.* [2] **41**, 332 (1890)] reported a similar behavior for 2,4,5-triphenyloxazole. In the present investigation, Laurent's observations were confirmed and it was found that *pure* 2,4,5-triphenyloxazole gives no such color test. Undoubtedly, the oxazole used by Leuckart was contaminated by traces of tetraphenylpyrazine.

in construction to an ordinary calorimeter bomb) containing about 200 cc. of liquid ammonia. After being heated (by steam) to 103°, the bomb was tilted and shaken so that the benzil and liquid ammonia might be mixed.[8] The reaction mixture was heated for twenty-four hours at 103°, after which the solvent was evaporated and the products separated by the procedure previously described. The results of experiments conducted in this manner are listed in Table I.

Reaction with liquid ammonia at 103° in the presence of ammonium chloride. Benzil (34.3 g.) was brought into contact with a solution of ammonium chloride (26.2 g.) in liquid ammonia (approximately 200 cc.) at 103° and the resulting mixture heated at this temperature for twenty-four hours. The method used in separating the products (see Table I) was the same as that previously described excepting that the weight of water-soluble material was corrected for the presence of ammonium chloride in terms of halide ion found (as AgCl).

TABLE I

THE AMMONOLYSIS OF BENZIL

TEMP. (°C.)	ACID OR BASE	WT. OF CRUDE PRODUCT (G.)	YIELD (%)[a]						
			Benzamide	Lophine	Tetraphenylpyrazine	Triphenyloxazole	Imabenzil	Benzilimide	Total
103[b]	none	10.3	21.7	45.7	0.5	20.0	—	—	87.9
103[c]	none	30.0	31.0	34.0	0.6	28.0	—	—	93.6
103[d]	NH_4Cl	34.1	30.5	39.3	0.5	20.5	—	—	90.8
103	KNH_2	20.6	65.0	19.0	trace	0.0	—	—	84.0
35	none	39.4	24.6	—	trace	10.0	29.8	13.4	81.1[e]
30	none	41.9	22.7	—	trace	7.0	40.0	4.1	75.8[f]
35	NH_4Cl	40.0	25.7	—	trace	8.3	27.0	16.4	84.1[g]
35	KNH_2	24.5	60.0	—	trace	0.0	11.0	16.0	87.0[h]

[a] All yield data are expressed as fractions of the total weight of dry crude product removed from the reaction vessel.

[b] Average values from two experiments. Reactions in sealed tubes.

[c] Average values from two experiments.

[d] Average values from three experiments.

[e] Total includes 3.3% of carbon disulfide-insoluble product.

[f] Total includes 2.0% of carbon disulfide-insoluble product.

[g] Total includes 6.7% of carbon disulfide-insoluble product.

[h] No carbon disulfide-insoluble product found in these experiments.

In the course of a series of these experiments, it was found that the yields of lophine and triphenyloxazole vary markedly with variation in the ratio of ketone to ammonia.

Reaction with liquid ammonia at 103° in the presence of potassium amide. A solution of the potassium amide from 17.2 g. of potassium in approximately 200 cc. of liquid ammonia, and 21.0 g. of benzil were brought together at 103° and thereafter heated for twenty-four hours. The yields of the products isolated (benzamide, lophine, and traces of tetraphenylpyrazine) are given in Table I.

Reaction with liquid ammonia at 35°. A series of experiments conducted at or near room temperature showed that the yields of the various products varied considerably with temperature differences of only a few degrees. Consequently, the remaining experiments were conducted in the calorimeter-type bomb just as described previously excepting that the

[8] Benzil is unreactive toward gaseous ammonia. The ketone was recovered unchanged after having been heated in a stream of anhydrous ammonia for six hours at 78°.

bomb and its contents were placed in a thermostat and brought to a temperature of 35° (or 30°) ± 0.2° before mixing the reactants and the temperature maintained throughout the reaction. In this manner, reproducible yield data were obtained readily.

Benzil (42.0 g.) and liquid ammonia (approximately 200 cc.) were mixed at 35° and held at this temperature for twenty-four hours. The solvent was evaporated and the dried and finely powdered crude product was stirred for one hour with 150 cc. of alcohol and filtered. The crude alcohol-insoluble imabenzil was recrystallized by dissolving it in the smallest possible volume of warm pyridine, followed by seven-fold dilution with toluene and cooling overnight in an ice-bath. This method of purification was found to be much more satisfactory than that of Japp and Wynne (10). The pure imabenzil appeared as a white, microcrystalline powder, m.p. 196°.

Anal. Calc'd for $C_{35}H_{28}N_2O_3$: N, 5.34. Found: N, 5.53.

The solvent was evaporated *in vacuo* from the alcoholic solution and the resulting hard, wax-like material was powdered and extracted with boiling water to remove benzamide, which was determined as benzoic acid. The water-insoluble material was extracted with carbon disulfide, and the small quantity of insoluble material (1.3 g.) was recrystallized from a large volume of alcohol; m.p. 184°. As yet, this product has not been identified. After evaporation of the carbon disulfide, the residues were stirred with 40 cc. of isopropyl ether[9] for one hour. The insoluble material melted at 139°. The identity of this product as benzilimide [N-desylbenzamide (2)] was established by a mixed melting point determination using benzilimide prepared by the method of Henius (11). The isopropyl ether was recovered and the residual material was recrystallized from alcohol and found to consist of triphenyloxazole. The results of experiments conducted at 35° and 30° are shown in Table I.

Reactions with liquid ammonia at 35° in the presence of ammonium chloride and potassium amide. Experiments similar to those involving ammonium chloride and potassium amide at 103° were conducted at 35°±0.2°, and the products were separated as described for the reactions with ammonia at 30° and 35°. The yield data are given in Table I.

The Radziszewski glyoxaline synthesis. A modification of Radziszewski's (12) synthesis of glyoxalines was carried out as follows. Benzil (14.0 g.) and benzaldehyde (7.20 g.) were treated with an excess of liquid ammonia for five hours at 35°. The solvent was removed and the crude product (23.2 g.) was extracted with water. The water-insoluble material was extracted with carbon disulfide. The carbon disulfide-insoluble material consisted of substantially pure 2,4,5-triphenyloxazole (lophine). Only traces of lophine could be isolated from the carbon disulfide solution. The yield was 9.75 g. or 42.0%. In a similar experiment conducted at 103° rather than 45°, 10.30 g. of lophine, corresponding to a 45.7 % yield, was isolated.

DISCUSSION

Two different mechanisms designed to account for the various products obtained from the interaction of benzil and ammoniacal media other than liquid ammonia have been proposed. Japp (10, 13) assumed an initial ammonolytic cleavage of benzil whereas the mechanism suggested by Davidson and co-workers (2) avoids this assumption. The latter mechanism was proposed primarily on the strength of the argument that Japp's explanation was inadequate in view of the unidirectional character of the reaction between benzil, benzaldehyde and ammonia in alcohol (Radziszewski's synthesis of glyoxalines). Since the present studies have shown that, *in liquid ammonia*, lophine is formed not quantitatively but only to the extent of 46 %, it seems reasonable to assume that neither of the previously proposed mechanisms will prove adequate finally to explain these apparently complex reactions in liquid ammonia. It is possible, of course, that

[9] The solubility of benzilimide was found to be 0.10 g./100 cc. of isopropyl ether.

reaction may occur simultaneously in accordance with both mechanisms. The relatively high yields of benzamide obtained in reactions employing potassium amide support Japp's assumption concerning the cleavage of benzil, since a simple ammonolytic cleavage should be expected to be promoted by an increase in the concentration of amide ion. That the reaction between benzil and liquid ammonia should not be strictly analogous to the interaction of the diketone and other ammonolytic media is not unanticipated. The absence of such an analogy has been amply demonstrated in other cases (14).[10]

A general criticism of earlier work in this connection lies in the fact that, to the best of the present writers' knowledge, all of the various reaction products formed at any given temperature have not previously been isolated from a single controlled reaction. Neither has there been much attention given to the relative quantities of the various products formed under different conditions of temperature. Accordingly, the studies described in this paper have been concerned largely with the problem of developing methods for the separation and estimation of the various products. The quantities of product unaccounted for in this work are of such magnitude that the losses may reasonably be attributed to mechanical losses resulting from the numerous separations required.

Tetraphenylpyrazine has not been observed previously as a product of the reaction between benzil and ammonia, but Japp and Wilson (16) have identified tetraphenylpyrazine among the products obtained from the reaction between benzoin and ammonia. Since the quantities of tetraphenylpyrazine found in the present investigation were always very small, it is entirely possible that the benzil employed contained quantities of benzoin too small to be detected by Scholl's color test.

From an inspection of the data of Table I, it is seen that (A) lophine is not formed in reactions effected near room temperature; (B) imabenzil and benzilimide do not appear as products of reactions conducted at 103°, and (C) triphenyloxazole is not produced in reactions involving potassium amide. In addition, experiments not reported in this paper have shown that the yield of lophine is a function of the concentration of ammonium chloride present. Until additional studies can be made, efforts to explain these facts could be little more than mere speculation. However, it is believed that the results reported here suggest and serve as a basis for lines of investigation which will eventually lead to a clarification of the entire question of the mechanism of the interaction of benzil and ammonia.

SUMMARY

1. The identification of the products produced by the interaction of benzil and liquid ammonia under several different experimental conditions has been reported.

2. Methods for the separation and estimation of these products have been described.

[10] For review and primary references see reference 15.

3. The Radziszewski glyoxaline synthesis has been shown to result in relatively low yields of lophine when liquid ammonia is used as the reaction medium.

AUSTIN, TEX.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

THE ACTION OF HYDROGEN BROMIDE IN ACETIC ACID ON UNSATURATED 1,4-DIKETONES

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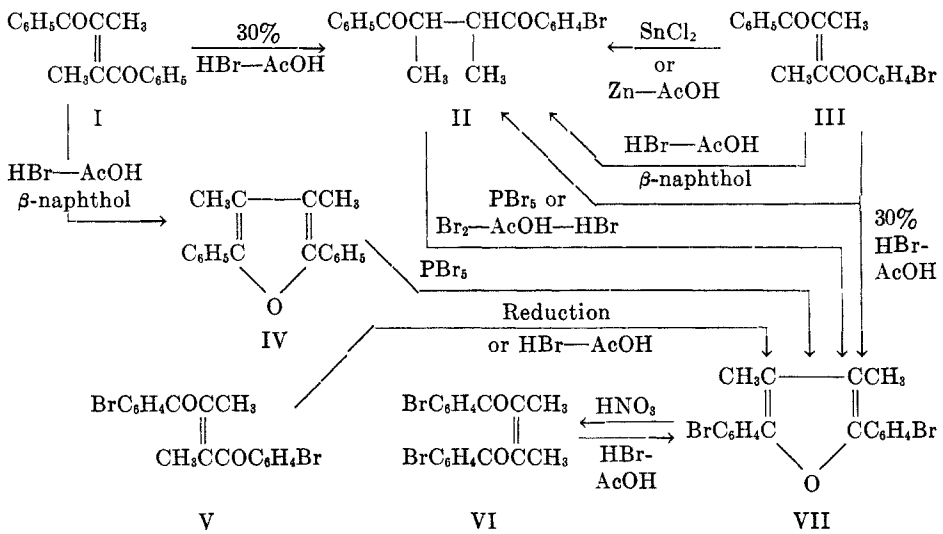
Some time ago a crystalline monobromo compound was obtained in good yield by the action of 30% hydrogen bromide in concentrated acetic acid on *trans* 1,2-dibenzoyldimethylethylene (I) (1). It was recognized that this was not a simple addition compound, because the halogen could not be removed by hydrolysis or reduction, and presumably therefore was in aromatic combination. Investigation of this compound revealed that the bromine had entered the para position of one of the phenyl groups and at the same time reduction had occurred. This report deals with experiments which were carried out in an attempt to gain an understanding of this interesting and unexpected reaction.



The first clue to the structure of the new product came through oxidation which gave a small amount of *p*-bromobenzoic acid. This demonstrated conclusively the location of the bromine. The saturated diketone structure (II) was then deduced from analysis and the stability towards hydrolyzing and reducing agents. The compound was not easily furanized, however, contrary to expectation based on the ease of formation of the furans (IV) and (VII). The structure was proved by synthesis from α-(*p*-bromobenzoyl)-α,β-dimethyl-

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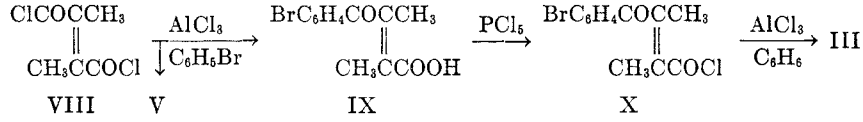
acrylic acid (IX) through conversion into the acid chloride (X), condensation with benzene by the Friedel-Crafts reaction, and reduction of the resulting unsaturated diketone (III).



In connection with this synthesis, it is interesting to note that the starting material, bromobenzoyldimethylacrylic acid (IX), has been made in a new way directly from dimethylfumaryl chloride (VIII) by the Friedel-Crafts reaction. This reaction slowly goes on to completion with the formation of the expected di(bromophenyl) unsaturated diketone (V).

The monobromo unsaturated diketone (III), prepared in the above described synthesis, was also treated with the 30% hydrogen bromide-acetic acid reagent. It was converted into a mixture of the corresponding saturated diketone (II) and di(bromophenyl)dimethylfuran (VII). The ratio of yields of the two products was 4:1, with reduction and dehydration the dominant reaction. At the same time the solvent must have undergone bromination to an extent equivalent to the amount of reduction.

The structure of the di(bromophenyl)dimethylfuran (VII) was demonstrated by synthesis in two ways; through bromination of dimethyldiphenylfuran (IV), and by reduction of the corresponding *trans* di(bromophenyl) unsaturated diketone (V). Consistent with this structure is the fact that the furan underwent the characteristic oxidative fission with nitric acid to give the *cis* unsaturated diketone (VI), which in turn could be reduced back to the furan with great facility.

Both the *cis* and the *trans* di(*p*-bromophenyl) unsaturated diketones (V and VI) have been treated with the hydrogen bromide-acetic acid reagent and gave the furan (VII) in good yield. These results involved both reduction and dehydration.

In connection with these experiments it should be noted that bromination of the saturated diketone (II) with an excess of free bromine in the hydrogen bromide-acetic acid reagent gave the di(bromophenyl)dimethylfuran (VII). No particular significance can be attached to this fact, however, because this reaction undoubtedly involved first bromination at an α-position to give the α-bromo diketone, followed by loss of hydrogen bromide. This reaction, therefore, is in the same category as that of the unsaturated diketone (III).

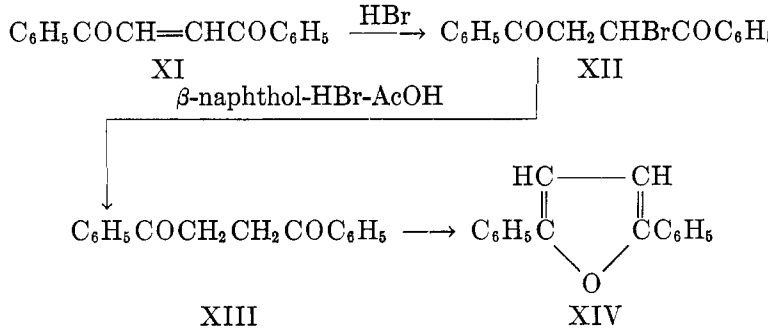
In none of the above described reactions between hydrogen bromide and the four unsaturated diketones (I, III, V, and VI) was there ever obtained any evidence of a compound containing more than two bromine atoms. Bromination occurred in two cases and involved only the para positions, and reduction occurred in all cases; no simple hydrogen bromide addition compound was isolated.

In these reactions it seemed probable that hydrogen bromide was adding re-

versibly to the molecule, the bromine then being transferred to the para position of the same or another molecule or to the solvent. The hypothetical hydrogen bromide addition compound would be an α-bromo ketone or an enol of it, and in the presence of hydrogen bromide would function as a brominating agent. It therefore seemed worth while to re-examine the action of the hydrogen bromide-acetic acid reagent on the unsaturated diketones (I and III) and also on dibenzoyl- and dimesitoyl-ethylenes (XI and XV), where hydrogen bromide addition compounds have actually been isolated, introducing into the various reaction mixtures a bromine acceptor such as β-naphthol to divert the brominating action and to confine the changes in the compounds in question to reduction.

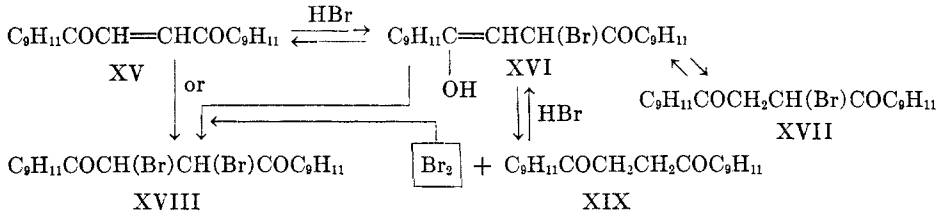
The reactions between hydrogen bromide-acetic acid and the unsaturated diketones (I and III) where both bromination and reduction had occurred, were repeated in the presence of β-naphthol. As was anticipated only the reduction products (IV and II, respectively) were obtained under these conditions, and α-bromo-β-naphthol could be isolated as a by-product.

Dibenzoylethylene (XI) is known to add hydrogen bromide in acetic acid; the addition compound, dibenzoylbromoethane (XII) crystallizes promptly from the reaction mixture in good yield. This reaction was repeated in the presence of β-naphthol, the mixture being allowed to stand until further reaction beyond the initial addition had occurred. 2,5-Diphenylfuran (XIV) and α-bromo-β-naphthol were isolated as the products. In an independent experiment it was shown that the saturated diketone (XIII) is readily dehydrated to the furan under the conditions of this experiment and undoubtedly was formed as an intermediate. The course of the reactions, disregarding equilibrations and intermediate steps, must be as follows:



The case of dimesitoylethylene (XV) is of interest in this connection. The hydrogen bromide addition compound (XVII) is unstable and not easily isolated, and it breaks up readily into the components. Here the reaction is slowly reversible, and in this respect occupies a position intermediate between those of dibenzoylethylene (XI) and dibenzoyldimethylethylene (I). It had previously been observed that in the reaction with dimesitoylethylene (XV) there was produced a small amount of dimesitoyldibromoethane (XVIII) (2). This product undoubtedly was formed by the action of free bromine which was generated through the interaction of hydrogen bromide and the addition compound

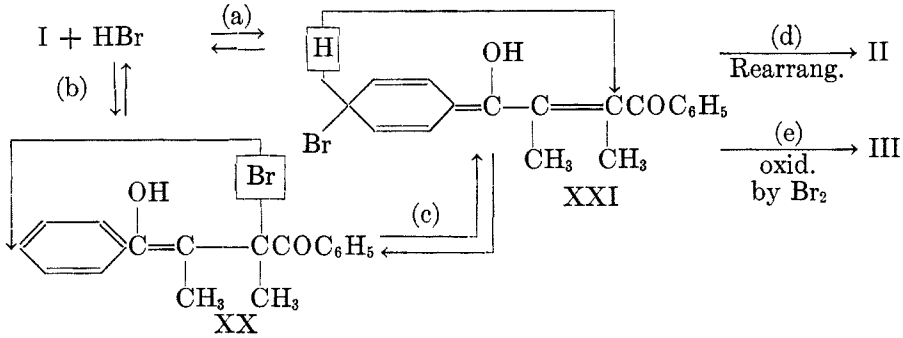
(XVI) or (XVII);[2] the bromine liberated would act upon the starting material (XV) or upon the intermediate enolic addition compound (XVI) which must be present also in equilibrium. This is pictured in the following diagram.



In the total reaction outlined above, the saturated diketone (XIX) should be formed in an amount proportional to that of the dibromide (XVIII) but its presence was not suspected at the time this experiment was performed (2). This experiment was therefore repeated with β-naphthol present to absorb the bromine and to prevent the formation of the dibromide. Under these conditions the saturated diketone (XIX) was obtained in good yield as the chief product.

It seems reasonable from the foregoing to assume that the diaryldimethyl unsaturated diketones (I, III, V, and VI) add hydrogen bromide reversibly, and that the hypothetical addition compounds or the enols resulting from 1,4-addition possess a very reactive bromine which to some extent may be transferred irreversibly to a para position. Probably free bromine is generated by the action of hydrogen bromide on the bromo diketone and is present in the equilibrium mixture. The entrance of the bromine into the para position rather than the meta, however, is a striking point. Obviously the saturated 1,4-diketones would not directly undergo para bromination; however, intermediate enols produced by 1,4-addition or enolization, or compounds resulting from addition at the carbonyl group, might well be able to do so.

An alternative and plausible mechanism for para bromination is reversible addition of hydrogen bromide to the conjugated unsaturated ketone system of the benzoyl group (path "a" in the diagram below), or a 1,7-shift of bromine of the enolic hydrogen bromide 1,4-addition compound (XX) from the chain



[2] The basis for assuming the reversible liberation of bromine is the recent work of Altschul and Bartlett (3).

to the para position to give XXI (path "b-c"). This would be followed by irreversible migration of the para hydrogen (step "d") or oxidation by the bromine in the equilibrium mixture (step "e").

Naturally in reactions such as those described above, where equilibria are involved throughout down to the fixation of the bromine in the para position of a phenyl group, it would be difficult to determine the specific mechanism involved. Conjugate additions and migrations are subject to elaboration and expression in electronic and ionic terms. Possibly various of the paths suggested are in reality equivalent; for example, (c) may occur indirectly through reversal of (b) followed by (a).

The results of this investigation serve as added illustration of the complications which may arise in reactions which involve α-halogeno ketones. Knowing of these complications it has been possible in several bromine additions (4) to improve the reactions markedly by taking care to remove the hydrogen bromide that was formed as the result of secondary or side reactions.

EXPERIMENTAL PART

trans *1-Benzoyl-2-*(p-*bromobenzoyl*)*-1,2-dimethylethylene* (III). *trans* 2-(*p*-Bromobenzoyl)-1,2-dimethylacrylyl chloride, prepared from 0.4 g. of phosphorus pentachloride and 0.5 g. of the parent acid, without removal of the phosphorus oxychloride produced, was taken up in 5 ml. of benzene. This solution was added dropwise at room temperature during 15 min. to a mechanically stirred mixture of 0.75 g. of aluminum chloride and 15 ml. of benzene. Stirring was continued with refluxing for 30 min. and the mixture was hydrolyzed by prolonged stirring in dilute hydrochloric acid. Separation and evaporation of the solvent gave a nearly quantitative yield of crude product (0.6 g.). Recrystallization from ethanol gave colorless needles of melting point 125°.

Anal. Calc'd for $C_{18}H_{15}BrO_2$: C, 63.0; H, 4.4; Br, 23.3.
Found: C, 63.1; H, 4.3; Br, 23.3.

4-(p-*Bromophenyl*)*-2,3-dimethyl-1-phenylbutanedione-1,4* (II). A mixture of 0.05 g. of the *trans* unsaturated diketone (III) and 0.1 g. of stannous chloride in one ml. of a 7:3 mixture of conc'd acetic and hydrochloric acids was refluxed for 30 min. On cooling, 0.04 g. of product separated; melting point 105–115°. Crystallization from ethanol-ethyl acetate mixtures raised the melting point to 125°. The compound showed no mixture melting point depression with the products obtained by the action of hydrogen bromide-acetic acid on dibenzoyldimethylethylene and by reduction of the *trans* unsaturated diketone (III).

trans *1,2-Di-*(p-*bromobenzoyl*)*-1,2-dimethylethylene* (V). (a) Ten grams of dimethylfumaryl chloride was added dropwise during one hour to a mechanically stirred and refluxing mixture of 17 g. of anhydrous aluminum chloride in 80 ml. of carbon disulfide and 26 g. (3 equiv.) of bromobenzene. After refluxing for another hour the mixture was hydrolyzed in ice and 35 ml. of conc'd hydrochloric acid. Fifteen grams of product was filtered off and an additional crop was obtained by evaporation of the solvent. Leaching with dilute alkali was necessary to free the material from acidic by-products. The yield of fairly pure compound was 80%; colorless prisms; melting point 172.5–173°.

Anal. Calc'd for $C_{18}H_{14}Br_2O_2$: C, 51.2; H, 3.3.
Found: C, 51.2; H, 3.3.

(b) In a second experiment, dimethylfumaryl chloride was added over 30 min. at room temperature to the carbon disulfide-bromobenzene-aluminum chloride mixture, using two equivalents of bromobenzene but with the other amounts of materials and conditions similar to those described in (a). There was isolated a 30% yield of 2-(*p*-bromobenzoyl)di-

methylacrylic acid (IX), a 14% yield of the unsaturated diketone (V) and a 4% yield of dimethylfumaric acid.

2,5-Di-(p-*bromophenyl*)-*3,4-dimethylfuran* (VII). A mixture of one gram of the *trans* unsaturated diketone (V) and 2 g. of stannous chloride in 10 ml. of 7:3 conc'd acetic and hydrochloric acids was refluxed for one hour. The resulting suspension was diluted with water, and gave a nearly quantitative yield of the furan, which crystallized from benzene as colorless hair-like needles of melting point 181°. Crystallization from ethanol-ethyl acetate mixtures in one experiment resulted in a monohydrate, which gave the expected analysis only after vacuum sublimation.

Anal. Calc'd for $C_{18}H_{14}Br_2O$: C, 53.2; H, 3.5.
Found: C, 53.3, 53.4; H, 4.0, 3.8.

The furan was obtained also in 30% yield upon refluxing a mixture of the *trans* unsaturated diketone (V), an equal weight of zinc dust and five times its weight of conc'd acetic acid. The remainder of the product in this experiment was accounted for as oils and a low-melting mixture presumably containing the expected saturated diketone. A more tractable mixture results from sodium hydrosulfite reduction, in which the saturated diketone could be seen under the microscope as characteristic compact hexagonal prisms.

The furan was also prepared in low yield by the action of phosphorus pentabromide both on 3,4-dimethyl-2,5-diphenylfuran (IV) and on 4-bromophenyl-2,3-dimethyl-1-phenylbutanedione-1,4 (II). Equal weights of starting material and phosphorus pentabromide were heated for 10 minutes on a steam-bath. The result was a mixture from which the furan was leached out by solvents and identified by mixture melting point.

cis *1,2-Di-*(p-*bromobenzoyl*)-*1,2-dimethylethylene* (VI). To 0.5 g. of di-(*p*-bromophenyl)-dimethylfuran (VII) and 10 ml. of propionic acid, in an ice-salt-bath, was added 2 ml. of a 3:1 mixture of propionic and conc'd nitric acids. After 15 minutes the reaction mixture was removed from the bath and diluted by the addition of ice. The crystals separating weighed 0.47 g. The compound was soluble in methanol and benzene. It was purified by recrystallizations from ligroin containing small quantities of ethyl acetate; melting point 138–139°.

Anal. Calc'd for $C_{18}H_{14}Br_2O_2$: C, 51.2; H, 3.34.
Found: C, 51.4; H, 3.76.

The action of HBr-CH$_3$*COOH on* trans *dibenzoyldimethylethylene* (I). Hydrogen bromide in acetic acid (30–32%) was used in these reactions and will be referred to as the hydrogen bromide-acetic acid reagent, or HBr-CH_3COOH. The inactivity of this reagent towards β-naphthol was shown by recovery of starting material in good yield after treatment for two hours at room temperature. A nearly quantitative yield of crude α-bromo-β-naphthol was obtained under similar conditions when one equivalent of bromine was added.

The conditions described by Lutz and Taylor (1) were found to be critical, since both heating and varying the ratio of materials resulted in a green resin. Purification of the product, *1-bromophenyl-4-phenyl-2,3-dimethylbutanedione-1,4* (II), was best effected by recrystallization from a 4:1 ethanol-ethyl acetate mixture, although this did not furnish material melting as high as that obtained by reduction of the corresponding unsaturated diketone. The purest sample obtained from the hydrogen bromide reactions melted at 118–119°, and was probably contaminated with the ortho-brominated isomer; the analytical results were satisfactory. The product is also crystallizable from acetic acid, ligroin, and isopropyl ether. An attempt to purify it by vacuum sublimation was fruitless, although the sublimed diketone was shown by analysis to have undergone no significant change. The various samples showed no mixture melting point depressions with each other.

Anal. Calc'd for $C_{18}H_{17}BrO_2$: C, 62.7; H, 5.0; mol. wt., 345.
Found: C, 62.6, 62.6; H, 4.75, 4.7; mol. wt. (Rast), 365.

In the most drastic attempt at hydrolysis, the saturated monobromophenyl diketone (II) was recovered in 75% yield after refluxing for 17 hours with 25 equivalents of alcoholic potassium hydroxide. A colorless oil accounted for the remainder of the starting material.

No reduction resulted from the action of refluxing zinc-acetic acid mixtures, or from prolonged catalytic hydrogenation with either platinum or palladium-barium sulfate catalysts.

Oxidation by hot conc'd nitric acid gave 0.9 mole of *p*-bromobenzoic acid (identified by mixture melting point). The same product was isolated from a more drastic potassium permanganate oxidation, and identified.

Furanization attempts met with surprising resistance. No furan was obtained upon treatment with boiling acetic anhydride containing sulfuric acid, or with boiling acetic acid saturated continuously with dry hydrogen chloride.

Bromination of 20 mg. of II by the action of one equivalent of bromine in 0.4 ml. of the hydrogen bromide-aceitic acid reagent, upon standing for one hour at room temperature, gave di(bromophenyl)dimethylfuran (VII) in good yield. Identification was by mixture melting point.

The reaction between HBr-CH_3COOH and dibenzoyldimethylethylene in the presence of β-naphthol. The action of 6 ml. of the hydrogen bromide-acetic acid reagent through contact at room temperature for one hour with 0.3 g. of *trans* dibenzoyldimethylethylene (I) and 0.33 g. of β-naphthol, gave upon filtration 0.2 g. of 3,4-dimethyl-2,5-diphenylfuran of melting point 116–117° (identified by mixture melting point with an authentic sample). Dilution of the filtrate with water brought the yield to 87%. The product gave a sharp mixture melting point depression with II which had been obtained by reaction in absence of β-naphthol.

The action of HBr-CH_3COOH on trans *1-benzoyl-2-bromobenzoyldimethylethylene* (III). Five-tenths gram of the unsaturated diketone was allowed to stand at room temperature, with 10 ml. of the hydrogen bromide reagent for one hour and the resulting precipitate was filtered off. Upon fractional crystallization of this product from ethanol containing a little ethyl acetate, there was obtained a small quantity of 2,5-di(bromophenyl)-3,4-dimethylfuran (VII) of m.p. 176–179°, and a larger amount of the more soluble saturated diketone (II) melting at 117–119°. Identifications were by mixture melting point; the ratio of VII:II was approximately 1:4.

The reaction in the presence of β-naphthol. Trans 1-benzoyl-2-bromobenzoyldimethylethylene (0.05 g.) was added to 1.0 ml. of the hydrogen bromide-acetic acid reagent containing 0.04 g. of β-naphthol. After standing for one hour at room temperature 0.04 g. of solid was filtered off and identified as 1-benzoyl-2-bromobenzoyldimethylethane (II) by the melting point 121.5–123.5° and by mixture melting point. No di(bromophenyl)dimethylfuran was found.

The action of HBr-CH_3COOH on trans *1,2-di(bromobenzoyl)dimethylethylene* (V). Nine milliliters of the hydrogen bromide-acetic acid reagent was added to 0.45 g. of the unsaturated diketone (V) and the mixture was stirred frequently for one hour at room temperature. Filtration gave 0.44 g. of product, which was crystallized from benzene and identified as 2,5-di(bromophenyl)-3,4-dimethylfuran (VII) by mixture melting point.

The reaction in the presence of β-naphthol. To 0.3 g. of *trans* di(bromobenzoyl)dimethylethylene was added 0.1 g. (approx. 1 equiv) of β-naphthol and 6 ml. of the hydrogen bromide-acetic acid reagent. After frequent stirring for one hour at room temperature the mixture was poured into water. The resulting mixture was made alkaline with sodium carbonate solution and was extracted with ether. Evaporation of the ether and leaching with 5% sodium hydroxide gave a residue weighing 0.34 g. From this product, melting at 145–162°, 2,5-di(bromophenyl)-3,4-dimethylfuran (VII) was isolated by crystallization from an ethanol-ethyl acetate mixture and was identified by mixture melting point. The aqueous layer from the ether extraction upon acidification gave 0.12 g. (78%) of α-bromo-β-naphthol which was identified by mixture melting point with a known sample.

The action of HBr-CH_3COOH on cis *1,2-di(bromobenzoyl)dimethylethylene* (VI). A mixture of 1 ml. of the hydrogen bromide-acetic acid reagent and 0.05 g. of the unsaturated diketone was allowed to stand for one hour at room temperature. The solid phase did not

disappear. Filtration gave 0.05 g. of product of melting point, 155–165°, which on crystallization from ligroin gave 0.02 g. of pure 2,5-di(bromophenyl)-3,4-dimethylfuran (VII) (identified by mixture melting point).

The reaction between HBr-CH_3COOH and trans *1,2-dibenzoylethylene (XI) in the presence of β-naphthol.* In each of three experiments the unsaturated diketone and β-naphthol were added in a weight ratio of 5:3 to 100 parts by volume of the hydrogen bromide-acetic acid reagent, and the mixtures were shaken at room tempeature. Solid dibenzoylbromoethane separated first and then gradually disappeared. Interruption of one experiment after 1.75 hours and filtering gave a mixture of starting material and the bromo saturated diketone (XII) in a combined yield of approximately 60%. Crystallization from ethyl acetate containing ethanol gave dibenzoylbromoethane in 18% yield; this was identified by a mixture melting point. From the filtrate, made alkaline and extracted with ether, was obtained a small quantity of diphenylfuran which was identified similarly. A second reaction mixture after six hours standing became a clear solution, from which an 80% yield of impure diphenylfuran was obtained by diluting the mixture with water, filtering, leaching the solid with 5% alkali, and crystallizing from methanol. The third mixture was allowed to stand for 17 hours, and upon diluting the clear reaction mixture, making alkaline, extracting thoroughly with ether, and acidifying the aqueous layer, a 71% yield of α-bromo-β-naphthol was obtained and identified by mixture melting point.

The action of HBr-CH_3COOH on 1,2-dibenzoylethane (XIII). A solution of 0.5 g. of dibenzoylethane in 10 ml. of the hydrogen bromide-acetic acid reagent was allowed to stand for 17 hours at room temperature. The solution was diluted with water and filtered to give 0.45 g. of impure diphenylfuran of melting point 83–90°. After one crystallization from methanol the melting point reached 90–92°, and the product was identified by a mixture melting point.

The action of HBr-CH_3COOH on trans *1,2-dimesitoylethylene (XV) in the presence of β-naphthol.* A mixture of 6 ml. of the hydrogen bromide-acetic acid reagent, 0.3 g. of dimesitoylethylene and 0.135 g. of β-naphthol was allowed to stand for 15 min. at room temperature. An immiscible oil formed. The mixture was diluted with water, made alkaline with sodium carbonate and extracted with ether. The ether extracts furnished a residue which was leached with cold 5% alkali and was again extracted with ether; 0.29 g. of alkali-insoluble pale yellow crystals was obtained. Recrystallization from ethanol yielded 1.65 g. of dimesitylbutanedione (XIX) of melting point 130–132°; it was identified by mixture melting point. Acidification of the aqueous solutions from the above procedure gave a 67% yield of α-bromo-β-naphthol, which was similarly identified.

Reactions with other unsaturated diketones. Conditions could not be found under which the hydrogen bromide-acetic acid reagent would give a crystalline product with *cis* 1,2-dibenzoyldimethylethylene. The reagent was without effect on *trans* 1,2-dibenzoyldibromoethylene after one hour under the usual condltions. The reagent, both with and without β-naphthol, quickly converted *trans* 1,2-dimesitoyl-1,2-dimethylethylene into an oil which has not been investigated further.

SUMMARY

Hydrogen bromide in acetic acid reacts with four 1,4-diaryl-2,3-dimethyl unsaturated 1,4-diketones. In two cases the result was essentially reduction, and in the other two the result was both reduction and bromination in the para position of a phenyl group.

The structures of the new compounds involved were demonstrated by interrelationship and by synthesis.

β-Naphthol when present in the reactions between hydrogen bromide and these four unsaturated 1,4-diketones and also in the reactions with dibenzoyl

and dimesitoylethylenes, served as a bromine acceptor; the reactions were confined to reduction (and furanization also in two cases).

A possible mechanism for the para bromination is suggested.

CHARLOTTESVILLE, VA.

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

CYCLIZATION OF DIENYNES. XIII. (1) SOME METHOXYCYCLOHEXENYLACETYLENE DERIVATIVES

C. S. MARVEL AND W. L. WALTON

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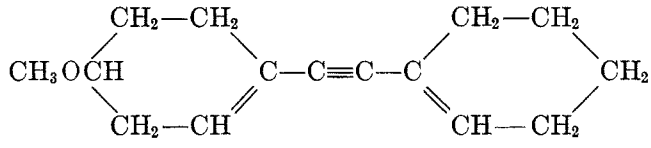
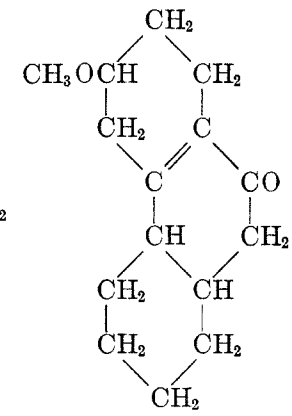
The occurrence of oxygen-substituted hydrophenanthrene rings in many natural products led us to study the cyclization of methoxy-substituted di-Δ^1-cyclohexenylacetylenes (such as I) in the hope that methoxyhydrophenanthrones (II) would result in sufficiently good yields to make this reaction a practical method of preparation for compounds in this series.



I

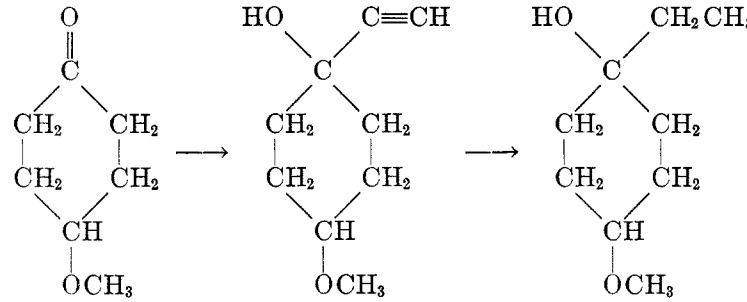


II

It has been found that the introduction of a group into one of the cyclohexene rings increases the number of isomers in this series to such an extent that separation of pure individuals becomes a tedious task. This does not promise to be a useful route to methoxyphenanthrones. We have obtained a number of acetylenic alcohols and glycols and their derivatives and have isolated some of the isomers in pure form. The cyclization reaction has been studied in some detail for the monomethoxydicyclohexenylacetylene, and evidence has been obtained that both spiranones and phenanthrones were produced.

4-Methoxy-1-cyclohexanone (III) was prepared by the method of Helfer (2) and converted to the corresponding acetylenic alcohol (IV) by the procedures used in previous work on related compounds (3). This alcohol was reduced by hydrogen over platinum oxide (4) to give 4-methoxy-1-ethylcyclohexanol (V) which, while having similar physical properties and giving a 3,4-dinitrobenzoate of almost the same melting point as that of alcohol obtained by the action of ethylmagnesium bromide on 4-methoxycyclohexanone (III), proved

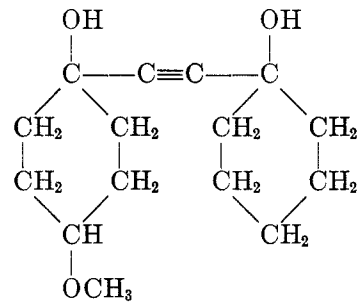
to be a stereoisomer of it. The acetylenic alcohol (IV) was condensed through its magnesium halide derivative by methods previously described (3) with



III IV V

cyclopentanone, 2-methylcyclopentanone, and 4-methoxycyclohexanone to give acetylenic glycols which in turn were converted to the corresponding dienynes. Due to the many isomers present, these glycols were not obtained crystalline.

The mixed acetylenic glycol (VI), was made from the Grignard derivative of 1-ethynyl-1-cyclohexanol (3) and 4-methoxycyclohexanone. Two isomeric

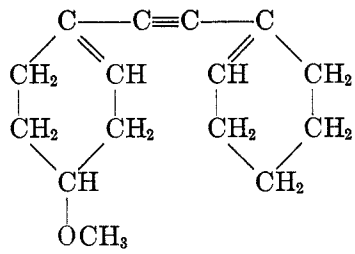


VI

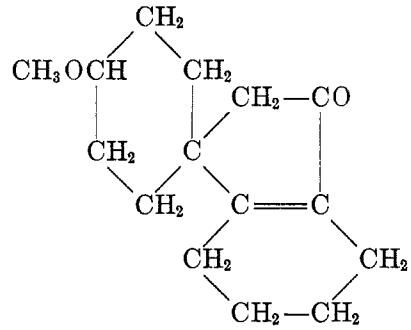
crystalline 3,5-dinitrobenzoates of this glycol were separated. Undoubedly these are the *cis-trans* isomers due to the 4-methoxy group and the hydroxyl group on one cyclohexane ring. By hydrolysis of these esters, the two isomeric glycols were obtained pure; one form proved to be crystalline.

It was thought that separation of the two glycols might simplify the problem of separating the products obtained in the cyclization reaction, but this did not prove to be the case. This is evidence that the first step in the cyclization reaction is dehydration, which thus converts either glycol into the same dienyne (VII). Attempts to dehydrate the unsymmetrical acetylenic glycol (VI) gave directly a mixture of cyclic ketones and other products. This mixture was reduced with hydrogen and platinum oxide (4) and then treated with 2,4-dinitrophenylhydrazine, to give a mixture of crystalline 2,4-dinitrophenylhydrazones, which was separated by chromatographic adsorption on alumina, to give three pure compounds. Two of these compounds gave correct analyses for derivatives of the expected cyclic ketone (II), but it is not possible to say

definitely whether they are stereoisomers of the phenanthrone or whether one is a phenanthrone and the other a spiranone[1] (VIII). The third 2,4-dinitrophenylhydrazone derivative proved to be identical with the corresponding derivative of the dodecahydrophenanthrone previously reported (6). Evidently



VII



VIII

the sulfuric acid treatment caused the loss of methyl alcohol from the methoxy derivative and the reduction saturated the resulting exposed double bond without reducing the buried double bond or the carbonyl group.

When more drastic cyclization treatment was tried, the amount of this unsubstituted ketone derivative increased at the expense of one of the methoxy-substituted derivatives. The loss of the methoxyl group must have occurred after cyclization, for if it were lost at the dienyne stage a dihydrobenzene derivative would have been formed. This would have gone over to a benzenoid molecule, and these do not cyclize (7).

The mixed ketones were dehydrogenated over palladium on charcoal (8) at 330°. The resulting mixture of dehydrogenation products was separated by chromatographic adsorption on alumina into four fluorescent bands.

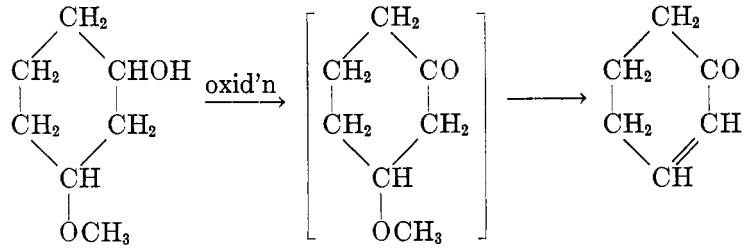
These bands were cut apart and the dehydrogenation products washed out of the adsorbent. The two major portions proved to be phenanthrene and 3-methoxyphenanthrene. The other two products isolated in about one-tenth the amount of the first two appeared to be anthracene and possibly a methoxyanthracene. The amounts obtainable were too small for definite identification. However, mixtures of phenanthrene and anthracene were prepared and separated by chromatographic adsorption. The rates of movement and color of the fluorescent bands of the known mixture were exactly those of the unknown.

This isolation of both phenanthrene and anthracene derivatives from the dehydrogenation of the cyclization products is an indication that at least one of the cyclization products may be a spiran derivative. Levitz, Perlman, and Bogert (9) have found that 15 parts of spirocyclohexane-1,1′-indane on dehydrogenation over a palladium-charcoal-asbestos catalyst gives about five parts of phenanthrene and one part of anthracene. The low ratio of anthracene deriva-

[1] Perlman, Davidson, and Bogert (5), have suggested that spiranones are probable products of this type of cyclization reaction.

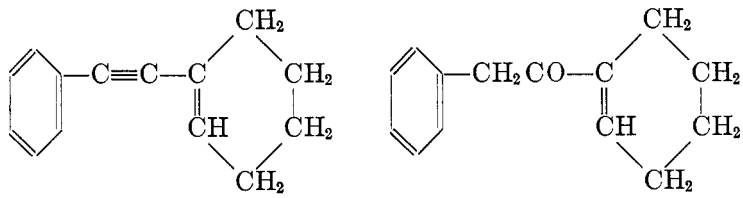
tives to phenanthrene derivatives in our dehydrogenation mixture is thus evidence that only a small amount of spiran derivative is present in our mixture.

Attempts to make compounds substituted with a methoxyl group in the 3-position were blocked by the instability of 3-methoxy-1-cyclohexanone (X). When 3-methoxy-1-cyclohexanol (IX) was oxidized, the only product which could be isolated was Δ^2-cyclohexenone (XI).

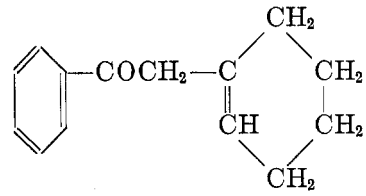


IX X XI

In the cyclization of a dienyne, hydration of the acetylenic group occurs, and in an unsymmetrical dienyne such as I, two isomeric products are possible, depending on the final position of the carbonyl group. It has been demonstrated (5) that the dienyne (XII) having one of the double bonds in a benzene ring, and the ketone XIII which would be formed by adding water to the triple bond in XII so that the carbonyl group remains conjugated with aliphatic unsaturation, do not cyclize. The isomeric ketone (XIV) has been described by Farrow



XII XIII



XIV

and Kon (10) who report it as being in equilibrium with α,α-cyclohexylideneacetophenone. When this ketone was prepared and submitted to mild cyclization conditions, it was recovered unchanged. Drastic treatment yielded acetophenone by degradation. These results indicate that the mechanism of our cyclization reaction must be somewhat different from the cyclodehydration reaction of Perlman, Davidson, and Bogert (5).

EXPERIMENTAL

4-Methoxycyclohexanone. Oxidation of 4-methoxy-1-cyclohexanol by essentially the method of Helfer (2) gave this ketone in 65% yields. The product boiled at 84–85°/14 mm.; n_D^{20} 1.4560. Its semicarbazone melted at 175–176.5° and the 2,4-dinitrophenylhydrazone at 150°. Helfer (2) reports the semicarbazone m.p. 178° and Ferrante and Bloom (11) give the melting point of the 2,4-dinitrophenylhydrazone at 150°.

4-Methoxy-1-ethynyl-1-cyclohexanol. The condensation of 4-methoxy-1-cyclohexanone and acetylene in the presence of potassium *t*-amoxide was carried out as previously described for the unsubstituted cyclohexanone (3). The yield of acetylenic alcohol b.p. 120–124°/22 mm.; n_D^{20} 1.4871 was 27%.

There was a small high-boiling fraction, which after repeated distillation boiled at 155°/4 mm.; n_D^{20} 1.5030. The analysis of this high-boiling material suggested that it was 4,4′-dimethoxy-2-cyclohexylidenecyclohexanone.

Anal.[2] Calc'd for $C_{14}H_{22}O_3$: C, 70.54: H, 9.31.
Found: C, 70.16: H, 9.02.

This product was evidently not quite pure and gave a mixture of 2,4-dinitrophenylhydrazones. An attempt was made to reduce it over platinum oxide catalyst but apparently only a purification was effected. The ketone treated in this fashion gave orange needles of a 2,4-dinitrophenylhydrazone from ethyl alcohol, m.p. 154–155°.

Anal. Calc'd for $C_{20}H_{26}N_4O_6$: N, 13.39. Found: N, 13.37, 13.43.

The acetylenic alcohol was purified by conversion to the 3,5-dinitrobenzoate. From 7.7 g. of the crude alcohol, 20 cc. of pyridine, and 11.38 g. of 3,5-dinitrobenzoyl chloride, by refluxing ten minutes and then diluting with water, a heavy oily ester was obtained. After washing with sodium carbonate solution and dissolving in hot ethyl alcohol, the ester was obtained, on cooling, as white crystals, m.p. 102–105°. The yield was 9.3 g. This product was further purified by crystallization from petroleum ether, ethyl alcohol, and methyl alcohol until there was no change in melting point. The pure ester melted at 112–114°.

Anal. Calc'd for $C_{16}H_{16}N_2O_7$: C, 55.15; H, 4.65.
Found: C, 54.96; H, 4.62.

The *p*-nitrobenzoate was similarly prepared. It was obtained as yellow needles from aqueous alcohol, m.p. 74.5–75.5°.

Anal. Calc'd for $C_{16}H_{17}NO_5$: C, 63.34; H, 5.65.
Found: C, 63.48; H, 5.75.

Hydrolysis of the 3,5-dinitrobenzoate gave the pure acetylenic alcohol, b.p. 121–122°/20 mm.; n_D^{20} 1.4880.

Anal. Calc'd for $C_9H_{14}O_2$: C, 70.09; H, 9.16.
Found: C, 69.50; H, 9.27.

Reduction of 4-methoxy-1-ethynyl-1-cyclohexanol to 4-methoxy-1-ethyl-1-cyclohexanol. A solution of 7.76 g. of the acetylenic alcohol in 150 cc. of ethyl alcohol was treated with 0.1 g. of platinum oxide catalyst (4) and hydrogen at 40 lbs. pressure for forty-five minutes. The catalyst was filtered off and the product distilled. The main fraction weighing 7.2 g. (90%) boiled at 114–116°/22 mm.; n_D^{20} 1.4689.

Anal. Calc'd for $C_9H_{18}O_2$: C, 68.29; H, 11.74.
Found: C, 68.29; H, 11.47.

This alcohol gave a 3,5-dinitrobenzoate which after crystallization from methanol melted at 117.5–118°.

Anal. Calc'd for $C_{16}H_{20}N_2O_7$: C, 54.52; H, 5.72.
Found: C, 54.58; H, 5.65.

Direct synthesis of 4-methoxy-1-ethylcyclohexanol. Ethylmagnesium bromide from 8.2 cc.

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[2] The analyses reported in this paper are microanalyses carried out by Mr. L. G. Fauble and Miss Mary S. Kreger.

of ethyl bromide and 2.6 g. of magnesium in 50 cc. of dry ether was treated with 12.8 g. of 4-methoxycyclohexanone. On working up the reaction mixture in the usual way, 9.48 g. (60%) of product boiling at 114–122°/22 mm., n_D^{20} 1.4687 was obtained. From this fraction a 3,5-dinitrobenzoate was prepared. After crystallization from methanol, it melted at 117–118°.

Anal. Calc'd for $C_{16}H_{20}N_2O_7$: C, 54.52; H, 5.72.
Found: C, 54.75; H, 5.68.

Strangely enough mixtures of equal amounts of this ester and the one of the same melting point prepared from the reduction product of the acetylenic alcohol melted at 99–100°. The two products must therefore be stereoisomers.

Rearrangement of 4-methoxy-1-ethynyl-1-cyclohexanol. Five drops of the acetylenic alcohol was added to 3 cc. of concentrated sulfuric acid at room temperature. The mixture became brown and heat was evolved. After fifteen minutes the solution was poured into water and the organic material was extracted with benzene. The benzene was removed by distillation and the residue treated with 2,4-dinitrophenylhydrazine. The ketone derivative was obtained as dark red needles which melted at 163–164° after two crystallizations from ethyl alcohol.

Anal. Calc'd for $C_{15}H_{18}N_4O_5$: N, 16.76. Found: N, 16.39.

ACETYLENIC GLYCOLS

From 1-ethynyl-1-cyclohexanol and 4-methoxycyclohexanone. The glycol (VI) was prepared from 196 g. of 1-ethynyl-1-cyclohexanol, with the ethylmagnesium bromide from 84.75 g. of magnesium and 385 g. of ethyl bromide in 1.5 l. of dry ether, and 205 g. of 4-methoxycyclohexanone, by the general procedure previously described for related glycols (3).

The crude glycol obtained by working up the reaction mixture, and distilling the solvent and all volatile material up to 150° at 3 mm., weighed 288 g. (78%); n_D^{20} 1.5163. It did not crystallize on cooling but was purified by conversion to the two isomeric solid 3,5-dinitrobenzoic acid esters which were purified readily by crystallization.

A solution of 10.28 g. of the crude glycol in 42 cc. of pyridine was added to a supersaturated solution of 35 g. of freshly prepared 3,5-dinitrobenzoyl chloride in 56 cc. of pyridine at 20°. The mixture was warmed for twenty minutes on a water-bath so that the temperature reached 90° in that time, and was then held at 90–95° for another twenty minutes. After the reaction mixture had been cooled slightly, the pyridine was washed out with dilute hydrochloric acid, and the crude ester was taken up in benzene and washed with sodium bicarbonate solution. Evaporation of the benzene left a thick syrup which crystallized when its solution in ethyl acetate was poured into ethyl alcohol. The original crop of solid ester was 22.5 g. By repeated recrystallizations from ethyl alcohol and ethyl acetate this ester was separated into 14 g. of a product slightly soluble in ethyl alcohol, m.p. 164–166°, and 3.1 g. of a product very soluble in ethyl alcohol, m.p. 128–130°. Further purification gave these materials in higher purity, m.p. 166–167° and 131–132° respectively.

Anal. Calc'd for $C_{29}H_{28}N_4O_{13}$: C, 54.36; H, 4.41.
Compound m.p. 131–132°. Found: C, 54.65; H, 4.51.
Compound m.p. 166–167°. Found: C, 54.47; H, 4.48.

Hydrolysis of 30 g. of the higher-melting ester in dilute alcoholic sodium hydroxide solution gave 9.85 g. of a brownish syrupy glycol which was distilled at 110°/10^{-5} mm. to give a light yellow syrup, n_D^{20} 1.5178.

Anal. Calc'd for $C_{15}H_{24}O_3$: C, 71.55; H, 9.59.
Found: C, 70.43; H, 9.59.

Hydrolysis of 10 g. of the lower-melting ester in the same way gave 4.28 g. of glycol which was also distilled at 10^{-5} mm. pressure to give a light yellow syrupy product, n_D^{20} 1.5177.

Anal. Calc'd for $C_{15}H_{24}O_3$: C, 71.55; H, 9.59.
Found: C, 71.55; H, 9.74.

A sample of this glycol crystallized after standing for five months at ordinary temperatures, and then melted at 60–62°.

From 4-methoxy-1-ethynyl-1-cyclohexanol and cyclopentanone. The Grignard complex from 5.17 g. of 4-methoxy-1-ethynyl-1-cyclohexanol was treated with 5.95 g. of cyclopentanone to yield 3.84 g. of brownish syrupy glycol, n_D^{20} 1.5269. Distillation at 110°/10^{-5} mm. pressure gave a pale yellow syrup, n_D^{20} 1.5277.

Anal. Calc'd for $C_{14}H_{22}O_2$: C, 70.53; H, 9.31.
Found: C, 74.21; H, 9.46.

The high carbon content indicates that some aldol condensation products were present in the glycol.

From 4-methoxy-1-ethynyl-1-cyclohexanol and 2-methylcyclopentanone. In a similar manner 19.25 g. of 4-methoxy-1-ethynyl-1-cyclohexanol and 12.25 g. of 2-methylcyclopentanone gave 24 g. of viscous syrupy glycol; n_D^{20} 1.5007. This glycol was not analyzed but converted to the dienyne.

From 4-methoxy-1-ethynyl-1-cyclohexanol and 4-methoxycyclohexanone. The Grignard complex from 19.25 g. of 4-methoxy-1-ethynyl-1-cyclohexanol was treated with 16 g. of 4-methoxycyclohexanone to give 30 g. of syrupy glycol. Treatment of this glycol with 3,5-dinitrobenzoyl chloride gave a mixture of solid mono- and di-esters and thus removed all by-products except the glycol. By hydrolysis of the mixture of solid esters, a red syrupy glycol was obtained. This was distilled at 110°/10^{-5} mm. pressure to give a light yellow syrup, n_D^{20} 1.5160.

Anal. Calc'd for $C_{16}H_{28}O_4$: C, 68.03; H, 9.29.
Found: C, 67.80; H, 9.32.

DIENYNES

$\Delta^{1'}$-Cyclohexenyl-Δ^1-4-methoxycyclohexenylacetylene. The crude glycol (37.5 g.) (VI) was first converted to the dibenzoate by treatment with 31 cc. of benzoyl chloride in 110 cc. of pyridine. This ester proved to be oily but by washing it with sodium carbonate and water and then dissolving in hot alcohol and precipitating the oily ester with water several times, a product was obtained which on hydrolysis gave 20 g. of glycol which was free of ketonic impurities as shown by a test with 2,4-dinitrophenylhydrazine.

Dehydration of 17.7 g. of this glycol by heating with a solution of 60 cc. of concentrated sulfuric acid in 60 cc. of water in an atmosphere of nitrogen for four and a half hours gave 11 g. (65%) of impure dienyne, b.p. 130–145°/2 mm. Redistillation gave a middle fraction b.p. 135–135.5°/2 mm., n_D^{20} 1.5404. The analysis and reactions of this fraction showed that some hydration of the triple bond and cyclization had occurred during the dehydration of the glycol.

Anal. Calc'd for $C_{15}H_{22}O$: C, 83.24; H, 9.33.
Found: C, 80.08; H, 9.43.

The product after reduction over platinum oxide gave ketonic derivatives with 2,4-dinitrophenylhydrazine which proved to be identical with those of the cyclization products described later.

Δ^1-4-Methoxycyclohexenyl-$\Delta^{1'}$-cyclopentenylacetylene. The crude glycol prepared from 65 g. of cyclopentanone and 120 g. of 4-methoxy-1-ethynyl-1-cyclohexanol was dehydrated by heating with a solution of 90 cc. of concentrated sulfuric acid in 240 cc. of water. The yield of dienyne was 93.5 g. (60%), b.p. 174–175°/19 mm., n_D^{20} 1.5492; $d_4^{18.5}$1.0187.

Anal. Calc'd for $C_{14}H_{18}O$: C, 83.12; H, 8.97.
Found: C, 79.90; H, 8.91.

Δ^1-4-Methoxycyclohexenyl-$\Delta^{1'}$-2-methylcyclopentenylacetylene. Fifteen grams of the corresponding acetylene glycol was treated with a solution of 20 cc. of concentrated sulfuric acid in 60 cc. of water for four hours at the boiling point under nitrogen. The yield was 7.1 g. (55%) of dienyne, b.p. 137–139°/3 mm., n_D^{20} 1.5449.

Anal. Calc'd for $C_{15}H_{20}O$: C, 83.27; H, 9.33.
Found: C, 83.21; H, 9.44.

DEHYDRATION AND CYCLIZATION EXPERIMENTS ON THE ACETYLENE GLYCOL (VII)

Many experiments were carried out on the crude glycol which will not be described, except to say that very complex mixtures of products resulted.

A mixture of 1.1 g. of the glycol prepared by hydrolysis of the 131–132°-melting *bis*-3,5-dinitrobenzoate, 20 cc. of water, 20 cc. of glacial acetic acid, and 1 cc. of concentrated sulfuric acid was heated under a reflux condenser for three hours. The mixture was cooled, neutralized with aqueous alkali, and extracted with ether. The ether was distilled, the residue dissolved in 20 cc. of ethyl alcohol and treated with 0.02 g. of platinum oxide catalyst and hydrogen at 40 lbs. pressure for a half hour. The catalyst and alcohol were removed. The residue was divided into two parts and one-half was treated with 2,4-dinitrophenylhydrazine. A mixture of products resulted. Recrystallization from alcohol gave a product melting at 160–163°. This was separated by chromatographic adsorption on alumina into three distinct derivatives.

A column was prepared by making a slurry of technical alumina in a mixture of equal volumes of benzene and petroleum ether (b.p. 65–110°) and pouring it into a tube approximately 4 by 50 cm. The solid was allowed to settle for fifteen to twenty minutes while solvent was slowly run through the tube to keep the adsorbent covered.

A solution of 0.2 g. of the mixed 2,4-dinitrophenylhydrazones in benzene and petroleum ether was run slowly onto the alumina column and developed with benzene. Three definite bands appeared. From the band with the slowest speed of movement the compound was obtained by eluting with ethyl acetate. The amount isolated was 0.058 g. (29%) of red needles, m.p. 190–191°.

Anal. Calc'd for $C_{21}H_{26}N_4O_5$: C, 60.84; H, 6.33.
Found: C, 61.02; H, 6.41.

The next compound, with an intermediate speed of movement in the alumina column, was obtained by developing it out of the column. After removal of the solvent and crystallization from ethyl alcohol, the yield was 0.065 g. (32.5%) of orange-red prisms m.p. 173–174°.

Anal. Calc'd for $C_{21}H_{26}N_4O_5$: C, 60.84; H, 6.33.
Found: C, 60.75, 61.54; H, 5.87, 6.76.

The third compound, which moved most rapidly in the column, was also obtained by developing it out of the tube. After removal of solvent and crystallization from alcohol, 0.050 g. (25%) of red needles, m.p. 227–228° was obtained.

Anal. Calc'd for $C_{20}H_{24}N_4O_4$: C, 62.47; H, 6.30.
Found: C, 62.62; H, 6.18.

This product proved to be identical with the 2,4-dinitrophenylhydrazone of the cyclization product of dicyclohexenylacetylene (6).

The glycol from the higher-melting *bis*-3,5-dinitrobenzoate gave essentially the same results.

The second half of the reaction mixture containing the above three ketones was treated with a hot solution of 5.5 cc. of concentrated sulfuric acid in 15 cc. of water for twelve hours and then worked up as before; no trace of the 2,4-dinitrophenylhydrazone melting at 173–174° was found. The ratio of the 2,4-dinitrophenylhydrazone melting at 190–191° to that of 2,4-dinitrophenylhydrazone melting at 227–228° (the product which had lost methanol) was about 1 to 2 in this material. This indicates that the ketone which gives the high-melting 2,4-dinitrophenylhydrazone is related in structure to the methoxy derivative which gives the 2,4-dinitrophenylhydrazone which melts at 173–174°.

Dehydrogenation of the mixed cyclic ketones. A 31.9-gram sample of crude glycol (VI) was dehydrated with 6.3 g. of potassium acid sulfate by heating in an oil-bath at 170°, and a fraction of 16 g. of dienyne boiling at 135–140°/2 mm. was collected. This was refluxed for fourteen hours with 70 cc. of 85% formic acid. After this treatment, the acid was neutralized with aqueous alkali and the mixed cyclization products distilled. Nine grams of product boiling at 140–155°/2 mm., n_D^{20} 1.5300 was obtained. A sample was reduced as above, and a chromatographic separation of its 2,4-dinitrophenylhydrazones showed that

this mixture contained the same ketones in approximately the amounts of 29 parts of the compound m.p. 190–191° to 32.5 parts of the compound m.p. 173–174° to 25 parts of the compound m.p. 227–228°.

Three grams of this ketone mixture was dehydrogenated over palladium on charcoal (8) at 330° for ten hours. Approximately 1.5 g. of dehydrogenated product was obtained. This was dissolved in 5 cc. of high-boiling petroleum ether and separated in an adsorbing column prepared from a slurry of alumina in high-boiling petroleum ether. The column was further developed with the same solvent. By viewing the column under filtered ultraviolet light four fluorescent bands were observed. In order of decreasing speed of movement, these were called A, B, C, and D. The bands were cut apart.

Band A was removed from the adsorbent with ether. The yield was 0.473 g. It gave a picrate, m.p. 140–141°, which on mixing with authentic phenanthrene picrate melted at 142–144°. Decomposition of the picrate with sodium carbonate solution gave a product melting at 94–95° which did not depress the melting point of an authentic sample of phenanthrene.

Band B was removed from the adsorbent with ether, and evaporation of the solvent gave 0.553 g. of oil. This gave a picrate, m.p. 124–125° and is assumed to be identical with 3-methoxyphenanthrene picrate, m.p. 124.5° (12).

Band C, as above, gave 0.038 g. of yellow oil which crystallized on standing. There were yellow and white crystals present and these could not be separated readily by solvents. A white crystal was separated mechanically and found to melt at 179–182° and gave a green color with chloroform and aluminum chloride (13). Too little of this material was found for further identification. But, it is apparently impure anthracene, which behaved similarly in a chromatographic adsorption experiment.

Band D gave only 0.022 g. of a yellow-brown syrup which did not crystallize nor give crystalline derivatives. It does give the color reaction noted above. It seems reasonable to believe that this is a methoxyanthracene derivative.

Oxidation of 3-methoxy-1-cyclohexanol. To 200 cc. of 15% aqueous sulfuric acid was added 50 g. (0.365 mole) of 3-methoxy-1-cyclohexanol. The mixture was stirred vigorously while a solution of 42.5 g. (0.143 mole) of crystallized sodium dichromate in 55 cc. of water was dropped in at such a rate that the temperature did not rise above 70°. Addition of the oxidant required thirty minutes, after which the stirring was continued for one hour with external heating to maintain a temperature of 65–70°. The mixture was then cooled and thoroughly extracted with benzene. A continuous extraction apparatus was employed after the first (and major) portion of the extract was removed. The combined extracts were treated with solid sodium bicarbonate, filtered, and distilled. The crude ketone, 13 g., distilling below 74°/16 mm. was a colorless, mobile liquid. Redistillation of the ketone yielded a product of b.p. 63°/14 mm., n_D^{20} 1.4818; semicarbazone m.p. 160–161°.

Courtot and Pierron (14) gave for Δ^2-cyclohexenone, prepared by oxidation of Δ^2-cyclohexenyl-1-chloride, b.p. 63°/14 mm. semicarbazone m.p. 161°.

The 2,4-dinitrophenylhydrazone was obtained as red needles, from ethyl alcohol, m.p. 165–166°; from ethyl acetate, m.p. 167.5–168°.

Anal. Calc'd for $C_{12}H_{12}N_4O_4$: N, 20.29. Found: N, 20.20.

The yield of Δ^2-cyclohexenone was evidently 75% or more, based on alcohol used up, as the higher-boiling material yielded 26.6 g. of unchanged alcohol and 3 g. of unidentifiable material.

Attempted cyclization of Δ^1-cyclohexenylacetophenone. Δ^1-Cyclohexenylacetophenone was prepared by the procedure of Farrow and Kon (10). It gave a 2,4-dinitrophenylhydrazone which separated from ethyl alcohol in golden-orange plates melting at 163–164°.

Anal. Calc'd for $C_{20}H_{20}N_4O_4$: C, 63.13; H, 5.28; N, 15.08.
Found: C, 63.45; H, 5.56; N, 15.14, 15.36.

Treating the ketone with cold acetic acid containing sulfuric acid, refluxing it with hot acetic acid containing small amounts of sulfuric acid, or refluxing it with fairly concentrated aqueous sulfuric acid failed to give cyclization products. The ketone was recovered un-

changed from the first two treatments. It was hydrolyzed to acetophenone by the third treatment.

SUMMARY

1. 4-Methoxy-1-cyclohexanone has been converted to 4-methoxyl-1-ethynyl-1-cyclohexanol, and acetylenic glycols have been prepared from this and 4-methoxy-1-cyclohexanone, cyclopentanone and 2-methylcyclopentanone. The last two glycols have been converted to the corresponding dienynes.

2. 1-Ethynyl-1-cyclohexanol has been condensed with 4-methoxy-1-cyclohexanone to give two isomeric glycols, which have been separated as 3,5-dinitrobenzoates. They have been dehydrated and cyclized to give a complex mixture of ketones which has been converted to mixed 2,4-dinitrophenylhydrazones. Three definite products have been isolated from this mixture by chromatographic methods. Dehydrogenation of the mixed ketone fraction over palladium on charcoal has given phenanthrene, 3-methoxyphenanthrene, and two less definitely characterized products which seem to be anthracene and a methoxyanthracene.

3. The isolation of the last two products in the dehydrogenation reaction indicates some spiran derivatives in the cyclization mixtures.

4. Oxidation of 3-methoxy-1-cyclohexanol with chromic acid has given Δ^2-cyclohexenone.

5. Attempts to cyclize Δ^1-cyclohexenylacetophenone with sulfuric acid were not successful.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF STANFORD UNIVERSITY]

THE DIRECT INTRODUCTION OF THE AMINO AND SUBSTITUTED AMINO GROUPS INTO THE AROMATIC AND HETEROCYCLIC NUCLEUS. VI. THE ACTION OF ALKALI DIPHENYLAMIDES ON SOME AROMATIC NITRO COMPOUNDS

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Although the nitro group is meta directive towards the entry into the benzene ring of atoms or groups such as NO_2, SO_2OH, Br, and Cl, and slows down the rate of their substitution, it is ortho-para directive if the entering group is one derived from a basic anion, and the rate of substitution is accelerated. Wohl (1) thus found many years ago that *o*-nitrophenol and a trace of *p*-nitrophenol were formed by gently warming nitrobenzene with dry powdered potassium hydroxide. de Montmollin and de Montmollin (2) obtained N-*p*-nitrophenylcarbazole by warming potassium carbazole with nitrobenzene, while Bradley and Robinson (3) prepared N-*p*-nitrophenylpiperidine by the simultaneous action of sodium amide and piperidine on nitrobenzene. It is logical to assume that the sodium salt of piperidine is an intermediate. Discussion of other reactions in which the nitro group is ortho-para directive will necessarily have to be omitted for lack of space (4).

It was thought that reactions of this type could very advantageously be carried out in liquid ammonia, since one may use this solvent for the preparation of salts of substances (such as carbazole) which show no acidic properties in water. In the present paper is described a study of the action of alkali metal diphenylamides on nitrobenzene and on the nitrotoluenes.

Nitrobenzene reacts fairly readily with a solution of sodium diphenylamide or potassium diphenylamide in liquid ammonia at $-33°$ to give *p*-nitrotriphenylamine in yields up to 45%. At room temperatures the reaction is sufficiently rapid to cause apparent solidification of the contents of the Faraday tube in a few minutes. The optimum yields of nitrotriphenylamine are obtained at $-33°$ with the use of an excess of nitrobenzene, whose function possibly is to remove sodium and hydrogen formed in accordance with the equation,

$$(C_6H_5)_2NNa + C_6H_5NO_2 \rightarrow (C_6H_5)_2NC_6H_4NO_2\text{-}p + (NaH)$$
$$(NaH) + C_6H_5NO_2 \rightarrow \text{reduction products of an indefinite nature.}$$

It will be recalled that Wohl (1b) was unable to obtain any reduction products of nitrobenzene in the reaction between potassium hydroxide and nitrobenzine, though he states that azoxybenzene was obtained by Lepsius (5). Since the mechanism of the reaction is at present unknown (however, see ref. 3), it is unwise to assume the elimination of sodium hydride as such; supposedly

reactions of this type could only occur if some substance (O_2, $C_6H_5NO_2$, etc.) was available to react with the (Na+H).

p-Nitrotriphenylamine can be prepared in ether and also in benzene, though in the latter solvent the reaction is far less complete and the yields of product are correspondingly poor. A small quantity of a higher-melting and as yet unidentified compound is formed in the room-temperature reaction in liquid ammonia; this is the only isolable product when excess potassium diphenylamide reacts with nitrobenzene under the same conditions.

It has been previously noted (6) that barium ion markedly catalyzes the reaction between barium amide and quinoline to give 2-aminoquinoline. Such a catalytic effect has not been observed in the present work, since barium diphenylamide reacts with nitrobenzene in liquid ammonia at room temperatures in the same manner as does sodium diphenylamide, though possibly a little more slowly.

o-Nitrotoluene and sodium diphenylamide react to give, among other substances, 2,2′-dinitrobibenzyl, which is apparently formed by oxidation of a sodium salt in accordance with the equations,

$$NO_2C_6H_4CH_3 + (C_6H_5)_2NNa \rightarrow NO_2C_6H_4CH_2Na + (C_6H_5)_2NH$$
$$2\ NO_2C_6H_4CH_2Na + (O) \rightarrow NO_2C_6H_4CH_2CH_2C_6H_4NO_2 + (Na_2O)$$
$$(Na_2O) + NH_3 \rightarrow NaOH + NaNH_2 \quad (7)$$

Similarly, *p*-nitrotoluene may be converted in very poor yield to 4,4′-dinitrobibenzyl, a compound that Bradley and Robinson (3) have previously prepared by treating *p*-nitrotoluene with sodium amide and piperidine. The well known reactivity of the hydrogen atoms of the methyl groups of *o*- and *p*-nitrotoluene is of course responsible for the observations recorded above.

Sodium diphenylamide slowly attacks *m*-nitrotoluene in liquid ammonia at −33° to form a substance that has been tentatively identified as 2-methyl-4-nitrotriphenylamine. No definite compounds have been obtained by the action of sodium diphenylamide on *o*-nitroanisole or on 1-nitronaphthalene.

EXPERIMENTAL

The preparation of *p*-nitrotriphenylamine under various conditions is described in Table I; the maximum yield recorded was obtained in the following manner (expt. 2, Table I):

In a 500-cc. round-bottomed flask about half full of liquid ammonia was dissolved 0.1 g. of ferric nitrate hydrate; 2.3 g. (0.1 atom) of sodium was then added. In the course of a few minutes the blue color of the sodium solution was replaced by the grayish color of a sodium amide-iron mixture. One-tenth mole (16.9 g.) of diphenylamine was slowly introduced, and this was followed in about ten minutes by 0.2 mole (24.6 g.) of nitrobenzene added dropwise from a separatory funnel. After the ammonia had evaporated (4–5 hours) alcohol was slowly added to destroy reactive sodium compounds, and then alcohol and nitrobenzene removed by steam distillation. The steam non-volatile oil, which slowly solidified, was crystallized from alcohol; yield, 13.1 g. (45%); m.p., crude, 139–145°; m.p. when recrystallized from alcohol, 141.5–142.0° (uncorr). Slightly purer material seems to be obtained by carrying out the reaction in the presence of benzene (expt. 7, Table I). Too long a time of reacton in liquid ammonia should be avoided.

Anal. Calc'd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.85; N, 9.64.
Found: C, 74.66; H, 4.82; N, 9.58.

Mixed with *p*-nitrotriphenylamine (m.p. 141.0–142.0°) prepared by the method of Piccard and Larsen (8) it melted at 141–142° (two mixtures).

The action of potassium diphenylamide in liquid ammonia on nitrobenzene at room temperatures (expt. 5, Table I). In the legs of a three-legged ammonia reaction tube[1] were placed respectively 4.22 g. (25 millimoles) of diphenylamine, 0.98 g. (25 milliatoms) of potassium, a pinch of iron oxide as catalyst, and 7.4 g. (60 millimoles) of nitrobenzene. Potassium diphenylamide was prepared by adding the potassium amide to the diphenylamine; the nitrobenzene was added to this solution. Within a few minutes the formation of an orange-brown solid had practically immobilized the liquid. After standing for one

TABLE I

EFFECT OF CONDITIONS ON THE YIELD OF *p*-NITROTRIPHENYLAMINE

NO.	(Na OR K) DIPHENYLAMIDE MILLIMOLES	NITROBENZENE, MILLIMOLES	TEMP., °C.	TIME OF REACTION, HOURS	YIELD[a] %
1	Na, 200	100	−33	8	27.9 x
2	Na, 100	200	−33	8	45.1 x
3	K, 15	20	20	18	29.1 z
4	K, 10	10	20	72	32.3 y
5	K, 25	60	20	24	39.7 x
6	Na, 100	150	−78	12	none
7	Na, 100	150	−33	3	29.0 x[b]
8	Na, 100	150	−33	12	21.6 y[c]
9	Na, 112	270	30	45	4.4 y[d]
10	Na, 30	72	20	19	29.3 xy[e]
11	Ba, 10	25	20	28	31.3 y[f]

[a] Approx. beginning of melting: x, 139°; y, 133°; z, 128°.

[b] Benzene (40 cc.) added with the nitrobenzene. The first crop of product was purer than in other runs.

[c] Ether (65 cc.) dissolved in the ammonia.

[d] Sodium diphenylamide was prepared by warming a benzene solution (200 cc.) of diphenylamine with sodium amide (Bergstrom, *Org. Syntheses*, John Wiley and Sons, New York, **1940,** Vol. 20, p. 86).

[e] Sodium diphenylamide was prepared in liquid ammonia, and this solvent, after evaporation was then replaced by 250 cc. of anhydrous ether.

[f] Potassium amide (10 millimoles) was added in a three-legged reaction tube to a solution of diphenylamine (10 millimoles) and barium thiocyanate (6.42 millimoles). The nitrobenzene contained in the third leg was then added to the resulting solution.

day, the ammonia was evaporated, the precipitate hydrolyzed with alcohol, and then crystallized from the same solvent. The yield was 3.57 g. (39.7%) m.p. 140–141°. When the compound was crystallized several times from alcohol, the m.p. was raised to 141.4–142.6°. A reaction time of over a day, or steam distillation of the product to remove nitrobenzene seemed to decrease the purity of the nitrotriphenylamine. In one experiment there was found a small amount of orange-red material, insoluble in alcohol, and melting at 199–201°.

When this reaction was repeated with the use of an excess of sodium diphenylamide (20 millimoles, together with 15 millimoles of potassium nitrate and 10 millimoles of nitrobenzene) only this high-melting material was obtained; yield, 0.79 g., m.p. when recrystallized from benzene, 201–212.5°. It has not yet been identified.

[1] For method of carrying out reactions in liquid ammonia at room temperatures, see (9).

Under the same conditions, barium diphenylamide reacted with an excess of nitrobenzene to form 31.3% of *p*-nitrotriphenylamine, together with some higher-melting material. The barium diphenylamide was prepared by adding potassium amide to a mixture of barium thiocyanate and an equivalent of diphenylamide in liquid ammonia.

Potassium anilide and nitrobenzene. Potassium anilide (50 millimoles, prepared by treating potassium amide with an equivalent of aniline in liquid ammonia at −33°) was allowed to react for two hours (at −33°) with 50 millimoles of nitrobenzene. An excess (3 g.) of ammonium chloride was added to stop the reaction. The yield of material, m.p. 132.5–133.5° (after crystallization from ligroin) was 0.11 g. It was identified by a mixed melting point with authentic *p*-nitrodiphenylamine. Large amounts of tar were formed in the reaction.

The reaction of potassium anilide (from 1.19 g. of potassium and 2.90 cc. of aniline) with 1.0 cc. of nitrobenzene and 1.49 g. of potassium nitrate for one day at room temperatures yielded 0.26 g. of unidentified material, m.p. 157–158° after crystallizing from benzene.

Sodium diphenylamide and o*-nitrotoluene.* *o*-Nitrotoluene (10.3 g.) was allowed to react with the sodium diphenylamide prepared from 8.45 g. of diphenylamine and an equivalent (1.15 g.) of sodium (ferric nitrate catalyst) in about 250 cc. of liquid ammonia at −33°. The reaction product, colored brownish in solution, was hydrolyzed with benzene and alcohol after evaporation of the ammonia. The undissolved solid was further extracted with hot benzene. Concentration of the combined extracts gave several crops of pale orange-brown prisms, m.p. 118–120°; yield, after recrystallization from alcohol, 2.46 g., or 36.2%, m.p. 120–121°.

Anal. Calc'd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29.
Found: C, 62.20; H, 4.48; N, 10.35.

2,2′-Dinitrobibenzyl is variously reported in the literature as white or yellow prisms with a melting point of 121° or 122° (9, 10). After standing for two months the melting point of the compound prepared in liquid ammonia had changed to 113–119°, but nine crystallizations from a variety of solvents only raised this to 118–121°. It was shown by mixed melting points to be identical with Lapworth's 2,2′-dinitrobibenzyl (11).

p-*Nitrotoluene and sodium diphenylamide.* The reaction of potassium diphenylamide or sodium diphenylamide with a liquid ammonia solution of *p*-nitrotoluene at −33° or at 20° gave a quantity of reddish-brown solid (after hydrolysis of the reaction mixture) of indefinite melting point (180° to above 315°), and low solubility in organic solvents (pyridine is the best). From this a small amount of 4,4′-dinitrobibenzyl m.p. 177.5–179°, was isolated and identified by a mixed melting point determination with material prepared by the method of Green, Davies, and Horsfall (12). Other crystalline fractions of doubtful homogeneity were also separated.

m-*Nitrotoluene and sodium diphenylamide.* Sodium diphenylamide and an excess of nitrobenzene react in liquid ammonia at −33° to form a compound melting, after repeated crystallizations, at 129.5–130.5°. The melting point with admixture of the 2-methyl-4-nitrotriphenylamine of Joszt and Lesnianski (13) was the same, but specimens so far analyzed are low in nitrogen. Further details are reserved for a future publication.

SUMMARY

1. Sodium diphenylamide and potassium diphenylamide, dissolved in liquid ammonia or in ether, react with nitrobenzene to form *p*-nitrotriphenylamine in yields as high as 45%. A solution of barium diphenylamide in liquid ammonia reacts similarly with nitrobenzene.

2. *o*-Nitrotoluene and sodium diphenylamide react to form 2,2′-dinitrobibenzyl in fair yield. Under similar conditions, *p*-nitrotoluene is converted to

a complex mixture from which a small amount of 4,4′,dinitrobibenzyl has been isolated. It is suggested that salts of the nitrotoluenes are intermediates in the reactions.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

THE RELATIONSHIP BETWEEN OPTICAL ROTATORY POWER AND CONSTITUTION OF THE STEROLS. II.

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In the first paper of this series (1) the application of the modern theories of optical rotatory power to steroids was discussed, and a method of calculation of the rotatory power of these compounds was developed. It is now our purpose to report the results of further studies on this problem especially as applied to certain derivatives, acetates, benzoates, etc. The method which has been employed is in principle the same as previously reported, but differs from it in the one respect that the rotatory power of the derivative is calculated directly from the value of the rotatory power of the corresponding free sterol itself. The discussion which follows has been limited to a consideration of sterol acetates, benzoates, and *m*-dinitrobenzoates, although of course by the same principle all other types of derivatives can be calculated.

Let us consider the change in rotation which occurs when cholestanol is converted to cholestanol acetate. The molecular rotation[2] of cholestanol is +8920 (1), and of cholestanol acetate is +4820. The difference in molecular rotation between these two compounds is 4100. Therefore, it follows from what has been said in Part I of this series that every acetate of this type (*i.e.* C_3—OH/C_{10}—CH_3, cis; C_5—H/C_{10}—CH_3, trans) will have a molecular rotation which is approximately 4100° less than that for the corresponding saturated sterol. This may be tested using stigmastanol, γ-sitostanol and their respective acetates.

Stigmastanol	= +10190(1)	γ-sitostanol	= +7650(1)
Stigmastanol acetate	= +7050	γ-sitostanol acetate	= +4120
	+3140		+3530

Since an error in the measurement of $[\alpha]_D$ of only 2.5° results in an error of about 1000° in $[M]_D$, we see that in these two cases our expectations are fully realized. This difference, however, of 4100° should not be the same when the environment around C_3 has been changed, *i.e.*, C_5—H/C_{10}—CH_3, cis, or a double bond at $C_{5:6}$. It is also to be noted that this difference would not be expected between the rotatory power of *epi*-cholestanol and its acetate.

It is now but a simple matter to calculate the molecular rotation of the acetate of any saturated sterol of the cholestanol type by substracting 4100 from the molecular rotation of the free sterol. We have represented the value, −4100,

[1] DuPont Fellow, 1940–1941.

[2] $[M]_D = [\alpha]_D \times$ molecular weight (C = 12, H = 1, 0 = 16). All molecular rotations have been rounded off in the last figure. All rotations recorded are for chloroform solution.

by the symbol Ac_{3Nt} which signifies an acetate group at the C_3 position of a sterol of the cholestanol type (C_3—OH/C_{10}—CH_3, cis or normal, and C_5—H/C_{10}—CH_3, trans). A general equation for the calculation of any acetate of this type then will be

$$[M]_D = [M]_{D_{sterol}} + Ac_{3Nt}$$

Application of this equation to the calculation of the molecular rotation of stigmastanol acetate gives

$$[M]_{D_{calc'd}} = +10190 - 4100 = +6090.$$

This calculated value for the molecular rotation gives a specific rotation, $[\alpha]_D$ of +13.3° which compares favorably with the observed value of +15.4°.

The same procedure may be applied to all other types of derivatives of sterols which may be saturated or unsaturated. In Table I are recorded the values,

TABLE I

DERIVATION OF CONSTANTS

SUBSTANCES USED IN CALCULATING CONSTANTS, STEROL AND STEROL DERIV.	$[M]_{D_{Deriv.}} - [M]_{D_{Sterol}}$ VALUE OF CONSTANT	SYMBOL FOR CONSTANT*
Cholestanol (1) and acetate (8)	−4100	Ac_{3Nt}
Cholestanol (1) and benzoate (8b)	0	Bz_{3Nt}
Stigmastanol (1) and *m*-dinitrobenzoate (9)	−2260	$DNBz_{3Nt}$
Cholesterol (1) and acetate (10)	−3500	$Ac_{3ND_{5:6}}$
β-Sistosterol (1) and benzoate (11)	+7800	$Bz_{3ND_{5:6}}$
β-Sistosterol (1) and *m*-dinitrobenzoate (11)	+8630	$DNBz_{3ND_{5:6}}$
Ergosterol (1) and acetate (12)	+11820	$Ac_{3ND_{5:6,7:8}}$
7-Dehydrocholesterol (1) and benzoate (8a)	+17660	$Bz_{3ND_{5:6,7:8}}$

* Legend: *Ac* = acetate; *Bz* = benzoate; *DNBz* = *m*-dinitrobenzoate.

Subscripts: 3 = C_3 of sterol molecule; *N* = cis or normal configuration at C_3 to C_{10}—CH_3; *t* = trans configuration of C_5—H to C_{10}—CH_3; *D* = double bond (numerical subscripts with this letter indicate positions).

and symbols for the various constants used in our calculations of the rotations of sterol derivatives. A general equation for the calculation of any sterol derivative will be

$$[M]_{D_{derivative}} = [M]_{D_{sterol}} + \text{Constant (symbol and value, Table I).}$$

Since there is now available an observed and a calculated value for the rotation of a sterol (1), two calculated values for the rotation of a sterol derivative are possible. These values for several acetates, benzoates, and *m*-dinitrobenzoates are recorded in Table II. In general the agreement between the observed and calculated values is excellent. In Table III are listed a number of compounds which have a double bond either at the $C_{8:14}$ (α-position) or the $C_{14:15}$ (β-position), and whose optical rotations have been calculated by use of the following derivative constants, Ac_{3Nt}, Bz_{3Nt}, and $DNBz_{3Nt}$. These constants have been previously used for the calculation of the rotatory powers of derivatives of saturated

sterols (see Table II). The results in Table III indicate that α- and β-stenol derivatives may be calculated successfully with these constants by assuming a negligible interaction between these double bonds and the C_3 region of asymmetry.[3] It should be pointed out in this connection, however, that nothing definite can be said at this time in regard to δ-(double bond at $C_{8:9}$) and γ-(double bond at $C_{7:8}$) stenol derivatives, since the number of such compounds known is too few to warrant a trustworthy conclusion. But a survey of the values of their rotatory power does indicate that δ- and γ-double bonds do influence appreciably the C_3 region of asymmetry.

TABLE II

OBSERVED AND CALCULATED ROTATIONS

COMPOUND	OBS. $[\alpha]_D$ ($CHCl_3$)	CALC. $[\alpha]_D$ ($CHCl_3$) (USING OBS. $[M]_D$ (1) OF STEROL)	CALC. $[\alpha]_D$ ($CHCl_3$) (USING CALC'D $[M]_D$ (1) OF STEROL)
Stigmastanol acetate	+15.4 (13)	+13.3	+13.4
γ-Sitostanol acetate	+9.0 (14)	+7.8	+8.2
Ergostanol acetate	+6.8 (15) (av.)	+4.8	+7.5
α_1-Sitostanol acetate	+39.4 (2b)	+15.6	—
Ergostanol *m*-dinitrobenzoate	+13.5 (9) (av.)	+6.6	+8.6
Stigmasterol acetate	−55.6 (16)	−51.3	—
β-Sitosterol acetate	−41.0 (11)	−40.5	−38.2
Brassicasterol acetate	−65.0 (9)	−64.7	−60.3
22,23-Dihydrobrassicasterol acetate	−45.5 (17)	−49.8	−45.8
γ-Sitosterol acetate	−46.1 (14)	−46.2	−47.8
22,23-Dihydrobrassicasterol benzoate	−19.0 (17)	−21.3	−19.7
γ-Sitosterol benzoate	−19.6 (18)	−18.8	−16.4
Brassicasterol *m*-dinitrobenzoate	−28.0 (9)	−27.5	−26.0
22,23-Dihydrobrassicasterol *m*-dinitrobenzoate	−17.1 (17)	−16.6	−15.3
Stigmasterol *m*-dinitrobenzoate	−21.5 (17)	−18.4	−20.1
22,23-Dihydroergosterol acetate	−74.8 (19)	−71.7	−75.7
7-Dehydro-β-sitosterol acetate	−71.0 (20)	−79.3	−67.2
7-Dehydro-β-sitosterol benzoate	−54.0 (20)	−58.3	−47.8
Ergosterol benzoate	−68.0 (21) −71.5 (22) −88.3 (23)	−67.9	—

By the use of these data which have been recorded, it is of interest to examine the results of the application of this method of calculation of the optical rotation of sterols and their derivatives to recent experimental results which have appeared in the literature. In their studies on the sitosterol complex Wallis and his collaborators (2) reported the isolation in a pure state of two new compounds which they at that time named α_1- and α_2-sitosterol respectively. Hydrogenation of α_1-sitosterol gave a saturated compound which they named α_1-sitostanol.

[3] In Part I (1) of this series calculations of these derivatives were made on the assumption that the influence of the double bonds at $C_{8:14}$ and $C_{14:15}$ on the C_3 center of asymmetry was not negligible. This assumption appears to be unnecessary.

Its acetate was also prepared and a specific rotation in chloroform, +39.4°, was recorded. In Table II is listed the calculated value of this acetate, using the observed molecular rotation of the free alcohol itself. In this instance a complete disagreement between the observed and calculated values is to be noted. Therefore, we are forced to one of three conclusions: (a) the method of calculation does not hold; (b) the reported rotatory power either of the free saturated alcohol or of its acetate is wrong; (c) the proposed structure of the compound itself and consequently of its acetate is incorrect. We are inclined to believe that the last conclusion is the most probable. Indeed, in our opinion if the use of the constants in Table I leads to calculated values which are in appreciable disagreement with those reported for molecules of the supposedly

TABLE III

CALCULATED ROTATIONS OF UNSATURATED STEROLS

COMPOUND	OBS. $[\alpha]_D$ ($CHCl_3$)	CALC'D $[\alpha]_D$ ($CHCl_3$) (USING OBS. $[M]_D$ (1) OF STEROL)	CALC'D $[\alpha]_D$ ($CHCl_3$) (USING CALC'D $[M]_D$ (1) OF STEROL)
α-Cholestenol acetate	+9.5 (8a, 24) (av.)	+8.9	—
α-Ergostenol acetate	0 (25)	+3.8	+5.2
β-Ergostenol acetate	+3.0 (15a)		
	+15.9 (15b)	+9.0	+17.0
	+10.0 (15e)		
α-Stigmastenol acetate	+15.5 (26)	+13.7	+11.2
Zymosterol acetate	+34.0 (8b, 22, 24, 27) (av.)	+34.0	—
Ergostadiene, 8:14,22:23-ol-3 acetate?	−20.0 (15c, 28)	−27.3	−9.1
β-Cholestenol benzoate	+32.2 (8a) (av.)	+26.8	—
α-Cholestenol benzoate	+7.5 (8) (av.)	+16.1	—
β-Ergostenol benzoate	+18.3 (29)	+16.0	+23.1
α-Stigmastenol benzoate	+11.0 (26)	+20.0	+17.8
α-Spinasterol benzoate	+2.3 (30)	0	—
Zymosterol benzoate	+36.4 (22, 31)	+38.1	—
	+44.1 (24)		
α-Spinasterol *m*-dinitrobenzoate	−3.5 (30) ($CHCl_3$?)	−3.7	+1.8

steroid type, then it is questionable whether such compounds are truly steroid in nature. If this conclusion be accepted, then it follows that another tool besides selenium dehydrogenation is available for indicating the presence of a cyclopentanoperhydrophenanthrene nucleus.

Attention is now called to certain experimental results reported by Fernholz and his collaborators (3). In the course of their studies on the sterol, campesterol, they reported the preparation and rotations of several derivatives. A proposed structure for this sterol was also given. In Table IV are recorded both the calculated values for the specific rotations of these derivatives, assuming the structure proposed by them, and the observed rotatory powers. These values are in excellent agreement.

Similar calculations have been made for the two sponge sterols, clionasterol

$C_{29}H_{50}O$ (one double bond) and poriferasterol, $C_{29}H_{48}O$ (two double bonds), and their derivatives, recently described by Valentine and Bergmann (4). These values are recorded in Table V. Our calculations indicate that in both of these compounds one double bond is at the $C_{5:6}$ position and in poriferasterol it appears to us that the second double bond may not be placed at $C_{7:8}$, $C_{8:9}$, $C_{8:14}$, or $C_{14:15}$ positions.

Certain results of Mazur (5) are of special interest from this point of view. This investigator has recently reported the isolation of a sterol from a fresh

TABLE IV

ROTATIONS OF CAMPESTEROL DERIVATIVES

COMPOUND	OBS. $[\alpha]_D$ ($CHCl_3$)	CALC'D $[\alpha]_D$ ($CHCl_3$) (ASSUMING STRUCTURE OF FERNHOLZ AND CO-WORKERS)
Campesterol	−33.0	−33.1
Campesterol acetate	−35.5	−37.8
Campesterol benzoate	−10.2 (av.)	−10.7
Campesterol *m*-dinitrobenzoate	−7.2 (av.)	−7.7
Campestanol	+31.0	—
Campestanol acetate	+18.3	+18.9
Campestanol *m*-dinitrobenzoate	+22.	+16.8
i-Campesteryl methyl ether	+62.	+60.7

TABLE V

ROTATIONS OF SPONGE STEROLS

COMPOUND	OBS. $[\alpha]_D$ ($CHCl_3$)	CALC'D $[\alpha]_D$ ($CHCl_3$)
Poriferastanol	+24.7	—
Poriferastanone	+46.7	+41.5
Poriferastanol acetate	+16.3	+13.5
Poriferastanol *m*-dinitrobenzoate	+17.1	+13.1
Poriferasterol	−49.7	—
Poriferasterol acetate	−53.0	−52.8
Poriferasterol benzoate	−22.0	−24.6
Poriferasterol *m*-dinitrobenzoate	−22.1	−19.6
Clionasterol (assumed to be dihydroporiferasterol)	−37.	−33.8
Clionasterol acetate	−41.9	−41.3
Clionasterol benzoate	−16.8	−14.5
Clionasterol *m*-dinitrobenzoate	−14.0	−11.0

water sponge to which he assigned the structure 5,6-dihydrostigmasterol. From the physical constants reported he has stated that he is of the opinion that clionasterol is identical with 5,6-dihydrostigmasterol. It appears to us that this latter statement can be questioned. In Table VII we have recorded the melting points of Mazur's compound together with those of a compound prepared by Marker and Wittle (6) and described by them as 5,6-dihydrostigmasterol. The bad agreement in these values clearly indicates non-identity. In Table VIII are recorded the calculated values for the optical rotations of 5,6-dihydro-

stigmasterol and its various derivatives together with those values recorded for these compounds reported by Mazur. Unfortunately similar values for the compound described by Marker and Wittle were not recorded and hence are not available. In our opinion the disagreement between the observed and calculated values is so striking that it may be safely concluded that the compound described by Mazur is not 5,6-dihydrostigmasterol. On the contrary the

TABLE VI

PREDICTED ROTATIONS OF α-ANHYDRO-UZARIGENIN DERIVATIVES

α-ANHYDRO-UZARIGENIN DERIVATIVE	PREDICTED $[\alpha]_D$ ($CHCl_3$)
Acetate	−52.7
Benzoate	−21.0
m-Dinitrobenzoate	−16.1

TABLE VII

DIHYDROSTIGMASTEROL

COMPOUND	MARKER AND WITTLE, M.P., °C.	MAZUR, M.P., °C.
5,6-Dihydrostigmasterol	187	136.5–137
5,6-Dihydrostigmasterol acetate	122	137

TABLE VIII

ROTATIONS OF DIHYDROSTIGMASTEROL DERIVATIVES

COMPOUND	OBS. $[\alpha]_D$ $CHCl_3$	CALC'D $[\alpha]_D$ ($CHCl_3$)
5,6-Dihydrostigmasterol	−41.8	+10.6
5,6-Dihydrostigmasterol acetate	−47.6	+0.6
5,6-Dihydrostigmasterol benzoate	−17.1	+8.5
5,6-Dihydrostigmasterol *m*-dinitrobenzoate	−18.3	+3.5

TABLE IX

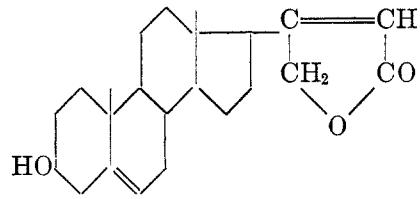
ROTATIONS OF MAZUR'S STEROL

MAZUR'S STEROL DERIVATIVE	OBS. $[\alpha]_D$ ($CHCl_3$)	CALC'D $[\alpha]_D$ ($CHCl_3$) (ASSUMING DOUBLE BOND AT $C_{5:6}$ POSITION)
Acetate	−47.6	−45.6
Benzoate	−17.1	−18.4
m-Dinitrobenzoate	−18.3	−14.3

values of the rotatory power reported for this sterol are in very good agreement with values obtained by our method of calculation if we assume that there be a double bond at the $C_{5:6}$ position (Table IX). It would therefore appear that the compound isolated by Mazur from a fresh water sponge is more probably identical with clionasterol, the properties of which have been described by Valentine and Bergmann.

Another illustration of the use of this method may be of interest.

In a recent paper by Ruzicka and co-workers (7) evidence is presented to establish that α-anhydro-uzarigenin and $\Delta^{5:6,20:22}$-3,21-dioxynorcholadienic acid lactone are identical.



$\Delta^{5:6,20:22}$-3,21-dioxynorcholadienic acid lactone

If α-anhydro-uzarigenin has one of its double bonds at the $C_{5:6}$ position, then one is able to calculate the optical rotation of several derivatives with the aid of the appropriate constants in Table I. Since these constants are characteristic for such a structure (β—OH at C_3, and double bond at $C_{5:6}$), agreement between the calculated and observed values would substantiate fairly conclusively the presence of such a structure. We have calculated the rotations of α-anhydro-uzarigenin acetate, benzoate, and *m*-dinitrobenzoate, assuming the above mentioned identity of α-anhydro-uzarigenin and $\Delta^{5:6,20:22}$-3,21-dioxynorcholadienic acid lactone, and the specific rotation, −49.1° ($CHCl_3$), reported by Ruzicka and co-workers (7) to be correct. The rotations of these derivatives of α-anhydro-uzarigenin are not known. Therefore our calculated values (Table VI) are to be considered as predictions.

SUMMARY

1. A simple method for the calculation of the optical rotatory power of steroid derivatives has been developed.

2. Application of this method as a structural tool has been made.

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[CONTRIBUTION NO. 66 FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF UTAH]

A SYSTEM CORRELATING MOLECULAR STRUCTURE OF ORGANIC COMPOUNDS WITH THEIR BOILING POINTS. VI. THE MONOHALOGEN DERIVATIVES OF THE VARIOUS HYDROCARBONS

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The boiling points of the monohalogen derivatives of the various hydrocarbons may be calculated using the boiling point equation developed previously (1) and the boiling point numbers (b.p.n.'s) for the halogen atoms given in Table I and the b.p.n.'s given for the hydrocarbons (2). The equation, while empirical, permits the correlation of the structure of organic molecules with their boiling points, and consequently it may be used to predict the boiling points of compounds from their structures.

The boiling points are calculated by substituting the molecular boiling point number (B.P.N.) into the boiling point equation

$$\text{B.P.} = 230.14\sqrt[3]{\text{B.P.N.}} - 543$$

or they may be obtained directly from the table of values published earlier (3). The B.P.N. for a molecule is obtained by summing up the atomic and structural b.p.n.'s for the various atoms and structural groupings in the molecule as described before (2).

The boiling point of a halogen derivative of a hydrocarbon depends not only upon the kind of halogen and the number of carbon and hydrogen atoms, but also upon the arrangement of the atoms. For example, primary, secondary, and tertiary halides have progressively lower boiling points. This property is accounted for by assigning appropriate b.p.n.'s to the halogens when occupying these characteristic positions. In like fashion, the boiling point is affected by the arrangement of the carbon atoms, and these structural differences should be considered in obtaining a B.P.N. for a substance, using the b.p.n.'s already assigned (2). The calculation of the boiling points of 1-, 2-, 3-, and 4-iodo-3-methylbutane demonstrates these points.

DERIVATIVE	B.P.N.	B.P. (CALC'D)	B.P. (OBS'D)
1-Iodo-3-methylbutane	3.2 + 8 + 3.05 + 13.0 = 27.25	149.6°	148.2°
2-Iodo-3-methylbutane	3.2 + 8 + 3.05 + 11.5 = 25.75	136.6°	138.0°
3-Iodo-3-methylbutane	3.2 + 8 + 3.05 + 10.2 = 24.45	125.1°	127.2°
4-Iodo-3-methylbutane	3.2 + 8 + 3.05 + 13.0 = 27.25	149.6°	148.0°

The attachment of a halogen to an unsaturated carbon atom always lowers the boiling point. This behavior is characteristic and has been taken care of

by assigning characteristic b.p.n.'s to the halogens when attached to doubly and triply bonded carbon atoms (Table I). This effect is shown by comparing

TABLE I

HALOGEN B.P.N.'S

TYPE	F	Cl	Br	I
1. RCH_2—X	3.3	7.5	9.7	13.0
2. R_2CH—X	2.7	6.5	8.7	11.5
3. R_3C—X	?	6.0	8.0	10.2
4. C=CHX	?	7.0	9.0	11.8
5. C=CXR	?	6.0	8.0	10.5
6. C≡CX	?	5.0	7.0	9.8
7. Alicyclic Halides: Use b.p.n.'s given above depending on the substitution. Where the halogen is attached to an unsubstituted ring (saturated or unsaturated) or to the opposite end of an unsubstituted chain (saturated or unsaturated) from an unsubstituted ring add, for cyclopropyl, 0.5; for all larger rings, 1.5.				
8. Aromatic Halides:				
Benzene	1.5	6.5	9.2	13.1
Naphthalene	0.9	7.4	10.3	15.0

Where the halogen is attached to the opposite end of an unsubstituted chain (saturated or unsaturated) from an aromatic ring, add 1.5.

TABLE II

BOILING POINTS OF THE CIS-TRANS ISOMERS

		B.P., °C.	HIGHER-BOILING ISOMER
1-Chloro-1-butene	cis	63.5	trans
	trans	68.1	
2-Chloro-2-butene	cis	66.8	cis
	trans	62.6	
1-Bromo-1-propene	cis	57.8	trans
	trans	63.3	
1-Bromo-1-butene	cis	86.2	trans
	trans	94.7	
2-Bromo-2-butene	cis	84.0	trans
	trans	92.5	
1-Iodo-1-butene	cis	168.0	cis
	trans	127.5	

2-chloro- and 3-chloro-1-butene, so chosen to avoid the complications of cis-trans isomerism.

DERIVATIVE	B.P.N.	B.P. (CALC'D)	B.P. (OBS'D)
2-Chloro-1-butene	3.2 + 7 + 1.5 + 6.0 = 17.7	56.8°	58.5°
3-Chloro-1-butene	3.2 + 7 + 1.5 + 6.5 = 18.2	62.3°	64.0°

Six pairs of cis and trans haloölefins and their boiling points at atmospheric pressure were found in the literature (Table II). In four cases, the trans isomer was reported as having a higher boiling point than the cis. This does not agree with the data obtained for those isomers whose structures have been determined with greater certainty, such as the esters of maleic and fumaric acids, the *s*-dihaloëthylenes, etc., in which the cis isomer has the higher boiling point. For the majority of the haloölefins reported in the literature, which theoretically should exist in the two geometrical forms, no attempt was made to isolate the isomers. Consequently, new and accurate data are needed badly in this field. It appears likely that in certain cases the cis isomer is higher-boiling and in others, the trans. Until more reliable data have been obtained, a b.p.n. for this type of isomerism will not be assigned.

The B.P.N.'s for the alicyclic halides are obtained by using the same b.p.n.'s for the halogens as for the analogous open chain derivatives. As an example, 1-chloro-1-methylcyclohexane may be used.

1-Chloro-1-methylcyclohexane

Cyclohexane, less 2 hydrogen atoms, 6 × 0.8 + 10.0 + 2.7	17.5
Methyl group attached to ring, 0.8 + 3.0	3.8
Chlorine, tertiary	6.0
B.P.N., calculated	27.3
B.P., calculated	150.0°
B.P., observed	149.5°

For those unsubstituted alicyclic halides which fit the formula, $R(CH_2)_nX$, where R is a further unsubstituted alicyclic ring and n may be any integer including zero, unusually high boiling points are always observed. A similar observation was made for the similarly constituted dicyclo derivatives, $R(CH_2)_nR$ (4). This structure seems to affect the boiling point in quite a uniform manner. Also, the effect upon the boiling point is quite marked, as the following derivative, which is isomeric with the 1-chloro-1-methyl-cyclohexane given above, shows.

Chloromethylcyclohexane

Cyclohexane, less one hydrogen atom, 6 × 0.8 + 11 + 2.7	18.5
Methylene group, 0.8 + 2.0	2.8
Chlorine, primary	7.5
B.p.n. for $R(CH_2)_n$ X structure	1.5
B.P.N., calculated	30.3
B.P., calculated	174.5°
B.P., observed	174.0°

Characteristic b.p.n.'s are used for the halogens attached to the benzene and naphthalene rings (Table I). These b.p.n.'s give satisfactory results regardless of whether alkyl groups are attached to the aromatic ring or not and should be used for both types of compounds. This behavior is different from that observed for the corresponding alicyclic derivatives and possibly is accounted for in the unique effect of the aromatic rings on the boiling point. However, the exaltation of the boiling point is observed for all other halogen derivatives which fit the formula, $R(CH_2)_nX$, where R is an unsubstituted aryl radical and n is any integer other than zero. The following examples demonstrate these points.

DERIVATIVE	B.P.N.	B.P. (CALC'D)	B.P. (OBS'D)
1-Bromo-2-ethylbenzene	18 + 6.6 + 9.2 = 33.8	201.1°	203.0°
(2-Bromoethyl)benzene	19 + 5.6 + 9.8 + 1.5 = 35.9	216.2°	217.5°

The boiling points of five halogen derivatives of biphenyl have been recorded in the literature. Two of these which are halogenated in the 4 position have high boiling points in a manner similar to that observed for the $R(CH_2)_nX$ compounds. Consequently for the 4-halobiphenyl derivatives the usual b.p.n. of 1.5 should be used as follows for 4-chlorobiphenyl:

B.P.N.	B.P. (CALC'D)	B.P. (OBS'D)
19 + 18 + 2.5 + 6.5 + 1.5 = 47.5	290.4°	291.2°

The atmospheric boiling points of a total of 437 monohalides were obtained from the literature and compared with the calculated values. None of the observed boiling points were discarded for any reason. For the total, the aver-

TABLE III

BOILING POINT DEVIATIONS

TYPE OF HALIDE	NO. OF HALIDES	AV. DEVIATION FROM THE CALC'D, IRRESPECTIVE OF SIGN, °C.	DEVIATION OF THE AV., CONSIDERING SIGN, °C.	% OF B.P.'S WITHIN ±10°C. OF CALC'D
Fluorides	26	4.08	+1.71	88.4
Chlorides	182	4.09	+0.80	90.6
Bromides	157	5.63	+1.63	84.1
Iodides	72	5.50	−0.43	86.1
Total	437	4.20	+0.91	87.4

age deviation was 4.18° disregarding the sign and +0.91 taking the sign into consideration (Table III). As might be expected, the best agreement was obtained with the fluorides and chlorides. However, there are many halides of all kinds for which the recorded boiling points are obviously out of line. These

TABLE IV

HALIDES WHOSE OBSERVED BOILING POINTS DEVIATE MORE THAN ±10°C. FROM THE CALCULATED

TYPE OF HALIDE	B.P. (CALC'D), °C.	B.P. (OBS'D), °C.	DEVIATION, °C.
Fluoride			
1. Fluoromethane	−100.6	−78.0	+22.6
2. Fluoroethane	−48.8	−32.0	+16.8
3. 3-Fluoro-1-propene	−13.2	+1.0	+14.2
Chloride			
1. 2-Chloro-2-methylheptane	161.2	145.0[dec]	−16.2
2. 1-Chloro-2-methyl-2-butene	102.4	117.5	+15.1
3. 3-Chloro-2-methylenepentane	110.6	122.0	+11.4
4. 1-Chloro-2-hexene	131.8	121.0	−10.8
5. 1-Chloro-2-butyne	93.0	82.5	−10.5
6. (1-Chloro-1-methylethyl)cyclopropane	113.0	132.5	+19.5
7. (1-Chloro-1-methylpropyl)cyclopropane	138.4	151.5	+13.1
8. 3-Chloromethyl-1,1,2-trimethylcyclopentane	187.3	175.0	−12.3
9. 2-Chloro-1-methyl-4-(1-methylethyl)cyclohexane	207.6	182.5	−25.1
10. 1-Chloro-1-phenylethane	180.7	194.0	+13.3
11. 1-Chloromethyl-4-methylbenzene	188.4	201.0	+12.6
12. Chlorohexamethylbenzene	300.9	285.0	−15.9
13. 1-Chloro-1-phenylethene	180.9	199.0	+18.1
14. 1-Chloro-2-phenyl-2-methylethene	203.7	214.0	+10.3
15. 1-Chloro-2-(4-methylphenyl)ethene	201.9	223.0	+22.1
16. 3-Chloroacenaphthene	296.3	309.0	+12.7
17. 5-Chloro-1,2,3,4-tetrahydronaphthalene	236.8	250.0	+13.2
Bromide			
1. 2-Bromo-3,3-dimethyl-1-butene	115.3	139.5	+24.2
2. 1-Bromo-3-methyl-2-butene	123.3	99.0	+24.3
3. 2-Bromo-3-methyl-2-butene	107.2	119.0	+11.8
4. 1-Bromo-2-pentene	135.3	123.5	−11.8
5. 1-Bromo-3-ethyl-2-pentene	176.1	153.0	−23.1
6. 1-Bromo-1-hexene	150.0	139.0	−11.0
7. 1-Bromo-1-heptene	172.9	162.0	−10.9
8. 1-Bromo-1-octene	194.4	179.0	−15.4
9. 2-Bromo-1,5-hexenyne	136.2	148.0	+11.8
10. 1-Bromo-2-propyne	76.4	89.0	+12.6
11. 1-Bromo-1-methylcyclopropane	84.8	99.5	+14.7
12. (1-Bromo-1-methylethyl)cyclopropane	131.3	152.5	+21.2
13. 1-Bromo-1-(1-methylethyl)cyclopropane	131.3	174.0	+42.7
14. (1-Bromo-1-methylpropyl)cyclopropane	155.4	167.5	+12.1
15. (1-Bromo-1-ethylpropyl)cyclopropane	175.3	186.5	+11.2
16. 1-Bromo-1-cyclohexene	154.9	165.0	+10.1
17. 2-Bromo-1-methylcyclohexane	172.1	158.0	−14.1
18. 1-Methyl-2-(bromomethyl)benzene	205.5	216.5	+11.0
19. 1-Methyl-4-(bromomethyl)benzene	205.5	219.0	+13.5
20. 4-Bromo-3-isopropyl-1-methylbenzene	235.2	224.0	−11.2
21. 6-Bromo-3-isopropyl-1-methylbenzene	235.2	225.0	−10.2
22. 1-Bromo-1-(3-methylphenyl)ethene	216.2	242.0	+25.8
23. 1-(4-Bromophenyl)-1-propene	227.3	240.5	+13.2
24. 6-Bromo-1,2,3,4-tetrahydronaphthalene	254.5	238.5	−16.0
25. 3-Bromoacenaphthene	306.6	335.0	+28.4

TABLE IV—*Concluded*

TYPE OF HALIDE	B.P. (CALC'D), °C.	B.P. (OBS'D), °C.	DEVIATION, °C.
Iodide			
1. 1-Iodo-2,2-dimethylpropane	139.7	128.0	−11.7
2. 3-Iodo-2-methylpentane	160.4	144.5	−15.9
3. 3-Iodo-2-methylheptane	203.7	170.0	−33.7
4. 2-Iodo-2-methylpentane	149.6	139.5	−10.1
5. *cis*-1-Iodo-1-butene	118.1	168.0	+49.9
6. 1-Iodo-1-propyne	77.5	98.0	+20.5
7. 4-Iodo-1,2-dimethylbenzene	235.5	225.0	−10.5
8. 4-Iodo-1-methyl-3-ethylbenzene	247.4	223.5	−23.9
9. 3-Iodo-1,2,4,5-tetramethylbenzene	277.4	287.5	+10.1
10. 6-Iodo-1-methyl-3-ter.-butylbenzene	276.8	264.5	−12.3

will be found among the compounds compiled in Table IV in which all of the compounds whose observed boiling points deviate from the calculated by more than ±10° have been listed. For example, the first of the chlorides in Table IV, 2-chloro-2-methylheptane, has been found to boil "with decomposition" at 145°, 16.2° lower than the calculated. This seems quite unlikely in view of the boiling point of 132° given for the homolog, 2-chloro-2-methylhexane, which is only 13° less than the boiling point given for the heptane. It is possible, of course, that the low boiling point of the heptane derivative is due to extensive decomposition. If this is the case, the value of 145° should not be considered as the true boiling point. The second chloride in Table IV has a recorded boiling point about 15° higher than the calculated. This, also, seems unlikely since the similarly constituted 1-chloro-2-methylenebutane has been found to boil at 102°, only 0.8° less than the calculated.

Many of the boiling points of the compounds appearing in Table IV may be compared with the boiling points of similar compounds and it appears that many of these boiling points have been determined incorrectly. Consequently, we intend redetermining the boiling points of the compounds appearing in Table IV. It is quite probable that certain ones of these have been determined correctly and for them new b.p.n.'s will be required, but for the others new data should be obtained.

SUMMARY

The observed boiling points of 437 organohalides obtained from the literature have been compared with the calculated boiling points. The average deviation of the total, regardless of the accuracy of the experimental value, was 4.18°. Those halides deviating from the calculated by more than ±10° have been listed and will be reinvestigated.

SALT LAKE CITY, UTAH

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

POLYCONDENSATION OF CERTAIN PEPTIDE ESTERS. I. POLYGLYCINE ESTERS[1]

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The importance of chemical synthesis of protein models, polypeptides of sufficiently high molecular weights, both for enzymatic studies and for investigation of chemical and physico-chemical properties can not be overemphasized. Since the time of the initial preparation of glycylglycine by Fischer and Fourneau (1) only two methods have been developed for the general synthesis of polypeptides, namely, the halogen acyl method of Fischer (2) and the carbobenzoxy method of Bergmann (3). Essentially, Fischer's method consists of utilizing the α-halogen acids; treatment with phosphorus pentachloride yields the α-halogen acyl chloride, which then can be coupled with the free amino group of any amino acid or peptide. Subsequent treatment with excess ammonia under controlled (4) conditions yields the corresponding free peptide. Higher peptides can be prepared by coupling the halide of another molecule of α-halogen acid to this product, or, according to Fischer, by treating the α-halogen acyl *peptide* with phosphorus pentachloride and coupling the resulting chloride with either another amino acid or a peptide. The classic example of this method is his synthesis of an octadecapeptide (5). In the carbobenzoxy method of Bergmann, the amino acid is used for coupling after protection of its amino group by combination with carbobenzoxy chloride. This is followed by treatment with phosphorus pentachloride to form the carbobenzoxy amino acid chloride, which is then coupled with amino acid esters or peptide esters in neutral solvent. Hydrogenation removes the carbobenzoxy group quantitatively with the formation of carbon dioxide and toluene to yield the free peptide.

Use of this procedure implied the addition to a peptide of only a single residue at a time, with yields normally lower than 50% because of the formation of the ester hydrochlorides as a result of liberation of hydrogen chloride from the coupling reaction. We attempted to avoid such laborious procedure by trying to prepare the acid chloride of carbobenzoxyglycylglycine as a preliminary to preparing the chlorides of other carbobenzoxy *peptides*. Our conditions were: slight excess of phosphorus pentachloride in ether at $-15°$; same at room temperature; excess thionyl chloride at 45–50°; mixing with slight excess of phosphorus pentachloride in the solid state; mixing with large excess in the solid state. In all cases much carbobenzoxyglycylglycine was recovered. Our products, consisting of a series of yellow oils when phosphorus pentachloride was used, and a reddish brown amorphous solid in the case of thionyl chloride, gave off fumes strongly, and attempts to couple them with leucine to obtain well-defined products failed. Inasmuch as the acid chlorides of several carbobenzoxy *amino acids* are pure crystalline compounds (3, 6), we attributed our

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failure to the presence of the reactive peptide link, which in all probability is attacked by the halogenating agents.

In view of this result, attention was turned to Fischer's halogenated peptide chlorides, all of which contain one or more peptide links. An examination of his procedures and analytical data strongly suggested that his chlorides were quite impure. In a series of experiments carried out in this Laboratory[3] on the simple compound chloroacetylglycylglycine, it has thus far proved impossible to obtain its acyl halide in a state even approximating purity; the reactivity of the peptide link was apparently indicated by the fact that phosphorus was present in the product. Since a survey of the literature revealed little mention of the use of this method of polypeptide synthesis since the time of Fischer, in all probability other observers have encountered the same difficulty. The 18-peptide (and others prepared in a similar manner) thrice involved the use of amorphous peptides and amorphous halides of questionable purity in the same series of reactions to yield an amorphous product, and likewise thrice involved the use of ammonia in a reaction known to yield large amounts of by-products. We are of the opinion that such "polypeptides" are so impure that they are worthless as scientific preparations or protein models, and only by the tedious method of adding one residue at a time to the amino end of a peptide can reasonably pure products be obtained. Hence, none of the well-established methods of synthesis, which have worked so well in the preparation of a wide variety of simple peptides, is adaptable to the production of protein-like substances.

After our failure to obtain pure polypeptides by these methods we turned our attention to the condensation reactions of the amino acids and peptides. These, under certain experimental conditions, lead to interesting products, some of which have been the subject of investigation early in the history of organic chemistry. An important method for the preparation of such products consists in heating the esters of the simple peptides and the amino acids under various conditions.[4] We have classified these reactions in four distinct types:

1. Intramolecular removal of one molecule of alcohol from one molecule of an amino acid ester gives a diradical, —NH·CH(R)·CO—, two of which combine in inverted position to yield the corresponding diketopiperazine. (We do not rule out the possibility of a dipeptide ester acting as an intermediate; our classification is for the purpose of system, not an expression of true reaction mechanism.) The heating of the amino acid ester is carried out most conveniently in a sealed tube (9, 10, 11).

2. The ester of a dipeptide loses one molecule of alcohol intramolecularly and the corresponding diketopiperazine (1, 12, 13) is formed by ring closure of the resulting —NH·CH(R)·CO·NH·CH(R)·CO— diradical. This cyclization proceeds extremely rapidly in the case of glycylglycine ester, the dry crystals of which change into diketopiperazine even at room temperature in ten days.

3. Conversion of a tripeptide ester into a hexapeptide ester. The condensation is best illustrated by intermolecular elimination of one molecule of alcohol from two molecules of the tripeptide ester and union of the resulting

[3] Unpublished data of E. Pacsu and Albert F. Chadwick.

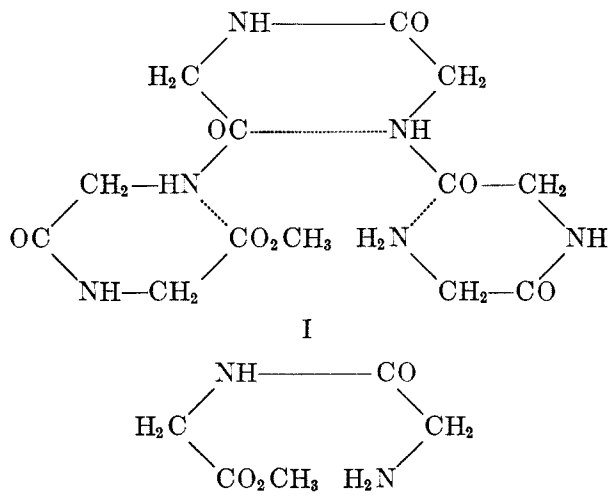
[4] Preliminary communications on this subject have been published by E. Pacsu (7, 8).

$H_2N \cdot CH(R) \cdot CO \cdot NH \cdot CH(R) \cdot CO \cdot NH \cdot CH(R) \cdot CO$— and —$NH \cdot CH(R) \cdot CO \cdot NH \cdot CH(R) \cdot CO \cdot NH \cdot CH(R) \cdot COOR'$ radicals. Until we undertook the present work, this reaction had been observed only with diglycylglycine methyl ester and *l*-alanylglycylglycine methyl ester (14), which give the corresponding hexapeptide esters and a small quantity of higher condensation products.

4. Tetrapeptide esters do not undergo any condensation at all (14).

In the course of the present work it was discovered that G_3M[5] in water solution suffers partial hydrolysis into methyl alcohol and diglycylglycine, and that simultaneously a considerable portion of G_3M changes into G_6M and a small quantity of other condensation products. It was also found that G_3M is unstable in non-aqueous solvents, since it condenses quite rapidly at room temperature, particularly in methanol solution, into the pure G_6M, which then precipitates out. This spontaneous change undoubtedly represents the most convenient method for the preparation of the latter compound in good yield and in excellent purity. Application to the esters of other tripeptides, however, does not give as good results, as will be pointed out in a second paper.

The initial purpose of the present work was to ascertain if a hexapeptide ester, when heated, would suffer any condensation and, if it did, to which type the reaction belonged. It is obvious that if, *e.g.*, the G_6M molecules were folded hexagonally on account of preformed hydrogen or "cyclol" bonds (I), then the ester could lose one molecule of methyl alcohol *intra*molecularly as readily as the G_2M (II) to give rise to the simplest model of "cyclol-6" postulated by the Wrinch theory (15, 16). On the other hand, the G_6M might not suffer any condensation at all, or it might undergo the reaction characteristic for the tripeptide esters. No prediction could be made as regards these possibilities, since the actual course of the reaction in all probability depends on the shape of the ester molecules, a property about which we have no information at present.



I

II

[5] To save space the tri-, hexa-, etc. peptide methyl esters of glycine will be designated by the symbols G_3M, G_6M, etc.

For the identification of the condensation products of a polypeptide ester with high molecular weight the analytical data for the elements are practically useless in that the calculated values do not differ sufficiently to allow a sharp distinction between the possible reaction products. For example, G_6M has C, 41.7, H, 5.9, and N, 22.5; the hypothetical "cyclohexapeptide" of glycine, $(NH \cdot CH_2 \cdot CO)_6$, contains C, 42.1, H, 5.3, and N, 24.6. For any possible condensation products the corresponding values would fall between these two sets of figures and, hence, well within the limits of error in the analysis. The present work was rendered possible by recognition that quantitative methoxyl determination was the only practical method of analysis.[6] From accurate methoxyl values one could draw inferences as to the course of the reaction, since *e.g.* G_6M contains 8.28% methoxyl, whereas a "cyclol-6" should not contain any.

TABLE I

CONDENSATION OF PENTAGLYCYLGLYCINE METHYL ESTER AT DIFFERENT TEMPERATURES

T = 102° ±1°		T = 112° ±1°		T = 130° ±1°	
Time, hrs.	Methoxyl, %	Time, hrs.	Methoxyl, %	Time, hrs.	Methoxyl, %
0	8.28	0	8.28	0.5	4.91
1	7.40	1	6.12	1.5	3.25
2	6.90	2	5.40	4.5	2.15
4	6.28	4	4.16	8	1.50
8	5.24	7	3.35	24	1.01
13	4.39	20	2.02	144	0.58
24	3.45	44	1.61	364	0.54
48	2.28	68	1.26		
72	1.80	140	0.97		
96	1.64				
168	1.25				
336	0.94				

Experiments were carried out by heating the pure G_6M below its melting point in a porcelain or platinum boat contained in a constant temperature oven; samples of the solid were withdrawn for methoxyl determination (17, 18) at known intervals of time. The results of the analyses are shown in Table I for samples heated at 102°, 112°, and 130°, respectively. In similar experiments G_8M (MeO, 15.26%) was heated at 80°, 102°, and 105°, respectively; the analytical data are given in Table II.

In order to obtain direct evidence as to the nature of the condensation products, samples of G_3M were heated at 100°±1° for different lengths of time and then analyzed for the products. The results are shown in Table IV. The analysis was carried out as follows. By repeated treatment of the samples,

[6] Amino nitrogen determinations were rendered extremely difficult because the insolubility of the products in most cases prevented introduction of samples into the reaction chamber of the Van Slyke apparatus.

contained in crucibles with sintered glass bottoms, with hot methyl alcohol the unchanged G_3M was removed from the reaction mixtures and its weight determined by the loss in weight of the samples. The washed-out G_3M was recovered in crystalline state and identified by methoxyl analysis. By subsequent and repeated treatment of the methanol-insoluble residues with warm (80°) water, the weight of the water-soluble condensation product was obtained by the loss in weight of the samples. The material recovered from the cooled filtrate was identified as pure G_6M, the result being confirmed by methoxyl analysis. From the methoxyl content of the water-insoluble residues we concluded that,

TABLE II

CONDENSATION OF DIGLYCYLGLYCINE METHYL ESTER AT DIFFERENT TEMPERATURES

T = 80° ±1°		T = 102° ±1°		T = 105° ±1°	
Time, hrs.	Methoxyl, %	Time, hrs.	Methoxyl, %	Time, hrs.	Methoxyl, %
0	15.26	0.17	15.50	0	14.40
1	15.01	0.33	14.10	72	1.93
2	14.86	0.50	13.59	117	1.20
3	14.66	1	13.26	360[a]	0.83
4	14.48	2	11.33	492	0.64
5	14.37	4	8.97	564	0.56
8	14.24	6	7.20		
24	13.46	11	5.67		
29.5	13.06	23	4.80		
50	12.63	47	3.62		
74	12.09	96	2.42		
98	11.67	192	1.56		
120	11.20	264	1.40		
240	8.89	432	1.14		
480	5.80				
720	4.40				
960	3.55				
1440	2.73				
2474	2.30				
2908	2.16				

[a] After 360 hours the temperature was raised to 112° ±1°.

after one hour of heating, the G_3M gave rise to almost pure $G_{12}M$ (found: MeO, 4.39; calc'd: MeO, 4.33) as the highest condensation product. This substance was first obtained in a similar manner by Fischer (14), who concluded from its carbon, hydrogen, and nitrogen content that it could be the $G_{12}M$. The gradual decrease in the methoxyl content of the insoluble residues indicated that the $G_{12}M$ underwent further condensation during the eight and twenty-four hours the respective samples of G_3M had been heated. Confirmation that the $G_{12}M$ undergoes further condensation was received from an experiment in which $G_{12}M$ prepared by the above method was heated at 110°±1°, samples being withdrawn and analyzed for methoxyl as usual. These data are included in

Table III. Had "cyclol-6" been formed in the condensation reaction of G_3M as well as G_6M, it could have been represented only by the insoluble residues, and the fact that the latter substances contained methoxyl ruled out this possibility. In addition, the insoluble residues could not have consisted of a mix-

TABLE III

CONDENSATION OF HENDECAGLYCYLGLYCINE METHYL ESTER AT 110° ±1°

TIME, HRS.	METHOXYL, %
0	4.39
3	3.47
6.4	3.07
12	2.69
24	2.39
48	2.07
96	1.89
192	1.61
226[a]	
394	0.77
1052	0.54

[a] Temp. raised to 130° ±1°; subsequent values at this temp.

TABLE IV

ANALYSES[a] OF SAMPLES OF DIGLYCYLGLYCINE METHYL ESTER HEATED AT 100° ±1° FOR DIFFERENT LENGTHS OF TIME

TIME, MIN.	LOSS METHYL ALCOHOL, %		G_3M, %	G_6M, %	$G_{12}M$ AND HIGHER, %	METHOXYL OF $G_{12}M$ AND HIGHER, %
	obs'd	calc'd				
0			98.94	1.06		
10	0.87		91.96	7.26	0.78	
30	1.73	1.52	81.05	15.72	3.22	
45	2.26	2.67	76.96	19.33	3.71	4.30
hrs.						
1	2.64	2.33	71.10	23.40	5.50	4.39
2	6.01	5.60	32.95	54.66	12.39	2.72
3	7.77	7.45	11.68	69.80	18.72	2.64
8	9.03		0.74	73.03	26.23	
24	9.24		0.38	67.08	32.54	

[a] The figures represent average values for several runs starting with initial samples of about 0.4 g. of G_3M. In each run the figures for G_3M and G_6M percentage represented the constant values obtained after three to five washings with hot methanol and 80° water, respectively.

ture of G_9M and $G_{12}M$, because the G_9M with 5.68% methoxyl could not lower the methoxyl content (4.33%) of the $G_{12}M$. We therefore interpret our data as indicating that the G_3M underwent a series of successive condensation reactions yielding G_6M, $G_{12}M$, $G_{24}M$, $G_{48}M$, and $G_{96}M$ with theoretical methoxyl contents of 8.28, 4.33, 2.21, 1.12, and 0.56%, respectively. Since there was no

appreciable difference in the experiments starting with G_3M, G_6M, or $G_{12}M$ between the methoxyl values of the last two samples taken at long interval of time, it appears very likely that the condensation reaction ends at the 96-peptide stage, yielding a nearly uniform product with a methoxyl content of 0.5%, and with the empirical formula $C_{193}H_{292}N_{96}O_{97}$ and molecular weight of 5504. From the nature of this type of condensation reaction, it follows that at the intermediate stages the figures of the methoxyl estimations represent the overall methoxyl content of the reaction products, which necessarily consist of mixtures of polypeptide esters. When the G_3M was heated at 80° the condensation reaction was so slow that after a total of four months heating the methoxyl reached only the value for $G_{24}M$ (found: MeO, 2.16; calc'd: MeO, 2.21). An amino nitrogen determination on the product, carried out under the obvious difficulty of introducing a large solid sample into the reaction chamber of the Van Slyke apparatus, gave a value of 0.680 mg. of nitrogen gas. The calculated value for the sample on the basis of the methoxyl content was 0.707 mg., showing excellent agreement. Accordingly, any possibility of a partial decomposition of G_6M or $G_{12}M$ into methanol and the corresponding free peptide, a reaction that might be thought to have caused the gradual decrease of the methoxyl content, is definitely ruled out, since the amino nitrogen value has suffered the same relative drop as the methoxyl content and the reaction must be tied up with the disappearance of free amino groups.

The absence of G_9M among the analyzed condensation products of G_3M is surprising. It would indicate that the reaction is not a random condensation between all of the peptides present, *e.g.*, G_3M and G_6M to yield G_9M, etc., but it proceeds according to a pattern which can be expressed by the simple formula 3×2^n, where $n = 1, 2, 3, 4$, and 5. Whether or not such selective condensation has anything to do with the presumably different shapes of the polypeptide ester molecules present, or with the oriented structure of the crystalline starting material, or with some unknown factors that may in general control the mechanism of reactions occurring in the solid state, at present we are unable to say. However, it does not seem to us unlikely that the rapid condensation of the amino acids in the living cell by the catalytic action of the enzymes takes place according to such economic pattern instead of random condensation.

All the polypeptide esters of glycine obtained in the course of this investigation were almost colorless substances, amorphous in appearance, and insoluble in alcohol but slightly (0.1–0.5%) soluble in water. They all give very strong biuret reaction and dissolve completely in cold conc'd hydrochloric acid, though only partly in dilute alkali solution. They are strongly reminiscent of denatured proteins, and like many of the latter substances are soluble in concentrated urea solution.

Although the inability of G_6M to form the simplest "cyclol-6" molecule by this method would seem to favor strongly the conception of a more or less open-chain structure, it should be pointed out that the tetrapeptide esters do not appear to undergo any type of condensation at all. There is thus an indication of some fundamental difference between the shape of the molecules of the di-,

tri-, and 3×2^n-peptide esters on the one hand, and that of the tetra- and probably penta-, hepta-, etc. peptides on the other. In addition, a 96-peptide is one-third of the Svedberg unit of 288; whether this has any significance we are not in a position to state at the present time.

EXPERIMENTAL

Preparation of diglycylglycine methyl ester. Fischer's procedure (11) was followed closely for the conversion of glycine ethyl ester hydrochloride into 2,5-diketopiperazine and for the preparation of chloroacetylglyclglycine from chloroacetyl chloride and the piperazine derivative. The exchange of the chlorine atom for an amino group in chloroacetylglycylglycine was carried out according to Abderhalden and Fodor (19), and the methyl ester hydrochloride of the resulting diglycylglycine was obtained by Fischer's method (11). For the preparation of the free tripeptide ester it became necessary to modify slightly Fischer's original procedure (11), which gave an unsatisfactory yield, due to rapid condensation of the liberated ester during the evaporation of the dilute methyl alcohol solution. The following procedure gave a pure crystalline product in nearly quantitative yield. To 4.8 g. (1/50 mole) of diglycylglycine methyl ester hydrochloride, suspended in 10 cc. of ice-cold methanol in a distilling flask, was added, drop by drop and under stirring at 0°, an approximately 2% methyl alcoholic sodium methoxide solution containing 3% less than the theoretical quantity of sodium. The reaction mixture was immediately concentrated *in vacuo* at 30° to a solid mass which was repeatedly extracted at 40° with 10 cc. portions of dry chloroform. The filtered extracts were united, and absolute ether or petroleum ether was added to the cold solution until turbidity developed. On standing at low temperature, the solution rapidly deposited the tripeptide methyl ester in groups of long needles; yield, nearly quantitative; m.p. and other physical properties agree with the data given by Fischer.

Anal. Calc'd for $C_7H_{13}N_3O_4$: OCH_3, 15.26.
Found: OCH_3, 15.40.

The methyl ester of diglycylglycine is soluble in cold water, giving a clear solution strongly alkaline to litmus. However, the solution rapidly develops turbidity, indicating the formation of water-insoluble condensation products. In a special experiment, 1 g. of pure ester was dissolved in 7 cc. of distilled water, and the clear solution was kept at room temperature for two days; heavy precipitation occurred during this time. The filtered substance was dried *in vacuo* over solid sodium hydroxide at room temperature; yield, 0.4 g. Although its methoxyl content (4.1%) corresponded to that of pure dodecapeptide methyl ester of glycine, the substance was a mixture of pentaglycylglycine and its methyl ester, both of which are soluble in warm water but only slightly soluble in cold. Addition of three volumes of absolute alcohol to the original filtrate of this substance gave crystalline diglycylglycine; yield, 0.3 g. This experiment showed that diglycylglycine methyl ester in water solution suffered partial hydrolysis into the tripeptide and partial condensation into the hexapeptide ester, the latter substance in turn being partly hydrolyzed to the free hexapeptide. In similar experiments carried out in boiling water, further condensation occurred, yielding substances insoluble in hot water and containing little methoxyl, besides large quantities of diglycylglycine.

Preparation of pentaglycylglycine methyl ester. The condensation of diglycylglycine methyl ester in non-aqueous solvents proceeded fairly rapidly, and the only product of the reaction was pure hexapeptide ester of glycine, which precipitated out immediately after it had been formed. Three grams of crystalline tripeptide ester was dissolved in 30 cc. of cold absolute methanol and the solution was filtered rapidly with activated carbon. Heavy precipitation was obtained by keeping the clear filtrate at room temperature for three days. The substance was filtered in a crucible with sintered glass bottom and washed with absolute methanol; yield, 1 g. of pure hexapeptide ester. From the filtrate, on standing for several days, a further quantity (0.7 g.) of the same substance was obtained.

Anal. Calc'd for $C_{13}H_{22}N_6O_7$: OCH_3, 8.28.
Found: OCH_3, 8.33.

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SUMMARY

A study of the condensation reactions which take place on heating the amino acid esters and simple polypeptide esters has been made, and the reactions have been classified into four distinct types.

It has been concluded that instead of cyclization to give the simplest model of a "cyclol-6" postulated by the Wrinch theory, the hexapeptide methyl ester of glycine, on being heated, undergoes the type of condensation characteristic for the tripeptide esters, in a series of successive reactions yielding 12-, 24-, 48-, and 96-peptide esters of glycine. The course of the reaction has been followed by methoxyl estimation on the samples withdrawn at certain intervals of time. Similarly, the condensation reactions of the tripeptide and dodecapeptide esters of glycine proceed according to the simple formula 3×2^n, where n represents whole numbers, to give 96 as the final stage of condensation.

From the results of the analyses of the condensation products it has been concluded that neither "cyclol-6" nor, in all probability, nonapeptide is formed when the tripeptide ester of glycine is heated. The polypeptides obtained are reminiscent of denatured proteins and give strong biuret reactions.

An improved procedure for the preparation of diglycylglycine methyl ester, and a new method for the preparation of pentaglycylglycine methyl ester have been given.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

POLYCONDENSATION OF CERTAIN PEPTIDE ESTERS. II. PROTEIN MODELS. NOTES ON THE PREPARATION OF TRIPEPTIDE METHYL ESTERS[1]

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In the preceding article[3] it was shown that the tripeptide methyl ester of glycine, on being heated, undergoes condensation in a series of successive reactions yielding the 96-peptide methyl ester of glycine as the final product. Application of the procedure to other tripeptide methyl esters has now been undertaken in order to open the way for the preparation of synthetic protein-like substances in accordance with the views postulated by Bergmann's periodicity hypothesis (1, 2, 3). It was hoped that substitution of different amino acids for glycine in the starting materials would lead to model substances not possessing the extreme insolubility of the glycine polypeptide esters. It should be pointed out that once the proper technique for the preparation of these various model substances has been established, synthetic products containing optically active amino acids linked together in known order can be made available for physiological and enzymatic studies.

A search of the literature for suitable starting materials revealed that, whereas several tripeptides had been prepared in pure state, both the methyl ester hydrochlorides and the methyl esters themselves were unknown. The only simple tripeptide methyl ester which had been prepared, other than G_3M,[4] was *l*-alanylglycylglycine methyl ester (4). In undertaking the preparation of such tripeptide esters considerable and unexpected difficulty was encountered for the reasons discussed in the following section. From the products finally obtained, only *dl*-alanylglycylglycine methyl ester (AG_2M) and *dl*-leucylglycylglycine methyl ester (LG_2M) were available in pure form.

I. THE PREPARATION OF METHYL ESTERS OF TRIPEPTIDES

For our experiments we decided to use the methyl esters of *dl*-alanylglycylglycine, *dl*-leucylglycylglycine, *dl*-alanyl-*dl*-leucylglycine (ALGM) and glycyl-*dl*-leucyl-*dl*-alanine (GLAM). We synthesized the free tripeptides in the same general manner in which they were originally obtained by Fischer (5, 6). In these syntheses, as one of the steps, ammonia is employed for the replacement of halogen by an amino group in the respective halogeno peptides, a reaction often resulting in the formation of large amounts of by-products (6). For instance, in

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[3] Paper I, Pacsu and Wilson, *J. Org. Chem.*, **7**, 117 (1942).

[4] See footnote 3, Paper I.

the ammonolysis of α-bromoisocaproylalanine the corresponding diketopiperazine is formed in considerable amount, as well as the hexenic acid derivative of alanine, $(CH_3)_2CH \cdot CH{=}CH \cdot CO \cdot NH \cdot CH(CH_3)COOH$, where hydrogen bromide was split off. The formation of a corresponding hydroxy acid, $(CH_3)_2 CH \cdot CH_2 \cdot CHOH \cdot CO \cdot NH \cdot CH(CH_3)COOH$, is likewise possible under the conditions of the experiment. Finally, the prolonged action of aqueous ammonia may be effective in splitting the peptide bond. It occurred to us that much of the by-product formation may actually take place *after* the amination has been completed, as a result of long contact of the product with strong ammonia. For this reason pilot experiments were run on most of the compounds we desired to aminate before subjecting the main part of the material to the treatment.

TABLE I

TIME NECESSARY FOR COMPLETION OF AMMONOLYSIS AS INDICATED BY HALOGEN ION ESTIMATIONS

SUBSTANCE	TIME (HRS.) AT 50° 9 *N* AMMONIA	TIME (HRS.) USED BY FISCHER. ABOUT 15*N* AMMONIA
α-Bromopropionylglycylglycine	4	0.5 (100°)
α-Bromoisocaproylglycylglycine	6.5	0.5 (100°)
α-Bromopropionylleucylglycine	2	24 (room temp.)
Chloroacetylleucylalanine	1	0.5 (100°)

TABLE II

AMINO NITROGEN CONTENT OF SYRUPS FROM ESTERIFICATION OF TRIPEPTIDES UNDER STANDARD CONDITIONS

SUBSTANCE	% AMINO N (CALC'D METHYL ESTER HYDROCHLORIDE)	% AMINO N (FOUND)
Alanylglycylglycine	5.52	8.62, 8.44
Leucylglycylglycine	4.74	5.94, 5.79
Alanylleucylglycine	4.52	5.42, 5.34
Glycylleucylalanine	4.52	7.28, 7.38

Samples were withdrawn from these pilot runs at known times and analyzed for halogen ion content; the end-point of the replacement reaction was thus ascertained. This technique in every case led to increased yields over those reported by Fischer, under milder conditions. As shown in Table I, the reaction is in general much more rapid than hitherto supposed.

Experiments for the preparation of the methyl esters of these tripeptides were based on the assumption that methyl alcoholic hydrogen chloride, so successfully employed in the case of G_3M and *l*-AG_2M, was the only methylating agent which could be used due to the insolubility of the peptides in organic solvents and the presence of a reactive amino group. Abderhalden (7) has given general rules for esterification, based largely on Fischer's original procedure for the above two tripeptide esters and for the amino acid esters themselves. Using this procedure, modified only by varying the percentage of hydrogen chloride in the esterifying

mixture from 2.5% to saturated, the following discouraging products were obtained after many different experiments. The GLA and ALG gave non-crystallizable syrups. The AG_2 and LG_2 gave syrups from which small amounts of fine needles slowly separated. This crystalline material, after purification, gave melting point and analytical data for methoxyl and chlorine content in perfect agreement with those of glycine methyl ester hydrochloride. Since it appeared from this that the tripeptides had undergone some fission, all syrups were converted into amorphous solids by trituration with dry ether and analyzed for amino nitrogen. The results given in Table II are typical of the products obtained from the various runs and indicate considerable splitting. Neutralization of the syrups with sodium methoxide yielded basic substances from which a volatile fraction, glycine methyl ester, was removed by distillation. From the residues a series of crystalline compounds were isolated. Their properties and analyses indicated that they represented the corresponding diketopiperazine derivatives, necessarily formed from the splitting off of the end-standing glycine residue in each case. We conclude, therefore, that esterification of the tripeptides under standard conditions leads to alcoholysis, resulting in the splitting of the molecules at the point between the end glycine residue and the remainder of the molecule. The resulting dipeptide ester hydrochlorides, when neutralized, rapidly cyclize to the corresponding diketopiperazines, while the free glycine ester is completely removed when the mixture is concentrated *in vacuo*. The results are summarized as follows.

$$\text{Alanyl-glycyl}\vdots\text{glycine} \xrightarrow[\text{HCl}]{\text{MeOH}} \text{AGM}\cdot\text{HCl} + \text{GM}\cdot\text{HCl}$$

$$\text{Leucyl-glycyl}\vdots\text{glycine} \xrightarrow[\text{HCl}]{\text{MeOH}} \text{LGM}\cdot\text{HCl} + \text{GM}\cdot\text{HCl}$$

$$\text{Alanyl-leucyl}\vdots\text{glycine} \xrightarrow[\text{HCl}]{\text{MeOH}} \text{ALM}\cdot\text{HCl} + \text{GM}\cdot\text{HCl}$$

$$\text{Glycyl}\vdots\text{leucyl-alanine} \xrightarrow[\text{HCl}]{\text{MeOH}} \text{LAM}\cdot\text{HCl} + \text{GM}\cdot\text{HCl}$$

It is interesting to note that previous to Abderhalden's general rules the same process of alcoholysis under nearly the same conditions was pointed out by Pribram (8); little has appeared on the subject since that time (9).

The importance of the time factor was now evident, and the easy preparation of G_3M and *l*-AG_2M under Abderhalden's conditions could be attributed to the rapid and easy crystallization of these particular ester hydrochlorides. Therefore our next series of experiments was run using freshly prepared saturated methyl alcoholic hydrogen chloride in order to ensure rapid esterification. The tripeptide was dissolved in this solution and the product *immediately* precipitated with dry ether, or the solution at once taken down *in vacuo*. The resulting substance was repeatedly taken up in methanol and thrown out of solution with dry ether, the liquid layer being decanted in order to remove as much hydrogen chloride as possible. The final product was dried over fresh sodium hydroxide.

In this manner the new pure crystalline hydrochlorides of AG_2M and LG_2M were obtained; the hydrochlorides of ALGM and GLAM would not crystallize although their analyses agreed reasonably well with the calculated values. Possibly this is due to the fact that they are composed of a mixture of diastereomers.

The hydrochlorides were neutralized with sodium methoxide in the usual manner to liberate the previously unknown free esters. Of these, the AG_2M was obtained in pure crystalline form, the pure LG_2M was a white amorphous powder, while the GLAM was at first an oil but turned into a slightly impure solid crystalline mass on standing; the ALGM could not be crystallized or solidified, and was unavailable for condensation experiments.

Experiments involving esterification of other polypeptides, as well as scission of protein molecules by methanolysis are now in progress in this Laboratory.

EXPERIMENTAL

dl-*Alanylglycylglycine methyl ester.* Fischer's procedure (5) for the production of α-bromopropionylglycylglycine was followed, using diketopiperazine and α-bromopropionyl bromide prepared according to Volhard (10). For the amination of this substance Fischer's method was modified as follows. To 1260 cc. of 9 *N* ammonia was added 168.5 g. of the bromo compound, giving a 0.5 molar solution of the substance. Since a pilot run indicated that at 50° under these conditions the bromide ion content reached the maximum in four hours, the amination was conducted in this fashion. The tripeptide was then worked up according to Fischer's procedure; yield, 100 g. or 78%. A second run gave a yield of 80.5%, whereas Fischer reported 57%; m.p. and physical properties were identical with those reported by him. Titration with alkali in aqueous solution, using thymol blue with the addition of three volumes of alcohol: 0.1368 g. required 6.63 cc. of 0.1 *N* alkali; calculated: 6.74 cc.

From the tripeptide the methyl ester hydrochloride was prepared as follows. To 17 g. of the tripeptide was added 170 cc. of a saturated methyl alcoholic hydrogen chloride solution freshly prepared from absolute methanol. The vessel was rotated while cooling until all the substance had dissolved, and the solution was immediately concentrated to dryness *in vacuo* at room temperature. The resulting syrup was repeatedly taken up in a small quantity of methanol and precipitated by the addition of dry ether, the liquid layers being decanted. After drying over solid sodium hydroxide *in vacuo* the syrup completely solidified. Two crystallizations from a methyl alcohol-ether mixture gave clusters of needles; yield, 20.4 g. or 96.2%. The crystals had the m.p. 154–157° (corr. 157–160°).

Anal. Calc'd for $C_8H_{16}ClN_3O_4$ (253.5): OCH_3, 12.22; Cl, 14.00.
Found: OCH_3, 12.24; Cl, 14.05.

For the liberation of the free methyl ester, a solution containing 2% less than the calculated quantity of sodium methoxide was added slowly to 7 g. of the hydrochloride dissolved in the minimum amount of ice-cold methanol. The mixture was immediately concentrated to dryness *in vacuo* at room temperature and the resulting cloudy syrup was extracted at once with several portions of hot ethyl acetate. On cooling the filtered ethyl acetate solution in ice, the ester separated in crystalline form; yield, 4.6 g. Addition of ether to the filtrate gave 0.4 g., a total yield of 83%. The needles melted at 86–88°, and in water solution were strongly alkaline to litmus, showing a positive biuret reaction. Titration of a 0.0959 g. sample using methyl red required 4.30 cc. of 0.1 *N* acid; calculated: 4.42 cc.

Anal. Calc'd for $C_8H_{15}N_3O_4$ (217): OCH_3, 14.28. Found: OCH_3, 14.22.

dl-*Leucylglycylglycine methyl ester.* The free peptide was obtained in the manner reported by Fischer (5). Diketopiperazine was converted to α-bromoisocaproylglycylglycine

by coupling with α-bromoisocaproyl chloride prepared from isoamyl alcohol according to Hass and Marshall (11). For amination to the tripeptide, a pilot run indicated maximum bromide ion concentration after six and one-half hours heating at 50° in 9 *N* ammonia. These conditions were used with excellent result; from 24.5 g. of starting material was obtained 15.6 g. or an 80.4% yield of the pure tripeptide, as compared with Fischer's 63% yield of unrecrystallized product; m.p. and properties indicated the tripeptide to be identical with Fischer's preparation. Conversion of one gram of the tripeptide to the new methyl ester hydrochloride was accomplished in a manner similar to that used for alanylglycylglycine methyl ester hydrochloride. The substance crystallized spontaneously on concentration of the original solution. It was washed with ice-cold methanol and dried over sodium hydroxide. Recrystallization from absolute methanol with the addition of ether gave fine needles; yield, 0.9 g.; m.p. 220–221° (corr. 227–228°) with decomposition.

Anal. Calc'd for $C_{11}H_{22}ClN_3O_4$ (295.5): OCH_3, 10.49; Cl, 12.01.
Found: OCH_3, 10.47; Cl, 11.94.

The free ester was liberated from the hydrochloride by the same procedure as used for the alanylglycylglycine methyl ester. The extraction was made with chloroform and from the solution, on concentration, a clear syrup was obtained. This was taken up in ether, the solution filtered from a trace of insoluble material, and the filtrate was again concentrated. The ester separated as a white solid which was removed by rubbing with dry petroleum ether and dried over sodium hydroxide; m.p. 70°. The substance was fairly soluble in ether.

Anal. Calc'd for $C_{11}H_{21}N_3O_4$ (259): OCH_3, 11.96. Found: OCH_3, 11.78.

Glycyl-dl-*leucyl*-dl-*alanine methyl ester.* The free peptide was obtained according to Fischer's procedure (6). For the conversion of the chloroacetylleucylalanine to the tripeptide the optimum condition was again determined by a pilot run. To 95 cc. of 9 *N* ammonia was added 13.3 g. of the chloroacetyl compound to give a 0.5 molar solution; this was kept at 50° for one hour, after which the solution was worked up according to Fischer. Yield, 10.8 g. or 88% as compared with Fischer's 70%. Molecular weight determination by electrometric titration gave 262.6; calculated, 259. The methyl ester hydrochloride was prepared by the same procedure as described for the two previous ester hydrochlorides. The product was obtained in solid form but could not be recrystallized; yield, 70%.

Anal. Calc'd for $C_{12}H_{24}ClN_3O_4$ (309.5): OCH_3, 10.01. Found: OCH_3, 10.32.

The free ester was obtained in the usual manner described above for the other tripeptide esters. The product was a clear oil soluble in ether; on standing or scratching, it readily crystallized. The crystalline product was only slightly soluble in ether, but could not be recrystallized from this or other solvents, since it always separated out as a slightly impure oil, the process of crystallization being evidently quite slow. Its aqueous solution is strongly alkaline to litmus, but gives only a faint biuret reaction; yield, 77%; m.p. 102–105°.

Anal. Calc'd for $C_{12}H_{23}N_3O_4$ (273): OCH_3, 11.35. Found: OCH_3, 10.90.

The *dl*-alanyl-*dl*-leucylglycine used in the experiments was prepared according to Fischer (6), except that the intermediate α-bromopropionylleucylglycine was aminated according to our new conditions. The usual pilot run indicated the reaction to be complete in two hours at 50° in 9 *N* ammonia; yield, 83.6% as compared with Fischer's 74%; m.p. and physical properties identical with those given by Fischer. Titration of a sample using the glass electrode gave a molecular weight value of 264.4; calculated, 259. Preparation of the ester hydrochloride and free ester from this substance according to the above conditions led only to impure syrupy products.

II. CONDENSATION EXPERIMENTS WITH NEW TRIPEPTIDE METHYL ESTERS

Attempts to prepare the hexapeptide ester from the crystalline AG_2M for use in condensation experiments by the same procedure as used for G_3M gave a different but interesting result. A 10% methyl alcoholic solution of AG_2M

(MeO, 14.28%) remained clear during a period of 24 days standing at room temperature. After this time the substance was precipitated in apparently amorphous form by addition of ether. The methoxyl content of the product was 6.98%, whereas the calculated value for AG_2AG_2M is 7.71%, indicating that, although the condensation does take place, the hexa-, and to some extent the higher peptide esters, unlike the G_6M, are soluble in methanol.

The AG_2M and LG_2M were then submitted to heating experiments, samples being withdrawn at known times for methoxyl determinations. For AG_2M, runs were made at 80°, 100°, and 110°; the results of the methoxyl analyses are given in Table III. With LG_2M, experiments were carried out at 100° and 110°; the

TABLE III

CONDENSATION OF *dl*-ALANYLGLYCYLGLYCINE METHYL ESTER AT DIFFERENT TEMPERATURES

T = 80° ± 1°		T = 100° ± 1°		T = 110° ± 1°		
Time (hrs.)	% OCH_3	Time (hrs.)	% OCH_3	Time (hrs.)	% OCH_3, 1st run	% OCH_3, 2nd run
0	14.28	0	14.28	0	14.28	14.28
1	13.79	0.4	13.10	0.25	12.42	
2	13.47	1	11.96	0.5	12.16	
4	12.67	2	10.88	1	10.58	10.71
7	11.74	4	7.34	1.5	8.80	
12	9.73	6	5.73	2	7.07	7.53
24	7.42	12	4.04	4	4.75	
48	6.34	24	3.47	6	3.69	4.15
72	5.99	48	2.57	12	2.77	
192	5.09	72	2.23	24	2.07	2.19
480	4.39	96	2.00	48	1.54	
		192	1.60	72	1.25	1.19
		312	1.33	96	1.11	0.86[a]
				264	0.70	
				408		0.55
				845		0.43

[a] This value is for 168 hours heating.

results of the methoxyl estimations are shown in Table IV. With the exception of the experiment at 80° on the AG_2M, all the runs were complicated by the fact that LG_2M melts at 70° and AG_2M melts at 86–88°. Consequently it was found necessary to weigh out the samples in advance in small individual tin cups; after heating, the cups with their contents were re-weighed and placed in the methoxyl apparatus. As with G_3M, G_6M, and $G_{12}M$, there occurred a general fall in the methoxyl contents to values fairly close to the calculated methoxyls for the respective 48- and 96-peptide esters. Some indication was obtained in the case of AG_2M at 110° that the condensation may have proceeded beyond the 96-stage; after 408 hours heating, the methoxyl content was 0.55%, while an additional 437 hours heating lowered the value to 0.43% as compared with the calculated value of 0.52%. Though this latter analysis is still within the experimental

error for the 96-peptide ester, it should be remarked that in all probability the condensation from the 96- to the 192-stage would be an extremely slow process.

We were able to obtain excellent confirmation of the validity of the methoxyl analyses in the following manner. A sample of AG_2M was heated at 80° until the methoxyl content was 4.39% (calc'd for the 12-peptide ester, 4.01%). This substance was completely soluble in water. Titration of a 0.1392 g. sample with 0.01 *N* hydrochloric acid, using the glass electrode, gave an end-point value of 18.6 cc.; the calculated value, assuming condensation for removal of the free amino group, is 19.1 cc. Amino nitrogen determinations on the same substance gave values of 2.13% and 1.97%, as compared with the calculated value of 1.98%.

Unfortunately, the washing-out experiments, used so successfully for the quantitative removal of G_3M and G_6M from the condensation products of the

TABLE IV

CONDENSATION OF *dl*-LEUCYLGLYCYLGLYCINE METHYL ESTER AT DIFFERENT TEMPERATURES

T = 100° ± 1°		T = 110° ± 1°	
Time (hrs.)	% OCH_3	Time (hrs.)	% OCH_3
0	11.96	0	11.96
1	10.90	1.5	9.12
2	9.95	3	7.73
4	8.71	5	5.73
11	5.96	9	4.54
27	4.70	24	3.06
50	3.80	72	2.40
96	2.80	168	1.85
217	2.34	264	1.84

earlier experiments, could not be applied as such to these latter products, as the high peptide esters possessed the unexpected property of being soluble in cold water at all stages. A series of experiments on products obtained by heating AG_2M showed the tripeptide ester to be soluble in warm ethyl acetate, and the hexapeptide ester to be insoluble in ethyl acetate but partly soluble in ethanol and completely soluble in methanol. While the unchanged tripeptide ester could be separated quantitatively from the other products by ethyl acetate, the hexapeptide ester could not be completely washed out with ethyl or methyl alcohol without appreciable removal of some products containing lower methoxyl values. Consequently, since recovered portions of hexapeptide ester usually showed lower methoxyl contents than the calculated for the pure hexapeptide ester, it is not possible to exclude the formation of 9-peptide ester on the basis of such experiments. The non-formation of "cyclol-6", however, is indicated by the following data. A sample of AG_2M heated at 80° for twenty-three hours contained 7.13% methoxyl (calc'd for the hexapeptide ester, 7.71%). Washing with warm ethyl acetate gave little loss in weight, indicating a negligible amount

of unchanged AG_2M at this stage. The residue was then boiled five minutes with methyl alcohol, and a small insoluble portion filtered off. This portion had a methoxyl content corresponding to that of a dodecapeptide ester (found: MeO, 4.53; calc'd: MeO, 4.01). From the alcoholic filtrate, on standing at 0°, a small fraction with 6.45% methoxyl value was recovered by filtration. Although this could be interpreted as being a mixture of 32% hexa- and 68% nona-peptide ester (calc'd for nonapeptide ester: MeO, 5.86), it is as likely that it consists of a mixture of hexa- and dodeca-peptide ester, and consequently no conclusion can be drawn on this point. The quantity of this fraction, however, is very small. The filtrate, on addition of ether, gave a large amount of almost pure hexapeptide ester containing 7.44% methoxyl. It is apparent, as in the case of the glycine peptide ester series, that had "cyclol-6" been the product, a substance containing no methoxyl rather than 4.53% should have been obtained.

It was also found that after heating AG_2M until its methoxyl content reached the calculated value for the hexapeptide ester, practically no unchanged AG_2M could be washed out from the condensation product with warm ethyl acetate. On the other hand, heating to a point midway between the calculated values for the tri- and hexa-peptide esters gave a mixture from which very nearly 50% unchanged AG_2M could be recovered by this treatment. This would seem to indicate that, at least in the earlier reactions, the condensation proceeds much more by stages than does the G_3M condensation. That is, when the methoxyl value reaches the theoretical for the hexapeptide ester of AG_2M, there is practically no tri- and very little dodeca-peptide ester present. If this is true of the later phases of the reactions, nearly uniform products could be obtained at the individual stages of the condensation reaction expressed by the formula 3×2^n.

An experiment was also made to determine if the rate of condensation of AG_2M in methanol solution could be influenced appreciably by heat. A sample was refluxed at 65° for four hours and then precipitated in crystalline state by the addition of ether; its methoxyl content was found to have fallen from 14.28% for the tripeptide ester only to 13.42%. The rate is apparently no faster than would have been the case in the solid state at 65°.

The fact that at 100° and 110° the AG_2M and LG_2M were in an intial molten state does not necessarily presuppose a different mechanism of condensation than that characteristic for G_3M, G_6M, and $G_{12}M$, and for AG_2M at 80°. The clear liquids, after two to four hours heating (that is, at the hexapeptide stage) turned into pink-white solids of apparently crystalline nature. In a trial run on another tripeptide ester, glycyl-*dl*-leucyl-*dl*-alanine methyl ester, a sample was heated at 80° for 114 hours. The methoxyl content dropped from the calculated value of 11.35% for the tripeptide ester to 9.06%. Inasmuch as the calculated value for the hexapeptide ester is 6.03%, a comparison with the results shown in Tables III and IV indicates that the condensation of this substance is very slow. No further experiments with this ester have been performed as yet.

The various polypeptide esters prepared during these condensations are white or slightly colored, apparently amorphous powders, all of which possess the surprising and valuable property of being easily soluble in cold water, in contrast to

the insoluble peptide esters of glycine. The higher peptide esters are insoluble in organic solvents. All give very strong biuret reaction. The importance of utilizing this procedure for the production of model substances is obvious. For instance, we believe that Bergmann's hypothesis of repeating amino acid units in the proteins finds the best synthetic approach in the almost numberless possibilities of order and arrangement which this method makes available. In this introductory paper alone compounds up to molecular weights of about 7000 containing long chains of repeating units such as —A·G·G·A·G·G·A·G·G·A·G·G·A·G·G·A·G·G·— and —L·G·G·L·G·G·L·G·G·L·G·G·L·G·G·L·G·G·— have been reported. The preparation of such substances by the use of Fischer's original method, included in almost every textbook on protein chemistry as the classical method for this approach, would have been a near impossibility.

Molecular weight determinations and other physico-chemical investigations on the water-soluble condensation products are to be carried out in this Laboratory and application of the condensation reaction to other tripeptide esters is being continued.

SUMMARIES

I

Tripeptides with glycine constituents used in this investigation suffer methanolysis under conventional conditions for esterification. The products are dipeptide methyl ester hydrochlorides and glycine methyl ester hydrochloride. Neutralization yields the corresponding diketopiperazines and glycine methyl ester.

A simple procedure is given for the preparation of the tripeptide methyl esters.

II

It has been shown that *dl*-alanylglycylglycine methyl ester and *dl*-leucylglycylglycine methyl ester, on being heated, undergo condensation in a series of successive reactions apparently according to the formula 3×2^n. The course of the reaction has been followed by methoxyl estimations. In the case of AG_2M the final product very likely represents the 96-peptide ester.

From the results of the quantitative analyses of the condensation products of AG_2M it has been concluded that "cyclol-6" is not formed in the reaction. No definite conclusion could be reached as to the formation or non-formation of a nonapeptide ester.

The substances are soluble in water and all give strong biuret reactions.

It has been pointed out that by this condensation reaction the way is open for the preparation of long-chain, high molecular weight protein models in agreement with the recurring structures postulated by Bergmann as existing in all proteins.

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Made in the United States of America

[CONTRIBUTION FROM THE LABORATORIO DE QUIMICA ORGÁNICA, FACULTAD DE CIENCIAS EXACTAS, FÍSICAS, Y NATURALES]

STUDIES ON ARGENTINE PLANTS. IV. ALKALOIDS FROM ERYTHRINA SPECIES

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The existence of alkaloids in the seeds of plants of the genus *Erythrina* was established long ago. Folkers and Unna (1) have revised the old literature on the subject.

The first product giving alkaloidal reactions and obtained as a pure substance, was hypaphorine, tryptophan betaine, isolated by Greshoff (2) from *E. hypaphorus*, and later from other species by several workers. Hypaphorine, which is relatively inactive, could not be the physiologically important substance present in the seeds, because the crude extracts had a curare-like action, and it was only in 1937 that the active alkaloids were isolated in pure condition from the seeds by Folkers and collaborators (3).

TABLE I

HYPAPHORINE AND FREE ALKALOIDS FROM ERYTHRINA SPECIES

SAMPLE	SPECIES	SEEDS, G.	PETROLEUM ETHER RESIDUE, %	METHANOL RESIDUE, %	HYPAPH. HCl, %	CRUDE FREE ALKALOIDS, %	CRYST. HI FREE ALK., MG.
I	*E. crista galli*	200	16.5	22	1.87	0.41	49
II	*E. crista galli*	420	—	—	—	0.3	420
III	*E. falcata*	220	12.4	25	2.11	0.35	20
IV	*E. falcata*	581	11.7	18.8	—	0.2	81
V	*E. dominguezzii*	165	15	23.6	2.06	0.33	12

They found that two types of alkaloids are present in the seeds of the *Erythrina* species. The so-called free alkaloids can be isolated by extraction of the crude extracts with organic solvents and are named erythraline, erythramine, and erythratine. The combined alkaloids, extractable only after liberation by hydrolysis are erysopine, erysovine, erysocine, erysodine, and erysonine. For each species the number of the different alkaloids isolated and the yield of each has been variable.

In Argentina, three *Erythrina* species are known: *E. crista galli*, *E. falcata*, and *E. dominguezzii*. The fact that Cicardo and Hug (4) had already demonstrated the curare-like activity of the extracts of seeds from *E. crista galli* induced us to study the alkaloids present in the Argentine species. Deulofeu, Hug, and Mazzocco (5) had already isolated hypaphorine from *E. crista galli* and Labriola (6) from *E. falcata* and *E. dominguezzii*. We have confirmed the existence of hypaphorine in those plants and the extracts, fractionated as described in the experimental part, have given free and liberated alkaloids.

The purification of the crude free alakaloid hydriodides gave crystalline com-

pounds but not one of the expected alkaloids was obtained in pure condition. Some of the liberated alkaloids were isolated as shown in Table II, where other data concerning the extraction are also given.

In the case of *E. falcata*, four of the five described liberated alkaloids could be isolated, but from two different samples of seeds. From *E. crista galli* and *E. dominguezzii* only erysovine, erysodine, and erysopine could be obtained.

When this work was already finished, a paper appeared by Folkers, Shavel, and Koniuszy (7) describing the isolation of the free and liberated alkaloidal fraction from the two last species, but only erysodine and erysopine were obtained.

TABLE II

LIBERATED ALKALOIDS FROM ERYTHRINA SEEDS[a]

SAMPLE	HYDROLYSIS									ISOLATED ALKALOIDS
	1st		2nd		3rd		4th			
	T.	R., g.	T.	R., g.	T.	R., g.	T.	R., g.	Total	
I	5	0.86	30	1.6	60	0.3	—	—	2.76	Erysopine, erysodine, erysovine
III	5	0.17	30	1.1	30	0.18	30	0.8	2.25	Erysopine, erysodine, erysovine
IV	30	2.61	30	2.75	30	1.28	—	—	6.64	Erysopine, erysodine, erysocine
V	5	0.34	30	0.74	30	1.3	30	0.38	2.76	Erysopine, erysodine, erysovine

T.: Time of hydrolysis, min.

R.: Residue from chloroform extraction.

[a] Sample II was not worked for combined alkaloids.

EXPERIMENTAL

The procedure employed for the isolation of the alkaloids was, with the exception of the second sample of *E. crista galli*, that described in the papers of Folkers and collaborators (3).

The seeds, dried in air and ground, were extracted in a Soxhlet apparatus, first with petroleum ether, and then with methanol. The methanol extract was filtered, concentrated in a vacuum, and the residue treated with dilute hydrochloric acid. The acid solution was then extracted with petroleum ether and chloroform, and the extracts discarded. It was then exactly neutralized with sodium bicarbonate and extracted many times with chloroform until a negative alkaloidal reaction was obtained in the extract.

The chloroform extracts were united and evaporated to dryness. The residue, "crude free alkaloids", was dissolved in a little absolute ethanol and treated with sodium iodide and acetic acid. By addition of absolute ether, an amorphous precipitate was produced, filtered, and ether added again to permanent turbidity. On standing, yellow needles were obtained, which after filtering and washing with a little absolute ethanol, melted from 236° to 247°, according to purity. A new but more impure fraction was obtained by concentration of the remaining solution and repeating the treatment. This crystalline hydriodide is a mixture of the free bases (yield, see Table I).

With sample II of *E. crista galli*, the hydriodide was further purified by recrystallization, and finally yellow needles melting at 245–247° were obtained with $[\alpha]_D$ + 186.4° (water, c = 0.072, l, 2 dm.).

Hypaphorine. After the extraction of the free alkaloids, the remaining solution was acidified with hydrochloric acid to *p*H 3.5, and after 24 hours, crystals of hypaphorine hydro-

chloride deposited in each case. The identity was established by melting point and preparation of the characteristic flavianate (5).

Liberated alkaloids. After separation of the hypaphorine hydrochloride, the solutions were boiled for 5 minutes, made alkaline with sodium bicarbonate, and extracted with chloroform. They were acidified again, boiled for 30 minutes, made alkaline with sodium bicarbonate, and extracted again with chloroform, the operation being repeated as described in Table II. The chloroform extracts were evaporated separately, the dried residue fractionated by crystallization, and purified as described. In Table II the conditions of hydrolysis and the yields obtained for the liberated alkaloids are stated.

Identification of the liberated alkaloids

E. crista galli

All the operations described refer to sample I.

Erysodine. By crystallization from ethanol of the residue of the chloroform extracts from the first, second, and third hydrolysis, a total of 415 mg. of crystals melting at 202–203° was obtained. By recrystallization, long prismatic crystals melting at 204–205°; $[\alpha]_D$ +250° (ethanol, c = 0.3212; l, 2 dm.). Erysodine melts at 204–205° and has $[\alpha]_D$ +248°.

Anal. Calc'd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68.
Found: C, 72.40; H, 7.58; N, 5.05.

Erysopine. The second and third hydrolysis deposited from the chloroform extracts an insoluble precipitate that was recrystallized from ethanol. Total yield, 641 mg. of white prisms, melting at 241°; $[\alpha]_D$ +265° [ethanol-glycerol (3:2), c = 0.0846; l, 2 dm.]. With ferric chloride the solution gives a green color. Erysopine melts at 241–242° and has in ethanol-glycerol $[\alpha]_D$ +265°.

Anal. Calc'd for $C_{17}H_{19}NO_3$: C, 71.55; H, 6.71; N, 4.91.
Found: C, 71.80; H, 7.05; N, 4.92.

Erysovine. During crystallization of the chloroform residue from the first hydrolysis, a small quantity of fine needles could be separated from the erysopine crystals. After recrystallization from ethanol, they melted at 175–176°. Erysovine melts at 178–179°.

E. falcata

The operations described, with the exception of the isolation of erysovine, refer to sample IV of the tables.

Erysodine. By crystallization from ethanol of the residue of the chloroform extracts from the second and third hydrolysis, crystals were obtained that were identical with erysodine; m.p. 204–205°, $[\alpha]_D$ +246° in ethanol.

Erysopine. This was separated as an insoluble precipitate from the chloroform extracts from the second and third hydrolysis. Recrystallized from ethanol, it gave crystals melting at 242°, and with $[\alpha]_D$ +250° in ethanol-glycerol. They gave in alcoholic solution a green color with ferric chloride.

Erysocine. The residue of the chloroform extract from the first hydrolysis was recrystallized from ethanol, giving fine needles of m.p. 160–161°; $[\alpha]_D$ +236.4° (ethanol, c = 0.059; l, 2 cm.). Erysocine melts at 162° and has in ethanol $[\alpha]_D$ +239.1°.

Erysovine. This base was obtained from the first hydrolysis of sample III. Recrystallization from ethanol of the residue from the chloroform extract gave 7 mg. of crystals melting at 178°.

Anal. Calc'd for $C_{18}H_{21}NO_3$: N, 4.68.
Found: N, 4.87.

E. dominguezzii

Erysodine. This base was obtained from the third and fourth hydrolysis. It represented the fraction of the chloroform residues easily soluble in ethanol; m.p. 204–205°.

Erysopine. This base was isolated from all four hydrolyses and represented the most nsoluble fraction in ethanol or in chloroform. It melted at 241–242°, and gave in solution a green color with ferric chloride.

Erysovine. This base was obtained from the first hydrolysis, and represented the fraction easily soluble in ethanol; it melted at 177–178°.

The same bases when isolated from different species did not give any depression of melting point when mixed. No depression was obtained when samples of erysopine and erysodine were mixed with pure samples kindly supplied by Dr. K. Folkers from the Merck Laboratories. We thank Drs. Mazzocco, Hug, and Descole, who kindly supplied the seeds for the work.

SUMMARY

The bases present in the seeds of the Argentine species of *Erythrina*, *E. crista galli*, *E. falcata*, and *E. dominguezzii* have been investigated.

All of these species contain hypaphorine, and the two fractions designated free and liberated alkaloids. Some of the alkaloids from the liberated fraction have been identified.

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TIEMANN'S "ISOCAMPHORPHORONE"[1]

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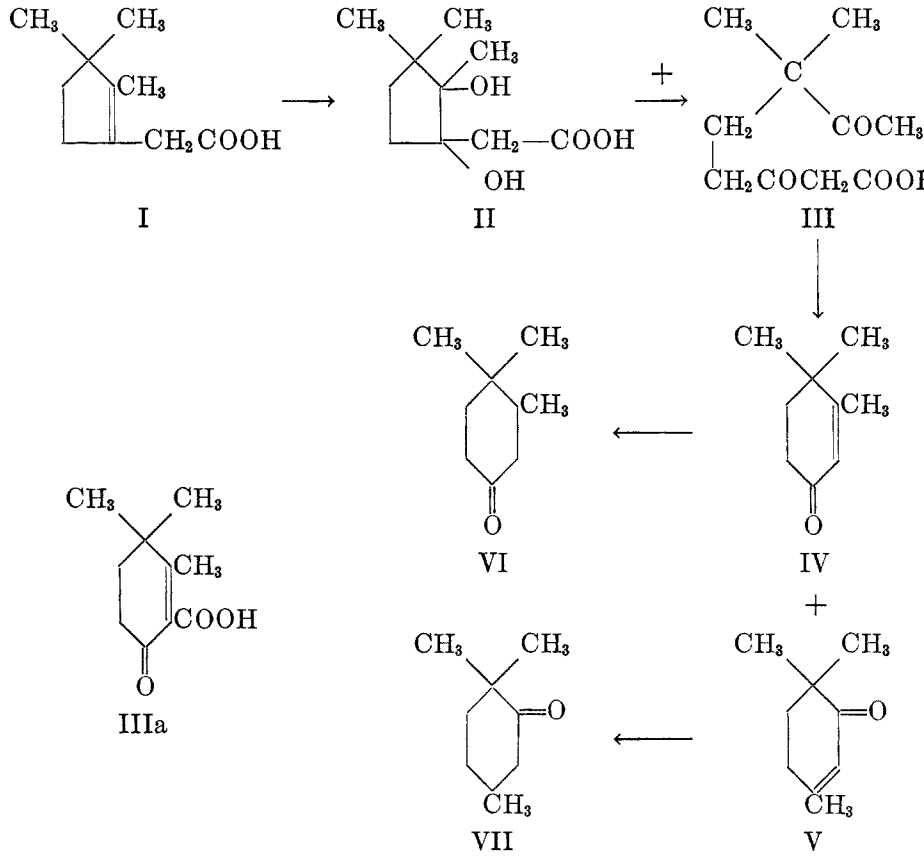
In 1897 Tiemann reported (3) that the permanganate oxidation of β-campholenic acid (I) yielded dihydroxydihydro-β-campholenic acid (II), small amounts of a ketonic acid ("campholonic acid") and a syrupy aliphatic acid which was not isolated in pure form. Under the conditions employed, this latter constituted the principal reaction product. Heating this material, either alone or in the presence of water, led to the elimination of carbon dioxide and water from the molecule with consequent formation of a ketone ("isocamphorphorone"). To this ketone, Tiemann assigned the structure (IV) based on a careful study of its oxidation products.



[1] The "β-camphorphorone" of Kerp and Müller (1) has also been referred to (2) as "isocamphorphorone."

At the time of these experiments, the structure of (I) was not known; it was impossible therefore correctly to interpret[2] the mechanism of formation of a compound having the structure (IV). Shortly after the publication of this work, however, the constitution of β-campholenic acid (I) became known (5) and Bouveault (5 b) postulated[3] formula (III) for Tiemann's syrupy acid, the precursor of (IV). Subsequently "isocamphorphorone" has been reported (7) only by von Braun and collaborators who prepared it according to the original directions.

The ketone (IV) was needed in this Laboratory as starting material for another investigation (8). Accordingly, the literature preparation (3) was repeated and it was found that the material resulting was not homogeneous but a mixture of isomers. This finding is not surprising, since two trimethylcyclohexenones, (IV) and (V) might be expected to result from the intermediate (III).[4] We were able to show that our isomers correspond in structure to (IV) and (V), and thus the essential validity of the Bouveault formulation may be regarded as established.

The mixture obtained by following carefully Tiemann's directions was fractionated *in vacuo* through a precision column to give the pure unsaturated ketones. The higher-boiling material was found to correspond to formula (IV); upon oxidation, it gave the dimethylketocaproic acid to be expected from this structure. The lower-boiling isomer was shown to be identical with 3,6,6-trimethylcyclohexen-2-one (V) previously synthesized by von Auwers (9). The reduction of (IV) led to the saturated ketone (VI) while (V) gave the known (10) inactive pulenone (VII).

The evidence, which is summarized in Table I, indicates that Tiemann obtained an "isocamphorphorone" preparation which consisted for the most part of (IV). However, some (V) was also present in the material which he investigated, since the oxime which he reported must have been derived from the latter. The von Braun preparation was also without doubt a mixture.

Since one of the objects of this work was to obtain the ketone (IV) for further synthetic operations, the utilization of (II) in this connection was studied. It was found that (II) was oxidized smoothly[5] by lead tetraacetate, and under conditions described in the Experimental Part, a ketonic product was obtained in which only the isomer (IV) could be detected. The action of hydrogen

[2] Tiemann's assumed intermediate (3) should be stricken from the literature (4) and replaced by (III).

[3] Bouveault's mechanism is not mentioned in "Beilstein" in connection with "isocamphorphorone" (6). Perhaps traceable to this oversight is von Braun's failure (7) to recognize (see below) that his "isocamphorphorone" was a mixture.

[4] Actually Bouveault (5b) assumed a second intermediate (IIIa), formed from (III) by loss of water. If dehydration of (III) were to precede decarboxylation, two isomeric unsaturated keto acids would result, only one of which would decarboxylate readily. Such a stepwise transformation would provide a plausible explanation for exclusive isolation of (IV) from (III). However there is no evidence that this mechanism obtains under the Tiemann conditions.

[5] The ready reaction indicates (12) that the OH groups in (II) are cis to each other, a structure in accord with the mode of formation of (II) and its inability to lactonize.

TABLE I

	"ISOCAMPHORPHORONE" TIEMANN (3)	IV[a]	V[b]	REDUCED "ISOCAMPHORPHORONE" VON BRAUN (7)	VI	VII[c]
Boiling point	b.p.$_{13}$ 97–99° b.p.$_{760}$ 217°	b.p.$_{13}$ 98°	b.p.$_{13}$ 86°	b.p.$_{11}$ 70–75° b.p. 184–188°	b.p.$_{13}$ 80–81°	b.p.$_{13}$ 66–67°
Density	d_4^{20} 0.9424	d_4^{25} 0.944	d_4^{25} 0.927		d_4^{25} 0.911	d_4^{25} 0.890
Refractive index	n_D 1.48458	n_D^{20} 1.4908 n_D^{25} 1.4889	n_D^{20} 1.4798 n_D^{25} 1.4780		n_D^{20} 1.4552 n_D^{25} 1.4535	n_D^{20} 1.4442 n_D^{25} 1.4425
Semicarbazone	m.p. 211°	m.p. 206.5–207.0° forms rapidly	m.p. 201.0–201.1° forms slowly	m.p. 177°	m.p. 208.0–209.0°	m.p. 176.0–176.3°
Derivative with hydroxylamine	hydroxylamino-oxime m.p. 153°	oxime m.p. 53.8–54.5°	hydroxylamino-oxime m.p. 156.5–157.0°	m.p. 100°	m.p. 72.5–73.5°	m.p. 94.5–94.8°
Derivative with *p*-nitrobenzaldehyde				m.p. 226°	di-*p*-nitrobenzal derivative m.p. 223.0–223.2°	mono-*p*-nitrobenzal derivative m.p. 117.5–118.0°
Reaction with bisulfite		none	none		reacts readily	none

[a] The data in this column do not fit the $C_9H_{14}O$ ketone described by Pringsheim and Schreiber (11) for which structure (IV) has been considered.

[b] von Auwers and Hessenland (9) found: b.p.$_{753}$ 208°, b.p.$_{15}$ 86–88°, $d_4^{16.5}$ 0.9317, $n_D^{16.5}$ 1.47958, semicarbazone, m.p. 200–201° (forms slowly).

[c] von Auwers and Hessenland (10) found: b.p.$_{39}$ 90–92°, semicarbazone, m.p. 176–177°. Cornubert and Humeau (10) found: b.p. 182–184°, d_4^{24} .8871, n_D^{24}0 1.4432, oxime, m.p. 93.5°, no reaction with bisulfite.

peroxide on (I) was also investigated. The major product resulting was shown to be a lactone derived from the stereoisomer (trans position of the OH groups) of (II) which has been obtained (13) by direct oxidation of dihydro-β-campholenolactone.

EXPERIMENTAL PART

β-Campholenic acid (I) (3). Three hundred grams of hydriodic acid (d = 1.7) was heated to boiling in a flask fitted with a reflux condenser, and 300 g. of d-camphor oxime (crude, containing some camphor) was added in 50-g. portions with manual shaking. After each addition, the mixture was refluxed for a few minutes to ensure complete reaction, and after the final addition, refluxing was continued for five minutes. Several such reaction mixtures were combined, diluted with water, extracted with ether, and the ether extract washed with sodium carbonate solution. The crude β-campholenonitrile obtained after removal of the ether was converted without further purification to (I). Crude nitrile (1476 g. from 1770 g. of camphor) was saponified by refluxing for 12 hours with a solution of 640 g. of sodium hydroxide in 1500 cc. of water and 2500 cc. of ethanol. Alcohol was removed by distillation, water was added, the solution acidified, and the liberated acid removed by repeated extraction with low-boiling ligroin (b.p. 30–60°). The ligroin solution was dried with sodium sulfate, saturated with dry ammonia, and the precipitated ammonium salt filtered off. Additional amounts were recovered from the mother liquors by washing with water, acidifying, taking up in ligroin, drying, and again saturating with ammonia. Ligroin was used here rather than ether (3) because of the hygroscopic nature of the crude ammonium salt. A total of 908 g. of ammonium salt of (I) was obtained (42% based on camphor, other runs gave on the same basis as high as 53%; distilled β-campholenonitrile yielded 82% of ammonium salt). The first crop of ammonium salt proved to be sufficiently pure for most purposes; recrystallization, attended by considerable loss, could be effected from isopropyl alcohol. The free acid was obtained from its salt by Tiemann's procedure, m.p. 50.2–50.7° from petroleum ether or methanol.

Permanganate oxidation of (I): (*a*) *Tiemann's conditions* (3). Eighty grams of pure (I) was dissolved in a solution of 20 g. of sodium hydroxide in 300 cc. of water, and a saturated solution of 81 g. of potassium permanganate in water was added over a period of about 15 minutes keeping the temperature at about 0° by addition of ice to the reaction mixture. Manganese dioxide was removed and the solution concentrated on the steam-bath to a small volume (evaporation *in vacuo* was not feasible due to excessive frothing). The organic acids were liberated and taken up in ether in the usual manner (3); after removal of solvent, the residue was recrystallized from benzene. The yield of dihydroxydihydro-β-campholenic acid (II) was 20 g. (20%); after repeated recrystallization from ethyl acetate and from isopropyl ether-alcohol, it melted at 141.0–142.0° [143.6–144.6° corr.; Tiemann (3) reported 146°]; the composition was checked by analysis.

The mother liquors from the dihydroxy acid were concentrated to a syrup and divided into two portions, each of about 25 g. One portion was distilled in a vacuum and the distillate, collected to 135° at 13 mm., carefully refractionated through a precision column. At 13 mm. there was obtained 4.1 g. of (V), b.p. 87–88°, 1.3 g. of an intermediate fraction, and 0.7 g. of (IV), b.p. 98–99°; no dihydro-β-campholenolactone (see below) could be detected in the residue. The other portion was placed in a flask with 300 cc. of 30% sulfuric acid and steam distilled. The organic matter in the distillate was separated by ether extraction and redistilled as above; 2.5 g. of (V), 0.9 g. of an intermediate fraction, and 1.7 g. of (IV) were obtained.

The higher-boiling material from this last experiment consisted for the most part of a fraction b.p. 127° at 13 mm. which was identified as dihydro-β-campholenolactone, owing its formation undoubtedly to the action of acid on (I). The lactone (analysis) gave a hydrazide (14), m.p. and mixed m.p. with an authentic sample 155.5–156.0° (from alcohol). Dihydro-β-campholenolactone was made [compare (13)] for comparison, by the action of 67% sulfuric acid on (I), b.p. (13 mm.) 126–127°, m.p. 37–38° (thermometer in melt) (15).

Tiemann's directions for obtaining "campholonic acid" were followed in detail but no material resulted which gave a semicarbazone under the usual conditions. To determine whether (II) could have been the precursor (16) of Tiemann's "campholonic acid", this substance was heated in sulfuric acid solution. Such treatment destroyed the dihydroxy acid, as shown by the fact that the product no longer reacted with lead tetraacetate; however no ketone derivative was obtained with semicarbazide.

(*b*) *Modified conditions.* It was found that oxidation of the ammonium salt of (I) gave results which could not be distinguished from those obtained with the free acid; all large-scale permanganate oxidations, therefore, were conducted with the more readily available salt. Amounts of permanganate larger than those used by Tiemann were employed, since the foregoing results indicate an incomplete oxidation, and since it seemed that an excess of oxidant would probably not react further upon (II) and (III) [confirmed experimentally for (II)]. Whereas the simplest procedure (3) leading directly to (IV) and (V) is to steam distill the strongly acidified filtrate from the permanganate oxidation, these conditions result in the destruction of any (II) present. The evaporation of the slightly alkaline solution resulting from the oxidation apparently involves a small loss of material; however this operation permits the convenient isolation of (II) and utilization of it for conversion into unsaturated ketone.

For preparation of the ketone mixture in quantity, the following procedure was adopted. One hundred eighty-five grams (1 mole) of ammonium salt was dissolved in 500 cc. of water and 60 g. of sodium hydroxide pellets dissolved in 100 cc. of water was added. The solution was poured on 2 liters of crushed ice, and 210 g. of potassium permanganate dissolved in about 4 liters of water was allowed to run in gradually over a period of about 10 minutes while the iced mixture was being constantly shaken by hand in a 12-liter flask. After coagulation of the manganese dioxide by heating and addition of "filter aid", the material was filtered with suction, the filter cake thoroughly stirred with hot water, filtered, and the two filtrates combined. The filtrates from several 1-mole portions were combined at this point and evaporated in a current of air at about 40–50°. From the acidified residue, crystalline (II) was obtained by continuous extraction with ether [it is not necessary to isolate (II); the total extract, after removal of solvent, may be treated as given for the mother liquors from (II)] in slightly better than 20% yield. The mixture of (II) and (III) present in the mother liquors was first treated with lead tetraacetate to convert (II) to (III) and the resulting reaction mixture then acidified with sulfuric acid and steam distilled. In this way a 9–14% yield of mixed ketones [approximately equal amounts of (IV) and (V)] was obtained directly, plus an additional 10% of (IV) from oxidation of the crystalline (II) (see below).

3,4,4-Trimethylcyclohexen-2-one (*IV*) was isolated by careful refractionation of the unsaturated ketone mixture, b.p. (13 mm.) 98°, d_4^{25} 0.944, $n^{20}D$ 1.4908, $n^{25}D$ 1.4889 (these constants are altered somewhat on standing, due perhaps to auto-oxidation).

Anal. Calc'd for $C_9H_{14}O$: C, 78.21; H, 10.21.
Found: C, 77.79; H, 10.20.

(IV) did not react when treated with aqueous bisulfite solution in the usual manner. The semicarbazone melted at 206.5–207.0° (from alcohol).

Anal. Calc'd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52.
Found: C, 61.73; H, 8.65; N, 21.66.

The oxime came out as an oil which crystallized after standing for two months. Recrystallized from petroleum ether at low temperature, it melted at 53.8–54.5°.

Anal. Calc'd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14.
Found: C, 70.87; H, 10.01; N, 9.43.

That no hydroxylaminooxime is formed must be ascribed to the steric effect of the *gem*-dimethyl grouping.

Three grams of (IV) was suspended in 40 cc. of water and a saturated solution of 9 g. of potassium permanganate in water was added slowly with shaking, in an ice-bath. The oxidation mixture was then heated to coagulate the manganese dioxide, filtered, and the filtrate evaporated at near room temperature to a small volume. The residue, after acidification with sulfuric acid, was extracted with ether, the ether extract dried and evaporated. From the oily acids was obtained a semicarbazone which gave analysis for $C_9H_{17}N_3O_3$, m.p. 182.5–183.0° decomp. (from alcohol-water). The keto acid was regenerated from the semicarbazone with oxalic acid and treated with hydroxylamine; the oxime was isolated by continuous extraction with ether and recrystallized from isopropyl ether, m.p. 95.3–95.8°. There has been reported (17) for 4,4-dimethylhexanon-5 acid: semicarbazone, m.p. 185°; oxime, m.p. 97–98°.

A smaller amount of oxidant gave a different result [compare (3)]. One and one-half grams of (IV) was oxidized with 1.0 g. of potassium permanganate in a manner similar to the above. After evaporation of the resulting solution, acidification of the residue precipitated an oil which solidified on cooling, m.p. 39.0–39.5°, from petroleum ether. Although the small amounts available prevented a thorough examination, this material must be regarded as 3,4,4-trimethylcyclohexandione-1,2 (18). The semicarbazone, m.p. 189–190° (from alcohol) turned yellow on standing [compare the monosemicarbazone of *p*-menthandione (19)].

Anal. Calc'd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89.
Found: C, 57.27; H, 8.46; N, 20.64.

3,6,6-Trimethylcyclohexen-2-one (*V*) was obtained as above, b.p. (13 mm.) 86°, d_4^{25} 0.927, $n^{20}D$ 1.4798, $n^{25}D$ 1.4780 (analysis). (V) did not react with bisulfite. The semicarbazone (analysis) m.p. 201.0–201.1° (from alcohol), formed very slowly (rate approximately 1/50 of that of formation of the isomer). With hydroxylamine, the 3-hydroxylamino-3,6,6-trimethylcyclohexanonoxime was readily obtained, m.p. 156.5–157.0° from alcohol.

Anal. Calc'd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04.
Found: C, 58.24; H, 9.59; N, 15.39.

3,4,4-Trimethylcyclohexanone (*VI*) was obtained in good yield by catalytic reduction of (IV) in methanol using a palladium-charcoal catalyst and a pressure above atmospheric of 30 lbs. per sq. in. The saturated ketone boiled at 80–81° at 13 mm., d_4^{25} 0.911, $n^{20}D$ 1.4552, $n^{25}D$ 1.4535.

Anal. Calc'd for $C_9H_{16}O$: C, 77.09; H, 11.50.
Found: C, 76.80; H, 11.13.

(VI) reacted readily with aqueous alcoholic sodium bisulfite solution giving a crystalline bisulfite addition compound from which (VI) was regenerated on treatment with alkali. The semicarbazone melted at 208.0–209.0° (from alcohol-water).

Anal. Calc'd for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71; N, 21.30.
Found: C, 60.64; H, 9.58; N, 21.21.

The oxime, after recrystallization from alcohol, melted at 72.5–73.5°.

Anal. Calc'd for $C_9H_{17}NO$: C, 69.63; H, 11.04.
Found: C, 69.96; H, 11.07.

A yellow di-*p*-nitrobenzal derivative was formed when (VI) was heated with *p*-nitrobenzaldehyde in the presence of aqueous alcoholic potassium carbonate; only one isomer could be detected, m.p. 223.0–223.2° (from benzene).

Anal. Calc'd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89.
Found: C, 68.42; H, 5.37; N, 7.15.

2,2,5-Trimethylcyclohexanone (VII) was obtained by reduction of (V) in the same manner as its isomer was obtained from (IV), b.p. 66–67° at 13 mm., d_4^{25} 0.8905, $n^{20}D$ 1.4442, $n^{25}D$ 1.4425, no reaction with bisulfite. The composition of (VII) and of its derivatives was checked by analysis; semicarbazone m.p. 176.0–176.3° (from alcohol), oxime, plates, m.p. 94.5–94.8° (from alcohol). The mono-*p*-nitrobenzal derivative was obtained by heating (VII) and *p*-nitrobenzaldehyde in alcohol with a few drops of aqueous sodium hydroxide, almost colorless crystals, m.p. 117.5–118.0° (from alcohol).

Anal. Calc'd for $C_{16}H_{19}NO_3$: C, 70.30; H, 7.01; N, 5.12.
Found: C, 70.67; H, 7.36; N, 5.22.

Lead tetraacetate oxidation of (II). To 63.5 g. of (II) dissolved in 150 cc. of glacial acetic acid, 160 g. of lead tetraacetate was added in portions, with stirring. A spontaneous rise in temperature took place; cooling of the reaction flask was effected by running tap water. After standing for 10 minutes, the reaction mixture was poured into 3.5 liters of water containing 105 g. of sulfuric acid and steam distilled. The distillate was neutralized, extracted thoroughly with ether, and the ether extract fractioned. Thirty and five-tenths grams of crude ketone was obtained, approximately 75% of which boiled at 97.5–98.0° at 13 mm. on redistillation through a precision column. The ketone (V) could not be detected; thus the yield of (IV) was 52%. In another experiment, 73 g. of lead tetraacetate was used to oxidize 63.5 g. of (II); a smaller yield of mixed ketones was obtained.

(II) was esterified by heating with ethanol and dry hydrogen chloride. The product, b.p. (2 mm.) 107–112° (analysis for $C_{12}H_{22}O_4$), in benzene solution reacted vigorously with lead tetraacetate.

Hydrogen peroxide oxidation of (I). Both the free acid (I) and its ammonium salt reacted readily with hydrogen peroxide to give, in each case the same major product. Eight and four-tenths grams of (I) was placed in a flask with 14 cc. of glacial acetic acid and 20 cc. of 30% hydrogen peroxide and heated to boiling for 2 hours. The reaction mixture was evaporated and water added to the residue; the oily, water-insoluble material resulting soon crystallized, yield 5.0 g. After recrystallization from isopropyl ether-alcohol, it melted at 143.0–143.5° and was identified as hydroxydihydro-β-campholenolactone (13) (analysis, lactone nature). No oxidation was observed on treatment of the lactone with lead tetraacetate or with chromic acid.

On heating the lactone with ethanol and dry hydrogen chloride, an oil was obtained, b.p. (2 mm.) 104–106°, (found: C, 67.0; H, 9.1) which did not react with lead tetraacetate. Saponification of the oil with alkali followed by acidification did not regenerate the parent lactone, indicating that deep-seated changes in the molecule had taken place.

SUMMARY

The synthesis of 3,4,4-trimethylcyclohexen-2-one, 3,6,6-trimethylcyclohexen-2-one, 3,4,4-trimethylcyclohexanone, and 2,2,5-trimethylcyclohexanone starting from β-campholenic acid has been described.

Tiemann's "isocamphorphorone" is a mixture of the two above-named isomeric unsaturated cyclic ketones.

PASADENA, CALIF.

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[CONTRIBUTION NO. 853 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

NAPHTHENIC ACID STUDIES. I. THE SYNTHESIS OF 3,3,4-TRIMETHYLCYCLOPENTANONE[1]

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As a degradation product of certain naphthenic acids, von Braun (1) obtained a ketone $C_8H_{14}O$ to which he assigned the structure (V). In spite of the importance of a verification by synthesis, all attempts (2) to prepare the trimethylcyclopentanone (V) have been unsuccessful.[2]

A number of possible methods for obtaining (V) were considered. These will be outlined here briefly as information on the synthesis of ketones of this type is rather widely scattered in the literature.

A. Conversion of β,β,β'-me_3-adipic acid (me_3 = trimethyl) to (V). While the transformation of me_3-succinic acid to the adipic acid fails (2), the conventional route *via* reduction by appropriate methods (4) of the anhydride of α,β,β me_3-glutaric acid (5) is still open. The desired acid may also be expected [compare formation (6) of β,β-me_2-adipic acid] to result from the oxidation of 3,4,4-me_3-cyclohexanone (I) [preparation from camphor (7); possible preparation from xylenol (8)] or of 3,3,4-me_3-cyclohexanone [possible preparation from me_3-dihydroresorcin (9)]. The preparation of adipic acids by oxidation of Diels-Alder adducts is undoubtedly general (10); conditions for obtaining the required adduct from me_3-ethylene and butadiene are however not yet established (11).

B. Ring contraction (12) of (I) or of 3,3,4-me_3-cyclohexanone. Two cyclopentanones are possible from each ketone; analogies (13) predict that in both cases (V) would be the chief product.

C. Shift (14) of the carbonyl group in 2,2,3-me_3-cyclopentanone (15) or in 2,3,3-me_3-cyclopentanone (15) to the neighboring position. The possibility of a Wagner rearrangement (compare 6 b) during the dehydration step impairs the value of this method.

D. Oxidative transformations starting from 1,1,2-me_3-cyclopentene-2 (16) [compare the formation (17) of cyclopentenone from cyclopentene]. Although the use of selenium dioxide is not indicated (18) here, auto-oxidation might be successful (19).

E. Modification of 3,3,4,4-me_4-cyclopentanone syntheses (20) to fit the present case.

F. See following communication.

It was decided to attempt the utilization of the trimethylcyclohexanone (I) as starting material for both methods (A) and (B). The steps which finally led to (V) are indicated on the chart. Although the direct oxidation of (I) to (IV) could not be accomplished, the adipic acid (IV) was easily obtained[3] (21) from the diketone (III) [or enol form of (III)], which was made *via* the dibromo ketone (II)[4] as intermediate [model experiments decided against direct oxidation

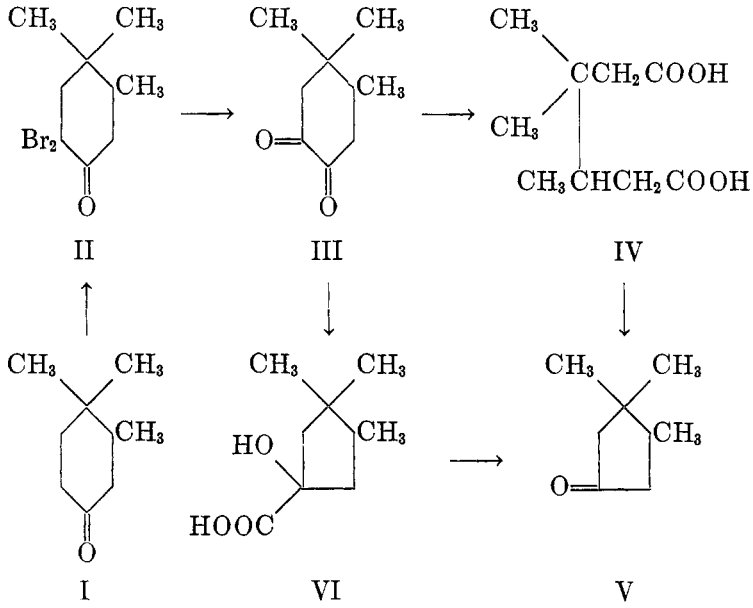
[1] The results contained in this paper were presented before the Pacific Division of the American Association for the Advancement of Science at the Pasadena meeting, June 18, 1941.

[2] The naphthene ketone has been referred to by von Braun (3) as "der Synthese leider nicht zugänglich".

[3] An alternative path leading to (IV) involves the oxidation (23) of the oxymethylene ketone from (I).

[4] We prefer to give this dibromide the structure (II) rather than that of a 3,4,4-trimethyl-2,6-dibromocyclohexanone, since we feel that Wallach's arguments (12 a) in favor of the latter formulation are inconclusive.

(22) of (I) to (III)]. (IV) was smoothly converted to the desired ketone (V). Whereas theoretically the steps leading from (I) to (III) could give rise to two isomeric diketones, the results (see Experimental Part) indicated that little, if any, of a second isomer was formed. That it is (III) which is obtained and not its isomer follows conclusively, aside from the fact that the isomer of (III),



3,4,4-trimethylcyclohexandione-1,2 is reported (7) to have other properties, from the demonstration of two unsubstituted α positions in our ketone (V). The synthesis of (V) by method (B) [(III) → (VI) → (V)] was also achieved; the properties of (V), made by both paths, agree.

TABLE I

	BOILING POINT	SEMICARBAZONE	OXIME	DI-*p*-NITROBENZAL DERIVATIVE
Ketone from naphthenic acids	172–174°	m.p. 162–163°	b.p.$_{14}$ 116–120°	m.p. 188–190°
3,3,4-Trimethylcyclopentanone	172–173°	m.p. 213.5–214.0°	m.p. 99.8–100.0°	α-form, m.p. 204.7–205.1° β-form, m.p. 202.0–202.5°

In Table I, these properties of the synthetic ketone (V) are compared with those given by von Braun (1, 3) for his naphthene ketone. The non-identity of the two substances is beyond question, as there is no doubt that the von Braun semicarbazone was accurately characterized. An unusual feature en-

countered in characterizing (V) was the isolation from it of two di-*p*-nitrobenzal derivatives (24); although four cis-trans isomers are possible, it is customary to encounter but one derivative in reactions of this type.[5]

It is obvious that since the structure assigned by von Braun to his naphthenic acid degradation product is in error, his structures for the parent naphthenic acids also are in need of revision. The correct formulation of the von Braun petroleum acids will be discussed in a future communication from this Laboratory.

EXPERIMENTAL PART

Preliminary experiments. 3,4,4-Trimethylcyclohexanone (I) was prepared from a mixture of 3,4,4-trimethylcyclohexen-2-one and 3,6,6-trimethylcyclohexen-2-one (7) by catalytic reduction and isolation over the bisulfite addition compound; its constants were the same as those found (7) for material prepared by reduction of pure unsaturated ketone. The oxidation of (I) was carried out with potassium permanganate and with nitric acid under conditions which lead to the formation of adipic acid from cyclohexanone. With permanganate, an oily mixture of organic acids was obtained from which no (IV) could be isolated even by the use of seed crystals. With nitric acid there was evidence that nitration took place.

2,2,5-Trimethylcyclohexanone (7) was oxidized (22) by heating with selenium dioxide in ethanol; no appreciable amount of diketone was obtained.

Cyclohexanone (20 g.) was brominated (12) with four atoms of bromine, and the product treated with alkali at room temperature. After acidification, the diketone was taken up in ether (12 b), the ether removed, and the residue mixed with 20 cc. of 30% hydrogen peroxide. The oxidation takes place only in the presence of alkali, which must be added cautiously, as the reaction is exothermic and accompanied by gas evolution. Sodium hydroxide solution was therefore added slowly to the diketone-hydrogen peroxide mixture until it remained strongly basic. After acidification of the reaction product, 2.5 g. of adipic acid was isolated by recrystallization (8% yield from cyclohexanone).

Twenty grams of cyclohexanone was brominated as before, and the product treated with alkali in two steps (12 a). The crude hydroxy acid formed was oxidized with potassium permanganate in dilute sulfuric acid solution (25), a procedure found to give better results than the lead dioxide method (12 a). Two and one-tenth grams of cyclopentanone was isolated, a 12% yield from cyclohexanone.

3,4,4-Trimethyl-6,6-dibromocyclohexanone (II). Two grams of (I) was dissolved in 8 cc. of glacial acetic acid, the solution cooled to 0°, and 4.6 g. of bromine was added slowly with continued cooling. The resulting pale orange solution was poured into ice-water and the organic phase separated by centrifuging; additional small amounts of crude dibromide were obtained by extraction of the aqueous layer with ether. Occasionally the dibromide started to crystallize during the washing with ice-water, otherwise it could be obtained crystalline by strong cooling of a dry petroleum ether-alcohol solution. Recrystallized from petroleum ether, it melted at 81.2–81.7°.

Anal. Calc'd for $C_9H_{14}Br_2O$: C, 36.27; H, 4.73; Br, 53.63.
Found: C, 36.27; H, 4.80; Br, 53.56.

4,4,5-Trimethylcyclohexandione-1,2 (III). The crude dibromide obtained from 2 g. of (I) was shaken vigorously for 1.5 hours with a solution of 2 g. of potassium hydroxide in 20 cc. of water. (Because of the insolubility of the dibromide, aqueous alcoholic sodium

[5] The di-*p*-nitrobenzal derivative from (I) for which the same number of forms are theoretically possible, was isolated (7) only in a single modification.

hydroxide was used in larger runs; this was added in portions and the reaction brought to completion by warming to about 35°.) The resulting yellow solution was filtered from small amounts of tarry matter using "filter aid", and acidified with 6 *N* hydrochloric acid. The oil which precipitated crystallized (in other experiments the oil was first steam distilled and the diketone isolated from the steam distillate) on strong cooling, was filtered, washed with water, and recrystallized from petroleum ether, *m.p.* 93.5–94.1°.

Anal. Calc'd for $C_9H_{14}O_2$: C, 70.10; H, 9.15.
Found: C, 69.79; H, 9.02.

β,β,β'-Trimethyladipic acid (IV). Pure (III) was almost quantitatively converted by alkaline peroxide oxidation to (IV); it was found convenient however to prepare (IV) from crude steam distilled (III). Crude (III) (3.3 g.) obtained from 10 g. of (I) was mixed with 30 cc. of 30% hydrogen peroxide in a 125-cc. flask, and 30% sodium hydroxide solution added cautiously until there was no further evidence of reaction. The reaction mixture was acidified and the precipitate, which crystallized very slowly, removed by filtration and washed with petroleum ether. The crude (IV) was recrystallized from a mixture of isopropyl ether and a little alcohol, seeding and allowing time for complete crystallization. Two crystal forms, triangular plates and rhombs, were noted, both melting at 127.3–127.6° (mixed m.p. same). The yield of pure (IV) [1.75 g. = 13% from (I)] corresponded closely to the weight of crude acid isolated from the acidified reaction mixture, indicating that crude (III) contained no appreciable amount of isomer.

Anal. Calc'd for $C_9H_{16}O_4$: C, 57.43; H, 8.57.
Found: C, 57.27: H, 8.72.

Preparation of 3,3,4-trimethylcyclopentanone (V) from (IV). One and one-half grams of pure (IV) and 0.13 g. of manganese carbonate were placed in a small distilling flask and heated in a metal-bath at 280–320° for one-half hour. One gram of (V) was obtained, which boiled almost entirely at 168–169° (172–173° corr.) at 742 mm., d^{25}_4 0.892, n^{25}_D 1.4386.

Anal. Calc'd for $C_8H_{14}O$: C, 76.14; H, 11.18.
Found: C, 75.95; H, 11.00.

The semicarbazone melted at 213.5–214.0° (from alcohol).

Anal. Calc'd for $C_9H_{17}N_3O$: C, 58.98; H, 9.35; N, 22.93.
Found: C, 59.38; H, 9.44; N, 22.76.

The oxime melted at 99.8–100.0° (from alcohol).

Anal. Calc'd for $C_8H_{15}NO$: N, 9.92. Found: N, 10.14.

The condensation between (V) and *p*-nitrobenzaldehyde was effected by heating the components in alcohol, either with a drop of aqueous sodium hydroxide or with a few drops of sodium carbonate solution; in both cases a mixture of isomers resulted. The separation of the α-form in the pure state was accomplished by several recrystallizations from benzene; orange-yellow needles, m.p. 204.7–205.1°. The isolated clusters of massive rhombs which constitute the β-form were mechanically separated from the tufts of needle crystals. They were slightly paler in color than the α-form, melted at 202.0–202.5° (from benzene), and when mixed with the latter depressed the m.p. considerably.

Anal. Calc'd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14.
Found: (α-form) C, 67.83; H, 5.13; N, 7.19.
Found: (β-form) C, 68.03; H, 5.44; N, 7.27.

A suitable adsorbent for a chromatographic separation of the two forms was not found.

1-Hydroxy-3,3,4-trimethylcyclopentanecarboxylic acid (VI). Twenty grams of (I) in 60 cc. of glacial acetic acid was cooled until crystals of solvent started to separate and, with

continued external cooling, brominated over a 25-minute period with 45.8 g. of bromine in 40 cc. of acetic acid. The product was washed with ice-water and the crude dibromide mixed with 50 cc. of water and 30 cc. of alcohol, cooled, and shaken with a solution of 40 g. of sodium hydroxide in 150 cc. of water (the latter being added slowly and with cooling). As soon as the dibromide had gone into solution, the reaction mixture was filtered, the tar dissolved in alcohol and treated anew with 10 g. of sodium hydroxide in 50 cc. of water, and this reaction product, after adding water to throw out insoluble material and filtering using "filter aid", was combined with the main filtrate. The combined filtrates were evaporated together with an additional 10 g. of sodium hydroxide on the steam-bath for 18 hours, excess 40% sulfuric acid was added to the residue, and the pale yellow oil which separated taken up in ether and the aqueous phase repeatedly extracted with the same solvent. The combined ether solutions on evaporation gave an oil which crystallized in part. The oil was filtered from the crystals (1.5 g.) and the mother liquors distilled *in vacuo*. The distillate (mostly boiling at *ca.* 125° at 2 mm.) also crystallized in part to give 1.9 g. of crystals [total yield of crystalline (VI) 13.5% from (I)]. The distilled crystals (1.9 g.) were recrystallized from petroleum ether-alcohol, yielding 1.0 g. of pure α-isomer m.p. 114.0–114.5° (in another experiment this higher-melting form was obtained by recrystallization of undistilled crystalline acid).

The undistilled crystalline acid above (1.5 g.) proved to be a mixture consisting of the acid just described together with a more slender needle-shaped variety. A small amount of the latter (β-isomer) was obtained in a pure form by repeated recrystallization from petroleum ether-alcohol, m.p. 109–110° (mixed m.p. with its isomer 88–96°).

Anal. Calc'd for $C_9H_{16}O_3$: C, 62.76; H, 9.37.
Found: (α-form) C, 62.90; H, 9.50.
Found: (β-form) C, 62.89; H, 9.57.

Preparation of (V) from (VI). A solution of 0.43 g. of potassium permanganate in 40 cc. of water and 2 cc. of concentrated sulfuric acid was added in portions to 0.70 g. of (VI) (pure α-form) heated to 40°. The reaction proceeded smoothly and the product was isolated by steam distillation in the usual manner, yield 0.45 g. (V) obtained in this way had the same properties as the ketone from (IV); the derivatives were identical (mixed m.p.'s). In another experiment, crude (VI), a mixture of oil and crystals, was oxidized with permanganate; not only was the ketone obtained very similar in properties to pure (V), but also in its behavior towards the usual ketone reagents it proved to be indistinguishable from the latter (indication for substantial purity of crude (III)].

SUMMARY

The synthesis of 3,3,4-trimethylcyclopentanone has been accomplished. This ketone is not identical with the $C_8H_{14}O$ ketone obtained by von Braun from naphthenic acids and consequently the formulation of certain naphthenic acids as related to this ketone is in error.

PASADENA, CALIF.

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CONTRIBUTION NO. 854 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY]

THE SYNTHESIS OF 3,3,4-TRIMETHYLCYCLOPENTANONE. II

HERBERT SARGENT

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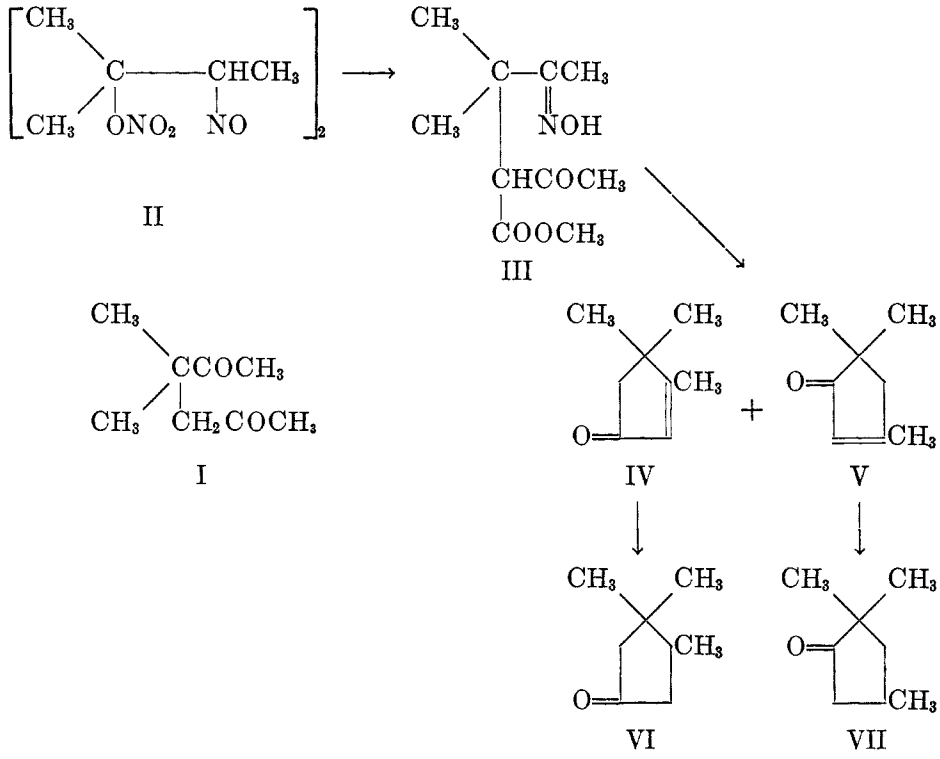
The preceding paper (1) reports the synthesis of the above-named ketone by two closely related paths; several possible alternative methods of synthesis are also listed. To these may be added the following: 3,3-dimethylhexandione-2,5 (I) on cyclization (2) should yield a mixture of (IV) and (V) from which the desired ketone (VI) could be obtained. (I) might conceivably be made by methylation of acetonylacetone or by the action of chloroacetone on sodium methyl isopropyl ketone.



The literature (3, 4) discloses that the equivalent of these reactions has already been carried out by Wallach. His synthesis started from "bis-trimethylethylene nitrosate" (II) which was condensed with sodium methyl acetoacetate to give the compound (III). Treatment of this latter with 50% potassium hydroxide yielded an unsaturated ketone fraction which, on the basis of analogy (5), would be expected to be a mixture of (IV) and (V). Actually Wallach (3) characterized but one trimethylcyclopentenone, which he regarded as (V);

reduction (4) of his crude ketone product gave a mixture of saturated isomers. While pointing out that these isomers[1] might correspond to (VI) and (VII), Wallach left open the question of assigning definite structures.

The repetition of these experiments led to the isolation from (III) of two isomeric unsaturated ketones, which were separated by careful fractionation; reduction afforded the corresponding saturated ketones. The structure of the higher-boiling saturated isomer is established by virtue of its identity with ketone (VI) obtained (1) from 3,4,4-trimethylcyclohexanone. The structures of the parent unsaturated ketone (IV) and of the related pair (V) and (VII) follow indirectly and find further substantiation in the properties of these substances (see Table I). A comparison of the Table with that in the paper next preceding

TABLE I

	IV[a]	V	VI[b]	VII[c]
Boiling point	b.p.$_{20}$ 87.5–88.0°	b.p.$_{20}$ 76.5–77.0°	b.p.$_{742}$ 173–175°	b.p.$_{742}$ 157–158°
Semicarbazone	m.p. 199.5–200.0° forms rapidly	m.p. 205.0–205.5° forms slowly	m.p. 213.5–214.0°	m.p. 171.0–171.3°
Derivative with hydroxyl amine	oil presumably an oxime	oxime m.p. 108.0–108.2°	m.p. 99.8–100.0°	m.p. 79.7–80.0°
Derivatives with *p*-nitrobenzaldehyde			di-*p*-nitrobenzal derivatives m.p. 204.7–205.1° m.p. 202.0–202.5°	mono-*p*-nitrobenzal derivative m.p. 99.3–99.5°
Reaction with bisulfite	none	none	reacts slowly	none

[a] Wallach (3) reported as a derivative of this compound the semicarbazone, m.p. 199–200°.

[b] Wallach (4) reported for this compound: b.p. 167–171°, semicarbazone, m.p. 214°, oxime, m.p. 110°.

[c] Wallach (4) reported for this compound: b.p. 162–168°, semicarbazone, m.p. 178°, oxime, m.p. 78°.

(5) brings out not uninteresting resemblances between the 5-ring ketones (IV), (V), (VI), and (VII) and their correspondingly numbered 6-ring analogs.

The author wishes to thank Dr. E. R. Buchman for suggesting this problem and for helpful advice in connection with the work.

EXPERIMENTAL PART

Preparation of unsaturated ketone mixture.[2] "Bis-trimethylethylene nitrosate" (II) was prepared as indicated in the literature (7) by passing oxides of nitrogen into a solution of 60 cc. of trimethylethylene in 150 cc. of glacial acetic acid which was kept cooled to the

[1] Chemisches Zentralblatt (6) refers to these as 2,2,4-trimethylcyclopentanone "Nr. 1" and "Nr. 2". It is thus understandable how any but the most thorough literature survey would have failed to disclose their bearing upon the naphthene ketone problem (1).

[2] No appreciable amount of 3-methylcyclopenten-2-one was obtained from the action of aqueous alkali on acetonylacetone; much tar was formed.

point where solid acetic acid separated. The nitrogen dioxide was generated by the action of nitric acid on copper turnings (superior to the action of concentrated nitric acid on arsenic trioxide); the passage of gas was stopped as soon as the solution turned green, and the crystals which had separated were filtered off and washed with acetic acid and with water. The resulting white crystalline material[3] was air dried (44% yield); further small amounts of crude (II) were precipitated from the mother liquors by addition of water.

The nitrosate prepared in this manner proved suitable for conversion into (III); Wallach (3) had claimed that a specially purified (II) was necessary. Nine and six-tenths grams of sodium was dissolved in 160 cc. of methanol, 52 g. of methyl acetoacetate added, and the solution cooled. Sixty-four grams of (II) was then added and the mixture heated cautiously to initiate the reaction which proceeded exothermally; cooling of the reaction flask with running tap water was necessary to prevent loss of solvent through the condenser. The reaction was complete in five minutes, at the end of which the solvent was removed *in vacuo* and the residue refluxed for four hours from a copper retort with 450 g. of potassium hydroxide and 450 cc. of water, and then steam distilled. In a parallel experiment, after the reaction was complete, the solution was filtered from the sodium nitrate which had separated, the filtrate evaporated and (III) isolated from the residue by recrystallization from alcohol-acetone; m.p. 148.5–149.0° (analysis), turns reddish on exposure to light.

The steam distillates from three of the above sized runs were combined, saturated with ammonium sulfate, extracted several times with isopropyl ether, the ether extracts dried over sodium sulfate and fractionated.[4] The main fraction, b.p. 75–90° at 20 mm., consisted for the most part of (IV) and (V) and amounted to 73 g., 49% yield from (II).

3,4,4-Trimethylcyclopenten-2-one (*IV*) was obtained in an 11% yield from (II) on refractionation of the unsaturated ketone mixture through a precision column, b.p. 87.5–88.0° at 20 mm., d_4^{30} 0.925, $n^{30}D$ 1.4720. Analysis and behavior on reduction disclosed the presence of a small amount of nitrogen-containing impurity; the constants given are therefore only approximately correct for pure (IV).

Anal. Calc'd for $C_8H_{12}O$: C, 77.37; H, 9.74.
Found: C, 76.64; H, 9.97.

(IV) did not react with aqueous sodium bisulfite solution. The oxime was obtained as an oil; the semicarbazone formed readily, m.p. 199.5–200.0° from ethanol.

Anal. Calc'd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19.
Found: C, 59.84; H, 8.31; N, 23.60.

3,5,5-Trimethylcyclopenten-2-one (*V*) was obtained as above in 12% yield from (II), b.p. 76.5–77.0° at 20 mm., d_4^{30} 0.906, $n^{30}D$ 1.4608.

Anal. Calc'd for $C_8H_{12}O$: C, 77.37; H, 9.74.
Found: C, 76.35; H, 9.87.

(V) also did not form a bisulfite addition compound. The product obtained with hydroxylamine was found difficult to purify by recrystallization; it was sublimed at 2 mm. and the crystalline sublimate recrystallized from isopropyl ether, needles, m.p. 108.0–108.2°.

Anal. Calc'd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06.
Found: C, 69.23; H, 9.41; N, 10.28.

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[3] Attention may be directed to the fact that (II) cannot be stored. An explosion occurred when a sample, which had stood in a stoppered bottle for 2½ weeks without noticeable alteration, suddenly decomposed completely.

[4] From the forerun was isolated about one-half gram of acetone oxime (analysis, mixed m.p.) b.p. *ca.* 61° at 20 mm., m.p. 61.0–61.2° from petroleum ether. With an equivalent amount of picric acid this substance gave a picrate, quite soluble in the usual solvents, m.p. 82.0–82.2° from isopropyl ether-alcohol (analysis). The addition compound lost its acetone oxime on drying *in vacuo* at room temperature.

The analysis discloses that the derivative is an oxime; higher molecular weight amorphous material also sublimed, so that the formation of hydroxylaminooxime cannot be excluded. By comparison with its isomer, the semicarbazone formed at an extremely slow rate; for its preparation the components were allowed to stand in aqueous solution at room temperature for two weeks, m.p. 205.0–205.5° from ethanol-water.

Anal. Calc'd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19.
Found: C, 59.96; H, 8.31; N, 23.53.

3,3,4-Trimethylcyclopentanone (*VI*) was prepared by catalytic reduction (5) of (IV), b.p. 169–171° (173–175° corr.) at 742 mm., d_4^{26} 0.892, $n^{26}D$ 1.4380 (analysis). The crude reduction product contained a small amount of volatile base, possibly ammonia, arising from the nitrogen-containing impurity in (IV). (VI) reacted slowly with saturated aqueous bisulfite solution [means of separation from (VII)]. The derivatives, including the di-*p*-nitrobenzal derivatives, were identical with those described (1) previously (mixed m.p.'s). The m.p. of the oxime (100.8–101.0° corr.) was unchanged after repeated recrystallization (Wallach reported 110°).

2,2,4-Trimethylcyclopentanone (*VII*) was formed by catalytic reduction of (V), b.p. 153–154° at 742 mm., d_4^{26} 0.871, $n^{26}D$ 1.4279.

Anal. Calc'd for $C_8H_{14}O$: C, 76.14; H, 11.18.
Found: C, 75.15; H, 11.26.

(VII) did not form a bisulfite addition compound. It reacted with semicarbazide somewhat less readily than its isomer; semicarbazone m.p. 171.0–171.3° from alcohol.

Anal. Calc'd for $C_9H_{17}N_3O$: N, 22.93. Found: N, 22.90.

The oxime was crystallized from alcohol and sublimed at 3 mm. for analysis, m.p. 79.7–80.0°; *in vacuo* it is noticeably volatile even at room temperature.

Anal. Calc'd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92.
Found: C, 68.02; H, 10.59; N, 10.11.

A pale yellow mono-*p*-nitrobenzal derivative was obtained in the usual manner, m.p. 99.3–99.5° from methanol.

Anal. Calc'd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40.
Found: C, 69.95; H, 6.93; N, 5.94.

SUMMARY

A convenient method for the synthesis of 3,3,4-trimethylcyclopentanone has been described.

3,4,4-Trimethylcyclopenten-2-one, 3,5,5-trimethylcyclopenten-2-one and 2,2,4-trimethylcyclopentanone have been characterized.

PASADENA, CALIF.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, AND THE NATIONAL INSTITUTE OF HEALTH]

A NEW DEGRADATION PRODUCT FROM MORPHINE[1]

LYNDON SMALL

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Morphine, its methyl ether, codeine, and other morphine derivatives of the same degree of unsaturation, undergo degradation to phenanthrene derivatives by two general methods, acetolysis, and exhaustive methylation. The nitrogen-free products are, respectively, methylmorphol (I) and methylmorphenol (II), or simple derivatives of these. The distinctive feature of the degradation is the loss of the entire ethanamine chain from the molecule, a phenomenon that led Gulland and Robinson (1) to propose a logical modification[2] of the Knorr-Wieland (2) formula, that subsequently found experimental support in the work of Schöpf (3). The extrusion of carbons 15 and 16 is so general that there is no instance of degradation of true morphine derivatives without loss of the ethanamine moiety, excepting where aromatization is blocked by hydrogenation, *e.g.*, dihydrothebainone and dihydrocodeinone derivatives (2, 4), or by nuclear substituents (5).

Studies in progress on methylmorphenol have necessitated the degradation of several kilograms of morphine through codeine methomethylsulfate, for which Mosettig and Meitzner (6) developed a modified Hofmann method, using sodium cyclohexoxide in cyclohexanol instead of alkali. As a by-product of the reaction, these investigators isolated a small amount of a new, nitrogen-free product, which has now been subjected to further study.

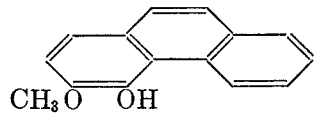
The new compound represents about 1% of the weight of morphine degraded, or about 2% of the total isolable degradation product. Analysis shows it to have the composition $C_{17}H_{14}O_2$, and to contain one methoxyl group. Since the compound is not phenolic, and gives no reactions for the alcoholic or ketonic groups, the second oxygen atom is probably in a cyclic ether linkage. These facts suggested formula III for the compound. This structure is hardly tenable, however, for the substance is indifferent to catalytic hydrogenation,[3] and, more important, is optically inactive. It reacts with but one mole of bromine, giving a monobromo substitution product.

[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General, U. S. Public Health Service.

[2] *Cf.* also Pschorr, *Ann.*, **373**, 64 (1910). The tendency towards aromatization as the driving force resulting in loss of the vinyl group was also recognized by Freund (5 b), although his reasoning was incomplete.

[3] That the vinyl group at C-13 in degradation products of this type is not sufficiently hindered to resist hydrogenation has been demonstrated in the reduction of the vinyl derivative obtained as end-product in the degradation of dihydrothebaine [Wieland and Kotake (2)].

Structure IV, which might have resulted from a cyclization of the thebenone type, is open to the same objections, and, moreover, involves two additional hydrogen atoms which our analytical procedure is capable of detecting.



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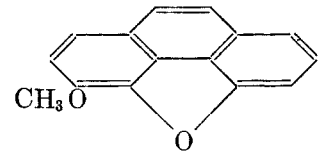

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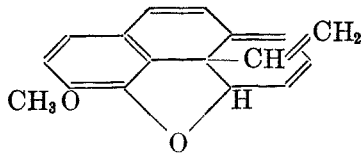
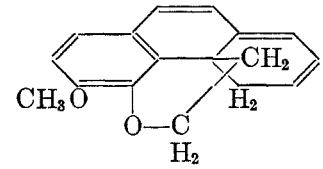


III



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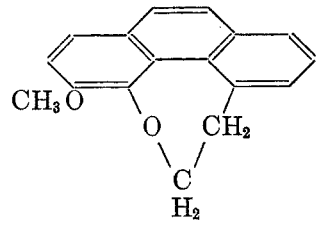

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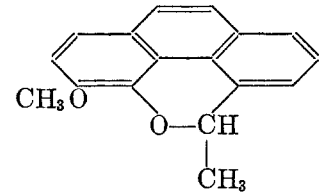
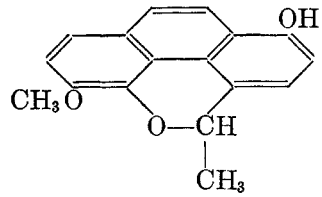


VI



VII

This brings formulas V or VI into consideration, either of which explains all of the observed facts. Of the two formulas, the six-membered ring structure of VI is the more probable. This idea finds confirmation in the results of a C-methyl determination, for which I am indebted to the kindness of Dr. R. T. Major and Mr. Douglass Hayman, of Merck and Co., Rahway, N. J. One C-methyl group is present, which probably excludes formula V. Although VI contains an asymmetric carbon atom, it would not be expected to be optically active, for the ring-closure undoubtedly took place after the morphine asymmetric centers had been destroyed by aromatization. Compound VI, 3-methoxy-5-methyl-5-phenanthro[4,5-bcd]pyran, (Ring Index 2795), is accordingly an analog of thebenol (VII), the end-product of exhaustive methylation of

thebenine (7). The six-membered heterocyclic ring structure in thebenol was first suggested without evidence by Gulland and Virden (8).

Whereas VI contains no group at which an optically active appendage might be attached to permit resolution, VII offers this possibility. Attempts to obtain an optically active derivative of thebenol have so far failed.

The structural concept of VI is supported by the results of zinc-dust distillation, which, like that of thebenol (7b, 9), yielded pyrene. While this is not conclusive proof of the position of the saturated chain, there is no instance of the formation of pyrene in the morphine group except from those compounds known to have the chain at the 5 position. Attempts to establish a direct relationship between VI and thebenol by elimination of the 8-hydroxyl group from the latter through the amino compound [method of Werner (10) or Bucherer (11)] failed. Thebenol was recovered unchanged from the attempted amination, or under more drastic conditions was decomposed. The ether ring of VI is exceedingly resistant to scission. Prolonged boiling with concentrated hydriodic acid in acetic anhydride resulted only in demethylation, with formation of 3-hydroxy-5-methyl-5-phenanthro[4,5-bcd]pyran. Opening the ring by alkali fusion was not attempted because of the exceedingly low yield recorded in the analogous reaction with methylmorphenol (12).

In addition to VI, the cyclohexoxide degradation of morphine yielded two other new products. One of these, a sparkling, colorless, mobile liquid, does not form a picrate, and its high hydrogen content indicates that it is probably derived from the cyclohexanol used. The second product (only 0.75 g. from 1.5 kg. of morphine), nitrogen-free, is high-melting and very sparingly soluble, and molecular weight values show that if it is derived from morphine, it must be dimolecular in nature. It is methoxyl-free, which fact, however, does not exclude its formation from the codeine methomethylsulfate used, since demethylation at C-3 has been observed under strenuous alkaline conditions.

It is very doubtful that the isolation of VI from an alkaline degradation of morphine methyl ether is of any significance for the morphine structural formula. The ethanamine chain has heretofore been observed to wander only under strongly acid conditions, and then only to C-8. In thebaine and codeinone, also under acid conditions, the chain may shift to 5, 14, or 8 (assuming the original position to be 13). A shift of the chain in a morphimethine, as implied by the appearance of VI, has never been observed. In view, however, of the well known lability of the ethanamine group in the morphine series, it is most reasonable to regard VI as the product of a rearrangement, and not as affording any evidence in favor of the Knorr-Wieland morphine formula.

EXPERIMENTAL

3-Methoxy-5-methyl-5-phenanthro[4,5-bcd]pyran (VI). The methanol mother liquors from purification of the methylmorphenol prepared by degradation of 1500 g. of morphine by the Mosettig-Meitzner method (6), gave on concentration 150 g. of black oil. This was treated with hot alcoholic picric acid. The mother liquors from crystallization of the picrate yielded a black oil (13 g., A). The picrate was decomposed with ammonia and extracted with ether, from which 31 g. of tan crystals (m.p. 60–91°, B) and 40 g. (C) of dark

oil were obtained. The crystalline fraction B was recrystallized several times from alcohol, and the melting point reached the constant level 82–93°. The material was sublimed slowly in a long tube at 100°, under an oil-pump vacuum. Two easily distinguishable zones were obtained; the one farthest from the heater, a dense layer of granular crystals, represented about half the sample, had the m.p. 58–60° (after purification, m.p. 63–65°), and was identified as methylmorphenol. The zone nearest the heater was a dense plug of acicular crystals, m.p. 115–116°; this was crystallized twice from ethyl acetate and resublimed. It had the m.p. 118.5°, $[\alpha]^{25}_{D}$ 0.0° (absol. alcohol, c = 1.00).

Anal. Calc'd for $C_{17}H_{14}O_2$: C, 81.57; H, 5.65; 1 OCH_3, 12.4; 1 C-CH_3, 6.0; m. w. 250.
Found: (average of 6 anal.) C, 81.44; H, 5.55; OCH_3, 11.8; C-CH_3, 5.00, 4.64; m. w. (micro-Rast), 248.

The compound was insoluble in aqueous alkali, and insoluble in alcoholic alkali beyond its solubility in alcohol alone; no ferric chloride reaction in alcohol. It gave no reaction with hydroxylamine. Catalytic hydrogenation (platinum oxide in alcohol) was completely negative. It was recovered unchanged from attempted dehydrogenation with palladium, refluxing in naphthalene. It was not oxidized by prolonged boiling with permanganate in acetone. From chromic acid oxidation a brilliant yellow powder was obtained that did not crystallize and could not be further characterized.

The *picrate* was prepared by mixing equal weights of the compound and picric acid and recrystallizing twice from boiling alcohol; long, deep purple rods, red-brown by transmitted light; m.p. 107–108°; unstable, turning black and resinous after a few weeks.

Anal. Calc'd for $C_{23}H_{17}N_3O_9$: N, 8.76.
Found: N, 8.75.

1(?)-Bromo-3-methoxy-5-methyl-5-phenanthro[4,5-bcd]pyran. A solution of 0.2 g. of VI in 3 cc. of glacial acetic acid was treated with bromine in acetic acid until the solution was faintly yellow. Calculated for 1 mole of bromine 0.127 g., used, 0.13 g. The slight excess of bromine was destroyed with sulfur dioxide, water was added (white emulsion) and the solution made alkaline with 40% sodium hydroxide. By ether extraction and crystallization from alcohol 0.23 g. of bromo derivative was obtained. After sublimation in a high vacuum at 110° (cold finger) it formed white needles, m.p. 104–105°.

Anal. Calc'd for $C_{17}H_{13}BrO_2$: C, 62.00; H, 3.98.
Found: C, 62.09; H, 3.97.

3-Hydroxy-5-methyl-5-phenanthro[4,5-bcd]pyran. When VI was boiled in 48% hydrobromic acid, intense purple color developed, and the compound went largely into solution. On dilution, the color disappeared, and VI was regained in a pure state. In an unsuccessful attempt to cleave the pyran ring, 0.2 g. of VI was refluxed for 15 minutes in a mixture of equal parts of acetic anhydride and hydriodic acid (sp. gr. 1.7). The red solution and resin was poured onto ice, extracted with ether, and the residue from the ether was dissolved in normal sodium hydroxide, from which lozenge-shaped crystals of the sodium salt separated. It was warmed into solution and carbon dioxide was run in. The viscous precipitate was taken into ether, from which an oil was obtained. This crystallized from petroleum ether (by evaporation), and the crystals were sublimed twice in a high vacuum at 125° (cold finger); icicle-shaped crystal masses, m.p. 84–84.5°.

Anal. Calc'd for $C_{16}H_{12}O_2$: C, 81.35; H, 5.12.
Found: C, 80.93; H, 5.08.

Degradation of VI. A mixture of 1 g. of VI with 10 g. of zinc dust was heated until all of the organic matter had been distilled (in a hydrogen stream) over a layer 15 cm. long of zinc dust (30 g.) heated to dull redness. The distillate was dissolved in ether, from which a brown oil was obtained; this was distilled onto a cold finger in a high vacuum at 110°, form-

ing yellow, waxy globules that crystallized in shining flakes when rubbed with alcohol; yield 100 mg., m.p. 118–122°. After seven crystallizations and two vacuum sublimations, it melted at 145–147°, mixed melting point with pyrene (m.p. 149°) 146–148°.

Anal. Calc'd for $C_{16}H_{10}$: C, 95.01; H, 4.99.
Found: C, 95.03; H, 5.16.

It yielded a picrate (unstable on long standing), red needles, m.p. 220–222°, no depression when mixed with pyrene picrate. The styphnate, orange needles (unstable to recrystallization) melted at 182–193°, and in mixture with pyrene styphnate (m.p. 189°) melted at 184–187°.

Composition of fraction A. The sirupy fraction A from the crude morphine degradation products did not form a crystalline picrate, even though it was found to contain about 16% of compound VI. The 13 g. of oil was rubbed well with 100 cc. of 60–70° ligroin, and the yellow solution was decanted from a pasty residue. The residue crystallized from ether (evaporation), giving 2.1 g. of VI. The ligroin was distilled under reduced pressure, leaving 9 g. of a mobile, red oil; insoluble in acid or alkali, alcoholic ferric chloride test brown with green tinge; nitrogen-free. In a high vacuum it distilled rapidly at 100° onto a cold finger, as a sparkling, colorless, mobile liquid, n^{25}_D 1.5613. Its odor was strong, and reminiscent of the cyclohexane series.

Anal. Found: C, 80.23; H, 10.42.

Composition of fraction C. The 40 g. of dark picrate-forming oil from the separation of the crude morphine degradation products, with alcoholic picric acid, gave 56 g. of a brown picrate, long needles. The mother liquor slowly deposited 4.5 g. of magnificent black crystals from which 2.5 g. of VI was obtained. The main crop of picrate gave 20.8 g. of methylmorphenol, m.p. 65°. During the recrystallization of this, 0.75 g. of very sparingly soluble white crystals was isolated. The compound was nitrogen-free, insoluble in acid or alkali, began to yellow at 265° and melted with darkening at 270–272°. It could be recrystallized from 50 cc. of ethyl acetate; $[\alpha]^{20}_D$ 0.0° (dioxane, c = 0.50). Colorless solutions in ethyl acetate or dioxane turned deep purple after a few hours exposure to air. It may be a dimolecular product derived from morphine, with a pseudomorphine-type linkage.

Anal. Found: C, 80.16, 80.36; H, 4.88, 4.83; m.w. (micro-Rast), 420, 448.

Thebenol. Attempts to convert thebenol (VII) to VI through the amino compound failed. It was regained unchanged after 30 hours at 140° with ammonia and ammonium sulfite (11). With sodium acetate, ammonium chloride, and acetic acid at 270° for 12 hours, it was decomposed to a black tar.

The pyran ring in thebenol could not be opened. Refluxing with acetic anhydride and hydriodic acid caused decomposition, with 32% hydrogen bromide in glacial acetic acid demethylation was the only change. Fusion with aniline hydrochloride (13) at 220° for 1 hour likewise gave only northebenol. In an attempt to obtain derivatives of thebenol that might be susceptible of resolution, reaction of the sodium salt with acetobromoglucose was unsuccessfully tried. The application of Helferich's method (14) with pentaacetyl-β-glucose in the presence of p-toluenesulfonic acid in xylene resulted in decomposition products.

SUMMARY

A new nitrogen-free degradation product from morphine is described, and evidence is advanced that it has the structure 3-methoxy-5-methyl-5-phenanthro[4,5-bcd]pyran.

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[CONTRIBUTION FROM THE DIVISIONS OF AGRICULTURAL BIOCHEMISTRY AND ORGANIC CHEMISTRY, UNIVERSITY OF MINNESOTA]

TECHNICS IN THE SYNTHESIS OF PORPHYRINDIN[1]

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Since the important oxidation-reduction dye, porphyrindin, is not commercially available, many laboratories interested in sulfhydryl studies need a means of synthesizing the indicator in the shortest time possible. Directions now available in the literature are abbreviated and omit precautionary measures with the result that attempted syntheses have been found unsatisfactory or unsuccessful.

The purpose of the present investigation was to study the steps of the synthesis in detail with a view to discovering and overcoming pitfalls responsible for failures and to coordinate the whole into a workable method.

Acetoxime (I), either as the Eastman product redistilled, or as prepared according to Semon (1), was found suitable for the preparation of the nitrile (II).

The Porter and Hellerman (2) method of preparing (II) was modified by drying the ether extracts of the reaction mixture with anhydrous sodium sulfate and by performing crystallizations and filtrations in a cold room at $-18°$. The product was exhaustively extracted with petroleum ether and used directly in the preparation of the imino ether (III) without further purification.

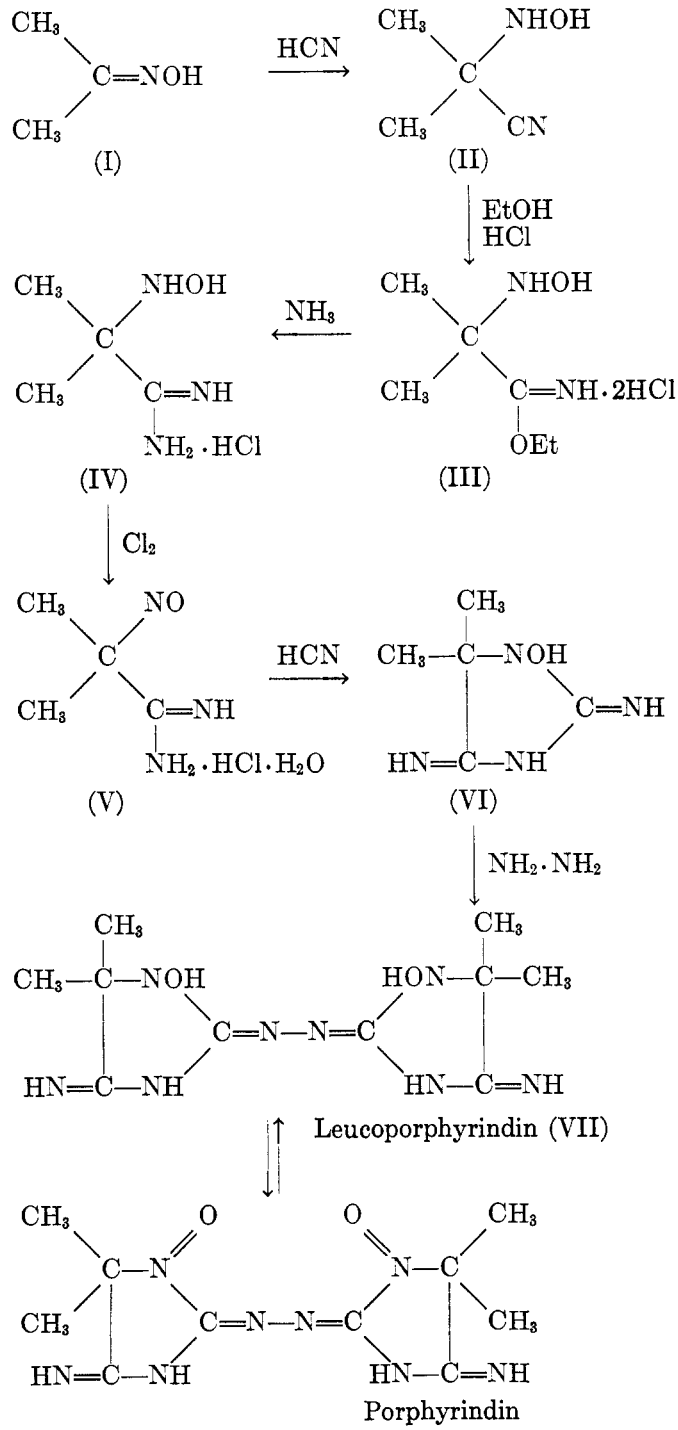
The preparation of (III) by the method of Piloty and Schwerin (3) was found to be successful only if extreme care is taken to exclude moisture from the operation. Commercial absolute alcohol was dried by refluxing over powdered magnesium methoxide and then distilled onto (II) to give a solution through which dried hydrogen chloride gas was passed to form (III). This entire step, including the drying and distillation of alcohol, as well as hydrogen chloride absorption, was carried out in a single closed system, exposure to the air being through desiccant traps. Rubber stoppers were found suitable for connections.

The preparation of the amidine (IV) by the method of Piloty and Schwerin (3) was found to lead largely to syrups which could not be used successfully as such in the next step of the synthesis. It was found that by proper treatment of the syrup with ether, crystalline amidine was obtained in satisfactory yields.

For the preparation of the nitroso compound (V), Kuhn and Franke (4) indicated that an acid solution of (IV) was treated continuously with chlorine until no more product precipitated. We have found that intermittent additions of chlorine followed by periods of standing are necessary because the product separates out very slowly. The intervening periods of rest allow time for separation without side reactions which take place when excess chlorine is present. Filtration of the product is carried out after each rest period before chlorine treatment is resumed.

[1] Herman Frasch Foundation for Research in Agricultural Chemistry, Paper No. 215. Paper No. 1940 Scientific Journal Series, Minnesota Agricultural Experiment Station.

[2] Frasch Fellow.


CH3
C=NOH
CH3
(I)
HCN
CH3
NHOH
C
CH3
CN
(II)
EtOH
HCl
CH3
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C
CH3
C=NH·2HCl
OEt
(III)
NH3
CH3
NHOH
C
CH3
C=NH
NH2·HCl
(IV)
Cl2
CH3
NO
C
CH3
C=NH
NH2·HCl·H2O
(V)
HCN
CH3
CH3—C—NOH
C=NH
HN=C—NH
(VI)
NH2·NH2
CH3
CH3—C—NOH
C=N—N=C
HN=C—NH
CH3
HON—C—CH3
HN—C=NH
Leucoporphyrindin (VII)
CH3
O
C—N
CH3
C=N—N=C
HN=C—NH
O
CH3
N—C
CH3
HN—C=NH
Porphyrindin

The reaction of potassium cyanide upon (V) to form the ring compound porphyrexin (VI) in the manner of Kuhn and Franke (4) was successful only when a rapid generation of gas took place. This was interpreted as a sign of the desired reaction occurring. Manner of addition and stirring were found to influence yield.

The preparation of leucoporphyrindin (VII) was successful only when a half mole of hydrazine hydrate per mole of (VI) was used, as suggested by Kuhn (4). Molar ratios in the manner of Piloty (5) gave syrups instead of the desired crystals. Leucoporphyrindin is relatively unstable, must be kept cool and in the dark, and should be prepared in small quantities as needed. Porphyrexin probably should be the stopping point in a commercial synthesis. It is stable and can be stored indefinitely.

EXPERIMENTAL

Preparation of α-hydroxylaminoisobutyronitrile (II). (I) (180 g.) was dissolved in 495 ml. of water and placed in a 5-liter flask equipped with a stirrer and dropping-funnel in an ice-bath in a hood. After adding 1190 g. of potassium dihydrogen phosphate (Mallinckrodt), stirring was begun and an ice-cold solution of 215 g. of sodium cyanide in 530 ml. of water was added dropwise. After complete addition of cyanide, the mixture was allowed to come to room temperature, was sealed with a rubber stopper, and kept in the hood for 18 hours with occasional shaking. The yellow oily layer was removed and the solution remaining was extracted with three 250-ml. portions of ether. The oily layer with added ether extracts was dried over anhydrous sodium sulfate, concentrated by the use of a stream of clean, dry air, and was crystallized by allowing the resulting syrup to stand 4–5 hours in a cold room at −18°. Using an oil-pump in the cold room, the crystals were filtered off. The mother liquor *in vacuo* in the cold room gave a second crop of crystals which was added to the first, and the combined crops were placed in a vacuum desiccator over activated alumina with suction being applied for an hour in the cold chamber. Suction was continued overnight in the laboratory at room temperature. The dried mass was extracted with petroleum ether until the extracts no longer gave acetoxime upon evaporation. The petroleum ether-insoluble residue was dried *in vacuo* over activated alumina overnight and was used directly in the synthesis of (III). Yield, 65 g. of nitrile; 110 g. of recovered acetoxime from petroleum ether extracts. Considering the recovered acetoxime apart from the reaction, the yield of (II) was 67%.

Preparation of α-hydroxylaminoisobutyro ethyl imino ether dihydrochloride (III). The closed system used is shown in Figure 1. The 65 g. of (II) was placed in the 2-liter round-bottom flask F. Commercial absolute ethyl alcohol was dried by refluxing in flask A with powdered magnesium methoxide for three hours using condenser B. Using condenser C, enough alcohol was distilled to dissolve (II). An ice-salt-bath was then applied to F, and hydrogen chloride, generated at K, was passed through the drying-bottles (sulfuric acid) J and I, the safety trap H, and the sintered glass gas distributor D, into the solution of (II) in alcohol. The alcohol became saturated in about 4 hours, as indicated by the fact that hydrogen chloride was no longer absorbed. Flask F was then removed, stoppered with a rubber stopper, and placed in a refrigerator. Crystals appeared within an hour, and after 48 hours were filtered off and placed in a vacuum desiccator over potassium hydroxide to remove excess hydrogen chloride. Yield, 125 g.; 90% of the theoretical, assuming (II) to be pure; sintered at 110°, melted at 180° with decomposition.

Preparation of α-hydroxylaminoisobutyroamidine hydrochloride (IV). In a hood, tank ammonia was passed slowly over 900 g. of cold absolute ethyl alcohol (magnesium methoxide dried) with stirring to effect solution. When approximately 65 g. of ammonia had been added, the total weight of solution was carefully noted and the whole was placed in

a cold room just above 0° and was sealed with a rubber stopper. By taking aliquot weight portions in the cold room, known amounts of ammonia could be measured.

Dry and powdered (III) (50 g.) was suspended in 250 ml. of absolute ethyl alcohol and then enough ammonia solution was added to give 2.5 molar ratio of ammonia to (III) (144 g. of solution if exactly 65 g. of ammonia had been added to 900 g. of alcohol). The mixture was stoppered and shaken for 5 hours at room temperature and, after removal of insoluble ammonium chloride, was concentrated *in vacuo* at room temperature to give a syrup. Ether was added to the syrup in sufficient quantity to precipitate a white sticky mass, which was converted into pure crystalline (IV) by scratching with a glass rod. Yield, 18 g. (51%) [Piloty (3) 50%; Kuhn (4) nearly quantitative]; m.p. 150° with decomposition.

Preparation of α-nitrosoisobutyroamidine hydrochloride hydrate (V). (IV) (10 g.) was dissolved in 50 ml. of water containing 1 ml. of concentrated hydrochloric acid. Tank chlorine was passed through the solution very slowly through a sintered glass gas distributor until the blue solution became turbid (about 15 minutes). The white precipitate

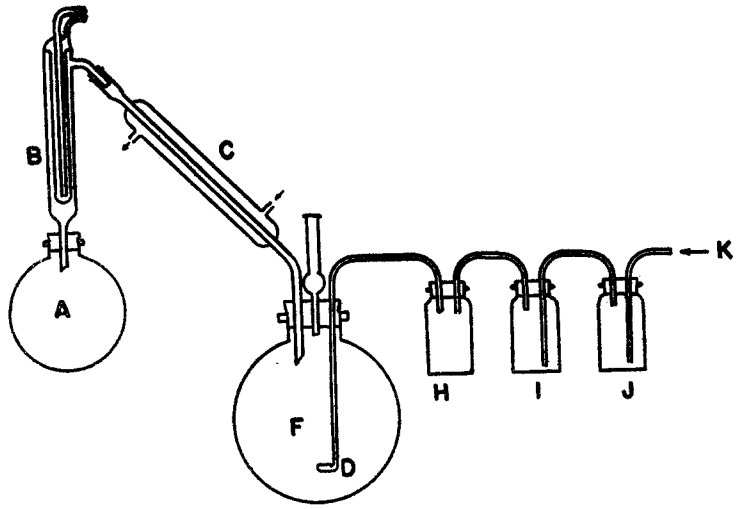

FIG. 1. SYSTEM USED IN THE PREPARATION OF IMINO ETHER (III)

formed on standing was filtered off and chlorine treatment was repeated. This process was repeated until no more precipitate formed on standing. The yield was the same whether the solution was treated with chlorine at 0°, or at room temperature. Yield, 8 g. (72%); m.p. 148°.

Preparation of porphyrexin(VI). A rapidly stirred solution of 1.1 g. of potassium cyanide in 3.5 ml. of water in a test tube was heated to 60° in a water-bath and 2 g. of (V) was added fairly rapidly. A brown solution resulted, and this was further stirred at 60° until a rapid generation of gas took place. [We have not been able to isolate (VI) when the frothing does not take place.] The solution was cooled and the precipitate formed was filtered off and dried in a desiccator over activated alumina. When the product was boiled with absolute ethyl alcohol, a trace of potassium chloride remained insoluble and, after filtration and evaporation of the filtrate to dryness, a mass of crystals of (VI) remained. Yield, 1.5 g. (89%); m.p. 249–50°.

Preparation of leucoporphyrindin (VII). (VI) (1 g.) was dissolved in 10 ml. of hot water and then 0.17 g. of hydrazine hydrate was added. The solution was boiled down to a thick syrup, which was cooled to give a solid mass of yellow crystals, which were suspended in absolute alcohol and filtered. Yield, 0.3 g. (30%); m.p. 277°.

SUMMARY

A study was made of the synthesis of porphyrindin. Necessary precautions, not directly specified in previous literature, have been developed and added to earlier methods. An improvement in the yield of nitrile from acetoxime was made possible by cold room techniques and by extractions with petroleum ether instead of recrystallization. It was found that the most difficult step (imino ether hydrochloride) gave excellent yields when extreme care was taken to ensure anhydrous conditions. Minor modifications in the last four steps have been applied to give some measure of success in place of the failures resulting from insufficient practice and knowledge of procedure. All knowledge, gained from the literature and from experiment, has been incorporated into a readily workable method.

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[COMMUNICATION NO. 841 FROM THE KODAK RESEARCH LABORATORIES]

SOME OBSERVATIONS UPON THE RELATION BETWEEN ABSORPTION SPECTRA AND CONSTITUTION OF CERTAIN ACID ANTHRAQUINONE DYES

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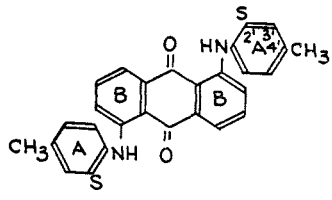
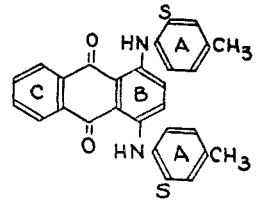
A sufficient amount of information is now available from the studies on isomers and homologs of the acid anthraquinone dye, Toluidine Blue (1, 2, 3), so that one may attempt to relate spectral absorption characteristics and molecular structure. This relation to be discussed in this paper is limited to the effects of groups in the blue and green dyes in the 1,4- and 1,5-series; it is only a part of the general topic of color and constitution of anthraquinone dyes, which is summarized in Houben (10). The blue and green series are of the general types I and II, respectively. The isomers and homologs are derived by varying the



I S = $NaSO_3$



II S = $NaSO_3$

nature of the groups in the rings A, B, and C. The older dyes considered (the formulas of which are not given in this paper) are the sodium salts of 1,5-di(2′-sulfo-4′-methylanilino)anthraquinone (Anthraquinone Violet) (4), 1,4-di-(2′-sulfo-4′-methylanilino)anthraquinone (Alizarin Cyanine Green) (5), 1,4-di-(3′-sulfo-4′-methylanilino)anthraquinone (Alizarin Direct Green) (6), 7,8-dihydroxy-1,4-di-(2′-sulfo-4′-methylanilino)anthraquinone (Alizarin Viridin) (7), and 1-amino-2-bromo-4-(2′-sulfo-4′-methylanilino)anthraquinone (Alizarin Pure Blue B) (8). Toluidine Blue is the sodium salt of 1,5-di-(2′-sulfo-4′-methylanilino)-4,8-dihydroxyanthraquinone, and Toluidine Green is the 1,4-isomer (1).

In Fig. 1 are shown the characteristic curves for four dyes, two in the 1,4- and two in the 1,5-series. The peaks of each are listed in Table I; it will be noted that there are two maxima in the longer wave lengths of all except the violet dye.[1]

An inspection of these curves reveals the great differences between the 1,4- and 1,5-series; thus, the differences between the second and third peaks in the green

[1] This dye may not be strictly comparable, for it appears to have four bands in the ultraviolet with a suggestion of a fifth at about 384 mμ. The band head at 330 has been assumed to be comparable to the third band in the other dyes, and the values in Table II are calculated from it.

series in the ultraviolet is more than double that in the blue series (125 *vs.* 35–55), the third peak in the former appearing in the visible.

The effect of the two hydroxyl groups in the 4,8- and 5,8-positions is also evident in Fig. 1. The difference between the first and second peaks (Table II) is approximately twice as great in the dyes containing these groups so arranged. Further, there is a much greater spread (50% more) between the third and fourth peaks in the blue series. That is, in this series, these hydroxyl groups have pushed the red absorption towards the longer wave lengths without greatly

TABLE I

MAXIMA OF ABSORPTION SPECTRA IN FIG. 1 (mμ)

I	Anthraquinone Violet (4)	246	272	308	330	560
II	Alizarin Cyanine Green (5)*	253	285	410	608	646
III	Toluidine Blue	244	300	335	654	696
IV	Toluidine Green	243	290	415	644	692

* The maxima of this dye, in methanol, are at 248, 286, 404, 602, and 642. The differences due to change of solvent are so small in comparison to those under discussion that the effect of the solvent has been disregarded. All the dyes were observed in aqueous solution.

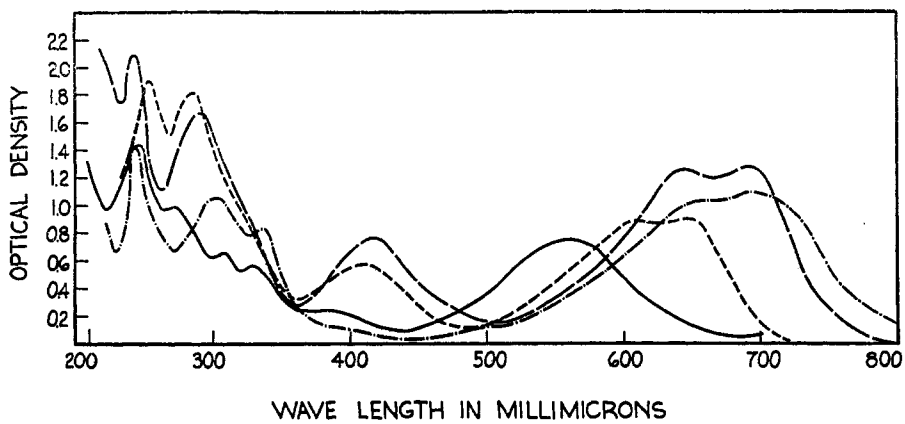


FIG. 1. ISOMERIC DYES IN 1,4- AND 1,5-SERIES

———, Anthraquinone Violet (1,5); ·····, Alizarin Cyanine Green (1,4); —·—·—, Toluidine Blue (1,5,4,8); — — —, Toluidine Green (1,4,5,8).

affecting the portion of the band in the ultraviolet. Further, the two hydroxyl groups in these positions have moved the red absorption towards the longer wave lengths; in the green series this amounts to 36 and 46 mμ (Table I), while in the blue it is of the order of 100 mμ. This effect seems to be confined to the 4,8- and 5,8-positions, for the 6,7- and 7,8-isomers resemble in the visible the unsubstituted Alizarin Cyanine Green (Fig. 2); even so, the effect is beginning to appear (12 and 8 mμ) in the 7,8-isomer (Alizarin Viridin), which has only one OH in an *alpha* position (Table III). Finally, the introduction of two OH groups into the 6,7-position of Alizarin Cyanine Green has moved the red

absorption in the opposite direction, slightly to the left (6 and 8 mμ) (Fig. 2) (Table III). If this latter can be considered to be the normal effect of introducing hydroxyl groups, then the large shift in the opposite direction observed in the Toluidine Green must be connected with a peculiarity of the *alpha* position. This feature is the possibility of chelation of the hydroxyl hydrogen with the

TABLE II

DIFFERENCES BETWEEN ABSORPTION MAXIMA OF TABLE I

Anthraquinone Violet	26	58	230	
Alizarin Cyanine Green	32	125	198	38
Toluidine Blue	56	35	319	42
Toluidine Green	47	125	229	48

TABLE III

COMPARISON OF HYDROXYLATED DYES (mμ)

NO.	DYE	OH	MAXIMA IN RED	
IV	Alizarin Cyanine Green		608	646
I	Toluidine Green	5, 8	644	692
II	Alizarin Viridin	7, 8	620	654
III	6,7-Dihydroxy-1,4-ditoluidinoanthraquinone	6, 7	602	638

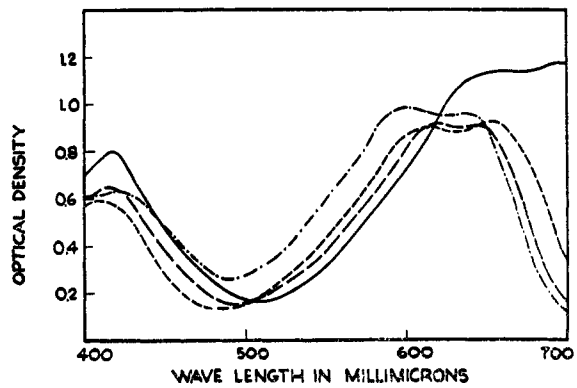


FIG. 2. ALIZARIN CYANINE GREEN AND THREE DIHYDROXY DERIVATIVES

———, Alizarin Cyanine Green; ———, Toluidine Green (5,8); ·····, Alizarin Viridin (7,8); —·—·—, 6,7-Dihydroxy isomer of Toluidine Green.

carbonyl oxygen. Further confirmation is thus afforded of the generally accepted idea of hydrogen bonding of *alpha*-hydroxylated anthraquinones (13).

In general, the introduction of halogen atoms into Alizarin Cyanine Green has a bathochromic effect, but their position in the molecule has a very great influence. In the case of the 5,8-dichloro derivative (α-series), in the ultraviolet, the distance between the peaks is 48 mμ, as compared to 32 mμ in the unsubstituted dye (Table IV). The 5,8-dichloro derivative thus resembles

Toluidine Green, where the difference is 47; that is, two chlorine atoms have an effect similar to two hydroxyl groups, when both are in the 5,8-positions (Fig. 3). From Table IV it will be noticed that it is a different head of each that is about the same as one of the parent dye, the hydroxyl group having moved the first peak towards the shorter wave lengths, whereas the chlorine atom has shifted the second in the opposite direction. The main band in the red, however, is greatly broadened by the chlorine atoms; the right head is moved 14 mμ to the longer

TABLE IV

ABSORPTION MAXIMA OF HALOGENATED DYES (mμ)

Alizarin Cyanine Green	253	285	410	608	646
5,8-Dichloro derivative	252	300	425	568	660
5,6,7,8-tetrachloro derivative	270		425	570	640
6,7-Dichloro derivative	266	(326?)	428	628	662
Toluidine Green	243	290	415	644	692
2,3-Dichloro derivative of Toluidine Green			420	600	643

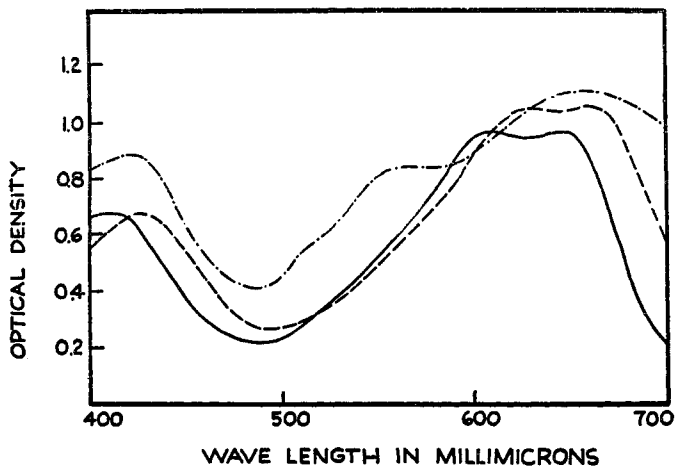


FIG. 3. ALIZARIN CYANINE GREEN AND TWO DICHLORO DERIVATIVES

———, Alizarin Cyanine Green; — — — —, 6,7-Dichloro derivative; —·—·—, 5,8-Dichloro derivative.

wave lengths (as compared to 46 for the 5,8-hydroxyl groups) but the left one is shifted 40 in the opposite direction, resulting in a wide band with a difference of 92 between the two maxima.

In the case of the 6,7-dichloro derivative (β-series), the introduction of the halogen has shifted the entire red band towards the longer wave length about 20 mμ, but otherwise has had no appreciable effect. So far, owing to side reactions leading to dyes of uncertain structure, a dye having chlorine atoms in the 2,3-positions has not been obtained. However, a 2,3-dichloro derivative of Toluidine Green has been prepared; the location of the maxima (Table IV) is about the same as in the unsubstituted Alizarin Cyanine Green, the halogen

having a very slight bathochromic effect. While this appears to be opposite to the 6,7-dichloro dye, a strict comparison cannot be made, since one has two hydroxyl groups in the *alpha* position. From these few examples, it may be said that when halogen atoms are present in the *beta* positions, they have much less influence upon the absorption than when they are in the *alpha* position.

Chlorine atoms in the benzene residue also have a bathochromic effect; comparisons with this type are made in the blue series (Table V). The ultraviolet is essentially the same in the 4′-chloro and 4′-methyl (Toluidine Blue) dyes, but the band in the visible, though of the same size, is not as far to the right in the case of the halogenated dye.

TABLE V

ABSORPTION MAXIMA OF DYES RELATED TO ANTHRAQUINONE VIOLET (IN mμ)

Anthraquinone Violet	246	272	330	560	
4′-Chloro-4,8-dihydroxy derivative	242	296	332	622	662
4′-Methyl-4,8-dihydroxy derivative (Toluidine Blue)	244	300	335	654	696

TABLE VI

COMPARISON OF BASES AND DYES*

FIG.	NO.	SUBSTANCE	MAXIMA IN THE VISIBLE			DIFF. LAST TWO	DIFF. BASE AND DYE
4	I	Alizarin Cyanine Green base	400	600	642	42	8, 4
4	II	Alizarin Cyanine Green dye	412	608	646	38	
6	I	Toluidine Green base	414	642	676	34	2, 16
6	II	Toluidine Green dye	416	644	692	48	
5	I	Toluidine Blue base		630	676	46	24, 20
5	II	Toluidine Blue dye		654	696	42	
7	I	Alizarin Pure Blue base		586	620	34	14, 10
7	II	Alizarin Pure Blue dye		600	630	30	

* The absorption of the bases was observed in dioxane solution, and of the dyes in water.

All the foregoing comparisons have been made on the dyes, which are salts of sulfonic acids. Since the unsulfonated quinones and dyes are not always dissolved by the same solvents, their curves may not be strictly comparable. Bearing this in mind, it can be said that the introduction of sulfonic acid groups into the toluidine residues has a relatively small effect (Figs. 4–7). This is towards the right (2–20 mμ) (Table VI) and is somewhat more pronounced in the blue series, being about double when the hydroxyl groups are present.

Sulfonation of the dye base always results in the introduction of the sulfonic acid group in the 2′-position of the toluidine residue (1, 5). The isomeric 3′-sulfonic acids can be secured by the use of sodium 4-aminotoluene-2-sulfonate under pressure (2, 3, 9). It is interesting to note that the isomeric 4-aminotoluene-3-sulfonate fails to react under the same conditions; this is undoubtedly

on account of its chelated structure. Comparison of the absorption curves of this variety of isomers (Figs. 8–10) shows small differences (Table VII). Of the two common dyes, Alizarin Cyanine Green and Alizarin Direct Green, there is a very small shift in the violet end, but the width of the main absorption band in the red end is quite different, the first having more blue absorption. More significant is the nature of the main absorption band in the red—it has but one

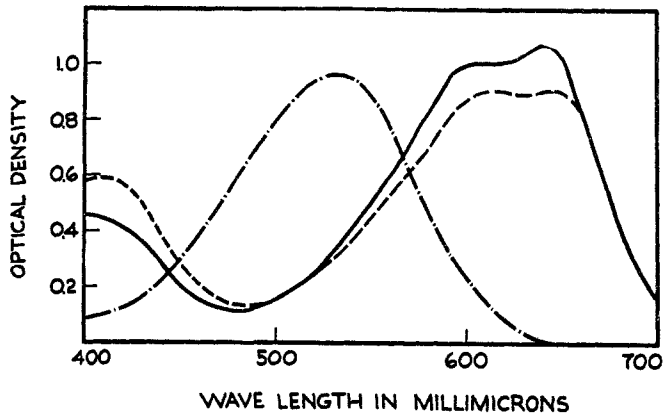


FIG. 4. EFFECT OF SULFONATION OF ALIZARIN CYANINE GREEN. COMPARISON OF 1,4- AND 1,5-DITOLUIDINOANTHRAQUINONES

———, Alizarin Cyanine Green, base in dioxane; ---------, Same, sulfonated; —·—·—, Anthraquinone Violet, base in dioxane.

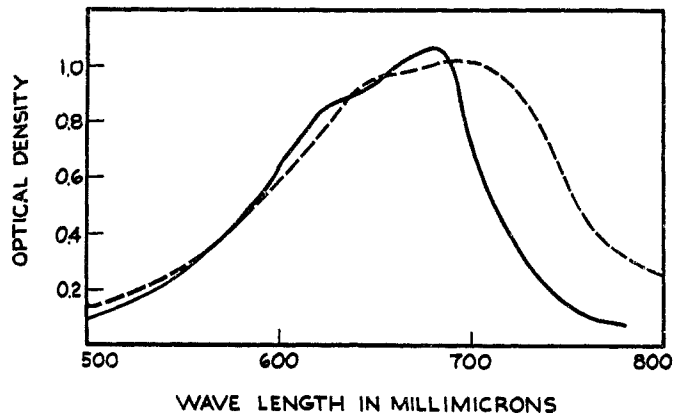


FIG. 5. EFFECT OF SULFONATION OF TOLUIDINE BLUE

———, Base in dioxane; — — — —, Same, sulfonated

peak, whereas with the 2′-isomer there are two maxima. Since the second peak is present in the unsulfonated 1,4-ditoluidinoanthraquinone, its presence in one sulfonated dye and its absence in the isomer must be related to the location of the sulfonic acid group. This same behavior is exhibited by the isomeric sulfonic acids of other dyes, and is discussed below.

Finally, 1,4-di-β-hydroxyethylamino-5,8-dihydroxyanthraquinone and its

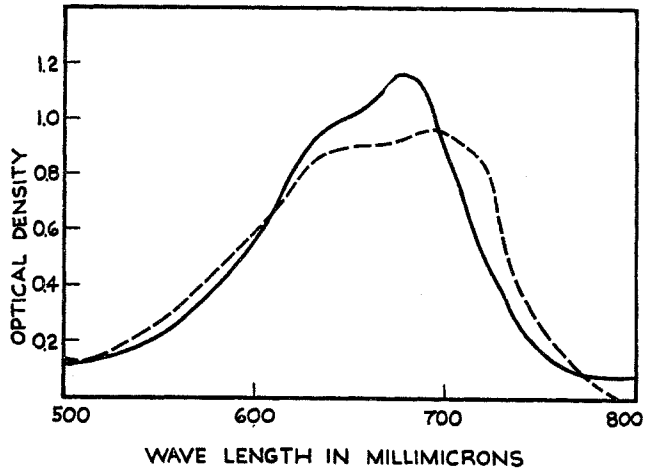


FIG. 6. EFFECT OF SULFONATION OF TOLUIDINE GREEN
———, Base in dioxane; — — — —, Same, sulfonated

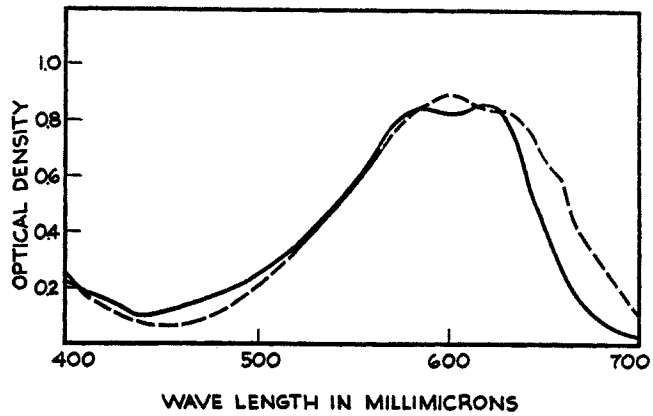


FIG. 7. EFFECT OF SULFONATION OF ALIZARIN PURE BLUE B
———, Base in dioxane; — — — —, Same, sulfonated

TABLE VII

MAXIMA OF ISOMERIC SULFONIC ACIDS

FIG.	DYE	SO_3H	MAXIMA				
8	Alizarin Cyanine Green	2′	253	285	410	608	646
8	Alizarin Direct Green	3′	254	282	414	620	
10	Toluidine Green	2′	243	290	415	644	692
10	Toluidine Green Isomer	3′	242	290	422	650	
9	Toluidine Blue	2′	244	300	325	654	696
9	Toluidine Blue Isomer	3′	240	294	338	660	

sulfato ester may be considered (Fig. 11 and Table VIII). Here it will be noted that there is no peak in the 325–425 range, from which it follows that the presence

of this probably depends upon the aromatic toluidine residues. There is just the suggestion of a head at about 566 (576), perhaps related to the aliphatic residues, as it does not appear in any of the other dyes.

It will also be noticed that the introduction of the sulfate group has had two effects: it has considerably depressed the peak farthest to the right, and it has

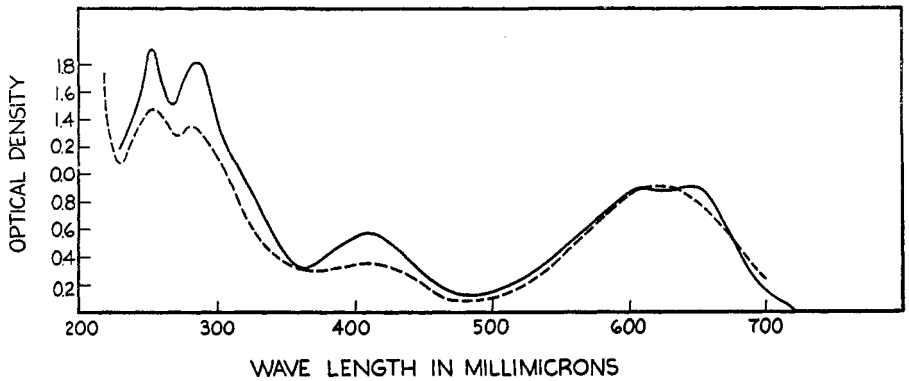


FIG. 8. EFFECT OF POSITION OF SULFONIC ACID GROUP

———, Alizarin Cyanine Green (2′—SO_3Na); — — — —, Alizarin Direct Green (3′—SO_3Na).

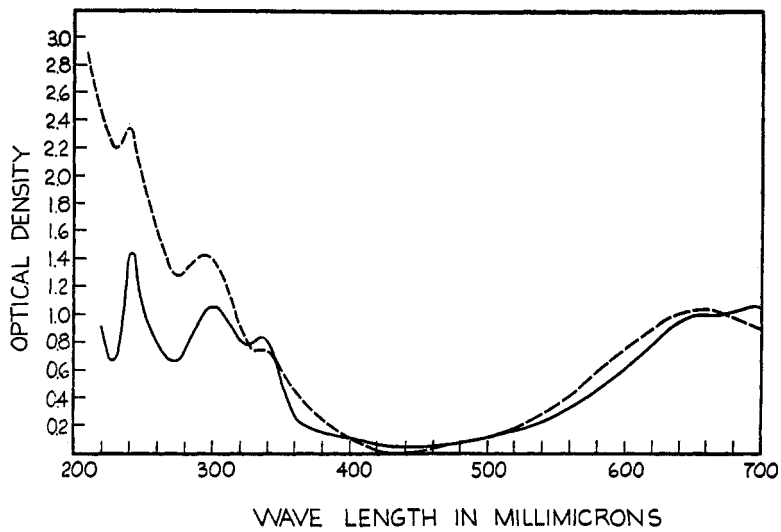


FIG. 9. EFFECT OF POSITION OF SULFONIC ACID GROUP

———, Toluidine Blue (2′—SO_3Na), — — — —, Isomer (3′—SO_3Na)

moved the entire red absorption about ten mμ to the left. The latter effect is ust opposite to what was observed in the aromatic-substituted anthraquinone. The depressing of the right-hand peak is insufficient to obliterate it, as seems to have happened with the 3′-sulfonic acids of the other series.

Even more instructive is the comparison between the 1,4-di-β-sulfatoethyl-

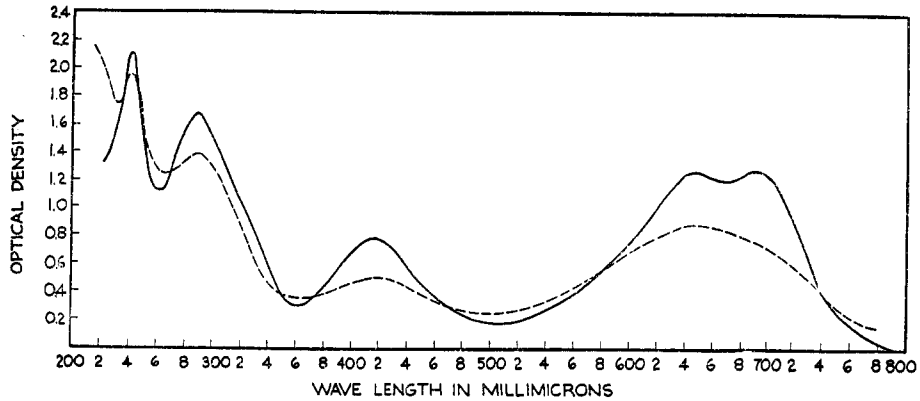


FIG. 10. TOLUIDINE GREEN AND ITS ISOMERIC SULFONIC ACID

———, Toluidine Green (2′—SO_3Na); — — — —, Isomer (3′—SO_3Na)

TABLE VIII

COMPARISON OF β-HYDROXYETHYLATED DYES

FIG.	DYE	MAXIMA					DIFFERENCE IN 1 AND 2, 4 AND 5	
11	Sulfated 1,4-Di-β-hydroxyethyl-aminoanthraquinone	258			588	628		40
11	5,8-Dihydroxy-1,4-di-β-hydroxy-ethylaminoanthraquinone, unsulfated			578?	624	676		
11	5,8-Dihydroxy-1,4-di-β-hydroxy-ethylaminoanthraquinone, sulfated	242	278	566?	614	664	36	50
1	Toluidine Green	243	290	415	644	692	47	46
1	Toluidine Blue	244	300	335	654	696	56	42

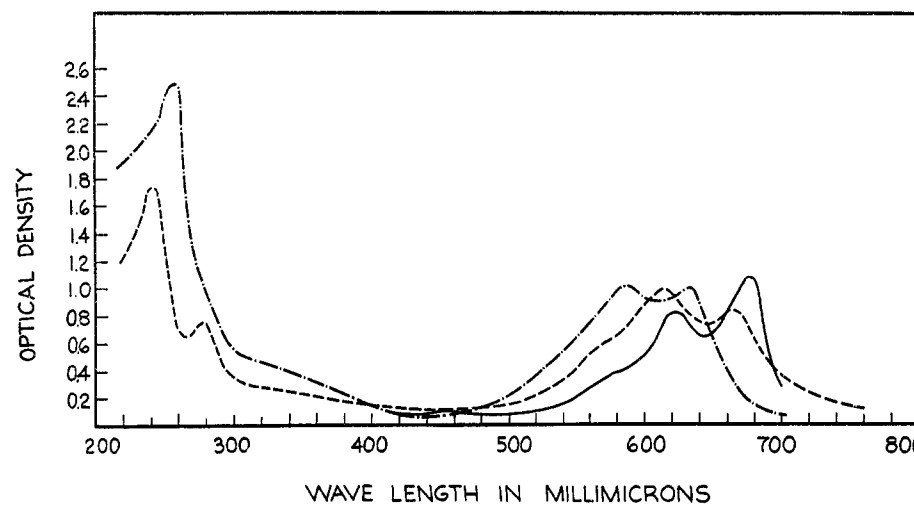


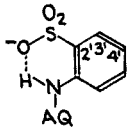
FIG. 11. DERIVATIVES OF 1,4-DI-β-HYDROXYETHYLAMINOANTHRAQUINONE

———, 1,4-Di-β-hydroxyethylamino-5,8-dihydroxyanthraquinone; ---------, 1,4-Di-β-sulfatoethylamino-5,8-dihydroxyanthraquinone; —·—·—, 1,4-Di-β-sulfatoethylaminoanthraquinone.

anthraquinones with (Fig. 11, Curve II) and without (Fig. 11, Curve III) hydroxyl groups in the 5,8-positions. In the latter there is but one peak in the ultraviolet, and the absorption in the red is considerably to the left; furthermore, the two peaks in the red are closer together, and of about equal magnitude. This might make it appear that the second peak in the ultraviolet was dependent upon the presence of the hydroxyl groups, but this cannot be true since both Anthraquinone Violet and Alizarin Cyanine Green, in which there are no hydroxyl groups, have double absorption in this region.

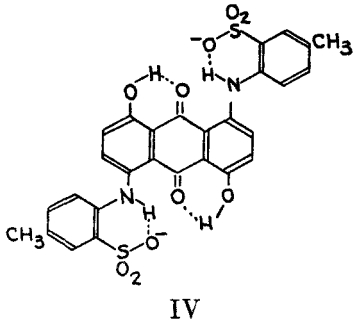
The effect of the 5,8-hydroxyl groups is just the same here as in the Toluidino series—the red peaks are moved to the right 26 and 36 mμ. There is no legitimate comparison in the ultraviolet, since it is unknown with which of the two bands of II the single peak of III corresponds.

The basal structure of acid anthraquinone dyes has long been accepted as that represented in general formula I; when aromatic groups occur in the amino side chain, it is known that they are preferentially attacked on sulfonation. In the first paper of this series (1), the structure of Toluidine Blue was written as having hydrogen bonds, with the sulfonic acid group represented by the letter S. From the examination of a number of dyes it has become evident that a sulfonic acid group in the 2′-position has a different effect from one in the 3′- or 4′-positions, as evidenced by the change in shape of the absorption curves; that is, the grouping $-SO_3M$ is not linked alike in the two instances. Now from an inspection of the formula, it is seen that while a $-SO_3^-$ group in the 3′- or 4′-positions could have no effect on the bonding, when the group is in the 2′-position, it can partake in ring formation with the imino hydrogen, making a different hydrogen bond system, as shown in III.

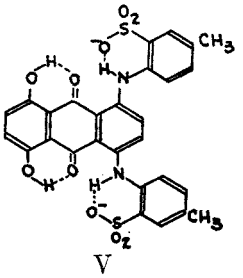


III

All dyes sulfonated in the 2′-position are now assumed to have the possibility of such a bond arrangement, and the formulas IV and V must be considered as contributing to the complete structures of Toluidine Blue and Toluidine Green,

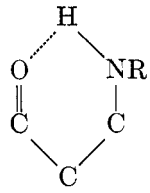


IV

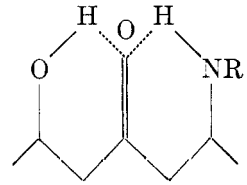


V

whereas in the isomeric sulfonic acids the imino hydrogen can only be bonded to the carbonyl oxygen as shown in the partial formula VI, VIa.



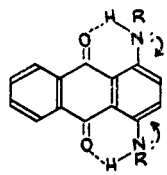
VI



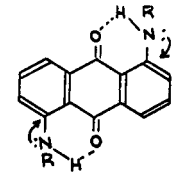
VIa

The absorption curves of these dyes, as well as others not shown in the figures, are of two general types, differing sharply in the nature of the main band in the visible. One type has a smooth curve while the other is characterized by a double head. The variations were first noticed among the isomeric sulfonic acids, and attributed to the location of the sulfo group, but later it was found that the unsulfonated "dye bases" themselves exhibited similar phenomena. Thus, 1,5-di-*p*-toluidinoanthraquinone has the smooth curve, whereas the 1,4-isomer shows two maxima on the main band (Fig. 4).

Based upon an inspection of a number of dyes, it has now been concluded that when there are in the 1- and 4-positions two groups which are able to furnish electrons by a mesomeric shift (VII), the main band of the absorption curve will have a double head. If but one group of this type is present (VIII), only a single head will be observed. The twofold shift of electrons, originating, for instance, with unshared pairs of electrons of nitrogen or oxygen atoms, appears to be responsible for the differentiation of the one head into two.



VII



VIII

This interpretation accounts in part for the nature of the curves of the 1,5- and 1,4-ditoluidinoanthraquinones.

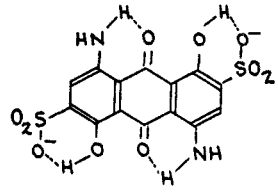
Now if the unshared pair of electrons in question on the nitrogen atom is restrained from a shift towards the anthraquinone nucleus, it is to be expected that the type of curve with a single head will result. Such a restraint can be effected by a sulfonic acid group in the benzene ring attached to the nitrogen atom. It has been found that sulfonation in the 3′- (*meta*) or 4′- (*para*) position has just this effect; the restraint is attributed to the strong inductive effect of the positive sulfur atom, which is transmitted through the aromatic ring system to the nitrogen atom and its unshared pair of electrons. However, when the sulfonic acid group is in the 2′-position (*ortho* to the imino nitrogen), a hydrogen bond will be formed by the sharing of an electron pair of an oxygen atom with the hydrogen

of the imino group (III). The hydrogen, in turn, will to some extent release its electrons shared with the nitrogen atom, so that the effect of the sulfonic acid group on the rest of the molecule will be diminished,—a sort of internal "short circuit".

This interpretation is supported by the absorption curves of the dyes having an aliphatic side chain, at the end of which is the sulfate group (Fig. 11). Since the effect cannot be transmitted (as readily) along an aliphatic chain, these dyes should have two maxima, and they do.

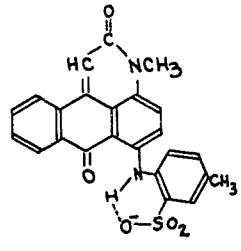
The conclusions discussed above were reached after a study of a large number of dyes, all of which were essentially of two general types; at the same time these were largely isomers (1,4- and 1,5-series). As a sort of test, it is now of interest to venture predictions as to dyes of other, less closely-related structures.

First, consider Alizarin Saphirol (IX), (11). The main band should have two heads, for the following reasons: (a) It was shown above that the differentiation of the absorption curve into a band with two maxima may be attributed to the twofold mesomeric shift of electrons into the anthraquinone system, these electrons originating with the substituents in positions 1 and 4. In IX, as in



IX

Toluidine Blue (IV), the NH_2 and OH are a suitable source of electrons. (b) A sulfonic acid group in position 2 or 3 of the anthraquinone nucleus, by its inductive effect, would not be expected to restrain, but rather, to enhance the shift of electrons towards the ring from positions 1 and 4, and the short circuit described above should work in the same direction. Hence, the introduction of a sulfonic acid group into position 2 or 3 of the anthraquinone system should result in dyes which do not exhibit the single but the more complicated double-headed absorption curve. This is, indeed, the case (Fig. 12). Second, consider



X

Alizarin Rubinol G (X), (12). In this dye, the necessary groups are present in the 1- and 4-positions, but the effect of the carbonyl oxygen is to counteract the

mesomeric shift of the electrons into the ring at position 1. Consequently, the absorption band would be expected to have a single head, as is actually the case (Fig. 12). In each figure, the abscissa is in millimicrons, while the ordinate is optical density; the latter is defined as $\log_{10} \frac{1}{T}$, where T = transmission. The solution was examined in a cell 1 cm. in thickness. We are indebted to Mr. E. E. Richardson and his staff for the absorption curves.

The dyes used were mostly those the preparation of which has been given in the earlier papers (1, 2, 3). Anthraquinone Violet (4) and Alizarin Pure Blue (7) were secured following directions from the patent literature, but using intermediates free from isomers. We are indebted to Dr. J. G. Baxter for a very pure specimen of 1,4-di-*p*-toluidinoanthraquinone, and to Dr. J. B. Dickey for the sodium 1,4-di-β-sulfatoethylaminoanthraquinone.

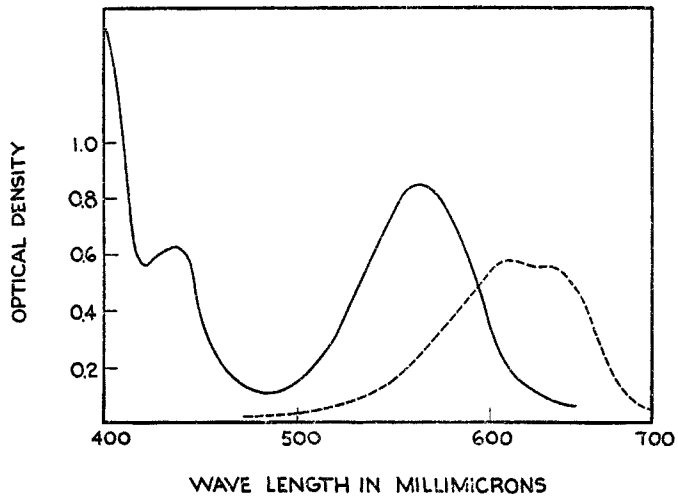


FIG. 12. PARTIAL ABSORPTION CURVES OF TWO DYES
———, Alizarin Rubinol G (1:4000); ---------, Alizarin Saphirol B (1:3000)

SUMMARY

The absorption spectra of a number of acid anthraquinone dyes have been recorded, and attention called to the effect of certain atoms or groups of atoms in various positions in the molecule.

An explanation has been suggested to account for the marked difference in the nature of the main bands in the visible. The influence of the position of the sulfonic acid group has been related to the possibilities of hydrogen bonding.

The correctness of the assumptions has been verified in two instances.

ROCHESTER, N. Y.

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

THE SYNERGISTIC ACTION OF SESAMIN WITH PYRETHRUM INSECTICIDES

H. L. HALLER, E. R. McGOVRAN, L. D. GOODHUE, AND W. N. SULLIVAN

Received December 27, 1941

In a recent patent, Eagleson (1) described the use of sesame oil as a "synergist" or "activator" when combined with insecticides containing pyrethrins, rotenone, and the like. The addition of sesame oil reduces the concentration of the insecticide required to give 100% mortality of houseflies, and prolongs the paralysis or torpor of such insects as are not killed by the spray. For example, Eagleson found that a pyrethrum insecticide containing a 0.001 molar concentration of pyrethrins in refined kerosene, when sprayed on houseflies in the apparatus described by him (2), produced a mean torpor of 50%. The addition of 0.5% by volume of sesame oil increased this value to 74%, and 5% of the oil with the pyrethrins gave a mean torpor of 95% of the flies. That the increase in toxicity is due to a synergistic or activator effect, and not to the addition of another insecticide, was shown by the failure of sesame oil alone to kill flies. Eagleson's results have been corroborated by us.

TABLE I

EFFECTIVENESS AGAINST HOUSEFLIES OF VARIOUS FRACTIONS OF SESAME OIL, ALONE OR AS AN ADJUNCT OF PYRETHRUM IN REFINED KEROSENE

(Two tests of about 150 flies each; concentration of pyrethrins 1 mg. and of sesame oil and its fractions 10 mg. per cc.)

MATERIAL	KNOCKDOWN IN 10 MIN., %	MORTALITY IN 48 HRS., %
Original sesame oil	0	2
Pyrethrins	99	21
Pyrethrins + original sesame oil	100	57
Pyrethrins + fraction I	100	100
Pyrethrins + fraction II	100	91
Pyrethrins + fraction III	100	21
Pyrethrins + fraction IV	100	29

The enhancement in toxicity of pyrethrum insecticides was not effected by other vegetable oils (3). It was deemed of interest, therefore, to determine the effect of several fractions of sesame oil in pyrethrum sprays. Accordingly 10 g. of refined sesame oil was separated by fractionation in a molecular still. Fraction I, distilling in a molecular vacuum up to 170°, consisted of 0.13 g. of waxy solid; fraction II, which distilled from 170° to 230°, was 0.2 g. of a viscous oil; and fraction III, which distilled from 210° to 220°, consisted of 3 g. of a mobile oil, similar in appearance to sesame oil itself. The part remaining in the still was regarded as fraction IV. Each fraction was separately added to pyrethrum insecticide in refined kerosene and tested against houseflies by the turntable

method of Campbell and Sullivan (4). The results obtained are shown in Table I.

From the combined first and second fractions, a crystalline solid was isolated, which was identified as sesamin (5). Table II records the results obtained when it was added to pyrethrins in a refined kerosene-acetone mixture and tested

TABLE II

EFFECTIVENESS AGAINST HOUSEFLIES OF FRACTIONATED SESAME OIL IN REFINED KEROSENE PLUS 10% ACETONE

(Two tests of 150 flies each; concentration of pyrethrins 1 mg. and of sesame oil fractions 2.5 mg. per cc.)

MATERIAL	KNOCKDOWN IN 10 MIN., %	MORTALITY IN 24 HRS., %
Pyrethrins	100	20
Sesamin (crystalline fraction)	0	5
Pyrethrins + sesamin (crystalline fraction)	100	85
Pyrethrins + noncrystalline residue	100	89

against flies (10% acetone in the kerosene is necessary to dissolve the sesamin). The effect produced by the non-crystalline fraction after removal of most of the sesamin is also given. It has not been possible to obtain from this active fraction any crystalline product other than sesamin. This fraction is being studied further, however. The results show clearly that sesamin increases the toxicity of pyrethrum insecticides when tested against flies.

WASHINGTON, D. C.

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

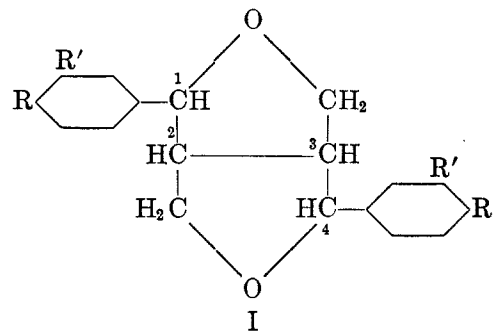
SOME COMPOUNDS RELATED TO SESAMIN: THEIR STRUCTURES AND THEIR SYNERGISTIC EFFECT WITH PYRETHRUM INSECTICIDES

H. L. HALLER, F. B. LAFORGE, AND W. N. SULLIVAN

Received December 27, 1941

A number of plant materials have been shown to contain members of a class of compounds having a common nucleus composed of two fused dihydrofuran rings with a substituted pyrocatechin group attached symmetrically to each of one of the carbon atoms adjacent to the ether oxygen atoms. The class includes sesamin (1, 2), found in sesame seeds and a minor constituent of sesame oil; asarinin (3, 4)[1] found in various oriental plants and in the bark of the American prickly ash (5); pinoresinol (6), a constituent of the exudate of spruce and related species; and eudesamin (7), a constituent of the kino gum from eucalyptus.

Within the last few years the chemical investigations of various workers have culminated in the determination of the structure of all these compounds and the establishment of their relation to one another.[2] They all contain the same structure with respect to the nucleus, but differ according to the configurational relations on their asymmetric carbon atoms and in the nature of the aromatic substituents. The compounds are represented by formula I.



I

R, R′ = O_2CH_2 (methylenedioxyl) for sesamin and asarinin; R = OH, R′ = OCH_3 for pinoresinol; R, R′ = OCH_3 for eudesamin.

The symmetrical structure of compounds represented by this general formula permits the theoretical existence of two optically inactive and two configurationally different active forms together with their optical antipodes (6).

Natural sesamin, which is dextrorotatory, is partly converted by boiling with alcoholic hydrochloric acid into an isomeric compound, isosesamin. This reaction involves the epimerization of the groups on carbons 1 or 4, is reversible, and results in an equilibrium mixture of isosesamin and sesamin, to whichever of the

[1] The name xanthoxylin-S was first given to this compound, but asarinin has been more generally accepted.

[2] The literature on this subject is so extensive that only the later references are given. For the most part the articles cited contain references to previous work.

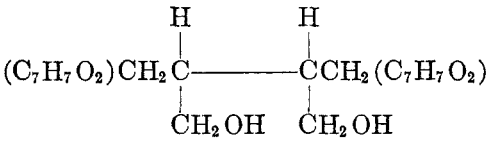
two compounds it is applied. Asarinin is levorotatory and is the optical antipode of isosesamin. Treatment with hydrochloric acid results in an equilibrium mixture of it and *l*-sesamin (3).

The correlation of these compounds with eudesamin and pinoresinol has been established by the conversion of asarinin (*levo*) to eudesamin (*levo*) by hydrolysis of the methylenedioxyl groups and methylation of the resulting phenolic derivative (8). By the same process, sesamin (*dextro*) was converted into pinoresinol dimethyl ether (*dextro*), the antipode of eudesamin. Epimeric forms of eudesamin and pinoresinol dimethyl ether have been obtained (7).

$$\text{Pinoresinol dimethyl ether} \longleftarrow \underset{[\alpha]_D = +68°}{\text{sesamin}} \overset{HCl}{\rightleftharpoons} \underset{[\alpha]_D = +122°}{\text{isosesamin}}$$
$$[\alpha]_D = +68°$$

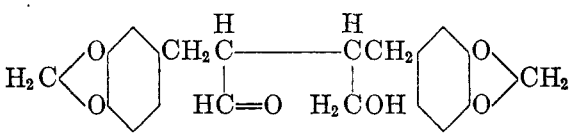
$$\text{Eudesamin} \longleftarrow \underset{[\alpha]_D = -122°}{\text{asarinin}} \overset{HCl}{\rightleftharpoons} \underset{[\alpha]_D = -68°}{l\text{-sesamin}}$$
$$[\alpha]_D = -68°$$

The nature of the nucleus in formula I was established in the case of sesamin and asarinin by hydrogenation to the 1,4-glycol of formula II (9),



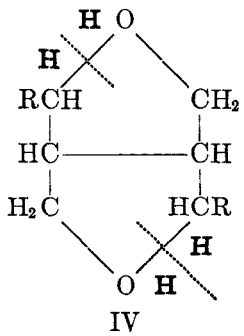
II

which was shown to be the antipode of the reduction product of the naturally occurring hydroxy aldehyde, cubebin, of known structure III.



III

The hydrogenation is interpreted as resulting in cleavage between the oxygen of the ether linkage and the carbon atoms to which the aromatic groups are attached, as shown in IV.



IV

The natural compounds described above and their derivatives and products of rearrangement have lately assumed a practical significance as a result of an important observation made by Eagleson (10). In experiments on the control of houseflies, Eagleson tested pyrethrum solutions in mixture with a number of vegetable oils, and found that sesame oil, to the exclusion of all others tried, markedly increased the effectiveness of the pyrethrins.

On the basis of the known fact that sesame oil contains sesamin, Haller and Goodhue isolated sesamin and prepared pyrethrum sprays to which it had been added. Sullivan then tested these solutions against houseflies by the turntable method and compared them with the solutions of the same pyrethrin content but

TABLE 1

SYNERGISTIC EFFECT OF SESAMIN AND RELATED COMPOUNDS ON THE INSECTICIDAL ACTION OF PYRETHRINS AGAINST HOUSEFLIES

(Turntable method; 3 tests using about 150 flies per test; solvent, refined kerosene with 10% acetone where needed to increase solubility)

MATERIAL	CONCENTRATION, %	AVERAGE % MORTALITY AFTER 24 HRS.
Sesamin and its isomers:		
Sesamin	0.2	4
Sesamin plus pyrethrins	0.2 + 0.05	84
Isosesamin	0.2	5
Isosesamin plus pyrethrins	0.2 + 0.05	87
Asarinin	0.18	14
Asarinin plus pyrethrins	0.2 + 0.05	88
Pinoresinol and derivatives:		
Pinoresinol	0.18	1
Pinoresinol plus pyrethrins	0.18 + 0.05	12
Dimethylpinoresinol	0.2	1
Dimethylpinoresinol plus pyrethrins	0.2 + 0.05	17
Diacetylpinoresinol	0.03	2
Diacetylpinoresinol plus pyrethrins	0.03 + 0.05	11
Pyrethrins (checks):		
Sample compared with sesamin and its isomers	0.05	25
Sample compared with pinoresinol and derivatives	0.05	19

without sesamin and with solutions of sesamin alone (11). These tests showed that, while sesamin alone was without effect, the addition of small quantities of it greatly increased the toxicity of the pyrethrins.

It then became of interest to test the other accessible related compounds with respect to their synergistic effect on the pyrethrins. Of the compounds available, and which we have so far prepared, isosesamin and asarinin are most closely related to sesamin. All have the same chemical structure, but differ with respect to the configuration on carbon atoms 1, 2, 3, 4 in formula I, asarinin being the optical antipode of isosesamin.

Of the other compounds named, pinoresinol dimethyl ether is, like sesamin, dextrorotatory and differs only with respect to the aromatic substituents, which are veratryl in pinoresinol dimethyl ether and piperonyl in sesamin.

When tested in combination with pyrethrum solutions, isosesamin and asarinin were as effective as sesamin, but pinoresinol dimethyl ether was without appreciable synergistic action, as were pinoresinol itself and its diacetyl derivative.

The results obtained are given in Table I. It may be concluded from these experiments that the nature of the substituents on the benzene ring is the only determining factor in the synergistic action of this class of compounds. This conclusion could be further tested by a systematic examination of a larger number of related compounds. The glycols obtained by hydrogenation of sesamin, isosesamin, and asarinin, and the various substitution products of pinoresinol fall into the scope of the investigation, as well as compounds of other structure but containing the piperonyl group. Of such common piperonylic compounds as have been tested, piperonal, safrol, and ethyl piperonylate were ineffective. From the results so far obtained, an important practical field has been opened that may lead to the discovery of other synergists, perhaps more active or more readily available than sesamin or asarinin.

WASHINGTON, D. C.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY AND FROM THE DEPARTMENT OF CHEMISTRY OF NORTHWESTERN UNIVERSITY]

CONDENSATION OF KETONES WITH ALCOHOLS IN THE PRESENCE OF MIXED CATALYSTS[1]

V. N. IPATIEFF AND VLADIMIR HAENSEL

Received July 3, 1941

The first investigation on the action of mixed catalysts upon primary alcohols carried out by one of us (1) showed that in the presence of a dehydrogenation catalyst (iron) and a dehydration catalyst (alumina) ethyl alcohol is converted into methyl ethyl ketone, methyl ethyl carbinol, isopropyl alcohol, and acetone. It was believed that the products were formed from acetaldehyde as intermediate; the first two by way of the aldol condensation and the last two by way of a Cannizzaro reaction.

In later investigations Dolgov and his co-workers (2) showed that upon passing ethyl alcohol over mixed catalysts (copper, nickel, zinc oxide, zirconium oxide, etc.) at atmospheric pressure and 250–275°, ethyl acetate is obtained in 40–45% yields. No mechanism of reaction was proposed.

In a patent issued to the E. I. duPont de Nemours and Company (3) it is stated that in the presence of mixed catalysts such as chromites of zinc, copper, and cadmium, certain secondary alcohols can be converted under pressure and a temperature of 325–350° into higher-boiling products consisting essentially of ketones having two and three times the number of carbon atoms of the original alcohol.

The present investigation was undertaken in order to clarify the mechanism of these condensation reactions. The experiments were carried out using both a high-pressure autoclave of the Ipatieff type (4) and a continuous flow high-pressure apparatus. The reactions between the following reactants were studied:

1. A secondary alcohol and a ketone
2. A secondary alcohol and a cyclic ketone
3. A primary alcohol and a ketone
4. A primary alcohol alone

The catalysts used in these condensations were copper-alumina and copper-zinc oxide-alumina. These were prepared by precipitating basic copper carbonate alone or together with zinc carbonate on powdered alumina and then reducing the washed and dried product at 225° with hydrogen. The reduced catalyst, consisting essentially of copper, zinc oxide, and aluminum oxide, was used as a powder in experiments employing the autoclave, while for continuous flow experiments the catalyst powder was pelleted in the form of $\frac{1}{8}$-inch cylindrical pills and used in that form in the reaction tube.

[1] Presented at the Atlantic City Meeting of the American Chemical Society, September, 1941.

The reaction between a secondary alcohol and a ketone was studied most extensively using isopropyl alcohol and acetone. It was found that the condensation in the case of these two compounds proceeded readily to give high yields of methyl isobutyl ketone and diisobutyl ketone. Table I gives the results obtained using a high-pressure autoclave. It will be observed that only those catalysts which possess both dehydrogenation and dehydration characteristics can effect the conversion. Furthermore, it will be noted that a mere mechanical mixture of the dehydrogenation and dehydration catalysts is not

TABLE I

REACTION BETWEEN ACETONE AND ISOPROPYL ALCOHOL. EFFECT OF CATALYST COMPOSITION UPON EXTENT OF REACTION

77.5 G. CH_3COCH_3 AND 80.5 G. $CH_3CHOHCH_3$ AND 12 G. OF CATALYST

	CATALYST CONSTITUENTS			
	ZnO:CuO:Al_2O_3	CuO:Al_2O_3	ZnO:Al_2O_3	Cu:Al_2O_3[a]
Catalyst composition, wt. ratios	1:1:3	2:3	2:3	2:3
Temperature, °C.	400	415	400	400
Time of heating, hours	3	3.25	3	3
Maximum pressure, atms.	101	111	120	108
Product:				
Gas, cc. (S.T.P.)	400	700	4500	800
Liquid, g.	155	155	153	153
Composition of anhydrous product, % by volume				
Unchanged $CH_3CHOHCH_3$ and CH_3COCH_3	38	33	89	90
Methyl isobutyl ketone	36	37	2[b]	6[c]
Diisobutyl ketone	13	18	3[b]	
Intermediate fractions	9	5	6	4
Residue + loss	4	7		
Total	100	100	100	100

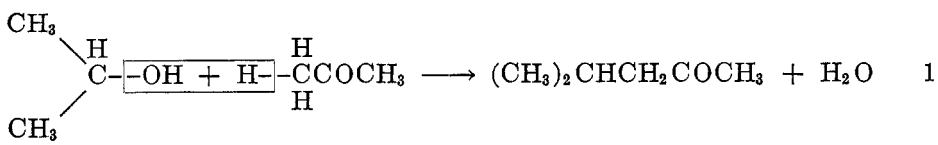
[a] Cu powder by reduction of CuO with H_2, mixed mechanically with Al_2O_3.

[b] Mesityl oxide and phorone.

[c] B.p. from 115-200°, product not identified.

sufficient, indicating that the two catalyst components must be in closer proximity.

Two possible mechanisms have been considered in an attempt to explain this condensation reaction. The first one is the direct interaction between the alcohol and the ketone with the elimination of one molecule of water:



The second mechanism involves a regular ketonic condensation of acetone to diacetone alcohol and a simultaneous hydrogen disproportionation between isopropyl alcohol and diacetone alcohol:

$$2\ CH_3COCH_3 \rightleftharpoons (CH_3)_2COHCH_2COCH_3 \qquad 2.$$

$$(CH_3)_2COHCH_2COCH_3 + CH_3CHOHCH_3 \rightarrow (CH_3)_2CHCH_2COCH_3 + CH_3COCH_3 + H_2O \qquad 3.$$

Our experiments indicate that the latter mechanism is the more probable. This is based on the following experimental evidence:

All ketones containing a methyl group next to the carbonyl group are easily condensed with isopropyl alcohol, and furthermore, only those alcohols which on dehydrogenation can yield ketones containing a methyl group next to the carbonyl group can condense with similar ketones. This is confirmed by the fact that diethyl carbinol does not condense with diethyl ketone and, similarly, isopropyl alcohol does not condense with either diethyl ketone or diisopropyl ketone.

It becomes apparent that the alcohol performs a two-fold action; first, it donates hydrogen so that the intermediate condensation product can be converted into a higher ketone and removed from the reaction; and second, it also donates a definite quantity of ketone which can undergo the condensation reaction. In the absence of the alcohol, acetone reacts to give only small amounts of mesityl oxide and phorone, while in the presence of the alcohol more than fifty per cent of the product consists of higher ketones.

From the above discussion, it appears logical that by varying the ratio of alcohol to ketone we are able to control the amount of hydrogen donated. Since the formation of the primary product of condensation (methyl isobutyl ketone) requires one mole of hydrogen while two moles of hydrogen are necessary for the formation of the secondary product of condensation (diisobutyl ketone), it should be possible to change the ratio of primary to secondary condensation products by changing the alcohol-ketone ratio in the charge.

The following table (Table II) shows the results obtained using different ratios of alcohol to ketone in the charge. The experiments were carried out using the continuous flow method in the presence of the copper-zinc oxide-alumina catalyst. It can be seen that by decreasing the amount of alcohol in the charge and, therefore, decreasing the amount of hydrogen that can be donated, the primary condensation product (methyl isobutyl ketone) is formed in considerably larger amounts than the secondary product of condensation (diisobutyl ketone).

Experiments carried out in the high-pressure autoclave showed that by using an excess of the alcohol increasingly larger quantities of methyl isobutyl carbinol are formed.

The problem of cross-condensing alcohols and ketones having different numbers of carbon atoms was of considerable interest. Methyl ethyl ketone and isopropyl alcohol were brought into reaction at 250° and under twenty atmos-

pheres pressure using a continuous flow method. The higher ketones produced by the condensation reactions constituted 41% by weight of the total product. The following equations show the reactions taking place, with the distribution in per cent by weight of the yields of the higher ketones.

TABLE II

REACTION BETWEEN ISOPROPYL ALCOHOL AND ACETONE. EFFECT OF VARYING FEED RATIOS UPON THE FORMATION OF THE PRODUCTS

Charge, grams			
Isopropyl alcohol	66.5	49.8	33.1
Acetone	33.5	50.2	66.9
Temperature, °C	250	249	251
Liquid space velocity[a]	2.3	2.3	1.9
Pressure, atms.	20	20	20
Product, grams			
Gas, hydrogen	0.1	0.0	0.0
Organic liquid	84.2	87.8	92.2
Water	15.7	12.2	7.8
Product, excluding H_2O, grams			
Acetone	12.3	22.9	46.8
Isopropyl alcohol	6.2	7.1	4.8
Methyl isobutyl ketone	27.3	32.2	28.8
Intermediate fraction (methyl isobutyl carbinol)	3.0	2.1	0.7
$C_9H_{18}O$ ketone	25.8	17.5	8.6
Intermediate	1.0	1.1	2.5
$C_{12}H_{24}O$ fraction	6.4	3.3	
Residue	2.2	1.6	
Total	84.2	87.8	92.2
Total acetone reacted	25.6	27.3	20.1
Total isopropyl alcohol reacted	55.9	42.7	28.3
Total alcohol + acetone reacted	81.5	70.0	48.4
Minus water obtained	65.8	57.8	40.6
Theoretical conversion to $C_6H_{12}O$, %	41.5	55.7	71.0
Actual conversion, %	33.5	46.0	59.5
Theoretical conversion to $C_9H_{18}O$, %	39.2	30.3	21.2
Actual conversion, %	31.6	25.0	17.8

[a] Unit volume of liquid charge per unit volume of catalyst per hour.

$$CH_3CHOHCH_3 + CH_3CH_2COCH_3 \rightleftharpoons CH_3COCH_3 + CH_3CH_2CHOHCH_3 \quad 4.$$

$$CH_3CHOHCH_3 + CH_3COCH_3 \rightarrow (CH_3)_2CHCH_2COCH_3\ (17\%) \quad 5.$$

$$CH_3CHOHCH_3 + CH_3COCH_2CH_3 \begin{matrix} \nearrow\ CH_3CH_2CH(CH_3)CH_2COCH_3\ (6\%) \\ \searrow\ CH_3CH(CH_3)CH_2COCH_2CH_3\ (33\%) \end{matrix} \quad 6.$$

$$CH_3CHOHCH_2CH_3 + CH_3COCH_2CH_3 \rightarrow CH_3CH_2CH(CH_3)CH_2COCH_2CH_3\ (18\%) \quad 7.$$

It will be observed that the yield of the cross-condensation product, that is of the two isomeric heptanones, is more than the combined yield of the C_6 and C_8 ketones. The remainder of the higher ketones consists of C_9, C_{10}, and higher ketones, these being the secondary condensation products. It will be noted that 3-methylhexanone-5 is formed to a much smaller extent than its isomer, 2-methylhexanone-4. This is easily explained by the fact that the first isomer is a methyl ketone, which can react further to give higher condensation products, while the second isomer is unable to do so. Therefore, the first isomer is no longer present in the heptanone range, although both isomers may have formed to an equal extent originally.

Since cyclic ketones behave like methyl ketones in their ability to undergo the regular ketonic condensation, it would be expected that cyclohexanone and isopropyl alcohol would condense under the same conditions. It was found that a somewhat higher temperature (350°) was required to effect this condensation using the continuous flow method. A sixteen per cent yield of cyclohexylacetone was obtained, along with an eighteen per cent yield of higher products. A side reaction taking place under the experimental conditions is the formation of cyclohexene, which proceeds through the hydrogenation of cyclohexanone to cyclohexanol followed by dehydration to cyclohexene.

The condensation of primary alcohols with methyl ketones was investigated using a number of alcohols. It was found that temperatures from 300–350° were necessary. Two concurrent reactions take place under the experimental conditions, the first one is the condensation reaction between the alcohol and the ketone and the second one is the Cannizzaro reaction. The reactions taking place are shown below using ethyl alcohol and acetone as an example:

$$C_2H_5OH \rightarrow CH_3CHO + H_2 \quad 8.$$

$$CH_3CHO + CH_3COCH_3 \rightarrow CH_3CH(OH)CH_2COCH_3 \quad 9.$$

$$CH_3CH(OH)CH_2COCH_3 + H_2 \rightarrow CH_3CH_2CH_2COCH_3 + H_2O \quad 10.$$

$$CH_3CHO + CH_3CH_2CH_2COCH_3 \xrightarrow{H_2} CH_3CH_2CH_2COCH_2CH_2CH_3 + H_2O \quad 11.$$

$$2\ CH_3CHO + H_2O \rightarrow CH_3CH_2OH + CH_3COOH \quad 12.$$

$$CH_3CH_2OH + CH_3COOH \rightarrow CH_3COOC_2H_5 + H_2O \quad 13.$$

It will be observed that the proposed mechanism in the case of a primary alcohol and a ketone is essentially the same as the one used in the case of a secondary alcohol and a ketone. The yield of pentanone-2, obtained upon reaction between ethyl alcohol and acetone at 310° and a pressure of 40 atmospheres, was 28%. The yield of di-*n*-propyl ketone was 10%, while the yield of ethyl acetate was only 7%. This indicates that in the presence of acetone the major reaction of the alcohol is that of condensation to give higher ketones rather than an esterification reaction. *n*-Butyl and *n*-propyl alcohols both

reacted in the presence of acetone give heptanone-2 and hexanone-2 as the condensation products. Varying amounts of ester were produced at the same time.

A series of experiments was carried out in investigating the reactions of primary alcohols alone in the presence of the dehydrogenation-dehydration catalysts. Isobutyl and *n*-propyl alcohols were brought into reaction, a number of experiments being made using the autoclave and a number using the continuous flow method. In the case of *n*-propyl alcohol, which was passed over the copper-zinc oxide-alumina catalyst at 350° and under a pressure of 48 atmospheres, the product contained unreacted alcohol along with a 21% yield of propyl propionate, a 16% yield of diethyl ketone and diethyl carbinol, and a 10% yield of amylene. The exit gas consisted of approximately 80% hydrogen, the remainder

TABLE III

REACTION OF ISOBUTYL ALCOHOL AT 400°C IN ROTATING BOMB

120 G. ALCOHOL + 12 G. CATALYST

EXPT. NO.	CATALYST	FINAL PRESS. ATMS.	YIELD OF LIQUID PRODUCT	COND. GAS, G.	NON-COND. GAS, LITERS	YIELD OF ESTER, %	COND. GAS COMPOSITION					NONCOND. GAS COMPOSITION				
							C_2H_6	C_3H_8	C_4H_8	C_4H_{10}	C_5+	CO_2	CO	H_2	PARAF.	PARAF. INDEX
1	$CuO\text{-}ZnO\text{-}Al_2O_3$	32	75	25	14	22	0	54.0	0	45.2	0.8	13.2	13.3	66.3	7.2	2.55
2	$CuO\text{-}Al_2O_3$	25	62	40	14	34	1.0	32.2	11.3	53.8	1.7	14.2	21.9	56.1	7.8	2.38
3	$ZnO\text{-}Al_2O_3$	42	56.3	30	28	20	32.2	18.4	0.8	48.1	0.5	10.5	20.2	59.2	10.1	2.05
4	CuO-ZnO	28	62.5	21.7	19.6	0	18.4	86.5	0.6	5.1	5.4	3.2	37.2	49.5	10.1	2 33
5	Al_2O_3	10	94	14.3	1.8	2.0	86.5	15.5	68.8	10.1	3.0	22.9	12.7	45.9	17.8	1.86

being primarily carbon dioxide with small amounts of carbon monoxide and paraffins. The following reactions are believed to take place:

$$6\ CH_3CH_2CH_2OH \rightleftharpoons 6\ CH_3CH_2CHO + 6\ H_2 \qquad 14.$$

$$6\ CH_3CH_2CHO + 3\ H_2O \rightarrow 3\ CH_3CH_2CH_2OH + 3\ CH_3CH_2COOH \qquad 15.$$

$$2\ CH_3CH_2COOH \rightarrow CH_3CH_2COCH_2CH_3 + CO_2 + H_2O \qquad 16.$$

$$CH_3CH_2COCH_2CH_3 + H_2 \rightarrow CH_3CH_2CHOHCH_2CH_3 \qquad 17.$$

$$CH_3CH_2CHOHCH_2CH_3 \rightarrow CH_3CH_2CH{=}CHCH_3 + H_2O \qquad 18.$$

$$CH_3CH_2COOH + CH_3CH_2CH_2OH \rightarrow C_3H_7OOCC_2H_5 + H_2O \qquad 19.$$

It will be observed that there is no over-all gain or loss of water during the reactions and, therefore, only an infinitesimal amount of water is required to start the reaction. Such an amount is undoubtedly either contained in the catalyst or is produced by very slight dehydration of the original alcohol.

Experiments using isobutyl alcohol in an autoclave indicated that under the experimental conditions considerable amounts of ester are formed. Table III gives the results obtained. It should be noted that in the presence of the zinc

oxide-alumina catalyst the ester is obtained in a 20% yield. However, it will be remembered from Table I that this catalyst did not effect the isopropyl alcohol-acetone condensation. As is known, zinc oxide is a good catalyst for the hydrogenation of the carbonyl linkage but it is not an active catalyst for either the hydrogenation of the ethylenic linkage or for the hydrogenation of keto alcohols to give saturated ketones.

It will be observed from Table III that a part of the alcohol reacts under the experimental conditions to give propane and butane (Expt. 1). The first product is formed through the decomposition of isobutyraldehyde, while the second one is obtained by the dehydration of the alcohol followed by the hydrogenation of the olefin.

EXPERIMENTAL PART

The experiments described below were carried out in either a rotating bomb of the Ipatieff type or in a continuous pressure apparatus. The bomb used in most cases had a capacity of 850 cc. In some experiments, a glass liner was inserted into the bomb. The continuous flow apparatus consists of high-pressure adjustable feed pump, a stainless steel reaction tube with a pressure gage, a release valve, a series of receivers, and a gasmeter. A perforated plate is used to hold the catalyst inside of the reaction tube. The volume of catalyst in the continuous flow experiments was 60 cc.

Experiments in rotating autoclave. (*a*) *Isopropyl alcohol and acetone.* Acetone (78 g.) and isopropyl alcohol (81 g.) were heated in an autoclave for 3 hours at 388–405° in the presence of 12 g. of catalyst (20% CuO, 20% ZnO, and 60% Al_2O_3 by weight, see below). No gas was evolved and 155 g. of liquid product was recovered. This product consisted of 9 g. of H_2O, 54 g. of unchanged acetone and isopropyl alcohol, 52 g. of methyl isobutyl ketone, 17 g. of diisobutyl ketone, and 14 g. of intermediate fractions and residue. The methyl isobutyl ketone fraction, b.p. 115–119°, gave a semicarbazone m.p. 133–134°, lit. m.p. 135°.

Anal. Calc'd for $C_6H_{12}O$: C, 72.02; H, 12.09.
Found: C, 71.80; H, 12.30.

The diisobutyl ketone fraction, b.p. 166–172°, n_D^{20} 1.4168; d_4^{20} 0.8063, gave a semicarbazone m.p. 116–118°, lit. m.p. 117°, 119°.

Anal. Calc'd for $C_9H_{18}O$: C, 76.00; H, 12.77.
Found: C, 76.20; H, 12.99.

This fraction was subjected to hydrogenation in the presence of the nickel on Kieselguhr catalyst (5) for 4 hours at 60–70°. The alcohol thus obtained distilled at 179°, n_D^{20} 1.4238.

Anal. Calc'd for $C_9H_{20}O$: C, 74.93; H, 13.91.
Found: C, 75.06; H, 13.56.

The α-naphthylurethan derivative had the m.p. 71–74°.

Anal. Calc'd for $C_{20}H_{27}NO_2$: N, 4.48.
Found: N, 4.72.

The alcohol was then passed over aluminum oxide at 370–400° to yield a fraction boiling at 131–132°; n_D^{20} 1.4126. This olefin was then hydrogenated using the nickel on Kieselguhr catalyst at 60–100° for two hours. The product distilled at 134–135° and had the refractive index n_D^{20} 1.4011; the constants for 2,6-dimethylheptane are b.p. 134–135°, n_D^{20} 1.3955, 1.4028. The yield of the paraffin based on the original alcohol was 80%.

(b) Using the same reactants and same conditions except that the heating was continued for 4 hours the yield of methyl isobutyl ketone was 50 g. The acetone-isopropyl alcohol mixture recovered from the product contained approximately 4 g. of a water-insoluble product, indicating that upon longer heating the side reactions begin to appear.

(c) One hundred fifty-eight grams of acetone was heated in an autoclave for 2 hours at 375–395° in the presence of 15 g. of catalyst containing equal parts of the three components, (CuO, ZuO, Al_2O_3). No gas was evolved and the liquid product contained 120 g. of acetone

and 17 g. of mesityl oxide. The remainder of the product consisted of intermediate fractions and a residue. The mesityl oxide was obtained in a pure state; b.p. 130°, n_D^{20} 1.4405.

Experiments using flow method. Table II describes the experiments using the continuous flow method. Although large quantities of product were obtained, all of the data were reduced to a basis of 100 parts by weight of charging material in order to simplify the tabulation of results. The products were dried with potassium carbonate and distilled using a 30-plate column. The catalyst used in these experiments consisted of 20% CuO, 20% ZnO, and 60% Al_2O_3 by wt. It was prepared as follows: 151.5 g. of $Cu(NO_3)_2 \cdot 3H_2O$ and 183 g. of $Zn(NO_3)_2 \cdot 6H_2O$ were dissolved in 1,000 cc. of water and added to a rapidly agitated suspension of 150 g. of powdered aluminum oxide in 2,000 cc. of water. The entire suspension was heated to 80–90° following which 142 g. of $(NH_4)_2CO_3 \cdot H_2O$ dissolved in 500 cc. of water was added. Upon reaching complete precipitation the suspension was cooled, washed by decantation, filtered, washed again, and finally dried at 250° for ten hours. This was followed by reduction at 225° for one hour using a mixture of hydrogen and nitrogen (app. 1:3).

The presence of methyl isobutyl carbinol (Table II, column 1) was proved by the 3,5-dinitrobenzoate derivative; m.p. 61°; mixed m.p. with derivative prepared from methyl isobutyl carbinol from complete hydrogenation of mesityl oxide, no change.

Experiments using methyl ethyl ketone and isopropyl alcohol. A number of experiments were made using methyl ethyl ketone and isopropyl alcohol as well as secondary butyl alcohol and acetone. The following experiment is described in detail; an equimolar mixture of methyl ethyl ketone and isopropyl alcohol was passed over a catalyst (10% CuO, 10% ZnO, 80% Al_2O_3 by wt.) at 274–280° and 20 atms. pressure. The space velocity was 4.1 cc. of liquid per cc. of catalyst per hour. No gas evolution was observed. The recovered liquid, after drying and distilling, was found to contain 59% by volume of unreacted acetone, isopropyl alcohol, methyl ethyl ketone, and sec.-butyl alcohol. The higher ketones fraction contained the following amounts of the various ketones: C_6, 17%; C_7, 39%; C_8, 18%; and C_9+, 26%. The octanone formed is 3-methyloctanone-5, b.p. 161°, semicarbazone m.p. 94°; lit. b.p. 161°, semicarbazone m.p. 96°. The C_7-ketone fraction can consist of two possible compounds: 4-methyl hexanone-2 and 5-methyl hexanone-3. The two compounds could not be separated by distillation and gave a semicarbazone melting over a range of 5 degrees. The crude C_7-ketone fraction was redistilled and a large cut boiling at 138.5–142° was obtained. This was hydrogenated using the nickel on Kieselguhr catalyst, to give a fraction boiling at 149–151°. The alcohol was then dehydrated over alumina at 380°, the products distilling in two fractions: 86–87°, n_D^{20} 1.4004; 87–88.5°; n_D^{20} 1.4020. These two fractions were combined and hydrogenated using the same catalyst, to give the following fractions: 90–90°, n_D^{20} 1.3858; 90–90.5°, n_D^{20} 1.3861. The two fractions were combined and a density measurement made: $d^{20.6}_4$ 0.6804; 2-methylhexane has the following constants: b.p. 89.7°, n_D^{20} 1.3851, d_4^{20} 0.6787, while for 3-methylhexane they are b.p. 91.8°, n_D^{20} 1.3887, d^{20} 0.6900.

Experiment using acetone and diisopropyl carbinol. Eighty-seven grams of acetone and 171 g. of diisopropyl carbinol were heated to 425° for 4 hours in a rotating bomb in the presence of the mixed catalyst; 10 g. of a condensable gas was collected. *Anal.*: C_3H_6, 7.2%; C_3H_8, 78.6%; n-C_4H_8, 3.5%; n-C_4H_{10}, 4.3%; C_5, 6.4%. No non-condensable gases were obtained. The lower-boiling fraction, b.p. 53–90°, consisted primarily of acetone and isopropyl alcohol along with small amounts of olefins. The main fraction, b.p. 123–129°, n_D^{20} 1.4010, semicarbazone m.p. 151.5–153.5°, consisted of diisopropyl ketone. A small amount of methyl isobutyl ketone was formed.

Experiment using cyclohexanone and isopropyl alcohol. Equimolar amounts of cyclohexanone and isopropyl alcohol were passed over the same catalyst at 350°, 21 atms. pressure and a liquid space velocity of 4.2. The exit gas contained 93% hydrogen. The liquid product was dried and distilled. It contained 13% cyclohexene, 3% methyl isobutyl ketone, 16% of fraction b.p. 192–201°, and 18% residue. The remainder of the product was unchanged cyclohexanone, acetone, and isopropyl alcohol. The fraction boiling at 192–

201° was redistilled to give a major cut, b.p. 200.5°, and a semicarbazone of m.p. 173–174°. This product could be either 2-isopropylcyclohexanone-1 or cyclohexylacetone. The product was hydrogenated to the corresponding alcohol b.p. 206–207°, n_D^{20} 1.4634, and completely hydrogenated with a nickel-alumina catalyst to give the corresponding alkyl cyclohexane. This product distilled at 152–156° and had n_D^{20} 1.4368. This corresponds to *n*-propylcyclohexane, n_D^{20}, 1.4371. The original compound is, therefore, most likely cyclohexylacetone.

Experiments using primary alcohols and acetone. (a) Equimolar amounts of *n*-butyl alcohol and acetone were passed over a catalyst containing 10% CuO, 10% ZnO, and 80% Al_2O_3 by wt. at 309°, 40 atmospheres pressure and a liquid space velocity of 2.3. The exit gas contained 91% hydrogen. The liquid product consisted of unchanged acetone and butyl alcohol, together with 7% of heptanone-2 and 11% of *n*-butyl *n*-butyrate. Small amounts of *n*-butyraldehyde were also found. Heptanone-2 was found in the fraction of b.p. 148–153°, and gave a sodium bisulfite addition product (plates from 90% alcohol); semicarbazone m.p. 119–120°, lit. m.p. 122°.

(b) Equimolar amounts of *n*-propyl alcohol and acetone were passed over the same catalyst at 350°, 54 atms. pressure, and a liquid space velocity of 2.6. The liquid product contained 63% unchanged acetone and *n*-propyl alcohol along with small amounts of propionaldehyde. Fraction b.p. 125–131° contained hexanone-2, which gave a sodium bisulfite addition product, semicarbazone m.p. 124.5–125.5° and dinitrophenylhydrazone m.p. 106°; lit. semicarbazone m.p. 118–119°, dinitrophenylhydrazone m.p. 106°. Propyl propionate was obtained in a 10% yield. Saponification followed by analysis of the silver salt confirmed the presence of the ester.

(c) Equimolar amounts of ethyl alcohol and acetone were passed over the same catalyst at 357°, 43 atmospheres pressure and a liquid space velocity of 3.3. Twenty-one liters of gas was obtained from 400 g. of charge. The gas analysis is as follows: CO_2, 8.0; C_2H_4, 1.1; C_3H_6, 14.2; CO, 0.4; H_2, 63.6; paraffins, 12.7. The liquid product contained 28% pentanone-2 and 10% di-*n*-propyl ketone. Pentanone-2, b.p. 100–103° gave a semicarbazone m.p. 107–108° and a sodium bisulfite addition product; lit. semicarbazone m.p. 110°. Di-*n*-propyl ketone distilled at 145–147° and gave a semicarbazone m.p. 133–134°; lit. m.p. 133°. Ethyl acetate was obtained in a 7% yield. The remainder of the product consisted of unchanged acetone and ethyl alcohol, with smaller amounts of acetaldehyde, methyl isobutyl ketone, and acetic acid.

Experiments using primary alcohols. (a) In order to determine the action of mixed catalysts upon primary alcohols under pressure in the absence of hydrogen, a series of experiments was carried out using isobutyl and *n*-propyl alcohols. At the same time the effect of catalyst composition upon the yield of the ester was determined. Isobutyl alcohol was used in the following experiments under these conditions: 120 g. of alcohol, 12 g. of catalyst; heating in rotating bomb at 400° for 4 hours. The data obtained are shown in Table III. The liquid product contained among the lower-boiling fractions isobutyraldehyde and unreacted alcohol. Fraction b.p. 140–150° consisted primarily of the ester, isobutyl isobutyrate. Following fractionation, cut 144–146° was saponified and the acid was converted into a silver salt.

Anal. Calc'd for $C_4H_7AgO_2$: Ag. 55.3. Found: Ag, 55.8.

In another experiment isobutyl alcohol was passed continuously over a catalyst consisting of 10% CuO, 10% ZnO, and 80% Al_2O_3 by wt. at 350°, 41 atmospheres pressure, and a liquid space velocity of 1 cc. of liquid per cc. of catalyst per hour. The liquid product contained 20% of a fraction b.p. 145–148° which was found to be isobutyl isobutyrate. Small amounts of isobutyraldehyde were found in the lower-boiling fraction. No condensable gas was produced, while the non-condensable gas contained 88% hydrogen.

In the next experiment, *n*-propyl alcohol was passed over the same catalyst at 349° and 48 atmospheres with a liquid space velocity of 1. Seventeen and six-tenths liters of gas was evolved per mole of alcohol charged. The gas contained the following: CO_2, 12.4; CO, 1.5; H_2, 78.6; total olefins 0.3; paraffins, 7.2. The liquid product was treated with water to

remove the *n*-propyl alcohol and part of the propionaldehyde. The remainder of the liquid product (60%) contained the following compounds: amylene 10%, propionaldehyde 9%, diethyl ketone and carbinol 16%, *n*-propyl propionate 21%.

The diethyl ketone gave a semicarbazone m.p. 136°; lit. m.p. 138°.

SUMMARY

The formation of higher ketones using a mixture of a secondary or a primary alcohol and a ketone has been investigated in the presence of a mixed dehydrogenation dehydration catalyst. The work was undertaken to approach the mechanism of the reaction, factors governing it, and the required catalysts for the reaction. It was found that ketones containing a reactive $-COCH_3$ group and alcohols containing as terminal groups either $-CH_2OH$ or $-CHOHCH_3$ react smoothly at temperatures above 200° and pressures ranging from 1 to 50 atmospheres to give large yields of higher ketones. These ketones contain the number of carbon atoms equivalent to the sum of the carbon atoms of the original ketone and alcohol. Only catalysts having both dehydrogenating and dehydrating properties can effect the condensation. The extent of reaction and purity of the product depend largely upon the initial alcohol ketone ratio.

There is no final conclusive proof of the mechanism of the reaction. It may, however, be stated that an intermolecular hydrogen disproportionation reaction is involved and that upon interaction of the alcohol and the ketone a molecule of water is eliminated. Primary alcohols and ketones give higher ketones by means of a similar mechanism. Primary alcohols alone in the presence of the same catalyst produce esters, the latter being formed through a Cannizzaro reaction.

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EVANSTON, ILL.

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[CONTRIBUTION FROM THE BUREAU OF ANIMAL INDUSTRY, UNITED STATES DEPARTMENT OF AGRICULTURE]

THE SYNTHESIS OF CONDENSED RING COMPOUNDS. IX. THE REACTION OF 5-ACETOXY-1,4-TOLUQUINONE WITH CONJUGATED DIENES, AND THE RULES OF ALDER[1]

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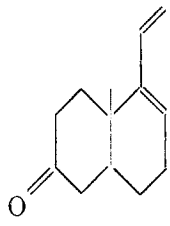
In order to prepare methylvinyloctalones similar to I for use in a projected synthesis of steroids (1) we have studied the reaction of 5-acetoxy-1,4-toluquinone (II) with 1,3,5-hexatriene. If the enol acetate (III) were a product of this reaction and were convertible to the isomer IV, we should have an intermediate useful for the synthesis of steroids with a hydroxyl or a keto group at position 3 and a methyl group at position 10, the type most frequently en-



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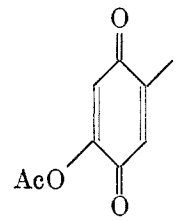

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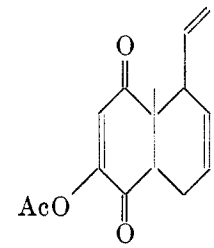

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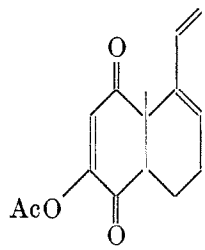

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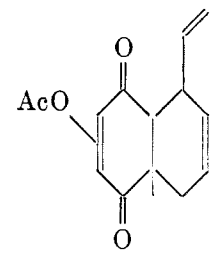

V

countered among naturally occurring steroids. We have already reported (2) the isolation of a substance $C_{15}H_{16}O_4$ from the products of this reaction and assumed that it had either structure III or V. It is still uncertain whether III can be readily converted to IV, and IV then condensed with a derivative of cyclopentene to produce a steroid. Dane and co-workers (3) in recent years have prepared several steroids by the addition of cyclopentene derivatives to

[1] This work was supported by an appropriation from Bankhead-Jones funds (Bankhead-Jones Act of June 29, 1935), and is part of an investigation of the animal metabolism of substances related to the steroid hormones being carried out under the Physiology of Reproduction Project, a cooperative project of the Bureau of Animal Industry and the Bureau of Dairy Industry. Not subject to copyright.

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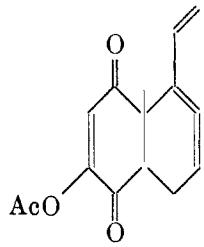
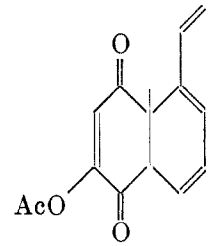
analogous vinyldihydronaphthalenes. The chances that the scheme of synthesis outlined in (1) may be practical are increased by the observations that 1,5-diene-3-ynes add maleic anhydride (4, 5) and quinones (6), because adducts from acetoxytoluquinone and dienynes, such as VI and VII, already would contain a reactive diene system, whereas III must be converted to IV. We wish at this time to present descriptions of the products formed in the reaction of acetoxytoluquinone with hexatriene, still incomplete descriptions, but demonstrating much of their structure and indicating what types of compound may be accessible through the reaction of the same quinone with dienynes.



VI

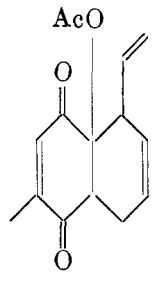


VII

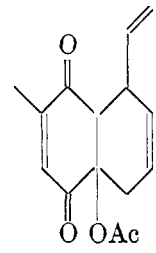
Although a Diels-Alder reaction of acetoxytoluquinone with hexatrien cane yield 16 primary products, four structural isomers each in four stereoisomeric (racemic) forms, we did not hesitate to utilize the reaction for synthetic purposes, since it is well known that it proceeds with a high degree of selectivity. This prognosis was found to be correct; two products were obtained in substantial yield (45% and 21%). This reaction of acetoxytoluquinone with hexatriene provides an interesting test of the relative reactivities of the acetoxyethene and methylethene systems. If the size of the substituent group at the dienophile double bond is the controlling factor, the chief products should be the enol acetates III and V. One or both of these is undoubtedly formed but it, or they, is extremely unstable, and only occasionally has an enol acetate been isolated although many batches were run. This instability of the enol acetates and some of the other products has complicated the study of the reaction. Its completion has been further hindered by the difficulty of preparing adequate quantities of hexatriene of assured purity. The preliminary work (2) was done with hexatriene prepared by the pyrolysis of *sym*-divinylglycol with formic acid according to van Romburgh (7). It was then found that the dehydration of 1,5-hexadiene-3-ol gave better yields of hexatriene (8) and most of the work here reported was done with hexatriene from this source. After much of the experimental work had been done, it was discovered (9) that this hexatriene probably contained some 1,3-cyclohexadiene, which would also in all likelihood react with acetoxytoluquinone to give products isomeric with those from hexatriene. The difficulties arising from this circumstance were controlled by including a study of the reaction of acetoxytoluquinone with pure 1,3-cyclohexadiene and with hexatriene prepared by the low temperature method of Kharasch and Sternfeld (10) which had appeared in the meantime.

It will be shown that three compounds, and possibly a fourth, can be isolated from the products of reaction of acetoxytoluquinone with hexatriene; that each of the three are formed both from hexatriene prepared by the method we previously described (8) and that of Kharasch and Sternfeld (10); and finally that each of these compounds differs from each of three which can be obtained by the reaction of acetoxytoluquinone with cyclohexadiene. The description of an adduct obtained from acetoxytoluquinone and 2,3-dimethyl-1,3-butadiene will also be given.

When acetoxytoluquinone and hexatriene are heated together in ethanol at 70° or 95° the colorless substance, $C_{15}H_{16}O_4$, previously (2) reported, cannot always be isolated from the product mixture, and when it is found, the quantity is much smaller than that of either of two other products which have since been obtained. The product obtained in highest yield (45%) is a faintly yellow crystalline compound, $C_{15}H_{16}O_4$, melting at 109–110°, which gives no color with ferric chloride and which could not be hydrolyzed to any product giving such a color. When heated at 200° at reduced pressure it gave acetic acid and tarry products which were not characterized. Enol acetates are usually not resistant to hydrolysis, and structures III and V probably do not represent this substance. Addition of hexatriene to the acetoxyethene link of the quinone would lead to compounds VIII and IX and these structures are compatible with the properties of the acetate melting at 109–110°. After the descriptions of the other compounds prepared in this work have been presented, it will be apparent that this substance, the major product of the reaction between acetoxytoluquinone and hexatriene, is an angular acetate, VIII or IX. The product formed



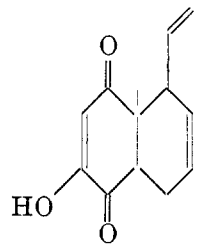
VIII



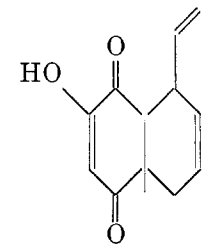
IX

in next largest amount is a colorless crystalline compound, $C_{13}H_{14}O_3$, which begins to decompose at 195° and melts at 206–210°. It dissolves in cold dilute aqueous sodium hydroxide and can be recovered unchanged from this solution by precipitation with hydrochloric acid. This behavior suggests an enolic structure, which is confirmed by the purple-black to brown-black solutions which the substance gives with ferric chloride. A part of the hexatriene has therefore added to the methylethene link in the quinone, and under the conditions of the addition reaction or the subsequent isolation of products the acetate thus formed has become hydrolyzed to an enol. Whether this enol has structure

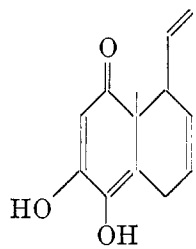
X or XI, XII or XIII, or one of a number of other tautomeric structures we do not know. The fact that the substance does not decompose until a rather high temperature (195°) is reached in the melting point determination perhaps indicates a dienol structure such as XII or XIII. The third compound, $C_{15}H_{16}O_4$, was isolated in very small quantity from only one batch. After recrystallization from ether it melted unsharply at about 135–140° and gave a deep green solution with ferric chloride. When heated with water for a short time, part of it dissolved and the filtered hot solution deposited a colorless material on cooling. This suspension gave a brown-black solution with ferric chloride similar to that obtained from the free enol. This enol was isolated from the part which did not pass into the hot water solution, and the close relationship of the acetate melting at 135–140° to the enol decomposing at 195° and melting at 206–210° was thus demonstrated. Whether the acetate has structure III or V or some tautomeric structure such as XIV cannot be decided on the basis of available evidence. It can be concluded, however, that the addition of hexatriene to acetoxytoluquinone does yield an enol acetate with an angular methyl group which is hydrolyzed with ease to an enol. On the basis of crystalline material actually isolated, this acetate appears to be a minor product and the angular acetate (VIII or IX) seems to be the chief product, but this apparently lower yield of enol acetate and enol may be due in part to the diffi-



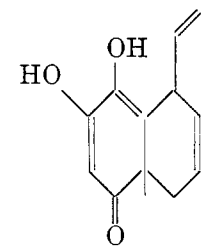
X



XI



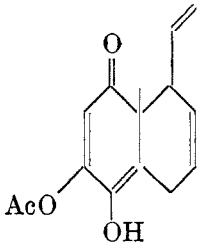
XII



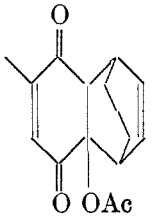
XIII

culty of isolating the enol acetate. The identity of the compound $C_{15}H_{16}O_4$ reported previously (2) is in doubt. When heated it decomposed at 161–162° to a yellow solid which melted at 192–195°. On the addition of tenth-normal aqueous sodium hydroxide it dissolved within a few minutes in the cold. Its behavior with ferric chloride was not observed. Since the solubility in

alkali indicated that the substance was an enol acetate, and since the melting point of the product of pyrolysis (at 161–162° in the capillary tube) was close to that of the enol $C_{13}H_{14}O_3$, which has been obtained pure and from many batches, it is suggested that it may have been largely converted to this enol during the melting point determination. The difficulty of purifying such enol acetates and of obtaining the two preparations in quantity has made it impossible to determine whether this compound previously reported and the acetate which melts at 135–140° are the same or isomeric.

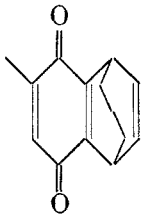


XIV

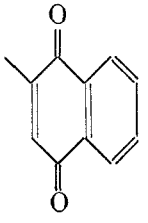


XV

When heated together at 65°, acetoxytoluquinone and cyclohexadiene gave three crystalline compounds which were different from those just described. Therefore, it would seem that the pyrolytic hexatriene used in this work contained little if any cyclohexadiene (9). The adduct obtained in largest yield (up to 55%) is faintly yellow, melts at 123–124° and has the composition $C_{15}H_{16}O_4$. This is not an enol acetate for it gives no colored solutions with ferric chloride, either before or after exposure to hydrolytic conditions, and does not dissolve readily in aqueous sodium hydroxide. The only probable structure is that represented by XV. This was conclusively shown to be correct by examination of the products of pyrolysis. It seemed likely that a compound XV



XVI

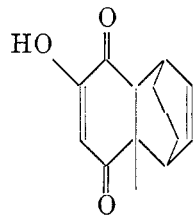


XVII

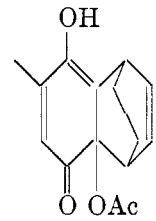
would split out acetic acid readily when heated to give XVI and it will be recalled (11) that compounds containing this 1,4-ethano-2,5-cyclohexadiene system are often decomposed at about 150° with the formation of ethylene and an aromatic ring. When we heated the substance melting at 123–124° at about 200° and under reduced pressure, acetic acid and 2-methyl-1,4-naphthoquinone (XVII) were obtained. Accordingly, under the conditions employed, cyclohexadiene adds to the acetoxyethene link of the quinone to a greater extent than

to the methylethene link. These conditions are mild and it would have been predicted that a group as large as the acetoxyl group would retard considerably the addition of the diene to the dienophile. Some other factor must therefore be present which facilitates this particular addition, and later on we will propose what this factor may be.

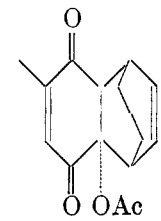
Under the same experimental conditions cyclohexadiene adds to the methylethene link, for it has been possible to isolate a very small quantity of an enol which must have structure XVIII or a tautomeric one. This substance, $C_{13}H_{14}O_3$, melted at 152–153°, was soluble in dilute aqueous sodium hydroxide and gave a brown solution with ferric chloride, and evidently had been formed by hydrolysis of an enol acetate. The third product from this reaction is a faintly yellow compound which melts at 84–87°. The highest yield obtained was 6%. The composition is that of the expected enol acetate, $C_{15}H_{16}O_4$, but this cannot be its structure for it not only fails to hydrolyze to the enol of melting point 152–153° or another enol, but it also decomposes on heating to give 2-methyl-1,4-naphthoquinone and acetic acid, just as does the isomer which melts at 123–124°. The structure of this substance must also be XV and we shall therefore call it XV-B.



XVIII



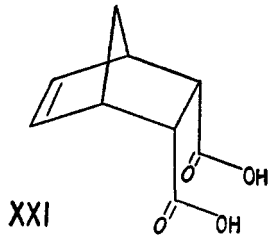
XIX



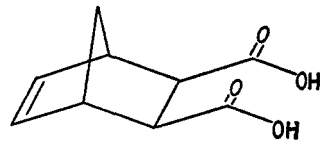
XX

Since neither XV-B nor the higher-melting isomer (XV-A) has enolic properties, their isomerism cannot be explained by assigning the tautomeric structure XIX to one of them. Nor can it be alleged that the one isomer is a trans-decalin type (XX), formed by conversion of the cis isomer which would be the primary product of the Diels-Alder addition. According to Alder and Stein, such a trans structure is probably incapable of existence because of the presence of the ethano bridge at the adjacent carbon atoms (12). The stereoisomerism here is probably of the endo-exo type discussed by Alder and Stein (13) in connection with the products of addition of dienophiles to cyclopentadiene and certain fulvenes.

Under a given set of conditions these workers found that cyclopentadiene and diphenylfulvene (the phenyl groups replacing the hydrogens of the methylene of fulvene) each reacted with maleic anhydride to give one compound in 100% yield. On the other hand, the analogous dimethylfulvene and pentamethylenefulvene each gave two compounds, one in about 60% yield and the other in about 40% yield. They were able to show conclusively that the compound from cyclopentadiene is the bicycloheptenedicarboxylic acid (XXI) which is quite different from the stereoisomer XXII which they obtained by another method.

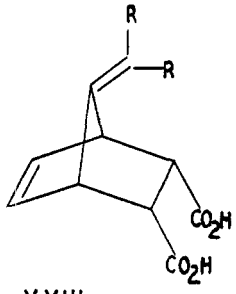


XXI

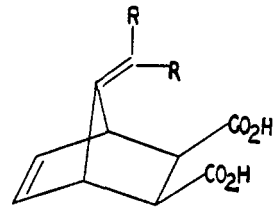


XXII

When, instead of cyclopentadiene, dimethylfulvene or pentamethylenefulvene reacts with maleic anhydride, the reaction no longer follows a single course, but proceeds to the formation of two stereoisomeric compounds in unequal amounts. This Alder and Stein attributed to the presence of the additional double bond. They proposed the hypothesis that in cases in which a diene and a dienophile can lead to more than one stereoisomer, the molecules of diene and dienophile prior to reaction tend to assume that relative orientation which corresponds to the maximum density of doubly bonded atoms. Upon reaction that isomer is formed which follows from this orientation. For this reason cyclopentadiene and maleic anhydride give only the endo isomer XXI in which the two carboxyls are relatively close to the annular double bond. In the attraction of the carboxyl groups, the methylene group offers no competition to the double bonds of the diene system. For a similar reason diphenylfulvene and maleic anhydride give only one product, XXIV (R is phenyl), in which the carboxyls are now oriented toward the C:RR group which contains seven double bonds. But in dimethylfulvene or pentamethylenefulvene the group R contains no double bonds; the carboxyls are attracted to both the diene system and the semicyclic double bond, two competing reactions ensue, and two products, XXIII and XXIV, are formed.



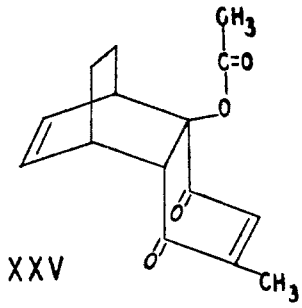
XXIII



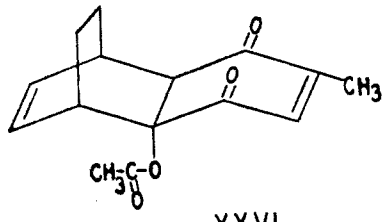
XXIV

The existence of the two forms, exo and endo, in this type of stereoisomerism depends on the rigidity of the molecules with the 1,4-bridge. Cyclohexadiene gives analogous products. Now in the reaction of acetoxytoluquinone and cyclohexadiene, structures are involved which could give rise to two isomeric angular acetates of the endo-exo type. In this case the competing unsaturated centers, the carbonyls and the acetoxyl, are in the dienophile reactant. Since

one of the competing systems has two double bonds and the other but one, the isomers can be expected in unequal yield. Actually 55% of the higher-melting compound (XV-A) and 6% of the lower-melting compound (XV-B) were isolated. Unlike Alder and associates, we have not proved the structures of the two isomers in this regard, but it will be subsequently shown that according to the rule of Alder and Stein the major product (XV-A) should have structure XXV. The acetate XV-B then must be XXVI.

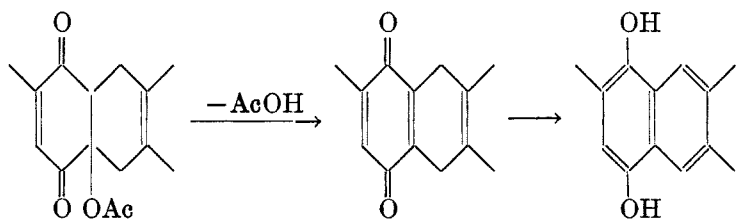


XXV



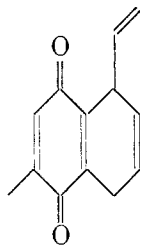
XXVI

Only one product was isolated from the reaction mixture from acetoxytoluquinone and 2,3-dimethyl-1,3-butadiene. This reaction was studied less thoroughly than the other two. It is being included because it has been found that here again the diene has added to the acetoxyethene link. The addition was carried out in ethanol at 95° and gave 42% of a faintly yellow crystalline compound which melts at 116–117°. This compound is an acetate, $C_{15}H_{18}O_4$, which is not converted to an enol by heating with dilute aqueous acetic acid. In view of the similarity in properties to some of the acetates from hexatriene and cyclohexadiene, we were curious to know how it would behave toward heat. At about 200° and under reduced pressure the products were acetic acid and a crystalline residue from which a small quantity of a nearly white compound was isolated. This melted at 170–175° and was soluble in hot water. Apparently it was a hydroquinone, but was not characterized further. The crude crystalline residue was oxidized with ferric chloride to give 2,6,7-trimethyl-1,4-naphthoquinone in good yield. The structure of the adduct is therefore to be represented by XXVII, and the probable course of the pyrolysis by XXVII → XXVIII.

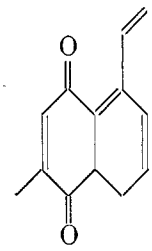


XXVII XXVIII

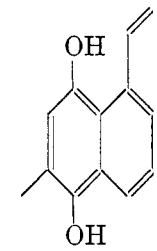
The outstanding result of this work is the observation that these dienes react with the acetoxyethene link of the quinone to an equal or greater extent than with the methylethene link. The methyl group at the dienophile link as a rule retards but does not prevent a Diels-Alder addition. The observation that dienes will add to an acyloxyethene link is not new. Nylén and Olsen (14) found that cyclopentadiene adds to acetoxymaleic anhydride, but not to ethyl *beta*-acetoxycrotonate. Alder and Rickert (15) were able to add vinyl acetate to many dienes. However, it was not to be expected that the acetoxyethene link would be the preferred site of reaction when a methylethene link is available. That this is the case was demonstrated by the preparation of 2-methyl-1,4-naphthoquinone from cyclohexadiene and 2,6,7-trimethyl-1,4-naphthoquinone from dimethylbutadiene just described. With the quantity of material on



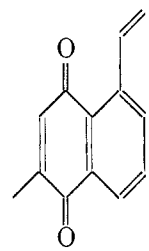
XXIX



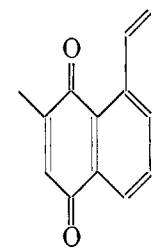
XXX



XXXI



XXXII



XXXIII

hand we could not find conditions suitable for the corresponding preparation of 2-methyl-5-vinylnaphthoquinone (XXXII) or 2-methyl-8-vinylnaphthoquinone (XXXIII) from hexatriene. Either the tetrahydronapthalenedione (VIII) or (IX) was recovered unchanged or dark, extensively decomposed products resulted from which no crystalline compounds could be isolated. This failure is perhaps to be charged to the probable instability of the vinyl derivatives (XXIX) (XXX) (XXXI) in the presence of the acetic acid formed in equivalent amount at the high temperature of the pyrolysis. In the pyrolysis of the dione (VIII or IX) two-thirds of the theoretical quantity of acetic acid was collected and determined by titration of the distillate. A comparison of the properties of the acetoxymethylvinyltetrahydronaphthalenedione of melting point 109–110° with the other compounds prepared (Table I) leaves no doubt that the substance has structure VIII or IX.

EXPERIMENTAL

The melting points for new compounds are corrected.

The ferric chloride enol test was performed by the addition of 2 drops of 0.15% $FeCl_3$ in ethanol to 1 cc. of dilute solution of the unknown substance.

5-Acetoxy-1,4-toluquinone (II). The procedure of Thiele and Winter (21) was followed. The quinone was used after three crystallizations from hexane; m.p. 75–76°.

Anal. Calc'd for $C_9H_8O_4$: C, 60.0; H, 4.5.
Found: C, 60.1; H, 4.6.

1,3,5-Hexatriene. (By Adam M. Gaddis.) Most of the hexatriene was made by the dehydration of 1,5-hexadiene-3-ol with phthalic anhydride at 160–200° (8). That employed

TABLE I

THE PROPERTIES OF COMPOUNDS FORMED IN THE REACTION OF 5-ACETOXY-1,4-TOLUQUINONE WITH 2,3-DIMETHYL-1,3-BUTADIENE (A), 1,3-CYCLOHEXADIENE (B), AND 1,3,5-HEXATRIENE (C)

COMPOUND	A-I	B-I	B-II	B-III	C-I	C-II	C-III
Melting point, °C.	116–117	123–124	84–87	152–153	109–110	135–140	206–210
Color	pale yellow	pale yellow	pale yellow	white	pale yellow	pale yellow	white
Soluble in cold aqueous 0.1 *N* sodium hydroxide	no	no	no	yes	no[b]	yes	yes
Color with ferric chloride	none	none	none	pink-brown	none	green	brown-black
Composition	$C_{15}H_{18}O_4$	$C_{15}H_{16}O_4$	$C_{15}H_{16}O_4$	$C_{13}H_{14}O_3$	$C_{15}H_{16}O_4$	$C_{15}H_{16}O_4$	$C_{13}H_{14}O_3$
Pyrolyzed to a naphthoquinone	yes	yes	yes		?[c]		
Position of maximum absorption in ultraviolet[a]	2360 Å	2300 Å	2350 Å		2350 Å		2560 Å

[a] Complete absorption curves for the ultraviolet region have been determined for these compounds by Russell E. Davis and Harry Bastron of the Bureau of Animal Industry. These will be published by Dr. Davis and Mr. Bastron in collaboration with us in a future paper dealing with the application of absorption spectra to some problems incidental to the synthesis of condensed ring compounds. It will be enough to recall here that Wassermann (27) found a maximum at 2220 Å for 5,8-methano-4a,5,8,8a-tetrahydronaphthalene-1,4-dione.

[b] Color becomes reddish-brown.

[c] Only acetic acid isolated.

for the preliminary (2) work was prepared according to Romburgh (7). A small quantity was prepared by the low-temperature method of Kharasch and Sternfeld (10); it was possible to convert this preparation[2] to 1-vinyl-9,10-anthraquinone (22).

1,3-Cyclohexadiene. This was prepared from cyclohexene by the procedure of Hofmann and Damm (23). The purified product boiled at 80–81°; n_D^{20} 1.474. Kistiakowsky (24) reported n_D^{20} 1.4740.

2,3-Dimethyl-1,3-butadiene. (By Adam M. Gaddis.) This was prepared according to the method of Fieser and Seligman (25). The product boiled at 66–71°.

[2] We are indebted to Mr. Melvin Goldberg for this preparation of hexatriene and for the conversion to vinylanthraquinone.

4a-Acetoxy-2-methyl-5-vinyl-4a,5,8,8a-tetrahydronaphthalene-1,4-dione (VIII) or its 8-vinyl isomer (IX). Three moles of hexatriene (from hexadienol) and acetoxytoluquinone in four volumes of ethanol were kept in sealed tubes filled with CO_2 at 66–74° for 39 hours. The products from six tubes (7.9 g. of hexatriene and 5.8 g. of acetoxytoluquinone) were worked up together. Removal of the more volatile components at 60° and reduced pressure gave 8.7 g. (10%) of crude products. Addition of benzene to this gave no crystalline material (except after long standing in the refrigerator, in which case crystalline enol $C_{13}H_{14}O_3$ separated), but addition of 2–3 cc. of ether gave 2.4 g. of crystals (A) which were filtered off. Removal of the ether and 0.5 g. of other volatile material by holding at 90° and 9 mm. for 2 hours failed to yield more crystals. Repeated extraction of this uncrystallized portion with hot heptane gave solutions which deposited 2 g. of crystalline product (B) upon cooling. A and B were identical and were combined; m.p. 103–104°, 45%. Two recrystallizations from petroleum ether gave 1.4 g., faintly yellow, m.p. 109–110°.

Anal. Calc'd for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2.
Found: C, 69.4; H, 6.5.

This compound becomes more deeply yellow in color and partially liquefied after storing in the dark for many months. This deteriorated product can be repurified by crystallization from hexane. Cold tenth-normal aqueous sodium hydroxide does not dissolve it. Hot aqueous alkalies slowly give deeply colored solutions. In ethanol it gives no colored solution with ferric chloride.

Pyrolysis of VIII (or IX). Upon heating 179 mg. at 200–215° and 80 mm. for 7 minutes, some material was driven off and the contents of the flask became very black. On reducing the pressure to 15 mm., solid acetic acid was condensed in a trap at −40°. Titration of this condensate with 0.05 *N* sodium hydroxide showed 30.84 mg. of acetic acid or 67%. Oxidation of the black residue with ferric chloride gave material from which no crystalline quinone could be isolated. When the period of heating was reduced to 2 minutes, unchanged starting compound was recovered, and again no solid products of pyrolysis were obtained.

2-Acetoxy-4a-methyl-5-vinyl-4a,5,8,8a-tetrahydronaphthalene-1,4-dione (III), its 8-vinyl isomer (V), or tautomer. Acetoxytoluquinone (4.2 g.) was heated with 5.5 g. or 3 moles of hexatriene (from hexadienol) in 33 cc. of absolute ethanol at 92–97° for 16 hours. The volatile components were removed at 50° under reduced pressure. Addition of 10 cc. of benzene to the residual gum (7.2 g.), boiling, and cooling gave no crystalline material (thus differing from some other experiments in which crystalline enol separated at this point). As further additions of benzene and refrigeration for several days yielded no crystals, the benzene solution (30 cc.) was poured into 800 cc. of petroleum ether and the resulting gum and dilute solution were separated. The gum weighed only 0.4 g. and was discarded. The petroleum ether was evaporated from the solution to give a partially crystalline residue. Trituration with 150 cc. of petroleum ether gave an insoluble fraction A and a solution B. Slow evaporation of B gave 0.6 g. of the angular acetate described in the preceding section (m.p. 105–106°, no color with ferric chloride) and 2 g. of oil which did not crystallize. A was purified by slow evaporation of its solution in 100 cc. of petroleum ether-diethyl ether mixture (2:1) which gave 0.4 g. of a crystalline compound, m.p. 135–140° (from ether), green color with ferric chloride.

Anal. Calc'd for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2.
Found: C, 69.2; H, 6.2.

This acetate (III, V, or tautomer) was hydrolyzed slowly by heating with water at 80–100°. A minor portion passed into solution and precipitated as colorless enol on cooling. The products of hydrolysis were dissolved in aqueous sodium hydroxide, the solution extracted with ether, hydrochloric acid added to the aqueous layer until red to litmus and Congo papers, the precipitate washed with water, dissolved in ether, and dried with sodium sulfate. Evaporation of the ether gave colorless crystals, m.p. 200–205°; m.p. of mixture with authentic enol (m.p. 206–210°), prepared as described below, was 203–207°; brown color with ferric chloride. This acetate, which was isolated from only one batch, is therefore

hydrolyzed with ease to the enol which was obtained from many batches, and it probably is the acetate of this enol, although the possibility of tautomerization during hydrolysis must be recognized.

2-Hydroxy-4a-methyl-5-vinyl-4a,5,8,8a-tetrahydronaphthalene-1,4-dione (X), its 8-vinyl isomer (XI), or a tautomer. One and three-tenths grams of acetoxytoluquinone, 1.7 g. of hexatriene from the hexadienol, and 10 cc. of absolute ethanol were heated in a sealed tube at 66–73° for 39 hours. Evaporation of the ethanol at reduced pressure in a stream of carbon dioxide gave a partly crystalline residue which was stirred with 5 cc. of warm benzene, cooled, and filtered. Concentration of the filtrate to 4 cc. gave another crop of crystalline enol. Yield, 0.4 g., 21%. Often separation of crystals did not occur until after addition of benzene and refrigeration of the benzene solution for several days. Two recrystallizations from benzene gave glistening white crystals, decomposing at 195°, m.p. 206–210°.

Anal. Calc'd for $C_{12}H_{14}O_2$: C, 71.6; H, 6.4.
Found: C, 71.6; H, 6.6.

This compound gives a brown-to-black color with ferric chloride in water or ethanol. It is soluble in hot water, from which solution it precipitates on cooling, and is soluble in cold 0.1 *N* aqueous sodium hydroxide. It can be recovered unchanged from the aqueous solution of the sodium salt. To 127 mg. of the enol was added 8.35 cc. of 0.1 *N* sodium hydroxide, whereupon a nearly colorless solution resulted in a few minutes. Addition of 0.09 *N* hydrochloric acid precipitated a solid which, after washing, drying, and recrystallizing from benzene weighed 70 mg., melted at 208–210° and did not depress the m.p. of the original enol.

Reaction of acetoxytoluquinone with hexatriene prepared from allyl chloride and sodamide in liquid ammonia (10). One gram of hexatriene, with the boiling range 75–90°, and 0.75 g. of acetoxytoluquinone were heated together in 10 cc. of absolute ethanol at 70° for 40 hours. The ethanol was removed and the residue was separated into a part soluble in benzene-petroleum ether mixture (1:4) (A), and a part insoluble therein (B). B on recrystallization from benzene gave 30 mg. of colorless product, which gave a brown-black color with ferric chloride and did not depress the melting range of a specimen of the enol of m.p. 206–210° described in the preceding section. Cooling the solution of A, filtering off a little impure enol, evaporating the filtrate to dryness, extracting the residue with 3 cc. of cold petroleum ether, and allowing this solution to stand for several days gave 30 mg. of faintly yellow crystals, m.p. 104–108°, which after being dried on tile gave no depression in melting point with the angular acetate, m.p. 109–110°, prepared from pyrolytic hexatriene.

The two diastereoisomeric 4a-acetoxy-5,8-ethano-2-methyl-4a,5,8,8a-tetrahydronaphthalene-1,4-diones (XV-A) and (XV-B), and 5,8-ethano-2-hydroxy-4a-methyl-4a,5,8,8a-tetrahydronaphthalene-1,4-dione (XVIII). Acetoxytoluquinone (1.4 g.), with 1.4 g. (2.3 moles) of cyclohexadiene in 4 cc. of absolute ethanol for 65 hours at 65° gave, after removal of the volatile components, a residue which crystallized well after seed had been obtained by grinding. The products were taken up in 10 cc. of ether and the solution was cooled well in a solid carbon dioxide-Cellosolve bath. The faintly yellow product (XV-A), m.p. 123–124° after recrystallization from methanol and ethanol, gave no color with ferric chloride in ethanol. Yield 1.0 g.; 55%.

Anal. Calc'd for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2.
Found: C, 69.1; H, 6.4.

The ether was removed from the mother liquor from XV-A, the residue was leached out with successive portions of warm ligroin (b. 60–70°), the ligroin evaporated from the combined extracts, and the residue therefrom taken up in a mixture of petroleum ether (b. 30–60°) and ether. When cooled very gradually, 100 mg. of crystals was deposited, m.p. 82–87°. Recrystallization from the same solvent mixture gave XV-B, faintly yellow, m.p. 84–87°; yield, 6%.

Anal. Calc'd for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2.
Found: C, 69.2; H, 6.2.

XV-B like XV-A gave no colored solution with ferric chloride. It was shown not to be a mixture of XV-A with an enol acetate, by an unsuccessful attempt to hydrolyze it to an enol. Ten milligrams was heated one hour in 6 cc. of ethanol and 3 cc. of 12 *N* aqueous hydrochloric acid. After careful neutralization with sodium hydroxide solution, the addition of ferric chloride failed to give a color. The enol acetate III or V was hydrolyzed to a chromogenic enol by merely heating with water. That the treatment with hydrochloric acid, or the presence of the sodium chloride resulting from the neutralization did not inhibit the customary enolic response to ferric chloride was demonstrated by a parallel experiment with the enol X or XI. In the latter case no color could be produced with ferric chloride in the presence of free hydrochloric acid, but after neutralization the usual colored solution was obtained.

Although no enol acetate was ever isolated from the reaction products of acetoxytoluquinone with cyclohexadiene, the enol XVIII was found in one batch. The material in the angular acetate mother liquor was distilled at 1–2 mm. At bath temperature 210–220°, a fraction of approximate b.p. 130° passed over and condensed to a red crystalline mass. Successive recrystallization from ether and petroleum ether-ether mixture gave white crystals, m.p. 152–153°. This substance was soluble in cold dilute sodium hydroxide and gave a pink-brown colored solution with ferric chloride in ethanol. It smelled of hickory wood smoke.

Anal. Calc'd for $C_{13}H_{14}O_3$: C, 71.6; H, 6.4.
Found: C, 71.3; H, 6.7.

Pyrolysis of XV-A to 2-methyl-1,4-naphthoquinone and acetic acid. Two hundred and twenty-two milligrams of XV-A, m.p. 123–124°, was heated in a small tubular flask attached to a receiver cooled to −40° for 20 minutes at 100–110 mm. and at bath temperature 210–215°. Trapping of the ethylene formed was not attempted, nor was a quantitative recovery of the acetic acid. After the period of heating, the flask was brought slowly to room temperature and the pressure reduced to 14 mm. for 10 minutes. In this way an amount of acetic acid was transferred to the receiver which required 11.30 cc. of 0.0505 *N* sodium hydroxide for neutralization. This is 34.2 mg. of acetic acid; 67% yield. The yellow oil on the sides of the flask and the charred residue at the bottom were worked up separately. The yield of 2-methyl-1,4-naphthoquinone, m.p. 103° from ether-ligroin was 51%; it did not depress the m.p. (105°) of an authentic specimen.

Pyrolysis of XV-B to 2-methyl-1,4-naphthoquinone and acetic acid. The isomer of m.p. 84–87° (XV-B) (114.6 mg.) was pyrolyzed in the same way as XV-A. The decomposition proceeded less smoothly than that of XV-A. The recovery of acetic acid as indicated by titration was 7.9 mg. or 29%. The yield of pure 2-methyl-1,4-naphthoquinone was smaller than that from XV-A. It melted at 102° (from ligroin); m.p. of mixture with the authentic specimen (m.p. 105°) was 103°.

4a-Acetoxy-2,6,7-trimethyl-4a,5,8,8a-tetrahydronaphthalene-1,4-dione (XXVII). (By Adam M. Gaddis.) Acetoxytoluquinone (3.6 g.), 2.4 g. (1.5 moles) of 2,3-dimethyl-1,3-butadiene, and 18 cc. of ethanol were heated at 95° for 14 hours. Concentration of the reaction mixture to one-half volume at reduced pressure gave 1.9 g. of crystalline material which after recrystallization from ether-hexane and then from hexane gave 1.29 g., faintly yellow, m.p. 116–117°. Evaporation of the original alcohol mother liquors, extraction of the residue with ether and hexane, and crystallization of the residue, obtained by the removal of solvents from this extract from methanol gave a further crop of the same product. Yield, 2.2 g.; 42%.

Anal. Calc'd for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9.
Found: C, 68.9; H, 7.2.

This compound does not dissolve completely in cold 0.1 *N* aqueous sodium hydroxide, gives no colored products with ferric chloride, and was not hydrolyzed to products giving such color with ferric chloride when heated with 30% acetic acid in water at 95° for one hour.

Pyrolysis of XXVII. Two hundred and sixty milligrams of XXVII, m.p. 116–117°,

was heated at 210–215° and 80–85 mm. for 15 minutes. While the reaction flask was cooling, the pressure was reduced to 15 mm. The condensed acetic acid required 16.1 cc. of 0.0505 *N* sodium hydroxide, which is equivalent to 48.8 mg. of acetic acid; yield, 80%. The residue from the pyrolysis crystallized on cooling.

A small portion was recrystallized from ether-ligroin, yielding a white substance with a tinge of violet, m.p. 170–175° with decomposition, which was soluble in hot water. This was not analyzed, but presumably was 2,6,7-trimethylnaphthalene-1,4-diol (XXVIII). For characterization the crude product of pyrolysis was oxidized by warming for a few minutes with 3 g. of ferric chloride hexahydrate in 15 cc. of ethanol. The ethanol solution was poured into 250 cc. of water, allowed to stand 15 minutes, the yellow crystals filtered off, and recrystallized successively from aqueous methanol and ligroin. Yield, 100 mg.; m.p. 107.5–108.5°. Bergmann and Bergmann (26) give m.p. 110° for 2,6,7-trimethyl-1,4-naphthoquinone.

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 78.0; H, 6.0.
Found: C, 78.0; H, 6.5.

APPLICATION OF THE RULE OF ALDER AND STEIN TO THE PREDICTION OF ISOMERIC PRODUCTS OF THE DIELS-ALDER REACTION

On the basis of about ten thoroughly investigated reactions, which were all of the type leading to products with endo bridges, Alder and Stein (13) proposed the following rule: *Upon mixing a 1,3-diene and a dienophile the molecules tend to assume that mutual orientation which corresponds to the greatest accumulation of double bonds, and that product is formed in larger amount which is to be expected from the preferred pre-reaction orientation.* The reactants of Alder and Stein presented only one dienophile link and could yield only two diastereoisomeric products. They were rather simple cases, and it was possible for Alder and Stein to apply the rule by merely inspecting the conventional structural formulas suitably juxtaposed. It is the purpose of this section to show how the rule may be applied to more complicated cases such as the reactions of acetoxytoluquinone. Three general cases will arise: (A) The maximal density of double bonds will be determinable by inspection of conventional formulas drawn to scale[3] and suitably juxtaposed. (B) The maximal density of double bonds cannot be determined as in (A), but can be determined by making measurements of such drawings and supporting these by simple calculations. (C) In the presence of double bonds in mobile groups, the position of nearest approach of the mobile double bond to the other double bonds must be determined, and the measurements and calculations then made as in (B).

Acetoxytoluquinone is a bifunctional dienophile, the two olefin links carrying different groups. Therefore, the reaction acetoxytoluquinone + 2,3-dimethylbutadiene could yield two products which are position isomers, and the relative amounts to be expected in the product-mixture might be predictable by the Alder-Stein rule. The reaction acetoxytoluquinone + hexatriene could give four position isomers as well as diastereoisomeric forms of each. Acetoxytoluquinone and cyclohexadiene could yield two position isomers, each in the endo and exo configuration. The pre-reaction orientations leading to these four

[3] By employing the currently available values for interatomic distances and interbond angles.

products are illustrated in Figure 1 by means of the type of representations used by Alder and Stein. An additional complication offered in the cases of reactions with acetoxytoluquinone or with hexatrene is that one of the orienting double bonds is a component of a freely rotating group. Therefore, in applying the

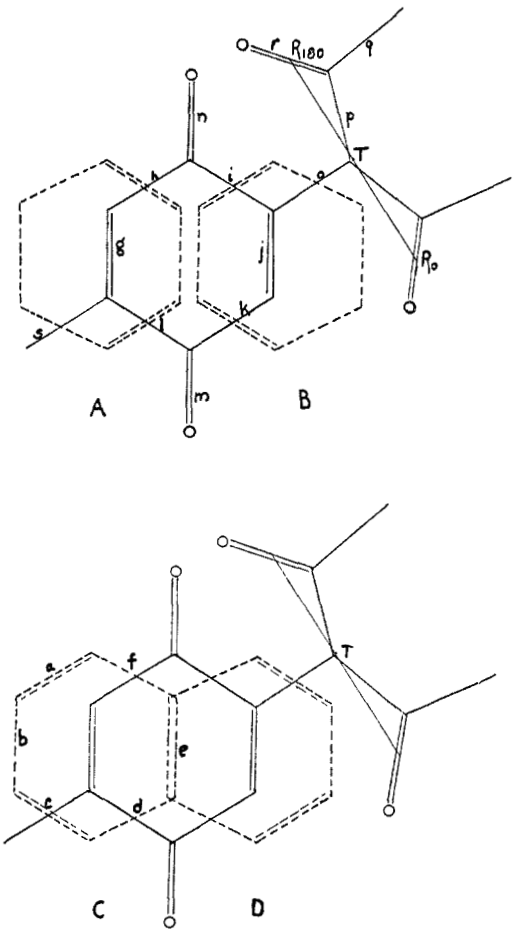


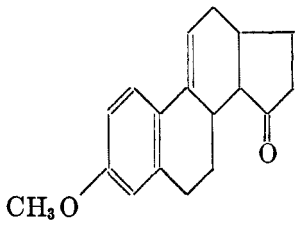
FIG. 1. THE FOUR ALDER-STEIN ORIENTATIONS OF CYCLOHEXADIENE AND ACETOXYTOLUQUINONE

Two coplanar positions of the acetoxyl group are shown. The line R_oR_{180} is the diameter of the circle described by the moving point R.

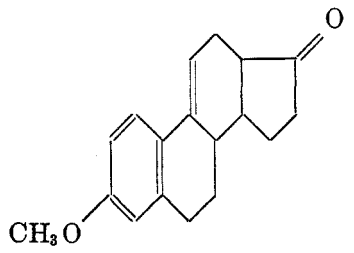
rule in these cases the probable position of the acetoxyl and the vinyl group must be determined and considered.

It might be profitable before analyzing the acetoxytoluquinone reactions to apply the rule to a case taken from the literature in which both position-isomeric and diastereoisomeric products are possible, but in which no mobile double bonds are involved. The reaction of cyclopentene-3-one with 1,2-dihydro-7-methoxy-

4-vinylnaphthalene studied by Dane and Eder (16) is of this type. The structure of the product isolated was not demonstrated or discussed by Dane and Eder, but Robinson and Rydon (17) had the following to say about it: "If, as seems probable, the Diels reaction is initiated by the coupling of the more anionoid end of the diene system with a cationoid β-carbon atom of a catio-enoid system, then the choice between these alternatives can be made if we can locate the more reactive anionoid C-atom in I"—the vinyldihydronaphthalene—"The circumstances are somewhat complex in this cross-conjugated system and the most that can be said is that the more aliphatic site of the vinyl group favors IV,"—here designated as XXXVI—"whereas the combined effect of two unsaturated conjugated centres on the naphthalene double bond, as well as the influenec of the methoxyl group, and any steric factor favors III"—(XXXVII).



XXXVI



XXXVII

It is noteworthy that Robinson and Rydon were not only unable to decide on a choice between the two position isomers, but also ignored the question of stereoisomerism, *i.e.*, the relative configuration at carbons 8 and 14 in both XXXVI and XXXVII.

Now the rule of Alder and Stein permits a prediction of the relative amounts of some of these four products by mere inspection of juxtaposed formulas[4] as in Figure 2. It can be readily seen that in orientation A, the accumulation of double bonds is greater than in orientations B, C, or D. Therefore the isomer XXXVI-A would be expected in greatest yield. It can also be seen that XXXVII-A (from orientation B) should be formed in larger amount than XXXVII-B (from orientation D). Likewise XXXVI-B should be formed in larger amount than XXXVII-B. It seems impossible to determine whether orientation B or orientation C corresponds to the greater density of double bonds by merely inspecting these formulas. It will therefore be necessary to use

[4] Neither Alder and Stein nor others have discussed application of the rule in any detail, and no complete critique will be given in this paper. However, the following assumptions seem to be implied in the rule as stated by Alder and Stein (13): 1. In directing orientation all types of double bonds, C=C, H—C=O, RO—C=O, etc., are quantitatively equivalent. 2. The effective directing force is localized at some point, *e.g.*, the midpoint of the double bond. 3. It is unnecessary to consider the many possible random orientations of the reactant molecules; only the standard orientations illustrated by the formulas in parallel planes as juxtaposed by Alder and Stein need be compared, in order to determine which correspond to the greater density of double bonds.

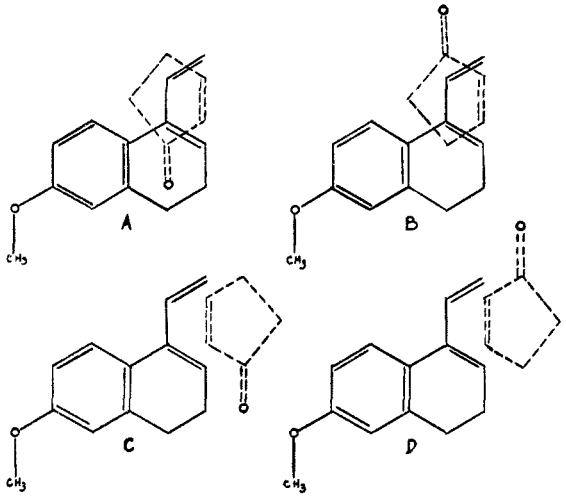
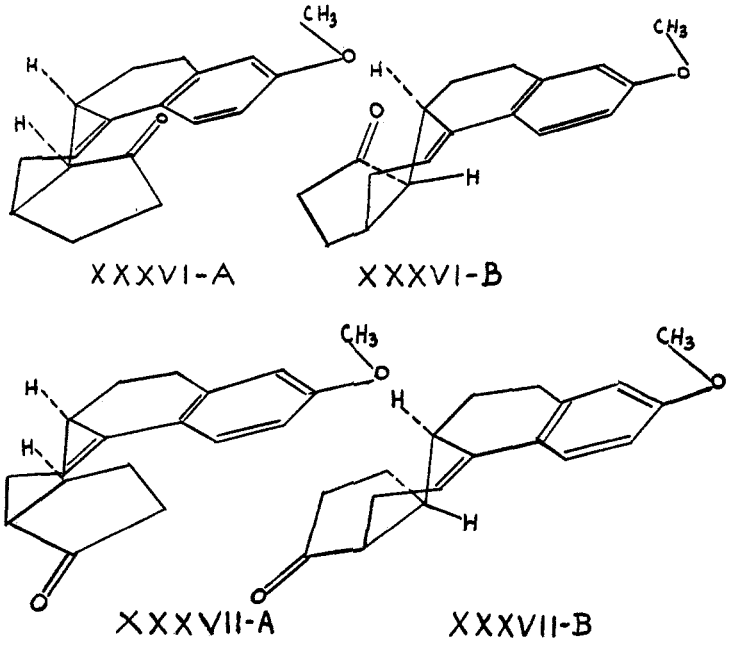
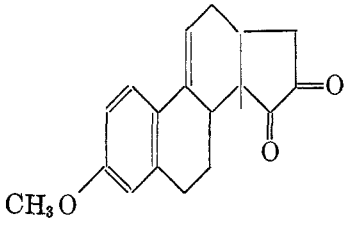


FIG. 2. THE FOUR ORIENTATIONS OF THE COMPOUNDS OF DANE AND EDER

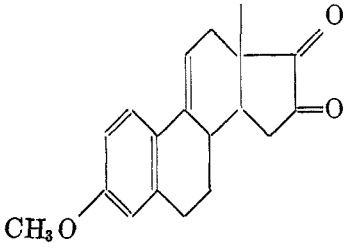
formulas drawn to scale and actually measure the double bond density in order to decide this point. A method of doing this is outlined below in connection with an analysis of the acetoxytoluquinone reactions. The Alder and Stein rule, therefore, predicts that the order of yields will be XXXVI-A > XXXVI-B > XXXVII-B, and XXXVI-A > XXXVII-A > XXXVII-B. Only a complete experimental study of the Dane-Eder reaction can demonstrate what validity the rule has in this case.



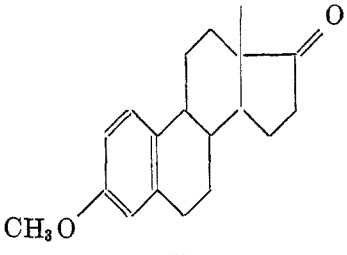
Dane and Schmitt (18) investigated the reaction of the same vinyldihydronaphthalene derivative with 1-methylcyclopentene-4,5-dione. This case can be analyzed in exactly the same way as the reaction of Dane and Eder. The rule predicts that the 8,14-cis stereoisomer of the steroid XXXVIII, with angular methyl at carbon 14, would be the chief product. Dane and Schmitt (28) by appropriate reactions converted the adduct which they obtained from this reaction to the corresponding non-olefinic 17-monoketone. The latter was not identical with the methyl ether of estrone (XL) and indeed could not be, aside from stereochemical considerations, if their adduct had structure XXXVIII rather than XXXIX.



XXXVIII



XXXIX

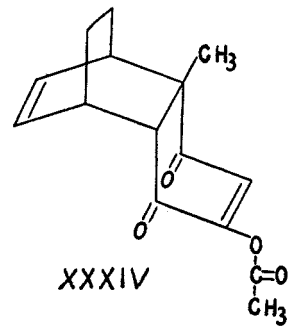


XL

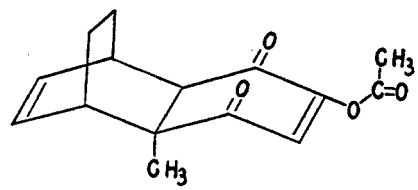
Another reaction in this same category was studied by Butz (2) with a view to the synthesis of 13-formyl steroids, namely the addition of cyclopentene-1-aldehyde to hexatriene. Here again, if the rule of Alder and Stein holds, the major product would be the intermediate (9-formyl-4-vinylhexahydroindene) of possible use in the synthesis, not of 13-formyl, but of 14-formyl steroids.

The reaction of acetoxytoluquinone and cyclohexadiene may yield four

acetoxyethanomethyltetrahydronaphthalenediones, two diastereoisomeric 2-acetoxy compounds, and two diastereoisomeric 4a-acetoxy compounds. At least three of these were formed: one product of addition to the acetoxyethene link (XV-A), yield 55% or more; another product of addition to the acetoxyethene link (XV-B), yield 6% or more; and a product of addition to the methylethene link, the acetate of the enol XVIII (XXXIV or XXXV), yield 39% or less. The evidence does not exclude the possibility that a second enol acetate was formed. Thus one compound was formed in larger amount than all others combined and 61% or more of the total reaction occurred at the acetoxyethene link. Could these results have been predicted on the basis of the Alder-Stein rule?



XXXIV



XXXV

By reference to Figure 1,[5] a choice can be made in the same way as in the case of the products of the reaction studied by Dane and Eder, *provided, that*

[5] In this figure the formulas are drawn to scale (one inch = one Ångstrom) using the following values for the bond lengths and interbond angles:

a = c = 1.36 Å	ab = bc = 121°
b = 1.46 Å	af = cd = 123°
d = f = 1.50 Å	de = ef = 116°
e = 1.54 Å	gh = ij = jk = lg = 121°
g = j = 1.32 Å	hi = kl = 118°
h = i = k = l = 1.50 Å	hn = in = km = lm = 121°
m = n = 1.14 Å	io = 117°
q = s = 1.54 Å	jo = 122°
o = p = 1.41 Å	op = 108°
r = 1.33 Å	pr = 122°

the carbon and oxygen atoms of the carbonyl part of the acetoxyl group are in the plane of the quinone ring. This will be true for only the two positions of the acetoxyl group which are shown in Figure 1. Since free rotation of the acetyl group about bond p and free rotation of the acetoxyl group about bond o are possible, the double bond r can take an infinitely large number of positions. For the position of r shown nearer to n, to be designated as R at 180° from an arbitrary origin, inspection of the figure shows that the order of orientation preference according to the Alder and Stein rule is B > A or D > C. It is found by actual measurement of the distances between double bonds in the figure that the order is B > A > D > C; while for the other position of r shown (in which r is more remote from n, R at 0°, *i.e.*, at the arbitrary origin), the preferred orientation order is B > A = D > C.

This result was arrived at as follows: Just prior to reaction, the essentially flat molecules of diene and quinone are found in two parallel planes with an interplanar distance x. The molecules become mutually oriented, partly according to A, partly according to B, etc., so that a line in the plane of the diene joining the terminal carbon atoms of the diene system when projected on the plane of the quinone coincides exactly with bond g or j. Designating the midpoints of the various bonds by capital letters corresponding to the bond letters in Figure 1, the fourteen distances between mutually movable double bonds which are needed for calculating the double bond densities can be designated as AG, MR, etc. These distances in the case of GR, JR, MR, NR, or their projections on the plane of the quinone ring (A'G, A'J, A'M, A'N, A'R, C'G, C'J, C'M, C'N, C'R) in the case of the remainder are measured directly from the drawings by dividers. The values found are recorded in columns A-I, B-I, C-I, and D-I (Table II). The interplanar distance x is then assigned a value, and the actual distances AG, AJ, etc., are calculated from A'G, A'J, etc., and are recorded in columns A-II, B-II, C-II, and D-II. The preferred orientation order will be the same for all values of x; x = 1.39 Å[6] was taken as a reasonable value. It is now possible by finding the sum of the distances in the II columns, to compare the double bond densities in the four orientations, A, B, C, and D. From Table II it is seen that, for this one position of R, the sum of distances between all the double bonds which are free to approach one another is smallest (40.17 Å) for orientation B. B is therefore the preferred orientation since it corresponds to the greatest density of double bonds. The values for the other orientations are A, 41.38 Å; D, 44.48 Å; C, 47.34 Å. C is therefore the least probable orientation.

Thus it is evident that by an operation consisting of drawing structural formulas to scale, measuring certain distances on the drawing and making some simple calculations, it has been possible to make a choice between orientations A and D for a particular position of the bond r. This choice appeared impossible by mere inspection of the drawings.

These are taken from "The Theory of Organic Chemistry" by Branch and Calvin (19) or are based upon the values for bond lengths and interbond angles in closely related compounds. A suitable value for b was obtained by calculation after the others were chosen. This was necessary in order to ensure a closed ring of required dimensions. Carbon-hydrogen bonds are omitted from the formulas but might have to be considered if any steric question should arise.

[6] Taking the carbon-carbon distance of the new bonds formed in the addition reaction as 1.54 Å, the interplanar distance will be 1.39 Å at the moment of formation of these new bonds.

For the second position of R in which r is coplanar wis the quinone ring (R more remote from N; called R_0 in a later discussion), it was found that B was again the most preferred orientation and C the least preferred. For this position of R, orientations A and D were found to be equally probable. The actual sums computed were: B, 41.45 Å; A, 43.79 Å; D, 43.62 Å; C, 50.17 Å. The difference of 0.17 Å between the sums in A and D is of about the same magnitude as the sum of errors involved in obtaining these sums (about 0.20 Å), and is therefore too small to be taken as indicative of a preference between the two orientations.

Thus it is seen that the numbers which have been taken as a measure of the density of double bonds are different in a given orientation for different positions

TABLE II

THE DISTANCES, IN ÅNGSTROM UNITS, BETWEEN FOURTEEN PAIRS OF DOUBLE BONDS IN FOUR MUTUAL ORIENTATIONS OF ACETOXYTOLUQUINONE AND CYCLOHEXADIENE AT R = 180°

(INTERPLANAR DISTANCE = 1.39 Å)

	ORIENTATION A		ORIENTATION B		ORIENTATION C		ORIENTATION D	
	I	II	I	II	I	II	I	II
AR_{180}	2.83	3.12	1.98	2.42	3.87	4.11	1.96	2.40
CR_{180}	4.60	4.87	4.12	4.35	5.32	5.50	4.13	4.36
GR_{180}	4.05	4.05	4.00	4.00	4.07	4.07	4.08	4.08
JR_{180}	2.94	2.94	2.92	2.92	3.07	3.07	3.04	3.04
MR_{180}	5.15	5.15	5.15	5.15	5.23	5.23	5.21	5.21
NR_{180}	1.72	1.72	1.75	1.75	1.76	1.76	1.77	1.77
AG	1.20	1.84	2.25	2.64	1.23	1.85	3.36	3.62
AJ	2.28	2.65	1.22	1.85	3.34	3.62	1.24	1.87
AM	3.15	3.44	3.17	3.44	3.60	3.86	3.60	3.88
AN	1.15	1.80	1.14	1.80	2.08	2.45	2.10	2.45
CG	1.25	1.87	2.30	2.69	1.25	1.87	3.33	3.62
CJ	2.27	2.64	1.25	1.87	3.33	3.62	1.22	1.85
CM	1.15	1.80	1.14	1.80	2.10	2.45	2.07	2.45
CN	3.20	3.49	3.20	3.49	3.63	3.88	3.60	3.88
Sum.....		41.38		40.17		47.34		44.48

of the double bond r. For one position, orientation A is definitely more probable than orientation D; for another position, the probability of A is about equal to that of D. Conceivably, therefore, there may be positions which r can take, in which the order of preference B> A> D> C> may not hold. In order to apply the rule of Alder and Stein in such cases, all the positions of r must be investigated.

What position does r have in acetoxytoluquinone alone and in the presence of cyclohexadiene (in orientations A, B, C, and D) in the absence of any additional solvent or in an indifferent solvent?[7] The reasonable assumption can be made

[7] A consideration of possible effects of the solvent on the orientation will be most interesting, but is outside the scope of this paper. All of the reactions with acetoxytoluquinone were carried out in nearly anhydrous ethanol, with the exception of one experiment with cyclohexadiene in which there was no additional solvent.

that in acetoxytoluquinone alone, the rule of Alder and Stein is already valid, and that in most of the molecules, the bond r is not necessarily in the plane of the quinone ring, but occupies whatever position corresponds to the maximum density of double bonds in the molecule. This position can be found from the following considerations, assuming that there is no rotation of the acetyl group about bond p from the position shown in Fig. 1:[8]

Let R_o be the midpoint of bond r when this bond is in the position coplanar with the quinone ring and more remote from N (Fig. 1). Now bond r (as a part of the acetoxyl group) can rotate freely about bond o, the midpoint R taking all possible positions on a circle (Fig. 3). As r rotates about o from the position stated, R passes through an arc of 180° until r again is coplanar with the quinone ring. This is the other coplanar position of r and r is now nearer to N. The midpoint of r in this position will be designated R_{180}. If a line R_oR_{180} be drawn connecting these two points, the midpoint T (Fig. 1) will be the center of the circle which R describes. These relationships are clearly seen from Figure 3.

The positions of R may now be described in terms of the angle ϕ which TR_ϕ makes with TR_o. In order to determine the approximate position of R in the acetoxytoluquinone alone, it is only necessary to determine the distances GR, JR, MR, and NR and find their sum for a sufficiently large number of values of ϕ. The distance TR_ϕ was measured from the

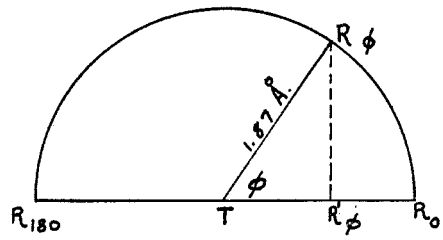


FIG. 3. CONSTRUCTION DRAWING FOR THE DETERMINATION OF RR′ FOR ANY VALUE OF ANGLE ϕ

drawing (Fig. 1) and found to be 1.87 Å. Since the projections of R on the plane of the quinone ring for different values of ϕ all fall on the line R_oR_{180}, the distances TR'_ϕ will be $1.87 \cos \phi$. Having calculated these and marked them off on R_oR_{180}, it was possible to measure GR′, JR′, MR′, and NR′ for various values of ϕ. GR, JR, MR, and NR could then be calculated since $RR' = 1.87 \sin \phi$. The results are given in the first column of Table III. It is seen that the sum of distances between double bonds is the minimum when ϕ is about 170°, *i.e.*, when the acetoxyl group is about 10° out of the plane of the quinone ring and near bond n.

[8] There is evidence from dipole moment data that such rotation will not occur (29). Vector addition of the ketone and ether moments in the acetoxyl group leads to the conclusion that rotation of the acetyl group about bond p is restricted with a single minimum in the position in which the moments are oppositely directed and the carbon and oxygen atoms of the acetoxyl group and the 5-carbon atom of the quinone ring are all in one plane. It would be interesting to calculate whether the same restriction in positions of the acetyl group would follow from the rule of Alder and Stein. Such a calculation would seem to require a knowledge of the position of some point U at which all the Alder-Stein effects of the several fixed double bonds could be considered localized. Once U were located, the distance RU could then be related to the angle ϕ (measuring rotation about the bond o) and an angle θ which would measure the rotation about bond p, and it should then be possible to determine the values for RU, ϕ, and θ at which RU is a minimum.

As the cyclohexadiene molecule approaches, the position of the acetoxyl double bond will change by virtue of the influence of two new double bonds, a and c. For any given distance of the plane of a and c from the plane of the quinone ring, *e.g.*, 1.39 Å, the minimum sum of distances between double bonds can be determined for different values of ϕ providing rotation about p does not occur or is adequately described.[8] The necessary distances are shown in Figure 4. For distances involving G, J, M, and N, it is only necessary to measure GR′,

TABLE III

THE SUMS OF THE DISTANCES BETWEEN THE DOUBLE BONDS IN ACETOXYTOLUQUINONE AND IN VARIOUS MUTUAL ORIENTATIONS OF CYCLOHEXADIENE AND ACETOXYTOLUQUINONE FOR VARIOUS VALUES OF ϕ

ϕ (DEGREES)	ACETOXYTOLUQUINONE ALONE	ORIENTATION OF ACETOXYTOLUQUINONE AND CYCLOHEXADIENE			
		A	B	C	D
0	15.09	43.79	41.45	50.17	43.62
15					
30	15.06	43.09	40.49	49.44	42.45
45	15.10	42.78	40.16	49.18	42.24
60	15.11				42.06
75	15.02	42.18	39.71	48.43	41.98
90	14.92	41.95	39.52	47.99	42.11
105	14.82	41.62	39.48	47.69	42.43
120	14.65	41.43	39.55	47.43	42.84
135	14.43	41.25	39.63	47.11	43.21
150	14.19	41.16	39.75	46.85	43.45
165	13.62	41.07	39.65	46.49	43.48
180	13.86	41.38	40.17	47.34	44.48

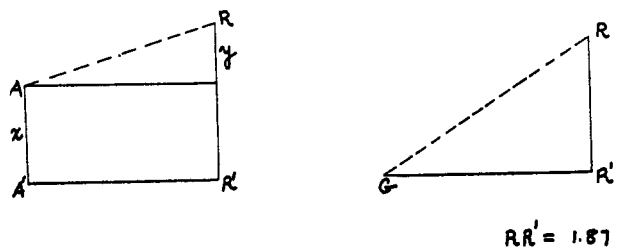


FIG. 4. CONSTRUCTION DRAWINGS FOR THE DETERMINATION OF AR, CR, AND GR, JR

JR′, MR′, NR′, A′G, etc. $RR_1 = 1.87 \sin \phi$. For the distances AR and CR, it is necessary to measure A′R′ and C′R′, and to calculate y which is RR′ − AA′ or $1.87 \cos \phi - 1.39$. The fourteen distances have been calculated for a number of values of ϕ and the results are given in Table III.

It is seen that at any value of ϕ which was investigated, B is the most preferred orientation; and therefore the rule says that the compound obtained in the largest yield is the angular acetate XXV.[9] Likewise at all values of ϕ, C was

[9] The values in Table III are plotted in Fig. 5. It is seen to be unlikely that the B curve would ever rise above the A, D, or C curves. Investigation of further values of ϕ is there-

the least preferred orientation. The relation of the sums in A and D change with ϕ, but at all angles from 105° to 180°, the sum of the distances is less in A; and therefore A can be considered the preferred orientation with respect to D, since ϕ is 170° just before reaction.

From the values in Table III or the curves in Figure 5 it is not possible to determine ϕ at the minimum sums of distances with precision because of the small variation in these sums with change in ϕ at some portions of the curves. Although precise values for these angles could possibly be determined by methods

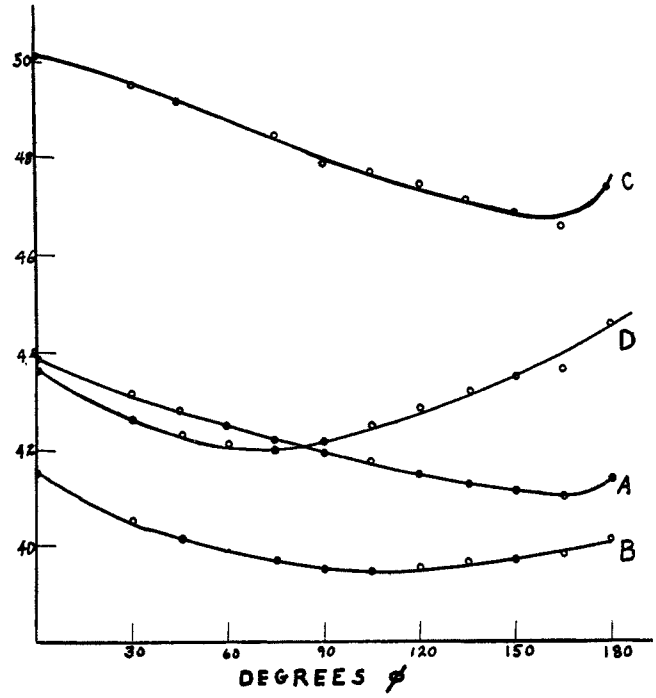


FIG. 5. GRAPHIC REPRESENTATION OF PART OF TABLE III

Abscissae: Values of angle ϕ in degrees. Ordinates: Sums of the distances in Å. units between the double bonds in various mutual orientations of cyclohexadiene and acetoxytoluquinone.

of calculus, such procedure may not be necessary in many cases to determine the order of preferred orientation.

DISCUSSION

According to the rule of Alder and Stein, on mixing acetoxytoluquinone and cyclohexadiene most of the molecules will become oriented according to B (Figure 1) with bond r lying in a plane nearly perpendicular to the planes of the rings. The angular acetate (XV-A) of m.p. 123–124° which was the chief prod-

fore unnecessary. Orientation C is seen to have a very low probability, while D is definitely more probable than A only in the range ϕ = 100° to 180°.

uct should therefore have structure XXV, and the angular acetate (XV-B) of m.p. 84–87° must be the isomer XXVI. The enol of m.p. 152–153° may be related to the acetate XXXIV, since this structure results from orientation A, and only one enol was isolated. The least probable product is the compound XXXV. The experimental findings in the case of this reaction are in good agreement with predictions which one could make from the rule.

It would next be valuable to analyze the reaction of acetoxytoluquinone and hexatriene from the standpoint of the rule since we wish to know which of the theoretically possible structures should be assigned to the angular acetate (some diastereoisomer of VIII or IX), obtained in 45% yield, and to the enol acetate (some diastereoisomer of IV or V), the enol of which was obtained in 21% yield.

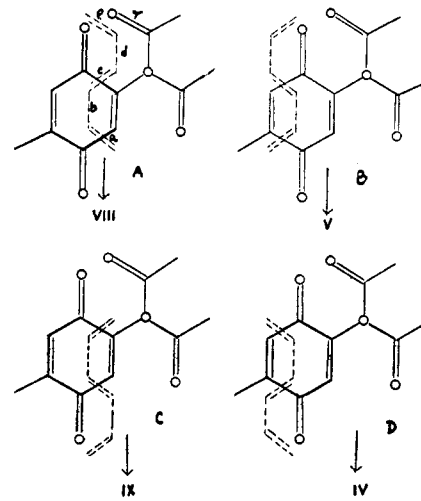


FIG. 6. FOUR ALDER-STEIN ORIENTATIONS OF TRANS-HEXATRIENE AND ACETOXYTOLUQUINONE

Two coplanar positions of the acetoxyl group are shown. The products to be expected from each are shown.

Such an analysis will be much more difficult than in the case of the acetoxytoluquinone–cyclohexadiene reaction, and it is still far from completed. In the first place it is unknown whether the hexatriene used consisted of the cis or trans isomer or a mixture of the two (10). The analysis will be somewhat simpler if it is assumed that trans-hexatriene is reacting. By inspection of formulas drawn to scale (Fig. 6), it can be seen that orientation A is preferred to C, and B is preferred to D. Here, in addition to the free rotation of the acetoxyl group already considered, free rotation is possible about bonds b and d of the triene molecule. It would appear that, in order to achieve maximal density of double bonds, the acetoxyl group would take some position corresponding to a considerably greater value of the angle ϕ than 90°, due to the presence of the double bond e which was not present in cyclohexadiene. Likewise the vinyl group would rotate about d so that the bond e would approach the acetoxytolu-

quinone molecule. This mutual approach of e and r would presumably cease some time before the distance ER became zero, because of the mutual interference in space between the acetoxyl and the vinyl groups. Rotation of the dienyl system abc about d and the vinyl group including a about b would also occur in the direction of the quinone molecule. Accordingly the hexatriene molecule, as well as the quinone molecule, would almost certainly not remain in the planar configuration which Figure 6 suggests. However, whatever the magnitude of these probable rotations, the orientations A and B appear the two most probable, and A is preferred to B.

Orientation A leads to the angular acetate VIII in which the acetoxyl group is ortho to the vinyl. Trans-hexatriene, therefore, is predicted to give more of VIII than of the position isomer IX; and since only one angular acetate was obtained, the compound of m.p. 109–110°, this substance may have structure VIII. VIII can exist in two diastereoisomeric forms; we have been unable to make a

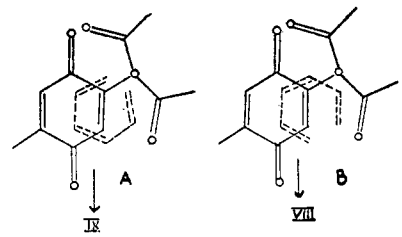


FIG. 7. TWO ALDER-STEIN ORIENTATIONS OF CIS-HEXATRIENE AND ACETOXYTOLUQUINONE

Two coplanar positions of the acetoxyl groups are shown. The products to be expected from each are indicated.

choice between these two by inspection of formulas and we leave this question open for future analysis.

Orientation B leads to the enol acetate V, which may represent the structure of the enol acetate, m.p. 135–140° which yields on hydrolysis the enol, m.p. 206–210°. These compounds can also exist in two diastereoisomeric forms; here again we feel unable to make a selection without comparing the sums of distances involved in various configurations of the reactant molecules.

The rule predicts then that trans-hexatriene will yield VIII rather than IX and V rather than IV. If structural analysis of the angular acetate and enol, which seems feasible, should confirm this prediction, we should have evidence that the hexatriene used was the trans isomer, for cis-hexatriene can be expected to give nearly equal amounts of VIII and IX (Fig. 7). Nearly equal amounts of IV and V should also be obtained from cis-hexatriene.

In this connection the dimerization of hexatriene observed by Kharasch and Sternfeld (10) is of interest because only one isomer was isolated and this in over 50% yield. The adduct was 4-butadienyl-3-vinylcyclohexene (Fig. 8). If the 3,5-isomer was not formed, this would be evidence, granting the validity of the Alder-Stein rule under the conditions of the dimerization, that only trans-

hexatriene reacted, for trans-hexatriene can give only the 3,4-dimer, while cis-hexatriene should give nearly equal amounts of the 3,4- and 3,5-dimers.

Alder and Windemuth (20) have found that diene additions occur selectively even when no double bonds are present other than the three which take part in the formation of the new ring. They suggest that in such cases there is a tendency for the reactant molecules to orient themselves so that there is a maximum accumulation of groups containing unshared electron pairs. This rule of Alder and Windemuth should be applied in conjunction with that of Alder and Stein. In many reactions both orienting double bonds and unshared electron pairs are present. In the case of the acetoxytoluquinone–cyclohexadiene reaction we venture to say that the unshared electron pairs (at the oxygen atoms) are so

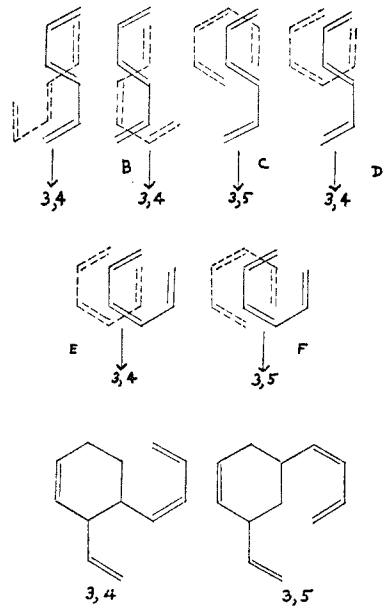


FIG. 8. ALDER-STEIN ORIENTATION DIAGRAMS SHOWING THE DIMERIZATION OF HEXATRIENE

A and B: trans-hexatriene plus trans-hexatriene. C and D: trans-hexatriene plus cis-hexatriene. E and F: cis-hexatriene plus cis-hexatriene. The expected butadienylvinylcyclohexenes are indicated.

placed that taking them into account will not appreciably alter the conclusions already drawn regarding the order of preferred orientations. However, this will not be true for all reactions.

SUMMARY

When 1,3-cyclohexadiene and 1,3,5-hexatriene react with 5-acetoxy-1,4-toluquinone, addition occurs at both the acetoxyethene and the methylethene links. The principal product is an angular acetate in each case. An angular acetate was the sole product isolated after reaction of 2,3-dimethyl-1,3-butadiene with acetoxytoluquinone. This preferred addition to the acetoxyethene link is predictable by application of the rule of Alder and Stein.

Three of the four theoretically possible isomers were isolated from the reaction products of cyclohexadiene and acetoxytoluquinone. Two of these were angular acetates and one was an enol. The structures of the endo and exo angular acetates were proved by conversion to 2-methyl-1,4-naphthoquinone. The structure of the angular acetate from dimethylbutadiene was proved by conversion to 2,6,7-trimethyl-1,4-naphthoquinone.

Hexatriene and acetoxytoluquinone gave an angular acetate and an enol in substantial yields. The structures were not proved. According to the rule of Alder and Stein the acetoxyl and vinyl groups should be *ortho* in the angular acetate and the methyl and vinyl groups *meta* in the enol.

It would seem profitable to employ the rules of Alder and Stein and Alder and Windemuth in the prediction of products and as a guide in structural analysis, when necessary by actual calculation of the distances between the various pairs of double bonds and unshared electron pairs.

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[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

THE SYNTHESIS OF *dl*-1,2-OCTADECANEDIOL AND SEVERAL OF ITS HOMOLOGS

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The higher molecular weight glycols are of considerable physiological interest, first because of their possible presence in lipid hydrolysates (1), second because of their relationship to sphingosine, a known component of many lipids, and third because of their possible role in intermediate fat metabolism.[1] As part of an investigation on the higher molecular weight glycols this communication will be confined to a description of the synthesis of several typical 1,2-glycols, and a brief account of some of their derivatives which may be suitable either for their characterization or their isolation and purification.

Applying the excellent procedure developed by Boord and his co-workers (4), the alkyl bromide, RCH_2Br, was converted into the alkene-1, $RCH_2CH=CH_2$, and the latter compound transformed into the 1,2-glycol, *via* the dibenzoate, with the aid of silver iodine dibenzoate (5). Of the three glycols synthesized by this procedure, one, 1,2-hexadecanediol, has been prepared before (6–8), but in this case the previous methods of preparation differed from that described above. The isopropylidine derivatives of the glycols were found to be quite satisfactory for the isolation and purification of the 1,2-glycols, whereas for purposes of characterization the diacetates and the di(N-phenylcarbamates) appeared to be more suitable. Mixed melting point determinations upon known mixtures of the glycols leave little doubt that these mixtures form solid solutions, but it is clear that the admixture of more than five per cent of a homolog containing two more or less carbon atoms can be detected by a melting point determination.

EXPERIMENTAL[2]

n-*Tetradecyl bromide.* Technical myristic acid was esterified with 2% methanolic hydrogen chloride and the resulting product fractionally distilled[3] to give 42% of methyl myristate, b.p./5 mm. 141.5–142.5°, f.p. 19.2°, n_D^{25} 1.4353. This ester was reduced with sodium and butanol (10) to give 60% of tetradecanol, b.p./3 mm. 128–132°, m.p. 38.5° (11). This alcohol was then converted into the bromide, following the procedure of Kamm and Marvel (12). The bromide, b.p./5 mm. 145.7–147.0°, was found to contain a small amount of unreacted tetradecanol. Fortunately the alcohol is quite insoluble in the bromide at the melting point of the latter compound, and after removal of the alcohol by filtration the

[1] Waelsch and Sperry (2) and Stetten and Schoenheimer (3) have shown that a close physiological relationship exists between acid and alcohol and the question therefore arises as to the possibility of a similar relationship between α-hydroxy acid and 1,2-glycol.

[2] Microanalyses by Dr. G. Oppenheimer and Mr. G. A. Swinehart.

[3] The apparatus used in this and all subsequent fractional distillations consisted of an electrically heated Vigreux column, 100 cm. in length, equipped with a total reflux variable take-off head. Pressures were kept constant with a sulfuric acid manostat (9).

n-tetradecyl bromide, f.p. 5.5°, n_D^{20} 1.4608, n_D^{30} 1.4565, was obtained in a 71% yield. Meyer and Reid (11) report the f.p. 5.67° for *n*-tetradecyl bromide.

Hexadecene-1. Three hundred grams of α,β-dibromoethyl ethyl ether (4) in 500 ml. of ether was added, with vigorous stirring, to a Grignard reagent prepared from 423 g. of tetradecyl bromide, 37 g. of magnesium, and 1500 ml. of ether, at such a rate that the temperature remained at or below 25°. The mixture was poured onto 4 kg. of ice, acidified with dilute hydrochloric acid, the aqueous phase discarded, and the ethereal phase washed with dilute hydrochloric acid and water. The residue remaining after removing the solvent from the dried ethereal phase was filtered, and the filtrate distilled to give 318 g. (60%) of α-tetradecyl-β-bromoethyl ethyl ether, b.p./0.2 mm. 145–165°, f.p. 23.5°. The solid recovered in the previous step proved to be *n*-octacosane, m.p. 61.5°, after repeated recrystallization from isopropyl ether. Egloff (13) gives the m.p. of *n*-octacosane as 61.6°. Two hundred eighty-five grams of α-tetradecyl-β-bromoethyl ethyl ether, 600 g. of zinc dust, and 600 ml. of *n*-butanol were refluxed, with stirring, for twenty-four hours, the mixture cooled, centrifuged, the precipitate washed with ether, and the washings and supernatant liquid combined. The solution was shaken with 75 ml. of water, filtered, the filtrate dried, and the butanol and ether removed *in vacuo* to give, after cooling, a residue of two phases. The upper phase was separated and distilled at 0.5 mm.; the distillate was then fractionally distilled at 3 mm. to give 120 g. of hexadecene-1, b.p. 122.0–122.5°. This product contained a small amount of tetradecanol as an impurity, but as the alcohol is insoluble in the hydrocarbon at a temperature just above the melting point of the latter compound, filtration gave 114 g. (62.5%) of hexadecene-1, f.p. 4.0°, b.p./3 mm. 122.0–122.5°, n_D^{20} 1.4410, n_D^{30} 1.4372. Egloff (13) gives the following constants for hexadecene-1, m.p. 4°, b.p./3 mm. 123°, n_D^{20} 1.4417. The tetradecanol was identified by a mixed m.p. with an authentic specimen of the alcohol.

1,2-Hexadecanediol. Applying the method of Prévost (5), 10.6 g. of iodine in 100 ml. of benzene was added, with shaking, to a suspension of 26.5 g. of silver benzoate in 150 ml. of benzene. To this solution was added, slowly and with shaking, 10.5 g. of hexadecene-1 in 50 ml. of benzene.[4] The mixture was refluxed for one hour, cooled, filtered, and the filtrate freed of solvent. The residual glycol dibenzoate was saponified by refluxing for three hours with 12 g. of potassium hydroxide in 75 ml. of ethanol and 25 ml. of water. The glycol was recovered by pouring the above hydrolysate into 500 ml. of hot water. After cooling, the crude glycol was collected, recrystallized from methanol twice, then from ligroin (b.p. 60–70°), and finally from methanol to give 4 g. (33%) of 1,2-hexadecanediol, m.p. 73.1–73.6°.[5]

Anal. Calc'd for $C_{16}H_{34}O_2$ (258.4): C, 74.4; H, 13.3.
Found: C, 74.4; H, 13.3.

n-*Hexadecyl bromide.* Methyl palmitate, b.p./5 mm. 163–163.5°, f.p. 29.0°, prepared from bayberry wax (14) was reduced with sodium and butanol (10) to give 67% of *n*-hexadecanol, b.p./3 mm. 144–146°, f.p. 49.0° (15). The alcohol was converted into the bromide (12), and after removing the unreacted alcohol by filtration at 20° the product was fractionally distilled to give 75% of *n*-hexadecyl bromide, b.p./1.5 mm. 153–154°, f.p. 17.8°, n_D^{20} 1.4627, n_D^{30} 1.4592 (11).

Octadecene-1. From 1.667 kg. of *n*-hexadecyl bromide, 134 g. of magnesium, and 1.125 kg. of α,β-dibromoethyl ethyl ether (4) we obtained 1.430 kg. (70%) of α-hexadecyl-β-bromoethyl ethyl ether, b.p./0.3 mm. 160–180°, f.p. 28.5–29.5°, and 32 g. of dotriacontane, m.p.

[4] All reagents and solvents were thoroughly dried.

[5] This m.p. was determined in a capillary tube immersed in a bath whose temperature was raised 0.25°/minute. The discrepancy between the above m.p. and the one reported by Krafft and Grosjean (6) (75–76°) is probably due to a variation in the technique of the m.p. determination as we were able to observe the m.p. 76–77° when the rate of heating was raised to 1°/minute.

69.0°, after repeated recrystallization from isopropyl ether. Egloff (13) gives 70.3° as the m.p. of dotriacontane. After 940 g. of α-hexadecyl-β-bromoethyl ethyl ether and 2 kg. of zinc dust in 2 l. of amyl alcohol had been refluxed for twenty-four hours, 300 g. of zinc dust was added and the suspension heated for an additional twenty-four hours. The reaction mixture was cooled, centrifuged, and 800 ml. of water added to the supernatant liquid. After precipitation was complete the precipitate was removed, and the alcohol phase dried over sodium sulfate. After removal of the solvent the crude octadecene-1 was distilled at 2.5 mm. and the distillate fractionally distilled at 3 mm. to give 289 g. (46%) of octadecene-1, b.p./3 mm. 144–146°, f.p. 17.5°, n_D^{20} 1.4448, n_D^{30} 1.4412. Egloff (13) gives the following constants for octadecene-1, m.p. 18°, n_D^{22} 1.4443, n_D^{32} 1.4411.

1,2-Octadecanediol. From 288 g. of octadecene-1, 620 g. of silver benzoate, and 290 g. of iodine (5) we obtained a crude dibenzoate which was saponified, with 300 g. of potassium hydroxide in 2 l. of ethanol and 700 ml. of water, to give 1,2-octadecanediol, 239 g. (73%), m.p. 79.0–79.5°, after alternate recrystallization from methanol and ligroin (b.p. 60–70°).

Anal. Calc'd for $C_{18}H_{38}O_2$ (286.5): C, 75.5; H, 13.4.
Found: C, 75.3; H, 13.2.

n-*Octadecyl bromide.* Technical methyl stearate (1.5 kg.) was hydrogenated, at 120° and 140 atm., over 50 g. of Raney nickel, and the resulting esters fractionally distilled to give 450 g. of methyl palmitate, b.p./1.5 mm. 140–145° and 350 g. of methyl stearate, b.p./1.5 mm. 164–167°, f.p. 37.0°. Three hundred forty-nine grams of methyl stearate, f.p. 37.0°, dissolved in ethanol, was hydrogenated at 250° and 225 atm., over 20 g. of copper chromite (16) to give, after removal of the solvent and subsequent distillation, 298 g. of octadecanol, b.p./5 mm. 165–170°. The alcohol was further purified by recrystallization from isopropyl ether to give 270 g. (85%) of octadecanol, m.p. 58.0° (15). The alcohol (270 g.) was converted into the bromide (12) and the latter fractionally distilled to give 247 g. (74%) of *n*-octadecyl bromide, b.p./1.5 mm. 168.0–169.5°, f.p. 27.4° (11).

Eicosene-1. α,β-Dibromoethyl ethyl ether (170 g.) in 500 ml. of ether was added to a Grignard reagent prepared from 247 g. of octadecyl bromide, 18.1 g. of magnesium, and 1 l. of ether. After hydrolysis of the reaction mixture with ice and dilute hydrochloric acid the ethereal phase was washed with saturated aqueous sodium sulfate, with water, filtered, and the filtrate dried over calcium chloride. Upon removal of the ether a dark, viscous residue was obtained, which was dissolved in twice its volume of isopropyl ether and decolorized with alumina to give a light red solution. Evaporation of the solvent gave 190 g. of crude α-octadecyl-β-bromoethyl ethyl ether.[6] Fourteen grams of hexatriacontane, m.p. 76° after repeated recrystallization from isopropyl ether, was obtained as a by-product of the Grignard reaction. Egloff (13) gives 76° as the m.p. of hexatriacontane. One hundred ninety grams of crude α-octadecyl-β-bromoethyl ethyl ether in 800 ml. of amyl alcohol was refluxed with 400 g. of zinc dust for twenty hours, then between the twentieth and forty-eighth hour of refluxing, 500 additional g. of zinc dust was added in three portions. The reaction mixture was cooled, centrifuged, the precipitate washed with isopropyl ether, and the washings and supernatant liquid added to 100 ml. of water. The suspension was shaken, the reddish solution recovered, distilled, and the distillate fractionally distilled to give 22 g. of eicosene-1, b.p./1.5 mm. 151°. This product contained a small amount of *n*-octadecanol,[7] which was removed by filtration at 30° leaving 18.2 g. of eicosene-1, b.p./1.5 mm. 151°, f.p. 28.5°, n_D^{30} 1.4440. The over-all yield from *n*-octadecyl bromide to eicosene-1 was 8.7%.

1,2-Eicosanediol. The glycol dibenzoate prepared from 18.2 g. of eicosene-1, 29.8 g. of silver benzoate, and 16.4 g. of iodine (5) was saponified in the usual manner. The crude glycol so obtained was alternately recrystallized from methanol and ligroin (b.p. 60–70°) to give 14.2 g. (70%) of 1,2-eicosanediol, m.p. 84.3–84.8°.

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[6] The bromo ether could not be distilled without decomposition.

[7] Identified by a mixed m.p. with an authentic specimen of *n*-octadecanol.

Anal. Calc'd for $C_{20}H_{42}O_2$ (314.5): C, 76.4; H, 13.5.
Found: C, 76.5; H, 13.4.

Glycol-acetone condensation products. One gram of the glycol in 10 ml. of acetone was shaken for six hours with 1.2 g. of anhydrous cupric sulfate. After filtering the suspension, the excess acetone was removed and the residue distilled at a pressure not greater than 0.2 mm. The distillate was allowed to stand at a temperature 1° above its melting point for

TABLE I

GLYCOL-ACETONE CONDENSATION PRODUCTS

COMPOUND	M.p. °c	ANALYSIS			
		Calc'd		Found	
		C	H	C	H
Isopropylidene-1,2-hexadecanediol	22.9	76.5	12.8	76.7	13.0
Isopropylidene-1,2-octadecanediol	31.3	77.2	13.0	77.1	13.0
Isopropylidene-1,2-eicosanediol	36.7	77.9	13.1	77.7	13.1

TABLE II

GLYCOL DIACETATES

COMPOUND	M.p. °c	ANALYSIS			
		Calc'd		Found	
		C	H	C	H
1,2-Diacetoxyhexadecane[8]	30	70.1	11.2	70.1	11.0
1,2-Diacetoxyoctadecane	40	71.3	11.4	71.4	11.7
1,2-Diacetoxyeicosane	47	72.4	11.6	72.4	11.8

TABLE III

GLYCOL DI(N-PHENYLCARBAMATES)

COMPOUND	M.p. °c	ANALYSIS					
		Calc'd			Found		
		C	H	N	C	H	N
1,2 - Hexadecanediol di(N-phenylcarbamate)	95	72.6	8.9	5.6	72.8	9.2	5.9
1,2 - Octadecanediol di(N-phenylcarbamate)	99.5	73.2	9.2	5.3	73.4	9.3	5.5
1,2 - Eicosanediol di(N-phenylcarbamate)	103.5	73.9	9.5	5.1	74.0	9.4	5.2

five hours and then filtered to remove any unreacted glycol. For analysis the isopropylidene compound was recrystallized from isopropyl ether. The yield of pure isopropylidene glycols was generally about 90%.

[8] Krafft and Grosjean (6) give the m.p. of 1,2-diacetoxyhexadecane, prepared from 1,2-dibromohexadecane and silver acetate, as 56–57°. Having in mind the possibility of an ortho ester type of structure, we repeated the synthesis of Krafft and Grosjean but were unable to confirm their results, as the diacetate so prepared had the m.p. 30° and was identical with the one described above.

The glycols were regenerated from the isopropylidene compounds by dissolving these in four times their weight of methanol, adding a 300% molar excess of water and a drop of conc'd hydrochloric acid, and heating the mixtures until they were homogeneous. Upon cooling, the glycols were recovered and recrystallized from methanol. The yield was generally about 90%. When specimens of recrystallized 1,2-hexadecanediol, 1,2-octadecanediol, and 1,2-eicosanediol were converted into their isopropylidene compounds and then regenerated, the melting points of the recovered glycols were identical with those of the corresponding original glycols.[9]

Glycol diacetates. One gram of the glycol in 4 ml. of pyridine was acetylated with 4 ml. of acetic anhydride. The reaction mixture was taken up in ether and the ethereal solution washed with aqueous sodium carbonate. After removal of the solvent the ester was recrystallized from methanol.

Glycol di(N-phenylcarbamates). Two grams of the glycol in 10 ml. of benzene was refluxed for six hours with 3.5 ml. of phenyl isocyanate, the excess benzene and phenyl isocyanate removed by distillation, and the residue recrystallized from isopropyl ether to constant melting point.

TABLE IV

MELTING POINTS OF GLYCOL MIXTURES[10]

GLYCOL A	GLYCOL B	M.p. °C[5]
100% C_{16}		73.1–73.6
75% C_{16}	25% C_{18}	69.2–70.2
50% C_{16}	50% C_{18}	69.3–71.2
25% C_{16}	75% C_{18}	73.7–74.7
	100% C_{18}	79.0–79.5
25% C_{20}	75% C_{18}	77.2–77.8
50% C_{20}	50% C_{18}	77.0–78.7
75% C_{20}	25% C_{18}	79.8–80.8
100% C_{20}		84.3–84.8

Melting points of glycol mixtures. In order to determine the melting point depression caused by homolog admixture, known quantities of the pure glycols were dissolved in methanol and the solutions slowly evaporated to dryness.[11]

Degradation of 1,2-octadecanediol. A mixture of 3.75 g. of 1,2-octadecanediol, 6 g. of lead tetraacetate, and 20 ml. of glacial acetic acid was shaken for five hours at 25°. The clear solution was then distilled and the distillate collected in 25 ml. of cold water. The addition of dimedon (17) to this solution resulted in the isolation of the formaldehyde-dimedon condensation product, m.p. 190°, in an 80% yield.

SUMMARY

1. The Boord alkene-1 synthesis has been extended to members of a homologous series containing sixteen, eighteen, and twenty carbon atoms. The preparation of eicosene-1 is described for the first time.

[9] Impure specimens of 1,2-glycols were readily purified by this process.

[10] Per cent by weight.

[11] As might be expected the glycols exhibit polymorphism and consequently the m.p. of any given preparation is dependent upon its previous history. We therefore have confined our investigations to the form which is obtained by crystallization from methanol though it is possible that in the course of the m.p. determinations a slow transformation from one form into the other was taking place.

2. 1,2-Hexadecanediol, 1,2-octadecanediol, and 1,2-eicosanediol have been synthesized, the latter two for the first time, and an account is given of some of their derivatives which are suitable either for their isolation or characterization.

PASADENA, CALIF.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

ALLYLIC REARRANGEMENTS. XII. THE ACTION OF DIOXANE ON BUTENYLMAGNESIUM BROMIDE[1]

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Previous work from this laboratory has shown that the preparation and hydrolysis of the Grignard reagent from either crotyl or methylvinylcarbinyl bromides (1a) and chlorides (1b) produces the same mixture of butenes. The rearrangement of butenyl radicals during the reaction may be attributed to two or perhaps three possibilities, (A) the formation of the same mixture of butenylmagnesium halides from all of the halides at the instant the halide reacts with the metal, due to resonance between the primary and secondary forms of an intermediate unfree carbonium ion or free radical in the activated complex; (B) the establishment of equilibrium between the primary and secondary butenylmagnesium halides after the Grignard reagent has been formed; or (C) rearrangement during the reaction of the reagent with water.

Process (B) would presumably result from establishment of the following equilibrium which has been postulated by many workers in recent years.

$$2RMgX \rightleftharpoons R_2Mg + MgX_2$$

However, if rearrangement of the butenyl radical is to result from establishment of equilibrium between RMgX and R_2Mg, it may be necessary to modify the equations to involve the formation of an ionic intermediate, a resonating butenyl carbanion, since recent work in this laboratory indicates that replacement reactions of allylic systems are normal if the reaction is a second order process but abnormal (involving rearrangement) if the reaction is first order (carbonium ion type).[2] The ionic equivalent of the equilibrium in process B is indicated as follows:

[1] This work was accomplished with the aid of a grant from the Board of Research of the University of California.

[2] We recognize the uncertainty involved in drawing this analogy between displacement reactions in which the allylic system is an electron acceptor and reactions of these Grignard reagents in which the allylic system is apparently an electron donor. However, until sufficient evidence is available to settle the question it seems reasonable to assume that abnormal reactions arise only when the carbon-magnesium bond becomes sufficiently ionic to allow resonance to occur. We also recognize that rearrangements during the formation and subsequent reactions of these Grignard reagents are not strictly allylic rearrangements since they may not involve an anionotropic shift. However, the starting materials and frequently the final products are true allylic isomers. Consequently it is appropriate to extend the term allylic rearrangement to include abnormal reactions of these Grignard reagents.

$$\text{Cr—MgBr} \rightleftharpoons \text{bu}^- + \text{MgBr}^+ \rightleftharpoons \text{Mvc—MgBr}$$

$$\text{bu}^- + \text{Cr—MgBr} \rightleftharpoons \left[\begin{array}{c}\text{Cr—Mg—Cr}\\ \text{or}\\ \text{Cr—Mg—Mvc}\end{array}\right] + \text{Br}^-$$

$$\text{bu}^- + \text{Mvc—MgBr} \rightleftharpoons \left[\begin{array}{c}\text{Cr—Mg—Mvc}\\ \text{or}\\ \text{Mvc—Mg—Mvc}\end{array}\right] + \text{Br}^-$$

where Cr = crotyl; Mvc = methylvinylcarbinyl and

$$\text{bu}^- = \left[\begin{array}{c}\text{H H H H}\\ \text{HC—C=C—C:}\\ \Updownarrow\\ \text{H H H H}\\ \text{HC—C—C=CH}\\ \cdot\cdot\end{array}\right]^-$$

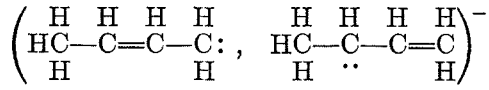
Hence possibility (B) represents a dynamic equilibrium between the secondary and the *cis* and *trans* primary forms of the butenyl Grignard reagent, while possibility (A) assumes the existence of *cis* and *trans* crotyl and methylvinylcarbinyl radicals bonded to magnesium in a more or less stable manner, these radicals being formed during the reaction of the butenyl bromide with the magnesium and retaining their identity thereafter. The latter possibility is favored by the fact that reaction of the Grignard reagent with oxygen to form alcohols (2) or with allyl bromide (3) to form heptadienes, leads to the same mixture of primary and secondary radicals as that produced by the action of water (1) on the reagent. The rate of reaction of the three forms of the Grignard reagent would not be the same with all reactants and consequently different mixtures would result if a rapidly established ionic equilibrium such as that required by postulate (B) actually existed. Possibility (C) requires that both the primary and secondary forms of the Grignard reagent,

$$\begin{array}{c}\text{H H H}\\ \text{HC—C=C—C—MgX}\\ \text{H H H}\end{array} \quad \text{and} \quad \begin{array}{c}\text{H H H H}\\ \text{HC—C—C=CH,}\\ \text{H}\\ \text{MgX}\end{array}$$

react by chelation at both the α and γ carbons to give the same proportion of primary and secondary radicals regardless of whether the reactant is water, oxygen, or butenyl halide. Since this mechanism (4) is the most satisfactory one yet proposed to account for the abnormal reactions of benzyl- and naphthylmagnesium halides it should not be overlooked. However, it seems unlikely that it would lead to the same ratios of primary an dsecondary radicals during reactions with the substances mentioned above. Furthermore it would not adequately account for the great difference in composition of butene mixtures obtained (5) from the reaction of butenyl halides with various metals. Even if the Grignard reagent is a mixture of the primary and secondary forms produced by possibility (A) it would be unlikely that a second rearrangement by possibility (C) would produce the same ratio of butenyl radicals when reacting

with the three different reagents. It is entirely possible, however, that carbonyl compounds such as formaldehyde, acetaldehyde, and ethylene oxide which react abnormally with benzylmagnesium chloride will also react abnormally with butenylmagnesium halides. Reactions of this type are being investigated.

Other evidence against the establishment of equilibrium between the butenyl radicals after formation of the Grignard reagent (possibility B) is found in the work of Noller and Raney (6), which indicates that the equilibrium between butylmagnesium chloride and dibutylmagnesium requires from 50–200 hours to be established. On the other hand we find that freshly prepared butenyl Grignard reagents give the same butene mixture on hydrolysis as those which have stood 50–100 hours. Cope (7), and Noller and White (8) have shown that the addition of dioxane causes the conversion of RMgX into R_2Mg, which remains in solution while the unreacted RMgX and MgX_2 are precipitated as dioxane complexes. The rapid formation of R_2Mg in this manner compared to the rate of establishment of the equilibrium studied by Noller and Raney (6), might be taken as indication that dioxane causes the production of a carbanion which reacts rapidly with RMgX to form R_2Mg. If this interpretation is correct we have an excellent way to test the relative merits of possibilities (A) and (B). The addition of dioxane to the butenyl Grignard reagent would produce the resonating butenyl carbanion



which could react with RMgX to form dibutenylmagnesium. If this butenyl carbanion were involved in the original rearrangement of the allylic system (possibility B) we would not expect the ratio of primary and secondary isomers to change during the formation of R_2Mg. However, if the original rearrangement resulted from resonance of the butenyl carbonium ion or free radical (possibility A) while the conversion of RMgX to R_2Mg involves resonance of the carbanion we would expect a change in the ratio of primary and secondary butenyl radicals.

In the present investigation it has been shown that the addition of dioxane to butenylmagnesium bromide produces a precipitate containing the butenylmagnesium bromide–dioxane complex and a solution of dibutenylmagnesium. Hydrolysis of the precipitate liberates the same butene mixture as the original Grignard reagent, while hydrolysis of the dibutenylmagnesium solution yields a butene mixture of different composition.

Discussion of Results

In the preliminary work (run 1) the butenylmagnesium bromide–dioxane precipitate was discarded and the solution containing the dibutenylmagnesium was converted to a butene mixture by hydrolysis, since it was from the dibutenylmagnesium portion of the reaction mixture that we expected to find evidence that dioxane had actually initiated the allylic rearrangement which was anticipated.

When analysis of the butene mixture from experiment 1 showed that the allylic composition of the butenyl radicals in the ether solution had changed, the following explanations were considered:

(I) That the addition of dioxane had initiated an allylic rearrangement during the formation of the dibutenylmagnesium. If this were true then the average composition of all radicals present in the R_2Mg and RMgX portions of the reaction mixture should differ from that found in the original Grignard reagent by butene analysis.

(II) That no allylic rearrangement was initiated by the treatment with dioxane, but the dioxane merely brought about a redistribution of the butenyl radicals between the RMgX and R_2Mg components by a bimolecular process in which the butenyl radicals are not free to resonate. In this case the composition of the butenes obtained from the dibutenylmagnesium would be different

TABLE I

ANALYSIS OF BUTENES FROM DIBUTENYLMAGNESIUM PRODUCED BY THE ADDITION OF DIOXANE TO BUTENYLMAGNESIUM BROMIDE

SOURCE OF BUTENEMIXTURE	K_2 OF DIBROMIDES CORRECTED	d_4^{25} OF DIBROMIDES	% 1-BUTENE	% *cis* 1-BUTENE	% *trans* 2-BUTENE	METHOD OF ANAL.
Dibutenylmagnesium from run 1[a]	.0566	1.7830	44.7	31.5	23.8	Reaction rate
Dibutenylmagnesium from run 2[a]	.0560	1.7831	44.0	33.2	22.5	Reaction rate
Dibutenylmagnesium from run 3[a]	.0564	1.7747[b]	44.8	32.0	23.2	Frey-Hepp
Average			44.5 ±.3	32.2 ±.3	23.2 ±.4	

[a] Each run consisted of two experiments on 0.4 mole quantities of the butenyl bromide, the dibromobutanes from each experiment being combined for analysis.

[b] A low density due probably to traces of impurity.

from that obtained from the RMgX–dioxane precipitate but the average composition of the radicals present in both phases would be identical with that in the original Grignard reagent.

In order to distinguish between explanations (I) and (II) a series of experiments were made in which both the dibutenylmagnesium and the butenylmagnesium bromide portions of the reaction mixture were converted into butenes for analysis. The results from the dibutenylmagnesium portion are listed in Table I. Butene samples from runs 1 and 2 were analyzed by the reaction rate method. The butene sample from run 3 was analyzed by the Frey-Hepp distillation method to furnish data by an independent analytical method. The results are in good agreement with those from runs 1 and 2.

The results of the analysis of the butene mixtures from the dioxane precipitate are listed in Table II. They are based on a combination of the reaction rate and Frey-Hepp method of analysis. It is difficult to get accurate densities on

small samples of dibromobutanes and equally difficult to make a good separation of the *cis* and *trans* 2-butenes by the Frey-Hepp distillation. Consequently the 1-butene content was measured by distillation, since the sharp break in the distillation curve made it easy to measure accurately. From a knowledge of the 1-butene content, the percentages of *cis* and *trans* 2-butenes in a given mixture can be estimated readily from the rate constant of the corresponding dibromide mixture, which can be accurately and readily measured. Table II shows the butene analysis based on the average rate constants and the 1-butene contents of samples from runs 2 and 3. The complete Frey-Hepp analysis of the sample from run 2 compares favorably with the analysis by the combined method.

TABLE II

ANALYSIS OF BUTENES FROM THE BUTENYLMAGNESIUM BROMIDE-DIOXANE PRECIPITATE

SOURCE OF BUTENE MIXTURE	K_2 OF DIBROMIDES CORRECTED	% 1-BUTENE	% *cis*-2-BUTENE	% *trans*-2-BUTENE	REMARKS
Ppt. from run 2.....	.0603	55.2	29.3	15.5	Analyzed by Frey-Hepp distillation
Ppt. from run 3.....	.0593	54.			1-Butene content obtained by Frey-Hepp distillation
Calc'd from average K_2 and 1-butene content.....	.0598	54.6	26.7	18.7	
Average.....		54.9	28.0	17.1	
Dibromides from butenylmagnesium bromide.....		56.4 ±2.0	26.5 ±1.4	17.2 ±3.3	Results of Young, Winstein, and Prater (1a) included for comparison

By comparison of the value obtained with those obtained for the original Grignard reagent it may be noted that the composition of the butenyl radicals in the precipitate has not been changed by the dioxane precipitation. This observation favors explanation I and rules out explanation II since a redistribution of radicals without rearrangement would require that the decrease in secondary radical (1-butene) found in the dibutenylmagnesium (Table I) would have to be offset by a corresponding increase in the secondary radical (1-butene) content of the butenylmagnesium bromide–dioxane precipitate. Consequently, it appears (a) that a mixture of *cis* and *trans* primary and secondary butenylmagnesium bromides is produced due to resonance at the instant the butenyl bromide reacts with the magnesium; (b) that the three forms of the butenyl radicals in the Grignard reagent are not the result of an equilibrium involving

resonance of a carbanion; (c) that dioxane causes a transfer of butenyl radicals forming the dibutenylmagnesium under conditions which produce resonance of the so-called butenyl carbanion and hence producing a different distribution of primary and secondary butenyl radicals than that produced during the formation of the Grignard reagent.

It should be noted that only one of the radicals undergoes rearrangement during conversion of the RMgX into R_2Mg. Since the butene mixture is formed from both radicals in the R_2Mg compound, the change in 1-butene content of 12% actually represents a change 25% in the composition of the butenyl radicals which were involved in the rearrangement due to addition of dioxane.

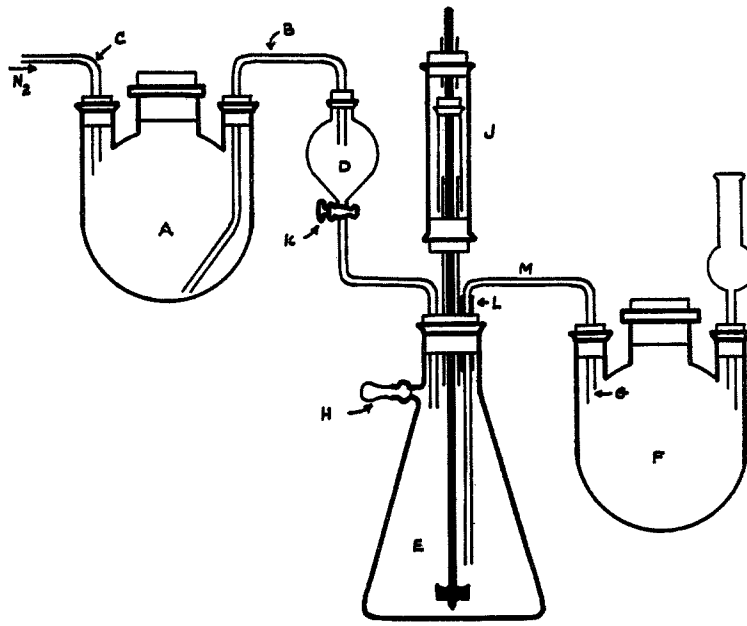


FIG. 1. APPARATUS USED FOR DIOXANE PRECIPITATION OF THE GRIGNARD REAGENT

EXPERIMENTAL PART

Preparation and hydrolysis of dibutenylmagnesium and butenylmagnesium bromide-dioxane complexes. Butenylmagnesium bromide was prepared in approximately 70–80% yields by the method of Young, Prater, and Winstein (9) starting with 0.4 mole of the equilibrium mixture of butenyl bromide (10). The relative mole quantities of the diethyl ether, magnesium, and butenyl bromide were 11, 3, and 1 respectively. The time of addition of the butenyl bromide was approximately 6 hours. The ether solution containing the butenylmagnesium bromide was transferred from the three-neck flask A (Fig. 1), in which it was prepared, into separatory funnel D and thence into flask E by means of glass siphon B. Plugs of glass wool inserted in the ends of siphon B freed the ether solution of bits of magnesium metal. Before the above transferring operation was carried out, flask F was detached and end G was closed by a rubber nipple while H was protected by a calcium chloride tube.

When all the Grignard reagent had been transferred to E, the siphon was removed and anhydrous dioxane was added to funnel D which was then protected by a calcium chloride

tube. The dioxane was then added in a slow stream to the gently stirred solution. A white precipitate formed immediately with the evolution of considerable heat. The dioxane was added in the ratio of 4 moles of dioxane to one mole of halide, according to the directions of Cope (7) for the preparation of dialkylmagnesium. All operations described were carried out in carefully dried apparatus under an atmosphere of dry nitrogen. When the dioxane had been added, stopcock K was closed and the calcium chloride tube removed from H and replaced by a dropper nipple.

The mixture was then stirred vigorously for about fifteen hours, after which the precipitate was allowed to settle for about an hour. The flask F was then attached as in Fig. 1, and nitrogen pressure was applied at H forcing the ether solution containing the dibutenylmagnesium into flask F. The system was so constructed that although joint L is gas-tight, the level of siphon M may be readily changed. In this manner most of the ether was removed and the solid material was not disturbed. Flask F was then removed and the nipples replaced at G and H. The precipitate, consisting of butenylmagnesium bromide-magnesium bromide-dioxane complexes was then stirred with 75 ml. of anhydrous dioxane which was siphoned off after the precipitate had settled for one hour. This washing process was repeated three times.

Two normal sulfuric acid was added dropwise to the washed precipitate which was being stirred. The evolved butene gas was led through the purification train described by Young, Winstein, and Prater (1a) and collected as dibromobutane.

The Flask F containing the ether-dioxane solution of dibutenylmagnesium was equipped for distillation and the ether and dioxane were removed at reduced pressure. It was necessary to raise the temperature of the heating-bath to 50–60° during the last portion of the distillation. A separatory funnel, a mercury sealed stirrer, and a Hopkins condenser were then attached to the flask F and the dibutenylmagnesium, now in the form of a gummy mass, was hydrolyzed and the resulting butene mixture converted into dibromobutanes as described above.

Analysis of the butene mixtures. The compositions of the butene mixtures obtained from the hydrolysis of the dibutenylmagnesium and from the butenylmagnesium bromide-dioxane precipitate were determined either by the dibromobutane reaction rate method of Dillon, Young, and Lucas (11) in which the necessary corrections were applied (5), or by distillation in a Frey-Hepp column modeled after the one used by Hurd and Goldsby (12). In some cases both procedures were used as a check on each other and in one case a combination of the two methods was used. The results of the analysis of the butene mixtures obtained from dibutenylmagnesium are recorded in Table I, while the analytical results for the butene mixtures obtained from butenylmagnesium bromide-dioxane complex are recorded in Table II.

Materials. The alcohol used in the preparation of the butenyl bromide was a mixture of crude crotyl alcohol and methylvinylcarbinol purchased from the Shell Chemical Co., Emeryville, California. The butenyl bromide was prepared by Method 2 described by Young and Lane (13). Commercial dioxane was refluxed for 15 hours over potassium hydroxide pellets. It was then redistilled from the potassium hydroxide and stored over sodium wire for several weeks. After this time it was redistilled and a middle fraction collected and stored over sodium wire. Commercial bromine was shaken with a solution of potassium bromide and distilled from concentrated sulfuric acid.

The authors are indebted to Dr. Saul Winstein for helpful suggestions during the preparation of the manuscript and to Mr. Richard Meier for assistance with Frey-Hepp analysis.

SUMMARY

Dioxane has been added to butenylmagnesium bromide in diethyl ether producing a solution of dibutenylmagnesium and a precipitate containing butenyl-

magnesium bromide–dioxane complex. Hydrolysis of the solution gives 44.5% 1-butene, 32.2% *cis* 2-butene, and 23.2% *trans* 2-butene and hydrolysis of the precipitate gives 55% 1-butene, 28% *cis* 2-butene, and 17% *trans* 2-butene.

A discussion of the reaction is presented showing that the formation of dibutenylmagnesium involves an allylic rearrangement.

Los Angeles, Calif.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

2-METHYL-*d*-ALTROMETHYLOSE AND ITS BEARING ON THE CONFIGURATION OF DIGITALOSE

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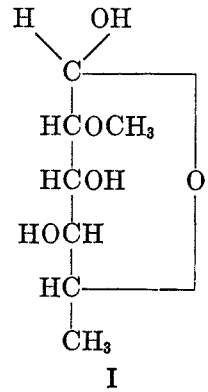
The question of the structure and configuration of digitalose has received attention from several investigators since its isolation from the products of hydrolysis of *Digitalinum verum* by Kiliani (1). Kiliani in several papers secured evidence which indicated that the sugar was a 2-methylhexomethylose but was unable to arrive at a configuration for it. Schmidt and Zeiser (2) degraded digitalose to *l*-arabotrimethoxyglutaric acid, thereby limiting the configuration of digitalose to one of the four possibilities, I–IV



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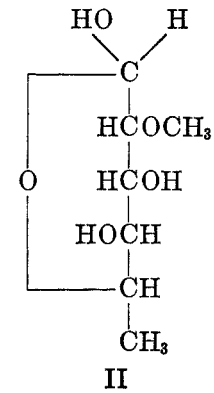

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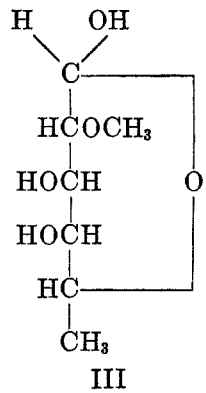

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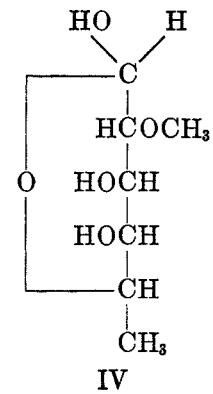


IV

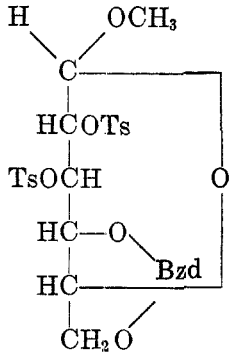
A review of the early literature on digitalose is given in the paper of Schmidt and Zeiser (2) and in a paper by MacPhillamy and Elderfield (3). The latter workers synthesized two of the four possibilities, namely, 2-methyl-*l*-rhamnose

(II) and 2-methyl-*d*-fucose (III) and showed that neither of these two sugars was identical with digitalose. In the present work we wish to report the synthesis of 2-methyl-*d*-altromethylose, the enantiomorph of one of the two remaining possibilities on the basis of previous work. The synthetic approach has been adopted in attacking the problem of the configuration of digitalose, in view of the extreme difficulty encountered in securing adequate amounts of the sugar for degradative studies.

Rather than attempt the preparation of 2-methyl-*l*-altromethylose (IV), we have prepared its optical enantiomorph, inasmuch as glucose can be conveniently used for the starting material in this preparation. The method used is based on the work of Robertson and co-workers (4) and proceeds from α-methylglucoside. This was converted into 2,3-ditosyl-4,6-benzylidene-α-methylglucoside (V). Upon detosylation of the latter, inversion takes place at carbon atom three with the formation of a 2,3-ethylene oxide bridge (VI), which, upon treatment with sodium methoxide, undergoes cleavage of the oxide and a second inversion at carbon atom two, accompanied by methylation of the hydroxyl group at carbon atom two, leading to 2-methyl-4,6-benzylidene-α-methyl-*d*-altroside (VII). Upon mild hydrolysis the benzylidene residue is removed from VII to give 2-methyl-α-methyl-*d*-altroside (VIII).

The problem then remained of converting the hexose derivative VIII to the desired hexomethylose. This was accomplished by simultaneous tritylation and acetylation of VIII to yield 2-methyl-3,4-diacetyl-6-trityl-α-methyl-*d*-altroside (IX). The trityl group of (IX) was removed by the action of hydrogen bromide in acetic acid, yielding 2-methyl-3,4-diacetyl-α-methyl-*d*-altroside, which was in turn tosylated in the open six position to yield (X). Replacement of the tosyl group in (X) by iodine followed by catalytic reduction of the resultant 2-methyl-3,4-diacetyl-6-iodo-α-methyl-*d*-altroside (XI) gave 2-methyl-3,4-diacetyl-α-methyl-*d*-altromethyloside, which by deacetylation furnished 2-methyl-α-methyl-*d*-altromethyloside (XII). The latter on hydrolysis of the glucosidic methyl group gave the desired 2-methyl-*d*-altromethylose.

The sugar thus obtained did not crystallize and could be obtained only as a syrup, which, however, furnished satisfactory analytical figures for the desired substance. We have been unable to obtain a crystalline derivative of the sugar by means of the usual reagents. Therefore, in order to establish its identity more definitely, it was prepared from 2-methyl-α-methyl-*d*-altroside (VIII) by the following alternative series of reactions. Upon unimolecular tosylation of the latter according to the method of Levene and Raymond (5), the 6-tosyl derivative (XIV) was formed. This, after conversion to the 6-iodo derivative (XV), led either to 2-methyl-3,4-diacetyl-6-iodo-α-methyl-*d*-altroside (XI) on acetylation of (XV), or to 2-methyl-α-methyl-*d*-altromethyloside (XII) on catalytic reduction. The two products thus obtained were identical in all respects with those obtained by the method described previously, and little doubt remains that any further inversions have taken place in the preparation of 2-methyl-*d*-altromethylose.



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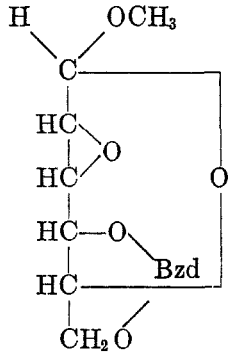

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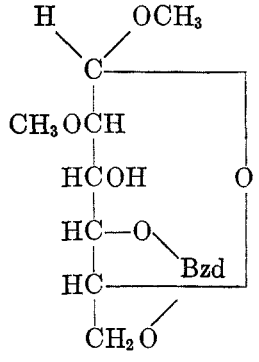

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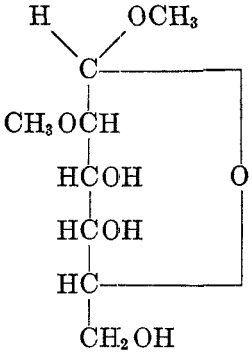

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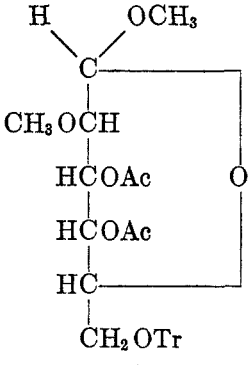

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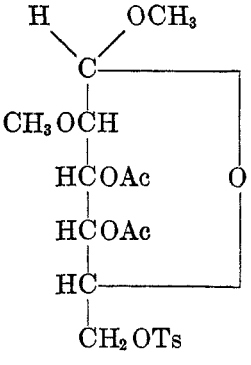
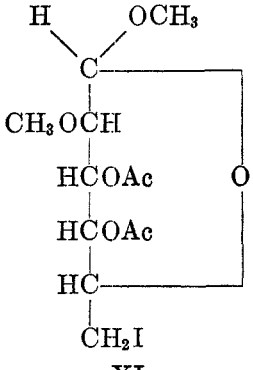


X



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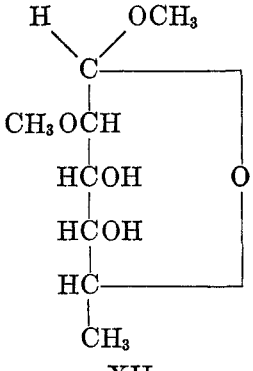

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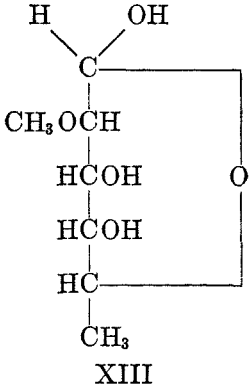

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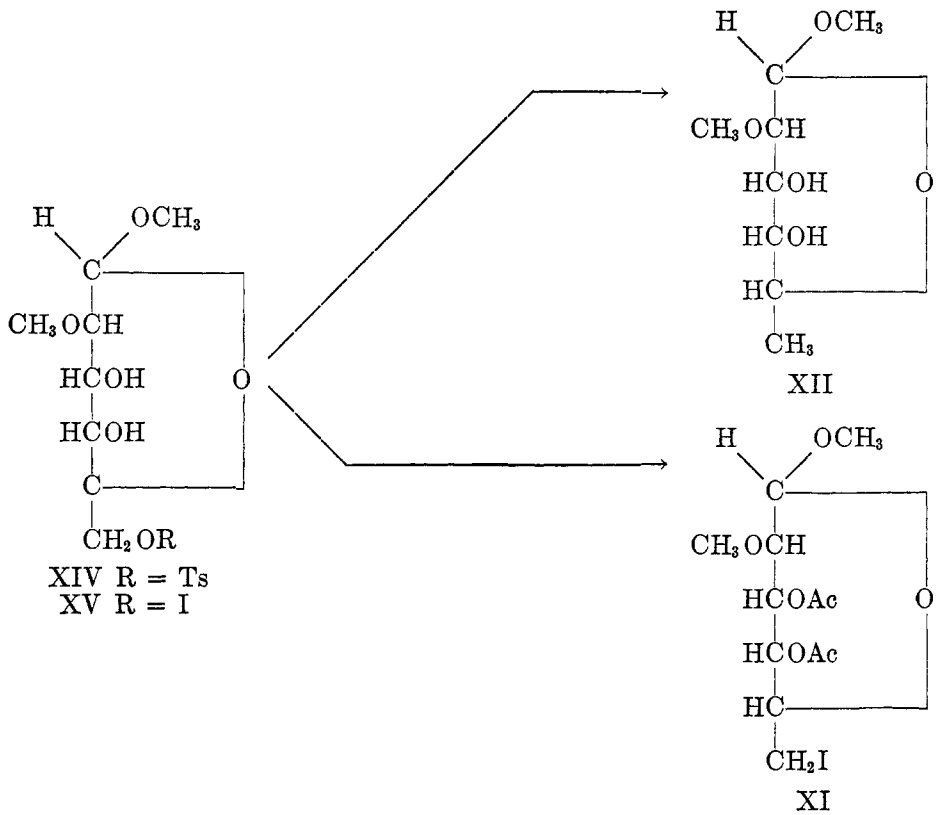

2-Methyl-*d*-altromethylose here described presents an interesting case of an altrose derivative in which anhydride formation between the one and six positions, as described by Richtmyer and Hudson (6) for altrose itself, as well as the 1,2-anhydride formation considered by these authors, is blocked. Hydrolysis of 2-methyl-α-methyl-*d*-altromethyloside proceeds in the normal fashion to give a sugar having reducing power.

The specific rotation of the syrupy 2-methyl-*d*-altromethylose thus prepared is 11.8°, which contrasts with the rotation reported by Lamb and Smith (7) of 106° for digitalose, and which can be taken as conclusive evidence of the non-identity of the two sugars. Three of the four possibilities for digitalose advanced by Schmidt and Zeiser (2) having thus been eliminated by direct synthesis, 2-methyl-*d*-gulomethylose (I) remains. However, there seems to be a good reason to doubt whether this actually represents the structure of digitalose. In Table I are given the values for the specific rotation of seven sugars, together with similar values for their 2-methyl derivatives.

It is at once apparent that methylation in the two position does not result in a pronounced change in the optical activity. The specific rotation of *d*-gulomethylose, as reported by Levene and Compton (19) is $-35.7°$. It is obvious, then, that a change of some 140° in this value will be necessary, in

order that methylation in the 2-position shall result in digitalose, a shift which is unlikely if considered in the light of similar changes, as noted in Table I. This point in turn raises a doubt as to the position occupied by the methyl ether in digitalose. Kiliani (20) suggested that this group is in the two position on the basis of the failure of digitalose to yield an osazone on treatment with phenylhydrazine. However, the experiment on which this conclusion was based was performed on the mixture of glucose and digitalose obtained by hydrolysis of *Digitalinum verum*, and glucosazone was the only product isolated in an analytically pure state. An impure substance considered to be the phenylhydrazone of digitalose was isolated from the mother liquors. Under the conditions of Kiliani's experiment it is surprising that an osazone of the parent sugar of digitalose was not formed by elimination of the methyl group if this is actually in the 2-position. One other point of evidence is at hand which can be taken as indicating that the methyl group under discussion may be

TABLE I

SPECIFIC ROTATIONS OF SUGARS AND THEIR 2-METHYL DERIVATIVES[a]

SUGAR	SPECIFIC ROTATION	SPECIFIC ROTATION OF 2-METHYL DERIVATIVE
d-Glucose	52.5° (8)	65.3° (9)
d-Galactose	81.7° (10)	82.6° (11)
d-Xylose	19° (12)	35.9° (13)
d-Arabinose	−105° (12)	−102° (14)
l-Rhamnose	8.9° (15)	31° (3)
d-Fucose	76.3° (16)	87.0° (3)
d-Altromethylose	18°[b]	11.8° (18)

[a] All values are for aqueous solutions, sodium D-line.

[b] Based on $[\alpha]_D$ −18° given for *l*-altromethylose by Freudenberg and Raschig (17).

more satisfactorily placed in the 4-position. Kiliani (1) prepared digitalonic lactone by oxidation of digitalose with bromine water. The latter on further oxidation with nitric acid led to a substance believed to be α,β-dihydroxy-α'-methoxyglutaric acid (21). There seems to be little doubt that a glutaric acid derivative is thus formed in view of the work of Schmidt and Zeiser (2). The formation of a glutaric acid derivative, therefore, can be taken to indicate that the stable lactone of digitalonic acid is the δ-lactone. Inasmuch as the γ-lactones are the stable forms of most sugar acid lactones, the possibility of the presence of a 4-methyl group, which would effectively block the formation of a γ-lactone of digitalonic acid, is not excluded. We are continuing this work with the view of clearing up these discrepancies.

The 2-methyl-*l*-rhamnose reported by MacPhillamy and Elderfield (3) has crystallized on long standing. It has been found to melt at 113–114° after crystallization from absolute alcohol and ether. Its non-identity with digitalose previously postulated, is thus confirmed by the melting point of the crystalline sugar.

We wish to acknowledge our indebtedness to Doctors C. S. Hudson and N. K. Richtmyer of the National Institute of Health, United States Public Health Service, for valuable advice during the course of this work.

EXPERIMENTAL

All boiling points and melting points are corrected for stem exposure.

4,6-Benzylidene-α-methylglucoside was prepared according to the method of Freudenberg, Toeppfer, and Andersen (22). The melting point of a sample recrystallized from water and then several times from a mixture of chloroform and ether was 163–164°. The rotation, 110.8° (c = 2.34 in chloroform), agrees with the value reported by Richtmyer and Hudson (23).

2,3-Ditosyl-4,6-benzylidene-α-methylglucoside (*V*). Crude 4,6-benzylidene-α-methylglucoside was tosylated according to the method of Ohle and Spencker (24), as modified by Richtmyer and Hudson (23). After recrystallization from chloroform-ether, it melted at 147–148°. The rotation was 12° in chloroform.

2,3-Anhydro-4,6-benzylidene-α-methyl-d-*alloside* (*VI*) was prepared by Richtmyer and Hudson's modification of the method of Robertson and Griffith (4). One hundred grams of 2,3-ditosyl-4,6-benzylidene-α-methylglucoside was dissolved in one liter of chloroform and the solution was cooled to 10°. Three hundred twenty cubic centimeters of 2.15 N sodium methoxide (4 mol. equivs.) in anhydrous methanol was added to the solution, which was then allowed to stand in the ice-chest for 3 days. The solution was allowed to stand an additional day at room temperature to destroy the excess of sodium methoxide by formation of methyl orthoformate. At the end of this time considerable amounts of sodium p-toluenesulfonate had separated. The chloroform solution was removed, washed once with water, dried over calcium chloride, and the solvent removed in a vacuum. During concentration 2,3-anhydro-4,6-benzylidene-α-methylalloside crystallized as white plates. The material melted at 200°, as reported by Robertson and Griffith (4). The rotation was 140° in chloroform. It is pure enough to use directly in the next reaction. The yield was 95%.

2-Methyl-4,6-benzylidene-α-methyl-d-*altroside* (*VII*) was prepared by the method of Robertson and Griffith (4). Twenty grams of 2,3-anhydro-4,6-benzylidene-α-methyl-*d*-alloside was dissolved in 400 cc. of anhydrous methanol containing 171 cc. of 2.28 N sodium methoxide solution. The solution was heated under reflux for 24 hrs., during which time the material went completely into solution. The solution was diluted with cold water and extracted exhaustively with chloroform. After drying, the solvent was removed under a vacuum, during which crystallization occurred. The material, after recrystallization from chloroform-ether, melted at 99°. The rotation was 104° in chloroform. The yield was 86%.

2-Methyl-α-methyl-d-*altroside* (*VIII*). Twenty-two and four-tenths grams of 2-methyl-4,6-benzylidene-α-methylaltroside was placed in a distilling flask with 200 cc. of water containing 10 cc. of 0.1 N hydrochloric acid. The mixture was distilled *in vacuo* below 40°, replacing the water lost by distillation, until the distillate no longer smelled of benzaldehyde. It was then neutralized to phenolphthalein with 0.1 N sodium hydroxide solution, and concentrated *in vacuo* to a heavy syrup. Since the material did not crystallize readily [Robertson and Griffith report the melting point 83° (4)], it was used directly in the next step. For this purpose the syrup was dried by repeated distillation with benzene.

2-Methyl-3,4-diacetyl-6-trityl-α-methyl-d-*altroside* (*IX*). To a solution of 11.3 g. of syrupy 2-methyl-α-methylaltroside in 175 cc. of dry pyridine was added 16.3 g. (1.1 mol. equiv.) of trityl chloride and the mixture was heated at 100° for three hours. The solution was then cooled and 60 cc. of freshly distilled acetic anhydride was added. It was allowed to stand at room temperature for three days and then was poured into ice-water, whereupon a heavy syrup separated which set to a solid mass of crystals overnight. The crystals were collected and washed with a small amount of ether. They were recrystallized from a mixture of chloroform and ether by careful addition of isopentane until the solution became

slightly turbid. It was then seeded and set to crystallize in the ice-chest. Crystallization was complete in three days. The aqueous-pyridine portion was extracted three times with chloroform, and the pyridine removed from the combined extracts by exhaustive washing with 20% copper sulfate solution. The extracts were dried and the solvent removed *in vacuo*. On addition of ether and isopentane to the thin syrup so obtained, a further crop of crystals was obtained. The total yield was 79%. The compound melts at 121–121.5°; $[\alpha]_D^{25}$ 63.4° (c = 2.012 in chloroform).

Anal. Calc'd for $C_{31}H_{34}O_8$: C, 69.6; H, 6.4; OCH_3, 11.6.
Found: C, 69.6; H, 6.2; OCH_3, 11.3.

2-Methyl-3,4-diacetyl-α-methyl-d-*altroside*. Fifteen grams of 2-methyl-3,4-diacetyl-6-trityl-α-methylaltroside was dissolved in 75 cc. of glacial acetic acid and cooled to 18°. Ten cubic centimeters of glacial acetic acid saturated at 0° with anhydrous hydrogen bromide was likewise cooled and added to the above solution with stirring. The mixture immediately became bright yellow, due to the formation of triphenylmethyl ion, and then, in a few seconds, a copious precipitate of trityl bromide separated. This was filtered on a sintered glass funnel and washed with cooled acetic acid. The filtrate was poured into 300 cc. of ice and water and this mixture was extracted with five portions of chloroform. The combined extracts were washed free of acid with sodium bicarbonate solution, dried, and the solvent removed *in vacuo*. The syrup remaining was taken up in a little anhydrous ether and isopentane was added until the solution became just turbid. The turbidity was discharged with a drop of ether and the solution was cooled. On standing overnight, 2-methyl-3,4-diacetyl-α-methyl-*d*-altroside crystallized as white needles. After recrystallization from ether-pentane the substance melted at 76–77°. The yield was 8.0 g. or 97%; $[\alpha]_D^{25}$ 127.8° (c = 1.850 in chloroform).

Anal. Calc'd for $C_{12}H_{20}O_8$: C, 49.3; H, 6.9; OCH_3, 21.2.
Found: C, 49.6; H, 7.0; OCH_3, 20.9.

2-Methyl-3,4-diacetyl-6-tosyl-α-methyl-d-*altroside* (*X*). Ten grams of 2-methyl-3,4-diacetyl-α-methylaltroside was dissolved in 25 cc. of anhydrous pyridine and 14 g. (2.1 mol. equivs.) of tosyl chloride was added. The mixture was allowed to stand at room temperature for three days, during which it was protected from atmospheric moisture by a calcium chloride tube. The mixture was poured into ice and water, and extracted with chloroform. The combined extracts were washed free from pyridine with cold dilute hydrochloric acid, then washed with sodium bicarbonate solution, dried, and the solvent removed *in vacuo*, leaving a clear, colorless syrup. All attempts to crystallize this syrup failed. A sample distilled at 10 mm. was still slightly contaminated, as shown by analysis. The product was used satisfactorily for the following reaction as directly obtained.

2-Methyl-3,4-diacetyl-6-iodo-α-methyl-d-*altroside* (*XI*). Fourteen and eight-tenths grams of syrupy 2-methyl-3,4-diacetyl-6-tosyl-α-methyl-*d*-altroside was heated with 50 cc. of acetone containing 11 g. of sodium iodide in a sealed tube, in a boiling water-bath for six hours. The acetone filtrate from sodium toluenesulfonate was concentrated to dryness *in vacuo* and portions of chloroform were repeatedly distilled from the dry residue to remove the last traces of acetone. The solid residue was extracted many times with boiling chloroform to separate the organic material from the excess sodium iodide. The chloroform solution was dried and the solvent removed *in vacuo*, leaving a rapidly crystallizing residue. This was recrystallized from a mixture of chloroform and isopentane. The substance formed large transparent prisms which melted at 54.5–55.5°. The yield was 77%; $[\alpha]_D^{25}$ 76.2° (c = 1.240 in chloroform).

Anal. Calc'd for $C_{12}H_{19}IO_7$: C, 35.9; H, 4.8; OCH_3, 15.4; I, 31.6.
Found: C, 36.2; H, 4.9; OCH_3, 15.0; I, 31.6.

2-Methyl-α-methyl-d-*altromethyloside* (*XII*). A solution of 6.6 g. of 2-methyl-3,4-diacetyl-6-iodo-α-methyl-*d*-altroside in 65 cc. of methanol and 20 cc. of 10% aqueous potassium

hydroxide solution was shaken with 1 g. of activated Raney nickel catalyst in an atmosphere of hydrogen. After 8 hrs. the calculated amount of hydrogen was absorbed. The potassium hydroxide was neutralized by passing carbon dioxide into the ice-cold solution and the solution was evaporated to dryness *in vacuo*. Since it was found difficult to remove acetate ion from this mixture, the altromethyloside was reacetylated by dissolving the crude, dry mixture in 50 cc. of anhydrous pyridine and adding 50 cc. of acetic anhydride. The solution was allowed to remain at room temperature for three days and then poured into ice-water. The product was extracted with chloroform and the solvent removed in the usual manner. The colorless syrup remaining consisted of 2-methyl-3,4-diacetyl-α-methyl-*d*-altromethyloside, which was not isolated as such but deacetylated directly by the method of Isbell (25). The syrup was dissolved in 100 cc. of anhydrous methanol and cooled to −10° in an ice-salt-bath, 3 cc. of 0.4 *N* barium methoxide solution was added and the mixture allowed to stand at 0° for four days. After addition of 20 cc. of water the barium was removed by saturating the solution with carbon dioxide. The solution was boiled for a few minutes to reprecipitate any barium bicarbonate formed and the inorganic salt was filtered off. Concentration of the aqueous methanol solution gave 2-methyl-α-methyl-*d*-altromethyloside as a colorless, very hygroscopic syrup. It was distilled at 0.55 mm. pressure, and boiled at 112–113°; n_D^{25} 1.4632. The yield was quantitative. $[\alpha]_D^{25}$ 91.1° (*c* = 2.262 in water).

Anal. Calc'd for $C_8H_{16}O_5$; C, 50.0; H, 8.4.
Found: C, 49.8; H, 8.4.

2-Methyl-d-*altromethylose* (*XIII*). 2-Methyl-α-methyl-*d*-altromethyloside was hydrolyzed by heating it at 50° with 7% hydrochloric acid for three days. At the end of this time the rotation of the solution had fallen to a constant value of +10.5°. Chloride ion was removed by stirring the solution with a paste of silver carbonate. Silver ion was removed with hydrogen sulfide and the solution was concentrated to a syrup below 30°. The syrup was dried by repeated distillation of absolute alcohol and benzene. All attempts to crystallize the sugar failed. For analysis the material was further dried at 80° and analyzed as such, although still impure.

Anal. Calc'd for $C_7H_{14}O_6$: C, 47.2; H, 7.9; OCH_3, 17.4.
Found: C, 47.5; H, 8.1; OCH_3, 16.2.

The syrup showed a value for $[\alpha]_D^{25}$ of 11.8° (*c* = 3.472 in water) and was strongly reducing to Fehling's solution. The sugar gave no crystalline phenyl-, *p*-bromo-, *p*-nitro-, or 2,4-dinitrophenylhydrazone, or *p*-tosylhydrazone.

2-Methyl-6-tosyl-α-methyl-d-*altroside* (*XIV*). 2-Methyl-α-methyl-*d*-altroside was treated according to the method of Levene and Raymond (5) for the unimolecular tosylation of monoacetone xylose. To a solution of 10 g. of dry 2-methyl-α-methylaltroside in 100 cc. of dry pyridine at 0° was added 10 g. (1.1 mol. equivs.) of tosyl chloride dissolved in 75 cc. of cold chloroform dropwise with stirring. The reaction mixture was kept at 0° for 5 hrs. and then for an additional 48 hrs. at room temperature. It was then poured into ice-water and the aqueous solution extracted with chloroform. The extracts were freed from pyridine in the usual manner and the solvent removed *in vacuo*. The colorless syrup remaining failed to crystallize.

2-Methyl-6-iodo-α-methyl-d-*altroside* (*XV*). A solution of 11 g. of syrupy 2-methyl-6-tosyl-α-methyl-*d*-altroside and 9 g. of sodium iodide in 50 cc. of acetone was heated at 100° for six hours in a sealed tube. The precipitated sodium toluenesulfonate was filtered off and the acetone removed from the filtrate by concentration under reduced pressure. The solid residue was extracted several times with boiling chloroform. Removal of the solvent left 8.5 g. of a clear, colorless syrup which could not be crystallized.

Acetylation of 2-methyl-6-iodo-α-methyl-d-*altroside*. One and eighty-five hundredths grams of syrupy 2-methyl-6-iodo-α-methylaltroside was acetylated in the usual manner

with acetic anhydride and pyridine. After extraction of the mixture with chloroform, the pyridine was removed in the usual manner. On concentration of the chloroform under reduced pressure crystallization occurred. After crystallization from ether-isopentane the substance melted at 55° and the melting point was not depressed on mixing with 2-methyl-3,4-diacetyl-6-iodo-α-methyl-*d*-altroside (XI) prepared as above. The yield was 1.1 g. or 47%. $[\alpha]_D^{25}$ 91.0° (c = 2.304 in water).

Attempted oxidation of 2-methyl-d-*altromethylose with bromine water.* Six-tenths of a gram of the sugar was dissolved in 20 cc. of water saturated with bromine. After standing at room temperature for 3 days the inorganic constituents were removed in the usual manner. Concentration of the aqueous solution *in vacuo* left a syrup which was still strongly reducing to Fehling's solution.

Oxidation of 2-methyl-d-*altromethylose with barium hypoiodite solution.* Four hundred eighty milligrams of the sugar was oxidized with 100 cc. of 0.1 *N* barium hypoiodite solution according to the method of Goebel (26). After removal of the inorganic constituents, the solution no longer reduced Fehling's solution. On removal of the solvent under vacuum, a syrup remained which failed to crystallize. Its phenylhydrazide was prepared but was not obtained in a crystalline condition.

Crystalline 2-methyl-l-*rhamnose.* A sample of the sugar prepared by MacPhillamy and Elderfield (3) has now crystallized. It was recrystallized from absolute ethanol-ether as long, colorless needles. Its melting point was 113–114°.

The microanalyses here reported were performed by Mr. Saul Gottlieb of this laboratory.

SUMMARY

1. 2-Methyl-*d*-altromethylose has been prepared and shown not to be identical with the enantiomorph of digitalose.

2. It is suggested that 2-methyl-*d*-gulomethylose, the only possible structure for digitalose remaining on the basis of hitherto accepted work, is open to question.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

THE PROPERTIES OF SOME PHENOXYACETONES

D. STANLEY TARBELL

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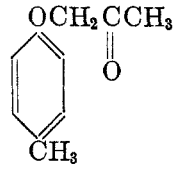
The atomic configuration $CH_2{=}CHCH_2OC{=}C$ is the group involved in the Claisen rearrangement of aryl allyl ethers, the two carbon atoms on the right being part of an aromatic nucleus (1). The analogous systems which have been shown to give rearrangement are $CH_2{=}CHCH_2OCH{=}NR$ (2), $CH_2{=}CHCH_2SC{=}C$ (3), $CH_2{=}CHCH_2SC{\equiv}N$ (4), and $CH_2{=}CHCH_2CC{=}C$ (5). In these examples, the $CH_2{=}CHCH_2$ group has not been altered, but it has been found that the systems $N{\equiv}CCH_2OC{=}C$ (6) and $HC{\equiv}CCH_2OC{=}C$ (7) do not give rearrangement of the Claisen type on pyrolysis.

The work described in this paper had its inception in an examination of the behavior of 4-methylphenoxyacetone (I) and related compounds upon pyrolysis, since they contain the group $O{=}C(CH_3)CH_2OC{=}C$.



I

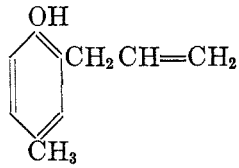
The results indicate that this group does not allow a rearrangement to take place, and that it should be classified with the last two systems mentioned in the first paragraph.[1]

The preparation of 4-methylphenoxyacetone, first made by Stoermer (8), was tried under a variety of conditions, using both chloroacetone and bromoacetone. In every case, even with an excess of haloacetone, much of the phenol was recovered unchanged and the yields were poor. The best method tried was that of Calaway and Henze (9, 10), according to which the sodium salt of the phenol in benzene is treated with bromoacetone, but even here the yields were below 50%.

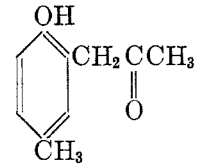
In reaction with *p*-cresol, the contrast between the reactions of the haloacetones and allyl bromide is striking; the former give a poor yield of a mixture of products, with acetone and potassium carbonate as the reaction medium, while allyl bromide gives excellent yields of the allyl phenyl ethers under the

[1] Since this article was submitted for publication, Hurd and Perletz have described the synthesis of phenoxyacetone and its behavior on heating to 650° (Abstracts of papers presented before the Organic Division, Memphis Meeting of the American Chemical Society).

same conditions (11). Furthermore, treatment of the sodium salt of a phenol with allyl bromide in benzene yields a large proportion of the C-alkylated product such as II, in addition to the ether (12). Bromoacetone under the same



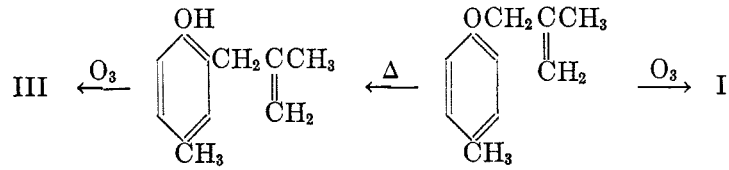
II



III

conditions gave a poor yield of the O-alkylated compound I but nothing corresponding to the C-alkylation product III could be isolated by careful distillation of the alkali-soluble fraction. The difference in behavior of the allyl and acetonyl compounds is probably due to the fact that the carbonyl group is electron-attracting and tends to make the halogen more "positive" than is the allyl halogen.

It was observed that the compound believed to be 4-methylphenoxyacetone showed some solubility in Claisen's alkali, and it seemed possible that this was because the product was actually the C-alkylated compound, 2-acetonyl-4-methylphenol (III). The insolubility of III in aqueous alkali might be due to formation of a stable hemiacetal. To prove the structure of the product, it was synthesized by another method which ruled out the possibility of C-alkylation. β-Methylallyl 4-methylphenyl ether (IV) was ozonized, and the semicarbazone



V IV

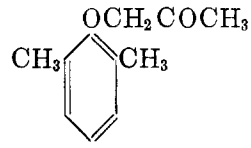
of the product shown to be identical with that of the product from *p*-cresol and bromoacetone. The ether IV was also rearranged to V, from which the acetonyl compound III was prepared in impure form by ozonization. Compound III was characterized by preparation of the semicarbazone.

When 4-methylphenoxyacetone which had been purified through the bisulfite compound was heated at 250° for two and one-half hours, most of it was recovered unchanged, but a small amount of *p*-cresol was recovered and identified. The purified 4-methylphenoxyacetone decomposes on long standing at room temperature and an alkali-soluble material is formed, presumably *p*-cresol.

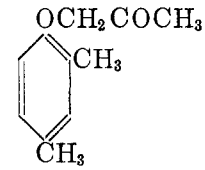
2,6-Dimethylphenoxyacetone behaved similarly when it was heated at 200° for one hour; there was some formation of an alkali-soluble substance, presumably 2,6-dimethylphenol, and much of the starting material was recovered unchanged. Pure 2,6-dimethylphenoxyacetone also decomposed slowly at room temperature, and 2,6-dimethylphenol was isolated from a sample which had stood for five weeks.

The results of the experiments at high temperatures indicate that the system O=C(CH_3)CH_2OC=C does not undergo a rearrangement analogous to the Claisen rearrangement.

The observation that 4-methylphenoxyacetone (I) can be partially extracted from petroleum ether and benzene solutions by Claisen's alkali [prepared from potassium hydroxide and dilute methanol (13)] was rather unexpected, and a number of substituted phenoxyacetones were prepared to determine the effect of substituents on the acidic character of the compound. The extraction is not due to a physical solubility effect. Blanks carried out on several compounds showed that extraction of the benzene solution with a mixture of water and methanol, richer in methanol than Claisen's alkali, did not remove as much of the ketone as Claisen's alkali. The ketones were changed to some extent by being dissolved in Claisen's alkali, since they were recovered as viscous oils. The semicarbazones could be obtained from the oil, however, showing that the condensation or resinification of the ketones was only partial.



VI

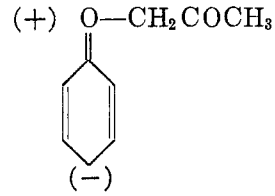


VII

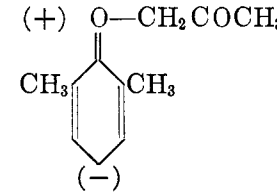
The substituted phenoxyacetones prepared were of two types. Several phenoxyacetones were prepared with groups which increase the acidity of phenols (nitro and bromo) to find whether they would also increase the acidity of the acid hydrogen in the phenoxyacetones. This is presumably the hydrogen on the carbon adjacent to the ether oxygen. The phenoxyl group has an electron-attracting inductive effect; phenoxyacetic acid has a dissociation constant 42 times greater than acetic acid (14).

The second class of compounds prepared included 2,6-dimethylphenoxyacetone VI, the 2,4-dimethyl compound VII and the nitro derivative of each, in order to see whether the phenomenon of damped resonance (15) would affect the behavior of the compounds greatly.

The resonance forms contributing to the structure of aromatic ethers include three in which the oxygen is attached to the ring by a double bond, with a positive charge on the oxygen and a negative charge in the ortho or para positions, as in VIII, in which the group attached to the oxygen lies in the plane of the



VIII



IX

ring. Two methyl groups in the ortho position should prevent the occurrence of a similar planar structure such as IX, *i.e.*, the resonance is damped or inhibited by steric factors. Such steric effects have been observed recently (16) in several instances involving amino and nitro groups as the resonating groups, and have also been used to explain the unusual reactions of di-ortho substituted benzoic acids (17).

The acidity of the phenoxyacetones was studied by extracting them from benzene with Claisen's alkali under uniform conditions and determining the amount extracted. This, of course, is a qualitative method only, because the relative solubilities as well as the intrinsic acid strength enter in. It was found that, while the methyl- and bromo-phenoxyacetones could be recovered unchanged from Claisen's alkali, at least in part, 4-nitrophenoxyacetone was cleaved very rapidly at room temperature by Claisen's alkali, yielding *p*-nitrophenol. The side chain was apparently polymerized after cleavage. There was no evidence that 4-nitrophenoxyacetone could dissolve in Claisen's alkali without cleavage. The statement by Stoermer and Brockerhof (18) that 4-nitrophenoxyacetone dissolves in aqueous alkali to give a yellow solution from which it can be recovered unchanged could not be confirmed, as the compound is insoluble in aqueous alkali. 2-Nitrophenoxyacetone was decomposed very rapidly by Claisen's alkali, but nothing could be isolated, not even *o*-nitrophenol.

The same results were obtained with 2,6-dimethyl-4-nitrophenoxyacetone and 2,4-dimethyl-6-nitrophenoxyacetone. The former was cleaved by Claisen's alkali giving 2,6-dimethyl-4-nitrophenol, while the latter was decomposed completely and nothing could be identified. 3-Nitrophenoxyacetone did not cleave, but was extracted to a greater degree than any of the methyl or the bromine substituted compounds; this must be due to the increased acidity of the compound caused by the inductive effect of the nitro group.

The results on the extraction experiments are given in Table I. The first column gives the percentage of the ketone remaining in benzene solution after three extractions with Claisen's alkali, the second the percentage extracted by Claisen's alkali but not cleaved by it, and the third the percentage of the ketone cleaved by Claisen's alkali. The procedure followed is described in the experimental part.

The results in the table show that the 4-bromo and the 3-nitro ketones are extracted by Claisen's alkali to a greater extent than the dimethyl ketones, and the solubility factor referred to above would probably operate in the opposite direction. These results must be due to the greater acidity of the compounds caused by the electron-attracting inductive effect of the bromine and the nitro groups substituted in the phenoxy group. The cleavage reaction shown by the 4-nitro ketones and the decomposition of the 2-nitro compounds in the presence of Claisen's alkali must be due to a resonance effect involving forms such as VIII and IX. If nothing but an inductive effect was operating, the 4-nitro compound should behave like the 3-nitro compound, except that the effect would be smaller in the former.

In order to study the cleavage reaction under more exactly defined conditions,

some rough quantitative tests were made of the cleavage reaction using 5% sodium methoxide in methanol. The procedure followed is described in the experimental part.

The poor recovery of material from 2-nitrophenoxyacetone was due to the fact that it formed a black material insoluble in ether. The results show that the 2,6-dimethyl-4-nitrophenoxyacetone is cleaved by sodium methoxide at a rate not much different from the unmethylated compound, while 2-nitrophenoxy-

TABLE I

EXTRACTION OF PHENOXYACETONES FROM BENZENE BY CLAISEN'S ALKALI

COMPOUND	% REMAINING IN BENZENE	% EXTRACTED WITHOUT CLEAVAGE	% CLEAVAGE
Phenoxyacetone[a]	77	19	1
4-Methylphenoxyacetone	86	9	0
2,4-Dimethylphenoxyacetone	86	2	4
2,6-Dimethylphenoxyacetone	90	3	1
4-Bromophenoxyacetone	86	14	1
2-Nitrophenoxyacetone	5	Only decomposition products	
3-Nitrophenoxyacetone	60	34	4
4-Nitrophenoxyacetone	29	1	56[b]
2-Nitro-4,6-dimethylphenoxyacetone	16	16	42[c]
4-Nitro-2,6-dimethylphenoxyacetone	84	—	8[d]

[a] Prepared by R. C. Mallatt. [b] *p*-Nitrophenol. [c] Red tar. [d] 2,6-Dimethyl-4-nitrophenol.

TABLE II

CLEAVAGE OF PHENOXYACETONES BY SODIUM METHOXIDE

COMPOUND	WEIGHT, G.	TIME	WEIGHT OF NEUTRAL MATERIAL, G.	WEIGHT OF ACIDIC MATERIAL, G.
4-Nitrophenoxyacetone	0.5	4.5 hrs.	0.28	0.14
2,6-Dimethyl-4-nitrophenoxyacetone	0.5	4.66 hrs.	0.34	0.09
2-Nitrophenoxyacetone	0.5	5 min.	0.01	0.03
4-Bromophenoxyacetone	0.6	19 hrs.	0.54	0.05

acetone is decomposed extremely rapidly under the same conditions. It is apparent that the steric inhibition of resonance which might be present in 2,6-dimethyl-4-nitrophenoxyacetone does not affect its properties very markedly compared to the unmethylated compound. In this connection it would be of considerable interest to compare the dissociation constants of 4-nitrophenoxyacetic acid and 2,6-dimethyl-4-nitrophenoxyacetic acid, because here the existence of damped resonance involving oxygen might be detected. Ingham and Hampson (19) found that the dipole moment of nitroethoxydurene was somewhat lower than that of *p*-nitroanisole, indicating damped resonance involving oxygen, but the effect was much smaller than with the nitroamino derivatives.

EXPERIMENTAL[2]

4-Methylphenoxyacetone (I). With chloroacetone and *p*-cresol in alcoholic sodium ethoxide and in aqueous sodium hydroxide, poor results were obtained (9), as was also the case with chloroacetone, sodium cresolate, and sodium iodide in acetone. Bromoacetone gave poor results in aqueous sodium hydroxide solution, and the most satisfactory method was found to be that of Calaway and Henze (10).

Thirty grams of bromoacetone in 25 cc. of benzene was added dropwise with stirring at room temperature to the sodium salt from 24 g. of *p*-cresol in 150 cc. of benzene. After refluxing for an hour on the steam-bath, the mixture was cooled, washed with water, with 10% sodium hydroxide solution, and the benzene solution concentrated on the steam-bath. The acidic material recovered from the sodium hydroxide washings amounted to 13.8 g. and was probably starting material. (In other runs, even with an excess of chloro- or bromo-acetone, considerable amounts of *p*-cresol were recovered. Fractionation failed to reveal any carbon alkylation product in the acidic portions and no haloacetone was recovered from the reaction mixture.) The benzene solution was shaken with saturated sodium bisulfite solution and allowed to stand several hours to complete the formation of the bisulfite addition product; this was isolated by filtration, washed with methanol, and the ketone recovered by heating the addition product with 15% sulfuric acid on the steam-bath for an hour. The yield of recovered ketone, b.p. 107–109° (5 mm.), n_D^{23} 1.5168, was 10 g. (27%). A forerun of 1 g. additional showed n_D^{23} 1.5160.

In another preparation carried out in essentially the same manner but omitting the formation of the bisulfite addition compound, 122 g. of *p*-cresol and 155 g. of bromoacetone yielded 69 g. (37%) of product, n_D^{25} 1.5162. The *p*-cresol recovered by distillation amounted to 55 g. (45%).

Preparation by ozonization. β-Methylallyl 4-methylphenyl ether (20) (10 g.) in 70 cc. of chloroform was ozonized for one hour, using a 40% excess of ozone. Saturated sodium bisulfite solution was added, the chloroform was evaporated off, and the bisulfite addition compound which formed on standing several hours was collected by filtration and washed several times with ether. The bisulfite addition compound was decomposed as above, yielding 2.7 g. of 4-methylphenoxyacetone.[3] Mixed melting point determinations showed that the semicarbazone of 4-methylphenoxyacetone prepared by ozonization was identical with that prepared by the method described above.

The *semicarbazone* of 4-methylphenoxyacetone crystallizes from methanol in shining white plates, m.p. 179–180°.

Anal.[4] Calc'd for $C_{11}H_{15}N_3O_2$: C, 59.7; H, 6.8.
Found: C, 59.6; H, 6.7.

Action of heat on 4-methylphenoxyacetone. 4-Methylphenoxyacetone, prepared from chloro- or bromo-acetone and not purified through the bisulfite compound, gave a vigorous decomposition reaction when heated at 200° for a few minutes. The liquid turned black, water was evolved, and *p*-cresol, identified as the phenylurethan, could be isolated from the reaction mixture by washing with sodium hydroxide solution. 4-Methylphenoxyacetone (1.21 g.), which had been purified through the bisulfite compound and freshly washed with sodium hydroxide solution, was heated for two and one-half hours at 250–260°. The dark product was cooled, taken up in ether, and extracted several times with 10% sodium hydroxide solution; the ether solution yielded 0.89 g. of neutral material which was shown to be starting material by preparation of the semicarbazone, identified by a mixed melting

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[2] All melting points corrected.

[3] Experiments of M. Insalacco indicate that better than 50% yields can be obtained in the ozonization by using ethyl acetate as solvent, and decomposing the ozonide with zinc and hydrochloric acid.

[4] Stoermer (21) reported that the b.p. of 4-methylphenoxyacetone was 255° and the m.p. of the semicarbazone was 187°, but gave no analyses.

point, in practically quantitative yield. Acidification and extraction of the alkaline solution gave 0.11 g. of viscous oil, which, on treatment with phenyl isocyanate and a drop of pyridine, gave 0.06 g. of crude phenylurethan of *p*-cresol. This product was recrystallized from petroleum ether, melting at 107–109°, mixed m.p. with a known sample, 107–111°. The ketone decomposes slowly on standing at room temperature, yielding alkali-soluble materials and giving a marked change in odor.

Preparation of 2-acetonyl-4-methylphenol. Five grams (0.031 mole) of 2-(β-methylallyl)-4-methylphenol (m.p. of *p*-nitrobenzoate 65–66°) (20) in 50 cc. of chloroform was ozonized for 25 minutes, using approximately 0.04 mole of ozone, and the ozonide decomposed with water. The semicarbazone of the product melted at 187–188° with decomposition after three recrystallizations from alcohol, and gave a depression when mixed with the semicarbazone of 4-methylphenoxyacetone.

Anal. Calc'd for $C_{11}H_{15}N_3O_2$: C, 59.7; H, 6.8.
Found: C, 59.7; H, 6.9.

2,6-Dimethylphenoxyacetone. Using the method described above, 30 g. of 2,6-dimethylphenol (0.25 mole), 5.64 g. of sodium (0.24 mole), and 48 g. (0.35 mole) of bromoacetone yielded 13.1 g. of crystalline starting material, and 5.5 g. of 2,6-dimethylphenoxyacetone. The product has the b.p. 110–113° (4 mm.), n_D^{20} 1.5097, and forms a semicarbazone, m.p. 163–165°. A sample which had stood for five weeks yielded crystalline 2,6-dimethylphenol when washed with sodium hydroxide solution. A sample (0.81 g.) of the purified ketone which had been heated at 200–205° for an hour yielded 0.15 g. of alkali-soluble material and 0.61 g. of starting material when worked up in the usual way.

Anal. (semicarbazone) Calc'd for $C_{12}H_{17}N_3O_2$: C, 61.3; H, 7.3.
Found: C, 60.8; H, 7.5.

2,4-Dimethylphenoxyacetone. 2,4-Dimethylphenol (30.5 g., 0.25 mole), 8 g. of sodium (0.35 mole), and 48 g. of bromoacetone (0.35 mole) yielded, following the usual procedure, 9.6 g. of the starting phenol, and 15.3 g. of 2,4-dimethylphenoxyacetone, b.p. 113–120° (5 mm.). When purified through the bisulfite compound, it had the following properties: b.p. 120° (6 mm.), n_D^{33} 1.5110, and formed a semicarbazone melting at 143–144.5° after recrystallization from dilute methanol.[5]

Anal. (semicarbazone) Calc'd for $C_{12}H_{17}N_3O_2$: C, 61.3; H, 7.3.
Found: C, 61.4; H, 7.3.

4-Bromophenoxyacetone. *p*-Bromophenol (34.6 g., 0.2 mole), 6.9 g. of sodium (0.3 mole), and 41 g. of bromoacetone (0.3 mole) yielded 17.3 g. of the starting phenol and 16.4 g. of 4-bromophenoxyacetone, b.p. 130–140° (6 mm.). The product crystallized on cooling, and when recrystallized from low-boiling petroleum ether, formed transparent rectangular plates, m.p. 42.5–44°.

Anal. Calc'd for $C_9H_9BrO_2$: C, 47.2; H, 4.0.
Found: C, 47.1; H, 4.0.

The *semicarbazone* was prepared and recrystallized from alcohol, melting at temperatures varying from 196° to 205° depending on the rate of heating.

Anal. Calc'd for $C_{10}H_{12}BrN_3O_2$: C, 42.0; H, 4.2.
Found: C, 42.0; H, 3.9.

2-Nitrophenoxyacetone. Potassium 2-nitrophenolate (17.7 g.), 9.3 g. of chloracetone, and 1.5 g. of sodium iodide were refluxed in 200 cc. of acetone for five hours. The solvent was evaporated, water was added, and the product taken up in ether. The ether solution was washed three times with 10% sodium hydroxide solution, which turned dark but yielded no solid on acidification. Ether extraction of this acid solution yielded a few grams of black tar. Evaporation of the ether yielded 11.7 g. of crystalline product, m.p. 65–66°; recrystallization from methanol-water gave 9.8 g., m.p. 67–69°. Stoermer (18) gave the m.p. as 69°.

3-Nitrophenoxyacetone. The sodium salt from 10 g. of 3-nitrophenol was prepared with

[5] Stoermer (ref. 21, p. 301) gave the b.p. of 2,4-dimethylphenoxyacetone as 263°, and the m.p. of the semicarbazone as 145°, but no analyses were reported.

sodium in methanol, and the dry salt was refluxed in 75 cc. of acetone with 6.7 g. of chloroacetone and a trace of sodium iodide for 7.5 hours. The reaction was worked up as described above, and 7 g. of crystalline product obtained, which, after washing with a little cold benzene and two recrystallizations from dilute methanol, melted at 79–81°.

Anal. Calc'd for $C_9H_9NO_4$: C, 55.4; H, 4.6.
Found: C, 55.2; H, 4.8.

Arnall (22) reported the melting point 83–84° but gave no analysis.

4-Nitrophenoxyacetone. Following the procedure described for 2-nitrophenoxyacetone, 16 g. of sodium 4-nitrophenolate, 9.3 g. of chloroacetone, and 1.5 g. of sodium iodide yielded 19.5 g. of 4-nitrophenoxyacetone, m.p. 74–80°. It was found that chloroform was a better solvent than ether for taking up the reaction product. The product was recrystallized from methanol, and 13.5 g. obtained, m.p. 79–81°. Stoermer (18) gives the m.p. as 81°. Aqueous sodium hydroxide does not dissolve the nitrophenoxyacetone (contrary to Stoermer's statement); 0.5 g. of the ketone was heated on the steam-bath for fifteen minutes with 10 cc. of 10% sodium hydroxide, and the solid removed by filtration after cooling; acidification of the filtrate gave no precipitate. In another experiment, 0.5 g. of the ketone dissolved in 10 cc. of ether was washed with three 10-cc. portions of 20% sodium hydroxide; acidification and extraction of the alkaline solution yielded only 0.02 g. of material.

2,4-Dimethyl-6-nitrophenol. To 3 g. of 2,4-dimethylphenol in 30 cc. of acetic acid kept in an ice-bath, a solution of 1.5 cc. of fuming nitric acid (sp. gr. 1.59) in 10 cc. of acetic acid was added dropwise. After the addition was complete, excess water was added to precipitate the product, and the mixture extracted several times with chloroform. The chloroform solution was steam-distilled and 2.2 g. of crystalline 2,4-dimethyl-6-nitrophenol isolated from the distillate by chloroform extraction. The pure product melts at 72° (23).

2,4-Dimethyl-6-nitrophenoxyacetone. The sodium salt from 2.12 g. of 2,4-dimethyl-6-nitrophenol was prepared with sodium in methanol and the dry salt treated with 1 cc. of chloroacetone and a trace of sodium iodide in acetone. The preparation was worked up as described above, and yielded 1.51 g. of crystalline 2,4-dimethyl-6-nitrophenoxyacetone; recrystallization from low-boiling petroleum ether yielded fine fiber-like crystals, m.p. 68–69°.

Anal. Calc'd for $C_{11}H_{13}NO_4$: C, 59.2; H, 5.9.
Found: C, 59.4; H, 6.0.

2,6-Dimethyl-4-nitrophenol. Numerous variations of the procedure of Auwers and Markovits (24) were tried, of which the following was the most satisfactory. One gram of 2,6-dimethylphenol dissolved in 5 cc. of acetic acid was added to 5 cc. of a solution made up as follows: 1 cc. of water, 20 cc. of acetic acid, and 3 cc. of fuming nitric acid (sp. gr. 1.59). When half of the phenol had been added, a red precipitate of the diphenoquinone (24) appeared; if instead, the nitric acid was added to the phenol, the quinone was formed with the addition of the first portion of acid. The reaction mixture was poured into excess water, and solid sodium carbonate added until the solution was distinctly alkaline. It was then filtered to remove the quinone, the filtrate acidified and the 2,6-dimethyl-4-nitrophenol (0.60 g.) collected by filtration. When recrystallized from dilute methanol, the phenol forms leaf-shaped crystals, m.p. 170–171.5°.

2,6-Dimethyl-4-nitrophenoxyacetone. The sodium salt from 2.47 g. of 2,6-dimethyl-4-nitrophenol was refluxed for two hours in 70 cc. of acetone with 1.37 g. of chloroacetone and 0.1 g. of sodium iodide. The reaction mixture was poured into excess water, and 1.63 g. of 2,6-dimethyl-4-nitrophenoxyacetone collected by filtration. From the filtrate 0.48 g. of the starting phenol was obtained on acidification. The yield of the phenoxyacetone obtained after recrystallization from methanol was 1.31 g., and the product melted at 111.5–113°.

Anal. Calc'd for $C_{11}H_{13}NO_4$: C, 59.2; H, 5.9.
Found: C, 59.4; H, 5.8.

The *semicarbazone* was prepared and crystallized twice from chloroform (in which it is only slightly soluble), m.p. 197–199° with decomposition.

The solubility of phenoxyacetones in Claisen's alkali. The phenoxyacetones were treated by the following general procedure: about 1 g. of the ketone in 50 cc. of benzene was extracted with three 10-cc. portions of Claisen's alkali, each portion of extract being run at once into excess dilute sulfuric acid. In some cases one-half of the above quantities of everything was used. [Claisen's alkali is prepared by dissolving 350 g. of potassium hydroxide in 250 cc. of water and diluting to 1000 cc. with methanol (13).] The acidified Claisen's alkali solution was extracted with ether and the ether solution washed with sodium hydroxide solution; any product contained in this alkaline solution (which would be the cleavage product) was obtained by acidification and extraction. As example of a blank test: 1.00 g. of 4-bromophenoxyacetone in 50 cc. of benzene was extracted with three 10-cc. portions of a mixture of 2 volumes of methanol and one of water. From the extract 0.02 g. was obtained, while with Claisen's alkali 0.14 g. was extracted (Table I).

The nitrophenols formed by cleavage were identified by mixed melting points. The ketones extracted by Claisen's alkali were transformed into the semicarbazones and mixed melting points were taken with the semicarbazones of the original ketones.

Action of sodium methoxide on phenoxyacetones. A given weight of the phenoxyacetone was dissolved in 30 cc. of 5% sodium methoxide in methanol and allowed to stand at room temperature for a definite time. The reaction mixture was then diluted with water, acidified with dilute sulfuric acid, extracted with ether and the ether extract washed with 10% sodium hydroxide to remove the phenol formed by cleavage. The phenol was recovered by the usual method. The ether solution was dried and evaporated to obtain the starting material; the identity of the nitrophenols formed by cleavage and of the neutral product was checked by melting point determinations. A small amount of *o*-nitrophenol seemed to be present in the mixture from 2-nitrophenoxyacetone, but it could not be characterized.

SUMMARY

Pure 4-methylphenoxyacetone and 2,6-dimethylphenoxyacetone do not rearrange on heating, although they do form a small amount of the corresponding phenol. Bromoacetone gives no C-alkylation when treated with the sodium salt of *p*-cresol in benzene. 4-Methylphenoxyacetone has been prepared by ozonization of β-methylallyl 4-methylphenyl ether, and 2-acetonyl-4-methylphenol by ozonization of 2-(β-methylallyl)-4-methylphenol.

The phenoxyacetones can be partially extracted from benzene or petroleum ether solution by Claisen's alkali. A series of substituted phenoxyacetones has been prepared including the following new ones: 2,6-dimethyl, 4-bromo, 2,6-dimethyl-4-nitro, and 2,4-dimethyl-6-nitro. The 4-nitro and 2,6-dimethyl-4-nitro compounds are cleaved by Claisen's alkali, giving the corresponding nitrophenols, while the 2-nitro and 2,4-dimethyl-6-nitro compounds are completely decomposed by Claisen's alkali. 3-Nitrophenoxyacetone is extracted from benzene without cleavage by Claisen's alkali, and its acidity is attributed to the increase of the electron-attracting effect of the phenoxy group by the nitro group, making the hydrogen on the carbon next to the ether oxygen more acidic.

The 4-nitro and the 2,6-dimethyl-4-nitro compounds are cleaved by sodium methoxide in methanol at room temperature at about the same rate, while the 2-nitro compound is decomposed very much more rapidly, and the 4-bromo compound is scarcely affected.

ROCHESTER, N. Y.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

MOLECULAR REARRANGEMENTS INVOLVING OPTICALLY ACTIVE RADICALS. XI. REARRANGEMENTS IN THE TRUXILLIC ACIDS AND THEIR BEARING UPON THEORIES OF MOLECULAR REARRANGEMENTS AND OPTICAL ROTATORY POWER

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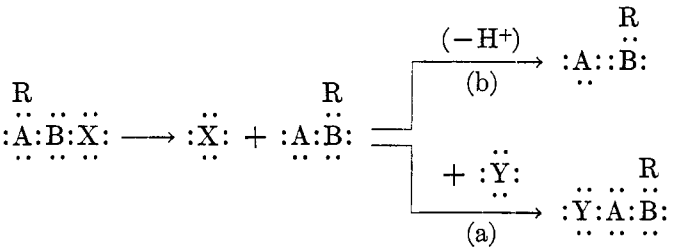
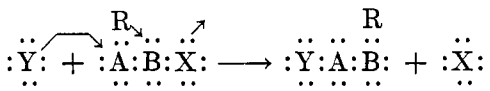
The modern electronic formulation for non-allylic molecular rearrangements as developed by Whitmore (1) may be illustrated by the following equation,

(I)



where A and B are atoms neither strongly electropositive nor electronegative, X and Y are strongly electronegative groups, and R is either an alkyl or aryl residue. The shifting of the group, R, follows simultaneously with the removal of $:\ddot{X}:$, R being apparently never completely free of either A or B (2). In rearrangements of the Wagner-Meerwein (retro-pinacolic) type, $:\ddot{Y}:$ may join the rearranged positive fragment (a), while in the pinacol rearrangement or in olefin formation, this fragment may lose a proton (b). It has also been pointed out (2 d, 3) that combination and rearrangement may be a single bimolecular process which can be formulated as follows,

(II)



analogous to substitution reactions of the S_N2 type (4), although at present there is no direct experimental evidence for this view.

Extensive studies in molecular rearrangements involving optically active groups have played an important role in the development and confirmation of the mechanism formulated in equation I. When R is an optically active group in which the asymmetric carbon atom is directly attached to A, it would be ex-

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pected on the basis of this mechanism to retain its complete activity. This has been shown to be true in earlier papers of this series (2 a, 5). Experimental studies have also shown that such a group not only retains its activity but also its configuration in conformity with an earlier suggestion in Part I (2 a) of this series. Thus, Noyes (6)[2] has shown in the *asymmetric* degradation of the camphoric acids that the rearrangement proceeds without inversion. A similar result has been obtained by Bartlett and Knox (8) in their studies of the Hofmann rearrangement involving hindered (bridge) systems, *i.e.*, the conversion of apocamphoric acid amide to the corresponding amine. A conclusive proof of this point for unhindered systems involving one asymmetric carbon atom is afforded in certain results (9) recently obtained in this laboratory on the Wolff rearrangement of optically active diazoketones.

For rearrangements of optically active molecules in which A is the asymmetric center, inversion or retention with more or less racemization would be expected from equation I, while inversion only should result from equation II. Experimental evidence is still somewhat confused. In certain studies (10) carried out in this laboratory of a retro-pinacolic type of rearrangement, partial racemization was observed. It should be noted, however, that this may have resulted from the unstable character of the tertiary chloride so produced. In considering the rearrangement of camphene hydrochloride to isobornyl chloride the results of kinetic studies are best explained by the bimolecular reaction of an intermediate positive camphene group and $P\,Cl^-$ where P is a chloride carrier such as H^+ or a phenol (3, 11). Thus, $R:\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}: \rightleftarrows R:\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}} + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}:$ is followed by the reaction

$$PCl^- + R:\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}} \rightarrow P + :\underset{\cdot\cdot}{\overset{Cl}{\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\underset{R}{B}}}:$$

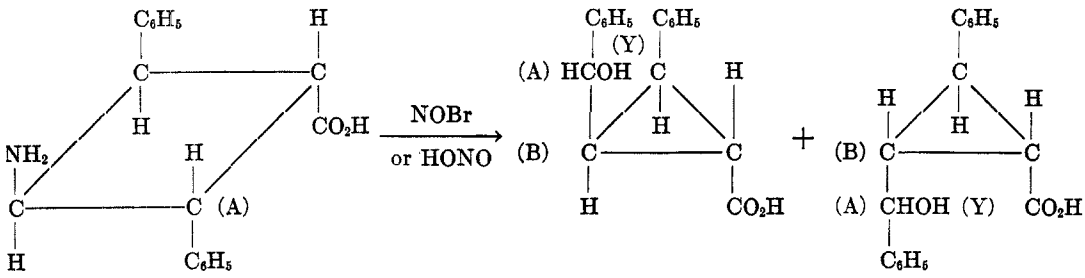
where the latter step, which is rate determining, is of the second order. It has been pointed out (3) that since bimolecular nucleophilic substitution reactions (4) occur with Walden inversion, inversion very probably occurs on the carbon atom holding the chlorine atom in isobornyl chloride.

The mechanism outlined above would also predict inversion of configuration involving carbon atom B. Kinetic studies (12) of the rearrangement of *cis*- and *trans*-7,8-diphenylacenaphthenediol-7,8 confirm this conclusion. Results of a similar nature were observed in kinetic studies (13) on the preparation of 2-indanone from both *cis*- and *trans*- indene glycol. Inversion of configuration has also been observed (14)[3] in the semipinacolic deamination of (−) 1,1-diphenyl-2-aminopropanol-1.

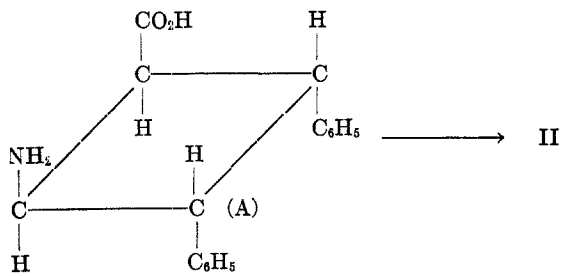
[2] Certain results of H. Fischer (7) obtained in the Curtius degradation of the amides of dihydroshikimic and quinic acids are of interest in this connection.

[3] In a recent paper by Kenyon and Young (*J. Chem. Soc.*, **1941**, 263), it is reported that (+) hydratropic azide is converted by the Curtius degradation into (−) α-phenylethylamine without appreciable racemization. We should like to point out at this time that this

In this paper we wish to present additional evidence for inversion at B. In part, this evidence has been obtained from a study of certain experimental researches of Stoermer and his co-workers (15) on the diazotization of the amino group in the truxillamic acids.[4] In an attempt to prepare certain hydroxyl derivatives of cyclobutane these investigators discovered that when the amino group in these acids was diazotized, a rearrangement occurred to give in each case various isomers of 1-carboxy-2-benzoxy-3-phenylcyclopropane, the configurations of which were determined. Thus,



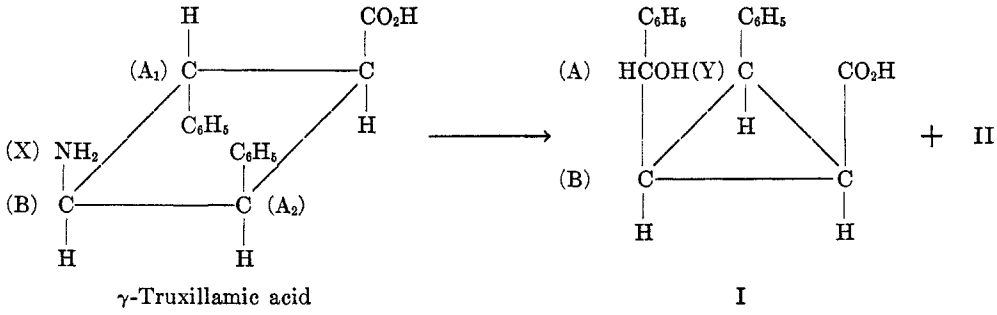
α-Truxillamic acid



β-Truxinamic acid

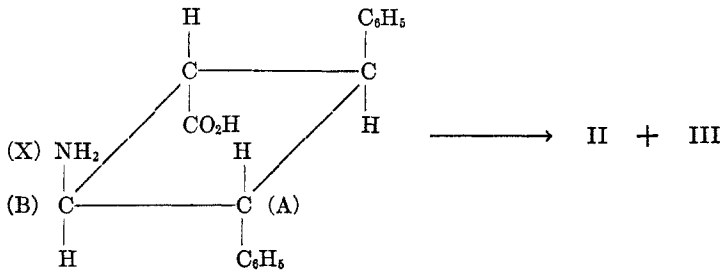
result is only a confirmation of the earlier work published from this laboratory in the first papers of this series. Moreover, for the particular molecule in question, the reaction was studied by Bernstein and Whitmore (14), reference to which was not made by Kenyon and Young. These investigators claim further to have submitted evidence to show that the course of the Beckmann transformation of optically active ketoximes is analogous to that of the Hofmann, Curtius, and Lossen rearrangements of related derivatives of optically active acids, a research project suggested by one of us in the title of Part I of this series. We find it regrettable that the investigation of Kenyon and Young has been conducted in so cursory a fashion as to permit no deductions concerning possible racemization during rearrangement. Indeed, it is not clear from these authors' experimental work whether optically pure starting materials were used, and granted that they were, no attempt was made to establish the degree of optical purity of the rearrangement product. We feel that the results of these authors must, therefore, be regarded as inconclusive and that a more precise investigation of the problem is necessary.

[4] These acids were prepared from the parent amido acid by the Hofmann degradation. In the light of our discussion on the asymmetric group, R, it is certain that the amino acids so produced are configurationally the same as the parent dibasic acids. The latter are well known. (See Rochussen and Niederländer in Richter's "Organic Chemistry", Nordemann Publishing Company, New York, **1939**, pp. 40–43.)

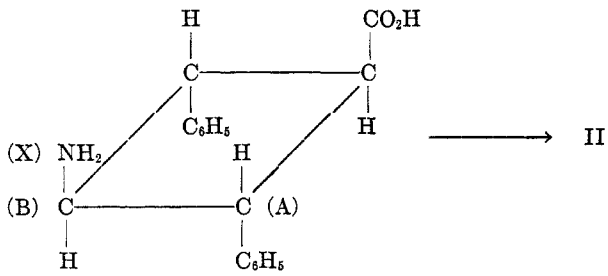


γ-Truxillamic acid

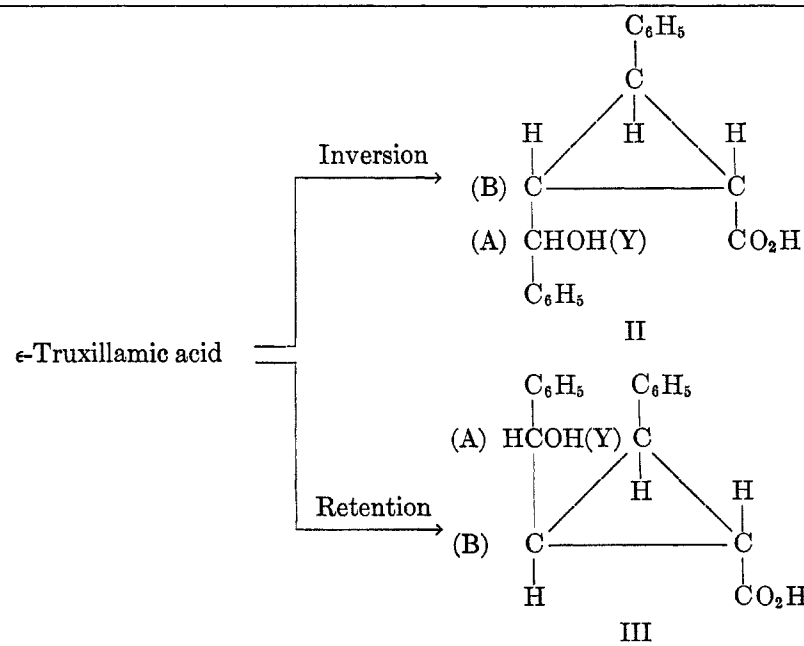
I



δ-Truxinamic acid



ϵ-Truxillamic acid



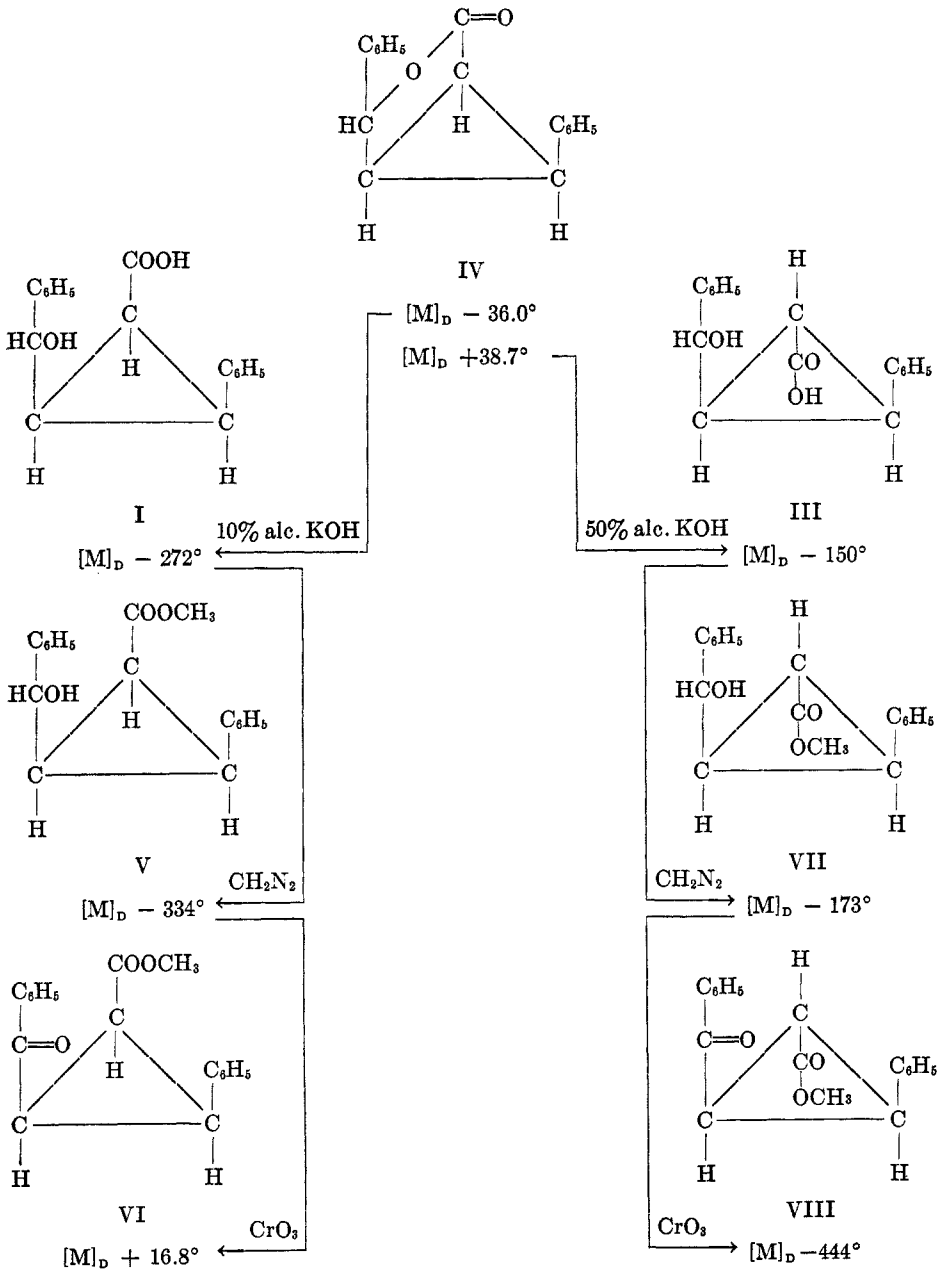
From a consideration of the spatial relationships involved, it can readily be seen that inversion or retention of configuration would lead to entirely different products. This is easily illustrated in the case of ϵ-truxillamic acid (see page 264.) Therefore, it is clear that with the β-, γ-, and ϵ-amino acids, all products of the rearrangement are the result of a rearward attack on the carbon atom holding the amino group. γ-Truxillamic acid yields both alcohols I and II because either a shift of the electron pair connecting the carbon atom, holding the carboxyl group, to the carbon atom holding the *trans* phenyl group, or a shift of the electron pair connecting the carboxyl-carbon atom to the one holding the *cis* phenyl group can take place. The β- and ϵ-amino acids having their phenyl groups *cis* to each other give only the one expected product.[5] In the rearrangement of α- and δ-amino acids, it is noted that two products, the same in each case, are also formed. Compound III which predominates results from an inversion of configuration. Compound II, found only in small quantities, is the product expected from a retention of configuration during rearrangement. Thus, a small amount of racemization occurs in these two cases at carbon atom B. This fact would suggest a small amount of preliminary ionization of R :A:B:X:. Indeed this has been suggested in some of the original formulations of this electronic theory (1, 2 a, 16) of rearrangements.

We now wish to describe the results of certain experiments that we have carried out, and that serve both as an extention and as a confirmation of the results of Stoermer and his co-workers (15). They also give information that is fundamental to the modern theory of optical rotatory power as applied to ring compounds (17). The rearrangement of γ-truxillamic acid was repeated using, however, both the *dextro* and *levo* forms of the optically active acid instead of the racemic modification. In our hands the (−) amino acid hydrochloride[6] yielded the pure (+) lactone (IV) of the (+) acid (I), while the (−) lactone was obtained when the (+) amino acid hydrochloride was diazotized with nitrosyl bromide. These facts are in accord with theory. It is also to be noted that with the optically active modifications no contamination of the products of rearrangement with diastereomers produced by racemization at either carbon atom A or B was observed. This also is as we might expect, since here we are carrying out the rearrangement under asymmetric conditions.

[5] It may be noted that Stoermer and his co-workers observed that the products I, II, and III as described above were always contaminated with small amounts of the corresponding diastereomer. These products, of course, result from a certain amount of racemization on carbon atom A.

[6] The (−) γ-truxillamic acid used in these experiments was prepared from the (+) γ-truxillamidic acid by a Hofmann degradation. The (+) amidic acid was obtained from the racemic compound by a simple resolution involving one crystallization of the morphine salt. The action of aqueous ammonia upon racemic γ-truxillic acid anhydride yielded the corresponding amide. The anhydride was made by refluxing α-truxillic acid with acetic anhydride. Certain difficulties were noted in the preparation of α-truxillic acid which will be discussed in a subsequent paper. The method finally used was essentially the same as that described by Kohler, *Am. Chem. J.*, **28**, 238 (1902).

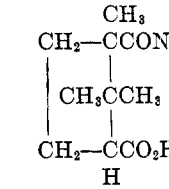
A number of reactions also were carried out starting with both the (+) and the (−) modifications of the lactone (IV). The results are listed in the accompanying chart, together with the molecular rotations of the various compounds which were prepared.



When these data are considered in terms of modern theory of optical rotatory power (17), the increase in the amount of rotation caused by the opening of the lactone ring is surprising, for Kauzmann and Eyring (17) have stated that "these influences which tend to restrict freedom of rotation and of orientation about bonds will tend to increase the order of magnitude of the optical activity." Thus, in general, hydroxy acids would be expected to have lower numerical

TABLE I

MOLECULAR ROTATIONS OF ACIDS AND THEIR CYCLIC DERIVATIVES

ACID	SOLVENT[a]	ACID $[M]_D$	ANHYDRIDE $[M]_D$	$(M_A)^-(M_A-H_2O)$[b]	REF
α-Isopropylglutaric	ether	(−) 27.5	(+) 5.6	+21.9	18
trans-Hexahydrophthalic	acetone	(+) 31.5	(−) 118.1	−86.6	19
trans-Δ^4-Tetrahydrophthalic	alcohol	(+) 196.0	(+) 10.0	+186	20
Camphoric	alcohol	(+) 192	(−) 14.0	+178	21
			Lactone		
2,2,3-Trimethyl-3[c]-cyclopentanol-1[c]-carboxylic	alcohol	(+) 87.5	(+) 13.1	+74.4	22
1,2,3-Trimethyl-3[c]-cyclopentanol-1[c]-carboxylic	alcohol	(+) 27.5	(−) 33.4	−5.9	23
α-(3-Methyl-3-cyclopentanol)-α,α-dimethylacetic	alcohol	(−) 6.5	(+) 29.5	−22.9	24
					
			Imide		
R = H	acetone	(+) 45	(−) 10.0	+35.1	21
n-C_5H_{11}	acetone	(+) 50.8	(+) 19.3	+31.5	
m-tolyl	acetone	(+) 89.0	(+) 47.0	+42.0	
α-naphthyl	acetone	(+) 24.2	(+) 80.7	−56.5	
β-naphthyl	acetone	(+) 210.9	(+) 55.2	+155.7	
			Lactam		
Aminocamphonanic	water	(−) 49.9	(−) 92.7	−42.8	25

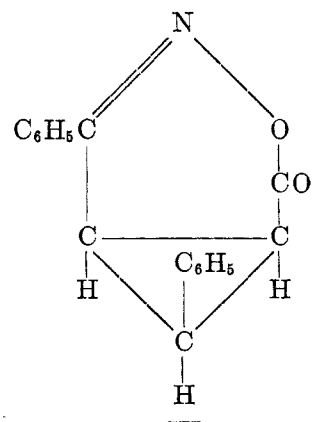
[a] Only compounds with which the rotations of both acid and anhydride have been taken in the same solvent are listed.

[b] Difference is numerical, not algebraic. The + indicates a higher value for the acid, the − for the anhydride.

molecular rotations than the corresponding lactones, since in the latter compounds rotation is more restricted. It is to be noted, however, that the examples given in Table I of their paper involve only the formation of monocyclic compounds from open chains, and that most of the substances listed are related to the sugars. Since in our case the noted exceptions involve the formation of a dicyclic system from a monocyclic derivative, it was thought pertinent to collect more data of this type. Some of these data are presented in Table I.

It is seen that in cases of this type the cyclization generalization of Kauzmann and Eyring (17) does not hold. It may be argued, however, that this failure does not affect the validity of the one electron theory of optical rotatory power, for if the rotatory power of the open chain compound be large, thus showing a considerable lack of asymmetry, cyclization would be much less likely to increase this asymmetry (26). It may be added that since monocyclic compounds, in general, have high rotations, which is in accord with theory, it is not surprising that shifts in rotation would be random on formation of the second ring.

In this connection it is of interest to consider another principle. It is seen from our experimental data that the (−) acid (I) is closely related configurationally to the (+) acid (III), the action of strong alkali converting the former compound into the latter. Since these two acids are so similar, one might think it possible to apply a principle analogous to the Freudenberg displacement rule (27) in order to demonstrate the configurational relationships involved. However, this can not be done. Although conversion of the acids to their respective keto esters causes a decrease in $[M]_D$, esterification of (I) results in a decrease in rotation, whereas the same reaction applied to (III) causes an increase. It is thus seen that no quantitative relationship in the shifts of the molecular rotations with similar chemical changes can be established. This is probably due to the close proximity (28) of the groups to each other. Indeed, this closeness of the groups attached to different carbon atoms in the cyclopropane ring is shown by the ease with which acid (I) is converted into its lactone (IV). If one acidifies the sodium salt of the acid with sulfuric acid, the lactone is produced on crystallization, no matter what the conditions are for carrying out the process. Only when hydrochloric acid is used does one get the hydroxy acid itself. Furthermore, under certain conditions the action of diazomethane brings about a dehydration to the lactone, a phenomenon that has also been observed in the sugars (29) and in folded rings of the bicyclo-(1,2,2)-heptane series (30). Finally, it may be noted that the keto ester (VI) is unusual in its behavior. Although actually a γ-keto ester, its reaction with hydroxylamine hydrochloride is similar to that undergone by 3-keto esters in the preparation of isoxazolones. Instead of an oxime, a cyclic dihydroörthoxazine derivative (IX) is produced, again indicating the closeness of groups on adjacent carbon atoms in the cyclopropane nucleus.



IX

EXPERIMENTAL

Preparation of (+) and (−) γ-truxillamidic acids. The optically active acids were prepared from the racemic modification by the method of Stoermer and Fretwurst (31). Racemic-γ-truxillamidic acid, m.p. 233–236°, was prepared in 75% yield according to the directions of these authors from α-truxillic acid, m.p. 274–276° (decomp.), which in turn, was prepared in 35% yield by the method of Kohler[6] from cinnamylidene malonic acid (32), m.p. 196–200°. From 18.7 g. of racemic acid was obtained 7.7 g. of (−) γ-truxillamidic acid, $[\alpha]_D^{20}$ −7° (*c* = 0.76, acetic acid), m.p. 254–256° when placed in the bath at 243°, and also 5.6 g. of (+) γ-truxillamidic acid, $[\alpha]_D^{20}$ +8° (*c* = 0.75, acetic acid). Stoermer and Fretwurst (31) report for the (−) acid $[\alpha]_D^{20}$ −11° (*c* = 0.70, acetic acid). In view of the inaccuracies attending the determination of this constant for a substance of such low rotatory power and slight solubility, we do not regard the discrepancy as serious. Moreover, the character of the products obtained from reactions of the acid which are subsequently to be described, indicated that it was essentially optically pure.

Preparation of (−) γ-truxillamic acid. This acid was prepared by a method analogous to that of Stoermer (15) for the preparation of the racemic acid. To 10.3 g. of (+) γ-truxillamidic acid was added 145 cc. of 0.5 *N* sodium hypochlorite solution. The reaction mixture was kept at 38–40° for two hours. At the end of this time it was cooled to room temperature, neutralized with dilute hydrochloric acid, and finally made just basic to litmus with dilute sodium hydroxide solution. The solution was filtered to remove a very small amount of insoluble material (m.p. 200–225°), and carbon dioxide was then passed through the filtrate until a precipitate began to form (at this point, if too much sodium hydroxide solution had been added, it was sometimes necessary to add a few drops of hydrochloric acid to induce precipitation). Carbon dioxide was passed through the solution for an additional hour, after which time 7.7 g. of pure (−) γ-truxillamic acid had separated. The product melted at 211–214° (decomp.) when placed in the bath at 200° and was insoluble in most solvents. Acidification of the aqueous mother liquor produced a white precipitate, which after recrystallization melted at 250° (decomp.) and was shown by a mixed melting point determination to be unchanged (+) γ-truxillamidic acid. Similar treatment of (−) γ-truxillamidic acid gave (+) γ-truxillamidic acid in 65% yield.

A small portion of the (−) amino acid on recrystallization from dilute hydrochloric acid was converted to the corresponding hydrochloride, m.p. 268° (decomp.); $[\alpha]_{6563}^{20}$ −16.6°, $[\alpha]_{5893}^{20}$ −22.7°, $[\alpha]_{5463}^{20}$ −28.8° (*c* = 1.145, methyl alcohol). From the analysis it is apparent that the crystalline salt contains one molecule of water of crystallization.

Anal. Calc'd for $C_{17}H_{18}ClNO_2$: C, 67.24; H, 5.94; N, 4.61.
Calc'd for $C_{17}H_{18}ClNO_2 \cdot H_2O$: C, 63.46; H, 6.28; N, 4.35.
Found: C, 63.90; H, 6.33; N, 4.28.

The (−) amino acid hydrochloride was readily converted to the corresponding methyl ester on being refluxed for three hours in a methyl alcoholic solution of hydrogen chloride. The ester, after recrystallization from methyl alcohol, melted at 269° (decomp.) when placed in the bath at 250°; $[\alpha]_{6563}^{20}$ −24.7°, $[\alpha]_{5893}^{20}$ −29.6°, $[\alpha]_{5463}^{20}$ −36.8° (*c* = 1.12, methyl alcohol).

Anal. Calc'd for $C_{18}H_{20}ClNO_2$: C, 68.05; H, 6.30; N, 4.41.
Found: C, 68.03; H, 6.27; N, 4.48.

Rearrangement of (+) γ-truxillamic acid to the lactone (IV). To 7 g. of (+) γ-truxillamic acid just covered with ether in an ice-salt-bath, was slowly added a solution of nitrosyl bromide [prepared by passing nitric oxide (33) into 200 cc. of dry ether containing 5.6 g. of bromine at −5°]. During the addition the temperature was kept below −5°. Vigorous evolution of nitrogen attended the addition of the first 100 cc. of solution, but the remainder could be added rather rapidly without an appreciable increase in temperature. When the evolution of nitrogen had ceased (about one hour after addition was complete), the white needles which had formed were removed by filtration, washed with ether, and dried: m.p. 133–135°. The dark brown ether solution was shaken with sodium bisulfite until colorless. The bisulfite layer was then extracted with ether and the combined ether extracts washed with dilute sodium carbonate. The carbonate layer was extracted with ether, and the

united ether extracts were dried over anhydrous potassium carbonate. On evaporation of the ethereal solution to a volume of 20 cc., an additional crop of crystals, m.p. 133–135°, was obtained. Finally the ether was removed from the mother liquor. The oil so obtained partially solidified on standing. The crystals were separated from the oil by filtration and washed with a small amount of ether. The three crops of crystals were united and recrystallized from benzene-petroleum ether (b.p. 60–75°) to give 3.08 g. of a pure product, m.p. 139°; $[\alpha]^{20}_{6563}$ −10.2°, $[\alpha]^{20}_{5893}$ −14.4°, $[\alpha]^{20}_{5463}$ −19.5°, $[M]^{20}_{D}$ −36.0° (c = 1.07, methyl alcohol); $[\alpha]^{20}_{6563}$ +30.6°, $[\alpha]^{20}_{5893}$ +35.2°, $[\alpha]^{20}_{5463}$ +41.8° (c = 1.05, benzene).

Anal. Calc'd for $C_{17}H_{14}O_2$: C, 81.59; H, 5.65.
Found: C, 81.8; H, 5.68.

Similar treatment of (−) γ-truxillamic acid gave the (+) lactone in 43% yield, m.p. 138°; $[\alpha]^{20}_{6563}$ +11.2° $[\alpha]^{20}_{5893}$ +15.5°; $[\alpha]^{20}_{5463}$ +19.6°, $[M]^{20}_{D}$ +38.7° (c = 1.25, methyl alcohol). Mixed m.p. of the (+) and (−) lactones 129–131°.

Preparation of 1^c-carboxy-2^c-benzoxyl-3^c-phenylcyclopropane (I). A mixture of 1.15 g. of the (−) lactone (IV) and 8 cc. of 10% alcoholic potassium hydroxide was heated for one minute longer than necessary to effect complete solution. It was then diluted with 35 cc. of water and filtered. The filtrate was carefully neutralized with dilute hydrochloric acid and the resulting precipitate separated by filtration, washed thoroughly with water, and dried. After two recrystallizations from benzene the product melted at 150° (decomp.) when placed in the bath at 141°; $[\alpha]^{20}_{6563}$ −78.4°, $[\alpha]^{20}_{5893}$ −101.4°, $[\alpha]^{20}_{5463}$ −121.4°, $[M]^{20}_{D}$ −272° (c = 1.02, methyl alcohol).

Anal. Calc'd for $C_{17}H_{16}O_3$: C, 76.14; H, 5.97.
Found: C, 75.80; H, 6.14.

Similar treatment of the (+) lactone (IV) gave the hydroxy acid (I) m.p. 146°; $[\alpha]^{20}_{6563}$ +75.4°, $[\alpha]^{20}_{5893}$ +96.6°, $[\alpha]^{20}_{5463}$ +116.6°, $[M]^{20}_{D}$ −259° (c = 1.18, methyl alcohol).

Action of diazomethane on the hydroxy acid (I). To a methyl alcoholic solution of the (−) acid (I) at the temperature of an ice-salt mixture was added slowly and with shaking an ethereal solution of diazomethane (34) until no more nitrogen was evolved, and the yellow color due to a slight excess of diazomethane was permanent. The solution was removed from the ice-salt-bath, allowed to stand for thirty minutes, and evaporated to dryness.

The residue was recrystallized from aqueous methyl alcohol: m.p. 137–139°; $[\alpha]^{20}_{6563}$ −10.6°, $[\alpha]^{20}_{5893}$ −14.9°, $[\alpha]^{20}_{5463}$ −20.1° (c = 1.04, methyl alcohol); mixed m.p. with the (−) lactone (IV) 137–139°. The same result was obtained when the foregoing operations were repeated, and also when an ethereal solution of diazomethane, distilled from anhydrous potassium hydroxide just before use, was employed.

In another experiment a solution of the acid was prepared in 20 cc. of methyl alcohol containing 5 drops of water, and to it was added according to the procedure described above, a distilled ethereal solution of diazomethane. The product so obtained was recrystallized from benzene-petroleum ether: m.p. 145° (decomp.); $[\alpha]^{20}_{6563}$ −89.4°, $[\alpha]^{20}_{5893}$ −118.5°, $[\alpha]^{20}_{5463}$ −141.7°, $[M]^{20}_{D}$ −334° (c = 1.27, methyl alcohol). By analysis and subsequent oxidation this product was proved to be the desired (−) methyl ester (V).

Anal. Calc'd for $C_{18}H_{18}O_3$: C, 76.60; H, 6.39.
Found: C, 76.80; H, 6.54.

The same product was obtained by the addition of ethereal diazomethane to an anhydrous ethereal solution of the acid, but the reaction was much slower.

In another experiment careful trituration with boiling petroleum ether (b.p. 60–75°) of the crude product resulting from the treatment of the (+) acid (I) in methyl alcoholic solution as described above, permitted separation of this product into two fractions. The more insoluble of these melted at 146° and was the desired (+) ester (V): $[\alpha]^{20}_{6563}$ +95°, $[\alpha]^{20}_{5893}$ +127°, $[\alpha]^{20}_{5463}$ +140°, $[M]^{20}_{D}$ +358° (c = 0.295, methyl alcohol).

Anal. Calc'd for $C_{18}H_{18}O_3$: C, 76.60; H, 6.39.
Found: C, 76.77; H, 6.39.

The more insoluble fraction melted at 115°. Analysis and specific rotation indicated

that it was an equimolar mixture of the lactone (IV) with the ester (V): $[\alpha]^{20}_{6563}$ +53.6°, $[\alpha]^{20}_{5893}$ +73.1°, $[\alpha]^{20}_{5463}$ +87.9° (c = 0.673, methyl alcohol).

Anal. Calc'd for $C_{18}H_{18}O_3 \cdot C_{17}H_{14}O_2$: C, 78.90; H, 6.06.
Found: C, 78.78; H, 6.22.

Preparation of the (+) methyl ester (VI) of 1^c-carboxy-2^c-benzoyl-3^c-cyclopropane. To 480 mg. of the (−) methyl ester (V) was added 250 mg. of chromic oxide in 5 cc. of glacial acetic acid. The mixture was cooled slightly at first and then allowed to stand at room temperature with frequent shaking for forty-eight hours. At the end of this time 60 cc. of water was added, causing the formation of a precipitate. The mixture was extracted with ether and the ether extract washed with sodium carbonate solution and dried over anhydrous sodium sulfate. Evaporation of the solution to a volume of 8 cc. followed by the addition of petroleum ether (b.p. 60–75°) caused the precipitation of a crystalline product, m.p. 95–110°. One recrystallization from ether gave the pure keto ester (VI): m.p. 109°; $[\alpha]^{20}_{6563}$ +5.4°, $[\alpha]^{20}_{5893}$ +6.0°; $[\alpha]^{20}_{5463}$ +7.21, $[M]^{20}_{D}$ +16.8° (c = 0.833, methyl alcohol).

Anal. Calc'd for $C_{18}H_{16}O_3$: C, 77.16; H, 5.72.
Found: C, 77.11; H, 5.61.

Preparation of the (+) dihydroörthoxazine (IX) of the (+) keto ester (VI). The (+) keto ester (VI) was refluxed for one day in 15 cc. of ethyl alcohol containing an excess of hydroxylamine hydrochloride. On cooling, the solution deposited long white needles, m.p. 177–179°. One recrystallization from methyl alcohol gave a product melting at 180°; $[\alpha]^{20}_{6563}$ +177°, $[\alpha]^{20}_{5893}$ +226°, $[\alpha]^{20}_{5463}$ +271°, $[M]^{20}_{D}$ +595° (c = 0.223, methyl alcohol). The analysis indicated that the product was a dihydroörthoxazine rather than an oxime:

Anal. Calc'd for $C_{18}H_{16}NO_3$: C, 73.21; H, 5.81; N, 4.74.
Calc'd for $C_{17}H_{13}NO_2$: C, 77.56; H, 4.99; N, 5.32.
Found: C, 77.87; H, 4.95; N, 5.25.

Preparation of 1^t-carboxy-2^c-benzoxyl-3^c-phenylcyclopropane (III). A solution of 900 mg. of the (−) lactone (IV) in 8 g. of 50% alcoholic potassium hydroxide was refluxed for ninety minutes and then evaporated almost to dryness. The residue was taken up in water, and the clear aqueous solution was acidified with dilute hydrochloric acid. The precipitate which resulted was recrystallized three times from dilute alcohol: m.p. 160° (decomp.); $[\alpha]^{20}_{6563}$ +43.2°, $[\alpha]^{20}_{5893}$ +56.4°, $[\alpha]^{20}_{5463}$ +68.3°, $[M]^{20}_{D}$ +151° (c = 1.13, methyl alcohol).

Anal. Calc'd for $C_{17}H_{16}O_3$: C, 76.14; H, 5.97.
Found: C, 76.13; H, 5.92.

Similar treatment of the (+) lactone (IV) gave the corresponding (−) acid (III): m.p. 161–162° (decomp.); $[\alpha]^{20}_{6563}$ −43.3°; $[\alpha]^{20}_{5893}$ −56.0°, $[\alpha]^{20}_{5463}$ −67.8° $[M]^{20}_{D}$ −150° (c = 1.10, methyl, alcohol).

Esterification of these acids with diazomethane gave the corresponding methyl esters (VII) as oils.

Methyl ester of the (+) acid, $[\alpha]^{20}_{6563}$ +47.3°, $[\alpha]^{20}_{5893}$ +60.6°, $[\alpha]^{20}_{5463}$ +73.2°, $[M]^{20}_{D}$ = +171° (c = 2.15, methyl alcohol).

Methyl ester of the (−) acid, $[\alpha]^{20}_{6563}$ −47.4°, $[\alpha]^{20}_{5893}$ −61.4°, $[\alpha]^{20}_{5463}$ −74.9°, $[M]^{20}_{D}$ −173° (c = 1.19, methyl alcohol).

Methyl alcoholic solutions of the (+) and (−) esters were mixed to give a solution of zero rotation. Evaporation of this solution gave the racemic ester, which after one recrystallization from ether-petroleum ether melted at 75° (Stoermer (15) reports m.p. 76°).

Preparation of the (−) methyl ester (VIII) of 1-carboxy-2-benzoyl-3-phenylcyclopropane. To the methyl ester (VII) prepared from 500 mg. of the (+) lactone (IV) was added a solution of 250 mg. of chromic oxide in 12 cc. of acetic acid. The mixture was heated on the steam-bath until the solution became green and was then diluted with 60 cc. of water. The resulting oil was extracted from the mixture with ether. The ether extract was washed with sodium carbonate solution and dried over anhydrous sodium sulfate. On evaporation of the ethereal solution an oil was obtained which was dissolved in 5 cc. of methyl alcohol and decolorized with animal charcoal. Evaporation to dryness of the clear solution so obtained gave an oil which gradually became crystalline. After one recrystallization from

ether-petroleum ether the product melted at 85°; $[\alpha]^{20}_{6563}$ −121.2°, $[\alpha]^{20}_{5893}$ −158.6°, $[\alpha]^{20}_{5463}$ −192.5°, $[M]^{20}_{D}$ −444° (c = 0.974, methyl alcohol).

Anal. Calc'd for $C_{18}H_{16}O_3$: C, 77.16; H, 5.72.
Found: C, 77.07; H, 5.63.

In conclusion we wish to thank the National Research Council for the grant of a fellowship to one of us for the year 1940–1941, and Merck and Co., Inc., Rahway, N. J., for the analyses published in this paper.

SUMMARY

(+) γ-Truxillamic acid has been shown to yield, on treatment with nitrosyl bromide, the (−) lactone of (−) 1^c-carboxy-α^c-benzoxyl-3^c-phenylcyclopropane. This result and other examples of Walden inversion attending the conversion of truxillamic and truxinamic acids to 1-carboxy-2-benzoxyl-3-phenylcyclopropanes are considered in terms of the electronic theory of molecular rearrangements.

The direction of the shift in optical rotatory power in the formation of dicyclic lactones, imides, and lactams from the corresponding monocyclic acids has been shown to be random. This behavior is discussed in the light of newer theories of optical rotatory power.

The preparation and certain reactions of the optically active *cis*- and *trans*-1-carboxy-2^c-benzoxyl-3^c-phenylcyclopropanes are described.

PRINCETON, N. J.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

THE BROMO DERIVATIVES OF 1,4-DIMESITYLBUTANE-1,2,4-TRIONE ENOL

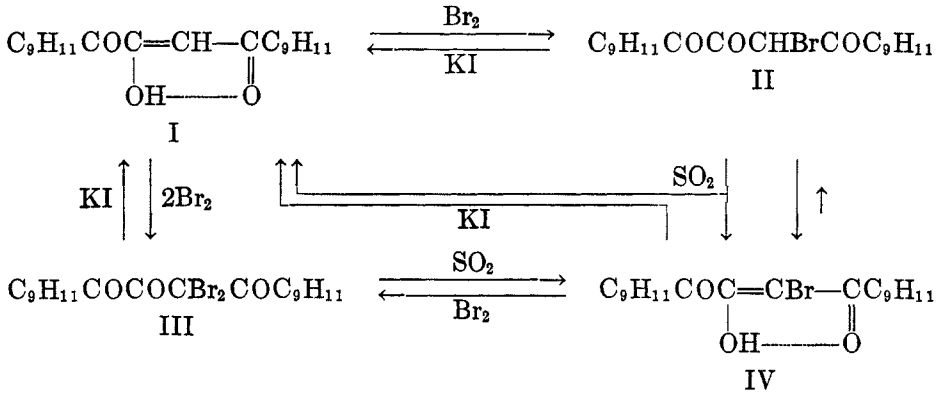
ROBERT E. LUTZ AND DANIEL H. TERRY[1]

Received January 14, 1942

This series of compounds, where cyclization to the hydroxyfuranone is blocked effectively by the steric hindrance of the mesityl groups, has been made in order to determine the effect of substitution of halogen on the 1,2,4-triketone-enol equilibrium.

The bromination of the triketone enol (I) in ethanol at −15° proceeded 23 per cent beyond one equivalent within a one-second interval between addition of an excess of bromine and the β-naphthol to stop further reaction; the absorption of the second molecule of bromine proceeded 57% in twenty seconds, 69% in thirty seconds, and was practically complete within five minutes. It was evident from these experiments that an easily enolizable bromo triketone (II) was the chief initial product of the reaction.

When exactly one equivalent of bromine was added to the enol under the above described conditions, the product consisted chiefly of the monobromo compound (II–IV); but along with this, small amounts of the dibromo derivative (III) and unchanged material (I) always could be isolated. This procedure therefore was unsuitable for the preparation of pure monobromo derivative. However, the dibromo derivative (III) could be obtained in good yield under these conditions by using a slight excess of two equivalents of bromine.



The monobromo derivative was best prepared by bromination in chloroform or carbon tetrachloride, where the reaction proceeded slowly and with a sharp demarkation between mono- and di-bromination. The product was found to

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consist chiefly of the labile bromo triketone (II). We were unable to free this compound completely from the enol form (IV) to which it rearranges with great facility, and we were unable to characterize it adequately. However, its existence in an impure state was demonstrated by the K. Meyer titrations, which indicated 30% enolization. Upon standing, slowly in the solid state or in solution and rapidly in electrolytic solvents, it underwent rearrangement to an equilibrium mixture which was shown by subsequent K. Meyer titrations to be approximately 80% enolized.

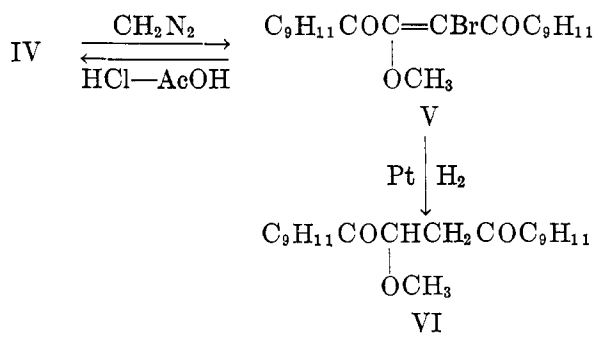
The pure monobromo enol (IV) was best obtained by acidification of the sodium salt. It gave a deep red color with alcoholic ferric chloride, reacted readily with diazomethane, and showed a high degree of acidity by reacting with sodium carbonate. Fresh samples were shown by the K. Meyer titration to be nearly completely enolized, and they reacted with an excess of bromine under these conditions to give the dibromo triketone (III). Samples of the enol after standing for several weeks showed a small but definite lowering in the percentage enolization to approximately 80%.

It is noteworthy that in this series, as expected, there is no evidence of cyclization to the hydroxyfuranone.

All three bromo compounds (II, III, and IV) were easily reduced by potassium iodide in acetic acid, in contrast with the diphenyl anologs where the last halogen was more difficult to remove because of cyclization to the hydroxyfuranone.

The reduction of the dibromo triketone (III) to the monobromo enol (IV) could be effected by means of sulfur dioxide. The monobromo triketone under similar conditions was converted into a mixture of the unsubstituted enol (I) and the monobromo triketone enol (IV) which evidently is unreactive under these conditions, as would be expected.

The bromo triketone enol (IV) reacted with diazomethane to give two methyl ethers, both of which could be hydrolyzed back to the enol by means of hydrochloric and acetic acids. One of these ethers was obtained in only very small amounts and was not studied further. The other, obtained in 71% yield, was shown to have the structure V as follows. Ozonization gave mesitylglyoxylic methyl ester and mesitoic acid; and catalytic reduction gave the non-crystalline dimesitylmethoxybutanedione (VI) which was characterized by pyrolysis to dimesitoylethylene (1).



From the above experiments it is evident that the bromination of the dimesitylbutanetrione enol (1) resembles the bromination of the enols of oxalylacetic ester, oxalylacetone, and oxalylacetophenone (2), and lies intermediate between the bromination of ordinary aliphatic enols and phenols. Furthermore, the substitution of a bromine atom affects the triketone-enol tautomerism in such a way as to diminish the preponderant stability of the enol form and to make possible the isolation of an unstable keto form.

EXPERIMENTAL

1,4-Dimesitylbutanetrione enol. The K. Meyer brominations described in the introduction were made in 95% ethanol at −15°, with addition of β-naphthol to stop the reactions after the time intervals noted. The titrations were carried out by adding potassium iodide and dilute hydrochloric acid, warming to 40° for 15 min., and titrating with sodium thiosulfate, using starch solution on a spot plate to determine the end point. Check runs were first made on acetoacetic ester and dibenzoylmethane. The following are some typical experiments:

1,4-DIMESITYLBUTANETRIONE ENOL (I)		BROMODIMESITYLBUTANETRIONE (II)	
Time in seconds*	Moles of I_2 lib. by KI	Time in seconds*	Moles of I_2 lib. by KI
1	1.23	1	1.36
2	1.30	3	1.42
10	1.54	60	1.73
30	1.69	600	1.89
120	1.84		
300	1.96		

* Between addition of bromine and β-naphthol to stop the reaction.

Samples of the bromo triketone (II) were (a) allowed to stand in the crystalline condition for three weeks, refluxed in 95% ethanol (b) for three hours and (c) for four hours, and (d) fused at 110–115° for fifteen minutes. Titration by the K. Meyer method as described above gave the following values for iodine liberated (in moles): (a) 1.67; (b) 1.76; (c) 1.82; and (d) 1.72.

A sample of the bromo enol (IV), freshly prepared and titrated immediately by the K. Meyer method, showed liberation of 1.98 moles of iodine. Samples allowed to stand in the crystalline condition for one, two, and three weeks and similarly titrated, showed liberation, respectively, of 1.91, 1.87, and 1.81 moles of iodine.

3-Bromo-1,4-dimesityl-1,2,4-butanetrione (II). A study of the bromination of dimesitylbutanetrione enol (I) under a variety of conditions led to the following procedures through which the production of the dibromo triketone was minimized.

One equivalent (2.38 g.) of bromine in carbon tetrachloride was added dropwise to a mechanically stirred carbon tetrachloride solution of 5 g. of the triketone enol (I) at 0°. When the color of the added bromine became distinct and persisted, the solvent was evaporated under reduced pressure. The residue was digested in conc'd acetic acid at 60° for 15 min. in order to dissolve out all of the monobromo compound. The dibromo triketone remained as an insoluble residue which was removed by filtration. On cooling the filtrate, 5.6 g. of nearly pure bromo triketone was obtained; m.p. 104–105°.

Products of nearly equal purity but in poorer yields were isolated in two similar procedures in which ethanol and conc'd acetic acid respectively were used as solvents instead of carbon tetrachloride. In the former case the product was precipitated by addition of small pieces of ice, and was then recrystallized. In the latter case, after filtering out the small

amount of dibromo triketone which crystallized, the monobromo triketone was precipitated by dropwise addition of water.

The monobromo triketone was purified by repeated crystallization from ethanol and from conc'd acetic acid. The yellow crystals melted at 105.5–106°.

Anal. Calc'd for $C_{22}H_{23}BrO_2$; Br, 19.0. Found: Br, 18.7.

The purest samples gave a pale red color with alcoholic ferric chloride; on standing, this color deepened to a purple. A sample which had been standing in the solid state for several weeks gave an immediate deep red or maroon color in the ferric chloride test.

Reduction of the monobromo triketone was accomplished in two ways.

(a) Sulfur dioxide was passed for one hour through an ethanol solution of 0.5 g. of the bromo triketone at room temperature. The solution was evaporated and the residual mixture extracted with ether. Upon shaking the ether solution with 5% sodium carbonate solution, 0.22 g. of the yellow sodium salt of dimesitylbutanetrione enol precipitated. From this upon acidification, 0.2 g. of the enol (I) was liberated and identified by mixture melting point. From the ether solution 0.21 g. of the monobromo triketone enol was recovered.

(b) A sample of the monobromo triketone in conc'd acetic acid was treated with potassium iodide. Iodine was liberated rapidly and upon dilution with water and addition of aqueous sodium bisulfite solution, the enol (I) was obtained in quantitative yield and identified.

3-Bromo-1,4-dimesityl-1,2,4-butanetrione enol (IV). A solution of 1.19 g. of bromine (one equivalent) in 20 cc. of chloroform was added dropwise to a mechanically stirred chloroform solution of 2.5 g. of the enol (I) at 15°. Aqueous sodium bisulfite solution was added to ensure removal of any excess bromine, and the chloroform solution was then washed several times with water. Evaporation under reduced pressure gave a yellow crystalline residue which was dissolved in ether. The ether solution was subjected to eight extractions with aqueous 5% sodium carbonate which removed all of the unchanged enol (I) and the monobromo enol (IV). The unchanged material, the enol (I), separated as the yellow sodium salt and was filtered and washed with water; acidification gave 0.22 g. of the enol (I) melting at 103–105°. The ether solution upon evaporation gave 0.07 g. of bright yellow crystalline dibromo triketone (III) which melted at 146–149°. The sodium carbonate solution was acidified and 2.43 g. of the monobromo enol (IV) separated as a yellow crystalline precipitate (m.p. 101–103°). Repeated crystallization from ethanol raised the melting point to 106.5–107.5°.

Anal. Calc'd for $C_{22}H_{23}BrO_2$: Br, 19.0. Found: Br, 19.3.

The monobromo enol (IV) gave a deep red color when treated with 1% ferric chloride in ethanol. The compound was stable and could be recovered unchanged after treatment for three hours with boiling ethanol, and for one hour in the presence of a small amount of added conc'd hydrobromic-acetic acid.

The compound was soluble in 5% aqueous sodium hydroxide or carbonate. The sodium salt proved to be very soluble in aqueous media, but could be extracted from 5% sodium carbonate by means of ethyl acetate, from which it was obtained as a solid residue upon evaporation of this solvent. It melted at 206–209° and was converted back into the monobromo enol (IV) when acidified. A bright yellow silver salt was precipitated by the addition of aqueous silver nitrate and then water to a methanol solution of the sodium salt; it was filtered and washed, but it darkened rapidly and became black within five minutes.

The 2-enol methyl ether of 3-bromo-1,4-dimesitylbutane-1,2,4-trione. (3-Bromo-1,4-dimesityl-2-methoxy-2-butene-1,4-dione) (V). A solution of 0.5 g. of diazomethane in 75 cc. of ether was added to 3.5 g. of the bromo enol (IV). After the immediate and vigorous evolution of nitrogen the solution was allowed to stand at room temperature for six hours and was then treated with 5% hydrochloric acid and washed with water. Evaporation of the ether under reduced pressure left a yellow solid which was crystallized from ethanol;

yield 2.55 g. (71%); m.p. 122–124°. Repeated and alternating crystallizations from conc'd acetic acid and from ethanol gave a pure product of m.p. 125.5–126°.

Anal. Calc'd for $C_{23}H_{25}BrO_3$: Br 18.6; OCH_3, 7.2. Found: Br, 18.8; OCH_3, 6.9.

Hydrolysis of 0.1 g. by conc'd acetic acid containing a few drops of conc'd sulfuric acid, (refluxing for a half hour) gave 0.08 g. of the enol (IV) which was purified and identified.

Potassium iodide in acidified ethanol solution at room temperature, and in conc'd acetic acid at 70°, was without action.

Catalytic reduction of 0.1 g. in 25 cc. of ethanol with 0.05 g. of platinum oxide proceeded with absorption of two molecules of hydrogen in three hours. Concentration of the solution after removing the catalyst by filtration gave an oil which could not be induced to crystallize. Fractional distillation of this oil in a vacuum oven at 110° onto a cold-finger condenser gave 0.65 g. of a clear, mobile and almost colorless oil of n_D^{27} 1.5480. This observed value corresponds closely to that of 1,4-dimesityl-2-methoxybutanedione-1,4 (VI) (1). The identity of this product was confirmed by redistillation at 190° at 8 mm. pressure, whereupon 0.42 g. of yellow crystals of dimesitoylethylene of m.p. 170–172° condensed on the cold finger and was identified.

Sunlight was without action on solutions of the ether (V) in methanol or in chloroform with a trace of iodine as a catalyst.

Ozonolysis. A stream of 5% ozone was passed through a solution of 2.7 g. of the ether (V) in 40 cc. of dry chloroform at 0° for 5 hrs. The solvent was then evaporated in a current of air, and 10 cc. of water was added. The mixture was brought to boiling to ensure complete hydrolysis of the ozonides. Sodium bicarbonate was added and the mixture extracted with ether to remove non-acid products. From the ether solution an oil was obtained which was shown to be the methyl ester of mesitylglyoxilic acid by hydrolysis with boiling 5% methanolic sodium hydroxide (refluxing for a half hour); acidification of the resulting solution gave a crystalline acid which was recrystallized from water and identified as mesitylglyoxilic acid (m.p. 113–115°; yield 0.17 g.). From the sodium carbonate extract of the products of ozonolysis, 0.67 g. of mesitoic acid was isolated by acidification and extraction by ether; this acid melted at 147–148° and was identified by mixture melting point with an authentic sample.

An isomeric methyl ether of 3-bromo-1,4-dimesitylbutane-1,2,4-trione enol. The residues from the above preparation of the 2-methyl ether (V) gave on fractional crystallization 0.27 g. of a second substance which was crystallized repeatedly from ethanol. It was obtained as colorless rhomboids of melting point 156–156.5°.

Anal. Calc'd for $C_{23}H_{25}BrO_3$: Br, 18.6; OCH_3, 7.2. Found: Br, 18.4; OCH_3, 7.96.

Hydrolysis of 0.1 g. by treatment for 15 min. with refluxing conc'd acetic and hydrochloric acids gave 0.07 g. of the monobromo enol (IV) which was identified. *Sunlight* was without action on solutions of the ether in methanol, or in chloroform with a trace of iodine as a catalyst.

3,3-Dibromo-1,4-dimesityl-1,2,4-butanetrione (III). Two equivalents (4.76 g.) of bromine in 25 cc. of ethanol was added dropwise with mechanical stirring to an ethanol solution of 5 g. of the triketone enol (I); the temperature was maintained at −10°. Upon concentration of the solution, 6.3 g. (86%) of yellow crystalline dibromo derivative separated; m.p. 146–148°. Repeated crystallizations alternately from ethanol and from ethyl acetate gave fine, bright yellow needles of m.p. 152–152.5°.

Anal. Calc'd for $C_{22}H_{22}Br_2O_3$: Br, 32.36. Found: Br, 33.19.

A sample of the dibromo triketone was recovered unchanged after being subjected to refluxing ethanol for four hours.

Reduction in conc'd acetic acid by potassium iodide proceeded readily with liberation of iodine, and a nearly quantitative yield of the triketone enol (I) was obtained.

Sulfur dioxide was passed through a solution of 0.5 g. of the dibromo triketone (III) at 70° for fifteen minutes; upon cooling, 0.3 g. (70%) of monobromo triketone enol (IV) of m.p. 103–105°, separated and was identified by mixture melting point.

Chlorination of the triketone enol (I) by phenyliodochloride in chloroform at room temperature (72 hrs.) gave a yellow product which was repeatedly crystallized from ethanol and from ethanol-ethyl acetate mixtures; long yellow needles; m.p. 142–142.5°.

Anal. Calc'd for $C_{22}H_{21}Cl_3O_3$: C, 60.00; H, 4.77.
Found: C, 61.2, 61.1; H, 4.8, 4.7.

SUMMARY

The bromination of 1,4-dimesitylbutanetrione enol gave a labile monobromo triketone which changed into the more stable enol form. An excess of bromine produced the dibromo triketone. This bromination resembles that of α-oxalyl ketones and esters.

Diazomethane converted the bromo enol chiefly into the 2-methyl ether, the structure of which was demonstrated.

CHARLOTTESVILLE, VA.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

REDUCTION OF THE *Cis* AND *Trans* 2-ENOL METHYL ETHERS OF 1,4-DIMESITYL-1,2,4-BUTANETRIONE

ROBERT E. LUTZ AND DANIEL H. TERRY[1]

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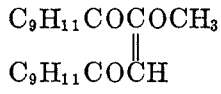
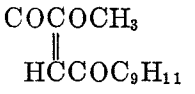
The reduction of 1,4-dimesityl-1,2,4-butanetrione enol (VII) follows a course which is different from that of the reduction of the diphenyl analog (1). It therefore seemed desirable to study the reduction of the enol ethers where fixed structures are involved. This paper deals with the *cis* and *trans* 2-enol methyl ethers (I and II) both of which are known (2).

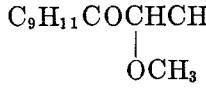


I

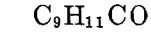


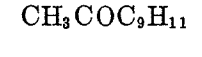
II

The reduction of these two ethers by means of sodium hydrosulfite proceeded in similar fashion and in both cases there were produced similar yields of the corresponding saturated methoxy diketone (III) and the fission products, mesitoic acid and acetomesitylene. In both cases the fission reaction was dominant.



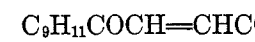
III



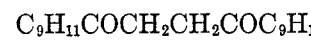


Two minor points of difference were noted in these reductions. In the case of the *cis* compound (I) a small amount of mesitylglyoxal hydrate was isolated whereas none was found in the reduction of the *trans* isomer; and in the case of the *trans* compound (II) there was produced a small amount of a new compound which has not been investigated.

The methoxy saturated diketone (III) was not obtained in crystalline form and the samples from the different sources were identified by boiling points, refractive indices and pyrolysis to dimesitoylethylene (IV).[2]



IV



V

It is a striking fact that in neither reduction was there isolated any dimesitylbutanedione (V) which might have been expected from reductive elimination of

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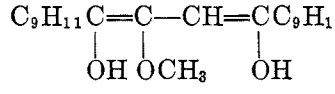
[2] It should be noted in this connection that the diphenyl analog is exceedingly difficult to crystallize and gives dibenzoylethylene and methanol on pyrolysis (3).

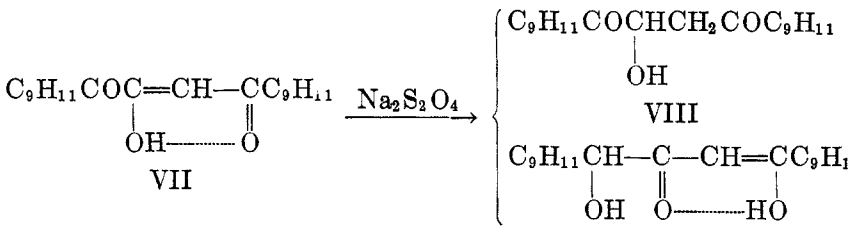
the methoxyl group. Except for the extent of cleavage involved, these reductions correspond to the reduction of the diphenyl analog (3), where reductive elimination of the methoxyl group occurs only to a small extent and where the methoxy saturated 1,4-diketone is the chief product.

It is probable that the reductions of the two enol ethers (I and II) involve intermediate di-enols such as VI—possibly stereoisomers—which undergo competing rearrangement to the saturated methoxy diketone (III) and hydrolytic fission.



VI

For purposes of comparison, the reduction of dimesitylbutanetrione enol (VII) was repeated with sodium hydrosulfite as the reagent. There were isolated from the reaction product a small amount of 2-hydroxydimesitylbutanedione-1,4 (VIII), a large amount of the isomeric 4-hydroxydimesitylbutane-1,3-dione enol (IX), and a trace of mesitylglyoxal hydrate. It is noteworthy that the extent of cleavage in this reduction was very small in comparison with that occurring in the corresponding reductions of the 2-enol ethers (I and II); on the other hand, as in the case of the 2-ethers, no reductive elimination of the 2-oxygen atom was observed.

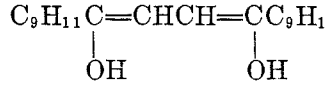


VII VIII IX

Catalytic reductions of the 2-enol ethers were carried out because it was anticipated that under these conditions the hydrolytic fission would be minimized. This proved to be the case. The *cis* and *trans* isomers reacted in very different ways, however. The *trans* isomer (II) absorbed approximately one molecule of hydrogen and gave a mixture from which a 65% yield of the saturated methoxy 1,4-diketone (III) and a 25% yield of dimesitylbutanedione (V) were obtained. The *cis* isomer (I) absorbed two molecules of hydrogen and gave dimesitylbutanedione (V) in almost quantitative yield. These results are to be contrasted with those of the sodium hydrosulfite reductions, in that elimination of the methoxyl group now appears as a prominent and in one case the dominant reaction, and as predicted, the hydrolytic fission has been almost completely suppressed.

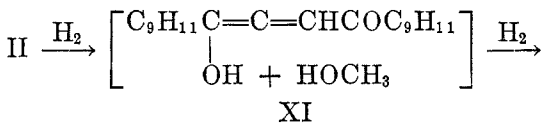
The striking difference in the behavior of the *cis* and *trans* isomers in catalytic reduction led to speculation concerning the mechanism of the reactions. The saturated methoxy diketone (III), once it is formed, is stable under the reducing

conditions; therefore the elimination of the methoxyl during reduction must occur directly or in an intermediate step. In one experiment a typical reduction of the *cis* ether was interrupted after addition of one molecule of hydrogen, and the resulting mixture was poured into alcoholic iodine to oxidize any di-enol produced; nevertheless the saturated diketone (V) was obtained in 36% yield. In a second and similar experiment in which the hydrogen absorption had been allowed to proceed to completion, there was produced a 96% yield of the saturated diketone (V). These experiments indicate that no di-enol of the type X was formed in the reduction unless it was an extraordinarily easily ketonized di-enol, stereoisomeric with that obtained in the reduction of dimesitoylethylene (IV) (4).

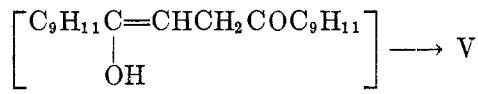


X

A possible mechanism which would account for the failure to form an oxidizable di-enol is 1,4-reduction of the α-methoxy ketone system followed by reduction of the 2-double bond of the resulting allenic enol (XI) and ketonization to the saturated diketone (V).



XI



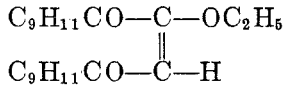
XII

The catalytic reduction of the *trans* ether (II) is best interpreted in terms of competing 1,4-reduction of the α-methoxy ketone system and 1,6-reduction of the unsaturated 1,4-diketone system. That the main course of the reduction did involve the 1,6-reaction mechanism to give the di-enol (VI) as the intermediate was shown by pouring the fresh reaction mixture into alcoholic iodine; in this experiment the starting material was regenerated and recovered in 75% yield, and quantitative determination showed that an approximately equivalent amount of iodine had been used up.

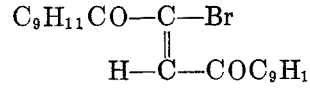
It is interesting to speculate as to why the *cis* ether (I) underwent reductive elimination of the methoxyl group so much more easily than did the *trans* isomer (II). One possible explanation is that, in the *cis* isomer as compared with the *trans*, steric hindrance is greater at the two carbonyls and less at the methoxyl; this would facilitate relatively that mode of reduction which involves the methoxyl oxygen. Another explanation would be in terms of interaction of the *cis* carbonyl groups in such a way as relatively to diminish the reactivity of the 4-carbonyl group in that compound.

EXPERIMENTAL

cis-1,4-Dimesityl-2-methoxy-2-butenedione-1,4 (I) (cf. Ref. 5). Three preparations of this ether are given. The first of these (a) involves the transformation of the *cis* ethyl ether (XIII) into the *cis* methyl ether (I). Evidently here, as also in the reaction with the *cis* and *trans* bromo unsaturated diketones (XIV), sodium methoxide adds 1,4 with subsequent elimination of sodium bromide or sodium ethoxide in such a way stereochemically as to produce consistently the *cis* configuration in spite of the greater energy content of this form.



XIII



XIV

(a) A methanol solution of 0.68 g. of the *cis* ethyl ether (XIII) and 0.1 g. of sodium hydroxide was refluxed for four hours. Upon cooling and acidification, 0.29 g. of the yellow enol (VII) separated and was identified. Dilution of the filtrate with water gave 0.3 g. (45%) of nearly pure *cis* methyl ether (I).

(b) A methanol solution of 0.75 g. of *trans* bromo unsaturated diketone (XIV) and a slight excess of sodium methoxide was allowed to stand with stirring for thirty minutes at room temperature. Dilution with water gave 0.45 g. (69%) of nearly pure *cis* methyl ether (I).

(c) In an experiment similar to (b) using the *cis* bromo unsaturated diketone (6) the *cis* ether (I) was obtained similarly in 84% yield.

Acid hydrolysis of 2 g. of (I) in 40 cc. of conc'd acetic acid, 10 cc. of conc'd hydrochloric acid, and 5 cc. of water at room temperature for three hours, produced 1.82 g. (94%) of almost pure enol (VII).

Reductions of the cis *2-methyl ether* (I). (a) Catalytic hydrogenation of 1 g. of (I) in ethanol with 0.05 g. of platinum oxide was stopped after absorption of one molecule, and the solution was immediately poured into alcoholic iodine solution. After diluting with water, the resulting oil was washed with sodium bisulfite and then with water, and was then taken up in ligroin from which 0.25 g. (35%) of dimesitylbutanedione (V) crystallized in nearly pure condition. The rest of the material was non-crystalline.

(b) In a similar experiment in which the reduction was allowed to go to completion with absorption of two equivalents of hydrogen, the solution was poured into an excess of alcoholic iodine. The product was isolated as before and proved to be the saturated diketone (V); yield 98%.

(c) In an experiment similar to (b), but bubbling oxygen through the resulting solution instead of using alcoholic iodine, the saturated diketone (V) was isolated in 76% yield.

(d) In another similar experiment in which the reduction mixture was treated with piperidine to hasten ketonization, the saturated diketone (V) was obtained in 94% yield.

(e) Hydrogenation with palladium on barium sulfate as catalyst was without result.

(f) The use of zinc dust and conc'd acetic acid or a mixture of conc'd acetic acid and acetic anhydride, at room temperature or at 60–70°, gave a mixture of products which included some mesitoic acid and the non-crystalline saturated diketone (III) [treated as described under (h)].

(g) Sodium bisulfite in 80% ethanol at refluxing temperature was without action.

(h) A number of reductions with sodium hydrosulfite were carried out. The following experiment is typical.

A mixture of 100 cc. of 80% ethanol, 45 g. of sodium hydrosulfite, and 15 g. of (I) was refluxed for half an hour with mechanical stirring. Upon cooling and diluting with water, an oil separated which was extracted by means of petroleum ether, from which 0.1 g. of colorless crystals was obtained on concentrating (m.p. 100–101°). This was identified by mixture melting point as mesitylglyoxal hydrate. Slow evaporation of the filtrate gave

mesitoic acid. Extraction of the filtrate three times with saturated sodium carbonate removed more mesitoic acid which was recovered upon acidification; total yield 2.6 g. (37%).

1,4-Dimesityl-2-methoxybutanedione-1,4. Final evaporation of the petroleum ether solution obtained in the preceding experiment left an oil (14 g.) which was distilled in a vacuum oven at 60° under 2 mm. pressure, and the distillate was collected dropwise on a cold-finger condenser. The fraction coming over at this temperature (3 g., 44%) was redistilled; it boiled at 126° under 7 mm. pressure and showed n_D^{23} 1.5170–1.5180 which corresponds closely to the value reported in the literature for acetomesitylene. The second fraction which came over at an oven temperature of 140–155° under 2 mm. pressure was 3.9 g. (26%). It was redistilled and showed n_D^{10} 1.5480 which is close to the value found for samples obtained in other reductions, including that of dimesitoylbromomethoxyethylene (7). This compound was not analyzed but its nature was demonstrated as follows. A portion was decomposed in two ways, one by distillation at 190–200° under partially reduced pressure, and the other by heating under an atmosphere of nitrogen at 240–260°. In both cases dimesitoylethylene (IV) was obtained in high yield and was identified.

Trans-*1,4-Dimesityl-2-methoxy-2-butenedione-1,4* (II). Hydrolysis of 0.6 g. of this ether in 20 cc. of conc'd acetic acid, 5 cc. of conc'd hydrochloric acid, and 2.5 cc. of water for three hours at room temperature gave 0.56 g. (97%) of nearly pure enol (VII).

Catalytic reduction of 1 g. of the *trans* ether (II) in 60 cc. of ethanol with 0.05 g. of platinum oxide involved rapid absorption of one molecule of hydrogen. The solution was poured into an alcoholic solution of an excess of iodine, and on working up the product in the usual way 0.75 g. of the methoxy unsaturated diketone (II) was recovered. When a similar reaction mixture from 2 g. of II was treated under hydrogen with two drops of piperidine and allowed to stand for five hours, 0.43 g. of the saturated diketone (V) was obtained. From the filtrates, 1.3 g. of an oil was obtained which was shown to be the methoxy saturated diketone (III) by redistillation at 130–140° under 2 mm. pressure, by refractive index (n_D^{25} 1.5460), and by pyrolysis as described above at 210° under partially reduced pressure, with the formation of dimesitoylethylene in 60% yield. Incidentally, a sample of the oil (III) was subjected to a catalytic reduction and was apparently unaffected; only a small amount of hydrogen was absorbed and a 6% yield of the saturated diketone (V) was isolated (obviously the result of partial reduction).

Sodium hydrosulfite reduction of 5 g. of (II) in 90 cc. of 80% ethanol and 15 g. of the reagent was carried out as described under (I). The oil obtained was dissolved in ligroin and extracted with three portions of sodium carbonate solution from which 0.26 g. of mesitoic acid was recovered upon acidification. The ligroin solution on evaporation left an oil which was distilled at 65° under 2 mm. pressure (yield 1.25 g., 55%); this was identified as acetomesitylene by refractive index; n_D^{25} 1.5205. The residue from the distillation of the acetomesitylene at a higher temperature in the vacuum oven gave a second and crystalline fraction (0.25 g.) which melted at 85° (upon repeated crystallization the melting point was 102°; this compound has not been investigated further). At a still higher temperature (130–140°) a viscous yellow oil distilled, the middle fraction of which showed n_D^{25} 1.5475 and evidently was the methoxy saturated diketone (III). It underwent pyrolysis at 200–220° under partially reduced pressure to give dimesitoylethylene (IV).

Reduction of 1,4-dimesityl-1,2,4-butanetrione enol (VII). A mixture of 5 g. of the enol (VII), 100 cc. of 80% ethanol, and 25 g. of sodium hydrosulfite was heated with stirring at 80–90° for four hours. On dilution with water, an oil was obtained which was dissolved in petroleum ether. Evaporation and digestion with ligroin, and standing, produced 1.15 g. of colorless crystals of m.p. 103–104° which was identified as 4-hydroxydimesitylbutane-1,3-dione enol (IX). Concentration of the filtrate gave 1 g. of the hydroxy saturated diketone (VIII) which was identified. The residue from evaporation of the filtrate was distilled in the vacuum oven at 120° and gave 0.97 g. of dimesitoylethylene (IV), which was identified.

SUMMARY

Sodium hydrosulfite reduction of the *cis* and *trans* 2-enol ethers of 1,4-dimesityl-1,2,4-butanetrione gave the methoxy saturated 1,4-diketone and large amounts of the cleavage products, mesitoic acid and acetomesitylene. Sodium hydrosulfite reduction of the triketone enol itself involved very little cleavage and gave a mixture of the hydroxy saturated diketone and the 4-hydroxy-1,3-diketone enol.

In catalytic hydrogenation the fission was minimized but the *cis* and *trans* ethers gave widely different results: the *trans* ether gave a mixture of the methoxy saturated diketone and the demethoxy compound, 1,4-dimesitylbutanedione; whereas the *cis* ether underwent complete reductive elimination of the methoxyl to give chiefly 1,4-dimesitylbutanedione.

The mechanism of these reactions is discussed and a possible explanation for the difference in behavior of the *cis* and *trans* isomers is offered.

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(6) LUTZ AND TERRY, results to be published shortly.
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES IN THE PYRIDINE SERIES. V. REACTIONS INVOLVING THE ORTHO EFFECT IN CERTAIN β,γ SUBSTITUTED PYRIDINES

MALCOLM J. REIDER AND ROBERT C. ELDERFIELD

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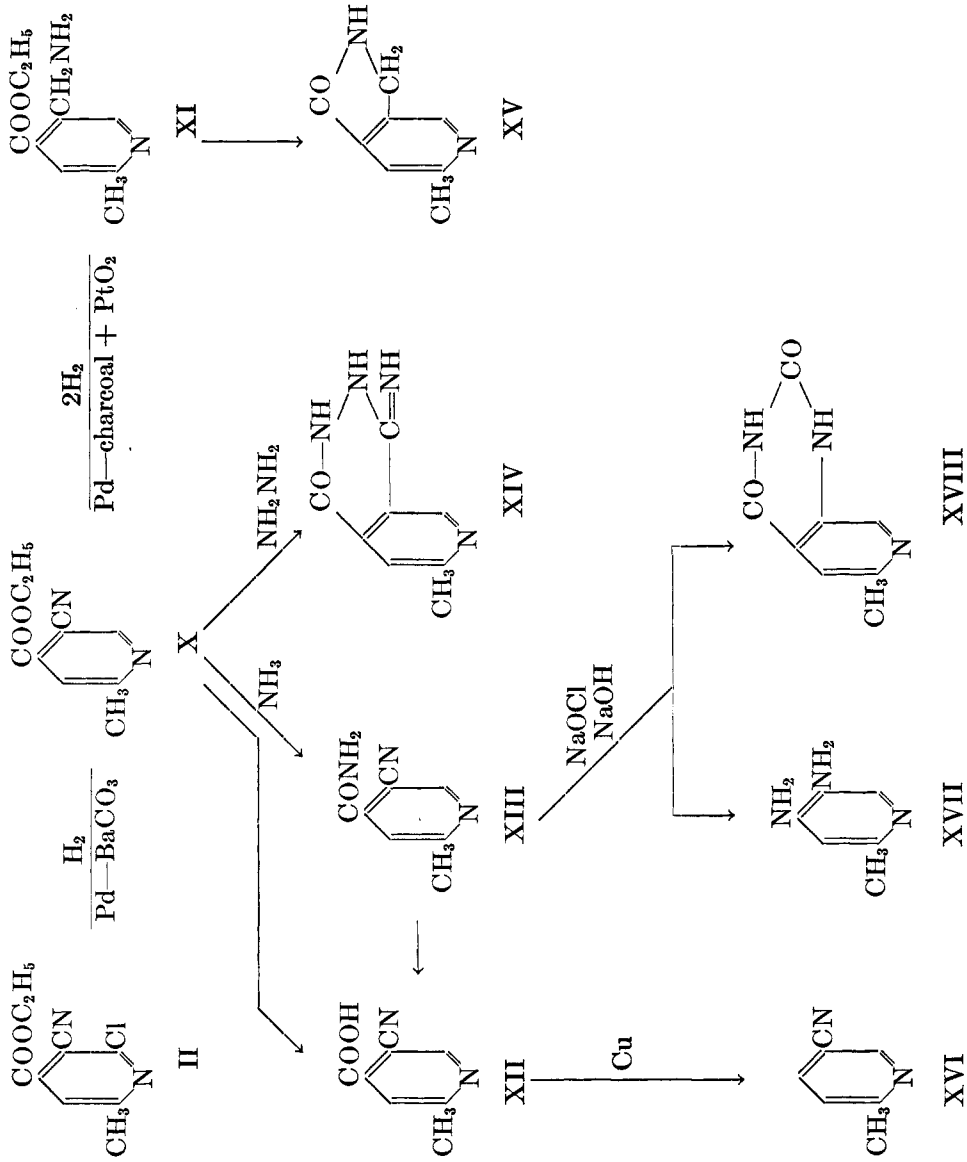
With the increasing importance which is being assumed by various derivatives of pyridine as a result of the recognition that these substances constitute integral parts of such physiologically important classes as the nucleic acids and the vitamin B complex, a fuller knowledge of the behavior of pyridine derivatives becomes desirable.

Most of the studies hitherto reported on pyridine derivatives are the result of work done some time ago, and frequently the observations on record leave considerable to be desired. Thus, in many cases insufficient data exist to enable one to predict the behavior of a given pyridine derivative under definite experimental conditions, except by analogy to corresponding benzene derivatives, a procedure often dangerous because of the difference in behavior of substituents in the α- and γ-positions of the pyridine nucleus compared with one in the β-position. Furthermore, the published data frequently omit yields, formation of by-products, etc., and are to a greater or less extent unsatisfactory. In order to clarify some of these points, it was felt that a study of certain transformations of pyridine derivatives containing substituents in the β- and γ-positions might be of help.

For this purpose, the 2-methyl-4-carbethoxy-5-cyano-6-pyridone described by Bardhan (1) forms a readily accessible substance. It carries two reactive groups in the desired β- and γ-positions, and possesses in addition a substituent in one of the α-positions which can be used to study the ortho effect on the adjacent group in the β-position. For the immediate purpose at hand this pyridone (I) was converted into the corresponding chloro derivative (II). Parallel experiments were then carried out on 2-methyl-4-carbethoxy-5-cyano-6-chloropyridine, in which the nitrile group in position 5 is sterically hindered by the chlorine atom in position 6 (hereafter designated as the hindered compound), and on the chlorine-free compound (X) in which the ortho effect is absent.

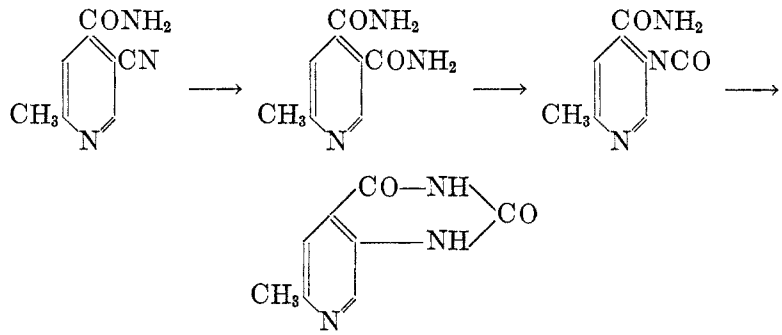
The first series of experiments dealt with the conventional Hofmann degradation of both the hindered and free cyano amides (III and XIII). These were readily prepared by treatment of the appropriate esters with ammonia. Hofmann degradations of isonicotinic acid amide and cinchomeronic acid 4-amide have been described in the literature (2, 3), with no yields reported. Dioxycopazoline has been obtained from the diamide of cinchomeronic acid by the same means (4, 5). In the benzene series, Hofmann degradation of the diamide

COOC2H5
CN
Cl
CH3
N
O
H
I
PCl5
POCl3
II
NH3
NH2—NH2
H+ or OH−
H2O
CONH2
III
CONHNH2
V
HNO2
C6H5CHO
CONHN=CHC6H5
VI
COOH
IV
H+
H2O
SOCl2
Cu
CH3OH
or
CH3ONa
Br
CH3ONa
CONHBr
VII
COOH
VIII
CN
IX
COCl
XIX


COOC2H5
CN
Cl
CH3
N
II
H2
Pd—BaCO3
COOC2H5
CN
CH3
N
X
2H2
Pd—charcoal + PtO2
COOC2H5
CH2NH2
CH3
N
XI
CO
NH
CH2
CH3
N
XV
NH2NH2
NH3
CO—NH
NH
C=NH
CH3
N
XIV
CONH2
CN
CH3
N
XIII
NaOCl
NaOH
CO—NH
CO
NH
CH3
N
XVIII
NH2
NH2
CH3
N
XVII
COOH
CN
CH3
N
XII
Cu
CN
CH3
N
XVI

of phthalic acid and of *o*-cyanobenzamide (6, 7) is reported as yielding benzoyleneurea by a reaction analogous to the formation of dioxycopazoline. It was of interest, therefore, to determine whether any differences between the benzene series, in which the positions are equivalent, and the pyridine series, in which the β- and γ-positions show differences in behavior, are apparent.

When the amide of 2-methyl-5-cyanoisonicotinic acid (XIII) was subjected to the Hofmann degradation using aqueous sodium hypochlorite solution (8), the products isolated were 2-methyldioxycopazoline (XVIII) and 2-methyl-4, 5-diaminopyridine (XVII) in the ratio of about 9 to 1. This contrasts with the degradation of *o*-cyanobenzamide which is reported as yielding no diamino derivative. We believe that the formation of 2-methyldioxycopazoline may be explained by the series of reactions:



The alternative scheme in which the nitrile is hydrated to the amide while the amide in the 4-position is converted to the isocyanate, seems unlikely on the basis of observations to be presented later on the stability of a haloamide in the γ-position of the pyridine ring. In any event, the formation of the dioxycopazoline arises by interaction of an amide group with an isocyanate group and parallels the observations of Jeffrys (9) on the formation of acyl-alkyl ureas as by-products of the Hofmann degradation in the aliphatic series.

When the degradation of the hindered amide of 2-methyl-5-cyano-6-chloroisonicotinic acid was investigated, a strikingly different behavior both of the amide and of the nitrile group was noted. As expected, the reactivity of the nitrile group was somewhat repressed in so far as hydration to an amide is concerned. However, the amide group in position 4 assumed an enhanced susceptibility to hydrolysis compared to the non-hindered compound discussed above. When the chloro derivative (III) was treated with cold aqueous alkaline hypobromite solution, the only product isolated was the sodium salt of 2-methyl-5-cyano-6-chloroisonicotinic acid, which obviously must arise by hydrolysis of the amide. As a result of the behavior of the free and hindered amides on acid hydrolysis, we believe that this apparent lability of the amide is due to the ortho effect of the chlorine atom on the nitrile group. When either amide is dissolved in cold dilute hydrochloric acid, the corresponding acid precipitates almost immediately. However, in the case of the free nitrile, under alkaline conditions, hydration of the nitrile to the amide apparently proceeds even faster than

hydrolysis of the amide in position 4. In the case of the hindered nitrile such hydration is repressed with the result that the nitrile continues to exert its activating influence on the amide in position 4. With the hydration of the nitrile in the unhindered compound, an amide results, which would not be expected to induce such rapid hydrolysis of a vicinal amide. A similar ease of hydrolysis of ester groups under alkaline conditions was noted in both series.

While the chlorine atom exerts an ortho effect on the nitrile sufficient to repress its hydration in the sense noted above, this is by no means as pronounced as might have been predicted. It is well known that di-ortho substituted nitriles in the benzene series are difficultly hydrolyzed, (10, 11, 12, 13), and to a lesser extent mono-ortho substituted nitriles, with the exception of those in which the ortho group is a carboxyl group (14). In the above chloronitrile acid, one would predict on the basis of recorded behavior of such compounds in the benzene series that the nitrile group would be moderately difficult to hydrolyze, in view of the hindering chlorine atom on one side and the activating carboxyl group on the other. Such is not the case, for merely recrystallizing the chloronitrile acid from acidulated water results in hydrolysis to the corresponding cinchomeronic acid derivative (VIII). Thus one is able to prepare at will 5-cyanoisonicotinic acids or cinchomeronic acids, by carrying out hydrolysis of the appropriate derivative under suitable conditions.

Decarboxylation of either of the above cyano acids by the copper method led to the corresponding nitriles (XVI and IX). However, when such decarboxylation was attempted in quantities larger than about one-half gram, the yield suffered markedly.

In view of the easy hydrolysis of the hindered amide when the Hofmann degradation was attempted in aqueous solution, the method of Jeffrys (9), based on the observation of Lengfeld and Stieglitz (16, 17) that sodium methoxide in anhydrous methanol converts bromo amides to urethans which can be subsequently hydrolyzed to amines, was applied to the hindered compound. When the general method of Jeffrys was applied, the amide was recovered unchanged. However, when the amide was treated with exactly one equivalent of bromine and sodium methoxide, a substantially quantitative yield of bromo amide (VII) was obtained. The bromine atom in the latter substance again displayed a remarkable lability. When the bromo amide was merely boiled with methyl or ethyl alcohol, bromine was rapidly liberated and the original amide was recovered. The bromo amide also resisted attempts to rearrange it to the urethan and decomposed to the original amide during all such experiments.

Attention was next directed to a study of the Curtius degradation as applied to both the free and hindered nitrile amides. Isonicotinic acid hydrazide is readily prepared, but available information is to the effect that conversion of the latter to the azide is accomplished only with poor yields (18). In the present case, the reactions of the two esters with hydrazine led to different products depending on whether the ortho effect of the chlorine atom in the 6-position was present or not. Ethyl 2-methyl-5-cyano-6-chloroisonicotinate reacted readily with hydrazine to yield the normal hydrazide (V). As such, a benzal derivative (VI) was readily

prepared. However, in the subsequent treatment of the hydrazide with nitrous acid, the same lability manifested itself as with the corresponding amide, and 2-methyl-5-cyano-6-chloroisonicotinic acid was formed by hydrolysis of the hydrazide. Amyl or butyl nitrite in non-aqueous solution were without effect on the hydrazide. Likewise, treatment of the acid chloride of IV with freshly crystallized sodium azide (19, 20, 21, 22) failed to yield the desired azide.

On the other hand, when ethyl 2-methyl-5-cyanoisonicotinate, in which the ortho chlorine substituent is absent was treated with hydrazine, a substance which furnished analytical figures corresponding to the expected hydrazide was obtained. However, this substance did not yield a benzal derivative when treated with benzaldehyde, and is accordingly assigned the structure XIV. Failure of the hydrazide of the hindered acid to react with the nitrile group may, therefore, be ascribed to the ortho effect of the chlorine substituent in the latter.

Finally, we wish to present some observations on the catalytic reduction of ethyl 2-methyl-5-cyano-6-chloroisonicotinate. The reduction of this compound proceeds smoothly in a stepwise manner in the presence of a palladium on barium carbonate catalyst, and one may stop at ethyl 2-methyl-5-cyanoisonicotinate if desired. However, if the reduction is carried farther in a sodium acetate-acetic acid medium, ethyl 2-methyl-5-aminomethylisonicotinate (XI) may be isolated as the picrate. If the reduction is carried out under strongly acid conditions as used by Kindler (23, 24), the reaction product consists of a mixture of the above amine (XI) and the lactam (XV) derived from it. The free amine when treated with cold dilute hydrochloric acid readily yields the hydrochloride of the lactam. Ring closure to the latter takes place so readily that it has not been possible to isolate the free amine. Treatment of the amine picrate with nitrous acid in the cold, in an attempt to obtain either the lactone or free alcohol, resulted in formation of the lactam.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Ethyl 2-methyl-5-cyano-6-chloroisonicotinate (II). To 100 g. of ethyl 2-methyl-5-cyano-6-hydroxyisonicotinate, prepared according to Bardhan (1), was added 200 g. of phosphorus oxychloride. To the mixture was added, in small portions, 200 g. of finely pulverized phosphorus pentachloride. When the evolution of hydrogen chloride slowed down, the mixture was warmed on the steam-bath until the solution cleared (45 minutes) after which heating was continued 15 minutes longer. The flask was then removed from the steam-bath and allowed to stand two hours, after which the phosphorus oxychloride was removed at reduced pressure and the syrup was poured onto 400 g. of cracked ice. After refrigerating overnight, the granular precipitate was filtered off and dried. The chlorinated product was extracted from unreacted pyridone with petroleum ether. The compound was recrystallized from petroleum ether or dilute alcohol. A very pure material was obtained by subliming the product at 0.1 mm. pressure, and 70°. The compound can also be purified by distillation through an apparatus equipped with a steam-jacketed condenser. The chloro derivative boils at 135–136.5° at 0.5 mm. pressure and melts at 62°. The yield was 50–70%. The compound is insoluble in water and in 10% hydrochloric acid, and soluble in alcohol, ether, benzene, chloroform, hot petroleum ether, and concentrated hydrochloric acid.

Anal. Calc'd for $C_{10}H_9ClN_2O_2$: C, 53.4; H, 4.1; N, 12.5.
Found: C, 53.8; H, 4.3; N, 12.4.

Ethyl 2-methyl-5-cyanoisonicotinate (*X*). One gram of ethyl 2-methyl-5-cyano-6-chloroisonicotinate and two grams of catalyst (5% palladium on barium carbonate) were suspended in 100 cc. of commercial absolute alcohol and shaken with hydrogen gas at atmospheric pressure until the calculated amount of hydrogen was taken up. The catalyst was filtered off, washed with alcohol, and the filtrate was concentrated *in vacuo* to 2 cc. Fifteen cubic centimeters of water was added and an oil separated which soon set to a mass of crystals. The compound was purified by sublimation at 0.1 mm. pressure and 70°. The substance, obtained in 95% yield, may also be recrystallized from dilute alcohol, and melts at 58°.

Anal. Calc'd for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3; N, 14.7.
Found: C, 63.3; H, 5.5; N, 14.9.

Amide of 2-methyl-5-cyanoisonicotinic acid (*XIII*). Ten grams of ethyl 2-methyl-5-cyanoisonicotinate was shaken with 400 cc. of ice-cold concentrated ammonia, keeping the flask in an ice-bath. After an hour a flocculent precipitate appeared. After three hours the amide was filtered off. The yield was 6 g., or 70% of the theory. The compound melts with decomposition at 275°.

Anal. Calc'd for $C_8H_7N_3O$: C, 59.6; H, 4.4; N, 26.1.
Found: C, 59.9; H, 4.7; N, 26.0.

Amide of 2-methyl-5-cyano-6-chloroisonicotinic acid (*III*). Fifty grams of ethyl 2-methyl-5-cyano-6-chloroisonicotinate was shaken at room temperature with 500 cc. of concentrated ammonium hydroxide until no more ester dissolved. The mixture was filtered and the solid was shaken with another 500 cc. of concentrated ammonium hydroxide. The mixture was filtered and the combined filtrates were concentrated at reduced pressure to 300 cc. The amide precipitated and was filtered off. The yield was 28.5 g. of amide which, when recrystallized from benzene or alcohol, melted at 233°. By working up the mother liquors, the yield may be raised to 80%.

Anal. Calc'd for $C_8H_6ClN_3O$: C, 49.3; H, 3.1; N, 21.5.
Found: C, 49.5; H, 3.3; N, 20.3.

Hofmann degradation of the amide of 2-methyl-5-cyanoisonicotinic acid. Methyldioxycopazoline (*XVIII*) *and 2-methyl-4,5-diaminopyridine* (*XVII*). Two grams of the amide was treated with 30 cc. of 10% potassium hydroxide solution and 11 cc. of freshly prepared normal sodium hypochlorite solution. The clear yellow solution was heated on the steam-bath to 80° for 30 minutes. A small amount of gas was evolved. The solution was chilled and extracted with ether. The ether solution, when dried and saturated with dry hydrogen chloride, yielded 5–10% of 2-methyl-4,5-diaminopyridine dihydrochloride, which melted with decomposition above 250°.

Anal. Calc'd for $C_6H_{11}Cl_2N_3$: C, 36.7; H, 5.6.
Found: C, 36.2; H, 5.6.

The cold aqueous solution was neutralized with acetic acid and yielded a copious precipitate of fine yellow needles which were recrystallized from alcohol or pyridine. The yield was 70% of methyldioxycopazoline which did not melt up to 310°.

Anal. Calc'd for $C_8H_7N_3O_2$: C, 54.2; H, 4.0; N, 23.7.
Found: C, 53.9; H, 4.0; N, 24.0.

2-Methyl-5-cyano-6-chloroisonicotinic acid (*IV*). Two grams of the amide of 2-methyl-5-cyano-6-chloroisonicotinic acid was treated with 50 cc. of water and 10 cc. of 6 *N* hydrochloric acid at room temperature. Solution was prompt and the acid separated almost immediately. The acid was recrystallized from water and melted at 198.5°. The yield was quantitative.

Anal. Calc'd for $C_8H_5ClN_2O_2$: C, 48.9; H, 2.5; N, 14.3.
Found: C, 49.2; H, 2.9; N, 14.3.

Alkaline hydrolysis of the ethyl ester of 2-methyl-5-cyano-6-chloroisonicotinic acid was equally striking. The ester was dissolved in the minimum amount of alcohol at room temperature. The theoretical amount of sodium hydroxide in 50% aqueous alcoholic solution was added, and the sodium salt of the acid precipitated at once. It was filtered off and then dissolved in water. Hydrochloric acid was added, which precipitated the nearly pure acid. The compound was recrystallized from water, during which the solution was boiled as little as possible. The acid melted at 198.5°. The yield was nearly quantitative.

The *methyl ester* of the above acid, prepared by means of diazomethane, melts at 168.5°, after sublimation at 0.2 mm. at 100°.

Anal. Calc'd for $C_9H_7ClN_2O_2$: C, 51.3; H, 3.4.
Found: C, 51.6; H, 3.5.

2-Methyl-6-chlorocinchomeronic acid (VIII). 2-Methyl-5-cyano-6-chloroisonicotinic acid was refluxed in 5% hydrochloric acid for one hour. The mixture was chilled and filtered and the acid was recrystallized from water; it melted at 205°. The same compound was isolated from the mother liquors from the recrystallization of 2-methyl-5-cyano-6-chloroisonicotinic acid.

Anal. Calc'd for $C_8H_6ClNO_4$: C, 44.7; H, 2.8; N, 6.5.
Found: C, 45.0; H, 2.7; N, 6.3.

The *dimethyl ester* was prepared with diazomethane, and melted at 85° after recrystallization from dilute alcohol.

Anal. Calc'd for $C_{10}H_{10}ClNO_4$: C, 49.3; H, 4.1.
Found: C, 49.3; H, 4.2.

2-Methyl-5-cyanoisonicotinic acid (XII). The ester (X) was treated with the theoretical amount of sodium hydroxide in alcohol, whereupon the sodium salt precipitated in quantitative yield. The sodium salt was dissolved in water and the solution was acidified with dilute hydrochloric acid. The acid was recrystallized from acidulated dilute alcohol. In a like manner the amide (XIII) was treated with enough cold 0.1 *N* hydrochloric acid to dissolve it. In one minute the acid came out as long flexible needles looking like tufts of cotton. It was recrystallized as above. The acid from either source melted at 230°.

Anal. Calc'd for $C_8H_6N_2O_2$: C, 59.3; H, 3.7.
Found: C, 59.6; H, 3.9.

Decarboxylation of 2-methyl-5-cyanoisonicotinic acid to 2-methyl-5-cyanopyridine (XVI). Two hundred and fifty milligrams of the acid was mixed with 2.5 g. of freshly reduced copper powder and placed in the short side of a 10 mm. diameter Pyrex tube which was bent at an angle of 120° about 5 cm. from the closed end. The charge was heated with a yellow Bunsen flame until no more liquid distilled around the bend in the tube. The distillate crystallized on cooling, and a small amount of this material was sublimed *in vacuo*. The compound melts at 84–85°, as reported by Räth and Schiffman (15) for 2-methyl-5-cyanopyridine. It was impossible to secure satisfactory analytical data for the compound.

Anal. Calc'd for $C_7H_6N_2$: C, 71.1; H, 5.1.
Found: C, 70.5; H, 5.3.

2-Methyl-5-cyano-6-chloropyridine (IX). This was prepared by the same method used for 2-methyl-5-cyanopyridine. The nitrile melts at 114.5–115.5°.

Anal. Calc'd for $C_7H_5ClN_2$: C, 55.1; H, 3.3; N, 18.4.
Found: C, 55.4; H, 3.4; N, 18.3.

Bromo amide of 2-methyl-5-cyano-6-chloroisonicotinic acid (VII). One gram of the amide (III) was suspended in 30 cc. of methyl alcohol and to this was added 0.2 cc. of bromine. To the mixture was added a solution of 0.2 g. of sodium in 10 cc. of absolute methyl alcohol. Following this 0.3 cc. of bromine was added. Solution occurred followed by the precipitation of a solid. The mixture was warmed five minutes on the steam-bath, chilled, and filtered. The precipitate was recrystallized from methyl alcohol and melted at 199.8°. The yield was nearly quantitative. Boiling in alcohol or chloroform caused the formation of free bromine. The bromo amide released iodine from an acidified potassium iodide solution.

Anal. Calc'd for $C_8H_5BrClN_3O$: C, 35.0; H, 1.8; N, 15.3.
Found: C, 35.5; H, 1.9; N, 14.6.

Attempts to rearrange the above bromo amide. Four hundred seventy milligrams of the bromo amide (VII) was refluxed 1.5 hours with a solution of 0.04 g. of sodium in 27 cc. of absolute methyl alcohol. The solvent was removed and the residue was recrystallized from benzene. One-tenth of a gram of bromine-free material was isolated. It melted at 235°, and when it was mixed with the amide (III) the melting point showed no depression. No other product could be isolated from the reaction.

Attempts were also made to form the bromo amide and rearrange it at the same time, but the results were the same as above.

1-Hydroxy-4-amino-7-methyl-2,3,6-pyridopyridazine (XIV). To 0.7 g. of ethyl 2-methyl-5-cyanoisonicotinate, dissolved in a sufficient quantity of a mixture of alcohol and ether (1:1), was added with cooling 0.15 g. of anhydrous hydrazine. Yellow crystals soon precipitated and were filtered off and dried. The yield was 77% of a material which may be crystallized from alcohol, and melts at 324°.

Anal. Calc'd for $C_8H_8N_4O$: C, 54.6; H, 4.6.
Found: C, 54.7; H, 5.2.

The above compound is basic and forms a brilliant red *hydrochloride.* This could not be recrystallized and on heating with alcohol or water decomposition occurred, resulting in the precipitation of the free base.

Anal. Calc'd for $C_8H_9ClN_4O$: C, 45.2; H, 4.3; N, 26.4.
Found: C, 45.3; H, 4.5; N, 26.6.

This compound did not form a derivative with benzaldehyde and, therefore, has been assigned the keto structure XIV.

Hydrazide of 2-methyl-5-cyano-6-chloroisonicotinic acid (V). To 20 g. of ethyl 2-methyl-5-cyano-6-chloroisonicotinate dissolved in the minimum amount of cold ether-alcohol mixture (1:1) was added 4.3 g. of anhydrous hydrazine. The solution was chilled and the cream colored plates were filtered off, washed with alcohol, and dried *in vacuo.* No suitable solvent could be found for recrystallization of this compound. It sublimed above 360°.

Anal. Calc'd for the dihydrate $C_8H_7ClN_4O \cdot 2H_2O$: C, 39.1; H, 4.5.
Found: C, 39.6; H, 4.8.

The *benzal derivative* (VI) of the above hydrazide melted at 282.5°, after recrystallization from alcohol.

Anal. Calc'd for $C_{15}H_{11}ClN_4O$: C, 60.3; H, 3.7.
Found: C, 60.6; H, 4.2.

2-Methyl-5-cyano-6-chloroisonicotinic acid chloride (XIX). One and four-tenths grams of 2-methyl-5-cyano-6-chloroisonicotinic acid was refluxed 6 hours with 20 cc. of thionyl chloride in an apparatus protected from atmospheric moisture with a calcium chloride tube. The excess thionyl chloride was removed at reduced pressure and the acid chloride

crystallized in small rosettes. A small sample was pressed on a clay tile and washed with a small amount of benzene. The compound so treated melts at 98–103°.

That the nitrile group was not attacked by this treatment was shown by preparation of the amide and ethyl ester from the acid chloride. The former melted at 233°, the latter at 62°, and neither showed a depression in melting point when mixed with varying proportions of known amide and ester respectively.

Ethyl 2-methyl-5-aminomethylisonicotinate (XI) and the lactam, 2-methyl-4,5-pyrrolidonopyridine (XV). To 1 g. of ethyl 2-methyl-5-cyano-6-chloroisonicotinate was added 1 g. of 5% palladium metal supported on charcoal, 50 mg. of Adams' platinum oxide catalyst, 0.4 g. of fused sodium acetate, and 100 cc. of redistilled glacial acetic acid. The mixture was shaken with hydrogen at atmospheric pressure and room temperature until 3 molar equivalents of hydrogen had been taken up. The catalyst was filtered off, washed with acetic acid, and the filtrate was concentrated at reduced pressure and room temperature to a syrup. This was taken up in hot alcohol, the inorganic salts were filtered off, and the filtrate was reconcentrated to a syrup. This was taken up in water, treated with saturated aqueous picric acid, and the precipitated picrate was filtered off. The yield was 60% of a compound melting with decomposition at 170°. Analytical figures corresponded with those for the *picrate* of ethyl 2-methyl-5-aminomethylisonicotinate.

Anal. Calc'd for $C_{15}H_{17}N_5O_9$: C, 45.3; H, 4.0.
Found: C, 45.3; H, 3.9.

Reduction of 22 g. of the same nitrile in a solvent composed of 125 cc. of glacial acetic acid and 7 cc. of concentrated sulfuric acid, yielded a mixture of 12.5 g. of the lactam picrate and 22.5 g. of the amine picrate when worked up as above. This represents an over-all yield of 77%. The two compounds could be separated by recrystallization from water. The *lactam picrate* is the less soluble of the two and melts at 205.5°.

Anal. Calc'd for $C_{14}H_{11}N_5O_8$: C, 44.6; H, 2.9; N, 18.6.
Found: C, 44.8; H, 3.1; N, 18.9.

If either of the above reduction mixtures was allowed to become warm while working them up, ring closure always occurred and the lactam picrate was the only product isolated.

Conversion of the picrate to the hydrochloride in the usual manner always yielded the *hydrochloride of the lactam* which sublimes above 285°.

Anal. Calc'd for $C_8H_9ClN_2O$: C, 52.2; H, 4.9.
Found: C, 52.0; 52.2; H, 4.9; 5.0.

The free *lactam* was prepared from the hydrochloride by neutralization with sodium hydroxide. This compound may be recrystallized from benzene or toluene and melts at 250° in a sealed tube.

Anal. Calc'd for $C_8H_8N_2O$: C, 64.8; H, 5.4.
Found: C, 65.1; H, 5.7.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. Catalytic reduction of ethyl 2-methyl-5-cyano-6-chloroisonicotinate leads either to ethyl 2-methyl-5-cyanoisonicotinate or to ethyl 2-methyl-5-aminomethylisonicotinate. The latter substance readily lactamizes and can be isolated only as its salts.

2. The ortho effect of a chlorine atom in the 6-position of the pyridine ring on

the behavior of a nitrile group in the 5-position has been studied from the standpoint of partial and complete hydrolysis of the latter group.

3. The usefulness of the Hofmann and Curtius degradations applied to various isonicotinic and cinchomeronic acid derivatives has been indicated.

4. New methods for the preparation of nicotinic and isonicotinic acid derivatives have been described.

NEW YORK, N. Y.

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

GRIGNARD REACTIONS INVOLVING THE BENZENE NUCLEUS

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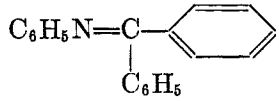
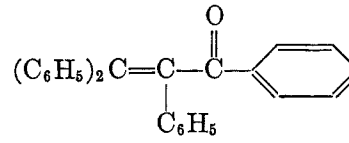
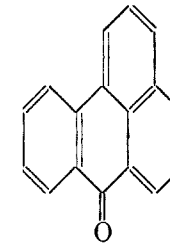
The Grignard reagent recently has been found to add in the 1,4 manner to the α,β-unsaturated ketone systems in α- and β-mesitoylfurans (1). These condensations are remarkable in that they involve a double bond of the furan nucleus. Reactions are known which involve a benzene ring. Phenylmagnesium bromide condenses in this manner with benzophenone anil (I) (2), α,β-diphenylbenzalacetophenone (II) (3), benzanthrone (III) (4), and naphthacenequinone.



I

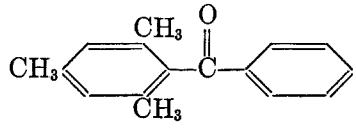


II

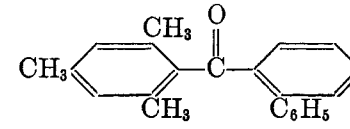


III

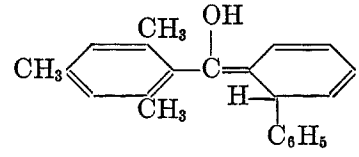
It has now been found possible to accomplish this type of reaction with mesityl aryl ketones. Benzoylmesitylene (IV) has been treated with phenylmagnesium bromide and it has been established that condensation occurs in the 1,4 manner and involves a double bond of a benzenoid ring. The product obtained in largest amount was 2-phenylbenzoylmesitylene (V).



IV



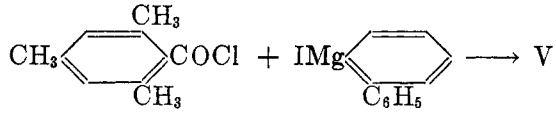
V



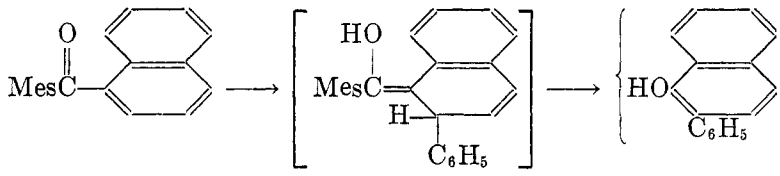
VI

The structure of this compound was established by degradation and synthesis. Cleavage with syrupy phosphoric acid produced *o*-phenylbenzoic acid. The

phenylated ketone (V) was synthesized from 2-xenylmagnesium iodide and mesitoyl chloride.

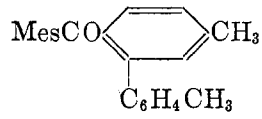


It (V) is presumably an oxidation product of the enol (VI) that would be expected. Although the enol could not be isolated, evidence of its formation was gained from work with other ketones. α-Mesitoylnaphthalene (VII),[1] for example, condensed with phenylmagnesium bromide to yield an oil from which mesitoic acid and 2-phenyl-1-naphthol could be obtained by exposure to air. These are the cleavage products to be expected for the enol (VIII).



VII VIII $MesCO_2H$

p-Tolyl mesityl ketone and *p*-tolylmagnesium bromide give rise to a compound that by analogy was identified as 2-mesitoyl-4′,5-dimethylbiphenyl (IX).



IX

Phenyl- and α-naphthyl-magnesium bromides condensed with *p*-bromobenzoylmesitylene to yield highly unsaturated products; the structure of these compounds was not established.

EXPERIMENTAL

Benzoylmesitylene and phenylmagnesium bromide. A solution of 50 g. of benzoylmesitylene in 150 cc. of dry ether was added slowly to a refluxing solution of phenylmagnesium bromide, prepared from 132 g. of bromobenzene and 21 g. of magnesium in 500 cc. of dry ether. After addition was completed the solution was stirred and refluxed for an additional five hours. The reaction mixture was then cooled and decomposed with dilute hydrochloric acid. The ether layer was washed with water and dried over calcium chloride. The ether was removed by evaporation. The resulting oil was distilled *in vacuo*. Biphenyl and benzoylmesitylene were found in the fore fraction.

The fraction boiling at 200–205° (4 mm.) was dissolved in methyl alcohol and a white compound was induced to crystallize. After two recrystallizations from ethanol, the 2-phenylbenzoylmesitylene melted at 89–90°; yield 8 g. or 18% of the theoretical.

Anal.[2] Calc'd for $C_{22}H_{20}O$: C, 88.00; H, 6.67.
Found: C, 87.59; H, 6.73.

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[1] Mes is used to represent the mesityl radical.

[2] Microanalyses by Miss Mary S. Kreger and Mr. L. G. Fauble.

One gram of 2-phenylbenzoylmesitylene was heated with 15 cc. of syrupy phosphoric acid for four hours. The mixture was poured into water, extracted with ether, and the ether layer extracted with 10% sodium carbonate solution. Acidification of this extract gave a small amount of a white material which when crystallized from ethanol melted at 112–113°. A mixed melting point with *o*-phenylbenzoic acid, m.p. 113°, showed no depression.

In addition to biphenyl, benzoylmesitylene, and 2-phenylbenzoylmesitylene, the original mixture contained a small amount of a very viscous liquid, b.p. 210–250° (4 mm.) from which was obtained a white crystalline compound, melting at 245–246°.

Anal. Calc'd for $C_{22}H_{22}O_2$: C, 83.02; H, 6.91.
Found: C, 83.43; H, 6.55.

An acetate of this compound was prepared by heating a small amount with acetic anhydride for one hour. The product was purified by recrystallization from methanol. It melted at 101° (cor.).

Anal. Calc'd for $C_{24}H_{24}O_3$: C, 80.00; H, 6.66.
Found: C, 79.98; H, 6.20.

The compound, $C_{22}H_{22}O_2$, and its acetate were not further investigated.

The distillation of the original reaction mixture left a large amount of tarry residue.

Synthesis of 2-phenylbenzoylmesitylene. 2-Iodobiphenyl was prepared according to the directions of Gilman, Kirby, and Kinney (2). One hundred and seventy grams of 2-aminobiphenyl yielded 195 g. (70%) of 2-iodobiphenyl; b.p. 169–170° (17 mm.).

2-Biphenylmagnesium iodide was prepared from 40 g. of 2-iodobiphenyl and 5 g. of magnesium in 120 cc. of dry ether; this solution was filtered into another flask. A solution of 24 g. of mesitoyl chloride (5) in 100 cc. of dry ether was added slowly to the clear solution of the reagent at such a rate that the ether refluxed gently. The reaction mixture was then refluxed and stirred for three hours, cooled, decomposed with ice and dilute hydrochloric acid, and worked up in the usual manner. After one recrystallization from ethanol, 32 g. (80% yield) of product was obtained; melting point and mixed melting point 89–90°.

Oxidation of enol intermediate obtained by the addition of phenylmagnesium bromide to benzoylmesitylene. To a solution of phenylmagnesium bromide prepared from 8.8 g. of bromobenzene and 1.35 g. of magnesium in 50 cc. of dry ether, was added slowly a solution of 10 g. of benzoylmesitylene in 30 cc. of ether. The remainder of the reaction was carried out in the usual manner. The reaction mixture was cooled in an ice-salt-bath and carefully decomposed with ice and hydrochloric acid. The ether layer was washed with ice-water and quickly transferred to a round-bottomed flask immersed in an ice-bath. A stream of dry air was passed through the solution for several hours, a little low-boiling petroleum ether being added from time to time to replace the solvent lost by evaporation. The ether was removed and its resulting dark brown oil was dissolved in absolute ethanol, which was allowed to evaporate slowly. A small amount of crystalline material separated and was isolated by dissolving the oil in a mixture of low-boiling petroleum ether and benzene and filtering the suspension. After two crystallizations from benzene the compound melted at 245° and gave no depression of melting point when mixed with the compound $C_{22}H_{22}O_2$ obtained previously; yield, 2.0 g.

The remaining oil was distilled, and from the distillate was obtained 3 g. (22% yield) of *o*-phenylbenzoylmesitylene, m.p. 84–88°.

α-Naphthoylmesitylene and phenylmagnesium bromide. A solution of 5 g. of α-naphthoylmesitylene in 50 cc. of benzene was added to the Grignard reagent prepared from 10.5 g. of bromobenzene and 1.6 g. of magnesium in 50 cc. of dry ether. Benzene was added to the reaction mixture and ether was allowed to evaporate until the temperature of the vapors reached 55°. The reaction mixture was refluxed and stirred for seventy-five hours. At the end of this time it was a light orange color. The solution was decomposed and worked up in the usual manner. The product was a black, sticky tar. The tar was dissolved in a

small amount of benzene, and the solution allowed to stand in an ice-box for several months. A white compound separated and was recrystallized from benzene; yield, 1 g., m.p. 210–211°.

Anal. Calc'd for $C_{16}H_{12}O$: C, 87.27; H, 5.45.
Found: C, 88.14; H, 5.11.

This compound was evidently 2-phenyl-1-naphthol; it underwent oxidation by atmospheric oxygen and other mild oxidizing agents to yield a brilliant red compound. Examination of the literature showed that 2-phenyl-1-naphthol had been prepared, though never purified, and was found to be easily oxidized to give a binaphthone, which melted at about 220°.

The oil from which the above compound was obtained was dissolved in ether and extracted with 10% sodium bicarbonate solution. Acidification of this solution gave 0.4 g. of mesitoic acid.

The ether solution was now extracted with 10% sodium hydroxide solution. This solution was nearly neutralized with acid and a dilute solution of potassium ferricyanide added. A voluminous deep purple precipitate formed, was extracted with benzene, and recrystallized from a benzene-ligroin mixture. A small amount of an almost black compound was obtained. It melted above 200° and was probably a binaphthone.

Preparation of p-*bromobenzoylmesitylene.* A solution of 160 g. of p-bromobenzoyl chloride in 500 cc. of carbon disulfide was added slowly to a well-stirred mixture of 106 g. of anhydrous aluminum chloride, 90 g. (105 cc.) of mesitylene, and 350 cc. of carbon disulfide. The addition was made over a period of two hours, and the reaction mixture was stirred at room temperature for five hours after the addition was completed. Most of the solvent was then distilled, and the pasty mass that remained was decomposed by pouring it into a mixture of ice and concentrated hydrochloric acid. The mixture was transferred to a separatory funnel, and the crude product was extracted with ether. The ether layer was washed with water, 10% sodium hydroxide solution, and again with water. The solvent was then evaporated and the crude product was recrystallized twice from 95% ethanol. Yield, 170 g. (75%); m.p. 72–73° (cor.).

Anal. Calc'd for $C_{16}H_{15}BrO$: C, 63.37; H, 4.95.
Found: C, 63.36; H, 4.39.

p-*Bromobenzoylmesitylene and phenylmagnesium bromide.* The reagent was prepared from 20 g. of bromobenzene and 4 g. of magnesium in 100 cc. of dry ether. This solution was filtered through glass wool and was added slowly to a solution of 30 g. of *p*-bromobenzoylmesitylene in 200 cc. of dry ether. The reaction mixture was refluxed gently and was well stirred during the addition, which was carried out over a period of two hours. The intense red solution which was obtained was refluxed and stirred for an additional five hours and decomposed with dilute acid. Removal of the solvent left an oily semi-solid product, which was washed with methanol. The yellow solid was crystallized once from methanol and melted at 119–120°; yield, 17 g. (43%). The pure compound melted at 121° (cor.).

Anal. Calc'd for $C_{22}H_{21}BrO$: C, 69.29; H, 5.51.
Found: C, 69.40; H, 5.69.

From the mother liquor was isolated a yellow solid which, when crystallized from methanol, melted at 131° (cor.).

Anal. Calc'd for $C_{22}H_{21}BrO_2$: C, 66.75; H, 5.28.
Found: C, 67.49; H, 5.27.

Properties of the compound $C_{22}H_{21}BrO$, *m.p. 121°.* This compound gives no precipitate with alcoholic silver nitrate. Treatment of the bromo compound with a 10% solution of sodium methoxide in methanol, produced a deep green solution.

Bromination. One gram of the compound was dissolved in 20 cc. of glacial acetic acid and 2.5 cc. of bromine added slowly to the solution. The reaction mixture became slightly warm and a small amount of hydrobromic acid fumes was noticed. The flask was allowed to stand at room temperature for thirty minutes. At the end of this time a white crystalline solid had separated; it was collected on a filter, washed with glacial acetic acid, and dried; yield, 1.25 g. After several recrystallizations from absolute ethanol it melted at 175° (cor.).

Anal. Calc'd for $C_{22}H_{19}Br_5O$: C, 37.71; H, 2.71.
Found: C, 37.47; H, 2.79.

The compound $C_{22}H_{21}BrO$ could not be acetylated or reduced and all attempts at dehydrogenation failed. It did not undergo a Diels-Alder condensation with maleic anhydride. A Zerewitinoff determination indicated that there was no active hydrogen.

p-*Bromobenzoylmesitylene and α-naphthylmagnesium bromide.* α-Naphthylmagnesium bromide was prepared from 18 g. of α-naphthyl bromide and 4 g. of magnesium in a mixture of 100 cc. of dry ether and 20 cc. of dry benzene. The reagent was filtered through glass wool and slowly added to a solution of 10 g. of *p*-bromobenzoylmesitylene in 50 cc. of dry ether. The reaction mixture was stirred and refluxed overnight and decomposed in the usual manner.

After removal of the solvent, the oily residue was subjected to steam distillation until a clear distillate was obtained. The residual dark colored oil hardened to an amorphous solid, which was difficult to crystallize. A small amount of the product was obtained crystalline by dissolving the oil in chloroform, adding low-boiling petroleum ether to the solution until it almost became turbid, and allowing the solvent to evaporate slowly. The solid was collected on a filter and washed with absolute ethanol. After several recrystallizations from ethanol it was obtained as colorless crystals melting at 195° (cor.).

Anal. Calc'd for $C_{26}H_{23}BrO$: C, 72.39; H, 5.34.
Found: C, 72.74; H, 5.40.

The filtrate was set aside and allowed to evaporate. After several weeks, part of the oil began to crystallize. The crystals were separated and the oil was taken up in alcohol and allowed to evaporate again. Eventually most of the oil crystallized. The compound was purified by recrystallization from absolute ethanol. It melted at 143° (cor.) and was the main product of the reaction.

Anal. Calc'd for $C_{26}H_{23}BrO$: C, 72.39; H, 5.34.
Found: C, 72.66; H, 5.42.

These two compounds are isomeric and have the composition of an addition product between *p*-bromobenzoylmesitylene and naphthalene.

p-*Toluylmesitylene and* p-*tolylmagnesium bromide.* A solution of 20 g. of *p*-toluylmesitylene in 50 cc. of dry ether was added slowly to a solution of *p*-tolylmagnesium bromide made from 2.8 g. of magnesium and 17.1 g. of *p*-bromotoluene in 60 cc. of dry ether. The mixture was refluxed for four hours and decomposed in the usual manner.

The thick yellow oil obtained was distilled *in vacuo*. The first fraction of 8.5 g. consisted of unchanged *p*-toluylmesitylene. A second fraction of 5.1 g. was an oil that failed to crystallize. From the final fraction was obtained yellow crystals melting at 101° (cor.). These had the composition of 2-mesitoyl-4',5-dimethylbiphenyl.

Anal. Calc'd for $C_{24}H_{24}O$: C, 87.75; H, 7.37.
Found: C, 87.78; H, 7.48.

SUMMARY

It has been shown that benzoylmesitylene condenses with phenylmagnesium bromide in the 1,4 manner to the conjugated system formed by the carbonyl group and a double bond of the benzene ring.

Similar results have been obtained with *p*-bromobenzoylmesitylene, α-mesitoylnaphthalene, and *p*-toluylmesitylene.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

SUCCESSIVE DIENE ADDITION AND DEHYDROGENATION IN NITROBENZENE SOLUTION WITHOUT ISOLATION OF THE HYDROAROMATIC INTERMEDIATE

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Occasionally the observation has been made that the diene reaction, when carried out in nitrobenzene solution, is accompanied by dehydrogenation of the primary hydroaromatic addition product. This behavior will be especially valuable if the addition product tends to dissociate again into its components; in this case, the dehydrogenation process removes the addition compound from the equilibrium mixture, and stabilizes the new product.

In a patent (1), the I. G. Farbenindustrie A. G. has shown that 2,3-dimethylbutadiene combines with naphthoquinone in nitrobenzene to give directly 2,3-dimethylanthraquinone. Clar (2) has reported that perylene and 2,3,10,11-dibenzperylene, which in xylene solution gave no trace of addition product with maleic anhydride, yielded the purely aromatic polycyclic system in nitrobenzene. The condensation between methyleneanthrone and maleic anhydride in the same solvent leads to the completely aromatic *bz*-benzanthrone-1,2-dicarboxylic acid with loss of four hydrogen atoms (3). More recently, Weizmann, E. Bergmann, and Berlin (4) have shown that a true benzoquinone derivative (I) is formed when phenylquinone acts upon bicyclohexenyl in nitrobenzene solution.

In the course of our synthetic experiments in the polycyclic series, we found it advisable to study the influence of nitrobenzene on the diene reaction more systematically. We have shown that nitrobenzene during these successive addition-dehydrogenation reactions is reduced to give water and aniline, which has been identified by the usual methods:

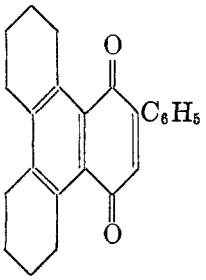
$$C_6H_5NO_2 + 3\ H_2 = C_6H_5NH_2 + 2\ H_2O.$$

Phenylated dienes, which have been investigated before with regard to their reactivity towards quinones (5), give, when the reaction is carried out in nitrobenzene solution, directly the anthraquinones: from 1-phenylbutadiene and benzoquinone, 1,5-diphenylanthraquinone is formed; from 1-phenylbutadiene and α-naphthoquinone, 1-phenylanthraquinone; from 1,4-diphenylbutadiene and benzoquinone, 1,4,5,8-tetraphenylanthraquinone; from 1,4-diphenylbutadiene and α-naphthoquinone, 1,4-diphenylanthraquinone.

In the same way the condensation between dienes and maleic anhydride in nitrobenzene solution gives substituted phthalic anhydrides instead of the tetrahydro derivatives. From 1,2-diphenylpentadiene-(1,3), 3,4-diphenyl-6-methylphthalic anhydride (II) (6) was obtained; from 1,2,4-triphenylbutadiene, 3,4,6-triphenylphthalic acid (III); and from 9-(1′-cyclopentenyl) phenanthrene, 1,2-cyclopentenotriphenylene-3,4-dicarboxylic acid anhydride

(IV), which so far (7) has been accessible only in a more complicated manner from the primary hydroaromatic addition product.

But this addition-dehydrogenation reaction is not generally applicable. If crotonic or cinnamic acid is condensed with bicyclohexenyl, the dodecahydro products V and VI are isolated from the nitrobenzene solution, whereas maleic anhydride leads to the octahydrophenanthrene derivative VII. It appears,



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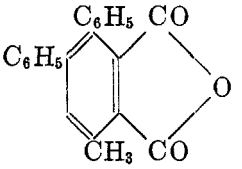

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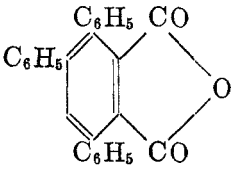

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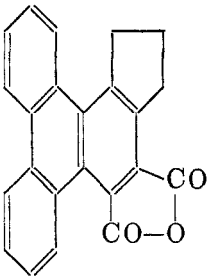

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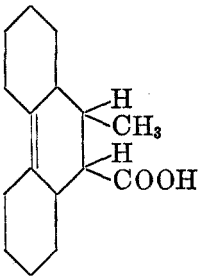

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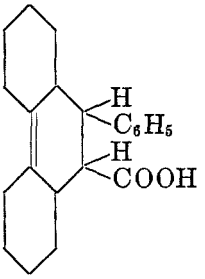

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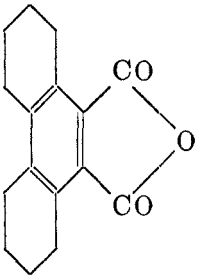

VII

therefore, that dehydrogenation is achieved only when two carbonyl groups substitute the "dienophile" olefin, and one may assume that enolization always precedes the splitting off of the hydrogen atoms.[1] By this process, the two enolized hydrogen atoms are removed, as in quinone I. The removal of the two remaining "hydroaromatic" hydrogens depends then on the stability of the intermediary dihydrobenzene nucleus, which is in most cases dehydrogenated spontaneously by a hydrogen acceptor in the reaction mixture, or by air.

[1] Weidlich (8), however, failed to obtain the aromatized condensation product from 1,1-bidialin and maleic anhydride in boiling nitrobenzene.

EXPERIMENTAL

1,5-Diphenylanthraquinone.[2] 1-Phenylbutadiene (13 g.), benzoquinone (5.5 g.), and nitrobenzene (20 cc.) were heated at 200° for 3 hours. The black, viscous mass was diluted with glacial acetic acid (20 cc.) and, after cooling, the quinone filtered. From nitrobenzene, greenish-yellow needles, m.p. 355°; yield, 7 g.

1-Phenylanthraquinone. 1-Phenylbutadiene (5 g.) and α-naphthoquinone (5 g.) in nitrobenzene (5 cc.), when heated at 180° in an oil-bath, reacted violently. The heating was continued for 5 minutes, then methyl alcohol (8 cc.) was added, the reaction product cooled and filtered. After distillation *in vacuo* (b.p. 180° at 0.2 mm.), the quinone had the m.p. 177°; yield, 5 g.

1,4,5,8-Tetraphenylanthraquinone. 1,4-Diphenylbutadiene (20 g.) and benzoquinone (5 g.) in nitrobenzene (25 cc.) were heated under slightly reduced pressure at the boiling point of the solvent. After 6 hours standing, the reaction product was cooled, filtered, washed with glacial acetic acid, and recrystallized from nitrobenzene; m.p. 355°; yield, 14 g.

1,4-Diphenylanthraquinone. 1,4-Diphenylbutadiene (5 g.) and α-naphthoquinone (2.2 g.) were boiled in nitrobenzene (10 cc.) for 2 hours. The reaction product crystallized on cooling and was purified as described previously (5); yield, 70%.

3,4-Diphenyl-6-methylphthalic anhydride (II). 1,2-Diphenylpentadiene-(1,3) (6) (5 g.) and maleic anhydride (3 g.) were heated for 3 hours in boiling nitrobenzene (15 cc.). The reaction product began to separate during the heating; after 48 hours standing it was collected and recrystallized from light petroleum (b.p. 130°); m.p. 161°.

Anal. Calc'd for $C_{21}H_{14}O_3$: C, 80.3; H, 4.5.
Found: C, 80.1; H, 4.3.

3,4,6-Triphenylphthalic acid (III). 1,2,4-Triphenylbutadiene-(1,3) (6) and maleic anhydride (1.5 g.) were heated at 100° in nitrobenzene (15 cc.) for 2 hours. On cooling, the reaction product separated, and was recrystallized from xylene; long rods, m.p. 172°. Analysis showed that the water formed during the reaction had hydrolyzed the anhydride system.

Anal. Calc'd for $C_{26}H_{18}O_4 + H_2O$: C, 75.7; H, 4.9.
Found: C, 75.7; H, 4.9.

1,2-Cyclopentenotriphenylene-3,4-dicarboxylic acid anhydride (IV) (7). 9-(1'-Cyclopentenyl)phenanthrene (0.5 g.) and maleic anhydride (0.5 g.) were heated for 2 hours in boiling nitrobenzene (10 cc.). The nitrobenzene was removed with steam, the residue isolated with chloroform and distilled *in vacuo*. The oil boiling under 0.1 mm. pressure at 300–310° solidified on trituration with acetone, and was recrystallized from ethyl benzoate; needles, m.p. 284°, which were identified by mixed melting point.

1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9-methylphenanthrene-10-carboxylic acid (V). Crotonic acid (4 g.) and bicyclohexenyl (8 g.) in nitrobenzene (25 cc.) were heated for 2 hours at 130–140°, then boiled for 6 hours. The solvent was removed with steam and the residue treated with ether, from which the acid was separated by extraction with sodium hydroxide. The crude acid was air-dried and distilled *in vacuo;* b.p. 180–200° at 3.5 mm. On trituration with acetone and ligroin, the syrup crystallized. From butyl acetate long rods were obtained, from petroleum ether (130°) and xylene, beautiful rhombohedra, m.p. 164°.

Anal. Calc'd for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7.
Found: C, 76.8; H, 10.0.

1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9-phenylphenanthrene-10-carboxylic acid (VI). Bicyclohexenyl (8 g.) and cinnamic acid (7 g.), after boiling for 5 hours in nitrobenzene

[2] For the discussion of the structural formula, see Weizmann, Bergmann, and Haskelberg (5).

(35 cc.), yielded a mixture of unreacted cinnamic acid and the condensation product. The latter was recrystallized from a mixture of xylene and petroleum ether (130°), m.p. 221°.

Anal. Calc'd for $C_{21}H_{20}O_2$: C, 81.3; H, 8.4.
Found: C, 81.2; H, 8.8.

1,2,3,4,5,6,7,8-Octahydrophenanthrene-9,10-dicarboxylic acid anhydride (VII). Bicyclohexenyl (3.2 g.) and maleic anhydride (2 g.) were boiled in nitrobenzene (10 cc.) for 5 hours. The solvent was removed *in vacuo* and the residue distilled, b.p. 220–240° at 1.5 mm. The syrup crystallized by trituration with acetone. From acetic anhydride the substance crystallized in needles of m.p. 305°, and was identified by mixed melting point with an authentic sample.

SUMMARY

The diene addition-dehydrogenation reaction, carried out in nitrobenzene solution, is described and discussed.

Phenylated dienes, with α-naphthoquinones and benzoquinones, give directly phenylated anthraquinones. With maleic anhydride, the phthalic anhydrides are obtained directly. Bicyclohexenyl with crotonic and cinnamic acid in nitrobenzene, however, yields the hydroaromatic compounds.

REHOVOTH, PALESTINE.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SWARTHMORE COLLEGE]

ARYLSULFONYL METHYLISOTHIOUREAS

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One of the reactions by which we attempted to prepare the arylsulfonyl ureas (1) was through the hydrolysis of the corresponding arylsulfonyl methylisothioureas. This reaction had already been successfully carried out in the pyrimidine series, when the ethylthiol group was transformed into the carbonyl group by means of warm dilute hydrochloric acid solution. In particular, Wheeler (2) and his co-workers converted 2-ethylthiol-6-oxypyrimidine-5-carboxylic acid to uracil-5-carboxylic acid. Ethyl mercaptan was the by-product. Several of the analogous derivatives of the arylsulfonyl methylisothiourea series have now been prepared and the hydrolysis of these has been studied. We were not able to prepare any pure specimens of the arylsulfonyl ureas by the hydrolysis of the corresponding isothiourea derivatives. While the amount of methyl mercaptan was in all cases practically quantitative, the main product proved to be a mixture of the arylsulfonyl amide and the arylsulfonyl urea.

The sulfonylisothioureas have not been recorded in the literature, and furthermore it has now been shown that the *p*-aminobenzenesulfonyl methylisothiourea has value in the treatment of streptococcal infection in mice. It is, therefore, considered of value to record some of the compounds of this series.[1]

EXPERIMENTAL PART[2]

Since the procedure for the condensation of the various sulfonyl chlorides with the methylisothiourea is practically the same for all the compounds prepared, only the detailed account of preparation of the *p*-acetaminobenzenesulfonyl methylisothiourea will be given. The hydrolysis of this is also described. The melting points and analyses are given in tabular review.

Preparation of p-*acetaminobenzenesulfonyl methylisothiourea.* In a three-liter flask provided with a motor stirrer were placed 400 g. of anhydrous potassium carbonate and one liter of acetone to which had been added 300 cc. water. The suspension was stirred and cooled in an ice-bath. To this was added a mixture of 153 g. (1.1 moles) of methylisothiourea sulfate and 234 g. (1.0 mole) of *p*-acetaminobenzenesulfonyl chloride[3] over a period of half an hour. After the addition, the ice-bath was removed and the reaction mixture stirred for four hours. The reaction contents were then poured while stirring into four liters of water, filtered, and washed with water. When dried, the crude product weighed 228 g. (80%). After crystallization from dilute acetic acid, small colorless needles were deposited which melted at 230–232°.

Preparation of p-*aminobenzenesulfonyl methylisothiourea.* Two hundred grams of *p*-

[1] Private communication from Professor Perrin H. Long, The Johns Hopkins Medical School.

[2] The author wishes to express this thanks to Mr. S. M. Raymond who prepared and analyzed some of the compounds.

[3] Grateful acknowledgement is made to the Monsanto Chemical Company for its generous supply of *p*-acetaminobenzenesulfonyl chloride.

acetaminobenzenesulfonyl methylisothiourea (crystallized once from dilute acetic acid) was suspended in 1200 cc. of 7% hydrochloric acid solution. The flask was lowered into a boiling water-bath and mechanically stirred until solution took place (30–45 mins.). The solution was then treated with charcoal, filtered while hot, and the filtrate diluted with one-half volume of water (to prevent the crystallization of the hydrochloride salt). It was then cooled in an ice-bath and made alkaline with ammonia (stirring). The crude product was filtered, washed, and dried (128 g., 75% yield). After a specimen was twice crystallized from dilute acetic acid it melted at 183–185° (colorless white needles).

TABLE

ARYLSULFONYL METHYLISOTHIOUREAS

$ArSO_2NHC(SCH_3)=NH$.

Ar.	M.P., °C.	FORMULA	NITROGEN %	
			Calc'd	Found
Benzene	159–160	$C_8H_{10}N_2O_2S_2$	12.16	12.23
Toluene	118–119	$C_9H_{12}N_2O_2S_2$	11.46	11.35
o-Xylene	136–137	$C_{10}H_{14}N_2O_2S_2$	10.84	11.04
m-Xylene	137–138	$C_{10}H_{14}N_2O_2S_2$	10.84	10.64
p-Xylene	144–145	$C_{10}H_{14}N_2O_2S_2$	10.84	10.60
p-Acetaminobenzene	230–232	$C_{10}H_{13}N_3O_3S_2$	14.62	14.81
p-Aminobenzene	183–185	$C_8H_{11}N_3O_2S_2$	17.13	17.06

SUMMARY

The preparation of arylsulfonyl methylisothioureas has been described, with particular reference to the preparation of *p*-acetaminobenzene sulfonyl and *p*-aminobenzenesulfonyl methylisothioureas.

The latter substance shows value in cases of streptococcal infection in mice, and it is to be further investigated in this connection.

SWARTHMORE, PA.

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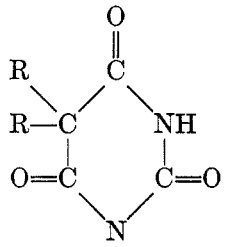
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

SYNTHESIS OF THE PYRIMIDINE ANALOG OF THIAMIN BROMIDE

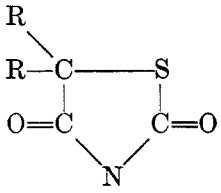
YOLANDA A. TOTA AND ROBERT C. ELDERFIELD

Received March 10, 1942

In 1937 Erlenmeyer and von Meyenburg (1) reported the preparation of analogs of the dialkyl barbiturates (I) in which a ring sulfur atom is substituted for the —CONH— group, giving heterocycles of the type shown by formula II. These sulfur compounds were found by the authors to possess hypnotic activity similar to that of the parent barbiturates.



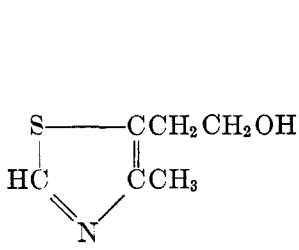
I



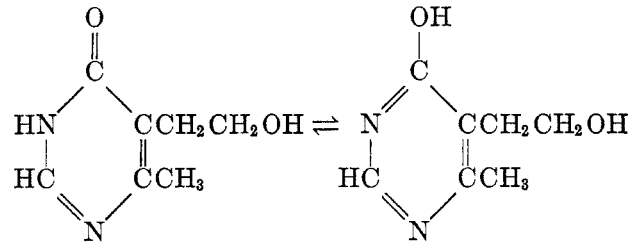
II

It seemed of interest, therefore, to determine whether this kind of substitution could be generalized and reversed, that is, whether the replacement of a ring sulfur atom in a physiologically active compound by a —CONH— group would yield a product exhibiting the same type of activity as the original compound.

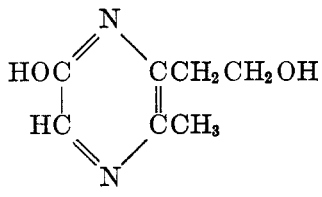
A suitable test substance for this purpose is thiamin, the thiazole portion of which is represented by III. If the sulfur atom in III is replaced by a —CONH— group, two structures are possible, 4-methyl-5-(β-hydroxyethyl)-6-hydroxypyrimidine (IV) and 2-methyl-3-(β-hydroxyethyl)-5-hydroxypyrazine (V), depending on the mode of substitution. In the present paper the synthesis of the pyrimidine analog of thiamin bromide is described.



III

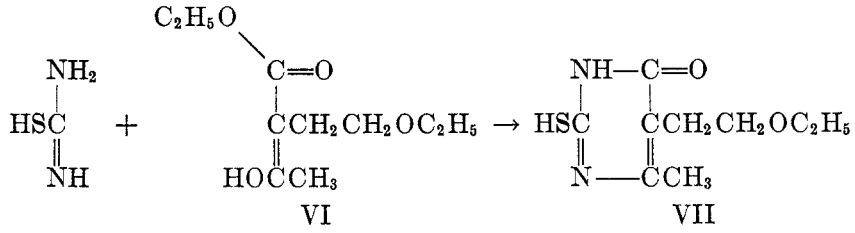


IV

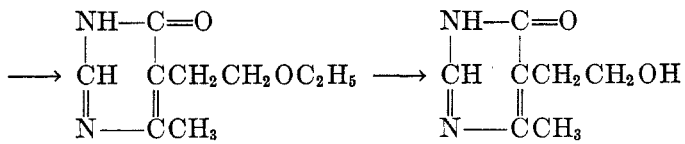


V

A suitable approach to the synthesis of the pyrimidine in question was suggested by the method utilized by Andersag and Westphal (2) for the synthesis of [6-methyl-4-hydroxypyrimidyl-(5)]-acetic acid. By condensation of thiourea with ethyl β-ethoxyethylacetoacetate (VI), 2-mercapto-4-methyl-5-(β-ethoxyethyl)-6-hydroxypyrimidine (VII) was readily formed. Oxidative removal of the mercapto group in VII led to 4-methyl-5-(β-ethoxyethyl)-6-hydroxypyrimidine (VIII), which on cleavage of the ether group led successively to the corresponding chloroethyl derivative and finally to IV.

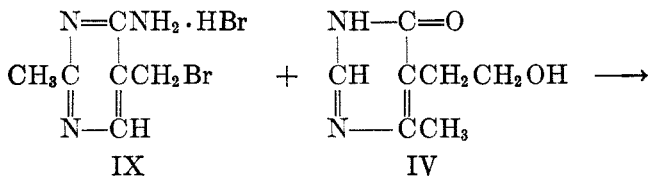


VI VII

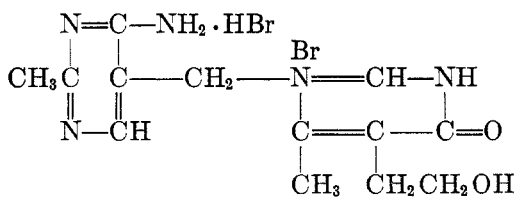


VIII IV

The pyrimidine IV condensed smoothly with 2-methyl-4-amino-5-bromomethylpyrimidine (IX) to yield a compound analogous to thiamin bromide. While it has not been definitely demonstrated which of the two nitrogen atoms of IV takes part in this condensation, it is logical to assume that the nitrogen atom in position 3 is the more basic, and hence is involved in the condensation. The thiamin bromide analog would then possess the structure X.



IX IV



X

The pyrimidine analog of thiamin bromide, as well as the pyrimidine IV, is being examined for activity and a report of this will appear elsewhere.

The synthesis of the pyridine analog of thiamin bromide, wherein the sulfur

atom of the thiazole ring is replaced by a —CH=CH— grouping, has been previously given (3) and a report of certain phases of its activity has recently appeared (4).

We wish to express our appreciation to Merck & Company, Inc. of Rahway, N. J. for the generous contribution of the 2-methyl-4-amino-5-bromomethylpyrimidine used in this work.

EXPERIMENTAL

All melting points are corrected for stem exposure.

2-Mercapto-4-methyl-5(β-ethoxyethyl)-6-hydroxypyrimidine (VII). A solution of 0.5 mole of sodium in 200 cc. of absolute alcohol was added to a solution of 100 g. of ethyl α-(β-ethoxyethyl)acetoacetate (3) and 40 g. of thiourea in 80 cc. of absolute alcohol. The reaction mixture was refluxed for 7 hrs. At the end of 30 min. the solution darkened and the pale yellow salt of the pyrimidine began to precipitate out. About 50 cc. of the alcohol was distilled off and the salt was centrifuged from the sticky red-brown solution and washed with absolute alcohol. The product was dissolved in water and the solution was acidified to Congo red with dilute hydrochloric acid. The colorless precipitate was filtered off and washed with water. The yield of the pyrimidine was 40.5 g. It melted at 202.5–203°. Further concentration of the alcoholic mother liquor and treatment as above gave an additional 15 g. of the pyrimidine, which was pale yellow in color. A small sample crystallized from a large volume of water in needles which melted at 203–203.5°.

Anal. Calc'd for $C_9H_{14}N_2O_2S$: C, 50.4; H, 6.6.
Found: C, 50.5; H, 6.6.

4-Methyl-5-(β-ethoxyethyl)-6-hydroxypyrimidine (VIII). A solution of 55 g. of the above pyrimidine in 850 cc. of hot glacial acetic acid was treated with 110 g. of lead acetate dissolved in 300 cc. of water. When the solution had cooled to 30°, 100 cc. of 29% hydrogen peroxide (Superoxol) diluted to 300 cc. was added at such a rate that the temperature did not rise above 40°. The reaction mixture was then heated at 50° for 3 hrs. The precipitated lead sulfate was filtered off through a layer of Norit and the excess lead was removed from the filtrate with hydrogen sulfide. The filtrate from the lead sulfide was then concentrated to dryness under reduced pressure and the residue was dissolved in a small volume of chloroform and the product was precipitated with ether. The first portion of the precipitate was less pure than the rest. Therefore it was collected separately, recrystallized from benzene, and combined with the purer ether precipitate, giving a total of 16 g. of product melting at 133.5–137.5°. As purification could be effected more readily in the subsequent step, the compound was used without further treatment. A small sample purified by recrystallization from benzene melted at 147.5–148°.

Anal. Calc'd for $C_9H_{14}N_2O_2$: C, 59.3; H, 7.7.
Found: C, 59.3; H, 7.9.

The *hydrobromide* melted at 126.5–127.5°, after recrystallization from chloroform and ethyl acetate.

Anal. Calc'd for $C_9H_{15}BrN_2O_2$: C, 41.1; H, 5.8.
Found: C, 41.3; H, 6.0.

4-Methyl-5-(β-chloroethyl)-6-hydroxypyrimidine hydrochloride. Five grams of the above pyrimidine was heated in a sealed tube for 3 hrs. at 150° with 35 cc. of concentrated hydrochloric acid (5). The solution was then diluted with water, filtered, and concentrated to dryness under reduced pressure with the addition of several portions of water, yielding 4.9 g. of crude product. Recrystallization from absolute alcohol and ether gave 4.2 g. of the hydrochloride, which melted at 167.5–168.5°. A small sample recrystallized once more from alcohol and ether melted at 168.5–169°.

Anal. Calc'd for $C_7H_{10}Cl_2N_2O$: C, 40.2; H, 4.8.
Found: C, 40.3; H, 5.0.

4-Methyl-5-(β-hydroxyethyl)-6-hydroxypyrimidine (IV). Three and seven-tenths grams of the above chloroethylpyrimidine salt was heated for 4 hrs. with 30 cc. of water in a sealed tube at 150°. Evaporation of the solution to dryness under reduced pressure gave 3.7 g. of crude material. On recrystallization from methanol and ether, 3.2 g. of the pure hydrochloride melting at 198.5–199° (with effervescence), was obtained.

Anal. Calc'd for $C_7H_{11}ClN_2O_2$: C, 44.1; H, 5.8.
Found: C, 44.3; H, 6.1.

The water-soluble base was liberated from its salt by stirring for 6 hrs. in aqueous solution with a 10% excess of freshly precipitated silver carbonate. The reaction mixture was then filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was recrystallized from absolute alcohol. The pure product melted at 154–154.5°.

Anal. Calc'd for $C_7H_{10}N_2O_2$: C, 54.5; H, 6.4.
Found: C, 54.5; H, 6.5.

The p-*nitrobenzoate* was prepared by warming the above pyrimidine for 2 min. with a slight excess of *p*-nitrobenzoyl chloride. After several recrystallizations from alcohol, it melted at 207.5–208°.

Anal. Calc'd for $C_{14}H_{13}N_3O_5$: C, 55.5; H, 4.3.
Found: C, 55.7; H, 4.6.

3-[(4-Amino - 2 - methyl)-5-pyrimidylmethyl]-4-methyl-5-(β-hydroxyethyl)-6-hydroxypyrimidinium bromide hydrobromide (X). A suspension of equivalent amounts of 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide and 2-methyl-3-(β-hydroxyethyl)-4-hydroxypyrimidine in light petrolatum was heated for 1 hr. at 100° with constant stirring. The amorphous precipitate was centrifuged off and washed with petroleum ether (Skellysolve B). After two recrystallizations from absolute alcohol, the product melted at 195–195.5°. It was slightly hygroscopic.

Anal. Calc'd for $C_{13}H_{19}Br_2N_5O_2$: C, 35.7; H, 4.4.
Found: C, 36.0; H, 5.0.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. 4-Methyl-5-(β-hydroxyethyl)-6-hydroxypyrimidine has been prepared.

2. Condensation of the above pyrimidine with 2-methyl-4-amino-5-bromomethylpyrimidine leads to an analog of thiamin bromide wherein the thiazole ring has been replaced by a pyrimidine ring.

NEW YORK, N. Y.

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(2) ANDERSAG AND WESTPHAL, *Ber.*, **70**, 2052 (1937).
(3) TRACY AND ELDERFIELD, *J. Org. Chem.*, **6**, 54 (1941).
(4) ROBBINS. *Proc. Natl. Acad. Sci. U. S.*, **27**, 419 (1941).
(5) CLARKE AND GURIN, *J. Am. Chem. Soc.*, **57**, 1879 (1935).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

A GENERAL SYNTHESIS FOR 2,3-DISUBSTITUTED AND 2,3,6-TRISUBSTITUTED 5-HYDROXYPYRAZINES

YOLANDA A. TOTA AND ROBERT C. ELDERFIELD

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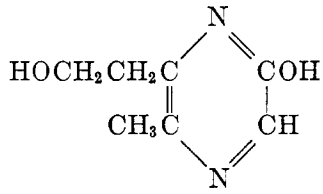
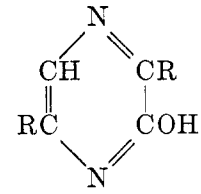
In the preceding paper the synthesis of the pyrimidine analog of thiamin bromide was described, and it was pointed out that a pyrazine analog is also possible on the basis of substitution of a —CONH— group for the ring sulfur atom of the thiazole of thiamin in accordance with the observations of Erlenmeyer and von Meyenburg (1) on similar substitutions with barbiturates. The pyrazine desired, therefore, is 2-methyl-3-(β-hydroxyethyl)-5-hydroxypyrazine (I),



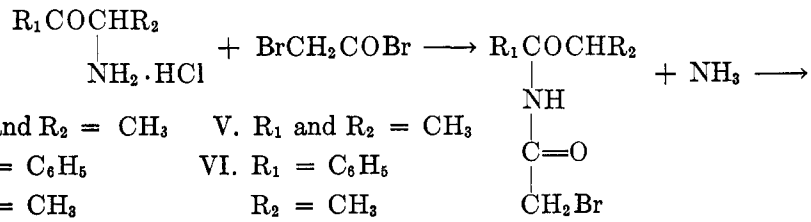
I



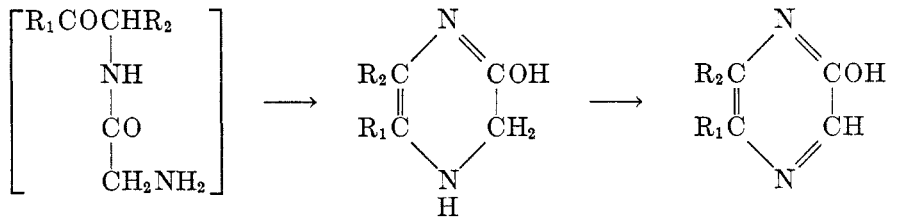
II

A survey of the literature revealed that existing methods for the preparation of substituted hydroxypyrazines lead exclusively to the formation of pyrazines of the type represented by II in which the two substituents are identical (2). Therefore attention was turned to the development of a general method for the preparation of other types of substituted hydroxypyrazines. In the present paper representative procedures are given by which one can obtain 2,3-disubstituted 5-hydroxypyrazines as well as 2,3,6-trisubstituted 5-hydroxypyrazines.

The method developed involves acylation of an α-amino ketone with chloroacetyl chloride or bromoacetyl bromide to yield the corresponding chloro- or bromo-acetyl amino ketone. The latter, in turn, on treatment with alcoholic ammonia in the presence of a small amount of sodium iodide, leads directly to the dihydropyrazine, presumably by way of the intermediate glycine derivative. The dihydropyrazine is then easily oxidized to the pyrazine by air.



III. R_1 and R_2 = CH_3
IV. R_1 = C_6H_5, R_2 = CH_3
V. R_1 and R_2 = CH_3
VI. R_1 = C_6H_5, R_2 = CH_3



VII VIII IX. R_1 and R_2 = CH_3
X. R_1 = C_6H_5
R_2 = CH_3

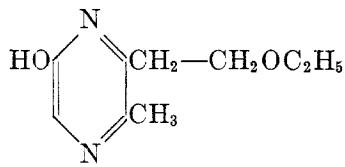
A further variation of the method furnished a convenient means for the synthesis of 2,3,6-trisubstituted 5-hydroxypyrazines. This involves merely use of an appropriate α-bromo acid halide instead of the α-bromoacetyl bromide used in the preceding cases, and details have been worked out for the preparation of 2-phenyl-3-methyl-5-hydroxy-6-ethylpyrazine.

The tendency of free α-amino ketones to condense with themselves with the formation of symmetrically tetrasubstituted pyrazines presented considerable difficulty in the first step of the above synthesis because of the necessity of liberating the base from its salt in order to accomplish the bromoacetylation. The first experiments were made with chloroacetyl chloride, but it later developed that the more reactive bromoacetyl bromide gave much better results. The procedure finally adopted was that in which the reactants were brought together in well-cooled chloroform solution in the presence of a small amount of water and an excess of solid calcium carbonate. The aqueous layer was thus maintained at a slightly acid *p*H. Yields as high as 99% of the desired product were obtained, particularly in cases where the amino ketones were the least soluble in water.

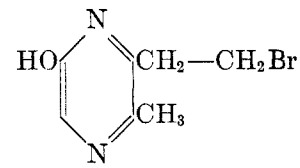
In the ring closure of the acylated amino ketones it was found that the bromo derivatives gave much better yields than the chloro derivatives, particularly in the presence of a small amount of sodium iodide. Isolation of the dihydropyrazines was not practical because of the ready oxidation of these substances by air. This oxidation to the pyrazine was accompanied by the formation of more or less dark oil, except in the case of 2-phenyl-3-methyl-6-ethyl-5-hydroxypyrazine, in which the presence of the substituent in the 6-position seems to stabilize the molecule. Attempts to carry out the oxidation of the dihydropyrazine with mild inorganic oxidizing agents gave only black oils. While warming the substances in the presence of air appears to be the best method of accomplishing the oxidation, attempts to accelerate it by bubbling air through the solution either produced no apparent change or else led to the formation of excessive amounts of oily products.

The above reactions appear to be general in their application to various pyrazine derivatives. The limiting factor is the availability of the requisite α-amino ketone.

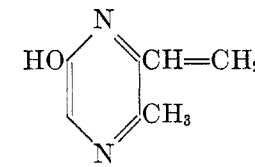
On the basis of the experience thus gained, attention was directed to the synthesis of 2-methyl-3-(β-hydroxyethyl)-5-hydroxypyrazine. 2-Methyl-3-(β-ethoxyethyl)-5-hydroxypyrazine (XI) was readily prepared by the above method. However, it has not been possible to accomplish cleavage of the ether group in XI in the desired sense to yield the hydroxyethyl derivative. When XI was heated with hydrochloric acid in a sealed tube under conditions which normally split the ether in the analogous thiazole, pyridine, and pyrimidine derivatives, the substance was completely decomposed. Treatment of the ether with hydriodic acid led to obscure iodine-containing complexes from which no



XI



XII



XIII

pure substance could be isolated. When the ether was heated with aqueous hydrobromic acid on the steam-bath, a portion of the material was recovered and the rest underwent extensive decomposition.

When XI was heated with a saturated acetic acid solution of hydrogen bromide on the steam-bath, a crystalline substance was obtained. However, the analytical figures obtained did not agree with those required by the expected β-bromoethyl derivative (XII). It is possible that this material is XII contaminated with a persistent impurity. Attempts to replace the bromine atom in the above substance by hydroxyl were unsuccessful. In only one experiment was a crystalline product obtained. When the bromine-containing substance was warmed with dilute sodium carbonate solution, a halogen-free substance was obtained which furnished analytical figures corresponding to 2-methyl-3-vinyl-5-hydroxypyrazine (XIII).

The exact nature of XII and XIII remains a subject of further investigation.

EXPERIMENTAL

All melting points are corrected for stem exposure.

3-Chloroacetaminobutanone-2. Biacetyl monoxime was reduced essentially according to the method of Künne (3). Thirty grams of the oxime was added in portions to a solution of 190 g. of stannous chloride (dihydrate) in 250 cc. of concentrated hydrochloric acid, cooling when necessary. The reaction mixture was finally warmed a short time on the steam-bath after the addition of metallic tin to reduce the stannic chloride. The solution was then diluted to 3 liters and saturated with hydrogen sulfide. The filtrate from stannous sulfide was evaporated to dryness at 20 mm. giving 34 g. of a colorless crystalline solid. The hydrochloride of 3-aminobutanone-2 is very hygroscopic and quite unstable, becoming red on standing.

A solution of 4.3 g. of the above amine salt in 20 cc. of cold water was added all at once to a vigorously stirred suspension of 12 g. of calcium carbonate in 20 cc. of chloroform surrounded by an ice-bath. Immediately a solution of 5.3 cc. (2 equivalents) of chloroacetyl chloride in 10 cc. of chloroform was added quite rapidly from a dropping-funnel. The reaction mixture was filtered and the excess calcium carbonate was thoroughly washed with

chloroform. The combined chloroform solution was washed with dilute hydrochloric acid, with sodium bicarbonate solution, and then with water. After drying over sodium sulfate and removal of the solvent at 20 mm., 3.3 g. of colorless crystalline product was obtained. On recrystalization from ether and ligroin (b.p. 77–116°, Skellysolve D) 3-chloroacetaminobutanone-2 melted at 54-55°.

Anal. Calc'd for $C_6H_{10}ClNO_2$: C, 44.1; H, 6.2.
Found: C, 44.1; H, 6.2.

3-Bromoacetaminobutanone-2 (*V*). A solution of 5 g. of 3-aminobutanone-2 hydrochloride in 25 cc. of cold water was added in 6-cc. portions to a cooled, well-stirred suspension of 20 g. of calcium carbonate in 70 cc. of chloroform, while 7 cc. of bromoacetyl bromide dissolved in 50 cc. of chloroform was rapidly added from a dropping-funnel. The reaction mixture was worked up as above, removal of the solvent giving a slightly yellow crystalline product contaminated with an oil. The oil and color were removed by washing with a small volume of cold ether. The yield of product melting at 64.5–66° was 4.6 g. A sample twice recrystallized from boiling ether and ligroin (Skellysolve D) formed fine needles melting at 71–71.5°.

Anal. Calc'd for $C_6H_{10}BrNO_2$: C, 34.6; H, 4.8: Br, 38.4.
Found: C, 34.9; H, 5.0; Br, 38.2.

The p-*nitrophenylhydrazone* melted at 169.5° after recrystallization from alcohol.

Anal. Calc'd for $C_{12}H_{15}BrN_4O_3$: C, 42.0; H, 4.4.
Found: C, 42.3; H, 4.4.

2,3-Dimethyl-5-hydroxypyrazine (*IX*). Four and one-half grams of the above bromoacetylated amino ketone was treated with 30 cc. of saturated alcoholic ammonia and 0.5 g. of sodium iodide for 48 hours at room temperature. The alcohol and ammonia were removed slowly on the steam-bath and the residue was extracted thoroughly with chloroform. After drying the extract over sodium sulfate, evaporation of the solvent, and recrystallization of the residue from ethyl acetate with the use of Norit, 0.9 g. of a tan crystalline product was obtained. It melted at 197.5–199.2°. Several recrystallizations from ethyl acetate gave a colorless product melting at 200–201°.

Anal. Calc'd for $C_6H_8N_2O$: C, 58.1; H, 6.5; N, 22.6.
Found: C, 58.2; H, 6.7; N, 22.6.

α-Chloroacetaminopropiophenone. α-Aminopropiophenone hydrochloride was prepared according to the method of Behr-Bregowski (4). A solution of 1.9 g. of this compound in 10 cc. of water was added to a suspension of 5 g. of calcium carbonate in 20 cc. of chloroform. The mixture was treated with 1.5 cc. of chloroacetyl chloride in 10 cc. of chloroform. Removal of the solvent gave 2.2 g. of a colorless syrup which crystallized on cooling in ice. It melted at 83–85°. On dissolving in a small volume of chloroform and precipitating with ligroin (Skellysolve D), 2.1 g. of a compound melting at 85–85.2° was obtained.

Anal. Calc'd for $C_{11}H_{12}ClN_2O_2$: C, 58.5; H, 5.4; Cl, 15.7.
Found: C, 58.5; H, 5.2; Cl, 15.8.

α-Bromoacetaminopropiophenone (*VI*). Seven and one-half grams of α-aminopropiophenone hydrochloride was treated as above with 7 cc. of bromoacetyl bromide. Nine and eight-tenths grams of crystalline product melting at 78–81° was obtained on removal of the chloroform. A small sample recrystallized from ether and ligroin (Skellysolve D) sintered at 80° and was completely melted at 82°.

Anal. Calc'd for $C_{11}H_{12}BrNO_2$: C, 48.9; H, 4.5; Br, 29.6.
Found: C, 48.6; H, 4.4; Br, 29.8.

1-Phenyl-2-methyl-5-hydroxypyrazine (*X*). Nine grams of the above bromoacetyl amino ketone was treated with 40 cc. of saturated alcoholic ammonia for 48 hours at room temperature. The solution was warmed on the steam-bath until the excess ammonia and about 15 cc. of the alcohol had evaporated off. On cooling, 2 g. of an orange product crystallized out. After washing with water and drying, the compound was recrystallized from chloroform and petroleum ether (b.p. 60–71°, Skellysolve B) with the use of Norit, and formed glistening yellow plates which decomposed at 250°. A small sample was recrystallized several times from ethyl acetate until it was colorless. It decomposed at 254°.

Anal. Calc'd for $C_{11}H_{10}N_2O$: C, 71.0; H, 5.4; N, 15.1.
Found: C, 71.3; H, 5.6; N, 15.2.

α-(α-Bromobutyryl)aminopropiophenone. A solution of 10 g. of α-aminopropiophenone hydrochloride in 30 cc. of water was added in portions to a cooled, vigorously stirred suspension of 25 g. of calcium carbonate in 70 cc. of chloroform while a chloroform solution of 12.7 g. of α-bromobutyryl chloride was added quite rapidly from a dropping-funnel. When the odor of the bromobutyryl chloride had disappeared, the reaction mixture was worked up as before, giving 16.5 g. of crude product as colorless crystals melting at 63–70°. After washing with cold petroleum ether (Skellysolve B) the compound weighed 14 g. and sintered at 72°, then melted at 82.5°. Recrystallization from boiling ether and petroleum ether (Skellysolve B) gave a product melting at 88.5–90°.

Anal. Calc'd for $C_{13}H_{16}BrNO_2$: C, 52.4; H, 5.4; Br, 26.8.
Found: C, 52.6; H, 5.6; Br, 26.7.

The p-*nitrophenylhydrazone* melted at 185–185.5°, after recrystallization from alcohol.

Anal. Calc'd for $C_{19}H_{21}BrN_4O_3$: C, 52.7; H, 4.9.
Found: C, 53.0; H, 5.1.

2-Phenyl-3-methyl-6-ethyl-5-hydroxypyrazine. Thirteen and one-half grams of the above compound was treated with 100 cc. of saturated alcoholic ammonia and 2 g. of sodium iodide for 3 days at room temperature. The alcohol was slowly evaporated on the steam-bath after the addition of 20 cc. of water, until an oil began to separate out. A few drops of methanol added to the hot solution dissolved the oil, and after cooling and standing in the ice-box several days, 4.9 g. of a crystalline product, covered with an oily film, appeared. At no time did the reaction mixture darken as in the preparation of those pyrazines having no substituent in the 6-position. Recrystallization of the crude product from benzene gave an almost colorless, nicely crystalline compound melting at 189–191°. Addition of water to the original reaction mixture, and two crystallizations of the precipitate gave an additional 0.3 g. of the product. For analysis the compound was further recrystallized from benzene; it melted at 192–193°.

Anal. Calc'd for $C_{13}H_{14}N_2O$: C, 72.9; H, 6.6; N, 13.1.
Found: C, 73.1; H, 6.6; N, 13.1.

2-Methyl-3-β-ethoxyethyl-5-hydroxypyrazine

α-Isonitroso-γ-ethoxypropyl methyl ketone. The method used was that outlined by Meyer and Züblin (5). To 20 g. of 5% sodium hydroxide solution was added 78 g. of ethyl α-(β-ethoxyethyl)acetoacetate and the mixture was stirred 9 hours. Twenty-six and six-tenths grams of solid sodium nitrite was then added and the orange solution was cooled in an ice-bath while a solution of 30 cc. of concentrated sulfuric acid in 80 cc. of water was slowly added from a dropping-funnel. The solution was allowed to stand overnight and was then made alkaline with 10% sodium hydroxide solution and extracted with ether. On acidification with sulfuric acid (saturation with carbon dioxide may be used) the product separated as a red-brown oil. The aqueous layer was extracted with ether and the combined oil and

extracts washed free of acid, dried over sodium sulfate, and distilled. The yield of product boiling at 108–113° at 2.3 mm. was 30 g. Amounts greater than 30 g. could not be distilled without decomposition. A small sample was redistilled and boiled at 116–116.5° at 1.4 mm. The freezing point was 29.5°.

Anal. Calc'd for $C_7H_{13}NO_3$: C, 52.9; H, 8.2; N, 8.9.
Found: C, 52.9; H, 8.4; N, 8.9.

The p-*nitrophenylhydrazone* melted at 182–183° after recrystallization from alcohol.

Anal. Calc'd for $C_{13}H_{18}N_4O_4$: C, 53.1; H, 6.2.
Found: C, 52.9; H, 6.4.

α-Amino-γ-ethoxypropyl methyl ketone hydrochloride. Sixty-five grams of the above oxime was reduced with stannous chloride and hydrochloric acid by the same procedure used for biacetyl monoxime. In this case the reaction was slower, however. The yield of colorless feathery crystalline product obtained on concentration to dryness was 63 g. The compound is very hygroscopic, changing to a dark syrup on exposure to air. It could be recrystallized only in small quantities because of its extreme sensitivity to heat. The uncrystallized product was used without further purification. A small sample recrystallized from ethyl acetate melted at 97–98°.

Anal. Calc'd for $C_7H_{16}ClNO_2$: C, 46.3; H, 8.9.
Found: C, 46.0; H, 8.9.

α-Bromoacetamino-γ-ethoxypropyl methyl ketone. Twenty-five grams of the above amino ketone was treated as above with 25 cc. of bromoacetyl bromide. Removal of the chloroform gave 40 g. of a crude oil. This could not be distilled, since it showed signs of decomposition even at 60° under reduced pressure. The crude product was crystallized by cooling in an ice-bath and then washed with Skellysolve B by inverted filtration, giving 34 g. of an almost colorless oil at room temperature. An analytical sample was prepared by recrystallization from ether and Skellysolve D (ligroin) by quickly centrifuging the cold mixture. It melted at 30–31.2°.

Anal. Calc'd for $C_9H_{16}BrNO_3$: C, 40.6; H, 6.1; Br, 30.0.
Found: C, 40.5; H, 6.2; Br, 29.9.

The p-*nitrophenylhydrazone* melted at 121–122° after recrystallization from alcohol.

Anal. Calc'd for $C_{15}H_{22}BrN_3O_4$: C, 44.9; H, 5.3.
Found: C, 45.3; H, 5.4.

2-Methyl-3-(β-ethoxyethyl)-5-hydroxypyrazine (XI). Seven grams of the above compound was treated with 40 cc. of a saturated solution of alcoholic ammonia and 1 g. of sodium iodide for 48 hours at room temperature. After adding 25 cc. of water, the alcohol and ammonia were removed on the steam-bath. On cooling, 1.3 g. of a yellow crystalline precipitate melting at 158–160° was obtained. The filtrate, on saturation with sodium chloride, precipitated a dark oil which crystallized in the ice-box giving an additional 0.2 g. of product. Recrystallization from ethyl acetate gave 1.2 g. of product melting at 160.2–161°. The aqueous reaction mixture on standing in air for several days gave a further precipitate of a dark oil which was extracted with chloroform, dried over sodium sulfate, and evaporated to dryness. On recrystallization from ethyl acetate an additional 0.3 g. of material melting at 157–159° was obtained.

Anal. Calc'd for $C_9H_{14}N_2O_2$: C, 59.3; H, 7.7; N, 15.4.
Found: C, 59.4; H, 7.6; N, 15.6.

Action of hydrogen bromide on 2-methyl-3-(β-ethoxyethyl)-5-hydroxypyrazine. When the above pyrazine was heated for 2 hours on the steam-bath with a solution of hydrogen bro-

mide in glacial acetic acid saturated at 0°, cleavage of the ether apparently took place. The resulting solution was concentrated under reduced pressure with the addition of water to remove the hydrogen bromide. The resulting dark aqueous solution was extracted with chloroform. After removal of the chloroform, the residue was recrystallized from ethyl acetate and gave a crystalline substance which melted at 159° after some decomposition at 156°. When mixed with the pyrazine XI, a depression of the melting point of 10–20° was noted. The material is sparingly soluble in water, easily soluble in chloroform, and soluble in sodium hydroxide solution (enolic hydroxyl group). It gives a precipitate with silver nitrate only after gentle warming. Samples from two different preparations gave identical carbon and hydrogen figures. However, the analytical figures obtained do not agree with those of the expected bromoethylpyrazine XII.

Anal. Calc'd for $C_7H_9BrN_2O$: C, 38.8; H, 4.2; N, 12.9; Br, 36.7.
Found: C, 40.2, 40.0; H, 4.4, 4.6; N, 12.4; Br, 39.3.

When the above bromine-containing substance was refluxed with 5 % sodium carbonate solution for one hour, a bromine-free compound was obtained. The solution was neutralized with hydrochloric acid, saturated with sodium chloride, and thoroughly extracted with chloroform. After removal of the chloroform, a bromine-free substance was obtained which melted at 139–140° after recrystallization from ethyl acetate. The compound decomposed after standing for a few days and decolorized bromine solution much more rapidly than the ethoxyethylpyrazine XI. The analytical figures agreed with those for 2-methyl-3-vinyl-5-hydroxypyrazine (XIII).

Anal. Calc'd for $C_7H_8N_2O$: C, 61.7; H, 5.9.
Found: C, 62.0; H, 5.8.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

NEW YORK, N. Y.

SUMMARY

1. A general synthesis for 2,3-disubstituted 5-hydroxypyrazines and for 2,3,6-trisubstituted 5-hydroxypyrazines has been developed.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

REDUCTION OF THE STEREOISOMERIC 4-ENOL METHYL ETHERS OF 1,4-DIMESITYL-1,2,4-BUTANETRIONE

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In the light of the varied results in the reductions of the stereoisomeric 1,4-dimesityl-1,2,4-butanetrione 2-enol ethers (*cf.* III) (1), it became of particular interest to complete the study of the reduction of the *cis* and *trans* 4-enol ethers (IV and V) which are α-diketones and have already been shown to be reducible to individual and persistent enediols (2). This report deals with some further experiments upon these and related compounds.

The *cis* and *trans* 4-enol ethers were first obtained in small amounts by the laborious separation of the mixture produced in the reaction between diazomethane and the triketone enol (I) (2). It is now possible by another method to obtain the labile form of these isomers (IV) in nearly pure condition and in yields of 70%, namely, by the action of methyl iodide on the silver enolate. This labile and presumably *cis* ether is easily converted into the stable and presumably *trans* isomer (V) by the action of acid, alkali, sunlight, or heat alone. Both of the 4-enol ethers are thus obtainable easily and in quantity.

It is noteworthy that the alkylation of the silver salt of the enol (I) resulted chiefly in oxygen-alkylation and involved the oxygen adjacent to the mesityl group rather than the 2-oxygen. Furthermore, there was isolated from the reaction mixture only a very small amount of the expected carbon-alkyl derivative (II) [to be described later (4)]. These results, therefore, are to be contrasted with the results of alkylation under similar conditions of the analogous diphenylbutanetrione silver enolate (3) where carbon alkylation is dominant.

The stereoisomeric 4-ethers (IV and V) were both easily hydrolyzed by acid to the enol. The reagents used, however, were such as would first convert the labile into the stable ether. Attempts to obtain individual oximes failed because hydrolysis occurred under the conditions involved and in each case the sole product was the oxime derived from the enol itself (2).

Both enol ethers absorbed one molecule of catalytic hydrogen to give individual and persistent enediols. These were readily oxidized back to the corresponding triketone enol ethers (IV and V) (2), and they underwent rearrangement into the α-hydroxy ketone forms (VI and VII), which have now been isolated. One of these reduction products (VI), that obtained from the labile triketone enol ether (IV), was found also to be labile and easily rearranged into the other (VII). Both underwent air oxidation at 200° to the same stable triketone enol ether (V).

The reactions of these two reduction products (VI and VII) and their mode of formation from known compounds (as outlined in the diagram) demonstrated

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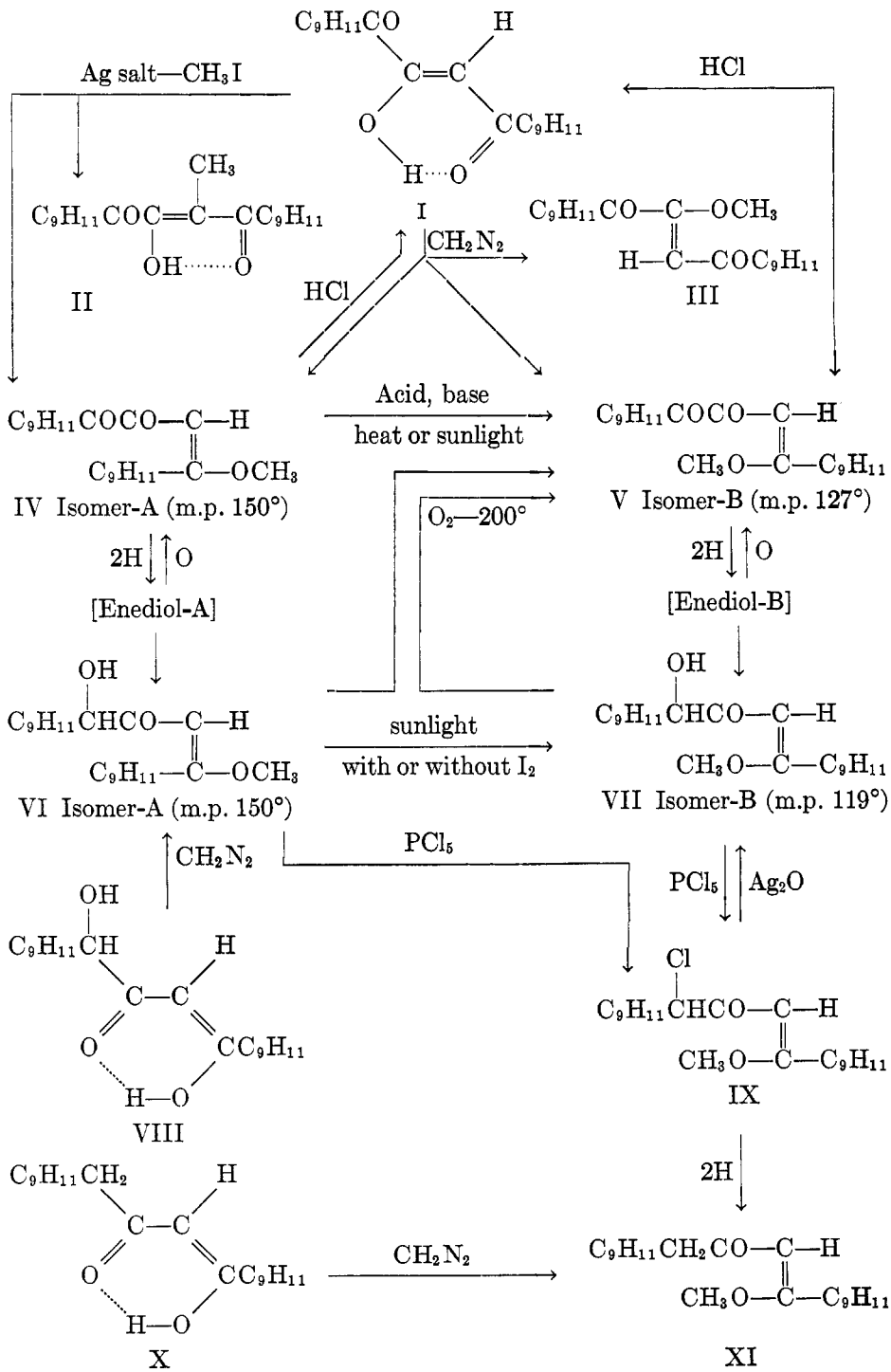

I

II

III

IV Isomer-A (m.p. 150°)

[Enediol-A]

V Isomer-B (m.p. 127°)

[Enediol-B]

VI Isomer-A (m.p. 150°)

VII Isomer-B (m.p. 119°)

VIII

IX

X

XI

satisfactorily that the isomerism involved is *cis-trans* with respect to the enol ether double bond, and is not structural isomerism of the acyloin type.

The labile reduction product (VI) has already been made by the action of diazomethane on 4-hydroxy-1,4-dimesitylbutane-1,3-dione enol (VIII) (2) and its structure is therefore certain.

Phosphorus pentachloride converted both enol ethers (VI and VII) into the same chloro derivative (IX), which therefore must have the stable configuration corresponding to that of (VII). Hydrolysis of the chloro compound with methanolic potassium hydroxide involved oxidation as well, and gave the stable triketone enol ether (V), but with silver oxide as the reagent, the reaction was confined to hydrolysis and there was produced the corresponding and stable hydroxy diketone enol ether (VII).

Reduction of the chloro compound (IX) by means of catalytic hydrogen gave the β-diketone enol ether (XI), which had previously been obtained by the action of diazomethane on the enol (X) (2). The chloro compound and the enol ether (XI) must have similar and stable configurations, because inversion would be unlikely under the conditions of the catalytic reduction. This reduction demonstrates that the chlorine atom in (IX) actually is located on the terminal carbon, and it demonstrates also, indirectly, the terminal location of the hydroxyl in the hydroxy diketone enol ether (VII) which is obtained from the chloro compound through hydrolysis with silver oxide.

It is obvious from the reactions outlined in the diagram that the enol ethers bear a consistent and definite configurational relationship to each other. It is unfortunate that there is no rigorous proof of the absolute configuration of any one of these compounds from which the configurations of the others would follow. However, it seems reasonable to assign configurations tentatively on the basis of the assumption that the more stable type will be that in which the bulkier groups, mesityl and mesitylglyoxyl, are *trans* with respect to each other. The formulations in the diagram have been written accordingly.

It is of interest to speculate on the mechanism of formation of the ethers from the enols through the action of diazomethane, and the bearing, if any, of a chelate ring structure for the enol on the configuration of the ethers produced. It is conceivable that the configuration of the ethers might be predetermined by the space arrangement of groups in the resonating chelated enol, and that there might be produced exclusively those ethers with the mesityl and mesitylglyoxyl groups (*cf.* V and VII) or the two mesitoyl groups (*cf.* III) *trans* with respect to each other. Actually a mixture of three ethers, including the *cis-trans* pair (IV and V) and the *trans* 2-enol ether (III), was formed in the methylation of the triketone enol (I). Of the two 2-enol methyl ethers the *trans* isomer (III) only was obtained, and this together with the *trans* 4-enol methyl ether-B (V) constituted the bulk of the products isolated; therefore in respect to the total yields of the ethers in this particular reaction, the dominant products appear to be *trans* as would be predicted on the basis of reaction directly with the chelated enol form. On the other hand, the action of diazomethane on the 4-hydroxy-1,3-diketone enol (VIII) and on the 1,3-diketone enol (X) proceeded in different

stereochemical senses. If the configurations assigned are correct, the reaction with the diketone enol (X) has gone in accordance with the configuration of a chelated form, and that with the hydroxy-β-diketone enol (VIII) contrary.

EXPERIMENTAL

cis-*1,4-Dimesityl-4-methoxy-3-butene-1,2-dione-A* (IV). Four grams of freshly prepared dimesitylbutanetrione silver enolate was dried in a vacuum dessicator over calcium chloride. It was suspended in 60 cc. of absolute isopropyl ether, and 10 cc. of methyl iodide was added dropwise with stirring. The mixture was then refluxed for two hours. After filtering to remove silver iodide, the solution was extracted three times with 25-cc. portions of 10% sodium hydroxide. Upon acidification of the aqueous extract, 0.22 g. (6.5%) of the yellow carbon-methyl derivative (II) separated and was identified by mixture melting point with an authentic sample (4). The ether solution upon evaporation left a bright yellow solid which was recrystallized from methanol; yield 1.84 g. (58%). This was purified and identified as (IV) by mixture melting point with an authentic sample.

In one reaction a small amount of the *trans* ether (V) was isolated from the enol fractions and its formation was accounted for by the action of the base used, on the labile *cis* form (IV).

In a second experiment, 2 g. of the enol (I) was dissolved in 30 cc. of methanol containing 0.3 g. of dissolved sodium (one equivalent). To this was added 3.5 cc. of methyl iodide. The solution was cooled to 0° and 80 cc. of 2% aqueous silver nitrate was added slowly with mechanical stirring. The mixture was stirred and allowed to come slowly to room temperature and then warmed on a steam-bath for fifteen minutes. The silver iodide was removed by filtration and the solution was diluted with water. An ether extract was then made; this was subsequently shaken six times with 25-cc. portions of saturated sodium carbonate. Evaporation of the ether layer gave a bright yellow residue which was crystallized from ethanol (1.47 g. or 67%) and identified by mixture melting point as the *cis* 4-enol ether (IV).

Treatment of 0.5 g. of (IV) in 20 cc. of conc'd acetic acid, 5 cc. of conc'd hydrochloric acid, and 2.5 cc. of water at room temperature for four hours gave 0.3 g. of almost pure enol (I).

The action of 0.5 g. of hydroxylamine hydrochloride on 0.5 g. of the enol ether (IV) in 15 cc. of pyridine (refluxing for seven hours) gave 0.42 g. (84%) of the oxime of the enol (I) which has already been described (2). It melted at 166.5–167° (*Anal.*, calc'd for $C_{22}H_{25}NO_3$: C, 75.2; H, 7.1; N, 4.0. Found: C, 75.3; H, 7.3; N, 4.0).

trans-*1,4-Dimesityl-4-methoxy-3-butene-1,2-dione-B* (V). Hydrolysis of 0.4 g. in 25 cc. of conc'd acetic acid, 5 cc. of conc'd hydrochloric acid, and 2.5 cc. of water (refluxed for 30 min.) gave 0.35 g. (91%) of almost pure enol (I). *Treatment with hydroxylamine hydrochloride* in pyridine under different conditions, including those described under the *cis* ether (IV), gave the oxime of the enol (I). *Reduction* with zinc and conc'd acetic acid at room temperature gave the 4-hydroxy compound-B (VII). Reduction with 20-mesh tin and a mixture of conc'd acetic and hydrochloric acids (refluxing for four hours) gave a small yield of 1,4-dimesitylbutanone-2, $C_9H_{11}CH_2COCH_2CH_2C_9H_{11}$. Reduction with zinc dust and hydrochloric acid in 85% ethanol (refluxing) gave a small amount of 1,4-dimesitylbutanedione-1,3 enol (X).

cis-*1-Hydroxy-4-methoxy-1,4-dimesityl-3-butene-2-one-A* (VI). This enol ether has been made by the action of diazomethane on the corresponding enol (2). A better method is as follows.

Hydrogenation of 0.5 g. of the *cis* 4-enol ether (IV) in 50 cc. of ethanol with a platinum oxide catalyst involved absorption of one molecule. Two drops of piperidine were added under hydrogen, and after standing for one hour the catalyst was removed by filtering. Evaporation gave 0.2 g. of colorless rhombic prisms; m.p. 145–146°; identified by mixture melting point as (VI). From the residual crystalline fractions a small amount of a second

product was isolated; this melted at 135–136° and was shown by mixture melting point to be identical with the by-product of the methylation of the enol (VIII) with diazomethane (2). This compound has not yet been investigated. It seems likely from the preparation by reduction of VI that it is a 4-methyl ether, possibly $C_9H_{11}COCH(OH)CH = C(OCH_3)C_9H_{11}$, although this formulation does not explain its formation in the methylation of the enol (VIII) by diazomethane.

Hydrolysis by passing dry hydrogen chloride through a solution of 0.2 g. in 10 cc. of conc'd acetic acid and 8 cc. of conc'd hydrochloric acid for three hours gave 0.15 g. of a new compound of m.p. 179.5–180°. Similarly another new compound of m.p. 91°, was obtained when 80% methanol was used in a similar experiment. These two compounds are being investigated. When treated with hydroxylamine and sodium acetate in dilute ethanol (boiling for 11 hrs.) largely unchanged material was recovered together with a small amount of the compound of m.p. 136–137° which was obtained as a by-product in the above described reduction (identification was by mixture m.p.). This product probably was the result of reduction of VI by hydroxylamine. The action of boiling pyridine and hydroxylamine hydrochloride converted the ether into the enol (VIII).

trans-*1-Hydroxy-1,4-dimesityl-4-methoxy-3-butene-2-one-B* (VII). Hydrogenation of 1 g. of the *trans* triketone enol ether (V) in 70 cc. of ethanol with 0.05 g. of platinum oxide as catalyst involved absorption of one molecule. Two drops of piperidine were added and the solution, still under hydrogen, was allowed to stand for five hours. Upon filtering and diluting with water, 0.9 g. (90%) of crystalline product separated. It crystallized in colorless rhombic prisms from ethanol; m.p. 120°.

Anal. Calc'd for $C_{23}H_{28}O_3$: C, 78.4; H, 7.95; OCH_3, 8.8.
Found: C, 78.35; H, 7.9; OCH_3, 8.64.

This compound was obtained also in other ways as follows: Reduction of 0.5 g. of (V) in 20 cc. of conc'd acetic acid with 0.5 g. of zinc dust for ninety minutes at room temperature gave 0.3 g. (60%) of the *trans* product (VII). This *trans* compound was obtained in almost quantitative yield from the *cis* isomer (VI) upon exposure in methanol to the sunlight for seven hours. Exposure of (VI) to sunlight in a chloroform solution containing a small crystal of iodine brought about a similar transformation.

Treatment in boiling ethanol (five hours) with hydroxylamine hydrochloride and sodium acetate was without effect.

A stream of air was passed for 2.5 hours over 0.1 g. of VII at 200° and the product was then distilled in the vacuum oven at 110°. The yellow crystalline product which collected on the cold-finger condenser was crystallized from ethanol and identified as (V).

Reduction of 0.1 g. of (VII) was brought about by means of a mixture of 10 cc. of conc'd acetic acid, 1 cc. of water, 0.5 g. of iodine, and 0.5 g. of red phosphorus at refluxing temperature for one hour. Upon taking up the product in ethanol, 0.01 g. of colorless crystals was deposited; m.p. 164–168° (not identified or studied further). From the filtrate 0.06 g. of 1,4-dimesityl-1,3-butanedione enol (X) separated and was identified by mixture melting point.

Reduction of 0.5 g. of (VII) was carried out by means of a mixture of 20 cc. of ethanol, 2 cc. of water, and 1.2 g. of 30 mesh zinc, under refluxing and continuous saturation with dry hydrogen chloride for two hours. The solution was decanted into water and the resulting product was extracted with ether. Upon evaporation and dissolving the residue in ethanol, 0.06 g. of colorless crystals of m.p. 227–229° separated (not identified or studied further). Concentration of the filtrate gave 0.25 g. (55%) of 1,4-dimesityl-1,3-butanedione enol (X), which was identified by mixture melting point.

Reduction of 0.15 g. of the *trans* enol ether (VII) by the combination, 5 cc. of conc'd acetic acid, 4 cc. of conc'd hydrochloric acid, and 2 g. of 20 mesh tin under refluxing for four hours, gave an oil which solidified on standing (0.08 g.). Upon purification by crystallization from ethanol, it was obtained as needles of m.p. 118.5–119.5°; it was identified by mixture melting point as 1,4-dimesitylbutanone-2 ($C_9H_{11}CH_2COCH_2CH_2C_9H_{11}$).

It is to be noted that these reductions of the enol ether (VII) involve demethylation and produce the same products as are obtained from the enols under similar conditions (2).

1-Chloro-1,4-dimesityl-4-methoxy-3-butenone-2 (IX). A solution of 0.5 g. of the *cis* enol ether (VI) in chloroform, cooled to 15°, was treated with 0.35 g. of phosphorus pentachloride, added portionwise with shaking. Reaction was evident from the evolution of hydrogen chloride. The solution was then warmed to 40° for five minutes and evaporated. The residue was treated with water and the organic material extracted with ether. The oil obtained from this upon evaporation was dissolved in ethanol and cooled; 0.3 g. (65%) of crystalline chloro compound separated. Repeated crystallization from ethanol brought the melting point of the product to 138.5–139°.

Anal. Calc'd for $C_{23}H_{27}ClO_2$: Cl, 9.6. Found: Cl, 9.9.

In two similar experiments using instead the *trans* enol ether (VII) yields of 57% and 76% respectively were obtained.

Catalytic reduction of 0.3 g. in 25 cc. of ethanol with 0.05 g. of platinum oxide involved absorption of one molecule of hydrogen and gave 0.13 g. (48%) of nearly pure product, which was recrystallized from ethanol and identified as the β-diketone enol ether (XI) by mixture melting point with an authentic sample.

Hydrolysis of 0.5 g. with 20 cc. of methanol and 0.25 g. of freshly prepared silver oxide (shaking for 24 hrs.) gave an oil which was dissolved in methanol; 0.01 g. of colorless crystals separated (m.p. 115–117°), and was identified by mixture melting point as *trans*-hydroxydimesitylbutanedione enol ether (VII).

Hydrolysis of 0.1 g. of (IX) in 15 cc. of 80% methanol and 4 cc. of 10% aqueous potassium hydroxide, refluxing for 30 min., gave 0.05 g. of yellow crystals of m.p. 125–126°, which was identified by mixture melting point as the *trans* triketone enol ether (V).

Refluxing pyridine containing 13% of water (two hours) was without action on the chloro compound (IX).

SUMMARY

The labile (*cis*) 1,4-dimesityl-1,2,4-butanetrione 4-enol ether has been prepared in quantity by alkylation of the silver enolate, and from this the stable (*trans*) isomer was obtained by inversion.

Reduction of these enol ethers proceeded through enediols to corresponding labile and stable 4-hydroxy-1,3-diketone 1-enol ethers, respectively. Both of these ethers have been oxidized back to the stable triketone 4-enol ether, and have been converted by phosporus pentachloride into the 4-chloro-1,3-diketone 1-enol ether.

There appears to be no consistent relation between the chelate enol form and the configuration of the products of methylation by diazomethane.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

SYNTHESES INVOLVING UTILIZATION OF ALLYLMAGNESIUM BROMIDE IN THE GRIGNARD REACTION

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Prior to 1928 the use of allyl bromide in the Grignard reaction required a procedure other than the usual one of independently preparing the alkylmagnesium reagent and then introducing the substance to which addition is desired. The method which actually had been used when the allyl group was to be utilized, involved the simultaneous mixing of allyl halide, anhydrous ether, the compound with which reaction was desired, and magnesium. This "batch" method (Barbier-Grignard procedure) had seemed necessary in view of the fact that previous attempts to form allylmagnesium bromide as such had resulted for the most part in the production of diallyl (1,2),[2] caused by interaction of the allylmagnesium compound and excess allyl bromide.

$$CH_2{=}CHCH_2Br + Mg \rightarrow CH_2{=}CHCH_2MgBr$$
$$CH_2{=}CHCH_2MgBr + CH_2{=}CHCH_2Br \rightarrow CH_2{=}CHCH_2CH_2CH{=}CH_2 + MgBr_2$$

However, in 1928, Gilman and McGlumphy (4) not only brought about the initial synthesis of allylmagnesium bromide, but also outlined a method for its preparation whereby a yield of eighty to ninety per cent of the theoretical might be expected in ordinary synthetic procedure. The method, as described, requires the use of a large excess of magnesium (three equivalents), a high dilution with anhydrous ether, vigorous stirring, and slow addition of the bromide; such factors allowing minimum contact of allyl bromide with the allylmagnesium bromide during formation of the latter. As an indication of the increased yields to be had through use of the preformed reagent, rather than of the aforementioned "batch" method, the amounts of products obtained by Gilman and McGlumphy in three typical reactions are tabulated. For purposes of comparison, yields of these products as previously prepared from the same reactants but by the "batch" method are included in Table I.

Subsequent to the pioneering work of Gilman, several investigators have made rather detailed studies of various factors which determine the optimum yield of allylmagnesium bromide and the results of these studies confirm Gilman's initial findings. Thus, Johnson and Adkins (8), testing the effect of copper upon the yields of Grignard reagents, found that allyl bromide reacts with copper-magnesium alloy to form only a six per cent yield of the reagent; using magnesium in essentially Gilman's proportion, however, they were able to obtain seventy-two per cent of the theoretical yield of allylmagnesium bromide.

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[2] Houben, Boedler, and Fischer (3) have shown that at best only twenty-five per cent of the theoretical yield of the allylmagnesium reagent may be obtained from the usual proportions of reactants.

Young, Prater, and Winstein (9), in an effort to determine the effect of solvent upon yields of crotyl- and allyl-magnesium bromides, found that for the latter the usual diethyl ether served more adequately than did ethers of higher molecular weight. In a study of the relative usefulness of RMgCl versus RMgBr, Zoellner (10) concluded that for most purposes the chloride is to be preferred to the bromide, but in the case of the allylmagnesium halide reagent the chloride is unsatisfactory, becoming colloidal and useless in the majority of instances, and recommended the bromide for routine synthesis.

In view of Gilman's work and of the wide application of the Grignard reaction in synthetic organic chemistry, it is surprising indeed to note the infrequency of use of allylmagnesium bromide. Apparently, the reagent has found its chief use in reactions of the type

$$\text{R-halide} + CH_2{=}CHCH_2MgBr \rightarrow RCH_2CH{=}CH_2 + MgBr_2 + Mg(\text{halide})_2$$

Shoemaker and Boord (11) have satisfactorily employed the reagent in an extensive study of the 1,4-diolefins, as have Summerbell and Bauer (12) in the

TABLE I

COMPARISON OF YIELDS OBTAINED FROM ALLYL BROMIDE IN THE GRIGNARD SYNTHESIS

Product	Percentage yields obtained using	
	RMgBr	"Batch"
Allyldiphenylcarbinol	74.9[a] (4,5)	60 (6)
Allylmethylphenylcarbinol	80.2 (4)	60 (6)
Butenoic acid	21.7 (4)	11 (7)

[a] In a repetition of the synthesis of this carbinol, Kharasch and Weinhouse (5) essentially duplicated this yield in obtaining 72%.

preparation of 2,3-diallyl-1,4-dioxane from 2,3-dichloro-1,4-dioxane. In this connection, however, Kogerman (13) was unable to bring about reaction between allylmagnesium bromide and vinyl bromide in an effort to synthesize 1,4-pentadiene.

Recently (14), in this Laboratory, we attempted to prepare an alkoxyalkyl allyl ketone by interaction of ethoxyacetonitrile and allylmagnesium bromide. Instead of the anticipated ketone, however, the product of the reaction was shown to be diallylethoxymethylcarbinamine. The same type of reaction occurred between allylmagnesium bromide and the methoxy- and isopropoxy-analogs. In view of this unexpected behavior of allylmagnesium bromide, and

$$ROCH_2CN + 2CH_2{=}CHCH_2MgBr \xrightarrow{(HOH)} ROCH_2\overset{\displaystyle NH_2}{\overset{|}{C}}(CH_2CH{=}CH_2)_2$$

because of the paucity of records of its use, it was desirable to study the reaction of the reagent, as prepared by Gilman (4), with a few common aldehydes,

ketones, esters, unsaturated aldehydes, and ketones, and then with a few compounds containing both carbonyl and ether groupings.

In this investigation, allylmagnesium bromide reacted with the following: propionaldehyde, *n*-butyraldehyde, *n*-valeraldehyde, acetone, ethyl methyl ketone, isobutyl methyl ketone, acrolein, crotonaldehyde, mesityl oxide, ethyl propionate, propyl ethoxyacetate, 1-methoxyethyl methyl ketone. Of these, all save the valeraldehyde and the two alkoxy derivatives, had previously been converted into the corresponding allyl carbinols, chiefly by the "batch" method with utilization of either zinc or magnesium. In general, the yields here reported equal or exceed those recorded elsewhere.

EXPERIMENTAL

The allyl reagent was prepared using a ratio of three equivalents of magnesium to one of allyl bromide and nine volumes of anhydrous ethyl ether. After six to seven hours of vigorous stirring at room temperature, the mixture was warmed for thirty minutes and then transferred rapidly into another flask by decantation through a coarse filter to remove the unreacted metal.[3] Slightly less than one equivalent (0.25 mole) of the appropriate carbonyl compound was diluted with an equal volume of dry ether and added to the chilled reagent. In some cases the addition product separated as a light gray solid, in others as an amber oil, but in a few instances remained in solution. The addition product was decomposed by action of crushed ice and chilled, dilute hydrochloric acid. After the usual procedure of ether extraction, washing and drying, the carbinols were fractionated for purification.

5-Hexen-3-ol. From 14.5 g. (0.25 mole) of propionaldehyde was obtained 15.6 g. (62% yield) of material boiling at 129–136°, but when purified by fractionation under 753 mm. boiling at 131.5–132.0° (corr.); 56–58° (33 mm.). The purified alcohol, a colorless liquid of penetrating, disagreeable odor, amounted to 13.2 g. (52% yield); n_D^{20} 1.4320; d_4^{20} 0.8409; γ^{20} 24.70 dynes/cm; M_R calc'd 30.97; M_R found 30.89; P calc'd 277.2; P found 265.4. A comparison of certain of these data with those previously reported in the literature follows:

TABLE II

PHYSICAL CONSTANTS, 5-HEXEN-3-OL

Boiling Range	Yield, %	d^t	n_D^{20}	Mol. Refract.	
				Calc'd	Found
130–132°[a]		d^{18} 0.843			
128–133°[b] 760–765 mm.	48				
130°[c]	50	d_4^{20} 0.8464	1.4330	30.97	30.71
131.5–132.0[d] 753 mm.	62	d_4^{20} 0.8409	1.4320	30.97	30.89

[a] Fournier (15) used a "batch" method with zinc and allyl bromide.
[b] Levene and Haller (16) used essentially and same method as in (*d*).
[c] Ou, K.-H. (17) used allylmagnesium bromide.
[d] This study.

[3] It was found to be more efficient to prepare the Grignard reagent in a flask with a glass tube attached off-center to the bottom. This tube was fitted with a stopcock and could be filled with a fine-mesh copper screen or glass wool as a filtering medium. The ether solution could this be transferred to another flask without exposure to the atmosphere.

1-Hepten-4-ol. Utilization of 36.0 g. (0.5 mole) of *n*-butyraldehyde yielded 37.7 g. (66%) of material boiling at 152.5–154.8° (743 mm.). Upon redistillation the carbinol boiled at 66° (20 mm.); 151.7–152.2° (corr.) (743 mm.); 57% yield; n_D^{20} 1.4342; d_4^{20} 0.8374; γ^{20} 25.43 dynes/cm.; M_R calc'd 35.58; M_R found 35.51; P calc'd 316.2; P found 306.2.

Anal. Calc'd for $C_7H_{14}O$: C, 73.63; H, 12.36.
Found: C, 73.36; H, 12.62.

1-Octen-4-ol. This compound, which had not been reported previously, was prepared from 43 g. (0.50 mole) of *n*-valeraldehyde. Upon first distillation of the product there was collected 53.8 g. (84% yield) of liquid boiling at 66–69° (10 mm.); upon redistillation the

TABLE III

PHYSICAL CONSTANTS, 1-HEPTEN-4-OL

Boiling Range		Yield, %	d_4^t	n_D^t	Mol. Refract.	
					Calc'd	Found
145–146°[a]						
59–60°[b]	20 mm.	35	$d^{22.1}$ 0.8384	n^{18} 1.4345	35.58	[35.50]
149.8–150.2°[c]			d^{20} 0.8412	n^{20} 1.4355	35.58	35.44
66°[d]	20 mm.	66	d^{20} 0.8374	n^{20} 1.4342	35.58	35.51

[a] Knorr (18) used a modified batch method in which some allyl chloride reacted with a large excess of magnesium; then were added allyl bromide, benzene, ether, and the aldehyde.

[b] Consden, Duveen, and Kenyon (19) reported "Considerable difficulty was experienced in the preparation of this alcohol." Addition of aldehyde to allylmagnesium chloride gave poor yields and much high-boiling material. Hence, an ether solution of allyl chloride and *n*-butyraldehyde was added very slowly to a well-stirred suspension of magnesium in ether. "On one occasion the yield was as high as 65%, but was generally only about half this amount. The crude alcohol, b.p. 58–59° (18 mm.), contained a variable amount of *n*-butanol."

[c] Karasev (20) used allylmagnesium bromide.

[d] This study.

alcohol (65% yield) boiled at 68–69° (10 mm.); 171.5–172.0° (corr.) (748 mm.); n_D^{20} 1.4383; d_4^{20} 0.8373; γ^{20} 26.00 dynes/cm.; M_R calc'd 40.22; M_R found 40.20; P calc'd 355.2; P found 345.7.

Anal. Calc'd for $C_8H_{16}O$: C, 74.94; H, 12.58.
Found: C, 74.67; H, 12.66.

2-Methyl-4-penten-2-ol. Twenty-six and eighth-tenths gram (70% yield) of this carbinol was obtained, from 22 g. (0.38 mole) of acetone, when collected at 115–117°. Upon redistillation, 20.3 g. (53% yield) boiled at 118.0–118.2° (corr.) (744.5 mm.); 46.0–46.5° (30 mm.); n_D^{20} 1.4263; d_4^{20} 0.8298; γ^{20} 24.12 dynes/ dm.; M_R calc'd 30.97; M_R found 30.94; P calc'd 277 .2; P found 267.5.

Anal. Calc'd for $C_6H_{12}O$: C, 71.95; H, 12.08.
Found: C, 71.68; H, 12.30.

3-Methyl-5-hexen-3-ol. By use of 18 g. (0.25 mole) of ethyl methyl ketone, 24.2 g. (84% yield) of product, boiling at 137–139°, was obtained. The purified alcohol boiled at 138.0–138.5° (corr.) (742 mm.); 60.5–61.0° (35 mm.); n_D^{20} 1.4370; n_4^{25} 1.4342; d_4^{20} 0.8442; d_4^{25} 0.8403; γ 24.42 dynes/cm.; M_R calc'd 35.58; M_R found 35.44; P calc'd 316.2; P found 300.7.

Anal. Calc'd for $C_7H_{14}O$: C, 73.63; H, 12.36.
Found: C, 73.74; H, 12.51.

4,6-Dimethyl-1-hepten-4-ol. Fifty-nine grams (83% yield) was obtained from 50.1 g. (0.50 mole) of isobutyl methyl ketone, the latter having been prepared by catalytic hydrogenation of mesityl oxide using the Adams catalyst. The alcohol was collected at 75°

TABLE IV

PHYSICAL CONSTANTS, 2-METHYL-4-PENTEN-2-OL

Boiling Range	Yield, %	d^t	n_D^t	Mol. Refract.	
				Calc'd	Found
119.5° (corr.)[a]		d_0^{18} 0.8307			
120° (atm. press.)[b]					
118.3–118.8°[c, d]	75				
118.5–119.5°[e]	39				
32–36° (12 mm.)	60–65	d_4^{17} 0.8326	n^{17} 1.4277	30.97	30.90
117–119° (775 mm.)[f]					
120°[g]		d_4^{20} 0.8270	n^{20} 1.4120	30.97	30.77
46.0–46.5° (30 mm.)	70				
118.0–118.2° (744.5 mm.)[h]	53	d_4^{20} 0.8298	n^{20} 1.4263	30.97	30.94

[a] Saytzeff and Saytzeff (21) used a "batch" mixture of zinc, allyl iodide and acetone.
[b] Courtot (22) used same procedure as in *h*.
[c] Jaworsky (23) dropped an ether solution of allyl chloride (or bromide) and acetone onto magnesium and obtained a 52% yield of material boiling at 115–125°.
[d] Jaworsky (24).
[e] Jaworsky (6) used allyl bromide in "batch" method.
[f] Bacon and Farmer (25) used allylmagnesium bromide.
[g] Ou, K.-H. (17) used allylmagnesium bromide.
[h] This study.

TABLE V

PHYSICAL CONSTANTS, 3-METHYL-5-HEXEN-3-OL

Boiling Range	Yield, %	d^t	n_D^{25}	Mol. Refract.	
				Calc'd	Found
138.5–139.5° (753 mm.)[a]		d_0^{20} 0.8421			
138–139° (atm. press.)[b]	52	d_4^{25} 0.8365	1.4309	35.58	35.33
138.0–138.5° (742 mm.)[c]	85	d_0^{25} 0.8442	1.4370	35.58	35.44

[a] Saytzeff (26) used zinc and allyl iodide.
[b] Milas and McAlevy (27) used allylmagnesium chloride.
[c] This study.

(26 mm.), b.p. 168.3–168.8° (corr.) (757.5 mm.); n_D^{20} 1.4402; d_4^{20} 0.8380; γ^{20} 25.16 dynes/cm.; M_R calc'd 44.82; M_R found 44.76; P calc'd 394.2; P found 380.1.

Anal. Calc'd for $C_9H_{18}O$: C, 75.99; H, 12.75.
Found: C, 75.75; H, 12.80.

1,5-Hexadien-3-ol. Fourteen grams (0.25 mole) of acrolein yielded 16.3 g. (66%) of crude product boiling at 126–136° (746 mm.); fractionation gave 14.4 g. (58.7% yield) of

alcohol distilling at 133.5–134.0° (corr.) (754 mm.); 60.5–61.5° (40 mm.); n_D^{20} 1.4471; d_4^{20} 0.8608; γ^{20} 25.08 dynes/cm.; M_R calc'd 30.50; M_R found 30.46; P calc'd 266.2; P found 255.1.

Anal. Calc'd for $C_6H_{10}O$: C, 73.43; H, 10.27.
Found: C, 73.27; H, 10.42.

1,5-Heptadien-4-ol. This carbinol was obtained in 82% yield (23.2g.) from 17.5 g. (0.25 mole) of crotonaldehyde, the crude material being collected at 72–75° (32.5 mm.). When

TABLE VI

PHYSICAL CONSTANTS, 4,6-DIMETHYL-1-HEPTEN-4-OL

Boiling Range	Yield, %	d^t	n_D^t	Mol. Refract.	
				Calc'd	Found
173.7° (corr.) (765 mm.)[a]	15.5	d_0^{20} 0.8355			
180–182° (753 mm.)[b]		d^{21} 0.823	n^{18} 1.4443	44.82	[45.93]
68–69° (20 mm.)[c]	60				
168.3–168.8° (747.5 mm.)[d]	83	d_4^{20} 0.8380	n^{20} 1.4402	44.82	44.76

[a] Marko (28) used "batch" mixture of zinc and allyl iodide.
[b] Bodroux and Taboury (29) used a "batch" mixture of magnesium and allyl bromide.
[c] Knorr (18).
[d] This study.

TABLE VII

PHYSICAL CONSTANTS, 1,5-HEXADIEN-3-OL

Boiling Range	Yield, %	d_4^t	n_D^t	Mol. Refract.	
				Calc'd	Found
133–134° (atm. press.)[a]		d^{25} 0.8596	n^{25} 1.4464	30.50	30.47
130–137°[b]					
130–131°[c]	About 50	d^{20} 0.8578	n^{20} 1.445	30.50	30.34
133.5–134.0° (754 mm.)[d]	58.7	d^{20} 0.8608	n^{20} 1.4471	30.50	30.46

[a] Levene and Haller (30) used zinc and allyl bromide, but reported "It can also be prepared by the action of acrolein on allyl magnesium bromide," and calc'd: C, 73.43; H, 10.20; found: C, 73.95; N, 10.39.
[b] Butz, Butz, and Gaddis (31) used allylmagnesium bromide. They reported the crude alcohol to boil at 45–65° (25 mm.) and calculated the yield as 74–79% (based on the acrolein used, and 41–44% based on the bromide). If the theoretical amount of acrolein was used, the yield was 35–40% (based on acrolein) while twice the quantity gave about 20%. About 90% of the product boiled 130–137° or 42–48° (17 mm.).
[c] Ou, K.-H. (17) used allylmagnesium bromide.
[d] This study.

fractionated at 15 mm., the alcohol boiled at 62.0–62.5° (corr.); 155–156° (742 mm.); n_D^{20} 1.4533; d_4^{20} 0.8590; γ^{20} 25.48 dynes/cm.; M_R calc'd 35.12; M_R found 35.32; P calc'd 305.2; P found 293.3.

4,6-Dimethyl-1,5-heptadien-4-ol. Sixty-three and eight-tenths grams (91% yield) of this compound, boiling at 169.7–170.2° (corr.) (750 mm.), was produced from utilization of

49 g. (0.50 mole) of mesityl oxide; b.p. 47–48° (4 mm.); 72° (18 mm.); n_D^{20} 1.4598; d_4^{20} 0.8622; γ^{20} 26.31 dynes/cm.; M_R calc'd 44.35; M_R found 44.53; P calc'd 384.2; P found 368.7.

Anal. Calc'd for $C_9H_{16}O$: C, 77.09; H, 11.50.
Found: C, 76.85; H, 11.33.

2,4-Dimethylheptan-4-ol. This alcohol was obtained through reduction:

A. Thirty and one-half grams (0.215 mole) of 4,6-dimethyl-1-hepten-4-ol was dissolved in an equal volume of absolute ethanol, mixed with 0.34 g. of the Adams catalyst, and

TABLE VIII

PHYSICAL CONSTANTS, 1,5-HEPTADIEN-4-OL

Boiling Range	Yield, %	d^t	n^t	Mol. Refract.	
				Calc'd	Found
68–90° (24 mm.)	16.5	$d_4^{14.8}$ 0.8668	$n_D^{13.7}$ 1.4553	35.12	35.07
156.0–156.7° dec. (765 mm.)[a]					
61–62° (15 mm.)[b]		d_4^{20} 0.8612	n_{He}^{20} 1.4541	35.12	36.26
54–55° (6 mm.)[c]	49				
59° (15 mm.)[d]		$d^{19.8}$ 0.8599	$n_D^{18.5}$ 1.4556	35.12	35.41
150–151°[e]	50	d_4^{20} 0.8598	n_D^{20} 1.4523	35.12	35.13
68.0–68.2° (24 mm.)[f]	50	d^{20} 0.8633			
62.0–62.5° (15 mm.)[g]	82.8	d_4^{20} 0.8590	n_D^{20} 1.4533	35.12	35.32

[a] Enklaar (32) used allyl bromide and zinc in a batch mixture.
[b] Auwers and Westermann (33) used allyl bromide and zinc in batch mixture.
[c] Knorr (18).
[d] Duveen and Kenyon (34) used allyl chloride and magnesium in a batch mixture.
[e] Ou, K.-H. (17) used allylmagnesium bromide.
[f] Pel'kis and Pazenko (35) used allyl bromide and magnesium in a batch mixture.
[g] This study.

TABLE IX

PHYSICAL CONSTANTS, 4,6-DIMETHYL-1,5-HEPTADIEN-4-OL

Boiling Range	Yield, %	d^t	n_D^t	Mol. Refract.	
				Calc'd	Found
168–170° (760 mm.)[a]					
71° (20 mm.)[b]	4	$d_4^{18.4}$ 0.8652	$n^{18.7}$ 1.4583	44.35	44.24
58° (2 mm.)[c]	75	d^{21} 0.8701			44.15
72° (18 mm.)[d]	91	d_4^{20} 0.8622	n^{20} 1.4598	44.35	44.53

[a] Jaworsky (6) used allyl bromide and magnesium in a batch mixture.
[b] Enklaar (36) used allyl bromide and zinc in a batch mixture.
[c] Pel'kis (37) used allylmagnesium bromide.
[d] This study.

reduced at room temperature with hydrogen at about 20 lbs./sq. in. Reduction was complete in about thirty minutes; b.p. 79° (26 mm.), 171.3–171.8° (corr.) (756 mm.); n_D^{20} 1.4298; d_4^{20} 0.8254; γ^{20} 24.75 dynes/cm.; M_R calc'd 45.29; M_R found 45.13; P calc'd 405.2; P found 389.8.

Anal. Calc'd for $C_9H_{20}O$: C, 74.93; H, 13.98.
Found: C, 74.85; H, 14.04.

B. From 38.5 g. (0.275 mole) of 4,6-dimethyl-1,5-heptadien-4-ol in the presence of 0.5 g. of the Adams catalyst with hydrogen under 20 lbs./sq. in., reduction was slow and incomplete; the catalyst was shown not to be poisoned and was extremely reactive in reduction of other substances, under these conditions of temperature and pressure. However, this mixture hydrogenated readily when shaken at 60° for ninety minutes with hydrogen under 900 lbs./sq. in.

1-Methoxyethyl methyl ketone. This ketone, needed in the synthesis of the following carbinol, was prepared by interaction of the appropriate Grignard reagent, produced from 8 g. (0.33 gram atom) of magnesium and 39 g. (0.28 mole) of methyl iodide, and 22.1 g. (0.26 mole) of α-methoxypropionitrile (39). The yield was 12 g. (45%) of 1-methoxyethyl methyl ketone (40) boiling at 114.0–114.5° (corr.) (745 mm.); n_D^{20} 1.3968; d_4^{20} 0.9063; M_R calc'd 26.94; M_R found 27.13.

TABLE X

PHYSICAL CONSTANTS, 2,4-DIMETHYLHEPTAN-4-OL

Boiling Range	d_t^{20}	n_D^t	Mol. Refract.	
			Calc'd	Found
170–171° (750 mm.)[a]	d^{20} 0.826	n^{18} 1.4318	45.29	[45.29]
75° (19 mm.)[b]	d_{20}^{20} 0.8230	n^{20} 1.4292	45.29	[45.08]
A 171.3–171.8°[c] (756 mm.)	d_4^{20} 0.8254	n^{20} 1.4298	45.29	45.13
B 171.2–172.2°[c] (751 mm.)	d_4^{20} 0.8261	n^{20} 1.4304	45.29	45.14

[a] Bodroux (29). The carbinol was prepared by the Grignard reaction, utilizing *n*-propylmagnesium iodide and isobutyl methyl ketone.

[b] Meyer and Tuot (38) likewise used the Grignard reaction.

[c] This study.

TABLE XI

PHYSICAL CONSTANTS, 4-ETHYL-1,6-HEPTADIEN-4-OL

Boiling Range	Yield, %	d^t	n_D^{20}	Mol. Refract.	
				Calc'd	Found
175–176° (743.5 mm.)[a]		d_0^{17} 0.8637			
175–176° (755.6 mm.)[b]	39	d_0^{20} 0.8688			
176.5–177.0° (750 mm.)[c]	73	d_4^{20} 0.8685	1.4587	44.35	44.11

[a] Smirensky (41) used zinc, an allyl halide, and ethyl propionate in "batch" method.

[b] Saytzeff (42) used zinc, allyl iodide and propionic anhydride in "batch" method.

[c] This study.

2-Methoxy-3-methyl-5-hexene-3-ol. Nine grams (0.088 mole) of 1-methoxyethyl methyl ketone was added to the reagent prepared from reaction of 8.8 g. (0.36 gram atom) of magnesium and 14.5 g. (0.12 mole) of allyl bromide. The crude product, weighing 8.9 g. (70% yield), was collected at 83–85° (40 mm.). Upon redistillation this new alcohol boiled at 166.0–166.5° (corr.) (737 mm.); n_D^{20} 1.4379; d_4^{20} 0.9080; γ^{20} 26.47 dynes/cm.; M_R calc'd 41.85; M_R found 41.68; *P* calc'd 275.2; *P* found 360.3.

Anal. Calc'd for $C_8H_{16}O_2$: C, 66.63; H, 11.18.
Found: C, 66.66; H, 11.20.

n-*Propyl ethoxyacetate*. This ester was formed in an 83% yield (104.5 g.) by saturating a solution of 73 g. (0.86 mole) of ethoxyacetonitrile (39) in 300 cc. of *n*-propyl alcohol with dry hydrogen chloride. After the usual procedures, the product was distilled with col-

lection of the fraction at 172–174°. Upon redistillation, the ester boiled at 173.5° (corr.) (748 mm.); n_D^{20} 1.4083; d_4^{20} 0.9594; γ^{20} 28.34 dynes/cm.; M_R calc'd 37.82; M_R found 37.62; P calc'd 356.2; P found 351.4.

4-Ethoxymethyl-1,6-heptadien-4-ol. The above ester (30 g. or 0.21 mole) was added to the Grignard reagent prepared from interaction of 50 g. (2.06 gram atoms) of magnesium and 80 g. (0.66 mole) of allyl bromide; the yield was 32.3 g. (90%) of tertiary alcohol boiling at 105.0–106.5° (36 mm.). Upon redistillation at 15 mm., the material boiled at 86–87°, 198.0–198.5° (corr.) (744.3 mm.); n_D^{20} 1.4500; d_4^{20} 0.9025; γ^{20} 26.07 dynes/cm.; M_R calc'd 50.61; M_R found 50.69; P calc'd 442.2; P found 426.2.

Anal. Calc'd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66.
Found: C, 70.49; H, 10.75.

4-Ethyl-1,6-heptadien-4-ol. One-fourth mole (25.5 g.) of ethyl propionate yielded 23.4 g. (66%) of material boiling at 81.5–86.0° (30 mm.); redistillation yielded the purified alcohol, b.p. 82–84° (32 mm.); 176.5–177.0° (corr.) (750 mm.); n_D^{20} 1.4587; d_4^{20} 0.8685; γ^{20} 26.21 dynes/cm.; M_R calc'd 44.35; M_R found 44.11; P calc'd 383.2; P found 364.8.

SUMMARY

Allylmagnesium bromide has been utilized in the Grignard reaction with representative saturated and unsaturated aldehydes and ketones, and alkoxy ketones and esters. A comparison of yields obtained in this study with those obtained in "batch" procedures, involving allyl halides, a carbonyl compound and zinc or magnesium, is unfavorable to the latter (and older) method.

AUSTIN, TEXAS.

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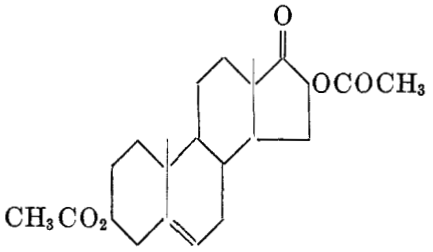
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY, AND THE DIVISION OF BIOCHEMISTRY, MAYO FOUNDATION]

STUDIES ON STEROID α-KETOLS. III. A PARTIAL SYNTHESIS OF 3,17-DIACETOXY-5-ANDROSTENE-16-ONE

FRANK H. STODOLA AND EDWARD C. KENDALL

Received April 8, 1942

In the course of the partial synthesis of 16-hydroxytestosterone, Butenandt and co-workers (1) prepared a diacetate with melting point 123° which has one of the following structures:



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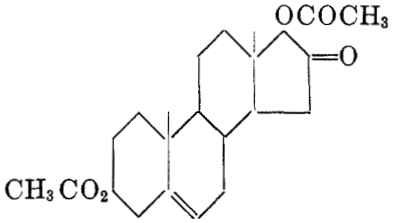
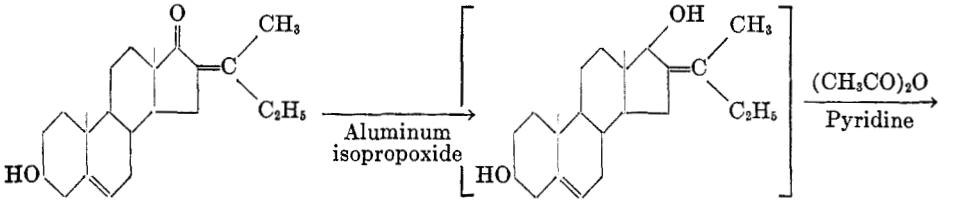
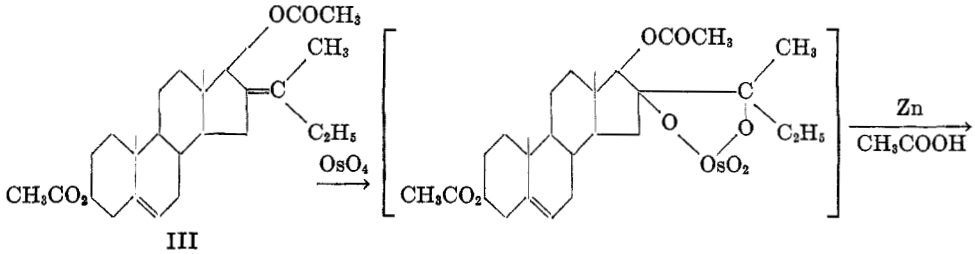


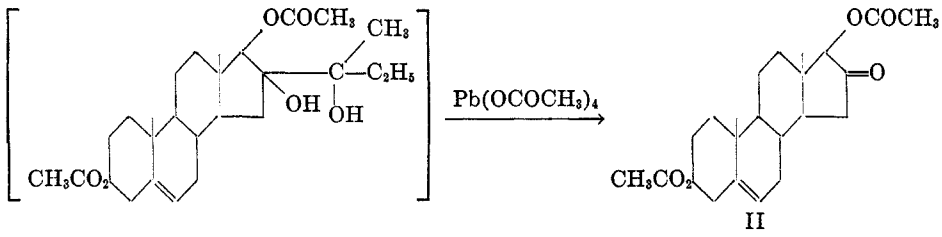
II

In the second paper (2) of this series a new method for the preparation of this compound in greatly increased yield by reduction of an isonitroso ketone was described, but the structure of the α-ketol was not established. Since it became a matter of importance to know the structure definitely, a compound with one of the two possible structures was prepared. The partial synthesis of 3,17-diacetoxy-5-androstene-16-one (structure II) was accomplished and it was shown by the method of mixed melting point that this compound is identical with the diacetate of Butenandt and co-workers with melting point 123°. The series of reactions for its preparation is as follows:





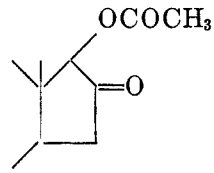
III



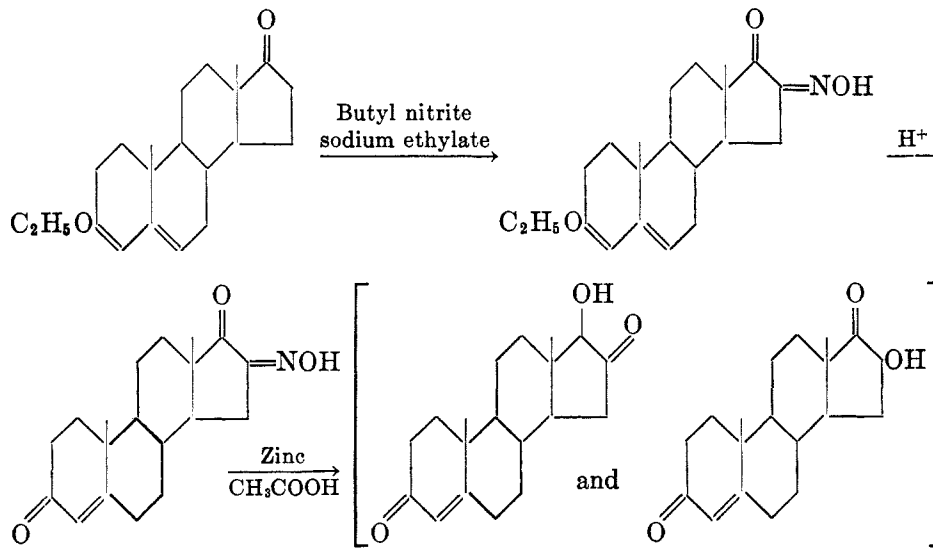
II

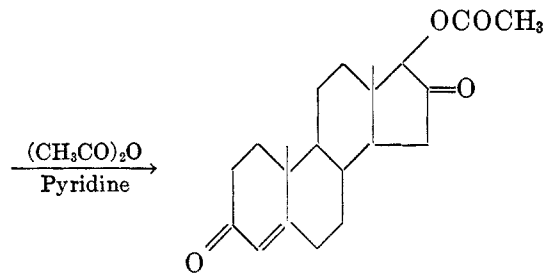
Although the synthesis gave the desired final product it was not entirely satisfactory because it was not possible to separate the glycol in pure form from the mixture obtained by reduction of the osmium addition compound. Accordingly a partial synthesis was carried through with similar but more easily available starting material, 16-benzaldehydroisoandrosterone. From this compound a fairly pure glycol was obtained which gave after treatment with lead tetraacetate the same final product as the earlier synthesis.

This independent determination of structure was of immediate value because it showed that mild reduction of isonitroso ketones provides a simple way for the preparation of steroids with the structure



The preparation of such a compound was described in the first paper of this series (3). The synthesis, however, was rather long, and we have now shown that it can be replaced by the following series of reactions in which the reduction of the isonitroso ketone is employed:





The final product of this synthesis was shown by the mixed melting point method to be identical with the 16-ketotestosterone acetate previously prepared (3).

EXPERIMENTAL

The diacetate (III). The condensation product with methyl ethyl ketone (2.41 g.), prepared by the method of Butenandt and co-workers (1), was dissolved in 8 cc. of dry isopropyl alcohol and added to 5 cc. of benzene which contained aluminum isopropoxide (0.31 g. per cc.). The solution was refluxed for two hours, concentrated to half its volume to remove acetone, and made up to its original volume with isopropyl alcohol. This process without alteration was repeated three more times. The solution of isopropyl alcohol was then concentrated to half its volume and the residue was concentrated several times with dry benzene to remove isopropyl alcohol. To the benzene solution, ether and 10 cc. of 5 *N* sulfuric acid were added. The ether-benzene solution was washed and then concentrated in a vacuum to an oil from which the last traces of water were removed with dry benzene by concentration in a vacuum. The residue was heated at 40° for thirty minutes with 10 cc. of pyridine and 10 cc. of acetic anhydride. After standing at room temperature overnight the acetyl derivative was isolated. Crystallization from acetone-methyl alcohol gave 1.18 g. of rosette crystals with melting point 120–130°. Repeated crystallization yielded 495 mg. of pure diacetate, m.p. 138–139°.

Anal. Calc'd for $C_{27}H_{40}O_4$: C, 75.67; H, 9.41.
Found: C, 75.67; H, 9.38.

The preparation and cleavage of the glycol. The diacetate (III) (255 mg.) was converted into the glycol through the OsO_4 addition compound as described in the first paper (3) of this series. Repeated crystallization of the crude glycol (260 mg.) from benzene-petroleum ether gave partial separation into a less soluble crystalline form of the glycol which melted at 195–205°,

Anal. Calc'd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15.
Found: C, 69.97; H, 9.19.

and a more soluble crystalline portion which melted at 150–152°.

Anal. Calc'd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15.
Found: C, 70.34; H, 9.22.

The lower-melting material (101 mg.) was treated in dry benzene with 115 mg. of lead tetraacetate. Eighty-five milligrams of oil was isolated and crystallized from acetone-petroleum ether to give 47 mg. of needles; melting point 124–125°. The melting point of a mixture of this compound with the one of the same melting point reported in the second paper of this series (2) showed no depression.

16-Benzaldehydroisoandrosterone. Dehydroisoandrosterone acetate (3.0 g.) and 1.5 molecular equivalents of benzaldehyde were refluxed for half an hour in 30 cc. of methanol with 1 molecular equivalent of sodium methoxide. A second mole of sodium methoxide

was added and refluxing continued for another half hour. The crystals which separated on cooling in ice weighed 2.90 g. A second crop weighed 0.2 g. After recrystallization from methanol the substance melted at 202–205°.

Anal. Calc'd for $C_{26}H_{32}O_2$: C, 82.93; H, 8.57.
Found: C, 83.00; H, 8.85.

This compound was first made by Dr. H. L. Mason. Grateful acknowledgment is given to him for permission to describe the details for its preparation in this paper.

3,17-Diacetoxy-16-benzal-5-androstene. Five grams of the benzal compound was reduced in benzene with aluminum isopropoxide and isopropyl alcohol by the method described. The reaction mixture was added slowly to a solution of 10 g. of potassium hydroxide in water and extracted twice with ether. The ether was washed and concentrated in a vacuum to a solid which was repeatedly crystallized from methanol. The crude product (2.63 g.) melted from 197° to 207°. This was heated on a steam-bath for three hours in a sealed tube with 12 cc. of pyridine and 9 cc. of acetic anhydride. The acetylated benzal derivative was isolated and crystallized from methanol in the form of blocks (weight 1 g., melting point 127–129°).

Anal. Calc'd for $C_{30}H_{38}O_4$: C, 77.89; H, 8.28.
Found: C, 77.86; H, 8.42.

Preparation of the glycol. The diacetate of the benzal derivative (232 mg.) was converted into the glycol through the addition of osmium tetraoxide as described in the first paper (3) of this series. Repeated crystallization of the crude glycol from acetone-water yielded 77 mg. of needles which melted at 204–206°.

Anal. Calc'd for $C_{30}H_{40}O_6$: C, 72.55; H, 8.12.
Found: C, 72.08; H, 8.17.

Cleavage of the glycol. The glycol (69 mg.) was treated in benzene with a 10% excess of lead tetraacetate and yielded 58 mg. of a pale yellow oil. This was dissolved in benzene, petroleum ether was added until turbidity was produced, and the solution was passed through a column of Al_2O_3 (1.8 g.). An oil was eluted from the column with petroleum ether. Crystallization from acetone-petroleum ether yielded 16 mg. of long needles melting at 124.5–125.5°. The melting point of a mixture of this compound with the one (m.p. 124–125°) reported in the second paper of this series (2) showed no depression.

16-Isonitroso-4-androstene-3,17-dione. Androstene-3,17-dione 3-enol ethyl ether (1.60 g.) was dissolved in 8 cc. of benzene and added to a solution of sodium ethoxide prepared from 0.44 g. of sodium and 11 cc. of alcohol. The solution was warmed at 35–40° for one minute and cooled to room temperature, and to it was added 0.58 cc. of freshly prepared *n*-butyl nitrite. After it had stood in the dark for two days there was a heavy orange precipitate. Ether, water, and 10 cc. of 5 *N* sulfuric acid were added.

After thorough shaking, the ether solution was brown and the water layer almost colorless. The ether was extracted twice with dilute sodium carbonate solution and concentrated in a vacuum to an oil. This was dissolved in ethyl alcohol which contained 1 g. of sodium hydroxide. Ether and water were added, and after thorough shaking the aqueous layer was removed. It was acidified with dilute sulfuric acid and extracted with ether. The ether was washed and concentrated in a vacuum to an oil which weighed 920 mg. This was warmed for ten minutes in 3 cc. of acetic acid and 3 cc. of water to complete the conversion of the enol ether to the ketone. Crystals started to come out of the warm solution. Addition of more water gave a precipitate of yellow crystals (633 mg.) sufficiently pure for the next step. For analysis 44 mg. was crystallized from ethanol-methanol to give 28 mg. of pale yellow blocks which sintered at 230° and melted at 237–238° with evolution of gas.

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44.
Found: C, 72.39; H, 8.14; N, 4.76.

Reduction of the isonitroso ketone. The isonitroso ketone (589 mg.) was dissolved in 11 cc. of acetic acid and 3 cc. of water was added. The solution was kept at 50° while 1.5 g. of zinc dust was added gradually. After one hour of refluxing, the unused zinc was removed by filtration and chloroform was added to the filtrate. Sufficient strong sodium carbonate solution was added to neutralize about 90% of the remaining acetic acid. After vigorous shaking the chloroform was drawn off and washed with 10 cc. of 1 *N* sulfuric acid and finally with 10 cc. of 1 *N* sodium hydroxide. The chloroform solution was washed until it was neutral, and concentrated in a vacuum to 500 mg. of oil. This was acetylated at room temperature with 3 cc. of acetic anhydride and 3 cc. of pyridine. From the acetylation mixture was isolated 570 mg. of pale yellow crystalline solid. This was recrystallized from petroleum ether-acetone to the constant melting point 194–195°. The yield was 360 mg. or an overall yield of 21.9% based on the weight of the enol ether.[1] The melting point of a mixture of this compound with the one prepared by the osmium tetroxide method described in the first paper (3) of this series showed no depression.

We wish to thank Dr. B. L. Josephy of Roche-Organon Company, Inc. for a generous amount of dehydroisoandrosterone.

SUMMARY

The diacetate of melting point 123° prepared by Butenandt and co-workers as an intermediate in the partial synthesis of 16-hydroxytestosterone has been shown to be 3,17-diacetoxy-5-androstene-16-one. An improved preparation of 16-ketotestosterone acetate is also described.

NEW YORK, N. Y.
ROCHESTER, MINN.

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[1] The over-all yield of the same product in the synthesis described in the first paper of this series was 9.3%.

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. X. CLIONASTEROL

C. ALBERT KIND AND WERNER BERGMANN

Received April 15, 1942

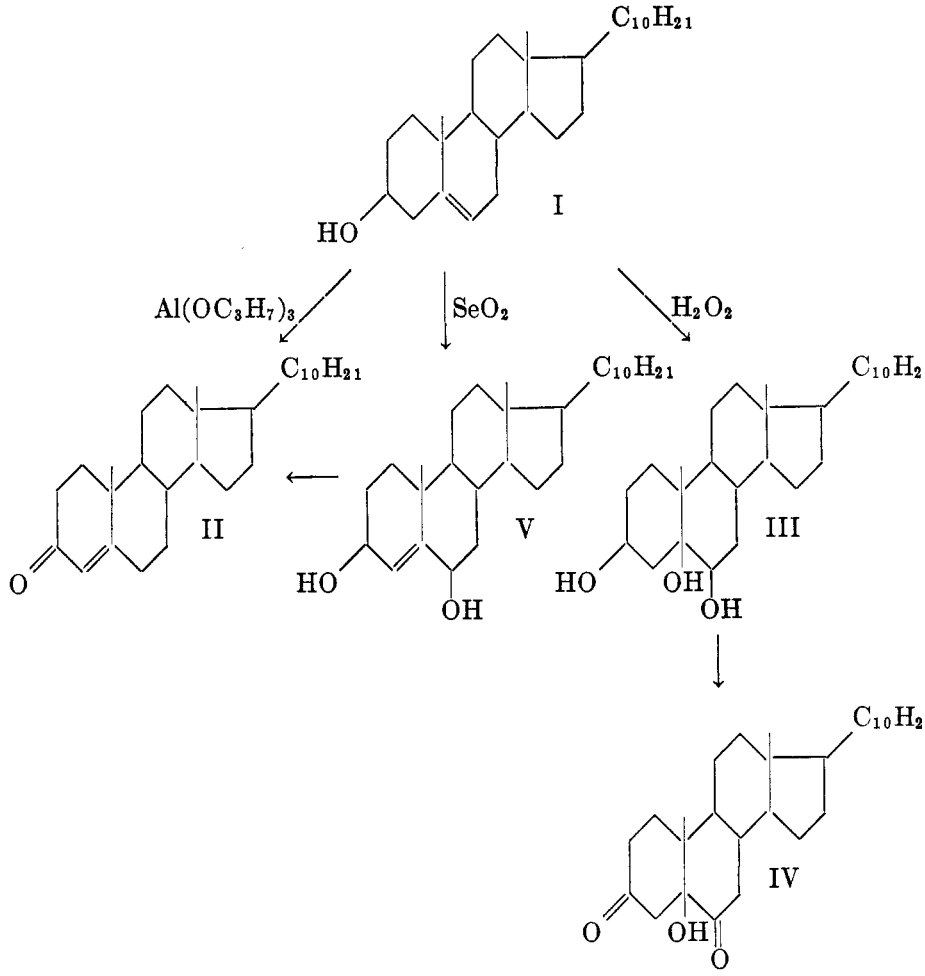
In a previous communication (1) it was pointed out that the sterol isolated by Dorée (2) from the marine sponge *Cliona celata* is a mixture of "phytosterol-like" sterols which may be separated into the mono-unsaturated clionasterol, $C_{29}H_{50}O$, and the di-unsaturated poriferasterol, $C_{29}H_{48}O$. Almost concurrently, Mazur (3) described the isolation of a sterol from the fresh-water sponge, *Spongilla lacustris*, the properties of which closely resemble those of clionasterol. Both Mazur and one of the present authors have therefore suggested the identity of the two sterols. In a more recent publication, Mazur (4) has now presented evidence intended to prove the identity of the spongilla sterol with 5,6-dihydrostigmasterol, and has implied that clionasterol is also identical with the latter. It is the purpose of the present publication to show that Mazur has incorrectly interpreted his results, and to prove the presence of a 5,6-double bond in clionasterol.

The properties of clionasterol and spongilla sterol are so different from the 5,6-dihydrostigmasterol prepared by Marker and Wittle (5) as to make their identity extremely unlikely. Since Marker's dihydrostigmasterol has been obtained by the reduction of stigmastenone it might be argued that it differs from the sponge sterol in the configuration at C^5. This, however, can not be the case since both sterols supposedly yield the same stigmastanol upon catalytic hydrogenation, which indicates identical configuration in the ring system.

Wallis and collaborators (6) have recently shown that Mazur's conclusions contradict the modern theories of optical rotatory power as applied to steroids, and have suggested on the basis of their calculations that the two sponge sterols possess a double bond in the 5,6-position. In a preliminary communication (7), the present authors have shown that they have arrived independently at the same conclusion on the basis of experimental evidence.

The presence of a 5,6-double bond in clionasterol (I) has been convincingly demonstrated by a series of oxidation reactions. Thus the Oppenauer oxidation of clionasterol yields clionastenone, $C_{29}H_{48}O$, (II), $[\alpha]_D^{25}$ + 80°, which shows the typical absorption spectrum of an α,β-unsaturated ketone. This observation coupled with the fact that conversion of the alcohol to the ketone is accompanied by a strong shift of the optical rotation in the positive direction suggests that the usual oxidation of a 5,6-en-3-ol to a 4,5-en-3-one has taken place. The 2,4-dinitrophenylhydrazone of clionastenone shows a specific rotation of + 232°, and the corresponding derivative of cholestenone one of + 241°. Such unexpectedly high rotations seem to indicate that these derivatives are heterocyclic compounds rather than hydrazones.

Oxidation of clionasterol with hydrogen peroxide gives a triol, $C_{29}H_{52}O_3$, in which the presence of an inert, tertiary hydroxyl group is indicated by the formation of a diacetate and dibenzoate. Formation of this triol is best explained by assuming the addition of two hydroxyl groups to a 5,6-double bond to give 3,5,6-trihydroxyclionastane (III). Oppenauer oxidation of the triol yields clionastanol-5-dione-3,6 (IV).



Rosenheim (8) and Butenandt (9) have shown that the oxidation of cholesterol with selenium dioxide gives rise to the formation of the two allylic isomers: 4-hydroxycholesterol, $[\alpha]_D - 60°$, and cholestene-4,5-diol-3,6, $[\alpha]_D + 6°$. Oxidation of clionasteryl acetate with selenium dioxide by Butenandt's method gives an acetate which upon hydrolysis yields a diol, $C_{29}H_{50}O_2$, $[\alpha]_D^{25} + 8°$. The relative insolubility of the diol and its positive rotation indicate that it is clionasten-4,5-diol-3,6 (V). Under the influence of acids the diol is dehydrated to

clionastenone (II), a reaction which is analogous to the dehydration of the selenium dioxide oxidation products of cholesterol to cholestenene.

In their theoretical considerations concerning the location of the double bonds in sponge sterols, Wallis and collaborators (6) have made the assumption that clionasterol and poriferasterol differ only in the presence of the double bond in the side chain of the latter. This assumption is justified, for catalytic hydrogenation of clionasterol gives a saturated sterol, $C_{29}H_{52}O$, which is identical with poriferastanol. In this connection it is of interest to note that Mazur (4) found that the slowness of this reaction indicates reduction of a 5,6-double bond rather than a 21,22-double bond which is known to absorb hydrogen readily.

EXPERIMENTAL[1]

Clionastenone. Eight grams of clionasterol and 9 g. of aluminum isopropoxide were dissolved in a mixture of 350 cc. of toluene and 85 cc. of cyclohexanone, and the solution was refluxed for two hours. After cooling, the mixture was shaken with 100 cc. of 3 *N* sulfuric acid, and the toluene layer washed successively with water, 5% sodium carbonate solution, and water. After drying, the toluene was removed *in vacuo*, and the remaining yellow oil digested with small amounts of methanol at 0°. A crystalline material was thus obtained which melted at 77–78° after several recrystallizations from methanol. The ketone was then distilled in a high vacuum and again recrystallized from methanol. The purified material melted at 79°; $[\alpha]_D^{25}$ + 80.2° (24.7 mg. in 3 cc. of chloroform).

Anal. Calc'd for $C_{29}H_{48}O$: C, 84.4; H, 11.7.
Found: C, 84.4; H, 11.7.

The 2,4-dinitrophenylhydrazone was prepared by refluxing 100 mg. of clionastenone with 10 cc. of Brady's reagent (10) for 30 minutes, and recrystallizing the crude product from alcohol and chloroform. It crystallizes in red needles of m.p. 227–228°, $[\alpha]_D^{25}$ + 232° (50.9 mg. in 3 cc. of chloroform).

Anal. Calc'd for $C_{35}H_{52}N_4O_4$: C, 70.0; H, 8.8; N, 9.45.
Found: C, 70.6; H, 8.85; N, 9.6.

Cholestenone 2,4-dinitrophenylhydrazone showed $[\alpha]_D^{25}$ + 240.8 (31.0 mg. in 3 cc. of chloroform.)

Clionastane-3,5,6-triol. To a solution of 5 g. of clionasterylacetate in 25 cc. of glacial acetic acid was added 5 cc. of 30% hydrogen peroxide in 0.5-cc. portions over a period of ten minutes. On each addition a flocculent precipitate was formed which subsequently went into solution. The mixture was then heated on the steam-bath for three hours, filtered from a small amount of precipitate, and poured into ice-water. Sodium chloride was added to facilitate the precipitation of the acetate mixture. The precipitate was collected and hydrolyzed by a 10% solution of potassium hydroxide in alcohol. Water was then added, and the triol filtered, dried, and recrystallized from a benzene-methanol mixture until the melting point remained constant at 237–238°.

Anal. Calc'd for $C_{29}H_{52}O_3$: C, 77.16; H, 11.7.
Found: C, 77.2; H, 11.7.

Triol monoacetate. Three hundred sixty milligrams of triol was refluxed with 5 cc. of acetic anhydride for one hour. The acetate which separated on cooling was recrystallized repeatedly from an ether-methanol mixture. On heating it softens at 235° and melts at 238°.

Anal. Calc'd for $C_{31}H_{54}O_4$: C, 75.9; H, 11.1.
Found: C, 76.0; H, 10.8.

[1] The authors are greatly indebted to Merck and Co., Rahway, N. J., for the preparation of the sponge sterols used in this investigation.

Triol diacetate. One hundred milligrams of triol was refluxed for 90 minutes with 4 cc. of acetic anhydride and 1 g. of fused sodium acetate. The diacetate which separated on cooling was filtered, washed with water and methanol, and crystallized from methanol until the melting point remained constant at 128–129°.

Anal. Calc'd for $C_{33}H_{56}O_5$: C, 74.4; H, 10.6.
Found: C, 74.05; H, 10.4.

Triol dibenzoate. Two cubic centimeters of benzoyl chloride was added to a solution of 225 mg. of triol in 5 cc. of dry pyridine. After standing at room temperature for eight hours the solution was poured into 2 *N* sulfuric acid, and the precipitate extracted with ether. After washing with water and carbonate solution, the extract was evaporated to dryness and the residue recrystallized from absolute alcohol. The dibenzoate melted at 225–228°.

Anal. Calc'd for $C_{43}H_{60}O_5$: C, 78.6; H, 9.2.
Found: C, 78.4; H, 9.35.

Clionastenol-5-dione-3,6. To a suspension of 400 mg. of triol in 30 cc. of dry acetone was added a solution of 1 g. of aluminum isopropoxide in 60 cc. of dry benzene, and the mixture was heated under reflux for ten hours. It was then cooled, 1 *N* sulfuric acid was added, and the benzene layer was washed with water and dried. Upon evaporation of the extract *in vacuo* there remained a colorless solid which was recrystallized several times from acetone. The diketone crystallized in small needles, and melted at 189–191°.

Anal. Calc'd for $C_{29}H_{48}O_3$: C, 78.3; H, 10.9.
Found: C, 78.0; H, 11.0.

Clionasten-4,5-diol-3,6. A solution of 4 g. of clionasterol in 100 cc. of acetic anhydride was heated for 30 minutes to 105–110°. With rapid stirring, a solution of 2.5 g. of selenium dioxide in 5 cc. of water was then added dropwise. After two hours the reaction product was precipitated with water, filtered, and washed repeatedly with hot water. The solid was then extracted with acetone, the extract filtered and poured into a 10% solution of potassium cyanide in water. After standing for several hours the mixture was extracted with ether, and the ether extract evaporated to dryness. The dark oily residue was refluxed for one hour with a 5% solution of potassium hydroxide in methanol. During the hydrolysis a copious crystalline precipitate appeared. It was filtered after cooling and crystallized first from a large volume of absolute ethanol, and then from ether by extraction from a thimble. The diol melted at 231–232°; $[\alpha]_D^{25}$ + 8.3° (47.0 mg. in 3 cc. of pyridine). It is difficultly soluble in most organic solvents with the exception of pyridine.

Anal. Calc'd for $C_{29}H_{50}O_2$: C, 80.9; H, 11.7.
Found: C, 81.1; H, 11.8.

Diol dibenzoate. The dibenzoate was prepared by treating the diol in pyridine solution with benzoyl chloride as described above. After several recrystallizations from absolute methanol it melted at 206–207°.

Anal. Calc'd for $C_{43}H_{58}O_4$: C, 80.8; H, 9.15.
Found: C, 80.6; H, 9.4.

Conversion of the diol to clionastenone. A small sample of the diol was refluxed with Brady's solution for five minutes. A 2,4-dinitrophenylhydrazone was formed which was recrystallized from a mixture of alcohol and chloroform. It melted at 229° and gave no depression with clionastenone-2,4-dinitrophenylhydrazone.

Hydrogenation of clionasteryl acetate. Eight hundred milligrams of acetate in 100 cc. of glacial acetic acid was hydrogenated at 60–70° in the presence of 0.3 g. of platinum oxide. The absorption of hydrogen was complete after 45 minutes. The reduction product gave a negative Liebermann test. The acetate was recrystallized from alcohol, m.p. 139°, $[\alpha]_D^{25}$ + 17.8° (30.4 mg. in 3 cc. of chloroform). Mixed with poriferastyl acetate of m.p. 140° it melted at 139.5–140°.

The alcohol prepared by hydrolysis of the acetate melted at 140–140.5°, $[\alpha]_D^{25}$ + 25° (30.4 mg. in 3 cc. of chloroform). Mixed with poriferastanol of m.p. 142–143° it melted at 141.5–142.5°.

The ketone prepared by oxidation of the alcohol with chromic anhydride melted at 159.5–160°; $[\alpha]_D^{25}$ + 43.1° (28.1 mg. in 3 cc. of chloroform). Mixed with poriferastanone of m.p. 161° it melted at 160.5–161°.

SUMMARY

Clionasterol has been shown to possess a double bond in the 5,6-position. It has been converted into clionastenone, clionastane-3,5,6-triol, clionastane-5-ol-dione-3,6, clionastene-4,5-diol-3,6, and poriferastanol. The structure of spongilla sterol has been discussed.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

FORMATION AND BEHAVIOR OF SOME CARBOARYLOXYAMINOANILINES

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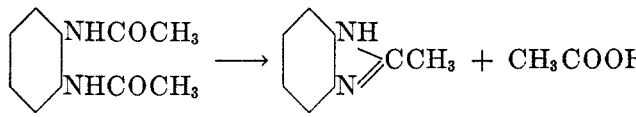
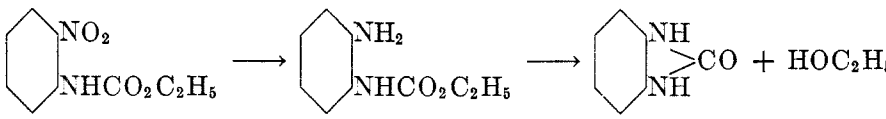
The formation of heterocyclic five-membered rings from certain ortho derivatives of benzene has frequently been observed. Ladenburg (1) found that heating *o*-phenylenediamine with glacial acetic acid and finally distilling the product gave 2-methylbenzimidazole. The intermediate in this case was probably the N,N′-diacetyl derivative of the diamine, because distillation of the latter by Rupe and Porai-Koschitz (2) was found to give the imidazole in quantitative yield. The conditions under which the imidazole is formed directly



from the monoacylated compound are indicated by later studies of Phillips (3), of Roeder and Day (4), and of Green and Day (5).

Ring closure may occur with other closely related derivatives of *o*-phenylenediamine. Rudolph (6) reduced 2-carboethoxyaminonitrobenzene to the related aniline and found that when the latter was heated above its melting point it lost the elements of alcohol and was converted into *o*-phenyleneurea. He also



noted that the urea may be formed during reduction of the nitro compound if the mixture is not kept cool. The structure of the final product has been established by Hartmann (7) who obtained it by the action of phosgene on the hydrochloride of *o*-phenylenediamine.

These observations and similar ones made by Ladenburg (8), by Groenvik (9) and by Raiford and Inman (10) on derivatives of 2-aminophenol, which also gave heterocyclic compounds, made it of interest to test the behavior of the related carboaryloxyaminoanilines and some of their substitution products. Attempts to obtain these compounds directly from the diamines gave diacyl derivatives, hence it was necessary to prepare first the carbophenoxyaminonitrobenzenes, and then reduce the latter to the desired products. The relations for the para compound are shown in Figure 1.

Although these reactions were carried through with the three nitroanilines, the behavior of derivatives of the ortho compound are of special interest. It was found that reduction of 2-carbophenoxyaminonitrobenzene with stannous

chloride and hydrochloric acid gave the related amino compound, which was isolated and for which a satisfactory analysis was obtained. This product was readily soluble in a 10% solution of caustic potash, and acidification of the resulting liquid precipitated a product that melted at 300–303° with apparent decomposition. The identity of this compound was established by comparing it with that obtained from the interaction of *o*-phenylenediamine and phosgene as described by Michler and Zimmermann (11). Analysis of the product here in question indicated that it was *o*-phenyleneurea, now designated as benzimidazolon (12), and first obtained by Hartmann (7), who reported the melting point 307–308°. The *m*- and *p*- carbophenoxyaminoanilines do not give cyclic ureas when treated with alkali under these conditions.

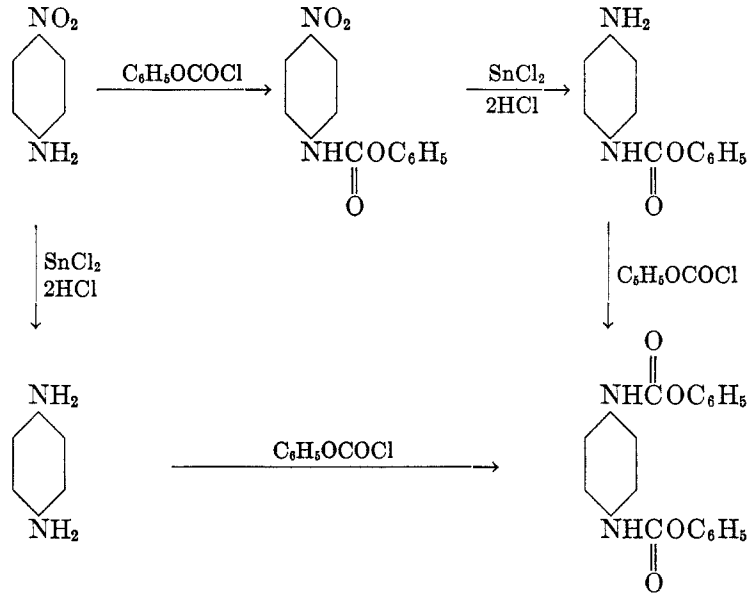


FIGURE 1. FORMATION OF MONO- AND DI-CARBOARYLOXYAMINO DERIVATIVES FROM PHENYLENEDIAMINES

The effect of substituents in the carbophenoxy radical was also tested. Repetition of the above experiment with 2-carbo-(2-chlorophenoxy)aminonitrobenzene was carried through. Reduction with stannous chloride and hydrochloric acid gave an amine hydrochloride that had a melting range of 175–180°. Analysis of the product showed the required amount of halogen and the compound seemed to be stable. Attempts to convert the hydrochloride into the free base by treatment with caustic alkali caused the loss of 2-chlorophenol and the formation of benzimidazolon. Treatment of a water solution of the hydrochloride with ammonium carbonate liberated the amino compound, which was removed by extraction with ether, but attempts to purify it caused the decomposition indicated above. In the ether extract the amino group was

acylated by benzoyl chloride and by 2-chlorophenyl chlorocarbonate, as shown in Figure 2.

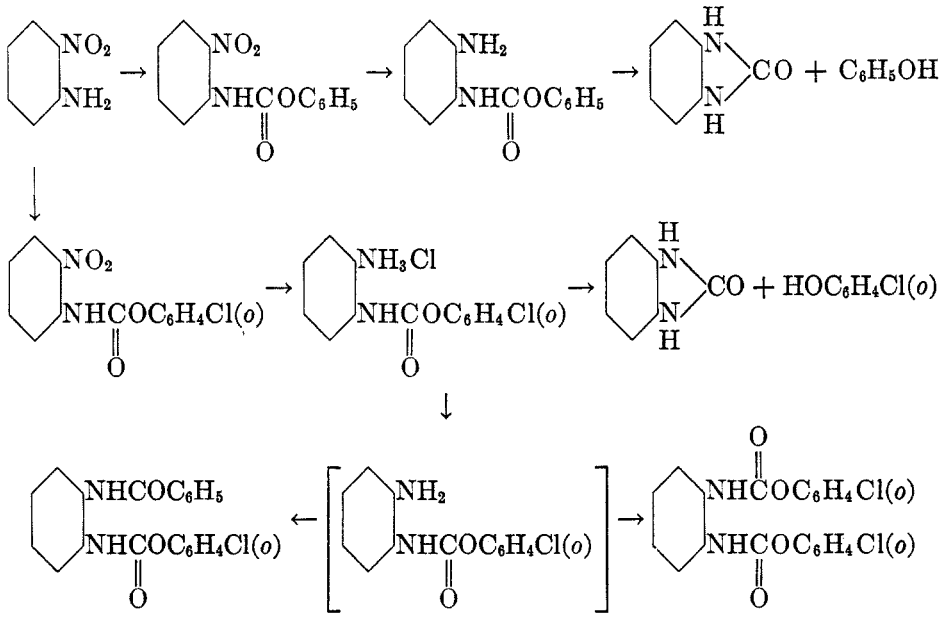


FIGURE 2. FORMATION OF A CYCLIC UREA FROM 2-CARBO-(2-CHLOROPHENOXY)-AMINOANILINE

The isomeric compounds having the substituted carboaryloxy residue in positions 3 and 4 were stable under these conditions.

EXPERIMENTAL

Carbophenoxy derivatives of the isomeric aminonitrobenzenes. Acylation was accomplished by adding gradually and with constant stirring, one molecular proportion of phenyl chlorocarbonate or its substitution product to an ether solution of two molecular proportions of the required nitroaniline, after which the mixture was allowed to stand for two hours. The hydrochloride of the aniline which had formed during this period was removed by filtration, the ether was distilled from the filtrate and the residue was crystallized from a suitable solvent. Analytical date and other properties are given in Table I.

Reduction of the nitro compounds. The general method may be illustrated by the preparation of the hydrochloride of 2-carbo-(2-chlorophenoxy)aminoaniline. Ten and seven-tenths grams of the related nitro compound, dissolved in hot alcohol, was reduced with a mixture of stannous chloride and hydrochloric acid. When the action was complete, the mixture was allowed to cool, and one volume of concentrated hydrochloric acid was added. The hydrochloride that separated was dissolved in the smallest possible amount of warm water, after which one volume of concentrated acid was poured in (13). The solid that was precipitated showed a melting range of 175–180°, and analysis indicated that the product was nearly pure.

Anal. Calc'd for $C_{13}H_{12}Cl_2N_2O_2$: Cl, 23.74, N, 9.36.
Found: Cl, 24.10; N, 9.09

Benzimidazolon. Three grams of 2-carbophenoxyaminoaniline was dissolved in 10% solution of caustic potash, and the resulting liquid was acidified with hydrochloric acid.

TABLE I

Acyl Derivatives of Aminonitrobenzenes

Composition and position of substituent	Yield, %	Solvent	Crystal form	M.P., °C	Formula	Analyses			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
2-Carbophenoxy-	73	Ligroin (65–67°)	Pale yellow needles	98–99	$C_{13}H_{10}N_2O_4$	—	—	10.85	11.01
2-Carbo-(2-chlorophenoxy)-	55	Alcohol	Pale yellow needles	113–115	$C_{13}H_9ClN_2O_4$	12.13	11.91	—	—
3-Carbophenoxy-	92	Toluene	Cream needles	123–124	$C_{13}H_{10}N_2O_4$	—	—	10.85	11.07
3-Carbo-(2-chlorophenoxy)-	76	Toluene	Colorless leaflets	136–137	$C_{13}H_9ClN_2O_4$	12.13	11.87	—	—
3-Carbophenoxy-4-methyl-	34[a]	Chloroform-ligroin	Colorless square prisms	128–130	$C_{14}H_{12}N_2O_4$	—	—	10.29	9.92
4-Carbophenoxy-	83	Toluene	Colorless needles	165–166	$C_{13}H_{10}N_2O_4$	—	—	10.85	10.90
4-Carbo-(2-chlorophenoxy)-	80	Toluene	Colorless needles	154–155	$C_{13}H_9ClN_2O_4$	12.13	11.70	—	—

[a] Refers to purified product. Starting material to the extent of 28% was recovered.

TABLE II

Carbophenoxyaminoanilines

Composition and position of substituent	Yield, %	Solvent	Crystal form	M.P., °C	Formula	Analysis nitrogen	
						Calc'd	Found
2-Carbophenoxy-	50	Alcohol	Pink needles	157–158 (decomp.)	$C_{13}H_{12}N_2O_2$	12.28	12.18
3-Carbophenoxy-	82	Alcohol	Colorless leaflets	178–179	$C_{13}H_{12}N_2O_2$	12.28	12.28
3-Carbo-(2-chlorophenoxy)-	32	Alcohol	Colorless leaflets	160 (decomp.)	$C_{13}H_{11}ClN_2O_2$	10.66	10.53
4-Carbophenoxy-	61	Toluene	Brown powder	134–135	$C_{13}H_{12}N_2O_2$	12.28	12.48
4-Carbo-(2-chlorophenoxy)-[a]	43	[b]	Pink powder	140 (decomp.)	$C_{13}H_{11}ClN_2O_2$	10.66	10.76

[a] The hydrochloride of this compound was isolated in colorless shining leaflets. *Anal.* Calc'd for $C_{13}H_{12}Cl_2N_2O_2$: N, 9.36. Found N, 9.28.

[b] No suitable solvent was found.

TABLE III

DICARBOPHENOXYDIAMINOBENZENE AND SUBSTITUTION PRODUCTS

COMPOSITION AND POSITION OF SUBSTITUENT	YIELD, %[a]	SOLVENT	CRYSTAL FORM	M.P., °C	FORMULA	ANALYSES			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
1,2-Dicarbophenoxy-	60	Alcohol	Colorless needles	189–190	$C_{20}H_{16}N_2O_4$	—	—	8.04	8.20
1,2-Di-(2-chloro-carbophenoxy)-	61	Dilute acetic acid	Colorless needles	170[b]	$C_{20}H_{14}Cl_2N_2O_4$	17.02	16.91	6.71	6.70
1,3-Dicarbophenoxy-	54	Dilute acetic acid	Colorless needles	163–165	$C_{20}H_{16}N_2O_4$	—	—	8.04	8.04
1,3-Di-(2-chloro-carbophenoxy)-	60	Acetic acid	Colorless leaflets	201–202	$C_{20}H_{14}Cl_2N_2O_4$	17.02	16.97	6.71	6.92
1,4-Dicarbophenoxy-	72	Alcohol	Pale brown leaflets	238–239	$C_{20}H_{16}N_2O_4$	—	—	8.04	8.06
1,4-Di-(2-chloro-carbophenoxy)-	67	Acetic acid	Colorless needles	223–224	$C_{20}H_{14}Cl_2N_2O_4$	17.02	17.08	6.71	6.63

[a] These figures represent purified materials.

[b] The product softened at 140°.

TABLE IV

MIXED DIACYL DERIVATIVES OF PHENYLENEDIAMINES

RELATIVE POSITIONS OF SUBSTITUENTS	ACYLS	YIELD, %[a]	SOLVENT	CRYSTAL FORM	M.P., °C	FORMULA	ANALYSES NITROGEN	
							Calc'd	Found
1,2-	Acetyl and carbophenoxy-	13	Ether[b]	Colorless powder	143–144	$C_{15}H_{14}N_2O_3$	10.37	10.19
	Benzoyl and carbophenoxy-	60	Alcohol	Colorless scales	146–148	$C_{20}H_{16}N_2O_3$	8.43	8.32
	Acetyl and carbo-(2-chlorophenoxy)-	85	[c]	Colorless leaflets	125–126	$C_{15}H_{13}ClN_2O_3$	9.19	9.41
	Benzoyl and carbo-(2-chlorophenoxy)-	80	[c]	Colorless powder	145–147	$C_{20}H_{15}ClN_2O_3$	7.64	7.82
1,3-	Acetyl and carbophenoxy-	41	Dilute alcohol	Colorless needles	144–146	$C_{15}H_{14}N_2O_3$	10.37	10.30
	Benzoyl and carbophenoxy-	60	Alcohol	Colorless fluffy masses	157–158	$C_{20}H_{16}N_2O_3$	8.43	8.55
	Acetyl and carbo-(2-chlorophenoxy)-	52	Dilute alcohol	Colorless needles	175–176	$C_{15}H_{13}ClN_2O_3$	9.19	9.42
	Benzoyl and carbo-(2-chlorophenoxy)-	28	Ether[b]	Gray powder	170–171	$C_{20}H_{15}ClN_2O_3$	7.64	7.52
1,4	Acetyl and carbophenoxy-	85	Dilute dioxane	Colorless powder	175–176	$C_{15}H_{14}N_2O_3$	10.37	10.35
	Benzoyl and carbophenoxy-	50	Alcohol	Pink leaflets	223	$C_{20}H_{16}N_2O_3$	8.43	8.43
	Acetyl and carbo-(2-chlorophenoxy)-	56	Dilute alcohol	Colorless leaflets	182–183	$C_{15}H_{13}ClN_2O_3$	9.19	9.23
	Benzoyl and carbo-(2-chlorophenoxy)-	60	Dilute alcohol	Colorless needles	195–196	$C_{20}H_{15}ClN_2O_3$	7.64	7.69

[a] These figures represent purified material.

[b] Ether was used to remove foreign matter.

[c] The product obtained by evaporation of ether was analyzed without further purification.

The precipitate that separated was crystallized from alcohol and was obtained as colorless plates that melted with apparent decomposition at 300–303°. The same product was obtained by the action of alkali solution on the hydrochloride of 2-carbo-(2-chlorophenoxy)-aminoaniline, in an attempt to secure the free amine, and also by the action of phosgene on a chloroform solution of *o*-phenylenediamine.

Anal. Calc'd for $C_7H_6N_2O$: N, 20.89. Found: N, 20.58.

Other carbophenoxyaminoanilines were prepared, and in most instances their salts were purified as indicated above. When it was not possible to free them from tin salts in the way specified, a solution of the salt was treated with hydrogen sulfide. In either case the solution of the amine hydrochloride was decomposed with ammonium carbonate solution in order to obtain the free bases, and these were purified by crystallization from suitable solvents. Analytical date and other properties are shown in Table II.

The carboaryloxyaminoanilines listed in Table II were further characterized by conversion into simple and mixed diacyl derivatives. The dicarbophenoxy compounds were obtained by treatment of one molecular proportion of the above-described monoacyl derivatives, in ether solution and in the presence of an equivalent amount of dimethylaniline, with one molecular proportion of the required acid chloride. When the free aniline was not available and it was necessary to use the hydrochloride, the latter was dissolved in water, the solution was mixed with ammonium carbonate, and the free base formed was extracted with ether. The resulting extract was then treated with the required acid chloride. The products were isolated and purified in the same general way as that described for the monoacyl derivatives tested above. The compounds thus were identical with those formed when the required phenylenediamines were treated directly with two molecular proportions of the necessary acylating agent. Analytical data and other properties of these substances are recorded in Table III.

To obtain the mixed diacyl derivatives the necessary acid chloride was added to an ether solution of the required amino compound in the presence of dimethylaniline to combine with the hydrogen chloride eliminated, the mixture was stirred for fifteen minutes, extracted with dilute hydrochloric acid, washed, dried over anhydrous sodium sulfate, and the ether distilled. The products were crystallized from suitable solvents. Data are given in Table IV.

SUMMARY

The carbophenoxyaminonitrobenzenes have been prepared and reduced to the related anilines, and the latter have been characterized. Heating the ortho aniline above its melting point causes the elimination of phenol and the formation of a cyclic urea. The presence of a "negative" substituent in the carbophenoxy radical makes the aniline less stable. It was possible to isolate the hydrochloride of 2-carbo-(2-chlorophenoxy)aminoaniline, but attempts to obtain the free aniline by treatment of the salt with an alkali caused elimination of 2-chlorophenol and the formation of the related cyclic urea. The isomers having the carbophenoxy radical in positions 3 and 4 are more stable.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

STRUCTURES OF THE MONO- AND DI-BROMOVERATRIC ACIDS

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In a study of the behavior of vanillin and some of its derivatives toward potassium permanganate and other oxidizing agents, which is still in progress, a number of halogenated veratric acids have been obtained. The monobromo compounds were readily prepared by oxidation of the related aldehydes which, in turn, were produced by methylation of the required vanillin substitution products (1). The 5,6-dibromo compound was not methylated directly under the conditions of these experiments, consequently the related acid was obtained indirectly as shown later.

The first dibromo acid isolated in the present work melted at 186–187°. Its structure was established by bringing it into relationship with the compounds indicated below. That bromovanillin XIX, which melts at 164°, proved by Dakin (2) to have bromine in position 5 (CHO = 1), was converted by methylation into 3,4-dimethoxy-5-bromobenzaldehyde, XX, previously obtained by Pschorr (3), and also by Jones and Robinson (4). Treatment of this aldehyde with fuming nitric acid gave a mononitro compound XXI, m.p., 139–140°, in which the nitro group must have entered position 2 or 6 and which was characterized by conversion into a number of derivatives. It was oxidized by potassium permanganate to the related nitrocarboxylic acid. This was reduced to the amino compound which was then diazotized, and the resulting diazonium salt was decomposed by cuprous bromide to give the dibromoveratric acid here in question, XXIV.

Compound XXI was quite different from an isomeric compound X, m.p. 69–70°, the structure of which was fixed by two routes, as shown below. In one of these the start was made with 5-bromovanillin. This was acetylated at position 4, the product was nitrated as indicated above, and again the nitro radical must have entered position 2 or 6. The acetyl group was removed by hydrolysis, the resulting hydroxyl was methylated to give compound X mentioned above. The position of the nitro radical in this product has been fixed by relating it to that nitrovanillin, IX, m.p. 137°, obtained by Pschorr and Sumuleanu (5). They methylated this substance and oxidized the product into a nitroveratric acid which was then reduced to the corresponding amino compound. The latter was diazotized, and when the resulting solution was treated with cuprous cyanide a nitrile was obtained. Hydrolysis of this gave hemipinic acid, which showed that the nitro compound IX was 2-nitrovanillin. In the present work bromination of the last-named compound gave a product which was found to be identical with XVI that had been obtained by nitration of acetyl-5-bromovanillin and subsequent removal of the acetyl group. Methylation of the resulting compound gave product X, which must therefore be 2-nitro-5-bromoveratralde-

hyde. This was converted into the corresponding dibromo acid XVIII, m.p., 186–187°, by methods outlined above for its isomer. A mixture of these acids showed a melting range of 154–162°. From this it follows that product XXI must be the 5-bromo-6-nitro compound and that the related dibromoveratric acid XXIV must be the 5,6-derivative.

Concerning the acid designated as XVIII, which is directly related to the nitrobromoveratraldehyde X, melting at 69–70°, it is to be noted that Beilstein (6) assigns positions 2 and 5 to the halogen atoms in a dibromoveratric acid, m.p. 182°, obtained by Boyen (7) by oxidation of a dibromo-3,4-dimethoxyallylbenzene with potassium permanganate. Boyen merely determined the composition of his product and did not even suggest a structure for it. This choice for the positions of halogen is questionable because it is based on the relation of the acid to a dibromoveratraldehyde, m.p. 122°, obtained by Hell (8) by oxidation of a dibromomethyleugenol dibromide acetyl derivative with chromic anhydride, and in which the halogen atoms are said to occupy position 2 and 5 (9), but for which no experimental proof was given. The positions of the bromine atoms in Hell's starting materials were indicated by Richter (10) as unknown. The positions recorded in the fourth edition of Beilstein rest solely on the suggestions of Zincke and Hahn (11) who assumed the structures indicated, though they provided no definite proof for the related products they studied. They refer for support to work in the same field by Auwers and Müller(12) but these men expressly state that the position of the second nuclear bromine atom in dibromoeugenol dibromide, to which Boyen's acid is directly related, is unknown. It has now been shown that Boyen's acid is 5,6-dibromoveratric acid. Dibromoeugenol dibromide was prepared as directed by Chasanowitz and Hell (13), and was found to melt at 120–121°. They reported 118°. Treatment of the alcoholic solution of this substance with zinc dust removed the bromine from the side chain, as they found. Methylation of the resulting dibromo compound resulted in an oil boiling at 210–220°/44 mm., that gave an acceptable analysis for halogen and which must have been identical with the dibromoeugenol methyl ether, m.p. 29.5°, described by Hell (14). The identity of our substances with Hell's compounds was further confirmed by comparison of the products obtained by the preparation of the methyl ether of dibromoeugenol dibromide by a route different from that which he used. Hell brominated the methyl ether of dibromoeugenol and obtained a product that melted at 65° and gave analysis for four bromine atoms. In the present work, methylation of dibromoeugenol dibromide gave a crystalline product that melted at 68–70°, and also gave values for a tetrabromo compound. The acid obtained by oxidation of Boyen's methyl ether of dibromoeugenol melted at 185°, and a mixture of this and the one of m.p. 186–187°, obtained by starting with 5-bromovanillin, and passing through product XXI, melted without depression.

The structure of the remaining acid, the 2,6-dibromo compound, was established as follows. Bromination of acetylvanillin gives the 6-derivative (15). Nitration of this product and subsequent removal of acetyl by hydrolysis gave a mononitrobromo compound. Methylation converted this into a product that

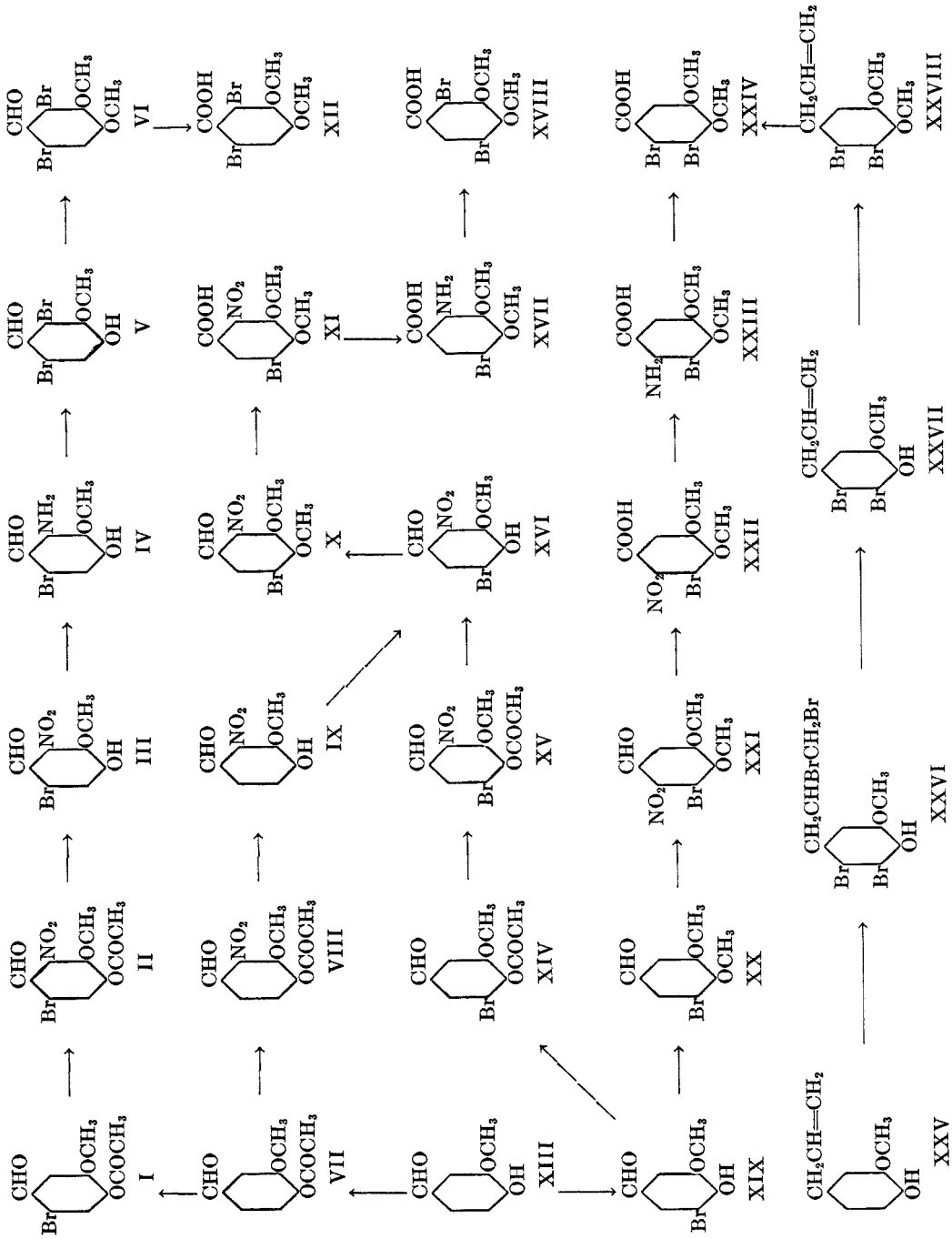

FIGURE 1. STRUCTURAL RELATIONS OF THE DIBROMOVERATRIC ACIDS

is isomeric with compounds X and XXI, but which melts at 117.5°. When it was carried through the required reactions to convert it into a dibromoveratric acid, it gave a product that melted at 123°. The relations involved in these changes are shown in Figure 1.

ACKNOWLEDGMENT

We are indebted to Mr. Don Floyd for assistance with the experimental work.

EXPERIMENTAL

Veratraldehyde, methylvanillin, has been prepared by many workers (16) with varying results as respects yields and purity of product. The most satisfactory method seems to be that of Buck (17), and a modification of his procedure was found suitable for substitution products of vanillin that could be methylated in this work. This modification involved dissolving the vanillin in warm methyl alcohol, after which alkali and dimethyl sulfate were added in about the way described by Buck. Analytical data and other properties for the monohalogenated compounds obtained are recorded in Table I.

TABLE I

VERATRIC ALDEHYDES OBTAINED BY METHYLATION OF VANILLIN SUBSTITUTION PRODUCTS[a]

SUBSTITUENT	YIELD %	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANALYSES HALOGEN	
						Calc'd	Found
2-Chloro-	79	Acetic acid	Colorless needles	69–70	$C_9H_9ClO_3$	17.70	17.41
5-Chloro-	80	Alcohol 70%	Long colorless needles	48–49	$C_9H_9ClO_3$	17.70	17.47
6-Chloro-	84	Alcohol 90%	Small nearly colorless needles	140–141	$C_9H_9ClO_3$	17.70	17.51
2-Bromo-	80	Dilute acetic acid	Colorless needles	84–85	$C_9H_9BrO_3$	32.65	32.34
5-Bromo-	88	Alcohol 70%	Colorless leaflets	59–60	$C_9H_9BrO_3$	32.65	32.35
6-Bromo-	96	Alcohol 70%	Colorless needles	145–146	$C_9H_9BrO_3$	32.65	32.08
5-Iodo-	76	Alcohol 70%	Nearly colorless needles	72–73	$C_9H_9IO_3$	43.49	43.21

[a] Though the bromine compounds only were here converted into acids, the methylation process was tested with other derivatives.

Veratric acid, first prepared by oxidation of eugenol methyl ether with dichromate mixture by Graebe and Borgmann (18), who recorded no yield, has now been obtained in 80% yield by oxidation of methylvanillin with potassium permanganate solution. A mixture of 5 g. of the vanillin and 100 cc. of approximately normal solution of the oxidizing agent was boiled for ten minutes, the mixture was filtered and the cold filtrate was acidified. Recrystallization of the precipitate from acetic acid gave fine, nearly colorless needles that melted at 179–180°, which agrees with previous work. Analytical data and other properties for the monobromo derivatives, obtained from related vanillin substitution products are given in Table II.

5-Bromo-6-nitroveratraldehyde was prepared in 85% yield by nitration of 5-bromomethylvanillin as directed by Jones and Robinson (4) who recorded no yield. Crystallization from acetic acid gave long, pale yellow needles that melted at 139–140°. Jones and Robinson

found 138°. Our product was further characterized by conversion into the nitroguanylhydrazone. Two grams of the aldehyde in 40 cc. of hot methyl alcohol was mixed with 20 cc. of a warm aqueous solution of 2 g. of nitroaminoguanidine, 10 cc. of acetic acid was added, and the mixture was cooled in an ice-bath. The solid that separated was crystallized from *n*-butyl alcohol and was obtained in small yellow granules that melted at 243–244°. The yield was 94%.

Anal. Calc'd for $C_{10}H_{11}BrN_6O_6$: Br, 20.46. Found: Br, 20.93.

5-Bromo-6-nitroveratraldoxime. A mixture of 12.5 g. of the required aldehyde, 3.6 g. of hydroxylamine hydrochloride, 2 g. of sodium carbonate, and 150 cc. of alcohol was boiled for an hour under reflux, filtered to remove salts, and the filtrate was allowed to cool. A small amount of unchanged starting material separated; this was removed by filtration and the filtrate was diluted. The yield was 97%. Crystallization from 50% alcohol gave long yellow needles that melted at 130–131°.

Anal. Calc'd for $C_9H_9BrN_2O_5$: Br, 26.22. Found: Br, 25.51.

3,4-Dimethoxy-5-bromo-6-nitrocinnamic acid. A mixture of 10 g. of the required veratraldehyde, 2.5 g. of anhydrous sodium acetate, and 50 cc. of acetic anhydride was heated in an oil-bath at about 170° for two hours, the hot mixture was poured slowly into several

TABLE II

MONOBROMOVERATRIC ACIDS

SUBSTITUENT AND POSITION	YIELD %	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	ANALYSES HALOGEN	
						Calc'd	Found
2-Bromo-	89	Dilute acetic acid	Colorless needles	205–206	$C_9H_9BrO_4$	30.65	31.08
5-Bromo-	89	Dilute acetic acid	Nearly colorless needles	192–193	$C_9H_9BrO_4$	30.65	30.41
6-Bromo-	98	Dilute acetic acid	Colorless needles	184–185	$C_9H_9BrO_4$	30.65	30.40

volumes of water, and the whole was allowed to stand in an ice-bath until the oil which separated at first had solidified to a dark mass. This was collected and repeatedly crystallized from acetic acid, and was finally obtained in nearly colorless needles that melted at 239–240°. The yield of purified material was 36%. Dilution of the collected mother liquors gave 5 g. of solid that was identified as unchanged aldehyde.

Anal. Calc'd for $C_{11}H_{10}BrNO_6$: Br, 24.09. Found: Br, 24.10.

5-Bromo-6-nitroveratric acid. Five grams of the required aldehyde was boiled for 10–15 minutes with a slight excess of potassium permanganate in about normal solution, manganese dioxide was removed by filtration, and the cold filtrate was acidified. Treatment of a water suspension of the manganese dioxide with sulfur dioxide gave an additional portion of acid. The total yield was 90%. Crystallization from 30% acetic acid gave small colorless needles that melted at 203–204°. It became colored on exposure to light and air.

Anal. Calc'd for $C_9H_8BrNO_6$: Br, 26.14. Found: Br, 25.85.

5-Bromo-6-nitroveratroyl chloride. A mixture of 5 g. of the above acid and slightly more than one molecular proportion of phosphorus pentachloride was warmed until action began and was then set aside for some hours at room temperature. The mixture was extracted with dry ether and the solvent was distilled off. Crystallization of the residue from ligroin, 68–70°, gave long, slightly colored needles that melted at 110–111°. A yield of 90% was obtained.

Anal. Calc'd for $C_9H_7BrClNO_5$: Hal., 35.59. Found: Hal., 35.53.

5-Bromo-6-aminoveratraldehyde. Twenty-five grams of the above nitroaldehyde was added slowly to a boiling mixture containing 250 g. of ferrous sulfate, 650 cc. of water, and

800 cc. of concentrated ammonia water, the boiling was continued for fifteen minutes, and the mixture was cooled and filtered. The residue was extracted several times with hot alcohol, the combined extracts were concentrated, and the liquid cooled. The solid that separated was crystallized from dilute alcohol, and was obtained in orange needles that softened about 150° and seemed to melt at 162–165°. A yield of 67% was obtained.

Anal. Calc'd for $C_9H_{10}BrNO_3$: Br, 30.76. Found: Br, 32.84.

5-Bromo-6-aminoveratric acid. Eight grams of the nitro acid was reduced by ferrous hydroxide as indicated above. Crystallization of the product from alcohol gave slightly colored needles that melted at 173–175°. The yield was 80%.

Anal. Calc'd for $C_9H_{10}BrNO_4$: Br, 28.98. Found: Br, 29.07.

5,6-Dibromoveratric acid. Six grams of the above amino acid was dissolved in a mixture of 15 cc. of concentrated hydrochloric acid and 10 cc. of water, the dark red solution was cooled to about 0°, and 3 g. of solid sodium nitrite was gradually added with stirring. Then a solution of 3 g. of freshly prepared cuprous bromide in 15 cc. of hydrobromic acid was added, the liquid was heated on the steam-bath for about two and one-half hours, 20 cc. of concentrated hydrochloric acid was poured in, and the mixture was cooled and filtered. Crystallization of the residue from 50% alcohol, with Norit to remove color, gave small colorless needles that melted at 186–187°. The yield was 71%.

Anal. Calc'd for $C_9H_8Br_2O_4$: Br, 47.06. Found: Br, 47.17.

Second method of preparation of 5,6-dibromoveratric acid. Dibromomethyleugenol, which had been prepared by a modification of Hell's method, was oxidized by a hot 4% solution of potassium permanganate, and gave an acid that in its crude form melted at 183–184°. Repeated crystallization from dilute alcohol gave colorless needles that melted at 185–186°, and which did not depress the melting point of the 5,6-dibromo acid prepared as described above.

Anal. Calc'd for $C_9H_8Br_2O_4$: Br, 47.06. Found: Br, 47.18.

2-Nitro-5-bromoveratraldehyde. Thirty grams of 2-nitro-5-bromovanillin, the structure of which was proved by Raiford and Stoesser (19), was dissolved by warming to about 85° in 280 cc. of water containing 50 g. of sodium bicarbonate, and 55 g. of dimethyl sulfate was added dropwise during a period of about two hours, while the temperature was held at about 85° and the liquid was stirred. To the mixture there was next added dropwise and simultaneously a solution of 40 g. of sodium bicarbonate in 250 cc. of water, and 40 g. of dimethyl sulfate, while the whole was stirred and heated for about two hours longer. The cooled mixture was extracted with ether, the solvent was distilled off and the remaining dark oil was cooled until it solidified. Crystallization from methanol gave slightly colored leaflets that melted at 69–70°. A yield of 38% was obtained.

Anal. Calc'd for $C_9H_8BrNO_5$: Br, 27.57. Found: Br, 27.77.

This product was further characterized by conversion into the nitroguanylhydrazone, as indicated above. Crystallization from *n*-butyl alcohol gave yellow granules that melted at 219–220°. The yield was 92%.

Anal. Calc'd for $C_{10}H_{11}BrN_6O_6$: Br, 20.46. Found: Br, 20.56.

2-Nitro-5-bromoveratric acid. Five grams of the related aldehyde was oxidized with hot potassium permanganate solution as previously described. Crystallization of the product from dilute acetic acid gave pale yellow needles that melted at 145–146°. The yield was 88%.

Anal. Calc'd for $C_9H_8BrNO_6$: Br, 26.14. Found: Br, 26.11.

2,5-Dibromoveratraldehyde. Twenty-three grams of 2,5-dibromovanillin (19) was dissolved in 75 cc. of methanol and placed in a three-necked flask, and methylation was carried out as indicated above, after which the mixture was cooled and acidified by dilute sulfuric acid to precipitate the product. The yield was 32%. Crystallization from alcohol gave colorless plates that melted at 145–147°. Hell's (8) product, obtained by the oxidation of a dibromomethyleugenol dibromide in which the positions of the nuclear bromine atoms were formerly listed as unknown (10) but have now been recorded (6) as 2 and 5, and which on that basis should be identical with the one here in question, was reported to melt at 122°.

Anal. Calc'd for $C_9H_8Br_2O_3$: Br, 49.38. Found: Br, 49.16.

2,5-Dibromoveratric acid. Five grams of the above-described aldehyde was suspended in 100 cc. of hot water, a hot 4% solution of potassium permanganate was run in until the purple color persisted, after which the color was discharged by sodium sulfite solution and the mixture was filtered. Acidification of the filtrate precipitated the product in 60% yield. Crystallization from 50% alcohol gave colorless needles that melted at 186–187°.

Anal. Calc'd for $C_9H_8Br_2O_4$: Br, 47.06. Found: Br, 47.17.

2-Amino-6-bromoveratraldehyde. Twenty-five grams of the related 2-nitro compound, m.p. 109–110°, prepared in 71% yield by directions of Jones and Robinson (4) who found 109° and reported no yield, was suspended in concentrated ammonia water and reduced as described by Sumuleanu (20). Crystallization of the product from alcohol gave orange needles that melted at 101°. The yield was 60%.

Anal. Calc'd for $C_9H_{10}BrNO_3$: Br, 30.76. Found: Br, 30.54.

2,6-Dibromoveratraldehyde. Twelve grams of the above amino compound was dissolved in a mixture of 50 cc. of concentrated hydrobromic acid and 50 cc. of water, the liquid was cooled to about 0°, diazotized by addition of 6 g. of sodium nitrate, and the diazonium salt was decomposed by cuprous bromide. A yield of 72% was obtained. Crystallization of the product from alcohol gave nearly colorless needles that melted at 136–137°, which agrees with that reported by Lock (21), whose product was made in a different way and gave good analytical data.

2,6-Dibromoveratric acid. Five grams of the required aldehyde was oxidized as explained above for the 2,5-compound. Crystallization from alcohol gave nearly colorless granules that melted at 122–123°.

Anal. Calc'd for $C_9H_8Br_2O_4$: Br, 47.06. Found: Br, 47.60.

SUMMARY

1. It has been shown that the monobromoveratric acids can readily be obtained by oxidation of the related aldehydes which, in turn, can be prepared by methylation of the corresponding vanillin substitution products.

2. The structures of the dibromo compounds have been established, and it has been found that the halogen atoms in Boyen's acid occupy positions 5 and 6, instead of 2 and 5 as previously recorded in the literature.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. VII. SYNTHESIS OF 3,14-BISDESOXYTHEVETIGENIN AND OF 14-DESOXYTHEVETIGENIN

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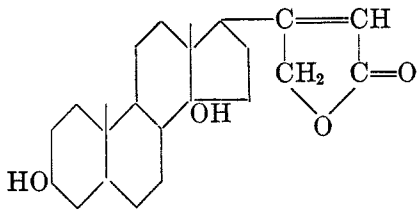
In preceding communications (1, 2), general syntheses for β-substituted $\Delta^{\alpha,\beta}$ -butenolides have been described and applied to the preparation of simple unsaturated lactones analogous to the cardiac aglycones. At the same time a study of the properties of the simple butenolides led to the suggestion that the side chain of the natural cardiac aglycones of the digitalis-strophanthus group is better represented as a $\Delta^{\alpha,\beta}$ -butenolide (3) than as a $\Delta^{\beta,\gamma}$ -butenolide. We have now extended this general study to the preparation of such butenolides containing the sterol ring system as a substituent on the β-carbon atom. The purpose in mind was two-fold: to substantiate the suggestion previously made concerning the position of the side chain double bond by a study of an unsaturated lactone containing a reduced cyclopentanophenanthrene substituent, and to gain information relative to the effect of structure of this group of drugs on physiological activity.

The simplest cardiac aglycones are digitoxigenin, thevetigenin, and uzarigenin. These are structurally identical but stereochemically different, and are represented by formula I.



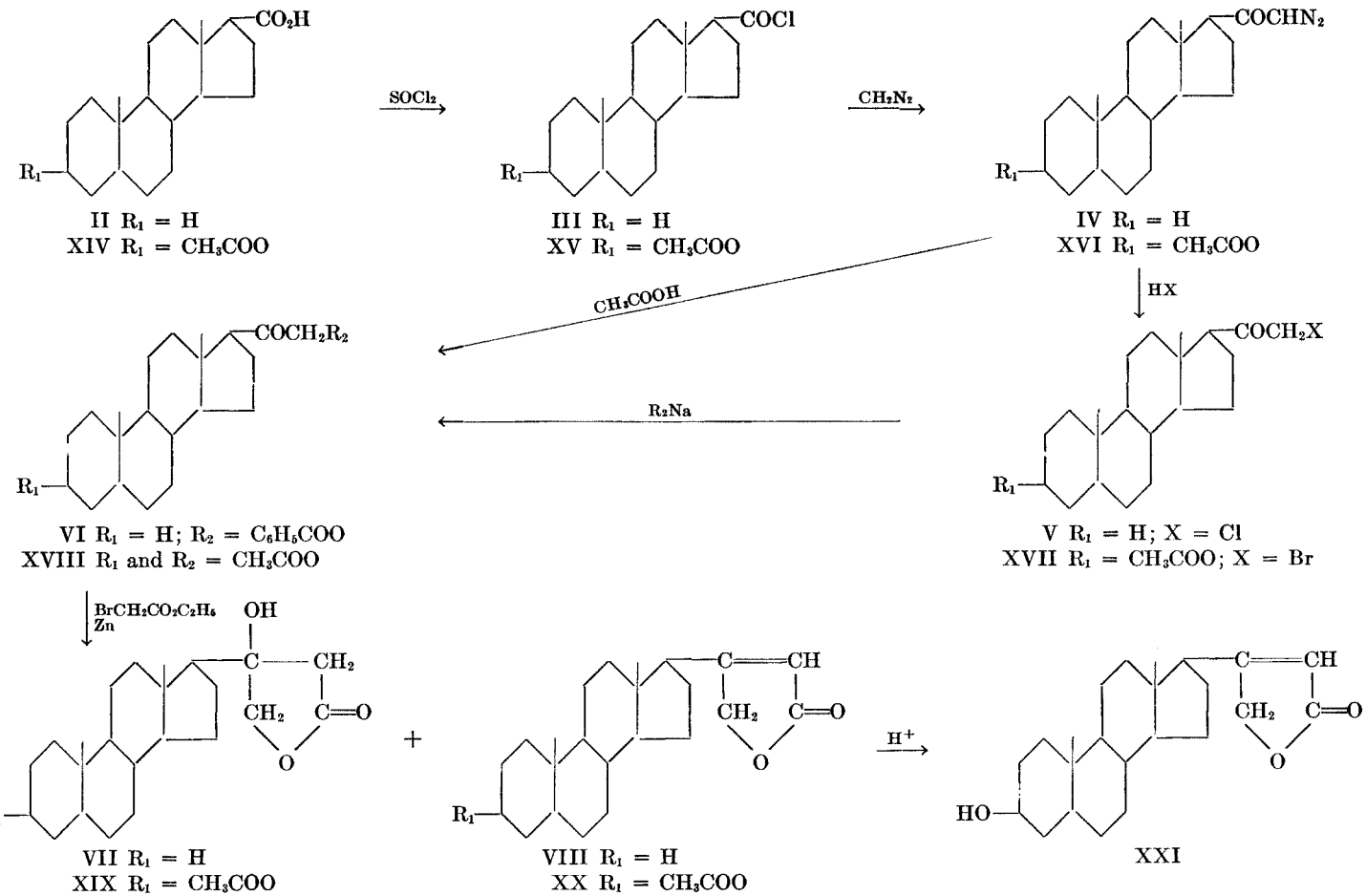
I

Stereochemical arrangement relative to C_{10}		
Digitoxigenin	*trans* 3,	*cis* 5
Thevetigenin	*cis* 3,	*cis* 5
Uzarigenin	*cis* 3,	*trans* 5

Of the three aglycones, digitoxigenin and thevetigenin show pronounced cardiotonic activity, whereas uzarigenin is comparatively much weaker in its action (4). It is therefore apparent that one should choose a steroid of the coprostane, or bile acid, series as the starting material for a synthetic lactone, if optimum activity is to be obtained, and that the configuration of the C-3 hydroxyl group is of comparatively minor importance.

The question of whether the presence of one or both of the hydroxyl groups is necessary for cardiotonic activity remains to be answered. There is no information at hand which can be used as a guide in the solution of this problem. Therefore we have prepared a lactone containing neither of the hydroxyl groups in question, and one containing the C-3 hydroxyl group. It is hoped to provide

[1] Eli Lilly post-doctorate fellow.


CO₂H
SOCl₂
COCl
CH₂N₂
COCHN₂
R₁
II R₁ = H
XIV R₁ = CH₃COO
III R₁ = H
XV R₁ = CH₃COO
IV R₁ = H
XVI R₁ = CH₃COO
CH₃COOH
HX
COCH₂R₂
R₂Na
COCH₂X
VI R₁ = H; R₂ = C₆H₅COO
XVIII R₁ and R₂ = CH₃COO
V R₁ = H; X = Cl
XVII R₁ = CH₃COO; X = Br
BrCH₂CO₂C₂H₅
Zn
OH
C
CH₂
C=O
O
+
CH
H⁺
HO
VII R₁ = H
XIX R₁ = CH₃COO
VIII R₁ = H
XX R₁ = CH₃COO
XXI

an answer to this question from the results of pharmacological tests of these lactones. A preliminary note dealing with the synthesis of the first of these substances has already appeared (5). During the course of the work here described the preparation of the lactone of 3,21-dihydroxy-$\Delta^{5,6;\ 20,22}$-norcholadienic acid was described by Ruzicka and co-workers (6). In order that the relationship of the synthetic lactones, here described, to the natural aglycones may be apparent, and in order to avoid unduly cumbersome names, we suggest that the lactone of 21-hydroxy-$\Delta^{20,\ 22}$-norcholenic acid be referred to as 3,14-bisdesoxythevetigenin (or digitoxigenin), and that the lactone of 3,21-dihydroxy-$\Delta^{20,22}$-norcholenic acid be referred to as 3-desoxythevetigenin.

The preparation of both of these lactones was accomplished using the method previously described (2). Etiocholanic acid, which was prepared by degradation of cholanic acid according to Wieland, Schlichting, and Jacobi (7) served as the starting material for the synthesis of 3,14-bisdesoxythevetigenin. It has been found that, if the reduction of dehydrocholic acid to cholanic acid be carried out in acetic acid solution, rather than in alcohol (8), an improved yield of a more easily purified product results. The reactions involved in passing from etiocholanic acid to the lactone are shown in formulas II–VIII. In the preparation of etiocholanyl chloride, it is vital that the reaction mixture be kept cold if a satisfactory yield is to be obtained. The reaction of etiocholanyl chloride with diazomethane to yield the diazomethyl ketone (IV) proceeded without difficulty. However, in attempts to prepare 21-acetoxypregnanone-20 in crystalline form, unexpected difficulties were encountered. When the diazomethyl ketone (IV) was warmed with acetic acid in the usual manner, no crystalline product could be isolated from the reaction mixture either before or after chromatographic purification. The reaction of IV with hydrogen chloride proceeded normally, leading to the well defined chloromethyl ketone (V), which after reaction with sodium or potassium acetate, likewise failed to yield a crystalline acetoxymethyl ketone. However, reaction of IV with sodium benzoate resulted in the formation of crystalline 21-benzoxypregnanone-20 (VI), which was used successfully for the subsequent Reformatzky reaction. The crude product of the reaction of VI with ethyl bromoacetate and zinc consisted of a mixture of the hydroxy lactone (VII) and the desired unsaturated lactone (VIII) from which VIII crystallized. The hydroxy lactone (VII) could be converted to VIII by treatment with a solution of hydrogen bromide in acetic acid, as was the case with the simpler lactones described earlier (2).

3,14-Bisdesoxythevetigenin (VIII) as thus prepared gives a strong, positive nitroprusside (Legal) color test, indistinguishable from that displayed by the natural cardiac aglycones. Its ultraviolet absorption curve is shown in Figure 1, together with the curves for strophanthidin, periplogenin, and β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide. The close similarity of the curve for the synthetic lactone with those for strophanthidin, provided allowance is made for the aldehyde group of the latter, and periplogenin, furnishes strong confirmation for assigning the side chain double bond of the natural aglycones to the $\Delta^{\alpha,\beta}$-position. In the earlier paper (3) a slight discrepancy existed between the curves for the

natural aglycones and that for β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide. This discrepancy has now been cleared up by the nature of the curve for the butenolide containing a substituent which is identical with that of the natural lactones, with the exception of the nuclear hydroxyl groups.

Catalytic reduction of the double bond of 3,14-bisdesoxythevetigenin resulted in the formation of the dihydrolactone, which was identical with that previously prepared by a number of workers from digitoxigenin (9), sarmento-

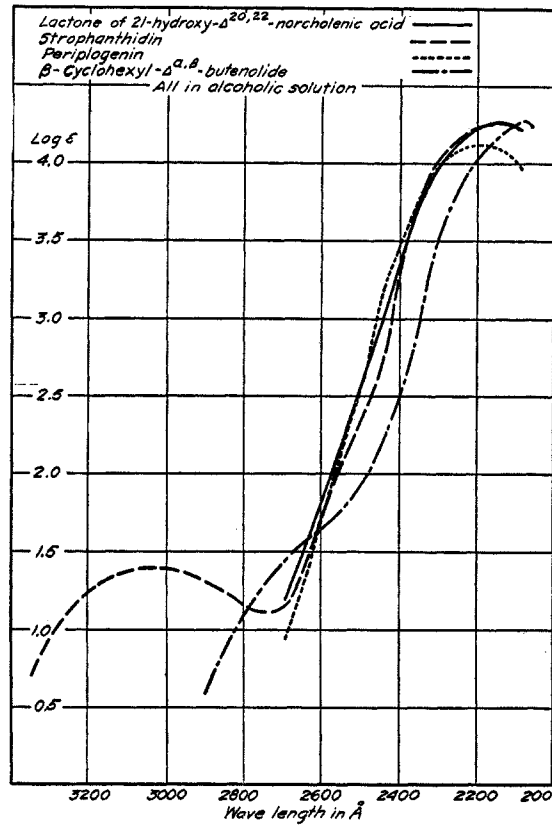
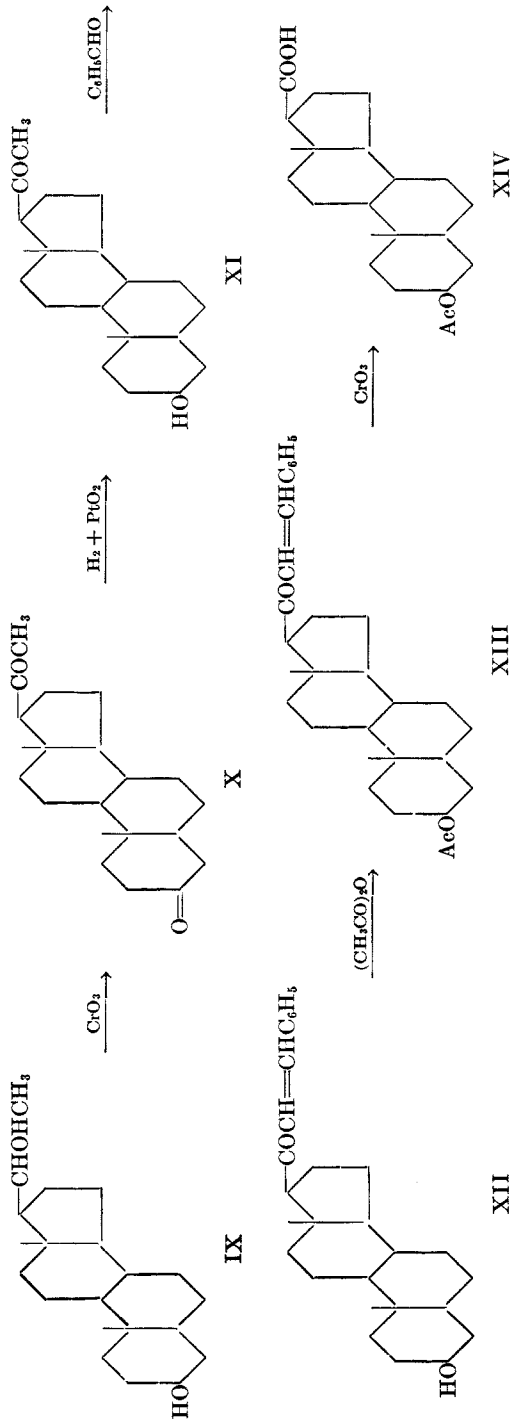


FIGURE 1

genin (10), or digoxigenin (11). A direct correlation between the bile acids and the cardiac aglycones with the carbon skeleton of the side chain of the latter intact, has therefore been accomplished.

The synthesis of 14-desoxythevetigenin was carried out in a similar fashion, proceeding from 3(β)-acetoxyetiocholanic acid. The latter has been described by Reichstein and Fuchs (12), who prepared it by catalytic reduction of methyl 3-keto-$\Delta^{4,5}$-etiocholenate. We have repeated this reduction, and according to our experience, methyl 3(β)-hydroxyalloetiocholanate is the predominating constituent of the fraction of the reduction product precipitated by digitonin.


CHOHCH3
HO
IX
CrO3
COCH3
O=
X
H2 + PtO2
COCH3
HO
XI
C6H5CHO
COCH=CHC6H5
HO
XII
(CH3CO)2O
COCH=CHC6H5
AcO
XIII
CrO3
COOH
AcO
XIV

However, too much significance cannot be attached to our failure to duplicate Reichstein and Fuchs' experience, in view of the pronounced effect on such reductions often caused by subjective variations in experimental conditions. In view of this difficulty we have prepared 3(β)-acetoxyetiocholanic acid by degradation of pregnanediol, using substantially the method of Marker and Wittle (13) for the degradation of pregnanediol to etiolithocholic acid.

Pregnanedione, prepared by oxidation of pregnanediol (14), was selectively reduced at carbon atom 3 to yield a mixture of isomeric pregnanolones (15). The pregnanol-3(β)-one-20 (XI) was isolated from this mixture by precipitation with digitonin and then condensed with benzaldehyde to yield XII (13). Oxidation of XII after protection of the hydroxyl group by acetylation, yielded 3(β)-acetoxyetiocholanic acid (XIV).

In the subsequent reactions (XIV–XXI) no unexpected difficulties were encountered. The diacetoxy ketone (XVIII) was prepared directly from the diazomethyl ketone (XVI) rather than by way of the intermediate halomethyl ketone (XVII) which was necessary in the above case. However, a discrepancy between the properties of 3(β),21-diacetoxypregnanone-20 prepared by us, and those of the same substance reported by Marker, Crooks, and Wagner (16) should be noted. These workers prepared their compound by a less direct and unambiguous method. Unfortunately we have been unable to secure a sample of the material described by these workers for direct comparison. However, apparently 3(β)-acetoxy-21-bromopregnanone-20 (XVII), as prepared by us from the diazomethyl ketone (XVI), agrees in properties with the same substance described by Marker *et al.* (16). It should be emphasized that the subsequent reactions carried out with our 3(β),21-diacetoxypregnanone-20 (XVIII) furnish convincing proof of the correctness of the structure assigned to it. The possibility of a rearrangement about carbon atom 17 is excluded by the results of the hydrogenation of 3,14-bisdesoxythevetigenin (VIII). If inversion had taken place, the reduction product should have been isomeric with the reduction product of the natural aglycones at carbon atom 17. Since the natural aglycones are known to possess the configuration of etiocholanic acid at this point (17), it follows that no inversion has occurred. The exact cause for this discrepancy remains to be worked out.

The Reformatzky reaction of XVIII with ethyl bromoacetate led to the usual mixture of the unsaturated lactone (XX) and the 20-hydroxy lactone (XIX). In this case separation of the two was easily accomplished by chromatographic adsorption of XIX on aluminum oxide. Under the conditions used, XX was not adsorbed. Finally, deacetylation of XX with dilute hydrochloric acid gave 14-desoxythevetigenin (XXI).

The pharmacological examination of these substances will be reported elsewhere.

We wish to express our appreciation to the Schering Corporation for the gift of the methyl 3(β)-$\Delta^{5,6}$-etiocholenate used in this work. Our thanks are likewise due to Parke, Davis and Company for the gift of the pregnanediol used.

EXPERIMENTAL

All melting points are corrected for stem exposure, except as noted.

Cholanic acid. Dehydrocholic acid was reduced in 40-g. runs by dissolving it in 450 cc. of glacial acetic acid and adding 300 g. of amalgamated zinc (20 mesh) and 450 cc. of concentrated hydrochloric acid. Dry hydrogen chloride gas was passed through the solution while refluxing for 30 hrs. The solution was then cooled and the cholanic acid solidified to a white crystalline mass on top of the liquid. The acid solution was decanted from the solid acid and the latter was thoroughly washed with water. The residual zinc was carefully washed with chloroform and the cholanic acid thus obtained was combined with the main crop and recrystallized three times from acetic acid. It melted at 163–164° (uncorr.). Wieland and Boersch (8) report the melting point 164° (uncorr.). From 300 g. of cholic acid, 113 g. of cholanic acid was obtained.

Etiocholanyl chloride (III). A mixture of 4 cc. of absolutely pure thionyl chloride and 500 mg. of etiocholanic acid was kept in the refrigerator at 0° with occasional shaking until all the acid had gone into solution. This required about 60 hrs., after which the solution was allowed to stand at room temperature for several hours. The thionyl chloride was then removed under reduced pressure with the aid of several concentrations with dry benzene. The acid chloride crystallized readily, was slightly yellow, and melted at 80–86°. It was used without further purification.

21-Diazopregnanone-20 (IV). Etiocholanyl chloride prepared from 500 mg. of etiocholanic acid was dissolved in 7 cc. of dry benzene and the solution was slowly added to a twice distilled solution of diazomethane, prepared from 5 g. of nitrosomethylurea, in 60 cc. of ether. The temperature during the addition was kept at −14° and the solution was kept in a freezing mixture for 2 hrs. longer, after which it was allowed to stand at room temperature for 12 hrs. The solution was filtered, and after removal of the solvent, the diazo ketone remained as a yellow crystalline solid which melted at 80–106°. It was used without further purification.

Attempted preparation of 21-acetoxypregnanone-20. One cubic centimeter of pure glacial acetic acid was added to the crystalline diazo ketone from 100 mg. of etiocholanic acid. The solution was then warmed on the steam-bath, during which it turned brown and evolved nitrogen. After heating for 30 min. a brown oil separated. Acetic acid was removed under reduced pressure and the non-crystalline residue was chromatographed over aluminum oxide. The acetoxy ketone could not be obtained crystalline.

In another experiment, 50 mg. of 21-chloropregnanone-20 (see below) was refluxed with 150 mg. of fused sodium acetate and 1 cc. of glacial acetic acid. Nothing crystalline could be obtained after chromatographing. In another experiment, 100 mg. of 21-chloropregnanone-20 was refluxed with 170 mg. of potassium acetate in 2 cc. of 90% alcohol for 4.5 hrs. The chloride ion in the reaction mixture was determined gravimetrically and 45 mg. of silver chloride was obtained. The calculated amount of silver chloride is 44 mg. Hence the reaction apparently took the desired course. However, the acetoxy ketone again could not be obtained crystalline.

21-Chloropregnanone-20 (V). A stream of dry hydrogen chloride was passed into an ice-cold solution of 21-diazopregnanone-20, from 100 mg. of etiocholanic acid, in 30 cc. of dry ether for 10 min. After evaporation of the ether, first on the steam-bath and then *in vacuo*, a yellow oil remained which crystallized on addition of a few drops of pentane. The chloro ketone was recrystallized from alcohol and formed colorless prisms which melted at 103–105°. The yield was 75 mg. $[\alpha]_D^{25}$ 125° ± 2° [c = 0.850 in chloroform].

Anal. Calc'd for $C_{21}H_{33}ClO$: C, 74.8; H, 9.9; Cl, 10.5.
Found: C, 75.0; H, 10.2; Cl, 10.7.

21-Benzoxypregnanone-20 (VI) A mixture of 68 mg. of pure 21-chloropregnanone-20, 62 mg. of sodium benzoate, 0.12 cc. of water and 1.2 cc. of absolute alcohol was refluxed for 5.5 hrs. Upon cooling, the benzoxy ketone crystallized as fine white needles. The mixture

was diluted and extracted with ether; the ether extract was washed with water and dried over sodium sulfate. On evaporation of the solvent the ketone remained as a colorless oil which quickly solidified. After two recrystallizations from absolute alcohol, it melted at 158–159°. The yield was 45 mg. $[\alpha]_D^{25}$ 113° ± 2° [c = 0.406 in chloroform].

Anal. Calc'd for $C_{28}H_{38}O_3$: C, 79.6; H, 9.1.
Found: C, 79.6; H, 9.1.

A small amount of unreacted chloro ketone was recovered from the mother liquors.

3,14-Bisdesoxythevetigenin (3,14-bisdesoxydigitoxigenin) (VIII). To a solution of 600 mg. of pure 21-benzoxypregnanone-20 and 1.8 g. of ethyl bromoacetate in 13 cc. of dry benzene, was added 900 mg. of 60 mesh granulated zinc. After distilling off some of the benzene in order to secure absolutely anhydrous conditions, the solution was refluxed for 30 min., after which an additional 0.2 cc. of ethyl bromoacetate and 200 mg. of zinc was added and refluxing was continued for 15 min. After the addition of 0.4 cc. of absolute alcohol the solution was boiled for another hour. The addition compound was broken up in the usual manner with dilute hydrochloric acid, and the lactone was extracted with ether. The residue, after evaporation of the ether, deposited crystals on standing several days in the refrigerator. The crystalline material was separated from adhering oil by careful washing with a mixture of pentane and ether. As thus obtained, the crystalline material represents a mixture of the two possible isomeric hydroxy lactones (VII) and the desired unsaturated lactone (VIII). After repeated recrystallization from alcohol, a small amount of the unsaturated lactone was obtained. Complete conversion of the original mixture into the butenolide was effected by dissolving 220 mg. of the crystalline material in a mixture of 2 cc. of glacial acetic acid and 4 cc. of glacial acetic acid saturated with dry hydrogen bromide, and refluxing for 1.5 hrs. with a bath temperature of 135–145°. The mixture was then poured into cold sodium bicarbonate solution and the lactone was extracted with ether. After evaporation of the ether, the unsaturated lactone was recrystallized from alcohol, using a small amount of decolorizing carbon. It crystallized as stout needles which melted at 167–168° and gave a strong positive nitroprusside (Legal) test. $[\alpha]_D^{25}$ 11° ± 1.5° [c = 0.316 in methanol].

Anal. Calc'd for $C_{28}H_{34}O_2$: C, 80.6; H, 10.0.
Found: C, 80.4; H, 10.1.

An additional amount of the lactone was obtained by treating the oil removed from the crystals by the ether-pentane washing with hydrogen bromide in acetic acid as before. After removing some colored amorphous material from the butenolide by solution in alcohol and chilling, the latter crystallized from the alcoholic solution on seeding.

Hydrogenation of 3,14-bisdesoxythevetigenin. An absolute alcoholic solution of 40 mg. of the above unsaturated lactone was hydrogenated in the presence of 20 mg. of platinum oxide. The product crystallized readily and was recrystallized repeatedly from absolute alcohol until the crystalline form no longer changed. There was thus obtained 12 mg. of long rectangular plates which melted at 187–189°. When mixed with hexahydrodianhydrothevetigenin [prepared from digitoxigenin (9)], which melted at 187–189°, the melting point was not depressed.

Anal. Calc'd for $C_{28}H_{36}O_2$: C, 80.3; H, 10.5.
Found: C, 80.4; H, 10.6.

The physical constants for this substance, which has been obtained from several natural aglycones, are shown in Table I, from which the identity of the lactone prepared from etiocholanic acid with those of plant origin, is obvious.

Pregnanol-3(β)-one-20 (XI). A solution of 2.6 g. of pregnanedione (X) in 40 cc. of 90% acetic acid was added to a suspension of 130 mg. of Adams platinum oxide catalyst, which had been previously reduced, in 40 cc. of 90% acetic acid. This mixture was then shaken in

an atmosphere of hydrogen until 185 cc. of wet hydrogen at 760 mm. and 24° had been absorbed. The solution of the hydrogenated product in 118 cc. of absolute alcohol was added to a solution of 5.2 g. of digitonin in 470 cc. of alcohol. After adding 200 cc. of water, the mixture was left at room temperature for 12 hrs. The crystalline digitonide was filtered, washed with ether, and decomposed by dissolving the dried material in 10 cc. of dry pyridine and precipitating the digitonin by addition of 120 cc. of dry ether. After removal of the pyridine by repeated washing with dilute hydrochloric acid, the ether solution was dried and the solvent was removed, leaving the crystalline pregnanolone, which was used for the next reaction without further purification. The yield was 30 to 35%.

An additional quantity of pregnanolone was obtained by isolating the other products of the reduction, reoxidizing them to pregnanedione and repeating the above procedure. For this purpose, the mother liquors from the digitonide precipitate were completely freed from alcohol *in vacuo*. The residue was then thoroughly extracted with ether, leaving digitonin undissolved. The material extracted by the ether was then reoxidized according to Butenandt (14).

21-Benzalpregnanol-3(β)-one-20 (*XII*) was prepared essentially according to Marker and Wittle (13), except that the method of working up the reaction mixture has been materially improved. After the reaction mixture had stood for 24 hrs., the crystalline benzal compound was filtered off and washed successively with small amounts of 95% alcohol, progressively more dilute alcohol, and finally with water to remove the alkali. In this manner

TABLE I

PHYSICAL CONSTANTS OF HEXAHYDRODIANHYDROTHEVETIGENIN

SOURCE	M.P., °C.	$[\alpha]_D$
Digitoxigenin	185 (9); 188–189 (10)	33.7° (9)
Sarmentogenin	189 (10)	35.4° (10)
Digoxigenin	185 (11)	34.5° (11)
Etiocholanic acid	187–189	33.0°

1.1 g. of pregnanolone yielded 900 mg. of the benzal compound, which melted at 169–174°. Another 350 mg. of less pure material was obtained by dilution of the mother liquors.

The *acetate* of the above compound was prepared by refluxing 1.92 g. of the substance with 18 cc. of acetic anhydride for 30 min. On cooling, the acetate crystallized readily as prismatic needles, which were collected and washed with a small amount of acetic anhydride. The yield of material melting at 172–174° was 1.72 g. An additional 150 mg. was obtained from the mother liquors.

3(β)-Acetoxyetiocholanic acid (*XIV*). To a solution of 1.2 g. of the above acetate in 150 cc. of glacial acetic acid, was added dropwise and with stirring, a solution of 2.25 g. of chromic acid in the minimum amount of water and 75 cc. of glacial acetic acid. The temperature was held at 50° until all the chromic acid had been added, after which it was raised to 60–70° and held at that point for 5 hrs. After destroying the excess chromic acid by addition of 5–10 cc. of alcohol, the solution was concentrated to a small volume *in vacuo*. The residual solution was diluted, acidified with dilute sulfuric acid, and extracted with ether. The ether extract was washed carefully with dilute potassium bicarbonate solution until no more acidic material could be detected in the aqueous washes. This treatment removes acetic, benzoic, and probably some phenylacetic acid. The remaining ether solution was washed with water, dried, and the solvent was removed. Crystallization of the residue from dilute methanol yielded 400 mg. of 3(β)-acetoxyetiocholanic acid as shining platelets which melted at 177–179°. Reichstein and Fuchs (12), who prepared the substance by catalytic reduction of methyl 3-keto-$\Delta^{4,5}$-etiocholenate, report the melting point 162–174°. An additional 50 mg. of slightly impure acid was obtained from the mother liquors.

3(β)-Acetoxy-21-diazopregnanone-20 (*XVI*) was prepared as described above. It was obtained as a yellow syrup (12).

3(β)-Acetoxy-21-chloropregnanone-20. To a solution of diazoketone, prepared from 80 mg. of 3(β)-acetoxyetiocholanic acid, in 10 cc. of dry ether, was added at 0° 10 cc. of a saturated solution of hydrogen chloride in dry ether. After standing 10 min. the ether was evaporated and the residual light brown oil was taken up in 10 cc. of a 1:1 mixture of benzene and isopentane. This solution was passed through a column of 2 g. of aluminum oxide (Brockmann), and the column was washed with 20 cc. of the same solvent. The colorless solution which passed through the column was concentrated, leaving the chloro ketone as a crystalline residue. After recrystallization from methanol it formed stout prisms which melted at 115–116°. The yield was 45 mg.

Anal. Calc'd for $C_{23}H_{35}ClO_3$: C, 69.9; H, 8.9; Cl, 9.0.
Found: C, 69.9; H, 8.8; Cl, 9.2.

3(β)-Acetoxy-21-bromopregnanone-20 (*XVII*) was prepared in a similar manner, except that a benzene solution of the diazoketone was used. The bromo ketone crystallized readily from methanol as stout prisms without chromatographing, and melted at 139–141°. Marker, Crooks, and Wagner (16), who prepared the substance by catalytic reduction of 3(β)-acetoxy-21-bromo-Δ^{16}-pregneneone-20, report it as crystallizing as fine needles from methanol and melting at 145–147°. No rotation was observed by these workers. For our substance: $[\alpha]_D^{29}$ 100° ± 5 [*c* = 0.100 in chloroform].

Anal. Calc'd for $C_{23}H_{35}BrO_3$: C, 62.9; H, 8.0.
Found: C, 62.9; H, 8.1.

Pregnanediol-3(β),21-one-20 diacetate (*XVIII*). The oily diazo ketone prepared from 500 mg. of 3(β)-acetoxyetiocholanic acid was heated on the steam-bath with 8 cc. of glacial acetic acid until evolution of nitrogen ceased. The solution was then concentrated to dryness under reduced pressure and the residue was dissolved in 5 cc. of methanol. After refrigerating overnight, the yellow solution was decanted from a small amount of amorphous material. The methanol was then completely removed *in vacuo* and the material was taken up in 40 cc. of benzene-isopentane (1:1). This solution was passed through a column of 10 g. of aluminum oxide (Brockmann), after which the column was washed with 40 cc. of the same solvent. After removal of the solvent from the combined effluent from the column, 300 mg. of an almost colorless oil, which was sufficiently pure for use in the next reaction, was obtained. A small part of the product was crystallized from methanol and formed prisms which obviously contained methanol of crystallization. The air-dried crystals softened at 50–60° and melted with evolution of vapors. After drying at 15 mm., first at room temperature and finally for 3 hrs. at 80°, the diacetate melted at 111–112°. The air-dried substance lost 3.64% of its original weight on vacuum drying. The calculated value for loss of 0.5 mole of methanol of crystallization is 3.68%. $[\alpha]_D^{27}$ 91° ± 4° [*c* = 0.138 in chloroform].

Anal. Calc'd for $C_{25}H_{38}O_5$: C, 71.7; H, 9.2.
Found: C, 71.7; H, 9.1.

The same substance is reported by Marker, Crooks, and Wagner (16) as melting at 145–146°. No value for optical rotation is given by these authors.

14-Desoxythevetigenin acetate (*XX*) *and the lactone of 3(β)-acetoxy-20,21-dihydroxynorcholanic acid* (*XIX*). The Reformatzky reaction was carried out essentially as described in the preceding case, using 350 mg. of pure pregnanediol-3(β),21-one-20 diacetate, 0.6 cc. of ethyl bromoacetate, and 500 mg. of 60 mesh zinc in 10 cc. of dry benzene. After 30 min., 0.1 cc. of ethyl bromoacetate and 200 mg. of zinc were added and like amounts of the reagents were added after 40 and 50 min. After 60 min., 0.3 cc. of absolute alcohol was added to decompose the very insoluble zinc complex, and the mixture was refluxed for another

hour. The reaction mixture was worked up in the usual way and the product was extracted with ether. The combined ether and benzene extracts, after washing and drying, were warmed to 50°, and 2.5 cc. of dry pyridine and 1.1 cc. of acetic anhydride were added. After standing overnight at room temperature, the dark brown mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in ether. The ether solution was washed successively with dilute hydrochloric acid and water and dried with sodium sulfate. The residue, after evaporation of the ether, was dissolved in 25 cc. of dry benzene and chromatographed over a column of 7 g. of aluminum oxide (Brockmann), using 50 cc. of dry benzene to wash the column. The effluent solution contained 14-desoxythevetigenin acetate (XX) and was concentrated to dryness under reduced pressure. The residual pale yellow oil crystallized rapidly on the addition of a few drops of alcohol. After several recrystallizations from alcohol, the acetate formed rectangular platelets which melted at 197–198° and gave a strong positive nitroprusside (Legal) color test. $[\alpha]_D^{28}$ 11.3° ± 1 [c = 0.708 in chloroform].

Anal. Calc'd for $C_{25}H_{36}O_4$: C, 75.0; H, 9.1.
Found: C, 75.0; H, 9.3.

The aluminum oxide column was eluted with 100 cc. of dry ether and the eluate was concentrated, leaving a residue which was the lactone of 3(β)-acetoxy-20,21-dihydroxynorcholanic acid (XIX). The substance was recrystallized from benzene, and formed fine needles which melted at 196–200°. The melting point was depressed to 170–185° when this substance was mixed with the unsaturated lactone described above.

Anal. Calc'd for $C_{25}H_{38}O_5$: C, 71.7; H, 9.2.
Found: C, 72.1; H, 9.3.

This hydroxy lactone was converted to 14-desoxythevetigenin acetate as follows (18): Thirty milligrams of the hydroxy lactone was refluxed with 3 cc. of acetic anhydride for 9 hrs. After removal of the acetic anhydride under reduced pressure, the residue was sublimed at 0.2 mm. pressure and a bath temperature of 200–220°. After several recrystallizations from alcohol, 15 mg. of pure 14-desoxythevetigenin acetate was obtained.

14-Desoxythevetigenin (XXI). A mixture of 35 mg. of 14-desoxythevetigenin acetate, 2 cc. of alcohol, 1.6 cc. of water, and 0.4 cc. of conc'd hydrochloric acid was refluxed for 2.5 hrs. Addition of water caused the formation of a crystalline precipitate which was extracted with chloroform. After washing and drying the chloroform extract, the solvent was removed under reduced pressure, leaving an oil which crystallized immediately upon the addition of a few drops of ethyl acetate. The lactone was recrystallized from a mixture of ethyl acetate and isopentane, or from dilute alcohol, and formed fine needles which melted at 220–222°. The substance gave a strong positive Legal test and an emerald green, as well as a blue ring, in the Keller-Kiliani test. $[\alpha]_D$ 11.5° ± 1.5 [c = 0.434 in chloroform].

Anal. Calc'd for $C_{23}H_{34}O_3$: C, 77.1; H, 9.6.
Found: C, 77.1; H, 9.5.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. 14-Desoxythevetigenin and 3,14-bisdesoxythevetigenin have been prepared from 3(β)-hydroxyetiocholanic acid and etiocholanic acid, respectively.

2. A more convenient preparation of 3(β)-hydroxyetiocholanic acid from pregnanediol has been described.

3. Hydrogenation of 3,14-bisdesoxythevetigenin yields a saturated lactone identical with that obtained from digitoxigenin, sarmentogenin, and digoxigenin.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. VIII. β-SUBSTITUTED-$\Delta^{\alpha,\beta}$-BUTENOLIDES OF THE NAPHTHALENE AND INDENE SERIES

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Two general syntheses for β-substituted-$\Delta^{\alpha,\beta}$-butenolides analogous to the cardiac aglycones have been described in previous communications (1, 2). These methods have been applied to the preparation of simple model lactones, as well as to the preparation of lactones containing a steroid ring system as substituent (3, 4). In the course of the pharmacological examination of the simpler lactones it was noted that β-(β-naphthyl)-$\Delta^{\alpha,\beta}$-butenolide exhibited a definite, although weak digitalis action toward frogs (5), while the corresponding α-naphthyl derivative was devoid of such activity. It becomes of interest, therefore, to explore the effect of structural changes on cardiac activity further. The present paper records the results of an investigation of the synthesis of such lactones the substituent of which is derived from naphthalene or indene derivatives. The results of the pharmacological testing of the substances prepared are also indicated, although a detailed account of the latter phase of the work will be left to a separate communication.

In the naphthalene series it was deemed of interest to investigate first the effect of the introduction of a hydroxyl group in the 6-position (the unsaturated lactone occupying the 2-position of the naphthalene ring system). Such a molecule would thus possess a hydroxyl group in the same relative position to the side-chain in the simple naphthalene system as does the hydroxyl group in the 3-position of the natural drugs. The effect of such a hydroxyl group in the β-naphthyl lactone could conceivably be important in view of the previously noted activity of the unsubstituted β-naphthyl lactone. Secondly, similar considerations indicated the desirability of investigating the completely reduced β-(2-decahydronaphthyl)-$\Delta^{\alpha,\beta}$-butenolide, particularly since in the natural drugs both of the rings in closest proximity to the unsaturated lactone side chain are completely saturated. Both of the desired lactones have been prepared.

In the natural drugs the unsaturated lactone can be regarded as being in the 1-position of a reduced indene ring system. Therefore, in view of the activity noted in the case of the β-naphthylbutenolide, an investigation of the simple bicyclic 1-indenyl butenolides appeared warranted. We, therefore, present our experiences in the syntheses, or attempted syntheses, of β-(1-indenyl)-$\Delta^{\alpha,\beta}$-butenolide, β-(1-indanyl)-$\Delta^{\alpha,\beta}$-butenolide, and β-(1-hydrindanyl)-$\Delta^{\alpha,\beta}$-butenolide together with a brief report on the pharmacological action of the latter. For the numbering system used see formula VII.

The synthesis of β-(6-hydroxy-2-naphthyl)-$\Delta^{\alpha,\beta}$-butenolide was explored both by the method of Rubin, Paist, and Elderfield (1) and by the method of

MgBr
CH3O
I
CH3OCH2CN
O
CCH2OCH3
CH3O
II
BrCH2CO2C2H5
Zn
OH
CCH2CO2C2H5
CH2OCH3
CH3O
III
HBr—AcOH
CH
C
CH2
C=O
O
CH3O
IV
CH2N2
CH
C
CH2
C=O
O
HO
VI
O
CCH2OCOCH3
CH3COO
V
BrCH2CO2C2H5
Zn

Linville and Elderfield (2). The latter is much to be preferred. The reactions involved are shown in formulas I–VI. The yield from the reaction between methoxyacetonitrile and I left considerable to be desired and it was not possible to cleave the ether group in III to the hydroxy lactone without extensive decomposition of the substance.

The 6-hydroxy-2-naphthoic acid used for making compound V was prepared from the easily accessible 6-methoxy-2-bromonaphthalene, a procedure which, although involving a rather large number of steps, nevertheless appears preferable to those heretofore described (6, 7). Carbonation of the Grignard reagent (I) gave a 50% yield of 6-methoxy-β-naphthoic acid (8) which was easily converted to 6-hydroxy-β-naphthoic acid by cleavage of the ether with hydrobromic acid. After acetylation of the latter, the 6-acetoxy-2-naphthyl acetoxymethyl ketone (V) was prepared *via* the acid chloride and diazo ketone according to Langenbeck and Baehren (9).

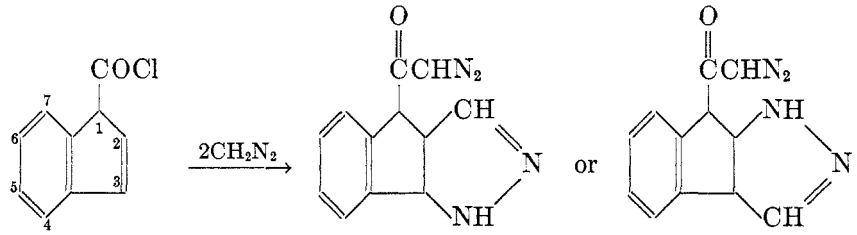
In accordance with previous experience (2), decomposition of the reaction mixture resulting from the Reformatzky reaction between V and ethyl bromoacetate resulted in cleavage of all acetyl groups present and gave the desired β-(6-hydroxy-2-naphthyl)-$\Delta^{\alpha,\beta}$-butenolide (VI). This was converted to the 6-methoxynaphthyl lactone by the use of diazomethane, which corroborated the structures of the substances obtained by both methods.

β-(2-Decahydronaphthyl)-$\Delta^{\alpha,\beta}$-butenolide was prepared from decahydro-β-naphthoic acid by conversion to the acid chloride, diazomethyl ketone, acetoxymethyl ketone, and reaction of the latter with ethyl bromoacetate and zinc. β-Naphthoic acid was reduced catalytically according to Ranedo and León (10) to the decahydro acid with difficulty using platinum oxide, but was more easily obtained by hydrogenating the ethyl ester in the presence of Raney nickel at higher temperature and pressure. The ester was subsequently saponified. No attempt was made to separate the isomers formed on reduction, pending the outcome of pharmacological tests. It was felt that, should such tests be positive, a determination of the effect of stereoisomerism could await further work.

In the indene series, the only unsaturated lactone which we have succeeded in preparing is the β-(1-hydrindanyl)-$\Delta^{\alpha,\beta}$-butenolide which was readily prepared from hydrindan-1-carboxylic acid exactly as in the case of the decahydronaphthyl lactone. In this instance the complete hydrogenation of indene-1-carboxylic acid was more easily accomplished with platinum oxide than in the case of β-naphthoic acid. The crude Reformatzky product after treatment with hydrogen bromide yielded a constant-melting lactone, which was apparently one of the stereoisomeric forms.

We have proceeded both from 1-indenylmagnesium bromide and from indene-1-carboxylic acid in the attempted preparation of β-(1-indenyl)-$\Delta^{\alpha,\beta}$-butenolide. In the former case, the reaction between the Grignard reagent and methoxyacetonitrile apparently did not take the desired course and the only product isolated was an unstable substance of obscure nature which was not further investigated. In the latter case the product from the reaction of indene-1-carboxylic acid chloride and diazomethane gave analytical figures corresponding

to a diazomethyl ketone of an indanodihydropyrazole to which either the structure VIII or IX may be assigned on the basis of the observations of earlier workers (11).



VII VIII IX

Catalytic reduction of indene-1-carboxylic acid in the presence of palladium black gave indan-1-carboxylic acid which served as a starting point for the attempted synthesis of the indanyl lactone. The acid chloride was easily prepared and its identity was demonstrated by conversion to indan-1-acid amide. Likewise the preparation of 1-indanyl-diazomethyl ketone appeared to proceed smoothly from the interaction of the acid chloride and diazomethane, as did the subsequent preparation of the acetoxymethyl ketone. However, difficulties were encountered when the Reformatzy reaction between the acetoxymethyl ketone and ethyl bromoacetate was carried out. The strong positive nitroprusside (Legal) test exhibited by the product of the reaction showed that the desired lactone had been formed, at least to a certain extent, but all attempts at purification resulted in the formation of obscure alteration products. It is not unlikely that the double bond of the lactone is easily pulled from its original position by the neighboring benzene ring, which would account for the complex mixture formed.

None of the butenolides synthesized were active when tested in frogs through the kind cooperation of Dr. K. K. Chen of the Lilly Research Laboratories.

We wish to acknowledge the kindness of the Barrett Company for the generous gift of the indene used in this work.

EXPERIMENTAL

All melting and boiling points are corrected for stem exposure.

Indene-1-carboxylic acid was prepared in 20% yield from the sodium derivative of indene and carbon dioxide according to Weissgerger (12) or in 56% yield from indenylmagnesium bromide and carbon dioxide according to Courtot (13). We have found that the acid may be more conveniently prepared from indenylsodium, which in turn can easily be obtained by treating a solution of 150 cc. of crude 70% indene (Barrett) in 300 cc. of dry dioxane with 4 cc. of dry pyridine and 18 g. of sodium. After refluxing the mixture in an atmosphere of nitrogen for 7–8 hrs., solution is substantially complete and carbonation is easily carried out. The relatively poor yield of acid, 20% based on the sodium used, is more than offset by the use of crude indene and by avoiding the necessity of handling the solid indenylsodium.

The acid prepared by either of these methods melted at 159.5–161°. It may be crystallized from benzene or aqueous alcohol, and an almost white product may be obtained by

sublimation at 140–150° and 0.2 mm. pressure. Courtot (13) reports the compound as melting at 161°, Weissgerger (12) at 156–157°, and Jacobi (14) at 160°.

Indene-1-carboxylic acid chloride. A mixture of 10 g. of acid, 20 cc. of pure thionyl chloride, and 20 cc. of benzene was allowed to stand at room temperature for two days or until all the crystals of acid were dissolved. It was found that warming caused the formation of tarry by-products. The excess thionyl chloride was removed in a vacuum with the aid of dry benzene. Dark crystals separated which melted at 74–76°. Inasmuch as purification was difficult, the identity of the acid chloride was established by conversion to *indene-1-carboxylic acid amide* in the usual manner. After recrystallization from alcohol the latter melted at 182–184°. Wislicenus and Hentrich (15) report the amide as melting at 180°.

Reaction of diazomethane with indene-1-carboxylic acid chloride. An ethereal solution of 5.24 g. (0.031 mole) of acid chloride was added dropwise at −5° to an ethereal solution of diazomethane made from 20.6 g. of nitrosomethylurea. Needles separated in about 30 minutes. After two crystallizations from alcohol the substance melted at 111–113° with decomposition. The analysis corresponded to the addition of two moles of diazomethane to the acid chloride with the formation of a pyrazoline derivative (VIII) or (IX).

Anal. Calc'd for $C_{12}H_{10}N_4O$: C, 63.7; H, 4.5; N, 24.8.
Found: C, 63.7; H, 4.6; N, 25.0.

Addition of methoxyacetonitrile to indenylmagnesium bromide. To a suspension of 10 g. of indenylmagnesium bromide, crystallized from toluene and ether, in ether was added 3.24 g. of methoxyacetonitrile with no apparent reaction, even after standing overnight. One hundred cubic centimeters of toluene was added, and the mixture was refluxed for four hours. After working up with dilute sulfuric acid there remained 1.5 cc. of dark oil. This distilled at 93° at 0.6 mm. pressure, giving a few drops of viscous yellow liquid which crystallized in white clusters from petroleum ether (b.p 60–71°, Skellysolve B) and melted at 49–50°.

Anal. Found: C, 81.4; H, 6.4.

The compound darkened and decomposed on standing and was not further investigated. The bulk of the reaction product remained as a tar in the distillation flask.

When indenyl sodium was brought into reaction with methoxyacetonitrile only indene itself was obtained.

Indan-1-carboxylic acid. A glacial acetic acid suspension of 4.1 g. of indene-1-carboxylic acid and 0.2 g. of palladium black was shaken with hydrogen. The theoretical amount of hydrogen was readily taken up, and all the crystals went into solution. The reduced acid was crystallized from petroleum ether (Skellysolve B) and melted at 57–58°. Tiffeneau and Orekhoff (16) report 59–60°.

Indan-1-carboxylic acid chloride was made from 2 g. of acid, 4 cc. of thionyl chloride, and 4 cc. of benzene. The mixture was allowed to stand two days, the excess reagent then being removed and the resulting oil used without purification.

Indan-1-carboxylic acid amide was prepared by adding a few drops of acid chloride to concentrated ammonia in the usual way. It was crystallized from alcohol and melted at 162–163°.

Anal. Calc'd for $C_{10}H_{11}NO$: C, 74.6; H, 6.9.
Found: C, 74.5; H, 6.9.

1-Indanyl diazomethyl ketone was prepared by adding an ethereal solution of acid chloride (0.009 mole) to a solution of 0.03 mole of diazomethane in 40 cc. of ether at 0°. After standing overnight, the solvent was removed and the residual oil was used without further purification.

1-Indanyl acetoxymethyl ketone. A solution of 0.06 mole of the diazomethyl ketone in 50 cc. of glacial acetic acid was warmed on the steam-bath for one hour, when the evolution of nitrogen ceased. The acetoxymethyl ketone was a dark oil which was distilled, b.p. 135° at 0.5 mm. pressure. The yield was 53% based on acid used; n_D^{25} 1.5287.

Anal. Calc'd for $C_{13}H_{14}O_3$: C, 71.5; H, 6.5.
Found: C, 71.3; H, 6.5.

Reaction of 1-indanyl acetoxymethyl ketone with ethyl bromoacetate. Twelve and eight-tenths grams of ethyl bromoacetate was added to a mixture of 13.9 g. of 1-indanyl acetoxymethyl ketone and 6.25 g. of zinc in 150 cc. of dry benzene. After refluxing for two hours and working up in the usual way, there was obtained 12 cc. of red oil which could not be induced to crystallize. The oil was distilled at 0.3 mm. from 110–180° in very poor yield. It gave a strong Legal test, thus indicating the presence of the desired lactone, but no pure product could be obtained from it. Treatment with hydrogen bromide in acetic acid resulted only in the formation of tarry products.

Hydrindan-1-carboxylic acid was prepared from indan-1-carboxylic acid by catalytic reduction with platinum oxide in acetic acid. The theoretical amount of hydrogen was taken up in about 40 hours, and the product solidified on removal of the solvent. After repeated crystallization from petroleum ether (Skellysolve B) one of the stereoisomers was apparently obtained; it melted constantly at 94–96°. The melting point range for the crude mixture was 80–91°.

This reduction was also carried out in one step from indene-1-carboxylic acid. From 20 g. of indene acid, 5.8 g. of twice recrystallized octahydro acid melting at 91–95° was obtained.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.5; H, 9.6.
Found: C, 71.8; H, 9.5.

Hydrindan-1-carboxylic acid chloride was prepared as in the preceding cases from the acid, which melted at 91–95° and was used without further purification. Its identity was shown by conversion to the *amide* which melted at 204.5–207° after crystallization from alcohol.

Anal. Calc'd for $C_{10}H_{17}NO$: C, 71.8; H, 10.0.
Found: C, 71.8; H, 10.2.

1-Hydrindanyl diazomethyl ketone was prepared in the usual manner. The substance formed a semi-solid crystalline mass and was used without further purification.

1-Hydrindanyl acetoxymethyl ketone was prepared exactly as in the case of 1-indanyl acetoxymethyl ketone. On removal of the excess acetic acid there remained a brown solid, which was most easily purified by sublimation at 0.3 to 0.4 mm. pressure and 100–130° bath temperature. The sublimate then crystallized from petroleum ether (Skellysolve B) in fine white needles melting at 59–61°. The yield from acid to acetoxy ketone was 73%.

Anal. Calc'd for $C_{13}H_{20}O_3$: C, 69.7; H, 9.0.
Found: C, 69.6; H, 9.1.

β-(1-Hydrindanyl)-$\Delta^{\alpha,\beta}$-butenolide. Three and seventh-tenths grams of ethyl bromoacetate was added to a mixture of 4.3 g. of the above acetoxymethyl ketone, 20 cc. of dry benzene, and 1.75 g. of zinc. The mixture was refluxed for two hours, and then worked up with dilute hydrochloric acid in the usual way. The crude product was next refluxed with 10 cc. of acetic acid and 10 cc. of acetic acid saturated with hydrogen bromide at 0° for 30 minutes. The oil from this reaction crystallized, and the lactone could be best purified first by sublimation at 0.3 to 0.4 mm. pressure and 100–130°, and then by crystallization from petroleum ether (Skellysolve B). It melted at 94–95° and gave a strong Legal test. The yield was 0.38 g.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 75.7; H, 8.8.
Found: C, 75.8; H, 8.7.

6-Methoxy-2-bromonaphthalene. 2-Bromo-6-hydroxynaphthalene was prepared from β-naphthol (17) and then methylated with dimethyl sulfate in the usual way. The yield from β-naphthol was 68%. The product melted at 106–107°. Franzen and Stauble (18) report 108°.

6-Methoxy-2-naphthyl methoxymethyl ketone (II). The Grignard reagent of 6-methoxy-2-bromonaphthalene was prepared according to Fries and Schimmelschmidt (8), using ethyl bromide to promote the reaction. The ether-benzene solution of the Grignard reagent was cooled in an ice-bath, and one equivalent of freshly distilled methoxyacetonitrile in benzene was added. A solid separated, and the mixture was left for 12 hours and then re-

fluxed for one hour. The addition product was decomposed in the usual way with ice and conc'd hydrochloric acid. On removal of the solvent the resulting oil solidified; it was sublimed at 2.4 mm. at 70–100°, yielding a fluffy white solid which melted at 63–69°. After five crystallizations from alcohol the substance melted at 97–98.5°.

Anal. Calc'd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1.
Found: C, 73.3; H, 6.1.

The yield from 50 g. of 2-bromo-6-methoxynaphthalene was 11 g. of crude solid, which gave 3.4 g. of pure 6-methoxy-2-naphthyl methoxymethyl ketone and 1.2 g. of 2-methoxynaphthalene. Also an impure compound melting at 145–146° was obtained in small amount. Its high carbon content indicates it may have been a coupling product of the Grignard reagent.

Anal. Found: C, 86.2; H, 6.0.

The substance was not further investigated.

Ethyl β-methoxymethyl-β-(6-methoxy-2-naphthyl) hydracrylate (III). This substance was prepared by the general Reformatzky procedure used in preceding cases. The crude product was distilled at 0.3 mm., and the fraction boiling at 180–185° was collected and crystallized on standing. After crystallization from petroleum ether or alcohol the substance melted at 53.5–54.5°. The yield was 38%.

Anal. Calc'd for $C_{18}H_{22}O_5$: C, 67.9; H, 7.0.
Found: C, 68.2; H, 7.1.

Reaction of ethyl β-methoxymethyl-β-(6-methoxy-2-naphthyl) hydracrylate with hydrogen bromide. Two and three-tenths grams of the above substance which was distilled at 180° at 0.3 mm. was heated with a mixture of 10 cc. of glacial acetic acid and 10 cc. of glacial acetic acid saturated with hydrogen bromide, at 130–140° for 20 minutes. The mixture turned very black, and gave a brown solid on pouring into water. If the dark solid was repeatedly extracted with ether, a portion giving a violet Legal test was extracted leaving most of the color behind. On removal of the ether an oil remained, which, when taken up in acetone and allowed to evaporate slowly, yielded large crystals. These were washed free of adhering oil with cold acetone and then readily recrystallized from alcohol. The substance formed light yellow needles melting at 152–153° and gave a violet Legal test. The yield was about 40 mg. of β-(6-methoxy-2-naphthyl)-$\Delta^{\alpha,\beta}$-butenolide (IV).

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0.
Found: C, 75.0; H, 5.3.

In another experiment 0.6 g. of the hydracrylic ester, distilled at 180° at 0.3 mm. was heated with 20 cc. of 48% aqueous hydrobromic acid and 20 cc. of glacial acetic acid on a steam-bath for one hour. When the mixture was poured into water, a pinkish solid came out, which, on treatment with acetone as in the previous case, gave about 20 mg. of crystals the melting point of which showed no depression with β-(6-methoxy-2-naphthyl)-$\Delta^{\alpha,\beta}$-butenolide, prepared as above. No other pure compound was obtained.

6-Methoxy-2-naphthoic acid. Since it was possible to get only the methoxy lactone by the above method, it was decided to try the longer synthesis from 6-acetoxy-2-naphthoic acid. This compound was made from the already available 2-bromo-6-methoxynaphthalene by carbonating the Grignard reagent according to Fries and Schimmelschmidt (8).

6-Hydroxy-2-naphthoic acid. A suspension of 8.4 g. of 6-methoxy-2-naphthoic acid in 33 cc. of acetic acid, 33 cc. of 48% aqueous hydrobromic acid, and 20 cc. of acetic acid saturated with hydrogen bromide, was refluxed for 2.5 hrs. On cooling, the phenol crystallized in 77% yield, and melted at 245–248° after one crystallization from boiling water. Butler and Royle (6) report 240–241° and Cason (7) reports 243–244°.

6-Acetoxy-2-naphthoic acid was prepared by acetylating the above phenol with acetic anhydride according to Butler and Royle (6). It melted at 222–224°. The above authors report 221–223° and Langenbeck and Baehren (9) report 217° (uncorr.). Cason (7) reports 223–224°.

The over-all yield from 40 g. of 2-bromo-6-methoxynaphthalene was 38%.

6-Acetoxy-2-naphthoic acid chloride was prepared by refluxing 6 g. of acid with 16 cc. of benzene and 16 cc. of thionyl chloride for 2 hrs. on a steam-bath, all of the solid going into

solution at the end. On removal of the excess reagent crystals formed which melted at 120–121°. Langenbeck and Baehren (9) report the melting point 124° for their acid chloride, made with phosphorus pentachloride.

6-Acetoxy-2-naphthyl diazomethyl ketone was made according to Langenbeck and Baehren's (9) procedure except that the acid chloride was added in benzene solution instead of ether, which required excessively large volumes. The yellow crystals melted at 118.5–120°. The above authors report 123°.

6-Acetoxy-2-naphthyl acetoxymethyl ketone (*V*) was prepared by treating acetic acid with the diazo ketone exactly according to Langenbeck and Baehren (9). The product melted at 115–117°, the above authors reporting 112°. The yield from acetoxy acid to 6-acetoxy-2-naphthyl acetoxymethyl ketone was 54%.

Reaction of 6-acetoxy-2-naphthyl acetoxymethyl ketone with ethyl bromoacetate. The Reformatzky reaction was carried out as in the preceding cases using 6.0 g. of acetoxymethyl ketone, 4.5 g. of ethyl bromoacetate, 3 g. of zinc, and 75 cc. of benzene. After refluxing the reaction mixture in benzene for 1.5 hrs., 4 cc. of absolute alcohol was added and the mixture was refluxed for 1 hr. longer. The benzene was removed and the residue was dissolved and suspended in 100 cc. of absolute alcohol and the solution was decanted from the zinc. The portions soluble and insoluble in absolute alcohol were worked up separately. The former gave a solid insoluble in ether, which after two crystallizations from alcohol gave 0.59 g. of β-(6-hydroxy-2-naphthyl)-$\Delta^{\alpha,\beta}$-butenolide (VI), which melted at 236–238° with decomposition.

Anal. Calc'd for $C_{14}H_{10}O_3$: C, 74.3; H, 4.5.
Found: C, 74.2; H, 4.7.

When 20 mg. of the 6-hydroxy lactone was treated in ether suspension with diazomethane, a compound was formed which melted at 152–153° and showed no depression when mixed with the 6-methoxy lactone (IV) previously described.

The insoluble portions gave only products of obscure nature, which were not further investigated.

Decahydro-β-naphthoic acid was prepared by catalytic reduction of β-naphthoic acid with Adams' catalyst in acetic acid, 0.04 g. of catalyst being used for 1.8 g. of β-naphthoic acid. The theoretical amount of hydrogen was very slowly taken up and the mixture of isomeric decahydro acids melted at 70–79°. Ipatieff (19) prepared the mixture of isomers by vapor-phase reduction of β-naphthoic acid over a nickel oxide catalyst. He gives the melting point 79–81° for the mixture of isomers. Borsche and Lange (20) report the melting point 80–82° for this mixture. Ranedo and León report 76–79° (10).

For the preparation of larger amounts it was found more convenient to reduce ethyl β-naphthoate in a bomb with Raney nickel catalyst. A solution of 91 g. of ester in 350 cc. of glass-distilled absolute alcohol and catalyst made from 10 g. of Raney nickel alloy were shaken in a bomb at 1780 lbs. pressure and 190°. After a day and a half of shaking no more hydrogen was taken up. The resulting decahydro ester was saponified and worked up, giving 53 g. of acid boiling at 120–136° at 10^{-3} mm. The yield from ester to the decahydro acid was 64.5%; n_D^{25} 1.5001. After long standing this acid partially crystallized, and the solid when rubbed on a clay plate melted at 65–78°.

Anal. Calc'd for $C_{11}H_{18}O_2$: C, 72.5; H, 10.0.
Found: C, 72.5; H, 9.9.

Decahydro-β-naphthoic acid chloride was prepared by warming the acid with a 4 molar excess of thionyl chloride for 2 hrs. on the steam-bath. The excess reagent was removed as usual and the chloride was used without further purification.

Decahydro-β-naphthyl diazomethyl ketone was prepared as in the previous cases by adding a benzene solution of the acid chloride to ethereal diazomethane.

Decahydro-β-naphthyl acetoxymethyl ketone was made as usual by warming the diazo ketone with acetic acid. It distilled at 108–130° at 0.2 mm. The yield was 81.5% from the decahydro acid to the acetoxymethyl ketone; n_D^{25} 1.4886.

Anal. Calc'd for $C_{14}H_{22}O_3$: C, 70.6; H, 9.3.
Found: C, 70.4; H, 9.1.

β-(Decahydro-β-naphthyl)-$\Delta^{\alpha,\beta}$-butenolide was prepared by the usual Reformatzky procedure from the acetoxy ketone. The zinc complex was soluble in benzene, and the use of alcohol was not necessary for working up. The crude product was refluxed for 2 hrs. with 3 parts of a solution of acetic acid saturated with hydrogen bromide and 2 parts of acetic acid. After working up, the oil was distilled, giving 32.6 g. of lactone, contaminated with halide, from 59.5 g. of ketone. It was possible to remove the halide by heating the crude product with 4 times its volume of quinoline for 4 hrs. at 220°. The base was removed by extraction with sulfuric acid and the lactone distilled as a light yellow oil at 100–118° at 10^{-4} mm. In order to get an analytically pure product it was necessary to redistill several times more with considerable loss; n_D^{25} 1.5210. The product was a mixture of stereoisomers. The yield from acetoxymethyl ketone to pure lactone was 31.5%.

Anal. Calc'd for $C_{14}H_{20}O_2$: C, 76.3; H, 9.2.
Found: C, 76.3; H, 9.2.

The microanalyses here given were carried out by Mr. Saul Gottlieb of these laboratories.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. IX. β-SUBSTITUTED-$\Delta^{\alpha,\beta}$-BUTENOLIDES OF THE NORCHOLANE SERIES

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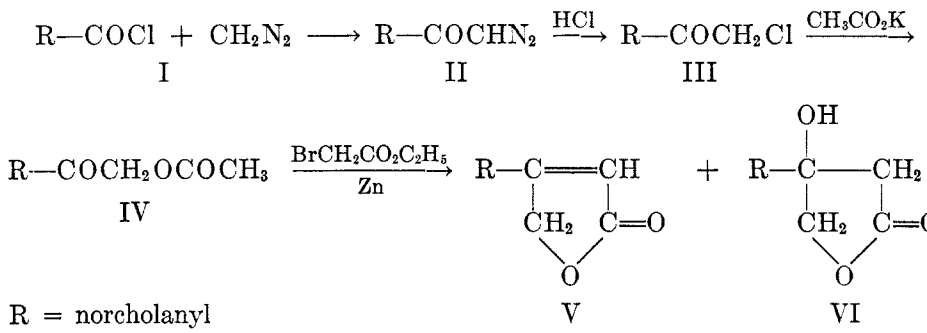
The synthesis of β-substituted-$\Delta^{\alpha,\beta}$-butenolides containing etiocholane or derivatives thereof as substituents has been described (1, 2). Pharmacological examination of at least one of these unsaturated lactones (the lactone of 21-hydroxy-$\Delta^{20,22}$-norcholenic acid) has shown that a pronounced cardiac activity in frogs can be obtained without the presence of the hydroxyl groups present in the natural cardiac aglycones (3). The question of the necessity for the presence of the etiocholane residue, therefore, arises. The preparation of such butenolides with a norcholanyl group or a derivative thereof as substituent is attractive principally because of the ready accessibility of the requisite starting materials, in contrast to the more difficultly obtainable etiocholane derivatives. We have, therefore, prepared β-norcholanyl-$\Delta^{\alpha,\beta}$-butenolide which has been subjected to pharmacological tests. At the same time the preparation of β-(3,7,12-trihydroxynorcholanyl)-$\Delta^{\alpha,\beta}$-butenolide has been explored with the object of ascertaining the effect of the three hydroxyl groups on activity. Although the latter lactone was not obtained in crystalline form, we should like to take this opportunity for presenting our experiences leading up to it.

The preparation of β-norcholanyl-$\Delta^{\alpha,\beta}$-butenolide proceeded smoothly according to the general method described in previous communications (1). The reactions involved are represented by formulas I–VI.



It was found preferable to prepare the acetoxymethyl ketone, IV, by way of the nicely crystalline chloromethyl ketone, III, rather than by the direct action of acetic acid on the diazomethyl ketone, II. In the dehydration of the hydroxy lactone, VI, to the unsaturated lactone, V, acetic anhydride has been found to offer advantages over the methods previously employed which involved the use of such vigorous reagents as hydrochloric or hydrobromic acid. The mode of action of acetic anhydride on such hydroxy lactones has been de-

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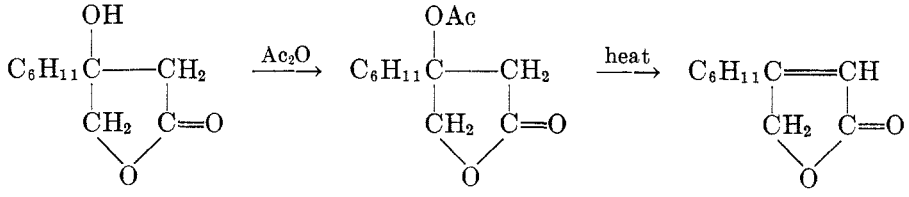
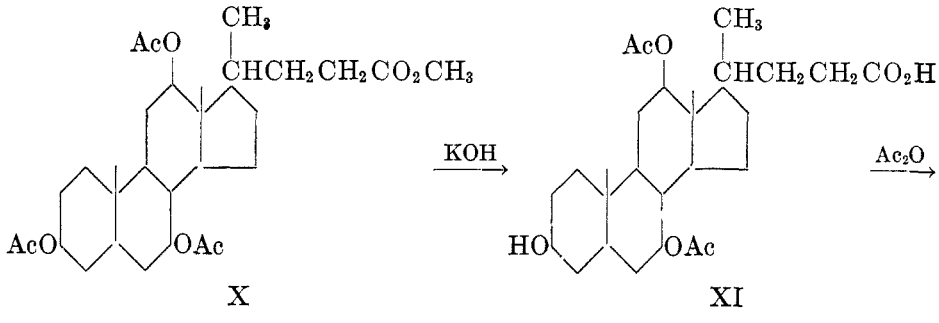
termined from a study of the model cyclohexylhydroxy lactone (VII). When this is refluxed with acetic anhydride the acetoxy lactone, VIII, is formed. The latter on heating was smoothly converted into β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide, IX.

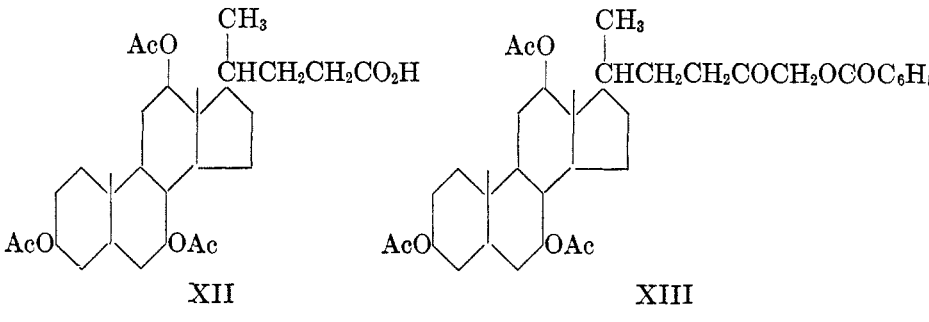


VII VIII IX

The preparation of β-(3,7,12-trihydroxynorcholanyl)-$\Delta^{\alpha,\beta}$-butenolide involves primarily the use of satisfactory protecting groups for the hydroxyl groups of cholic acid. For this purpose acetyl groups are eminently satisfactory from the standpoint of ease of removal at the end of the synthesis. However, the two reported syntheses of triacetylcholic acid in the literature (4, 5) by direct acetylation were later shown by Wieland and Kapitel (6) to be in error. These attempts had yielded only 3,7-diacetylcholic acid. We have found that, by careful saponification of methyl triacetylcholate (X) as suggested by the above authors, the nicely crystalline 7,12-diacetylcholic acid (XI) was easily obtained. This in turn was then reacetylated to the desired triacetyl compound (XII). Although XII was not obtained in crystalline form it yielded the crystalline methyl ester (X) on treatment with diazomethane, and when converted *via* the acid chloride, diazo ketone, and chloro ketone to triacetylnorcholyl benzoxymethyl ketone (XIII), a crystalline product was obtained.



X XI



XII XIII

Attempted direct acetylation of cholic acid with ketene in the presence of a trace of sulfuric acid yielded obscure alteration products.

Formyl groups are also satisfactory for the protection of the hydroxyl groups of cholic acid during the formation of the acid chloride. When the acid chloride of triformylcholic acid is treated with diazomethane, the expected reaction with the acid chloride group occurs, and a non-crystalline diazomethyl ketone is formed. Whether the formyl groups are methylated simultaneously was not determined. However, after alkaline saponification of the diazomethyl ketone and subsequent treatment with hydrogen chloride, norcholyl chloromethyl ketone is formed.

When the benzoxy ketone, XIII, was subjected to the usual Reformatzky reaction with ethyl bromoacetate, the desired lactone was obviously formed as shown by the strong nitroprusside (Legal) color test given by the reaction product. However, despite the use of a variety of schemes, it was not possible to isolate the hydroxy lactone in crystalline form.

β-Norcholanyl-$\Delta^{\alpha,\beta}$-butenolide showed no activity in frogs when tested at the Lilly Research Laboratories through the kind cooperation of Dr. K. K. Chen.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Cholanic acid chloride was prepared from 3.5 g. of cholanic acid and 10 cc. of thionyl chloride. The mixture was allowed to stand 2 hrs. at 0°, and 2 hrs. at room temperature The excess reagent was removed as usual with benzene, leaving dark crystals which were not purified. This acid chloride has also been prepared by Borsche (8).

Norcholanyl diazomethyl ketone (II) was prepared by adding dropwise a benzene solution of the acid chloride to a 3 molar excess of ethereal diazomethane at −5°. After standing for 12 hrs. the solvent was removed, leaving an amorphous residue.

Norcholanyl chloromethyl ketone (III) was prepared by passing dry hydrogen chloride into an ethereal solution of the diazomethyl ketone, cooled at 0°, until nitrogen was no longer evolved. On removal of the solvent a yellow solid separated, which was recrystallized first from petroleum ether (b.p. 60–71°, Skellysolve B) and then from alcohol. The chloromethyl ketone remained quite yellow even on liberal treatment with Norit. The yield from cholanic acid was 61% and the melting point was 109–110°. $[\alpha]_D^{27}$ 24° [c = 1.019 in chloroform].

Anal. Calc'd for $C_{25}H_{41}ClO$: C, 76.4; H, 10.5.
Found: C, 76.6; H, 10.5.

Norcholanyl acetoxymethyl ketone (IV). A solution of 2.2 g. of the chloromethyl ketone and 3 g. of dry potassium acetate in 30 cc. of acetic acid was refluxed for 8 hrs. On removal of the solvent in a vacuum and subsequent addition of water, crystals separated, which were recrystallized from a small amount of alcohol. The yield of acetoxy ketone was 81% from the chloro ketone, and the melting point after very thorough drying was 81.5–82.5°. $[\alpha]_D^{27}$ 22° [c = 2.074 in chloroform].

Anal. Calc'd for $C_{27}H_{44}O_3$: C, 77.7; H, 10.6.
Found: C, 77.8; H, 10.7.

β-(Norcholanyl)-$\Delta^{\alpha,\beta}$-butenolide (V). The usual Reformatzky procedure was followed, using 1.6 g. of acetoxymethyl ketone, 16 cc. of dry benzene, 2.4 g. of zinc, and 3.2 g. of ethyl bromoacetate. The mixture was refluxed 40 minutes and then 1 cc. of absolute alcohol was added and refluxing was continued for 1 hour longer. At this point 20 cc. more of absolute

alcohol was introduced, and the zinc was filtered off. The product was worked up as usual, except in this case it was not possible to remove the acidic by-products, always present in the Reformatzky reaction, since the ether solution formed bad emulsions with bicarbonate. The color was completely removed by passing the benzene solution of the reaction product through a column of 10 g. of aluminum oxide and eluting thoroughly with acetone. The residue from the combined eluates yielded 460 mg. of crude lactone and hydroxy lactone crystals. This was treated with a mixture of 5 cc. of acetic acid and 5 cc. of acetic acid saturated with hydrogen bromide, for 1.5 hrs. at 135–140°. The yield of lactone after recrystallization from alcohol was 155 mg. It melted at 162–163°. $[\alpha]_D^{25}$ 21° [c = 0.760 in chloroform].

Anal. Calc'd for $C_{27}H_{42}O_2$: C, 81.3; H, 10.6.
Found: C, 81.0; H, 10.6.

β-Cyclohexyl-β-acetoxybutyrolactone (*VIII*) was prepared by refluxing a mixture of 200 mg. of β-cyclohexyl-β-hydroxybutyrolactone and 5 cc. of acetic anhydride for 8 hrs. The product was worked up to give a solid, which crystallized from petroleum ether (Skellysolve B) and melted at 93–95°. When mixed with β-cyclohexyl-β-hydroxybutyrolactone it melted at 74–90°. The acetoxy lactone gave as strong a Legal test as the unsaturated lactone.

Anal. Calc'd for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0.
Found: C, 63.9; H, 8.2.

This compound sublimed easily at 170° and 50 mm. However, when heated at atmospheric pressure at 200°, acetic acid was lost and an oil was obtained which was identical with the previously described β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (9).

Reaction of acetic anhydride with the crude Reformatzky reaction mixture from norcholanyl acetoxymethyl ketone. The Reformatzky product made from 0.405 g. of ketone was mostly decolorized by passing through 2 g. of aluminum oxide in a column and eluting with large amounts of acetone. The resulting light yellow oil was refluxed with 10 cc. of acetic anhydride for 6 hrs. and worked up to give an oil which sublimed at 190–210° at 0.5 mm. The solid sublimate, after repeated crystallization from alcohol yielded 0.063 g. of a compound which melted at 161–162° and showed no depression when mixed with β-(norcholanyl)-$\Delta^{\alpha,\beta}$-butenolide previously described.

Methyl triacetylcholate (*X*) was prepared according to Wieland and Kapitel (6) by treating methyl cholate with pyridine and acetic anhydride. A yield of 67% of a product which melted at 89–91° and showed $[\alpha]_D^{27}$ 77° [c = 0.996 in methanol] was obtained. Wieland reports the melting point to be 94° and $[\alpha]_D^{25}$ 78°.

7,12-Diacetylcholic acid (*XI*) was prepared from the above methyl triacetylcholate by partial saponification as suggested by Wieland and Kapitel (6). One gram of the methyl ester (0.00182 mole) was dissolved in 20.0 cc. of 0.451 *N* alcoholic potassium hydroxide and allowed to stand at 26° for 1.25 hrs. Back titration required 52.2 cc. of 0.1028 *N* sulfuric acid. The calculated amount for saponification of two groups is 52.4 cc. The bulk of the alcohol was evaporated in a vacuum and the acidified solution was extracted with ether. The acidic components were removed by extraction with bicarbonate, and on reacidification crystals of 7,12-diacetylcholic acid separated. The acid formed white prisms from ethyl acetate, and melted sharply at 204–204.5°. $[\alpha]_D^{28}$ 71° [c = 1.79 in methanol].

Anal. Calc'd for $C_{28}H_{44}O_7$: C, 68.3; H, 9.0.
Found: C, 68.6; H, 9.2.

Triacetylcholic acid (*XII*) was made from 1.5 g. of 7,12-diacetylcholic acid, 18 cc. of acetic anhydride, and 22 cc. of pyridine according to the method of Reichstein (10). The mixture was allowed to stand at room temperature for 48 hrs., then was warmed 30 minutes on the steam-bath. After the addition of 6 cc. of water the mixture was heated for two hours and then evaporated in a vacuum. The ether solution of the residue was extracted

with ice-cold sodium carbonate solution. Acidification of the extract gave a light yellow oil which could not be crystallized. For characterization, a portion of this was treated with ethereal diazomethane. The resulting oil crystallized on seeding with methyl triacetylcholate and gave no depression of melting point when mixed with this compound.

In another experiment 0.5 g. of 7,12-diacetylcholic acid was acetylated with 0.3 g. of acetyl chloride and 5 cc. of acetic acid, but this method gave no crystalline product.

When cholic acid was brought into reaction with ketene in acetone to which a small drop of conc'd. sulfuric acid had been added, and the mixed anhydride thus formed was decomposed with warm water, only non-crystalline products were obtained.

Triacetylcholic acid chloride. A mixture of 0.026 mole of amorphous triacetylcholic acid and 19 cc. of pure thionyl chloride was allowed to stand for 12 hrs. at 0°. On working up, a light colored oil was obtained, which was used without further purification.

Triacetylnorcholyl diazomethyl ketone was prepared as in previous cases by adding the benzene solution of the acid chloride to ethereal diazomethane. This product did not crystallize.

Triacetylnorcholyl chloromethyl ketone was prepared from the above non-crystalline material with dry hydrogen chloride as in the case of norcholanyl chloromethyl ketone. It did not crystallize even with repeated chromatographing. *Triacetylnorcholyl acetoxymethyl ketone* was likewise prepared by warming the diazomethyl ketone with acetic acid. It also did not crystallize with chromatographing.

Triacetylnorcholyl benzoxymethyl ketone (*XIII*) was prepared by refluxing the oily chloromethyl ketone in aqueous alcohol with excess sodium benzoate for 7.5 hrs. After dilution, the mixture was extracted with ether. Evaporation of the ether extracts left a dark oil. When this oil was repeatedly extracted with hot ligroin, b.p. 77–116° (Skellysolve D), most of the color remained undissolved. On cooling the extracts, both crystals and oil came out. The crystals were purified from alcohol, and melted at 178–180.5°. By re-treating the oily residues with sodium benzoate and reacetylating 1.8 g. more ketone could be obtained giving an over-all yield of 26.5% based on the 7,12-diacetylcholic acid. It was later found that if the chloro ketone was first purified by chromatographing, it was much easier to get the pure benzoxy ketone, and the yield was just as good. This method gave a pure white product, melting at 178–180.5°. $[\alpha]_D^{27}$ 63° [c = 0.646 in chloroform].

Anal. Calc'd for $C_{38}H_{52}O_9$: C, 69.9; H, 8.0.
Found: C, 69.8; H, 8.1.

Reaction of triacetylnorcholyl benzoxymethyl ketone with ethyl bromoacetate and zinc. This reaction was carried out in just the same manner as with norcholanyl acetoxymethyl ketone. The zinc complex was very insoluble in benzene and it was necessary to use a very large excess of zinc, and also to work up as previously described with the aid of absolute alcohol. In this instance it was very easy to extract most of the color with bicarbonate. Although the product of the reaction gave a strong Legal test, we have been unable to bring it to crystallization. Chromatographing, both before and after reacetylation of any hydroxyl groups which might have been uncovered during the reaction was unsuccessful in this respect.

Finally the crude lactone was saponified under conditions which would lead to the unsaturated hydroxy acid from the side chain (11). It was hoped thereby to deacetylate completely the substance and thus obtain the trihydroxy lactone. However, after relactonization, the substance could not be crystallized, although it still gave a strong Legal test.

Finally, 3,7-diacetylcholic acid, prepared according to Borsche (4), was used for the lactone synthesis in the hope that the C-12 hydroxyl group would be sufficiently unreactive to withstand the reactions involved. However, when this substance was brought into reaction with thionyl chloride, only black tars were formed.

Action of diazomethane on triformylcholyl chloride. Exactly one equivalent of an ethereal solution of diazomethane was added gradually to a benzene-ether solution of triformylcholyl chloride prepared according to Cortese and Bauman (7) at 0°. It was hoped thereby

to avoid methylation of the formyl groups. When the diazomethane had all reacted, dry hydrogen chloride was passed into the solution to form the chloro ketone. A white amorphous product was obtained which could not be crystallized.

In another experiment triformylcholyl chloride was treated with 6 moles of diazomethane in the expectation of methylating all of the formyl groups. Since the diazo ketone was amorphous, it was hydrolyzed with methyl alcoholic potassium hydroxide cold for 6 hrs. (12). Water was added and the methanol evaporated. Chloroform extracted from this dark reaction mixture a small amount of crude crystals which behaved like a hydrate. This product was treated in the usual way with dry hydrogen chloride and gave a brown powder, which was chromatographed in acetone solution over ten times its weight of aluminum oxide. The effluent solution yielded crystals, which melted at 191.5–192.5° after recrystallization from acetone and petroleum ether. The analysis corresponded to *norcholyl chloromethyl ketone* $[\alpha]_D^{27}$ 39° [c = 0.712 in methanol].

Anal. Cal'd for $C_{25}H_{41}ClO_4$: C 68.1; H, 9.4.
Found: C, 68.0; H, 9.5.

The microanalyses here reported were carried out by Mr. Saul Gottlieb of these laboratories.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

INVESTIGATIONS ON LOCO WEEDS. IV. A PRELIMINARY STUDY OF THE CONSTITUENTS OF *Astragalus wootoni*. (1)

WILLIAM S. KNOWLES AND ROBERT C. ELDERFIELD

Received May 5, 1942

In preceding communications (1, 2) the results of a preliminary investigation of the constituents of Big Bend loco weed (*Astragalus earlei*) have been reported. We have commenced a similar study of another variety of loco weed, *Astragalus wootoni*, which is reported to be especially toxic to sheep. From the latter weed, pinite, betaine, choline, and trigonelline have been isolated. The active constituent or constituents have not been obtained as yet and work on the Wooton loco weed is being held temporarily in abeyance pending further experience with the more easily obtainable Big Bend loco weed.

The dried powder of the whole Wooton loco plant was extracted with seventy per cent alcohol and the extract was freed from large amounts of inert substances by precipitation with basic lead acetate exactly as was done with Big Bend loco (2). The concentrate from this treatment was then extracted with absolute alcohol, in which the active material was soluble. From the alcohol extract *d*-pinite crystallized, although the amount of this sugar present was much less than had been obtained from Big Bend loco weed.

After removal of the pinite, the fraction extracted by absolute alcohol was precipitated with phosphotungstic acid. At this point a further difference from the Big Bend weed was noted. Whereas in the latter, practically all of the activity is found in the phosphotungstic acid filtrate, in the present case about half of the activity is precipitated. After decomposition of the phosphotungstic acid precipitate, crystallization of any bases present as salts was still difficult. The solution of the bases was, therefore, freed of additional amounts of extraneous material by use of silver oxide according to the method of Kiesel (3). The bases obtained after such purification were readily brought to crystalline form. Trigonelline crystallized directly as the half-picrate from alcoholic picric acid, and choline and betaine were obtained from the mother liquors of the trigonelline picrate by chromatographic adsorption of the picrates on alumina.

We have also made a few general observations on the nature of the poison of Wooton loco weed. The activity is not destroyed by boiling with four per cent sulfuric acid, and such treatment does not indicate the occurrence of the poison as an acid-hydrolyzable substance. The poison does not have a large molecular weight since it readily diffuses through a Visking membrane. The poison apparently is not absorbed on alumina. Furthermore, the weed contains less than one part per million of selenium by the method of Williams and Lakin (4).

We have used cats in following the course of the activity of the various fractions. In general there is no appreciable difference in the symptoms caused by Wooton loco weed and those caused by Big Bend loco weed. A fuller report of this aspect of the work will appear separately.

We wish to acknowledge the kindness and cooperation of Dr. A. L. Hershey, of the New Mexico State College of Agriculture, in securing the weed with which this investigation was carried out. We also wish to express our appreciation to S. B. Penick and Company, of New York City, who kindly carried out the first extraction of the weed.

EXPERIMENTAL

All melting points are corrected for stem exposure.

The finely ground whole weed was exhaustively percolated with 70% alcohol and the alcoholic extract thus obtained was evaporated under reduced pressure to a syrup. After dissolving the syrup in water, the solution was precipitated with basic lead acetate, and the filtrate from the lead precipitate was freed from lead by means of hydrogen sulfide. The filtrate from the lead sulfide precipitate was then concentrated under reduced pressure and the resulting syrup was dried by azeotropic distillation with benzene. The carefully dried syrup was then exhaustively extracted with boiling absolute alcohol, a procedure which was shown by cat assays to extract all the active principles.

The absolute alcoholic extract after long refrigeration deposited a small amount of crystalline material which was shown to be d-*pinite* contaminated with potassium chloride, in which the weed appears to be quite rich. After repeated extraction of the material with absolute alcohol and recrystallization of the soluble portion from 95% alcohol, a very small amount of *d*-pinite was obtained which melted at 182–184° and showed no depression in melting point when mixed with a known sample of *d*-pinite which melted at 182–183°; $[\alpha]_D^{25}$ 62.5° ± 2° [*c* = 0.630 in water]. The reported value for *d*-pinite is 65° (2, 5).

After replacement of the alcohol in the extract obtained above by water, the aqueous solution was precipitated with phosphotungstic acid. About half of the original activity of the weed was found in the solution obtained by decomposition of the phosphotungstic acid precipitate as usual with barium hydroxide. The remainder of the activity was not precipitated and the filtrate from the phosphotungstic precipitate has not been investigated as yet.

Isolation of trigonelline, choline, and betaine. An aqueous solution of the bases precipitated by phosphotungstic acid from 15.4 kg. of dried weed was evaporated to dryness under reduced pressure and the residue was taken up in 125 cc. of absolute alcohol, in which it was completely soluble. On the addition of 25 cc. of ether, a dark oil separated, from which the clear red supernatant liquor was removed by decantation after refrigeration. At this point no crystalline precipitate could be obtained from the material in the supernatant liquor by precipitation of test portions with either picric acid or mercuric chloride in either alcoholic or aqueous solution.

The solvent in the above alcoholic-ether solution was replaced by water and the aqueous solution was made acid to Congo red with sulfuric acid. Then, following the procedure of Kiesel (3), 10 g. of silver oxide was stirred into the solution, which was always kept acid to Congo red during the addition. For this purpose about 25 cc. of *N* sulfuric acid was required. After stirring the solution for 30 min., a saturated solution of barium hydroxide was added with vigorous agitation until the mixture was strongly basic. The barium and sulfate ions were then balanced out and the precipitate was filtered and thoroughly washed.

The clear filtrate thus obtained was concentrated to dryness under reduced pressure and the residue was taken up in 95% alcohol. A saturated alcoholic solution of picric acid was added until the solution was just neutral to bromphenol blue. The solution was warmed to 50–60° and refrigerated overnight, during which circular clusters of needles separated which, when added to a second crop obtained by concentrating the mother liquor, amounted to 0.58 g. The *picrate* thus obtained melted at 238.5–240° and a mixture of it with choline picrate melted at 202–208°. Analyses corresponded to the *half-picrate of trigonelline.*

Anal. Calc'd for $(C_7H_7NO_2)_2 \cdot C_6H_3N_3O_7$: C, 47.7; H, 3.4; N, 13.9.
Found: C, 47.8; H, 3.9; N, 13.9.

The identity of the base as trigonelline was confirmed by the preparation of the *hydrochloride* which melted at 243–244.5° with darkening and decomposition.

Anal. Calc'd for $C_7H_7NO_2 \cdot HCl$: C, 48.4; H, 4.6; Cl, 20.5.
Found: C, 48.2; H, 4.7; Cl, 21.0.

The *chloraurate*, after recrystallization from water containing excess gold chloride and hydrochloric acid, melted at 197–197.5°.

Anal. Calc'd for $C_7H_7NO_2 \cdot AuCl_3 \cdot HCl$: C, 17.6; H, 1.7; Au, 41.3.
Found: C, 18.0; H, 1.9; Au, 41.0.

On recrystallization three times from water the above normal chloraurate changed to the *basic chloraurate* which melted at 186–187°.

The *normal picrate* was obtained by recrystallizing the half-picrate obtained as above from alcoholic picric acid solution. The picrate thus obtained was more soluble than the half-picrate and melted at 198–200°.

Anal. Calc'd for $C_7H_7NO_2 \cdot C_6H_3N_3O_7$: C, 42.6; H, 2.7.
Found: C, 42.7; H, 2.7.

Trigonelline hydrochloride, normal chloraurate, basic chloraurate, and normal picrate are reported as melting respectively at 245–250° with decomposition, 197–198°, 185–186°, and 197–199°, uncorr., or 201–203° corr. (6).

After no more trigonelline picrate could be obtained from the mother liquors of the above, benzene was added to the solution until a saturated solution of the picrates still present was formed. This benzene-alcohol solution was then chromatographed over a column of 11 g. of Merck's aluminum oxide (Brockmann). The effluent solution yielded fine needles which, after recrystallization from alcohol, melted at 245–246.5° and showed no depression of melting point when mixed with *choline picrate*.

The aluminum oxide was eluted with difficulty with hot alcohol and the eluate yielded a mixture of picrates. Therefore it was passed again through a new column. From the effluent solution, an additional amount of choline picrate was obtained. Elution of the aluminum oxide yielded a picrate which melted at 243.5–244° but which showed a marked depression in melting point when mixed with both trigonelline picrate and choline picrate. The melting point of the picrate was quite variable. After many recrystallizations from alcohol, it melted at 181–183° and gave no depression in melting point when mixed with *betaine picrate*.

Anal. Calc'd for $C_5H_{11}NO_2 \cdot C_6H_3N_3O_7$: C, 38.2; H, 4.1.
Found: C, 38.5; H, 4.1.

The *hydrochloride* was prepared from the above picrate and melted at 240–242° with decomposition after recrystallization from aqueous alcohol. Betaine hydrochloride is reported as melting at 248° with decomposition (7).

Anal. Calc'd for $C_5H_{11}NO_2 \cdot HCl$: C, 39.1; H, 7.9.
Found: C, 39.3; H, 7.7.

The microanalyses here reported were carried out by Mr. Saul Gottlieb of these laboratories.

NEW YORK, N. Y.

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

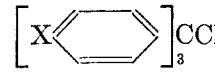
THE DISSOCIATION OF HEXAARYLETHANES. XIII. HALOGEN SUBSTITUENTS[1]

C. S. MARVEL, FREDERICK C. DIETZ, AND CHESTER M. HIMEL

Received May 22, 1942

The influence of alkyl groups introduced into the aryl residues on the dissociation of substituted hexaphenylethanes has been shown to be dependent on the size, position, and number of these groups (1). The effect is most marked when the group is in the ortho position and this has been interpreted as steric. The weight of the group and the symmetry of the radical are important when the group is in either the meta or para position. The present study of halogen derivatives of hexaphenylethanes was undertaken to see whether the halogen atoms would show effects different from those of alkyl groups.

The compounds most suitable structurally for comparison with the corresponding alkyl substituted hexaphenylethanes which have been studied would be the hexa-*p*-halophenylethanes. However, Gomberg and Cone (2) have shown that treatment of a tri-*p*-halophenylmethyl chloride (I) with silver results in removal



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of the halogen from the ring at almost the same speed as the removal of the chlorine. On the other hand, it has been found possible (2, 3) to obtain with ease dihalohexaphenylethanes of known structure, and these compounds are stable enough for determination of their dissociation by the magnetic susceptibility method used in this Laboratory (4). Radicals with para halogen substituents were rather unstable, whereas the radicals with ortho and meta halogen substituents were relatively long-lived. Thus, di-*m*-bromophenyltetraphenylethane showed no change in magnetic susceptibility over a seven-day period.

The dihalogenated hexaphenylethanes whose magnetic susceptibilities were determined together with the degree of dissociation of 0.1 *M* solutions in benzene are given in Table I.

All of the ethanes in Table I have been described in the literature, but with one exception, no mention has been made of the degree to which these ethanes are dissociated. Bowden and Watkins (5) have estimated by molecular weight methods that di-*p*-fluorophenyltetraphenylethane is dissociated to the extent of 20 $\pm 2\%$ in 0.041 *M* solution in benzene at the freezing point of the solution. This high observed value in their experiments may be due in part to some disproportionation of the radical.

Our results indicate that the influence of a halogen atom in the ring is very much like that of an alkyl group. In the ortho position the weight of the halogen atom is important. The influence of an ortho halogen atom is greater than that

[1] For the twelfth communication in this series see *J. Am. Chem. Soc.*, in press.

of the same halogen atom in either the meta or para position. A meta halogen atom has a greater influence than a para halogen atom. All ethanes containing para halogen substituents dissociate to a greater extent than does hexaphenylethane but there is little difference between the individual halogen derivatives. The monoalkyl derivatives show this same behavior (1).

The effect of radical symmetry is shown by the 7.0 ±1% dissociation of tetra-*p*-bromophenyldiphenylethane in 0.1 *M* solution in benzene as compared to 5.0 ±1% for the di-*p*-bromo compound. An attempt was made to study a hexahalotriaryl derivative in tetra-*p*-bromophenyldi-*p*-chlorophenylethane. This showed a 2.5% dissociation of a 0.1 *M* solution in benzene. It is not certain, however, that this ethane is the simple one obtained by the first coupling reaction. Hexa-*m*-substituted products are needed to make it possible to clear up some of these points.

TABLE I

DISSOCIATION OF DIHALOGENATED HEXAPHENYLETHANES

HALOGEN	% DISSOCIATION OF 0.1 *M* SOLUTION OF ETHANE IN BENZENE AT 25° WITH SUBSTITUENT		
	Para	Meta	Ortho
Fluorine	3.5 ±1		7.5 ±1
Chlorine	5.0 ±1	6.5 ±1	12.0 ±1
Bromine	5.0 ±1	7.0 ±1	17.0 ±1
Iodine	6.0 ±1		

EXPERIMENTAL

Monohalogenated triphenylcarbinols. The carbinols were made from the proper halobenzoic ester and phenylmagnesium bromide. In each case the Grignard reagent was prepared in ether and then the ether distilled off and replaced by thiophene-free benzene. The ester was then added to the benzene solution of the Grignard reagent and the mixture stirred and refluxed for four hours. The carbinols were purified by steam distillation of the reaction mixtures, followed by crystallization of the solid carbinols from petroleum ether. In some cases this solution had to be treated with "Darco" in order to get a crystalline product. Only two new carbinols were prepared.

m-Chlorophenyldiphenylcarbinol melted at 53–55°.

Anal. Calc'd for $C_{19}H_{15}ClO$: C, 77.4; H, 5.09.
Found: C, 77.7; H, 5.37.

p-Iodophenyldiphenylcarbinol melted at 73–74°.

Anal. Calc'd for $C_{19}H_{15}IO$: C, 59.1; H, 3.90.
Found: C, 59.6; H, 4.22.

Di- and tri-halogenated triphenylcarbinols. Di-*p*-bromophenyl-*p*-chlorophenylcarbinol was obtained from 85 g. of *p,p'*-dibromobenzophenone and *p*-chlorophenylmagnesium bromide made from 72 g. of *p*-bromochlorobenzene. The carbinol was difficult to purify and the yields were low. After six recrystallizations from petroleum ether this carbinol melted at 115–116°.

Anal. Calc'd for $C_{19}H_{13}Br_2ClO$: C, 50.4; H, 2.87.
Found: C, 50.9; H, 3.10.

Phenyl-di-*p*-bromophenylcarbinol was obtained from phenylmagnesium bromide and *p,p'*-dibromobenzophenone. Our product melted at 123–124° whereas the literature has reported the melting point at 113.5° (6).

Halogen substituted triphenylchloromethanes. These were all made from the carbinols and acetyl chloride (7). All have been previously reported except *m*-chlorophenyldiphenylchloromethane, m.p. 55–57°.

Anal. Calc'd for $C_{19}H_{14}Cl_2$: Active chlorine, 11.33.
Found: Active chlorine, 11.12.

As a matter of record it may be stated that the halogen substituted triphenylchloromethanes used in this work had melting points very close to those previously recorded in the literature. Melting points are recorded in Table II only as a record of the purity of our compounds.

TABLE II

MELTING POINTS OF CERTAIN TRIPHENYLCHLOROMETHANES

TRIPHENYLCHLOROMETHANE	FOUND M.P., °C.	LIT. M.P., °C.
o-fluoro	109–110	110–111 (8)
p-fluoro	91–92	91–92 (5)
o-chloro	133–134	136 (9)
m-chloro	55–57	
p-chloro	87–88	90 (10)
o-bromo	118–119	116–118 (11)
m-bromo	67–68	67 (12)
p-bromo	113–114	114 (13)
p-iodo	126–127	125 (13)
di-*p*-bromo	101–102	100 (2)
di-*p*-bromo-*p*-chloro	134–135	135 (14)

TABLE III

DISSOCIATION OF HALOGEN SUBSTITUTED HEXAPHENYLETHANES FOR 0.1 *M* BENZENE SOLUTIONS AT 25

HEXAPHENYLETHANE	$\chi_{sol} \times 10^6$	% ETHANE	α, %
di-*o*-fluoro	0.6844	5.9	7.5 ±1
di-*p*-fluoro	.6950	5.9	3.5 ±1
di-*o*-chloro	.6715	6.26	12.0 ±1
di-*m*-chloro	.6848	6.26	6.5 ±1
di-*p*-chloro	.6896	6.26	5.0 ±1
di-*o*-bromo	.6521	7.25	17.0 ±1
di-*m*-bromo	.6793	7.25	7.0 ±1
di-*p*-bromo	.6850	7.25	5.0 ±1
di-*p*-iodo	.6775	8.20	6.0 ±1
tetra-*p*-bromo	.6741	8.92	7.5 ±1
tetra-*p*-bromo-di-*p*-chloro	.6851	9.60	2.5 ±1

Magnetic susceptibility measurements. The analytically pure triarylchloromethanes were dissolved in dry benzene and shaken with silver in the apparatus previously described (4). In separate experiments the time of shaking was varied from fifteen minutes to two hours. The resulting solutions were filtered from the silver, and the residual silver

was then washed by distilling small amounts of benzene back into this part of the apparatus. The solutions thus prepared were measured immediately and remeasured at various time intervals. From these results it was concluded that, in agreement with previous reports, the preparation of the radical is essentially quantitative in less than thirty minutes. Subsequent disproportionation of the free radical solutions was slow but was appreciable in twenty-four hours, as shown by change in the magnetic susceptibility of the solutions. The *p*-iodo substituted free radical was the least stable. The *o*- and *m*-halogen substituted free radicals were most stable. All measurements were made in 0.1 *M* solution. These measurements and the calculated dissociations of the ethanes are collected in Table III.

Characterization of new ethanes. All of the ethanes were characterized by conversion to the corresponding peroxide by air oxidation. The ethanes which did not disproportionate gave 60–80% yields of pure crystalline peroxide after the magnetic susceptibility measurements were completed.

Four new peroxides were characterized: *o*-Fluorophenyldiphenylmethyl peroxide after crystallization from benzene and alcohol melted at 155–156°.

Anal. Calc'd for $C_{38}H_{28}F_2O_2$: C, 82.31; H, 5.05.
Found: C, 82.18; H, 5.28.

m-Chlorophenyldiphenylmethyl peroxide after crystallization from benzene and alcohol melted at 159–160°.

Anal. Calc'd for $C_{38}H_{28}Cl_2O_2$: C, 77.69; H, 4.77.
Found: C, 77.67; H, 3.78.

o-Bromophenyldiphenylmethyl peroxide was crystallized by dissolving in benzene, at room temperature, adding alcohol, and slowly evaporating the cold solution. It seemed to decompose in hot solution. It melted at 145–146°.

Anal. Calc'd for $C_{38}H_{28}Br_2O_2$: C, 66.47; H, 4.08.
Found: C, 67.65; H, 4.77.

p-Chlorophenyldi-*p*-bromophenylmethyl peroxide after recrystallization from acetone melted at 194–195°.

Anal. Calc'd for $C_{38}H_{24}Cl_2Br_4O_2$: C, 50.50; H, 2.65.
Found: C, 50.36; H, 2.66.

SUMMARY

Nine dihalohexaphenylethanes have been prepared and their degrees of dissociation measured by the magnetic susceptibility method. Ortho halogen atoms are more effective in producing dissociation than are meta, and meta are more effective than para. In the ortho position the bromine atom is more effective in producing dissociation than is a chlorine atom and this is more effective than a fluorine atom. In general, halogen substituents in hexaphenylethane seem to have about the same influence on dissociation as do alkyl substituents.

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THE ESSENTIAL OIL OF *CUPRESSUS MACROCARPA*

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A number of essential oils of the genus *Cupressus* have already been examined, including *C. sempervirens*, *C. sempervirens pyramidalis*, *C. aromatica*, *C. Goweniana*, *C. funebris* (1), *C. torulosa* (2), *C. lusitanica* (3). *Cupressus macrocarpa*, Hartweg (syn. *C. Lambertiana*, Carr.) or Monterey cypress has probably the most restricted range of any conifer, growing naturally only at Monterey and on the island of Guadaloupe, while at Monterey the main grove occupies an area only 2 miles long and 200 yards wide. It has been introduced into many parts of the world, including New Zealand, where it is grown extensively. The essential oil has not been previously examined in detail, Schimmel and Co. (4) reporting the physical constants, d_{15} 0.8656, $[\alpha]_D$ +31.35°, chemical constants, acid value 1.5, ester value 13.9, ester value after acetylation 50.82, and it was suggested without chemical confirmation that the oil contained citronellal and *p*-cymene.

A complete examination of the essential oil has now been made, ten different constituents being isolated with certainty, including two new compounds, a sesquiterpene alcohol and a diterpene, while at least five other unidentified constituents are also present. The winter oil, obtained in 0.20% yield from the leaves and terminal branchlets, is yellow in color and has the following constants: d_4^{25} 0.8607, n_D^{25} 1.4718, $[\alpha]_D^{25}$ +11.31°, acid number 1.0, saponification number 1.4, saponification number after acetylation 33.7. Phenols are absent, and the combined aldehyde and ketone content is less than 0.3%.

When an attempt was made to fractionate the oil at atmospheric pressure, decomposition occurred with apparent liberation of water, so that nearly all the fractionations were carried out at 10 mm. A typical preliminary distillation gave the fractions listed in Table I.

The fractions boiling below 65°/10 mm. were then systematically fractionated, twice at 10 mm. and finally at atmospheric pressure, the fractionation being controlled by the boiling point, as well as by the refractive index, density, and rotation, graphs being drawn of these four constants as the fractionation proceeded.

After the fourth fractionation it was apparent that some obvious mixtures were not being separated further, and separation and identification was then carried out by chemical means. The fractions boiling above 65°/10 mm. were also repeatedly fractionated at 10 mm., the solid separating in the higher-boiling fractions being filtered off before refractionation. In all cases where the molecular refraction indicated a hydrocarbon unmixed with any appreciable quantity of oxygenated compounds, the final distillations were carried out in the presence of sodium.

No attempt has been made to identify the constituents in each fraction but only those have been examined which a consideration of their physical properties

showed to be reasonably homogeneous, or in some cases mixtures of constituents practically impossible to separate by fractionation. The numbers of the following fractions refer to those in Table II.

TABLE I

Fractionation of Cupressus Oil

FRACTION	B.P./10 MM., °C	n_D^{25}	d_4^{25}	$[\alpha]_D^{25}$	%
1	<45	1.4640	0.8473	+1.34	31.6
2	45–50	1.4672	.8431	+15.9	19.5
3	50–55	1.4712	.8373	+17.0	8.0
4	55–65	1.4757	.8459	+4.35	17.4
5	65–90	1.4770	.9228	+17.7	10.7
6	Residue	Solidified on cooling			9.1
	Loss				3.7
					100.0

TABLE II

FRACTION	B.P., °C	MM.	n_D^{25}	$[\alpha]_D^{25}$	d_4^{25}	WEIGHT, G.	FRACTION, %	CUMULATIVE, %
1	152–154	757	1.4612–1.4622	−19.64	0.8461	25.5	4.15	4.15
2	154–155.5	757	1.4622–1.4623	−14.57	0.8484	113	18.4	22.6
3	155.5	757	1.4623–1.4630	−7.29		49.1	7.9	30.5
4	155.5–156	743	1.4630–1.4639	−5.15		41.4	6.75	37.3
5	156–157	743	1.4639–1.4640	+4.54		45.2	7.36	44.7
6	157–157.5	743	1.4640–1.4651	+19.41	0.8457	24.4	3.98	48.6
7	157.5–163	743	1.4651–1.4675	+30.02	0.8420	29.7	4.85	53.5
8	163–164	743	1.4675–1.4680	+36.46	0.8366	37.4	6.10	59.4
9	164	743	1.4680–1.4688	+35.96	0.8373	13.3	2.16	61.8
10	164–167	749	1.4688–1.4720	+30.03	0.8360	35.9	5.85	67.5
11	167	749	1.4720–1.4722	+19.68	0.8332	11.3	1.84	69.4
12	167–170	749	1.4722–1.4735	+16.33	0.8352	22.2	3.54	73.0
13	170–174	754	1.4735–1.4748	+10.02	0.8381	29.9	4.87	77.9
14	174–176	754	1.4748–1.4755	+8.34		13.2	2.16	80.0
15	176–177	754	1.4755–1.4761	+4.68	0.8439	55.5	9.05	89.0
16	55–57	10	1.4761–1.4768	+1.41		37.6	6.10	95.1
17	58	10	1.4768–1.4778	+0.62		15.2	2.48	97.5
18	58	10	1.4778–1.4808	+0.26	0.8513	13.9	2.26	100
19	Residue		Red gummy mass					

The larger fraction 2 consisted mainly of a mixture of *dl*- and *l*-α-pinene, since it yielded the inactive nitrosochloride and *dl*-pinonic acid on oxidation with permanganate.

The constants of fraction 8 suggested the presence of sabinene, confirmed by oxidation with alkaline permanganate to the insoluble sodium sabinenate and hence to the free acid. Ozonization yielded sabina ketone, which was converted

to an apparent mixture of isomeric dinitrophenylhydrazones, which could not, however, be conveniently separated into the pure optical isomerides. No trace of β-pinene could be detected in this or other fractions.

A minimum in the density curve indicated the presence of some acyclic terpene in fraction 10. Treatment with maleic anhydride furnished a mixture of adducts of myrcene and α-terpinene, separated by crystallization of their related potassium salts and the corresponding acids. The presence of α-terpinene in this case, is due probably to isomerization of sabinene under the conditions of the experiment, since there was no other evidence for its occurrence.

Treatment of fraction 15 with hydrogen chloride in glacial acetic acid furnished terpinene dihydrochloride, which might be derived from a number of terpenes, including the terpinenes, sabinene, thujene, and possibly the phellandrenes. The presence of α-phellandrene was confirmed by the preparation of the nitrosite (yield $< 1\%$) while the same fraction furnished the nitrosochloride (yield $< 5\%$) and the related nitrolpiperidide of γ-terpinene. *p*-Cymene was shown to be definitely absent, since the fraction was completely oxidized with very dilute permanganate. From the small yield of derivatives from this fraction it would appear that other terpenes besides α-phellandrene and γ-terpinene are also present, but neither a solid bromide nor a nitrosate could be isolated.

Oxidation of the highest-boiling terpene fraction 18 with dilute permanganate confirmed the presence of both γ-terpinene and terpinolene through the isolation of the corresponding erythritols, m.p. 236–237° and m.p. 149–150° respectively. Bromination with two moles of bromine yielded terpinolene tetrabromide, m.p. 117°, confirmed by mixed melting point with an authentic specimen, while with one mole, terpinolene dibromide, m.p. 69°, was formed. The presence of terpinolene is therefore definitely established and this is possibly the first authentic record of terpinolene existing in a naturally occurring oil. Clover (5) reported the presence of terpinolene in the oils distilled from two samples of resin from *Canarium luzonicum* but nineteen other samples of resin from different trees gave oils which contained no terpinolene. Bacon (6), however, examined over one hundred specimens but found no trace of terpinolene. The abstract of Clover's paper does not give the evidence for the identification of terpinolene. The occurrence of terpinolene in the oil of coriander (7) is listed in the abstract with a question mark. Escourrou (8) claimed to have proved as a result of experiments on the oxidation by ozone of limonene from oil of sweet oranges, that even the purest limonene is always a mixture of limonene, terpinolene, and α-terpinene. If Escourrou's claim is correct then the occurrence of terpinolene in essential oils would be as widespread as that of limonene (dipentene), which is second only to α-pinene in number of source species. The presence of terpinolene in Escourrou's limonene was not shown by the formation of derivatives, and the possibility of isomerization under the experimental conditions employed must be considered. However, in this oil terpinolene has been isolated and identified in the usual way and although attempts have been made to detect limonene, these have been fruitless.

The combined fractions, b.p. 65–90°/10 mm., after repeated fractionation

gave a forerun of higher-boiling terpenes and a last fraction of sesquiterpenes but the bulk of the material passed over at 83–87°/10 mm. with practically no change of physical constants. The identity of this constituent was confirmed as *d*-terpinen-4-ol by oxidation with permanganate to the corresponding glycerol, hydration by means of dilute sulfuric acid to terpinene-terpin, and the formation of the corresponding naphthylurethan.

Since sabinene can be hydrated to terpinen-4-ol, this process also probably occurs in the plant, as sabinene is found in all the oils in which the alcohol occurs.[1] Simonsen (9) draws attention to the fact that 1,4-cineole also occurs where both sabinene and terpinen-4-ol are present in the same oil. 1,4-Cineole could not be detected, however, in this oil; if present, it would have revealed itself by its high density and low refractive index in the appropriate boiling fraction and by its characteristic odor.

The fractions boiling above 90°/10 mm., including all those from the refractionations, were united and separated into two main fractions, (a) b.p. < 115°/5 mm. and (b) b.p. > 115°/5 mm. The first fraction was refractionated at 10 mm. and from the curves derived from the physical constants the presence of at least five constituents was indicated but so far none of these have been identified.

The specific refraction, and the evolution of hydrogen with sodium, indicated the presence of an unsaturated monocyclic alcohol in the first fraction, b.p. *ca.* 100°/10 mm., which is apparently tertiary, since it does not form a naphthylurethan but is readily dehydrated. No solid phthalic ester could be formed, and the action of 5% sulfuric acid yielded no solid hydrated product.

The second fraction, b.p. *ca.* 110°/10 mm., had an ester value of 40.2, indicating the presence of about 15% of ester (as $C_{10}H_{15}OCOCH_3$). This corresponded to about one gram of ester in the fraction, and no attempt has been made to identify it.

The next three small fractions, b.p. 115–117°/10 mm., b.p. 120–121°/10 mm., b.p. 124–127°/10 mm., respectively, had physical constants agreeing with dicyclic sesquiterpenes and each gave a different color reaction with bromine in chloroform solution. Although dicyclic, however, the first and last fractions failed to yield a naphthalene or azulene hydrocarbon on treatment with palladized charcoal. The first fraction yielded no solid hydrochloride, and the third fraction also did not give a solid hydrochloride, nitrosochloride, nitrosite, or nitrosate. There was insufficient of the second fraction for examination. Although no solid derivatives have been obtained from these sesquiterpene fractions the physical constants approximate most closely those of the caryophyllenes.

A crystalline solid separated from the next higher-boiling fraction, b.p. 130–150°/5 mm., which when purified had the m.p. 108°, $[\alpha]_D^{25}$ +25.4°. This we believe to be a new saturated tricyclic sesquiterpene alcohol, $C_{15}H_{25}OH$, for

[1] Sfiras (3), however, did not isolate salinen from the oil of *C. lusitanica* but reported the presence of terpinen-4-ol.

which we suggest the name macrocarpol. It was characterized as its naphthylurethan, m.p. 88–91°, purified with difficulty, and as a readily purified 3,5-dinitrobenzoyl ester, m.p. 157–158°. The alcohol did not react with chromic acid, nor did it form a chromate under conditions described by Wienhaus (10); it gave no coloration with tetranitromethane and was recovered unchanged after attempted hydrogenation with a platinum oxide catalyst. The melting point and rotation are both higher than those of the isomeric alcohols, ledol, m.p. 105°, $[\alpha]_D$ +7.98° (chromate, m.p. 92°) (11) and maalyl alcohol, m.p. 105°, $[\alpha]_D$ +18.33° (chromate, m.p. 111°) (12), and the crystalline form is also significantly different.

All the higher-boiling fractions from all the distillations deposited a crystalline solid on cooling, which proved to be almost entirely the diterpene, isophyllocladene, m.p. 112°, $[\alpha]_D^{25}$ +23.7° (in chloroform), identified by mixed melting point with an authentic specimen, and by the preparation of the hydrochloride, m.p. 106–107°, and dibromide, m.p. 133–133.5°. Isophyllocladene is not produced from phyllocladene in the course of distillation and isolation, since it could readily be isolated from the oil obtained in a pilot experiment after the more volatile constituents had been allowed to evaporate off, and it was also deposited in the condenser towards the end of the steam distillation. This is the first record of the occurrence of isophyllocladene in essential oils but the unidentified diterpene (13) from *Sciadopitys verticillata*, m.p. 111–112°, $[\alpha]_D$ −24.5°, (hydrochloride, m.p. 105–107°, dihydro derivative, m.p. 71–72°) is almost undoubtedly the levo form of isophyllocladene. It is possible too, that the diterpene, mirene, from *Podocarpus ferrugineus* (14), m.p. 105°, $[\alpha]_D$ −27.15° (hydrochloride, m.p. 97–98°, dihydro derivative, m.p. 73–74°) is also the levo modification of isophyllocladene. The *d* form also occurs with phyllocladene in the leaf-oil from *Phyllocladus trichomanoides* (unpublished results).

Systematic fractionation of the liquid diterpene fraction and crystallization of the solids separating furnished more isophyllocladene and a new diterpene, $C_{20}H_{32}$, m.p. 74–75°, $[\alpha]_D^{25}$ +59.2° (in chloroform), for which the name cupressene is suggested. Cupressene is more soluble in methyl and ethyl alcohol than isophyllocladene; it is tricyclic with two double bonds, forming a tetrahydro derivative, m.p. 56–57.5°, a hydrochloride, m.p. 80–85°, and is unchanged after boiling with either alcoholic sulfuric or alcoholic hydrochloric acid. The only product isolated from an attempted dehydrogenation with palladium charcoal was isophyllocladene in 30% yield. The isophyllocladene may have been formed by the action of the catalyst on cupressene but on the other hand it is quite conceivable that the isophyllocladene was present as an original impurity, for although the sample of cupressene used in this experiment had the m.p. 73–74°, the presence of isophyllocladene (or phyllocladene) causes practically no depression on the melting point of cupressene. There was insufficient material for the experiment to be repeated on an analytically pure specimen.

The small amount of liquid diterpene fraction remaining had $[\alpha]_D^{25}$ +25.7°. Experiments on the constitution of isophyllocladene are in active progress.

EXPERIMENTAL

The leaves and terminal branchlets of *Cupressus macrocarpa* growing in Auckland and collected during July were steam distilled in the usual way in three batches, the yield being 0.20% one day after cutting and 0.18% after two days.

The physical and chemical constants already recorded were determined by the standard methods. Four systematic refractionations were carried out, the fractionating column consisting of a 30-cm. jacketed Widmer column with a 10:1 reflux ratio, the pressure being maintained constant with an electrically controlled manostat. The results of the final fractionation of the constituents boiling below 65°/10 mm. are recorded in Table II.

α-Pinene. The nitrosochloride, m.p. 107°, was prepared from fraction 2 by Wallach's method (15) in 9% yield, undepressed by an authentic specimen, m.p. 110°. A liquid acid, b.p. 155–161°/5 mm., was obtained in 38% yield on oxidation with dilute permanganate according to Delépine (16), which deposited crystals of *dl*-pinonic acid on cooling, and after recrystallization from benzene had the m.p. 104–105° (*dl*-pinonic acid has the m.p. 103–104°). The low yields of these products and the low density of this fraction indicate the presence of another constituent.

Sabinene. The yield of sodium sabinenate (4.4 g. from 5 g. of sabinene) obtained by oxidation of fraction 8 with alkaline permanganate according to Short and Read (17) suggests a sabinene content in this fraction of 55%. Only the active acid, m.p. 56.5–57°, was isolated after acidification and crystallization from water, but none of the *dl*-acid, m.p. 84–85°. Wallach (18) records the m.p. 57° for the active acid. Ozonization of this fraction gave in 18% yield sabina ketone, b.p. 85–87°/10 mm., d_4^{25} 0.9472, n_D^{25} 1.4611, $[\alpha]_D^{25}$ −2.4°, which furnished a mixture of dinitrophenylhydrazones, separated from chloroform-methyl alcohol into two fractions, (a) m.p. 98–101°, and (b) m.p. 116–117°. Short and Read give 124.5° as the melting point of the pure derivative, but when the compound is derived from less pure ketone the melting point is markedly lower. The low rotation of the above ketone indicates that it is far from being optically pure.

Myrcene and α-terpinene. Ten grams of fraction 10 and freshly sublimed maleic anhydride (2 g.) were heated at 100° for 0.5 hour. Distillation at 10 mm. removed the terpenes and excess of maleic anhydride, followed by a mixture of adducts, b.p. 170–177°/5 mm., yield 4.24 g., forming a greasy solid on cooling, m.p. 25–28°. Saponification gave a mixture of potassium salts, one comparatively insoluble and the other freely soluble in water. The latter, after acidification followed by repeated crystallization from acetone-water and acetonitrile, furnished the pure acid, m.p. 123–124°, derived from the myrcene adduct, melting point undepressed by an authentic specimen. Diels and Alder (19) record the m.p. 122–123° for this acid.

The above insoluble potassium salt was twice recrystallized, and on acidification gave the free acid, m.p. 134.5–135°. Goodway and West (20) and Sfiras (21) record melting points of 134° and 131° respectively from the acid derived from the maleic anhydride adduct of α-terpinene, but Diels, Koch, and Frost (22) record the m.p. 158° for apparently the same compound. Repeated crystallization of the acid from acetonitrile raised the melting point to 141.5–143.5° but when heated at 130°/2 mm. for 1.5 hours it partly sublimed to a solid of m.p. *ca.* 60° and then had the m.p. 147–148°. Treatment of this product with acetyl chloride gave the anhydride, b.p. 155–165°/5 mm., which after repeated crystallization from light petroleum (b.p. 80–100°) had the m.p. 61–62°, unchanged by further recrystallization. Goodway and West (20), Sfiras (21), and Diels, Koch, and Frost (22) record melting points of 62°, 65–66°, and 66–67° respectively for this anhydride. Goodway and West were unable to raise the melting point of the anhydride above 62° and that of the acid above 134°. Although we cannot duplicate the high melting points of Diels, Koch, and Frost we have reconverted the above anhydride, m.p. 61–62°, into the acid of m.p. 135–140°, again raised after drying over phosphorus pentoxide at 100°/vac. to 147–148° with gas evolution.

α-Phellandrene and γ-terpinene. Fraction 15 (2 g.) when treated with dry hydrogen chloride in cooled glacial acetic acid gave a crystalline solid (yield 180 mg.) which after

repeated crystallization from chloroform-methyl alcohol had the m.p. 51.5–52°. Wallach (23) records the m.p. 51–52° for terpinene dihydrochloride. The nitrosite prepared from this fraction (5 g.) in the usual way (yield 50 mg.) after repeated crystallization from chloroform-methyl alcohol and acetone had the m.p. 110–111°, undepressed by an authentic mixture of the α- and β-nitrosites of α-phelandrene, m.p. 110.5–111.5°. There was insufficient material to separate into the pure α- and β- forms, which exhibit marked mutarotation (24).

The same fraction gave a nitrosochloride in <5% yield, which after repeated crystallization from chloroform-methyl alcohol had the m.p. 108–109°, and the related nitrolpiperidide after crystallization from alcohol had the m.p. 148–149°. Richter and Wolff (25) record the m.p. 111° and m.p. 149° for these derivatives respectively for γ-terpinene.

γ-Terpinene and terpinolene. Fraction 18 (4.3 g.) was mixed with an ice-cold solution (400 cc.) of potassium permanganate (3.25 g.) and potassium hydroxide (1 g.) and shaken mechanically for one hour, and allowed to stand for two days. One and one-tenth grams of unchanged oil was separated and reoxidized separately as above. The combined filtrates were evaporated to dryness and extracted with alcohol. On concentration of this extract, γ-terpinene erythritol separated, which after repeated crystallization from aqueous alcohol melted at 236–237°. Wallach (23) records the m.p. 235–236° for this derivative.

The alcoholic mother liquors from the original extract were evaporated to dryness, the residue dissolved in water, and then repeatedly extracted with ethyl acetate. On concentration, terpinolene erythritol separated, and after repeated crystallization from ethyl acetate-ether had the m.p. 149–150°. Wallach (26) records 148–150° for this derivative.

Fraction 18 (0.85 g.) was dissolved in a mixture of amyl alcohol (1 cc.) and ether (2 cc.) and cooled in a freezing mixture. A cooled solution of bromine (2 g.) in ether (2 cc.) was slowly added. On removal of the ether a light yellow solid separated (0.95 g.), which after repeated crystallization from chloroform-methyl alcohol had the m.p. 116.5–117.5°, undepressed by an authentic specimen of terpinolene tetrabromide similarly prepared from terpinolene derived from terpineol by dehydration (27). Wallach (28) and Henry and Paget (29) record the m.p. 116° and m.p. 119° respectively for this derivative.

In a similar experiment using one gram of bromine, long needles of terpinolene dibromide separated (380 mg.), which after many crystallizations from chloroform-methyl alcohol and from acetone melted at 69°. Baeyer (27) records the m.p. 69–70° for the dibromide.

d-Terpinen-4-ol. By refractionation of the combined fractions, b.p. 65–90°/10 mm., an almost pure fraction was obtained, b.p. 86–87°/10 mm., d_4^{25} 0.9285, n_D^{25} 1.4765, $[\alpha]_D^{25}$ +21.36° corresponding to *d*-terpinen-4-ol which has the b.p. 92.5–94°/10 mm., d^{19} 0.9265, n_D^{19} 1.4785, $[\alpha]_D$ + 25.2° (30). Oxidation of this fraction with permanganate according to Wallach (30) gave *p*-menthane-1,2,4-triol hydrate, which after crystallization from ethyl acetate and then from chloroform melted at 112–113°. After heating at 100° for 24 hours the anhydrous compound was obtained of m.p. 128–129°. Wallach records 114–116° and 128–129° respectively for these derivatives. Hydration of this fraction with 5.5% sulfuric acid according to Wallach (31) gave terpinene-terpin, crystallizing from hot water in colorless crystals, m.p. 137.5–138.5° (lit. m.p. 137–138°).

The naphthylurethan prepared in the usual way was crystallized repeatedly from methyl alcohol and then had the m.p. 107–108°. Penfold (30) records m.p. 104–105° for this compound.

Terpene alcohol, terpene ester, and sesquiterpene fraction. The material boiling above 90°/10 mm. was separated into two major fractions, (a) b.p. below 115°/5 mm., and (b) b.p. above 115°/5 mm. The first portion was again fractionated, the physical constants indicating the presence of five constituents as in Table III.

Fraction A1 did not give a precipitate with Brady's reagent but liberated hydrogen on the addition of sodium, indicating the presence of an alcohol. When an attempt was made to prepare the naphthylurethan, dinaphthylurea was the only solid product which could be isolated. Similar attempts to form the phthalic ester and a hydrate with 5% sulfuric acid

yielded no solid product. Calculation of the molecular refraction on a basis of formulas $C_{10}H_{16}O$ and $C_{10}H_{18}O$ indicated that it was a monocyclic alcohol with two or one double bonds respectively.

The second fraction A2 contained a small quantity of ester as already described.

The three sesquiterpene fractions gave pale green, reddish-brown, and deep blue colorations respectively with bromine in chloroform solution.

No aromatic nor azulene hydrocarbon could be obtained from the sesquiterpene fractions A3 or A5 using a palladized charcoal catalyst capable of yielding 520 mg. of cadalene from one gram of authentic cadinene (32).

In order to investigate the use of chloranil as a dehydrogenating agent in the sesquiterpene field, cadinene was treated as described by Arnold and Collins (33), but a yield of only 750 mg. of cadalene could be obtained from 2.7 g. of cadinene.

TABLE III

FRACTION	B.P./10 MM., °C	d_4^{25}	n_D^{25}	$[\alpha]_D^{25}$	$[R_L]_D$	YIELD, G.
A1	91–106	0.9149	1.4770	+6.62		10.6
A2	106–115	0.9028	1.4820	+4.86		7.0
A3	115–117	0.8965	1.4935	+7.34	66.4	6.9
A4	120–121		1.5020			1.7
A5	124–127	0.9031	1.5015	+16.83	66.6	2.4

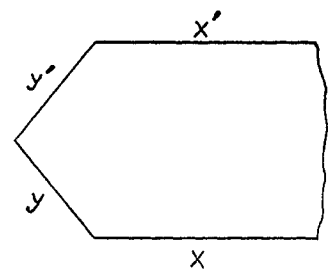
Macrocarpol. Refractionation of the second major fraction, b.p. above 115°/5 mm., gave a fraction of b.p. 130–150°/5 mm., which deposited a crystalline solid on cooling. Repeated crystallization from aqueous alcohol or light petroleum (b.p. 60–70°) furnished tabular crystals, m.p. 108°, $[\alpha]_D^{25}$ +25.4° ($l = 1$, $c = 5.24$ in alcohol). Yield *ca.* 0.5 gram.

Anal. Calc'd for $C_{15}H_{26}O$: C, 80.97; H, 11.79.

Found: C, 80.82, 80.95, 80.72; H, 11.55, 11.65, 11.49.

Molecular weight (Rast) 223, $C_{15}H_{26}O$ requires 222.

The optic axial angle of the crystals (2v) = 30° ± 1°, with the optic sign negative. The crystals are tabular in habit, bounded by edges having the following supplementary angles of intersection as seen under the microscope



x to y = x′ to y′ = 50.5° ± 1

y to y′ = 79° ± 1

The compound is freely soluble in the common solvents with the exception of water and light petroleum.

The naphthylurethan prepared from 250 mg. separated as a gummy solid and could only be purified with difficulty from light petroleum as crystals of m.p. 88–91°.

The 3,5-dinitrobenzoyl ester prepared in the usual way from 140 mg. readily crystallized from alcohol and after repeated crystallization formed colorless needles, m.p. 157–158°.

Anal. Calc'd for $C_{22}H_{28}N_2O_6$: C, 63.42; H, 6.78.
Found: C, 63.60; H, 6.63.

Isophyllocladene. The fraction boiling above 150°/5 mm. deposited a considerable quantity of crystalline material, which after repeated crystallization from methyl and ethyl alcohol formed needles several centimeters long, m.p. 112°, $[\alpha]_D^{25}$ +23.7° (l = 1, c = 7.596 in chloroform). The melting point was not depressed by an authentic specimen formed by the isomerization of phyllocladene with alcoholic sulfuric acid (34).

The crystals are probably orthorhombic and prismatic or acicular in habit, elongated parallel to c. Interfacial angles, measured in the prism pinacoid cone only gave the following values (± 5′)

110 to 1 $\bar{1}$ 0 = 87° 42′
110 to 0 1 0 = 46° 9′

Optical properties: Optic axial angle (2v) = 18° ± 4°
Optic sign positive with β parallel to c.

The hydrochloride was prepared according to Uota (35), and after two crystallizations from ether-methyl alcohol had the m.p. 106–107°, undepressed by an authentic specimen.

The dibromide crystallized from alcohol in needles, m.p. 133–133.5°. Uota records 133–134°.

Cupressene. Systematic fractionation of the final diterpene liquid fractions, and crystallization of the solids separating on standing yielded more isophyllocladene and a further diterpene, m.p. 74–75°, separated from isophyllocladene by its greater solubility in methyl and ethyl alcohol (yield < 1 gram). $[\alpha]_D^{25}$ +59.2° (l = 1, c = 1.908 in chloroform).

Anal. Calc'd for $C_{20}H_{32}$: C, 88.24; H, 11.76.
Found: C, 88.14; H, 11.66.
Molecular weight (Rast) 309, $C_{20}H_{32}$ requires 272.

It gives a yellow coloration with tetranitromethane in chloroform solution.

Tetrahydrocupressene. Cupressene (180 mg.) was hydrogenated in glacial acetic acid at 45 lb. pressure for 20 hours in the presence of Adams' catalyst (30 mg.). Most of the acetic acid was removed by distillation *in vacuo*, the tetrahydro derivative being then precipitated by addition of water, crystallizing from alcohol in plates and needles. When crystallized from chloroform-methyl alcohol it formed plates, m.p. 56–57.5°, while from the mother liquors on standing, needles separated of approximately the same melting point; $[\alpha]_D^{17}$ (micro-tube) +62° (l = 1, c = 6.58 in chloroform).

Anal. Calc'd for $C_{20}H_{36}$: C, 86.96; H, 13.04.
Found: C, 86.93; H, 13.00.

The melting point was depressed on admixture with authentic β-dihydrophyllocladene (34) of m.p. 57–58°, $[\alpha]_D^{25}$ +12.5°.

Cupressene hydrochloride. Dry hydrogen chloride was passed through a solution of cupressene in ether in a freezing mixture. The solid product formed after the removal of ether was repeatedly crystallized from alcohol-ether and then had the m.p. 80–82°. The only analytical sample was unfortunately lost in the censoring of the mail.

A mixture of cupressene, m.p. 73–74°, (500 mg.) and active palladized charcoal (50 mg.) was heated in a stream of nitrogen at 270–280° for 3.5 hours. The catalyst was filtered off after dilution with ether, and the product after removal of the ether crystallized from ethyl acetate in needles, m.p. 98–100° (yield 150 mg.). Repeated crystallization from ethyl acetate raised the melting point to 107–108°, undepressed by an authentic specimen of isophyllocladene; $[\alpha]_D^{25}$ +25° (l = 1, c = 0.781 in chloroform).

Anal. Calc'd for $C_{20}H_{32}$: C, 88.24; H, 11.76.
Found: C, 88.10; H, 11.82.

The isophyllocladene was also confirmed by the preparation of α-dihydrophyllocladene (34), m.p. 73°, undepressed by an authentic specimen.

All melting points are uncorrected. The analyses are by Dr. Burger.

We are greatly indebted to Dr. F. J. Turner, Otago University, for the crystal measurements, to the Chemical Society and the Australian and New Zealand Association for the Advancement of Science for grants, and one of us (M. D. S.) for a National Research Scholarship.

SUMMARY

The essential oil from the leaves of *Cupressus macrocarpa* has been shown to consist of the following constituents expressed in approximate percentages:

1. Terpenes: α-pinene, 40%; sabinene, 15%; myrcene, 3%; α-phellandrene, 4%; α-terpinene (?)—; γ-terpinene and terpinolene, 6%; unidentified terpenes, 12%.

2. Sesquiterpenes: (a) unidentified sesquiterpene, b.p. 115–117°/10 mm., (b) b.p. 120–121°/10 mm., (c) 124–127°/10 mm., 0.7%.

3. Diterpenes: isophyllocladene, 3.5%; cupressene, 0.1%.

4. Alcohols: *d*-terpinen-4-ol, 8.8%; unidentified alcohol, b.p. *ca.* 100°/10 mm., 0.8%, macrocarpol, 0.1%.

5. Ester: unidentified ester, b.p. *ca.* 110°/10 mm., 0.5%.

6. Acids, aldehydes, ketones: traces.

7. Other compounds, including residue: 5.5%. Total, 100%.

Macrocarpol is probably a new sesquiterpene alcohol, $C_{15}H_{26}O$, m.p. 108°, while cupressene is a new diterpene, m.p. 74–75°. This is the first record of isophyllocladene and possibly terpinolene in essential oils.

AUCKLAND, NEW ZEALAND

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

AMINO ALCOHOLS. XI.[1] ARYLGLYOXYLOHYDROXAMYL CHLORIDES[2]

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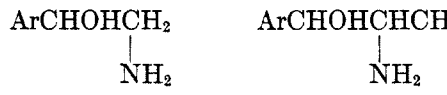
INTRODUCTION

In previous studies of the relationship between chemical structure and physiological activity of the primary amines belonging to the epinephrine-ephedrine series, it was shown that optimum circulatory activity is found in the arylethanolamines (I) and arylpropanolamines (II).



(I) (II)

Amino alcohols of both the ethane and propane derivatives may be readily obtained by the catalytic hydrogenation of the corresponding isonitroso ketones (1–4). The intermediary isonitrosopropiophenones are readily prepared by allowing the propiophenone in ether solution to react with an alkyl nitrite in the presence of hydrogen chloride,

The nitrosation reaction, which gives better than 70% yields in the case of propiophenone itself, may be employed in cases where the phenyl nucleus is substituted, even to the hydroxypropiophenones (3). Higher homologs of isonitrosopropiophenone may be prepared in a similar manner from higher alkyl aryl ketones, but unfortunately this is not true of the lower homolog, acetophenone. Consequently, it has been difficult to obtain as complete a series of arylethanolamines as has been possible in the case of the arylpropanolamines. This is regrettable, since a more complete pharmacological comparison of the amino alcohols of the corresponding ethane series is desirable. Available information on the favorable pressor activity of phenylethanolamine (5–7) and also that of norepinephrine (arterenol) (8–10)—the primary amine corresponding to that of epinephrine—indicates the desirability of a suitable general method which might be employed for the synthesis of amines of the entire arylethanolamine series.

[1] For Amino Alcohols, X, see *J. Am. Chem. Soc.*, **57**, 1091 (1935).

[2] This paper is constructed in part from a dissertation presented by Nathan Levin to the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in June, 1941. A portion of this paper was presented before the Division of Organic Chemistry at the Baltimore meeting of the American Chemical Society, April, 1939.

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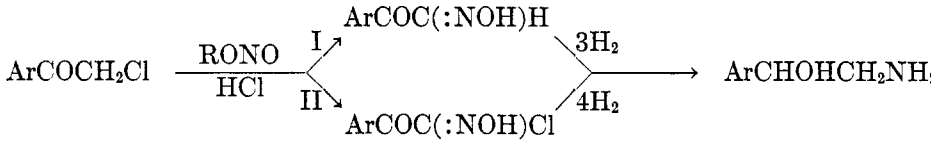
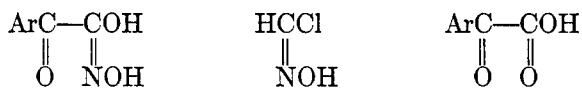
The chief objection to the use of isonitrosoacetophenones as intermediates in the synthesis of the phenylethanolamines is that these derivatives cannot be readily prepared. Thus, isonitrosoacetophenone, $C_6H_5COC(:NOH)H$, may be obtained in approximately 25% yields by allowing an absolute alcoholic solution of acetophenone, an alkyl nitrite and sodium alkoxide to stand in the cold for several days;[4] with acetophenone bearing unprotected phenolic hydroxyls, the reaction does not proceed at all. When nitrosation is carried out in the presence of hydrogen chloride, the yields of the isonitroso ketone are low or negligible (2, 11).

In quest for a procedure more broadly applicable or available for the preparation of intermediates that may readily be transformed into the corresponding arylethanolamines, the reaction between phenacyl chloride and alkyl nitrites was investigated. Nitrosation might proceed in one of two directions, either product being a potential intermediate for reduction to the arylethanolamine:



Results show that in each instance, compounds of type II, chloroisonitrosoacetophenones, are formed in excellent yields.

Structurally, these chloroisonitroso ketones form an interesting class of compounds; they are, strictly speaking, chlorides of keto-hydroximic acids of the type (III). Further, they may be considered either as aroyl derivatives of



(III) (IV) (V)

formhydroximic acid chloride (IV) or as the hydroximic acid chloride of arylglyoxylic acid (V). Accordingly, the compound, $C_6H_5COC(:NOH)Cl$, may be designated as benzoylformhydroxamyl chloride or phenylglyoxylohydroxamyl chloride,—either name is correct (12).

The first compound of this type was reported by Glutz (13), who, in 1870, treated chloroacetone with concentrated nitric acid and obtained methylglyoxylohydroxamyl chloride, $CH_3COC(:NOH)Cl$. Claisen (14) prepared the first arylglyoxylohydroxamyl chloride by saturating a cooled mixture of acetophenone and amyl nitrite with hydrogen chloride. By this method, there was obtained a small quantity of a colorless crystalline product, m.p. 133–134°, which, when heated above its melting point, decomposed with the liberation of hydrogen chloride; Claisen assumed that the reaction product was an addition compound of isonitrosoacetophenone and hydrogen chloride. Subsequently Claisen and Manasse (15) repeated the reaction and reported the isolation, in

[4] Results obtained in this laboratory. The higher yields reported by Edkins and Linnell, [*Quart. J. Pharm. Pharmacol.*, **9**, 75 (1936)], could not be duplicated.

small amounts, of both chloroisonitrosoacetophenone and isonitrosoacetophenone. They explained the formation of these products on the basis of the following reactions,

$$RONO + HCl \longrightarrow ROH + NOCl$$

$$C_6H_5COCH_3 + NOCl \longrightarrow C_6H_5COC(:NOH)H + HCl$$

It was further indicated that any nitrous acid which might be liberated, could oxidize hydrogen chloride to "free" chlorine and this might also possibly account for the formation of the chloroisonitroso ketone (16).

Such chlorination has been successfully applied in the preparation of both phenyl- and *p*-methylphenyl-glyoxylohydroxamyl chlorides (16–18); extension of this method of synthesis is limited, however, in view of the difficulty encountered in preparing the necessary isonitrosoacetophenones themselves. Recently, Rheinboldt and Schmitz-Dumont (19) developed a process called "nitrosochlorination," which involves essentially the reaction of nitrosyl chloride with a methyl ketone,

$$RCOCH_3 \xrightarrow{NOCl} RCOC(:NOH)Cl$$

Except in the case of *tert.*-butyl methyl ketone, which formed yields of 70%, the reaction did not prove encouraging; *e.g.*, the phenyl- and *p*-tolyl- ketones gave yields of 24 and 32% respectively; the *p*-chlorophenyl ketone formed the isonitroso ketone but not the chloroisonitroso ketone.

In the present study, the nitrosation reaction was applied to phenacyl chloride and its derivatives in which the phenyl is substituted by various groups such as halogen, alkyl, alkoxyl, and hydroxyl. The yields are highly satisfactory and there is no reason to believe that the reaction is not generally applicable.

The arylglyoxylohydroxamyl chlorides dissolve in concentrated sulfuric acid with the formation of a yellow color. Heating with dilute sulfuric acid causes degradation to the corresponding benzoic acid. In cold, dilute aqueous sodium hydroxide, they dissolve slowly, forming a yellow solution; heating causes decomposition with the formation of the benzoic acid. With hydroxylamine, the arylglyoxylohydroxamyl chlorides may be converted to chloroglyoximes, $ArC(:NOH)C(:NOH)Cl$, and with aniline they form characteristic anilides of the general formula, $ArCOC(:NOH)NHC_6H_5$. With pyridine, all of the arylglyoxylohydroxamyl chlorides form a wine-red color with simultaneous liberation of heat; the color gradually deepens and after several minutes decomposition sets in; this characteristic color test is not obtained with oximes or other oximino ketones.

The reduction of arylglyoxylohydroxamyl chlorides to arylethanolamines is of particular interest. Suffice it to say for the present, phenylglyoxylohydroxamyl chloride has been reduced to phenylethanolamine (yields quantitative except for manipulative loss), according to the equation,

$$\underset{\displaystyle \overset{\|}{NOH}}{C_6H_5COCCl} + 4H_2 \xrightarrow[HCl]{Pd} \underset{\displaystyle \overset{|}{NH_2 \cdot HCl}}{C_6H_5CHOHCH_2} + HOH$$

The first two molecules of hydrogen are taken up rapidly with the formation of a product characterized as an α-amino ketone, which on treating with aqueous ammonia gives 2,5-diphenylpyrazine; the third molecule generally is taken up more slowly, and the fourth enters with considerable difficulty. A more detailed description of this reduction procedure will be given later.

EXPERIMENTAL

Preparation of chloromethyl ketones. Phenacyl chloride and its various derivatives were prepared by either the Friedel-Crafts reaction or the Fries rearrangement from appropriate starting materials. The data are summarized in Table I.

3,4-Dihydroxyphenacyl chloride. This important intermediate has been prepared in varying yields (40–65%) by various modifications of the reaction between catechol, chloroacetic acid, and phosphorus oxychloride (20). The extensive study by Ott (20), which indicates that ketone formation is catalyzed by the presence of phosphorus oxychloride, suggested a further modification of the previously described procedures. In the course of this investigation it was found that yields of 60% of pure, colorless product may be consistently obtained by the following procedure: A mixture of 83.3 g. (0.4 mole) of phosphorus pentachloride and 42.5 g. (0.45 mole) of chloroacetic acid is allowed to react by refluxing in a boiling water-bath for three hours. The clear solution thus obtained is distilled and the portion coming over up to 115° is added to a suspension of 44.0 g. (0.4 mole) of catechol in 200 cc. of benzene (anhydrous). After refluxing on a water-bath for fifteen hours, the solvent is recovered by distillation, using slightly reduced pressure toward the end. The dark purple residue thus obtained is then dissolved in 400 cc. of boiling water; on cooling and with rapid stirring, the crude product crystallizes out. After standing overnight in the refrigerator, the precipitated material is filtered off and dried with suction; recrystallization from boiling water with the addition of 5.0 g. of Norit, gives 41.5 g. (60%) of colorless needles, decomposing at 173°.[5]

TABLE I

CHLOROMETHYL KETONES[a]

KETONE	M.P., °C	PER CENT YIELD
Phenacyl chloride	56–57	88.2
p-Methylphenacyl chloride	55–56	82
p-Phenylphenacyl chloride	124–126	84
p-Chlorophenacyl chloride	100–101	88.5
p-Methoxyphenacyl chloride	97–98	65
p-Hydroxyphenacyl chloride	147–148[b]	28.2
3,4-Dihydroxyphenacyl chloride	173[b]	60

[a] These ketones are described in Beilstein.

[b] Decomposes on heating.

Nitrosation of chloromethyl ketones. The general procedure adopted for the preparation of arylglyoxylohydroxamyl chlorides is as follows: In a three-neck, round-bottom flask (of suitable size), provided with a sealed mechanical stirrer, a reflux condenser (connected to a gas-absorption trap), a delivery tube for hydrogen chloride, and a small dropping-funnel, is placed the chloromethyl ketone and ether (U.S.P.). The stirrer is set in motion, and after (complete or partial) solution of the ketone, anhydrous hydrogen chloride is intro-

[5] All melting points reported were taken with an Anschütz thermometer (entire stem immersed in bath).

duced into the reaction mixture at the rate of 2–3 bubbles per second, stirring and addition of hydrogen chloride being continued throughout the reaction. Then freshly-distilled alkyl nitrite (in slight molecular excess) is added from the dropping-funnel, in 0.5–1.0-cc. portions. After addition of the first portion, the reaction mixture becomes an orange-brown and after several minutes, light yellow in color; after this, a second portion of nitrite is added and a similar color change takes place, whereupon a third portion is added. The reaction mixture gradually warms up and the ether begins to reflux gently. After all of the nitrite is added (about thirty to forty minutes are usually required), stirring and addition of hydrogen chloride are continued for another fifteen minutes, after which the reaction mixture is allowed to stand for one to two hours, or overnight if more convenient. The reflux condenser is then inverted, stirring is resumed, and the solvent recovered by distillation from a bath maintained at 60–80°. When practically all of the solvent is removed, distillation is continued using slightly reduced pressure, until no further appearance of crystals is noted. The residue is then allowed to stand until dry in a vacuum desiccator over concentrated sulfuric acid, soda-lime, and anhydrous calcium chloride. The crude product is recrystallized from a suitable solvent.

This procedure may be employed for the nitrosation of the various ketones. Where the chloromethyl ketone is not readily soluble in ether, suspensions of the material nitrosate equally well; solution gradually takes place during the course of reaction since the products are, in general, more soluble than the ketones from which they are prepared. Any alkyl nitrite may be employed as nitrosating agent; in this reaction, isopropyl nitrite is preferred because it is a liquid, may be conveniently handled and moreover, the alcohol which it forms boils relatively low and hence may be removed with comparative ease.

Oximation. The chloroglyoximes are prepared by treating 0.02 mole of the arylglyoxylohydroxamyl chloride in 25 cc. of alcohol with a solution of 0.04 mole of hydroxylamine hydrochloride dissolved in 25 cc. of water. Sufficient alcohol is then added, drop by drop, until a clear solution results. After allowing the reaction mixture to stand for three to four days, crystals begin to precipitate out; after two weeks, the product is filtered off and dried with suction. The glyoximes prepared in this investigation are colorless, crystalline compounds, melting with decomposition.

Phenylglyoxylohydroxamyl chloride. Nitrosation of phenacyl chloride, 15.5 g. (0.1 mole), using 12.6 cc. (0.11 mole) of butyl nitrite in 100 cc. of ether, gives 15.7 g. (85.6%) of phenylglyoxylohydroxamyl chloride, after recrystallization from boiling carbon tetrachloride, m.p. 130–133°. A second recrystallization gives long, glistening colorless needles, m.p. 132–133°.

The chloroglyoxime, after recrystallization from hot isoamyl alcohol, decomposes at 186–187° (19).

p-*Methylphenylglyoxylohydroxamyl chloride.* From 50.6 g. (0.3 mole) of *p*-methylphenacyl chloride, 36.7 cc. (0.32 mole) of butyl nitrite in 200 cc. of ether, there is obtained, after recrystallization from hot carbon tetrachloride, 44.0 g. (74.2%) of chloroisonitroso ketone, m.p. 119–126°; a second recrystallization forms long, colorless needles, m.p. 126–128°.

Anal. Calc'd for $C_9H_8ClNO_2$: N, 7.10. Found: N, 6.88.

p-Tolyl chloroglyoxime, recrystallized from hot isoamyl alcohol, decomposes at 185–186°.

Anal. Calc'd for $C_9H_9ClN_2O_2$: N, 13.17. Found: N, 12.7.

p-*Xenylglyoxylohydroxamyl chloride.* *p*-Phenylphenacyl chloride is nitrosated by treating a rapidly-stirred suspension of 23.1 g. (0.1 mole) of ketone in 300 cc. of ether with 11.6 cc. (0.11 mole) of isopropyl nitrite. As reaction proceeds, the ketone gradually goes into solution, and after approximately three-fourths of the required nitrite is added, a homogeneous solution results. Recrystallization of the crude product from boiling benzene gives 21.2 g. (81.6%) of pale yellow crystals of *p*-xenylglyoxylohydroxamyl chloride, which forms a red melt at 157–158°.

Anal. Calc'd for $C_{14}H_{10}ClNO_2$: N, 5.4. Found: N, 5.32.

p-Xenyl chloroglyoxime, prepared in the usual manner, is recrystallized from hot butyl alcohol; dec. 177°.

Anal. Calc'd for $C_{14}H_{11}ClN_2O_2$: N, 10.2. Found: N, 10.08.

p-*Chlorophenylglyoxylohydroxamyl chloride.* From 19.0 g. (0.1 mole) of *p*-chlorophenacyl chloride, 11.6 cc. (0.11 mole) of isopropyl nitrite, and 200 cc. of ether, pale yellow crystals of crude product are obtained, which after recrystallization from boiling carbon tetrachloride gives 16.7 g. (76.6%) of colorless, glistening needles, m.p. 120–121°. *p*-Chlorophenylglyoxylohydroxamyl chloride is soluble in cold alcohol and ether; in benzene and toluene, on heating, but insoluble in petroleum benzine and ligroin.

Anal. Calc'd for $C_8H_5Cl_2NO_2$: N, 6.42. Found: N, 6.3.

The chloroglyoxime forms colorless platelets from hot glacial acetic acid; dec. 181–182°.

Anal. Calc'd for $C_8H_6Cl_2N_2O_2$: N, 12.01. Found: N, 12.14.

p-*Methoxyphenylglyoxylohydroxamyl chloride.* When nitrosation is applied to *p*-methoxyphenacyl chloride, the characteristic color changes are not observed, and reaction does not appear to occur. It was found that the addition of a few drops of water is necessary to initiate nitrosation; thereafter reaction proceeds as usual. The yield of *p*-methoxyphenylglyoxylohydroxamyl chloride obtained from 9.2 g. (0.05 mole) of ketone, 5.8 cc. (0.055 mole) of isopropyl nitrite, and 100 cc. of ether (to which is added 0.2 cc. of water), is 8.8 g. (82.0%), after recrystallization from hot carbon tetrachloride. The colorless needles thus obtained melt at 137–139°, and are soluble in ether, alcohol, and ethyl acetate, but dissolve in ligroin, benzene, and carbon tetrachloride only on heating.

Anal. Calc'd for $C_9H_8ClNO_3$: N, 6.56. Found: N, 6.65.

p-*Hydroxyphenylglyoxylohydroxamyl chloride.* To a suspension of 17.1 g. (0.1 mole) of *p*-hydroxyphenacyl chloride in 250 cc. of ether is added 12.6 cc. (0.11 mole) of butyl nitrite. Recrystallization of the crude product from ether-benzin (1:3) gives 18.5 g. (95.5%) of fine, colorless crystals, decomposing at 158–159°. *p*-Hydroxyphenylglyoxylohydroxamyl chloride is characterized by a violent sternutatory action. The chloroisonitroso ketone is readily soluble in alcohol, ether, acetone, and ethyl acetate; in *n*-amyl acetate on heating, but is insoluble in benzene, toluene, and carbon tetrachloride.

Anal. Calc'd for $C_8H_6ClNO_3$: N, 7.02. Found: N, 7.01.

Oximation by the general procedure gives colorless crystals of *p*-hydroxyphenyl chloroglyoxime, which, after recrystallization from a mixture of dioxane and heptane, decomposes at 183–184°.

Anal. Calc'd for $C_8H_7ClN_2O_3$: N, 13.52. Found: N, 13.33.

3,4-*Dihydroxyphenylglyoxylohydroxamyl chloride.* Eighteen and seven-tenths grams (0.1 mole) of the dihydroxyphenacyl chloride suspended in 400 cc. of ether (to which is added 3 cc. of water) is treated with 12.6 cc. (0.11 mole) of butyl nitrite according to the general nitrosation procedure. The reaction mixture darkens gradually as the nitrite is added; complete solution of the ketone occurs after approximately one-half of the required nitrite is added. The reaction mixture is then concentrated to one-half its volume by distillation from a water-bath and 200 cc. of benzene is added to precipitate the chloroisonitroso ketone. The yield of yellow crystals obtained is 17.8 g. (82.4%); dec. 184–185°.

Anal. Calc'd for $C_8H_6ClNO_4$: N, 6.47. Found: N, 6.38.

Isolation of the chloroglyoxime, when the general procedure is employed, proved difficult.

Alkaline decomposition of the arylglyoxylohydroxamyl chlorides. Decomposition of the arylglyoxylohydroxamyl chlorides, by refluxing with aqueous alkali, gives excellent yields of the corresponding benzoic acids, varying from 80–99%; attempts to prepare protocatechuic acid by the decomposition of the glyoxylohydroxamyl chloride, however, proved difficult, due to the ease of oxidation of the acid and also its extremely high solubility in water.

Arylglyoxylohydroximic acid anilides. The general procedure employed for the preparation of these anilides, is essentially that of Rheinboldt and Schmitz-Dumont (19). To 0.03 mole of arylglyoxylohydroxamyl chloride dissolved in 100 cc. of anhydrous ether is added 0.06 mole of freshly-distilled aniline. The flask is securely stoppered and allowed to stand at room temperature, with occasional shaking, for four days. The precipitated aniline hydrochloride is filtered off with suction and the filtrate evaporated to dryness in

a vacuum desiccator. Recrystallization from an appropriate solvent gives a pure product. The anilides obtained from *p*-hydroxy- and 3,4-dihydroxyphenyl-glyoxylohydroxamyl chlorides are insoluble in ether; these are freed of the precipitated aniline hydrochloride by washing with cold water.

Arylglyoxylohydroximic acid anilides melt with decomposition; with concentrated sulfuric acid, cold, they decompose, with the formation of a dark purple color. On heating with dilute aqueous alkali, the anilides yield isocyanides, recognized by the characteristic odor; a similar observation is made in attempts to recrystallize these from the higher-boiling solvents, *viz.* xylene, amyl acetate, etc. A summary of the various arylglyoxylo-hydroximic acid anilides is presented in Table II.

TABLE II

ARYLGLYOXYLOHYDROXIMIC ACID ANILIDES

Ar=	M.P. (DEC) °C.	RECRYSTALLIZED FROM	CRYSTALLINE FORM	FORMULA	ANAL., N	
					Calc'd	Found
C_6H_5— [a]	145-146	Toluene	Yellow flakes	$C_{14}H_{12}N_2O_2$		
p-$CH_3C_6H_4$—	163-164	Isopropyl alcohol	Fine, colorless needles	$C_{15}H_{14}N_2O_2$	11.02	11.00
p-$C_6H_5C_6H_4$— [b]	135-136	Isopropyl alcohol	Yellowish-brown flakes	$C_{20}H_{16}N_2O_2$		
p-ClC_6H_4—	145-146	Isopropyl alcohol	Large, yellow flakes	$C_{14}H_{11}ClN_2O_2$	10.2	10.01
p-$CH_3OC_6H_4$—	148-150	Dilute alcohol (50%)	Fine, pale yellow needles	$C_{15}H_{14}N_2O_3$	10.4	10.22
p-HOC_6H_4—	164-165	Dilute alcohol (50%)	Fine, pale yellow needles	$C_{14}H_{12}N_2O_3$	10.9	11.10
3, 4-$(HO)_2C_6H_3$—	155[c]	Acetone-toluene (1:3)	Small, yellow needles	$C_{14}H_{12}N_2O_4$	10.26	10.0

[a] Previously described by Rheinboldt and Schmitz-Dumont (19).

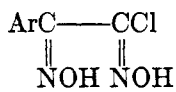
[b] Not pure for analysis

[c] Darkens at this temperature.

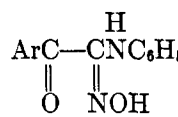
SUMMARY

1. A general method is described for the preparation, in good yields, of aryl-glyoxylohydroxamyl chlorides by the nitrosation of chloromethyl ketones.

2. These products may be converted into glyoximes of the general structure,



3. Arylglyoxylohydroxamyl chlorides show properties of acid chlorides, *e.g.*, they react with amines; with aniline, they form characteristic anilides of the type,



4. Preliminary studies indicate that arylglyoxylohydroxamyl chlorides are of value as intermediates, by catalytic hydrogenation, for the synthesis of phenyl-ethanolamine and its phenyl substituted derivatives.

BALTIMORE, MD.

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

CONSTITUENTS OF PYRETHRUM FLOWERS. XV. PRESENCE OF THE CUMULATED SYSTEM IN THE PYRETHROLONE SIDE CHAIN

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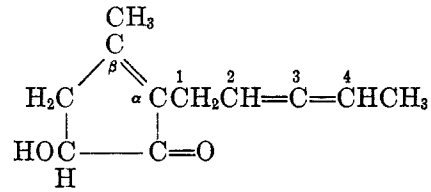
Received June 12, 1942

The original structures of the two pyrethrins proposed by Staudinger and Ruzicka (1) have since been confirmed by subsequent researches, with the exception of one minor feature. Pyrethrolone, the alcoholic-ketonic component common to both pyrethrins, was found to contain a third double bond located in the alpha,beta-position in the nucleus in addition to the two double bonds in the five-membered side chain (2).



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According to the original formula this side chain consisted of a 2,3-pentadienyl group. The evidence was furnished by the isolation of malonic acid from the oxidation products of pyrethrolone, and the production of acetaldehyde on ozonization (3). The last-mentioned result locates with certainty one of the double bonds in position 3, and proves the presence of a terminal methyl group. Many unsuccessful attempts to obtain further direct proof of the arrangement of the double bonds in the pyrethrolone side chain were subsequently made in this Bureau.

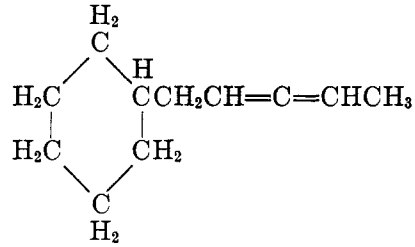
Since the cumulated system had never been encountered in nature, additional confirmation of its existence in pyrethrolone seemed necessary. A natural alternative supposition was that the conjugated system so common in nature might be present (4). However, very convincing indirect evidence against this theory and in support of the cumulated system has been obtained.

With one double bond definitely located in position 3, the absence of the other one in position 1 (*i.e.*, the exclusion of a conjugated system) would be positive evidence for the existence of the cumulated arrangement, since only position 2 would then remain.

Pyrethrolone and its desoxy derivative, pyrethrone, do not react with maleic anhydride or *alpha*-naphthoquinone, and they do not add hydrogen on treatment with aluminum amalgam, by which method pyrethrone was prepared from pyrethrolone (5). In indifferent solvent, pyrethrolone and pyrethrone readily add 1 mole of bromine, and the dibromo derivatives are reconverted into the original compounds by zinc reduction (5, 6). A 1,4-addition of halogen had therefore not occurred, as would have been likely were the conjugated system

present, for the zinc reduction of dibromopyrethrone would then have furnished jasmone (4) having only one double bond, located in position 2. When pyrethrone was treated with bromine in an alcoholic solvent, the main product was an alkoxybromo addition compound formed together with some of the dibromo derivative. Both products furnished the original pyrethrone on zinc reduction (5, 6).

In order to compare these halogen addition reactions with an authentic 2,3-pentadienyl derivative, 1-cyclohexyl-2,3-pentadiene (formula II) was prepared (6) and examined with respect to its behavior toward bromine in the two types of solvents (7).



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The results of the halogen addition and of the subsequent reduction were found to be parallel to those obtained with pyrethrone.

Finally, the absorption spectrum of pyrethrone was compared with that of 1-cyclohexyl-2,3-pentadiene, with the following results:[1] Pyrethrone showed the typical absorption of an *alpha,beta*-unsaturated ketone ($\lambda_{max.}$ 235 mμ log ϵ = 4.2). The position of the maximum excludes a formula in which a conjugated system of double bonds in the side chain is in conjugation with the keto group and a double bond of the ring system. If such were the case, pyrethrone should possess a maximum of absorption considerably above 240 mμ. The presence of a cumulated system in the side chain, on the other hand, has little, if any, effect on the absorption of the *alpha,beta*-unsaturated ketone. The 1-cyclohexyl-2,3-pentadiene, for example, was found to possess practically no absorption above 250 mμ and only slight general absorption below. The absorption results thus exclude the possibility of a double bond in position 1, while the formation of acetaldehyde on ozonization fixes one double bond in position 3, at the same time excluding position 4 and leaving only position 2 as the location of the remaining double bond.

The presence of a three-membered ring is excluded as an unlikely possibility because this group does not easily hydrogenate, nor does it readily add bromine.

Formula I may therefore be accepted as representing the correct structure of pyrethrolone.

BELTSVILLE, MD.

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[1] Our appreciation is expressed to F. Hirschmann, for making the spectrographic observations while at Yale University, August, 1939.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

FURTHER ACYLATION EXPERIMENTS WITH SULFANILAMIDE AND HETEROCYCLIC AMINES

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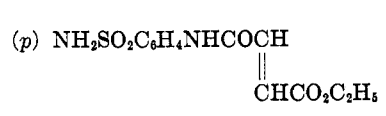
PART II

In a previous communication (1) some rules were suggested for the condensation of aromatic amines with dicarboxylic acid anhydrides. It was found that heterocyclic amines in general behave like their isocyclic analogs, with the exception that maleic anhydride failed to give imide derivatives, which are formed with such extreme ease with succinic or phthalic anhydrides. This exception was especially surprising in the sulfanilamide series, where it was observed that citraconic anhydride yielded as the only reaction product the cyclic imide (2). It seemed worth while to investigate further the peculiar position of maleic anhydride.

It was first suspected that the compounds of the series RNHCOCH=CH-COOH derived from maleic anhydride might possess trans structure. It is admitted that cis-trans isomerization has never been observed under the influence of a sulfonamido group. On the other hand, it is known (3) that pyridine is an excellent catalyst for this transformation, so that a similar effect of the tertiary nitrogen in sulfapyridine or 6-methoxy-8-aminoquinoline (1) was not *a priori* to be excluded. However, condensation of fumaroyl chloride ethyl ester with sulfanilamide yielded a substance (I) entirely different from the esterification product of maleamidosulfanilamide. Moreover, in the latter reaction a small amount of the imide II was formed. Again, the same series of reactions with 6-methoxy-8-aminoquinoline revealed the essential difference between the cis and trans forms of III. On the other hand, we now find that citraconic anhydride behaves as predicted, in that the amide acids IV and VI are formed at room temperature and at 50°, and are cyclized to the corresponding imides V and VII at about 100° and 80° respectively. In previous experiments (2) recrystallization from boiling water was sufficient to effect the cyclization of IV.



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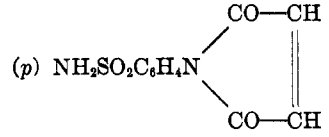

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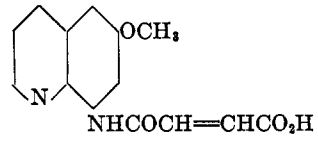
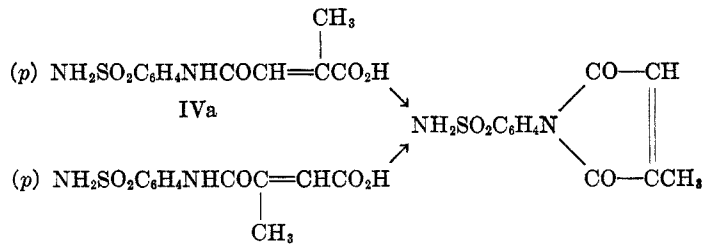
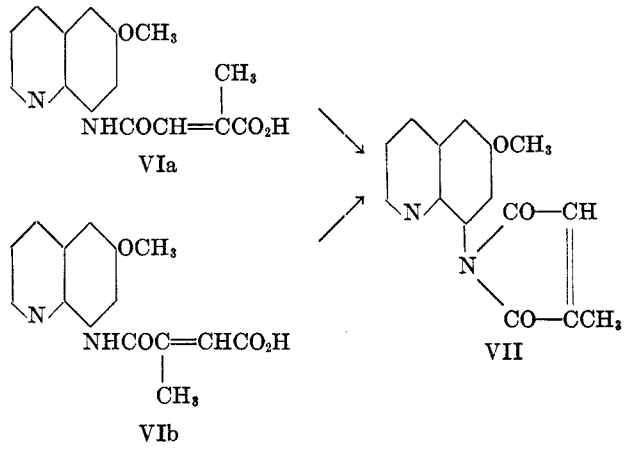


III



The different behavior of maleic and citraconic anhydrides probably must be ascribed to the influence of the methyl substituent. It has been found by Ashton (4) that the ratio of the two dissociation constants is, respectively, for maleic acid $\frac{K_1}{K_2} = \frac{1}{6.2 \times 10^{-5}}$ and for citraconic acid $\frac{K_1}{K_2} \times \frac{1}{1.3 \times 10^{-4}}$ for 0.01 molar solutions. It can be concluded that the larger difference in acidity between the two carboxyl groups of maleic acid causes their different ability to condense with amino groups. We feel, however, that this explanation is unsatisfactory, and shall attack the problem by physical methods.



In view of the low toxicity of the sodium salt of N^4-sulfanilamidomaleic acid, it was of interest to determine the corresponding figure for the trans isomer. Both derivatives show about the same toxicity in white mice: Lethal dose of the cis form, 4.5 g./kg.; lethal dose of the trans form, 4.0 g./kg.

EXPERIMENTAL

Ethyl N^4-sulfanilamidomaleate. Condensation between sulfanilamide (17.2 g.) and maleic anhydride (11 g.) (5) was easily effected in acetone (150 cc.). The solution turned immediately yellow and became warm. The maleamidosulfanilamide crystallized soon in quantitative yield; m.p. 209–210°. Esterification of this compound (13.5 g.) was carried out in boiling absolute ethanol (100 cc.) with 2 cc. of sulfuric acid. In the course of one hour the amide acid went completely into solution. After twelve hours standing, a small amount of white crystals settled down (II). These, when recrystallized from butanol-

pyridine, formed colorless prismatic rods, without a definite melting point. After sintering at 220°, the substance remained semi-solid to about 285°, when it decomposed.

Anal. Calc'd for $C_{10}H_8N_2O_4S$: C, 47.6; H, 3.2; N, 11.1.
Found: C, 47.5; H, 2.8; N, 11.2.

The filtrate of II was concentrated on a steam-bath and the ester precipitated by addition of water. From butanol, yellowish leaflets, m.p. 204–205° (cis form of I).

Anal. Calc'd for $C_{12}H_{14}N_2O_5S$: C, 48.3; H, 4.7; N, 9.4.
Found: C, 48.6; H, 4.9; N, 9.5.

Condensation of sulfanilamide with maleic anhydride in boiling dioxane or xylene likewise yielded the amide acid of m.p. 209°. Melting of the two components at 150–160° gave a yellow powder, which was soluble only in pyridine and could not be recrystallized.

Ethyl N^4-sulfanilamidofumarate. To a solution of fumaroyl chloride ethyl ester (4 g.) in acetone (15 cc.) was added dropwise a solution of sulfanilamide (4.5 g.) in acetone (25 cc.) and pyridine (2 cc.). After evaporation of the solvent, the residue crystallized. Recrystallization from ethyl benzoate with a little pyridine yielded the ester (I) as a white, microcrystalline powder, m.p. 219°.

Anal. Calc'd for $C_{12}H_{14}N_2O_5S$: N, 9.4; OC_2H_5, 15.1.
Found: N, 9.2; OC_2H_5, 15.1.

The ester was saponified easily with sodium hydroxide at room temperature, and the trans acid precipitated with hydrochloric acid. It was purified by several reprecipitations, and finally by recrystallization from glacial acetic acid; m.p. 295°.

Anal. Calc'd for $C_{10}H_{10}N_2O_5S$: C, 44.4; H, 3.7; N, 10.4.
Found: C, 44.5; H, 3.7; N, 10.5.

Condensation of sulfanilamide with citraconic anhydride (IV and V). Sulfanilamide (8.6 g.) was dissolved in dioxane (40 cc.) and a solution of citraconic anhydride (5.6 g.) in dioxane (10 cc.) was added dropwise at +5°. The reaction product was filtered off after twelve hours standing. It is easily soluble in cold sodium carbonate solution, and therefore represents the acid (IV a or b); yield quantitative. After reprecipitation of the sodium salt of IV with hydrochloric acid, the acid IV shows the m.p. 175°. At the melting temperature gas is evolved (water), the product solidifies, and melts again at about 210°. Recrystallization of the acid IV from 50% acetic acid gave only the imide V as fine needles, m.p. 217–218° (2).

Anal. of acid (IV). Calc'd for $C_{11}H_{12}N_2O_5S$: C, 46.5; H, 4.2.
Found: C, 46.8; H, 4.4.

6-Methoxyquinoline-8(N-maleamido acid) ethyl ester (III, —$COOC_2H_5$ in place of —COOH). Condensation is best accomplished by dissolving 6-methoxy-8-aminoquinoline and maleic anhydride in acetone and boiling for two minutes. The mixture solidifies immediately, and the acid III (cis form) is obtained in quantitative yield; m.p. 225°.

Four grams of this amide acid in ethanol (35 cc.) was boiled with 2 cc. of concentrated hydrochloric acid for six hours. The reaction product crystallized slowly; from butanol, long yellow rods, m.p. 212° (with decomp.). This hydrochloride of the ester of III retains half a molecule of water, which cannot be removed by drying without loss of hydrogen chloride. For analysis, the substance was dried at 56°.

Anal. Calc'd for $C_{16}H_{16}N_2O_4 \cdot HCl + 0.5\ H_2O$; C, 55.7; H, 5.2; N, 8.1.
Found: C, 55.8, 55.9; H, 5.5, 5.4; N, 8.4.

The free ester-base was obtained by trituration of the above product with cold ammonia. Recrystallization was extremely difficult and could be effected only by short boiling with nitrobenzene, prolonged boiling causing decomposition; long fine needles of m.p. 177°.

Anal. Calc'd for $C_{16}H_{16}N_2O_4$: C, 64.0 H, 5.3; N, 9.3.
Found: C, 63.85; H, 5.0; N, 9.1.

6-Methoxyquinoline-8(N-fumaramido acid) ethyl ester (trans form of III, —$COOC_2H_5$ in place of —COOH). Fumaroyl chloride ethyl ester (4 g.) was dissolved in acetone (20 cc.) and added dropwise to a solution of 6-methoxy-8-aminoquinoline (4 g.) in acetone (15 cc.). Every drop produced a yellow precipitate of the hydrochloride. The product was filtered

off and recrystallized from butanol; sharp rods, m.p. 195° (decomp.), yield quantitative. During recrystallization, partial hydrolysis of the hydrochloride occurred; therefore it was necessary to add a few drops of hydrochloric acid to the recrystallization mixture.

Anal. Calc'd for $C_{16}H_{16}N_2O_4 \cdot HCl$: N, 8.3; $OCH_3 + OC_2H_5$, 22.3.
Found: N, 8.4; $OCH_3 + OC_2H_5$, 21.6.

The free ester-base was obtained by treating the above hydrochloride with ice-cold ammonia and was recrystallized from isopropanol; rods, m.p. 105°.

Anal. Calc'd for $C_{16}H_{16}N_2O_4$: C, 64.0; H, 5.3; N, 9.3; $OCH_3 + OC_2H$, 25.3.
Found: C, 64.3; H, 5.7; N, 9.4; $OCH_3 + OC_2H_5$, 25.6.

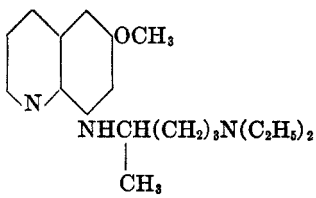
The ester-base was not saponified by sodium hydroxide at room temperature. At 100° only the free aminoquinoline was obtained.

6-Methoxyquinoline-8-citraconimide (VII). The quinoline base (1.7 g.) and citraconic anhydride (1.2 g.) were dissolved in acetone (15 cc.). A red color appeared immediately, and the mixture solidified after two minutes. After washing with ethanol, the crystals showed the m.p. 131°; yield 90%. No method other than reprecipitation was found to purify the acid VI. Even from methyl ethyl ketone, the imide VII was obtained in beautiful prisms, m.p. 179°. From 30% ethanol, there was first precipitated a mixture of VI and VII, which was converted completely into VII by longer boiling.

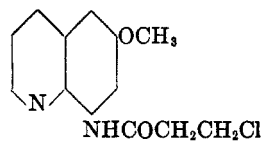
Anal. of VII. Calc'd for $C_{15}H_{12}N_2O_3$: C, 67.2; H, 4.5; N, 10.4.
Found: C, 67.1; H, 4.3; N, 9.9.

PART III

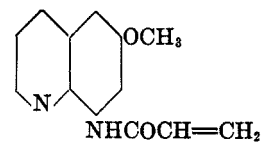
In the search for derivatives of 6-methoxy-8-aminoquinoline with antimalarial activity, it was soon found (6) that the aliphatic chain introduced into the amino group must possess a strong basic center, in order to give the substance sufficient solubility in the body fluids, and in this way plasmoquine (VIII) and its homologs were developed (7). The question arises, how far the specific structure of the side chain in (VIII) is necessary for the desired chemotherapeutic effect. We therefore attempted to replace the —$NHCH_2$— group by the —NHCO— grouping. Condensation of 6-methoxy-8-aminoquinoline with β-chloropropionyl chloride yielded the acyl amide of IX, but our attempts to exchange the β-chlorine with diethylamine invariably led to the acroyl derivative X by splitting off hydrogen chloride. When the derivative IX was heated alone in ethanol for 10 hours, it was recovered unchanged. Therefore, it is concluded that the elimination of hydrogen chloride is due to the action of diethylamine and not to the influence of the tertiary quinoline nitrogen.



VIII



IX



X

The behavior of the β-chloropropionyl compound IX is surprising, in view of the fact that ethyl β-chloropropionate easily exchanges its halogen with dialkylamines (8), and that even ethyl acrylate is transformed at 100° into ethyl β-diethylaminopropionate (9).

EXPERIMENTAL

6-Methoxy-8(β-chloropropionylamido)quinoline (IX). To a solution of 6-methoxy-8-aminoquinoline (4.4 g.) in benzene (25 cc.) was added dropwise β-chloropropionoyl chloride (3.5 g.) in benzene (10 cc.) at 0°. After twelve hours, the crystals (6.5 g.) were removed by filtration. The crude hydrochloride of IX melted at 185–190° and was converted into the free base by trituration with sodium carbonate; from 90% ethanol, needles m.p. 104°.

Anal. Calc'd for $C_{13}H_{13}ClN_2O_2$: N, 10.6. Found: N, 10.8.

6-Methoxy-8-acroylaminoquinoline (X). Five grams of IX in methanol (20 cc.) and diethylamine (4 cc.) was boiled for 3 hours. After evaporation of the solvent, the residue was shaken with ether and soda solution, and the ethereal layer dried over sodium carbonate. The base X was purified by distillation, b.p. 210° (0.4 mm.). The yellow oil was triturated with methanol and recrystallized with ethanol; prismatic rods, m.p. 119–120°.

Anal. Calc'd for $C_{13}H_{12}N_2O_2$: N, 12.3; OCH_3, 13.6.
Found: N, 12.5; OCH_3, 13.3.

The hydrochloride of X was precipitated from ethanol solution by addition of ethanolic hydrogen chloride. Recrystallization from ethanol gave prismatic plates, m.p. 208°.

When the acroyl derivative X was dissolved in chloroform and bromine added, a vigorous reaction occurred. The residue which was left after evaporation of the solvent was triturated with cold sodium hydroxide and recrystallized from butyl acetate; long, yellowish needles, m.p. 171–172°.

Anal. Calc'd for $C_{13}H_{12}Br_2N_2O_2$: C, 40.2; H, 3.1.
Found: C, 40.7; H, 2.9.

SUMMARY

1. Condensation of sulfanilamide and 6-methoxy-8-aminoquinoline with maleic or fumaric acids, respectively, gives different reaction products. The geometrical structure of the unsaturated acid remains, therefore, unaffected.

2. Citraconic anhydride, in contrast to maleic anhydride, shows a very pronounced inclination to form cyclic imides. The theoretical basis for the different behavior of the two unsaturated homologs is discussed.

3. Attempts to introduce the side chain $—COCH_2CH_2N(C_2H_5)_2$ into the amino group of 6-methoxy-8-aminoquinoline failed.

REHOVOTH, PALESTINE

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XI. THE OCCURRENCE OF OCTADECYL ALCOHOL, BATYL ALCOHOL, AND CETYL PALMITATE IN GORGONIAS[1]

C. ALBERT KIND AND WERNER BERGMANN

Received June 29, 1942

It has been shown in previous communications (1, 2) that coral-reef building animals contain significant quantities of unsaponifiable matter. The suggestion has been made (1) that this material is eventually removed from circulation by becoming embedded in the ever-growing reef, acting like a vast storehouse of compounds, which may be looked upon as potential precursors of petroleum. Gorgonias have long been recognized as contributors to the formation of reefs. The organic chemistry of these animal colonies has been the subject of a number of investigations; these have been concerned, however, almost exclusively with the iodine-containing horny stem. This part of the colony contains only small amounts of ether-acetone-soluble material. The bulk of the fatty substances is concentrated in the living, calcareous, external layers, from which they may readily be extracted by lipid solvents. As far as the authors are aware, no information concerning the composition of these lipids appears to be available at present.

In connection with systematic studies on the distribution of sterols among marine invertebrates, which are in progress in this laboratory, a quantity of non-steroid alcohols was obtained from the unsaponifiable fraction of the gorgonia, *Plexaura flexuosa*. This material had been obtained by first removing the sterols by means of digitonin, and by subsequent subdivision of the remainder into an alcoholic and non-alcoholic fraction by way of the sulfuric acid esters of the alcohols. This method of separation, which has already been shown by one of the authors (3) to give satisfactory results, is analogous to the one, first used by Natelson and Sobel (4) for the isolation of sterols from mixtures. Recently Sobel and Spoerri (5) have recommended a modified procedure as a cheap and convenient substitute for the digitonin method in the isolation and quantitative determination of sterols. The fact, however, that this sulfate method may also be used with advantage for the isolation of alcohols other than sterols, makes it obvious, that in its present form it may replace the digitonin method only in such cases where the presence of non-sterol alcohols is definitely contra-indicated. The alcohols were recovered from the sulfates by acid hydrolysis as recommended by Butenandt and Westphal (6).

The crude, sterol-free, alcoholic fraction from *Plexaura flexuosa* was a colorless, wax-like material. It was at first believed to consist principally of cetyl alcohol, as did the corresponding fraction from corals (2). Fractional distillation of the material *in vacuo*, however, showed that it contained two principal components. The first fraction, representing more than fifty per cent of the

[1]The material in this paper constitutes part of a dissertation submitted by C. A. Kind in partial fulfillment of the requirements for the Ph.D. degree, Yale University, June 1942.

material, melted at 55–56° after repeated recrystallizations. Analysis of the alcohol agreed well for $C_{18}H_{37}OH$, or octadecyl alcohol for which the m.p. 58° has been reported. The phenylurethan of the gorgonia alcohol melted at 76° or about three degrees below the melting point reported for octadecylphenylurethan. Mixtures of the corresponding alcohols and phenylurethans melted between the melting points of the respective substances. It was assumed therefore that this gorgonia alcohol was octadecyl alcohol containing small amounts of impurities. The correctness of this assumption was borne out by the fact that the *m*-dinitrobenzoate, m.p. 76.5°, of the gorgonia alcohol analyzed accurately for octadecyl *m*-dinitrobenzoate, and that treatment of the alcohol with hydriodic acid gave octadecyl iodide, m.p. 34°, which gave no depression of the melting point when mixed with an authentic sample. As far as the authors are aware, this is the first time that octadecyl alcohol has been isolated from lower marine invertebrates.

The second fraction from the fractional distillation of the gorgonia alcohols was a mixture, which will be discussed below. The residue from the distillation represented about fifteen per cent of the mixture. Treatment of the material with phenylisocyanate yielded a compound of m.p. 101–102°, which analyzed satisfactorily for the bis-phenylurethan of an alcohol of the formula $C_{21}H_{44}O_3$. The data agree well with those reported for the bis-phenylurethan of batyl alcohol, m.p. 101–102° (7), and a mixture of the two compounds showed no depression of the melting point. Hydrolysis of the bis-phenylurethan of the dihydric gorgonia alcohol gave batyl alcohol, $HOCH_2CHOHCH_2O(CH_2)_{17}CH_3$, m.p. 68–69°, which like the batyl alcohol from fish oils (8) and bone marrow (7) showed a small positive rotation of $(\alpha)_D^{25} + 1.4°$. The identity of the dihydric gorgonia alcohol with batyl alcohol was finally established by the conversion of the former into octadecyl iodide, m.p. 34°, which gave no depression of the melting point when mixed with an authentic sample. As far as the authors are aware this is the first time that the presence of batyl alcohol in lower marine invertebrates has been definitely established.

The second, or middle fraction, from the distillation melted at 64°, and gave a phenylurethan of m.p. 95–96°. The physical properties and analytical data of this fraction and its derivatives indicated that it was a mixture of batyl alcohol and some octadecyl alcohol. In this connection it is of interest to note that Drummond and Baker (9) have reported the melting point 64° for a sample of batyl alcohol isolated from a mixture containing octadecyl alcohol. These authors have emphasized the difficulties encountered in separating such a mixture.

Quite different results were obtained with the gorgonia, *Xiphogorgia* sp. The calcareous layers of this colony are rather thin, and their separation from the stem is difficult. The entire material was therefore extracted with acetone.[2] Treatment of the acetone extract with alcohol led to the separation of a greenish wax, which after purification melted at 50–50.5°. It was identified as cetyl palmitate by direct comparison and by its hydrolysis to cetyl alcohol and palmitic

[2]The authors express their gratitude to Merck and Co. for the extraction of the material.

acid. The sterol-free, alcoholic fraction of the unsaponifiable matter of this gorgonia, prepared as described above, consisted almost entirely of cetyl alcohol. The results obtained with *Xiphogorgia* are therefore quite analogous to those obtained with corals (2).

EXPERIMENTAL

All melting points are corrected.

Preparation and fractionation of the non-sterol alcohols from Plexaura flexuosa. Twenty-five grams of sterol-free unsaponifiable matter was dissolved in 150 cc. of chloroform and 75 cc. of pyridine. The solution was cooled in an ice-bath, and a solution of 7.5 cc. of chlorosulfonic acid in 50 cc. of chloroform was added dropwise under vigorous stirring. The mixture was left standing at room temperature overnight and then refluxed for two hours on the steam-bath. Most of the chloroform was then distilled off, and ether was added to the remainder. The suspension was then shaken vigorously with 150 cc. of 2 *N* sodium carbonate solution until the sodium salts of the sulfuric acid esters had largely separated. Concentrated sodium chloride solution was then added, and the ether layer separated, a process which was greatly facilitated by centrifugation. The salts were filtered, dried *in vacuo*, and exhaustively extracted with ether. They were then refluxed for six hours with 200 cc. of ethanol and 100 cc. of 5 *N* sulfuric acid. The alcohols, which separated as an oily layer on the surface of the liquid, solidified at room temperature. They were extracted with ether, and the ether extract was washed, dried, and evaporated to dryness. The crude alcohols (12 g.) were then transferred into a small distilling flask with a built-in Widmer column and subjected to fractional distillation at about 0.5 mm. The first fraction, A, came over at a distilling temperature of 100–105° and a bath temperature of 152–155°, and the second fraction, B, at 135–140° and 180–185° respectively. The distillation was then interrupted and the residue, fraction C, removed from the flask.

Isolation of octadecyl alcohol. Fraction A, (7 g.) came over as an almost colorless oil which solidified at room temperature. After repeated recrystallizations from acetone it melted at 56–57°; the mixed melting point with octadecyl alcohol of m.p. 58° was 56–58°.

Anal. Calc'd for $C_{18}H_{38}O$: C, 79.92; H, 14.16.
Found: C, 79.94; H, 13.88.

Octadecylphenylurethan. The alcohol was refluxed for three hours with a solution of phenylisocyanate in benzene. The solution was then evaporated to complete dryness *in vacuo* at 100°, and the residue recrystallized from benzene and methanol; m.p. 76°. The mixed melting point with octadecylphenylurethan of m.p. 78–79° was 77–78°.

Anal. Calc'd for $C_{25}H_{43}NO_2$: N, 3.60. Found: N, 3.70.

Octadecyl m-*dinitrobenzoate.* The alcohol was treated with *m*-dinitrobenzoyl chloride in dry pyridine. The crude, reddish product was dissolved in low-boiling petroleum ether and decolorized with Norit. After several recrystallizations from petroleum ether the compound was obtained in the form of small, colorless needles, m.p. 76.5°. The *m*-dinitrobenzoate of authentic octadecyl alcohol was prepared in an analogous manner. It melted at 77.5°, and a mixture of the two compounds melted at 76–77°.

Anal. Calc'd for $C_{25}H_{40}N_2O_6$: C, 64.63; H, 8.68.
Found: C, 64.53; H, 8.68.

Octadecyl iodide. Five hundred milligrams of the alcohol, 20 mg. of red phosphorus, and 25 mg. of freshly sublimed iodine were heated for four hours at 145–150°. After cooling, the mixture was treated with ether, and the ether extract washed successively with water, 5% sodium hydroxide solution, and water, dried, and evaporated to dryness. The residue was recrystallized several times from an acetone-ethanol mixture, m.p. 33–33.5°. The mixed melting point with an authentic sample of octadecyl iodide of m.p. 34° was 33–34°.

Batyl-bis-phenylurethan. Fraction C was treated with phenylisocyanate in the manner described above, and the reaction product was recrystallized several times from methanol;

m.p. 100.5–101°. The mixed melting point with an authentic sample of batyl-bis-phenylurethan[3] of m.p. 100–101° was 100–101°.

Anal. Calc'd for $C_{35}H_{54}N_2O_5$: C, 72.16; H, 9.28.
Found: C, 72.10; H, 9.53.

Batyl alcohol. The alcohol was prepared by refluxing the bis-phenylurethan for six hours with 5% sodium hydroxide in methanol. After several recrystallizations from dilute acetone it melted at 68–69°. The mixed melting point with an authentic sample of batyl alcohol[3] of m.p. 70° was 68–70°. $(\alpha)_D^{25}$ +1.4° (45.1 mg. in 3.0 cc. of chloroform).

Anal. Calc'd for $C_{21}H_{44}O_3$: C, 73.25; H, 12.79.
Found: C, 73.01; H, 12.69.

Octadecyl iodide. The alcohol was refluxed for 150 minutes with hydriodic acid, spec. gr. 1.7, and the iodide was isolated according to Heilbron and Owens (10); m.p. 33–34°. The mixed melting point with octadecyl iodide of m.p. 34° was 33–34°.

Anal. Calc'd for $C_{18}H_{37}I$: C, 56.83; H, 9.80.
Found: C, 56.86; H, 9.72.

Fraction B. After four recrystallizations from acetone, fraction B gave 0.8 g. of a colorless, crystalline substance of m.p. 62–64°. (Calc'd for $C_{21}H_{44}O_3$: C, 73.25; H, 12.79; Found: C, 74.39; H, 13.19.) The phenylurethan of the substance melted at 95–96°. (Calc'd for $C_{35}H_{54}N_2O_5$: C, 72.16; H, 9.28; Found: C, 71.70; H, 9.49.) It appears therefore that this fraction is a mixture of batyl and octadecyl alcohols and probably some other constituents.

Isolation of cetyl palmitate from Xiphogorgia *sp.* The acetone extract of *Xiphogorgia* sp. was diluted with twice its volume of warm ethanol, and the undissolved material was filtered. It represented a greenish wax, which was subjected to repeated treatments with Norit in acetone. A colorless material of m.p. 50–51° was eventually obtained, which gave no depression of the melting point when mixed with an authentic sample of cetyl palmitate. The compound was identified as cetyl palmitate by its hydrolysis to cetyl alcohol, m.p. 49°, and palmitic acid, m.p. 62.5° (2).

SUMMARY

Octadecyl alcohol and batyl alcohol have been isolated from the unsaponifiable material of the gorgonia, *Plexaura flexuosa*. Cetyl palmitate has been isolated from the acetone extract of the gorgonia, *Xiphogorgia* sp.

NEW HAVEN, CONN.

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[3] The authors are indebted to Drs. H. N. Holmes and N. Kornblum for a sample of this compound.

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XII. THE OXIDATION OF PORIFERASTEROL[1]

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As has been shown in a previous communication (1), the sterol mixture obtained from the marine sponges *Cliona celata* and *Spheciospongia vesparia* contains two principal components, the mono-unsaturated clionasterol, $C_{29}H_{50}O$, and the di-unsaturated poriferasterol, $C_{29}H_{48}O$. It has also been shown (2) that the two sterols are closely related to each other, since they both give the same poriferastanol upon catalytic hydrogenation. The poriferasterol may be separated from the sterol mixture by way of its difficultly soluble acetate tetrabromide. Partial debromination of this tetrabromide by the method of Fernholz and Stavely (3) gives poriferasteryl acetate dibromide. Since this behavior is quite analogous to that of stigmasteryl acetate tetrabromide, it was assumed that poriferasterol possesses one double bond in the ring system, and another in the side chain. The correctness of this assumption has now been established by the oxidation and ozonization of poriferasterol.

Like clionasterol (2), poriferasterol has a nuclear bond in the 5,6-position. This was first established by the oxidation of poriferasterol with aluminum isopropoxide and cyclohexanone. During the oxidation the usual shift of the double bond to the 3,4-position takes place to give poriferastenone, $(\alpha)_D^{25} + 57°$, which shows the typical absorption spectrum an α,β-unsaturated ketone. The ketone was characterized by its 2,4-dinitrophenylhydrazone, m.p. 232–234°, and its semicarbazone, m.p. 229–230°.

Because of the similarity of the behavior of the stigmasteryl and poriferasteryl acetate tetrabromide it was first assumed that the side chain double bond of poriferasterol occupied the 22,23-position.[2] Doubts as to the correctness of this assumption, however, were raised, when it was found that preliminary ozonization experiments with poriferasterol failed to give an aldehyde identifiable as a semicarbazone. Further investigations along this line have now demonstrated the correctness of the original assumption. Ozonization of poriferasteryl acetate 5,6-dibromide according to the directions of Fernholz and Stavely (4) gave an acid, which after debromination and hydrolysis yielded 3(β)-hydroxy-5,6-bisnorcholenic acid, m.p. 291–292°. The acid was identified by its physical properties and analysis, its methyl ester, m.p. 140°, and methyl ester acetate 137.5°, and by comparison with authentic material.

This observation proves what so far has been only an assumption, namely, that the sponge sterols are true sterols. It also proves definitely the presence

[1]The material in this paper constitutes part of a dissertation submitted by A. M. Lyon in partial fulfillment of the requirements for the Ph.D. degree, Yale University, June 1942.

[2]In a previous communication (1) this position has been erroneously called the 21,22-position.

of the hydroxyl group in the 3(β)-position, and the presence of a double bond in the 5,6-position. Since poriferasterol differs from clionasterol only by the presence of a double bond in the 22,23-position, the latter must be regarded as 22,23-dihydroporiferasterol. The results also demonstrate that poriferasterol differs from the isomeric stigmasterol only in the arrangement of the terminal seven carbon atoms of the side chain. All attempts to elucidate the structure of this final group have so far met with little success. Ozonization of poriferasterol yielded a volatile substance which gave fuchsin-aldehyde reaction. The fragment, however, was more water-soluble than the aldehydes obtained by the ozonolysis of stigmasterol and ergosterol, and it failed to give an insoluble semicarbazone. The volatile compound reacts readily with 2,4-dinitrophenylhydrazine to give a hydrazone, m.p. 113°, $(\alpha)_D^{25}$ 0°, which analyzed satisfactorily for a derivative of $C_7H_{14}O$. This derivative therefore represents the final seven carbon atoms of the side chain. Decomposition of the 2,4-dinitrophenylhydrazone with oxalic acid regenerated the volatile product, which again failed to give an insoluble semicarbazone, but reacted readily with 2,4-dinitrophenylhydrazine. Lack of material has made necessary a temporary abandonment of the study of this fragment.

In this connection it is of interest to note that Mazur (5) obtained upon ozonization of the spongilla sterol an aldehyde, $C_7H_{14}O$, which was identified as its 2,4-dinitrophenylhydrazone of m.p. 109°. It appears likely that this compound is identical with the corresponding substance obtained from poriferasterol, but it seems at present unlikely that it is identical with the 2,4-dinitrophenylhydrazone of ethylisopropylacetaldehyde. Since the data for the spongilla sterol lie between those of clionasterol and poriferasterol, and since a separation of a possible mixture by way of the acetate bromides had not been carried out, it appears likely that the spongilla sterol is a mixture of clionasterol and poriferasterol. Ozonization of such a mixture would lead to the formation of the fragment $C_7H_{14}O$, characterized by its 2,4-dinitrophenylhydrazone of m.p. 113°.

EXPERIMENTAL[3]

All melting points are corrected.

Poriferastenone. One gram of poriferasterol and 1 g. of aluminum isopropoxide were dissolved in a mixture of 35 cc. of dry toluene and 10 cc. of cyclohexanone, and the solution was refluxed for four hours. The ketone was then isolated as previously described (2). The crude ketone was dissolved in alcohol and treated with 10 cc. of a 1% digitonin solution to remove a small amount of unreacted sterol. The filtrate from the digitonide was evaporated to dryness *in vacuo* and the residue extracted with petroleum ether. The extract was taken to dryness, and the residue recrystallized several times from acetone; m.p. 111–112.5°; $(\alpha)_D^{25}$ + 56.7°; maximum of absorption in the ultraviolet 240 mμ.

Anal. Calc'd for $C_{29}H_{46}O$: C, 84.81; H, 11.30.
Found: C, 84.89; H, 11.62.

Poriferastenone 2,4-dinitrophenylhydrazone. It was prepared by refluxing equal parts of the ketone and 2,4-dinitrophenylhydrazine for several minutes in alcohol and adding a

[3]The authors are greatly indebted to Merck and Co., Rahway, N. J. for the preparation of the sponge sterols, and for a grant in aid of the investigation.

drop of conc'd hydrochloric acid. The hydrazone, which separated immediately, was recrystallized first from chloroform-ethanol and then twice from ethanol; m.p. 231.8–234.5°.

Anal. Calc'd for $C_{35}H_{50}N_4O_4$: C, 71.17; H, 8.53; N, 9.48.
Found: C, 71.17; H, 8.54; N, 9.53.

Poriferastenone semicarbazone. This derivative was prepared in the usual manner and recrystallized from alcohol; m.p. 229–230°.

Anal. Calc'd for $C_{30}H_{49}N_3O$: C, 77.03; H, 10.56.
Found: C, 76.89; H, 10.66.

3(β)-*Hydroxybisnorcholenic acid.* Poriferasteryl acetate was dissolved in chloroform, and sufficient bromine in chloroform was added to satisfy one double bond. After more than twice the theoretical amount of ozone had passed through the solution, which was cooled by an ice-bath, it was evaporated *in vacuo* below 35°, and the residue debrominated with zinc and glacial acetic acid. Water was then added, the mixture extracted with ether, and the extract washed with water and an excess of 2 *N* sodium hydroxide. The precipitate which formed on the interphase was washed with 2 *N* sodium hydroxide and ether. The salt was then decomposed with 6 *N* sulfuric acid, and the acid extracted with ether. The ether was evaporated and the residue refluxed with a 5% solution of potassium hydroxide in methanol. Water and 2 *N* sulfuric acid were then added and the mixture extracted with a large amount of ether. The ether residue was first recrystallized from ether in a thimble and then from glacial acetic acid, m.p. (decomp.) 291–292°. The mixed melting point with an authentic sample of 3(β)-hydroxybisnorcholenic acid showed no depression.

Anal. Calc'd for $C_{22}H_{34}O_3$: C, 76.23; H, 9.91.
Found: C, 75.76; H, 9.81.

3(β)-*Hydroxybisnorcholenic acid methyl ester.* The methyl ester was prepared from the acid with diazomethane and recrystallized from aqueous methanol, m.p. 140–141°.

Anal. Calc'd for $C_{23}H_{36}O_3$: C, 76.58; H, 10.10.
Found: C, 76.21; H, 10.06.

3(β)-*Acetoxybisnorcholenic acid methyl ester.* The methyl ester described above was allowed to stand overnight with pyridine containing 10% of acetic anhydride. The solvent was then removed under diminished pressure and the residue recrystallized from methanol; m.p. 137.5°. The mixed melting point with an authentic sample of 3(β)-acetoxybisnorcholenic acid methyl ester showed no depression.

Ozonization of poriferasteryl acetate. One gram of the acetate was suspended in 20 cc. of glacial acetic acid, which had been distilled three times from chromic anhydride. Ozone was passed through the suspension, which became clear after 15 minutes. After one hour the solution was poured into 100 cc. of water, and the mixture distilled into a solution of 2,4-dinitrophenylhydrazine sulfate until one-quarter of the original volume remained. The reagent solution was prepared by dissolving 0.5 g. of 2,4-dinitrophenylhydrazine in 2 cc. of concentrated sulfuric acid and diluting with 100 cc. of ethanol. An amorphous yellow precipitate formed, which was allowed to coagulate overnight. The crude product was purified by percolation of its benzene solution through activated alumina according to the directions of Mazur (5). It was recrystallized three times from alcohol; m.p. 113–114°; $(\alpha)_D^{25} \pm 0°$.

Anal. Calc'd for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04.
Found: C, 52.85; H, 6.26; N, 19.24.

SUMMARY

Poriferasterol has been oxidized to poriferastenone. Poriferasterol has been degraded by ozonization to a C_{22} acid, identified as 3(β)-hydroxybisnorcholenic acid. A volatile C_7 fragment from the side chain has been isolated in form of its 2,4-dinitrophenylhydrazone. Clionasterol has been shown to be 22,23-dihydroporiferasterol.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

INVESTIGATIONS ON LOCO WEEDS. V. FURTHER STUDIES ON THE CONSTITUENTS OF *ASTRAGALUS EARLEI*

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In preceding communications (1, 2) the results of a preliminary investigation of the constituents of Big Bend loco weed (*Astragalus earlei*) have been reported. While the isolation of the toxic principle, or principles, was not accomplished, two nitrogenous substances called at that time "α- and β-earleine" were separated from the weed along with considerable amounts of *d*-pinite. With the limited quantity of weed available at the time the early work was carried out, and because of the very small yield of the two bases, it was not possible to characterize them further.

In the meantime an additional supply of weed has been obtained and a further study of the two bases, as well as an extension of the general study of the constituents of the weed, has been carried out. The general preliminary extraction of the weed was the same as that used in the earlier work. After extraction of the ground whole weed with 70% alcohol, extraneous inactive material was removed by precipitation with basic lead acetate. The filtrate from this precipitate, after removal of lead as lead sulfide, was concentrated to a syrup which was thoroughly extracted with absolute alcohol, a procedure which has been shown to remove the active substance. The concentrate from the absolute alcohol extract (fraction A) has been used for the work here described.

At the outset, further investigation with larger quantities of the so-called "α- and β-earleines" showed that they were identical with betaine and choline respectively, and a preliminary note to this effect has already appeared (3). A study of the thermal decomposition of the latter provided the clue to its identity. When "β-earleine" was heated, trimethylamine and acetaldehyde were isolated from the decomposition products as the picrate and 2,4-dinitrophenylhydrazone respectively. From this the identity of "α-earleine" with betaine was surmised and the identity of both bases with choline and betaine was further confirmed by preparation of other derivatives. "β-Earleine" produced a typical choline effect on mice (4).

As additional experience with the weed has accumulated, it has been found that the precipitation of the toxic constituent with phosphotungstic acid may possibly be explained by adsorption of the poison on the rather bulky precipitate. In common with the earlier work (1), a considerable amount of activity has been found in the filtrate from the phosphotungstic precipitate. In order to show that the toxicity of this solution was not due to unprecipitated choline, the total nitrogen content of the fraction was determined by the Kjeldahl method. On the assumption that all the nitrogen thus found was due to choline, an amount of choline chloride corresponding to the nitrogen value found, was fed to cats in the same dosage as obtained with the weed extracts. In no case

did this produce any symptoms of locoism in the animals, although one cat died. On autopsy the cause of death appeared to be starvation.

Attention was then turned to the filtrate from the phosphotungstic acid precipitation. In the more recent work particular attention has been paid to thorough washing of this precipitate, with the result that a larger portion of the activity of the weed is found in the filtrate, although it has not been conclusively demonstrated that such activity as is found in the precipitate is adsorbed. However, this now appears to be likely.

The extreme solubility of the active material in water and alcohol suggests that the molecule is strongly polar and that it probably is highly hydroxylated. If one assumes that the appearance of the active material in the phosphotungstic acid precipitate is due to adsorption, then the further statement can be made that it is not truly precipitable by this reagent. It was felt that acetylation of the substances found in the phosphotungstic acid filtrate would render them soluble in other organic solvents and hence more amenable to separation. Accordingly the filtrate (fraction C) was freed of phosphotungstic acid with barium hydroxide and the resulting solution was concentrated to dryness. The residue was then acetylated in pyridine with acetic anhydride and the product after such treatment was then separated by extraction with chloroform into a chloroform-soluble fraction (D) and a fraction not extracted by chloroform from water (fraction E).

The entire fraction D was deacetylated with barium methoxide and yielded a mixture which was not active in cats. However, fractional distillation of the acetylated material yielded three substances, acetyl *d*-pinite, glycerol triacetate, and a diacetoxyvalerolactone, or an isomer thereof.

The presence of three saponifiable groups in the so-called diacetoxyvalerolactone was established by a quantitative determination. Furthermore, two of these groups were characterized as acetyl groups by the method of Elek and Harte (5). This diagnosis was confirmed by a study of the product obtained by deacetylation of the acetyl lactone by means of either barium methoxide or hydrochloric acid. The product thus obtained was neutral, and on saponification, one equivalent of alkali was consumed. The hydroxy lactone was further characterized by the preparation of a phenylhydrazide of the corresponding acid.

With the limited amount of material available it has not been possible to establish the exact structure of the lactone. The following evidence is offered in a preliminary sense, pending the accumulation of larger quantities of the substance. The possibilities to be considered are α,β-dihydroxy-γ-valerolactone, β-δ-dihydroxy-γ-valerolactone, β,γ-dihydroxy-δ-valerolactone, α,δ-dihydroxy-γ-valerolactone and α,γ-dihydroxy-δ-valerolactone, or branched chain isomers thereof. On the assumption that a straight chain is present, β,δ-dihydroxy-γ-valerolactone and β,γ-dihydroxy-δ-valerolactone can be eliminated because of the failure of the lactone to undergo dehydration under the conditions attending deacetylation of the acetoxy lactone with hydrochloric acid. Under such conditions, these β-hydroxy lactones would be expected to suffer dehydration and to lead to the corresponding unsaturated lactone. Evidence

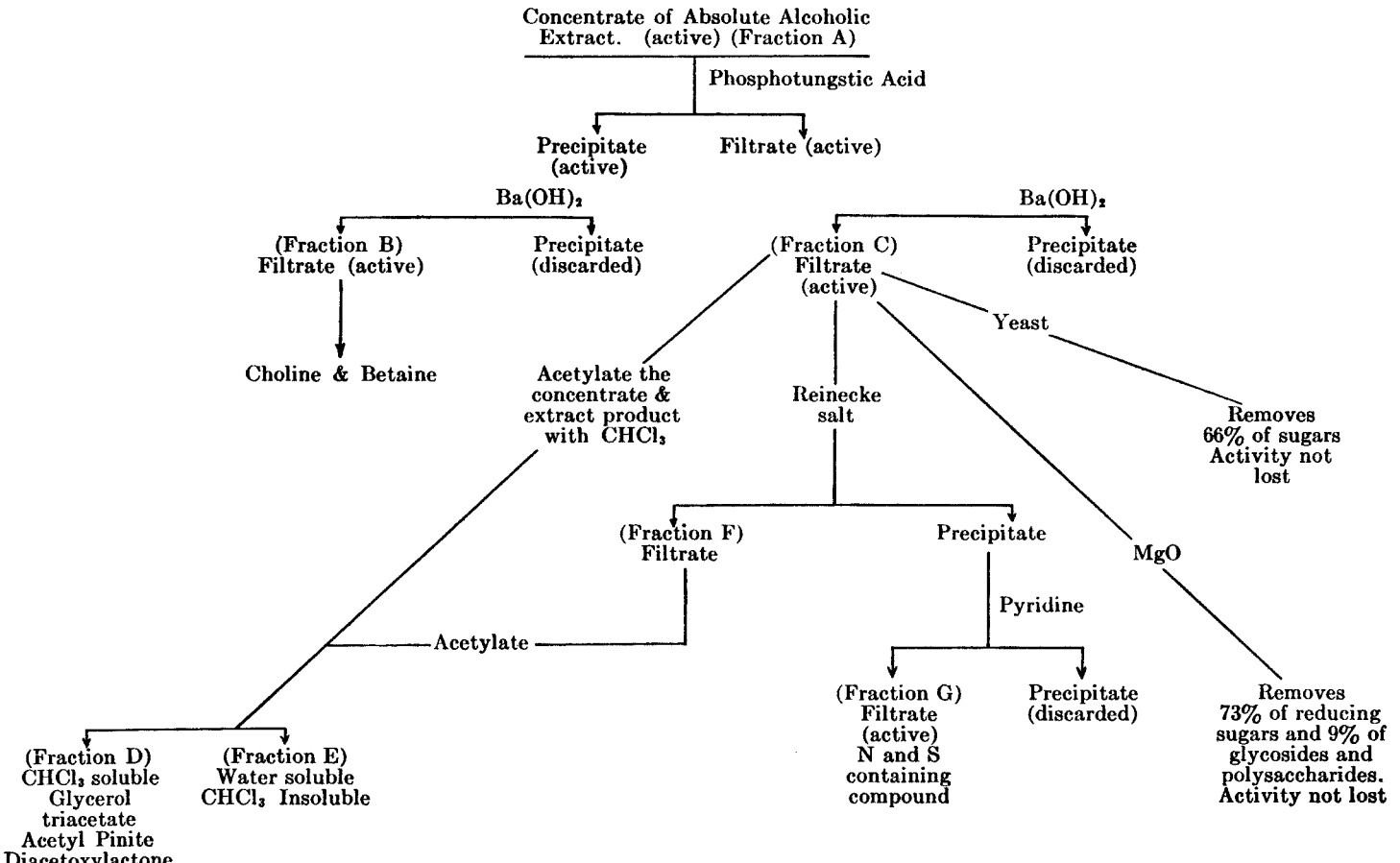
Concentrate of Absolute Alcoholic Extract. (active) (Fraction A)
Phosphotungstic Acid
Precipitate (active)
Filtrate (active)
Ba(OH)₂
Ba(OH)₂
(Fraction B) Filtrate (active)
Precipitate (discarded)
(Fraction C) Filtrate (active)
Precipitate (discarded)
Choline & Betaine
Acetylate the concentrate & extract product with CHCl₃
Reinecke salt
Yeast
Removes 66% of sugars Activity not lost
(Fraction F) Filtrate
Precipitate
MgO
Pyridine
Acetylate
(Fraction D) CHCl₃ soluble Glycerol triacetate Acetyl Pinite Diacetoxylactone
(Fraction E) Water soluble CHCl₃ Insoluble
(Fraction G) Filtrate (active) N and S containing compound
Precipitate (discarded)
Removes 73% of reducing sugars and 9% of glycosides and polysaccharides. Activity not lost

FIGURE 1

secured by a study of the action of lead tetraacetate on the lactone points to the presence of vicinal hydroxyl groups in a *trans* relationship to each other. In Figure 2 is shown the curve representing the course of the oxidation of the lactone by lead tetraacetate according to the method of Hockett and McClenahan (6), together with curves obtained by these authors for other sugar derivatives. If this interpretation is correct, the structure of the lactone in question narrows down to one of the isomeric α,β-dihydroxy-γ-valerolactones. Such an assumption appears to be warranted by the observed failure of the lactone to display mutarotation in aqueous solution, a behavior which would be expected in the cases of α,δ-dihydroxy-γ-valerolactone and α,γ-dihydroxy-δ-valerolactone. Eight possible stereoisomers of α,β-dihydroxy-γ-valerolactone may occur, namely, *d*- or *l*-arabomethylonic lactone, *d*- or *l*-xylomethylonic lactone, *d*- or *l*-lyxomethylonic lactone, and *d*- or *l*-ribomethylonic lactone.

l-Arabomethylonic lactone is reported as melting at 123° and showing a value for $[\alpha]_D$ of $-44.7°$ in water (7). The lactone in question melts at 52–53° and shows a value for $[\alpha]_D$ of $-64.7°$ in water. We have prepared the phenylhydrazide of *d*-xylomethylonic acid, which melts at 132–133° and shows a value for $[\alpha]_D$ of 33°, which compares with constants of 114–115° and 42° for the phenylhydrazide of the acid corresponding to the lactone under consideration. The new dihydroxy lactone, therefore, is not an arabo- or xylo-methylonic lactone. Neither of the ribomethyloses or their lactones have been described in the literature. *d*-Lyxomethylonic lactone is reported by Votoček (8) as showing a value of $[\alpha]_D$ of 44.2°. However, Clark (9) reports *l*-lyxomethylonic lactone as melting at 111° and showing a value of $[\alpha]_D$ of $-63.65°$. In view of this conflict of data, it does not appear warranted to exclude a lyxose configuration for the unknown lactone. On the assumption that the unknown lactone is one of the straight-chain methyltetronic acids, the configuration of *l*-lyxonic lactone would seem to be probable on the basis of Hudson's lactone and phenylhydrazide rules. Definite corroboration for this suggestion awaits accumulation of larger amounts of the lactone and reconciliation of the conflicting data on lyxomethylonic lactone. These points are under investigation.

Whether this hydroxy lactone is a primary constituent of the weed or whether it is formed by transformation of some precursor during the isolation process must be left open for the present, although the comparatively mild treatment undergone by the extract up to the acetylation would hardly be expected to cause degradation of other carbohydrate constituents. However, the possibility that the lactone is an artifact cannot be overlooked.

The other constituents of the acetylated fraction were identified as glycerol triacetate and acetyl-*d*-pinite. The latter obviously arises from traces of pinite carried along mechanically in the solutions. The presence of glycerine, taken together with the occurrence of choline, suggests the unlikely possibility that phosphotides might have been originally present in the active extracts. However, phosphorus determinations on both the original absolute alcohol-soluble part, and the material unextracted by absolute alcohol, showed the absence of phosphorus.

Fraction E, which was not extracted by chloroform, was concentrated and yielded a mixture of substances which was highly toxic to cats. While this fraction still gave a positive Molisch test, it no longer reduced Fehling's solution. It gave a reddish-blue ninhydrin test. It was obvious, therefore, that a considerable concentration of the activity had been achieved. On destructive distillation of the residue from concentration of fraction E, the vapors gave an intense, red, pine-splinter test for pyrrole and a deep purple color with Ehrlich's reagent. In contrast to this, an aqueous solution of fraction E gives no pine-splinter test and a faint green color with Ehrlich's reagent. The color tests are, therefore, due to decomposition products of the bases present. The apparent inability of phosphotungstic acid to precipitate all of the nitrogenous material, taken together with the above color tests, indicates the presence of nitrogen in a non-basic compound of the pyrrole series.

Since not all of the nitrogen present in the weed is basic, it was of interest to determine the distribution of the nitrogen in each fraction. This was done as given in the experimental part, and at least 11% of the total nitrogen in the weed was shown to be non-basic nitrogen. Whether the total activity is to be found in this non-basic nitrogen fraction remains to be seen.

Since apparently the nitrogen in the active material is non-basic, and since some indication had been obtained that a derivative of pyrrole was involved, the use of precipitants such as Reinecke salt or ammonium rhodanilate was suggested. When the filtrate from the phosphotungstic acid precipitate, after being freed from phosphotungstic acid (fraction C), was treated with Reinecke salt, a precipitate was obtained which after decomposition with pyridine in the usual manner, gave an almost colorless, highly active solution (fraction G). The solution gave a positive ninhydrin test and on concentration yielded a residue from which crystalline material was obtained. On thermal decomposition the crystalline material gave off an odor of a lower aliphatic amine and the vapor showed a strong pine-splinter test for pyrrole. Elementary analysis showed the presence of nitrogen and sulfur in this substance, along with carbon, hydrogen, and oxygen. The sulfur is neither disulfide nor sulfhydryl sulfur, and the absence of sulfate and thiocyanate groups was shown. No primary amine groups are present and the compound gave a negative ninhydrin test. The substance is also precipitated by ammonium rhodanilate, and may likewise be obtained from fraction E. With the limited amount available, it has not been possible to characterize this material further. Furthermore, it has not been possible to demonstrate conclusively whether this sulfur-containing substance is responsible for the activity of the weed or whether the active material is to be found in the part of fraction G which gives the ninhydrin test.

In our attempts to isolate the active constituent of the weed, the presence of large amounts of carbohydrate material, and possibly glycosides, has occasioned much difficulty. It was, therefore, felt that, if some method could be found whereby this inert material could be removed, the separation of nitrogenous components would be facilitated. For this purpose we have applied the procedure of Rabaté (10), which consists in gently heating the dry mixture of carbo-

hydrate material with magnesium oxide. It was found that, when this treatment was applied to the mixture extracted by 95% alcohol, 73% of the reducing sugars had been removed along with 9% of the sugar occurring as glycosides and polysaccharides, while the activity of the extract was comparatively unaffected. However, the ease of isolation of nitrogenous constituents was not improved by such treatment.

Crawford (11) reports that *Astragalus lambertii* has been used by the Mexicans for making beer, and that in some cases symptoms of locoism developed. If this indication that fermentation does not affect the activity of the weed is true, then a simple way for eliminating some of the carbohydrate material is offered. The phosphotungstic acid filtrate (fraction C) was, therefore, fermented with yeast and the resulting solution, after removal of proteins, was fed to cats. The activity was not decreased and 66% of the sugars present, determined as glucose, had been removed. Likewise Kjeldahl determinations revealed no change in nitrogen content. Despite this removal of the bulk of the sugars, the isolation of nitrogenous constituents was not facilitated. It is interesting to note that the absolute alcoholic extract before precipitation with phosphotungstic acid did not ferment with yeast, possibly because of the presence of an inhibitor precipitated by phosphotungstic acid.

The filtrate from the phosphotungstic acid precipitate (fraction C) contains glycosides, possibly of the active material. Therefore, attempts were made to determine the effect of enzymatic hydrolysis on the activity of this fraction. By following the increase in reducing power of solutions under the action of taka-diastase and emulsin respectively, at least one glycosidic linkage has been found. The activity of the fraction was not decreased by such treatment, but the evidence as to whether the toxic material occurs as a glycoside, was inconclusive.

In the above work we have used cats as experimental animals, although there is a great need for a more satisfactory assay method. The present method requires from four to six weeks for definite symptoms to appear. In order to try to provide a more satisfactory laboratory animal, we have fed an active extract of the weed to guinea pigs, with no effect. Subcutaneous injections of the extract in chicks, starting when they were a day old, did not affect either growth or stability. Finally, although adult cats react well to the weed, kittens did not react when fed active extracts.

We wish to acknowledge our appreciation for the kind cooperation of S. B. Penick & Company of New York City, and of Parke, Davis and Company of Detroit, Michigan, in carrying out preliminary extraction of the weed, which was secured with the aid of Dr. Frank P. Mathews of the Loco Weed Laboratory, Alpine, Texas. Our thanks are also due to the American Academy of Arts and Sciences for a grant for technical help in this investigation.

EXPERIMENTAL

All melting and boiling points are corrected for stem exposure.

The concentrate used in this work was obtained exactly as described by Pease and Elderfield (1). The concentrate of the absolute alcohol extract of the resin was used.

Identification of choline and betaine. The picrates of the bases formerly called "α- and β-earleine" were isolated as previously described (1). When free "β-earleine" was thermally decomposed in a stream of nitrogen, trimethylamine and acetaldehyde were isolated from the decomposition products. The picrate of the former melted at 228–229° and gave no depression of melting point when mixed with a known sample.

Anal. Calc'd for $C_3H_9N \cdot C_6H_3N_3O_7$: C, 37.5; H, 4.2; N, 19.5.
Found: C, 37.8; H, 4.2; N, 19.7.

Acetaldehyde was identified as the 2,4-dinitrophenylhydrazone, which melted at 164°.

Anal. Calc'd for $C_8H_8N_4O_4$: C, 42.9; H, 3.6; N, 25.0.
Found: C, 43.1; H, 3.4; N, 24.8.

TABLE I

Choline Picrate	
Anal.	Calc'd for $C_5H_{14}NO \cdot C_6H_3N_3O_7$: C, 39.8; H, 4.8; N, 16.9
	Found: C, 39.8; H, 4.7; N, 16.9
M. P.	Reported: 240° (uncorr.) (12); found: 247°
Acetylcholine Picrate	
Anal.	Calc'd for $C_7H_{15}NO_2 \cdot C_6H_3N_3O_7$: C, 41.7; H, 4.8; N, 15.0
	Found: C, 42.0; H, 4.9; N, 15.1
M. P.	111.5–112.5°
Choline Chloroplatinate	
Anal.	Calc'd for $(C_5H_{14}NO)_2 \cdot H_2PtCl_6$: C, 19.4; H, 4.9; Pt, 31.5
	Found: C, 20.0; H, 5.1; Pt, 31.8
M. P.	Reported: 234–235° (dec.) (13); found: 234–236° (dec.)
Betaine Picrate	
Anal.	Calc'd for $C_5H_{11}NO_2 \cdot C_6H_3N_3O_7$: C, 38.2; H, 4.1; N, 16.2
	Found: C, 38.3; H, 4.1; N, 15.6
M. P.	Reported: 183° (14); found: 184°
Betaine Styphnate	
Anal.	Calc'd for $C_5H_{11}NO_2 \cdot C_6H_3N_3O_8$: C, 36.5; H, 3.9; N, 15.5
	Found: C, 36.8; H, 4.1; N, 15.0
M. P.	186–188° (dec.)
Betaine Hydrobromide	
Anal.	Calc'd for $C_5H_{11}NO_2 \cdot HBr$: C, 30.3; H, 6.1; N, 7.0; Br, 40.4
	Found: C, 30.8; H, 6.2; N, 7.0; Br, 40.1
M. P.	Reported: 233° (15); found: 225°

From this it appeared likely that "β-earleine" in reality is choline, and it could be surmised that "α-earleine" in reality is betaine. This interpretation was confirmed by reexamination of the data at hand, both old and new, on the two bases as shown in Table I. In cases where there was no decomposition, mixed melting points of known samples with the derivatives were taken, and no depressions were noted.

Acetylation of the phosphotungstic acid filtrate (fraction C). An aqueous solution of the phosphotungstic acid filtrate equivalent to 25 lbs. of dry weed was concentrated to dryness *in vacuo* and dried by two distillations with absolute alcohol and benzene. The residue was extracted by stirring with 400 cc. of dry c.p. pyridine on the steam-bath. A small amount did not go into solution. This residue was reextracted with 100 cc. of pyridine and the combined pyridine extracts were cooled in ice to 0°. Four hundred cubic centimeters of acetic anhydride was added slowly. The solution warmed up slightly during the addition. After all of the acetic anhydride had been added, the solution was allowed to remain at room temperature for seven days. It was then poured into 1.5 liters of ice and allowed to stand for 2.5 hours with occasional stirring. The aqueous solution was then extracted several times with chloroform. The combined chloroform extracts were washed several times with 2.5 *N* hydrochloric acid to remove pyridine, the solution being cooled with ice

during the washing. Excess acid was then removed by shaking with a saturated sodium bicarbonate solution. The chloroform solution was dried over calcium chloride, filtered, and the chloroform removed by distillation *in vacuo*. The residue was then distilled at a pressure of about 5×10^{-3} mm. and the following fractions were collected: 1, up to 100°, 2, 100–130°, 3, 130–150°. These fractions were then redistilled.

Fraction 1. This was a slightly brownish mobile liquid which was redistilled; it boiled at 85–89° at 0.15 mm. It furnished analytical figures corresponding to glycerol triacetate.

Anal. Calc'd for $C_9H_{14}O_6$: C, 49.5; H, 6.4.
Found: C, 49.8; H, 6.5.

The acetate obtained as above was deacetylated by use of barium methoxide. To an ice-cold solution of 4.5 g. of the acetate in 125 cc. of absolute methanol was added 5 cc. of 0.5 *N* barium methoxide solution in absolute methanol. After standing for 2 days in the refrigerator, barium was removed as the sulfate, and the filtrate from barium sulfate was concentrated to yield a viscous syrup. This was benzoylated with benzoyl chloride in pyridine and yielded glycerol tribenzoate, which melted at 72–73° after crystallization from alcohol, and showed no depression in melting point when mixed with a known sample.

Anal. Calc'd for $C_{24}H_{20}O_6$: C, 71.4; H, 5.0.
Found: C, 71.4; H, 5.3.

Fraction 2. This fraction amounted to about 11 cc. It was redistilled at 0.2 mm., and the material boiling from 124–130° was collected. On standing, the heavy oil crystallized. After recrystallization from aqueous alcohol, 2.0 g. of an acetate which melted at 86–87° was obtained. Analyses indicated the presence of two acetyl groups and one lactone. $[\alpha]_D^{25}$ −7.09° (c = 2.822 in chloroform); 25.2° (c = 2.124 in alcohol).

Anal. Calc'd for $C_9H_{12}O_6$; C, 50.0; H, 5.6; 2 CH_3CO, 39.8.
Found: C, 50.0, 50.3; H, 5.5, 5.8; CH_3CO, 38.8, 38.9.
Molecular weight (Rast method in camphor) Calc'd: 216. Found: 195.

The saponification equivalent from 0.1102 g. of substance was obtained using 0.1 *N* sodium hydroxide in dilute acetone at 0° and back titrating with 0.1 *N* sulfuric acid. Calculated for 3 equivalents: 15.30 cc. of 0.1 *N* NaOH; found: 15.38 cc.

The acetyl lactone was deacetylated either with hydrochloric acid or barium methoxide. In the former case, 0.3 g. of the substance was heated at 60° with 60 cc. of 0.5 *N* hydrochloric acid. The substance slowly dissolved and was completely in solution after an hour. After four hours, the solution was concentrated to dryness under reduced pressure, and the residue was thoroughly dried by azeotropic distillation with absolute alcohol and benzene. On crystallization from ether-petroleum ether (Skellysolve B) long white needles were obtained which melted at 52–53°. $[\alpha]_D^{25}$ −64.7° (c = 0.580 in water). No change after two days.

Anal. Calc'd for $C_5H_8O_4$: C, 45.5; H, 6.1.
Found: C, 45.4; H, 6.2.
Saponification equivalent, calc'd: 132; found: 131.

The deacetylated lactone obtained by the more cumbersome barium methoxide method was identical in all respects with that obtained with hydrochloric acid.

The *phenylhydrazide* of the hydroxy acid corresponding to the lactone was prepared by heating the lactone with a slight excess of phenylhydrazine on the steam-bath for one hour. After cooling, the oily material was rubbed up with ether until it solidified, and then washed several times more with ether. On recrystallization from benzene-alcohol, it formed clusters of needles which melted at 114–115°. $[\alpha]_D^{28}$ 42° ± 2° (c = 0.558 in methanol); 45° (c = 0.462 in water).

Anal. Calc'd for $C_{11}H_{16}N_2O_4$: C, 55.0; H, 6.7.
Found: C, 54.9; H, 6.6.

d-*Xylomethylonic acid phenylhydrazide* was prepared in a similar manner from *d*-xylomethylonic acid prepared by oxidation of *d*-xylomethylose with bromine water. The phenylhydrazide crystallized as plates from benzene containing a trace of alcohol and melted at 132–133°. $[\alpha]_D^{28}$ 33° (c = 0.640 in methanol); 21° (c = 0.398 in water).

Anal. Calc'd for $C_{11}H_{16}N_2O_4$: C, 55.0; H, 6.7.
Found: C, 54.9; H, 6.7.

Oxidation of the hydroxy lactone with lead tetraacetate. The procedure was that of Hockett and McClenahan (6). To a solution of 35 mg. of the lactone in about 70 cc. of glacial acetic acid was added 25 cc. of 0.1288 *N* lead tetraacetate in glacial acetic acid and the resulting solution was made up to exactly 100 cc. At intervals, 5-cc. samples were removed, added to 10 cc. of a solution of sodium acetate and potassium iodide, and the liberated iodine was titrated with 0.02 *N* thiosulfate. The course of the oxidation is shown in Figure 2, together with a curve obtained similarly by Hockett and McClenahan for β-methyl-*d*-xylopyranoside and α- and β-methyl-*d*-glucopyranoside. From the similarity of the curves it is suggested that the hydroxyl groups in the lactone are *trans* to each other.

Fraction 3. This was an extremely viscous oil distilling at 137–145° at 10^{-2} mm. It was obtained crystalline from ether-ligroin and melted constantly at 97–98°. It was identified as acetyl pinite by mixed melting point and rotation. $[\alpha]_D^{25}$ 7.0° (c = 1.920 in alcohol).

Isolation of the nitrogen and sulfur compound. To a solution of 75 g. of Reinecke salt in 800 cc. of absolute methanol cooled in an ice-bath, was added with vigorous stirring, 1 liter

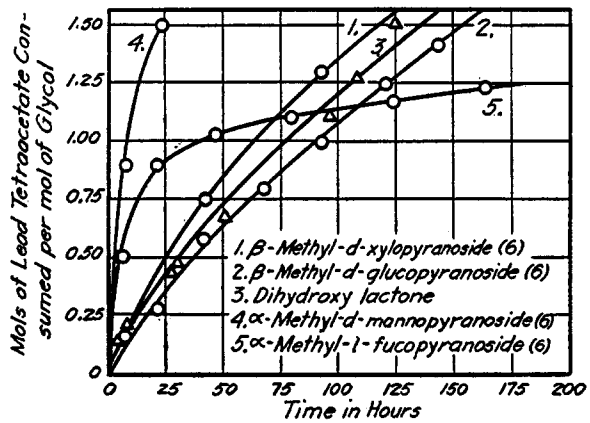

FIGURE 2

of an aqueous solution of the filtrate from the phosphotungstic acid precipitate (fraction C) which had been freed from phosphotungstic acid by treatment with barium hydroxide. This was equivalent to 25 lb. of dry weed. A precipitate formed almost immediately. After refrigerating overnight, the precipitate was filtered off and suspended in 200 cc. of water. After the addition of 6 cc. of pyridine, the mixture was shaken for an hour and filtered. Several drops of acetic acid were added to the filtrate to remove the last of the Reineckate, the solution was filtered again and the filtrate was concentrated to dryness under reduced pressure. The residue was taken up in absolute methanol and the solution deposited crystals on standing. After several crystallizations, both from methyl and ethyl alcohol, the substance appeared homogeneous and formed glistening white plates. The substance does not show a sharp melting point but decomposes about 320°. The yield was 50 mg. The analytical data, obtained from two different preparations, are difficult to reconcile with a satisfactory formula at present.

Anal. Found: C, 33.0, 33.0; H, 7.1, 7.1; N, 6.5; S, 17.7, 17.1.

The compound is optically inactive, extremely soluble in water, but sparingly soluble in cold alcohol. Its aqueous solution shows no turbidity with barium chloride, and a negative nitroprusside test for sulfhydryl and disulfide sulfur. The ninhydrin reaction is negative and no amino nitrogen can be detected by the Van Slyke procedure. That the sulfur did not come from the Reinecke salt was shown by a negative ferric chloride test for thiocyanate. On thermal decomposition, a strong odor of a lower aliphatic amine appears, and the vapors give a strong pine-splinter test for pyrrole.

While the solution obtained on decomposition of the Reineckate produces typical locoism in cats, due to the extremely small amount of material available, it has not been possible to demonstrate whether the above compound is responsible for such symptoms or whether a still unisolated substance carried down in the precipitate is the active material. This point is under active investigation.

The methanol filtrate, after removal of the Reinecke precipitate, was concentrated under reduced pressure, the residue was taken up in water and freed from Reinecke salt by use of pyridine in the usual manner. Concentration of the final filtrate left a syrup, which, on acetylation, yielded the same three acetates described above.

Ammonium rhodanilate can be used for the above precipitation, but it is not as satisfactory and does not give as clean a product as Reinecke salt.

TABLE II

FRACTION	MG. N PER LB. OF DRY WEED
Absolute alcohol extract	306
Filtrate from phosphotungstic acid precipitate (fraction C)	98
Above filtrate after a second phosphotungstic precipitation	68
Unacetylated part (fraction E)	34

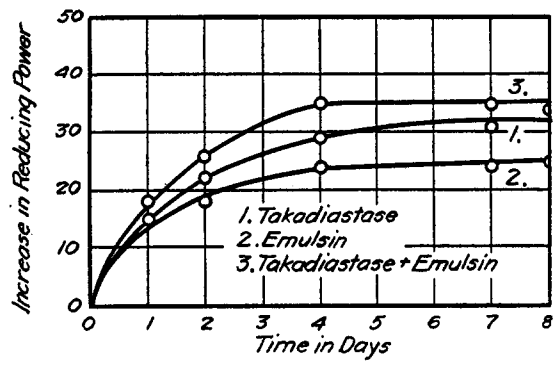

FIGURE 3

Enzymatic hydrolysis of the phosphotungstic acid filtrate (fraction C). The substrate used was a solution of the filtrate, freed from phosphotungstic acid, of which 25 cc. corresponded to 0.022 lb. of dry weed. The following solutions were used:

(a) 25 cc. of substrate, 2 cc. of $M/5$ acetate buffer, 2 cc. of 1% takadiastase (Wallerstein), and 2 cc. of water. *p*H of the solution: 4.70.

(b) Same as (a) except that 2 cc. of 1% emulsin (prepared from almonds) was used instead of the takadiastase. *p*H of the solution: 4.59.

(c) Same as (a) except that 2 cc. of 1% emulsin and 2 cc. of 1% takadiastase were used. *p*H of the solution: 4.65.

The solutions were kept in a thermostat at 35° ± 0.05° and 2 cc. samples were removed at intervals. Reducing sugar was determined by the Hanes modification of the Hagedorn-Jensen method (16). The results are shown in Figure 3.

Action of magnesium oxide on the phosphotungstic acid filtrate (fraction C). The method of Rabaté (10) was used in an effort to remove some of the troublesome carbohydrates. A portion of fraction C equivalent to 0.08 lb. of dry weed was found to contain 48 mg. of reducing sugar determined as glucose by the Hanes, Hagedorn, Jensen method. This solu-

tion was stirred up into a paste with magnesium oxide and dried in an oven at 38°. The dry powder was pulverized and extracted with alcohol; the solution thus obtained contained 13 mg. of reducing sugar, indicating that 73% of free reducing sugar had been removed. A larger run was then made, and the product produced typical symptoms of locoism in cats.

In order to ascertain whether appreciable amounts of glycosides and polysaccharides had been removed, the following control experiment was done. A solution of fraction C equivalent to 0.08 lb. of dry weed was made 0.2 *N* in sulfuric acid and refluxed for 5 hrs. An exactly similar experiment was run on the material after magnesium oxide treatment. After the acid hydrolysis the untreated phosphotungstic acid filtrate contained 82 mg. of reducing sugar calculated as glucose, an increase of 34 mg., and the filtrate from the magnesium oxide treatment contained 44 mg. of reducing sugar, an increase of 31 mg. From this it is apparent that about 9% of the glycosides and polysaccharides have been split during the magnesium oxide treatment.

While this method for concentrating the activity has shown signs of great usefulness, it has not been pursued further at present because of the more convenient Reinecke precipitation which apparently requires no preliminary concentration other than precipitation of choline and betaine with phosphotungstic acid.

Distribution of nitrogen in extracts of the weed. Since not all of the nitrogen isolated thus far from the weed is basic, it became of interest to follow the distribution of the nitrogen in the various fractions. This was done by the Kjeldahl method and the results are shown in Table II. From this it is apparent that at least 11% of the nitrogen originally present in the weed may be accounted for as non-basic nitrogen. Evidence at present available points to the occurrence of the active substance in this fraction.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. The substances previously called "α- and β- earleine" have been shown to be identical with betaine and choline respectively.

2. It appears likely that the reported precipitation of the active constituent of *Astragalus earlei* by phosphotungstic acid is due to adsorption on the precipitate.

3. Reinecke salt precipitates a highly active fraction from which a crystalline substance has been isolated.

4. Bases which give a strong ninhydrin test are also precipitated by Reinecke salt.

5. A dihydroxyvalerolactone, or an isomer thereof, has been isolated from extracts of the weed along with glycerine. Possible structures for the lactone are discussed.

6. Enzymatic action of yeast, takadiastase, or emulsin affects the carbohydrate constituents of the weed, but does not apparently affect the activity.

7. A practical method for removing most of the reducing sugars from an extract of the weed without affecting the activity is suggested.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. X. SYNTHESIS OF SIMPLE HYDROXYLATED β-SUBSTITUTED $\Delta^{\alpha,\beta}$-BUTENOLIDES

EDWIN R. MARSHALL, J. A. KUCK, AND ROBERT C. ELDERFIELD

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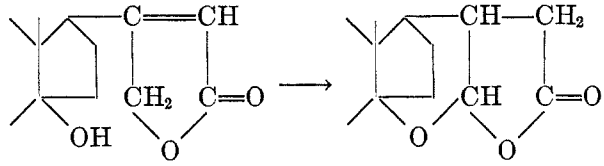
Syntheses of simple unsaturated lactones analogous to the naturally occurring cardiac drugs have been described in previous publications (1, 2), and by application of these methods, such lactones containing steroid ring systems have also been prepared (3). As a result of a study of the properties of the synthetic β-substituted $\Delta^{\alpha,\beta}$-butenolides and comparison of them with the naturally occurring drugs, the conclusion has been reached that the side-chain double bond in the latter is in the α,β-position (4). With this revision in structure, a number of reactions of the natural drugs require amplification before the factors involved become fully understood. Among these, the formation of the so-called iso-aglycones from the aglycones under the influence of alkali (5) is perhaps most interesting. The reaction involved may be represented in an over-all sense by



In order to secure the change, it is apparently necessary that a hydroxyl group be located in reactive proximity to carbon atom 21 of the side chain, and, further, that such a hydroxyl group be in the proper stereo-relationship to the side chain.

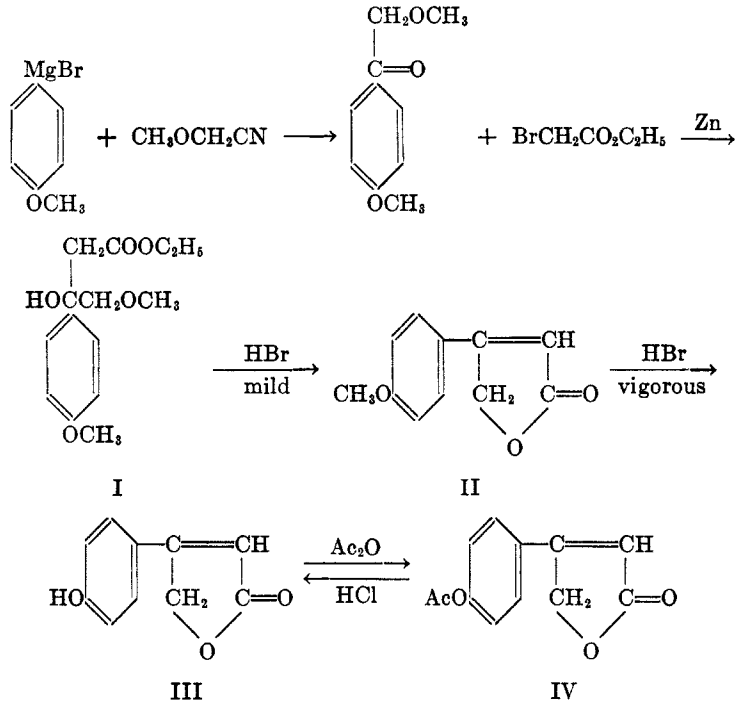
During the course of pharmacological examination of the simpler lactones, a slight but distinct activity in frogs has been noted in some cases (6). It is of interest, therefore, to prepare several lactones containing different substituent groups on the β-carbon atom of the lactone, in order to ascertain if possible the factors determining cardiotonic activity.

In the present communication we wish to present the results of a study of the synthesis of simple hydroxylated β-substituted $\Delta^{\alpha,\beta}$-butenolides. The study was confined to relatively simple and accessible substances in order that general methods could be worked out, and that the limitations inherent in the present available synthetic methods could be noted. At the same time information bearing on the question of structure and activity was secured. Reactions which can be expected to lead to the three isomeric β-(hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolides have been investigated in detail, and a preliminary study of the corresponding hydroxycyclohexyl butenolides has been started. The latter substances are particularly useful as models for the study of iso-compound formation.

Two general syntheses have been used, that of Rubin, Paist, and Elderfield (1), which proceeds from methoxymethyl ketones, and that of Linville and Elder-

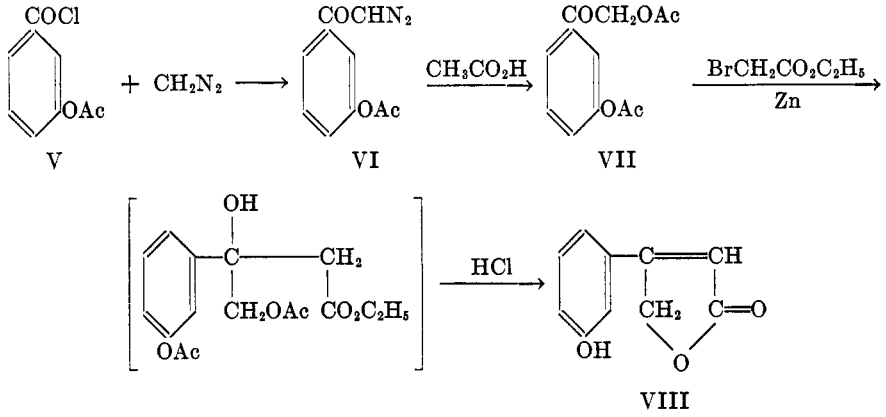
field (2), which proceeds from acetoxymethyl ketones. Inasmuch as it is necessary to block any hydroxyl groups present in either synthesis, a choice of ether or acyl blocking groups is thus afforded, and the relative merits of the two procedures will be apparent.

The reactions involved in the preparation of β-(4-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide by the first of the above methods, are shown in the formula scheme.



The reactions noted proceeded without difficulty. The ester, I, was converted directly to the unsaturated methoxy lactone, II, by relatively gentle treatment with hydrobromic acid, although the over-all yield appeared to be slightly better if the ester was saponified prior to ring closure of the lactone. More vigorous treatment with hydrobromic acid was necessary to remove the blocking methyl group on the phenolic hydroxyl group. Under the best conditions it was not possible to secure the hydroxy lactone free from contaminating methoxy lactone, and because of the similarity in solubilities of the methoxy lactone, II, and the hydroxy lactone, III, purification of the latter by fractional crystallization was difficult. However, it was possible to prepare the acetoxy lactone, IV, from the mixture of II and III. This was then easily purified, and, on deacetylation by treatment with hydrochloric acid, gave pure β-(4-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide. The hydroxy lactone as thus obtained gave a strong nitroprusside color test, but no color with ferric chloride. The presence of the phenolic hydroxyl group was shown by acetylation to yield IV, and by methylation with diazomethane to yield II. The lactone also rapidly decolorized an alcoholic solution of bromine.

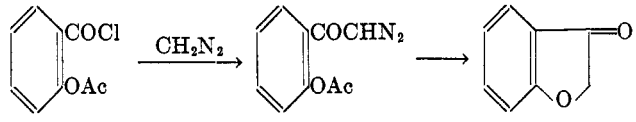
In view of the difficulty encountered in splitting the blocking ether group in the methoxy lactone (II) the method of Linville and Elderfield (2) appeared to be better adapted for the purpose in hand, inasmuch as the nuclear hydroxyl group could be blocked by an acetyl group. This method was, therefore, used for the preparation of β-(3-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide. The 4-hydroxyphenyl lactone, III, was also prepared in this way in order to check the products of the two syntheses. The steps in the synthesis of the 3-hydroxyphenyl lactone are shown in formulas V–VIII.



V VI VII VIII

β-(3-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (VIII) gives a strong nitroprusside color test, a red color with ferric chloride, readily decolorizes bromine water, and on methylation with diazomethane, yields the corresponding methoxy lactone. β-(4-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide prepared by this method is identical with the lactone prepared from *p*-bromoanisole, and on treatment with diazomethane, yields a methoxy lactone identical with II.

When the preparation of β-(2-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide by either of the above methods was undertaken, it was found that ring closure to coumaranone or derivatives of coumaranone occurred at some stage in the series of reactions under all conditions tried. Acetylsalicylic acid chloride, IX, on treatment with diazomethane apparently yielded the expected diazomethyl ketone, X. However, when X was treated with glacial acetic acid coumaranone, XI, was the only product isolated. The behavior of the reaction mixtures indicated



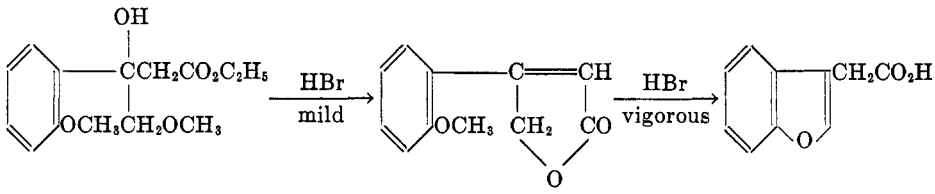
IX X XI

that the desired ω,*o*-diacetoxyacetophenone probably was formed, but underwent ring closure, possibly by loss of acetic anhydride, on working up and attempted purification. This easy ring closure finds a parallel in the observation of Wiedenhagen and Herrmann (7) that *o*-hydroxy-ω-chloroacetophenone yields

coumaranone on treatment with sodium acetate. Likewise Clibbens and Nierenstein (8) found that *o*-acetoxy-ω-chloroacetophenone yields coumaranone on distillation.

In view of the easy removal of the blocking *o*-acetyl group in the reactions discussed above, it was felt that a less easily cleaved ether group might serve better for blocking purposes. Accordingly, *o*-methoxy-ω-diazoacetophenone was prepared. Surprisingly enough, when this was treated with acetic acid, formation of coumaranone proceeded more readily and cleanly than was the case with the acetyl derivative.

Finally the preparation of the desired β-(2-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide was attempted, starting from ω,*o*-dimethoxyacetophenone. On reaction with ethyl bromoacetate in the presence of zinc, the glycol ether ester, XII, was readily obtained. This gave β-(2-methoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide, XIII, when treated in the usual manner. However, all attempts to remove the blocking ether group resulted in the formation of coumaronyl-3-acetic acid, XIV.



XII XIII XIV

In the cyclohexyl series attention has been concentrated on the preparation of β-(2-hydroxycyclohexyl)-$\Delta^{\alpha,\beta}$-butenolide. This substance possesses the desired arrangement of functional groups to serve as a model for studies of the iso-compound transformation. For the purpose in mind, salicylic acid or one of its derivatives forms a readily available source of material. No attempt has been made to separate the various stereo and optical isomers encountered, since it was felt that the usefulness of existing synthetic methods could be evaluated with the mixture of isomers, provided analytically pure substances were secured. The resolution of such substances could then be carried out at such a time as the desired synthetic materials had become available. Because of this approach it should be pointed out that in most cases the physical constants of many of the substances encountered are not well defined and represent those of mixtures. Furthermore, failure to secure crystalline derivatives in some cases, as well as the formation of complex mixtures in some reactions may be ascribed to the same cause.

2-Acetoxyhexahydrobenzoic acid chloride apparently reacted normally with diazomethane to yield ω-diazo-2-acetoxyhexahydroacetophenone. However, when the diazo ketone was treated with acetic acid, extensive resinification occurred and no well defined substance could be isolated from the reaction product. It therefore appeared that the acetoxy group was unsuitable for the protection of the nuclear hydroxyl group during the reactions involved. A similar series of reactions proceeding from 2-methoxyhexahydrobenzoic acid

was then investigated. Again, while the intermediate diazomethyl ketone appeared to be formed in the normal manner, reaction of the latter with acetic acid again led to unidentifiable compounds.

However a more promising approach to the 2-hydroxycyclohexyl butenolide was opened up by the observation that ethyl β-(*o*-methoxyphenyl)-β-methoxymethylhydracrylate (XII), in contrast to its precursors, could be reduced catalytically with platinum oxide to yield the corresponding cyclohexyl compound, although some cleavage of the ether groups present, and possibly of the ester apparently took place during the reduction. The yield of desired cyclohexyl compound was consequently poor. However in this substance the troublesome steps encountered in the attempts to arrive at it from cyclohexane carboxylic acid and its derivatives have been overcome, and all that remains to be done in order to secure the desired lactone is to split the ether groups and close the lactone in the usual manner. When the cyclohexylhydracrylic ester was treated with hydrobromic acid in acetic acid, conversion of the side chain to the unsaturated lactone apparently occurred, as evidenced by the strong positive Legal test shown by the crude product. However the formation of much tar accompanied the ring closure and it was impossible to isolate more than a fraction of a per cent of product by distillation. Apparently the nuclear hydroxyl group was removed leaving a double bond under this rather severe treatment, with resultant formation of large amounts of resinous substances. Better success attended the use of aqueous hydrochloric acid for cleavage of the ethers and ring closure. When the hydracrylic ester was refluxed with concentrated hydrochloric acid, a substance which gave a strong Legal test and contained chlorine was obtained; this is probably β-(2-chlorocyclohexyl)-$\Delta^{\alpha,\beta}$-butenolide. This was then heated with water in a sealed tube in order to replace the chlorine atom by hydroxyl. The product thus obtained still gave the Legal test, but also still contained chlorine. However the analytical figures obtained indicated that, while the desired replacement of chlorine by hydroxyl had occurred, simultaneously dehydration involving the nuclear hydroxyl group had also taken place to some extent. A suitable synthesis for this type of lactone must remain for future investigation.

None of the lactones described showed cardiac activity when tested in frogs through the kind cooperation of Dr. K. K. Chen of the Lilly Research Laboratories.

EXPERIMENTAL

All melting points are corrected for stem exposure.

ω,4-Dimethoxyacetophenone was prepared from *p*-bromoanisole and methoxyacetonitrile according to the method of Pratt and Robinson (9) who report a yield of 30% (based on the methoxyacetonitrile) of material boiling at 185–190° at 35 mm. and melting at 40°. We obtained a yield of 42% of material boiling at 145° at 7 mm. and melting at 41–42°.

Ethyl β-methoxymethyl-β-(4-methoxyphenyl)hydracrylate (*I*). A mixture of 40.7 g. (0.23 mole) of ω,4-dimethoxyacetophenone, 20.9 g. (0.32 mole) of 20-mesh zinc, and 175 cc. of anhydrous benzene was heated to refluxing. This mixture was stirred vigorously and kept refluxing for 1.25 hours, during which time a solution of 35.0 g. (0.21 mole) of ethyl bromoacetate in 25 cc. of anhydrous benzene was added dropwise. Refluxing and stirring were

continued for 3 hours longer. The cooled benzene solution was decanted from the excess zinc, and the zinc was washed with ether. The combined benzene and ether solutions were washed with dilute hydrochloric acid, and dried over anhydrous magnesium sulfate. Distillation yielded 43 g., or 70%, of a slightly yellow viscous oil which boiled at 152–160° at 0.6 mm.

Anal. Calc'd for $C_{14}H_{20}O_5$: C, 62.7; H, 7.5.
Found: C, 63.0; H, 7.8.

When the glycol ether ester was dissolved in glass-distilled alcohol, and shaken with Adams' catalyst in an atmosphere of hydrogen, no hydrogen was absorbed.

β-Methoxymethyl-β-(4-methoxyphenyl)hydracrylic acid. Twenty-eight grams of the above ester was saponified by refluxing for 1.5 hrs. with a solution of 38 cc. of 10% aqueous sodium hydroxide in 40 cc. of absolute alcohol. After distillation of the alcohol, the aqueous solution was washed with ether, acidified with 10% hydrochloric acid, and extracted with ether. This extract was dried over anhydrous magnesium sulfate, and the ether was removed to yield a reddish-yellow oil which soon crystallized. Recrystallization from benzene gave the acid as small white plates which melted at 102.5–103.5°. The yield was 11.5 g. By dissolving the magnesium sulfate with water and recrystallizing the undissolved solid from benzene, an additional 9.5 g. of the acid was obtained. The total yield was 21.0 g. or 84%.

Anal. Calc'd for $C_{12}H_{16}O_5$: C, 60.0; H, 6.7; OCH_3, 25.8.
Found: C, 60.0; H, 6.9; OCH_3, 21.1.

When an alcoholic solution of this acid was shaken with Adams' catalyst in an atmosphere of hydrogen, no hydrogen was absorbed.

β-(4-Methoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (II). A mixture of 4.8 g. of the above acid and 16 cc. of glacial acetic acid, which had been saturated with dry hydrogen bromide at 0°, was heated at 110–120° for thirty minutes. When the cooled solution was poured with stirring into 100 cc. of ice-water, a pinkish solid separated. After repeated recrystallization from dilute alcohol the lactone formed very long, thin, white needles which melted at 120°. The yield was 2.0 g. or 53%. This compound gave a positive Legal test and a negative ferric chloride test. An alcoholic solution of it did not decolorize bromine water. It was soluble in chloroform and in hot alcohol, and slightly soluble in ether, benzene, and hot water.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3; OCH_3, 16.3.
Found: C, 69.8; H, 5.6; OCH_3, 15.8.

β-(4-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (III). A mixture of 2.7 g. of the above methoxy lactone, 23 cc. of a saturated solution of dry hydrogen bromide in glacial acetic acid, 12 cc. of constant boiling hydrobromic acid, and 45 cc. of glacial acetic acid was heated at 120–140° for 3.5 hrs. The solution was concentrated under a partial vacuum, and poured into ice-water to yield 2.0 g. of a chalky solid. After repeated recrystallization from dilute alcohol, with liberal use of decolorizing carbon, feathery clusters of short white needles which melted at 250–256.3° in a sealed tube (the substance decomposed upon heating in an open tube) were obtained. These needles gave a positive Legal test, and a negative ferric chloride test. An alcoholic solution of them decolorized bromine water. The substance has a limited solubility in the ordinary solvents, but is insoluble in choloroform.

A sample which had been purified by vacuum sublimation gave the following analysis, from which the presence of a small amount of methoxy lactone is indicated.

Anal. Calc'd for $C_{10}H_8O_3$: C, 68.2; H, 4.6; OCH_3, 0.0.
Found: C, 68.7; H, 5.1; OCH_3, 2.3.

This same lactone, mixed with the methoxy lactone, was prepared directly from the hydracrylate, (I) in a similar manner. Twenty-six grams of the ester was heated at 130–140° for 3.5 hrs. with a mixture of 100 cc. of acetic acid solution of hydrogen bromide, 100 cc. of constant-boiling hydrobromic acid, and 100 cc. of glacial acetic acid. The reaction mixture was worked up in the same manner as before to yield a purple solid which was dissolved in acetic acid and repeatedly boiled with decolorizing carbon. Removal of the solvent yielded a buff-colored solid which melted from 110–170°. Digestion of this material with hot chloroform gave two fractions. The insoluble fraction was recrystallized from

alcohol and formed white needles which melted at 247–257.4°. The melting point was not depressed when the substance was mixed with the lactone (III), prepared as above. The yield was 5.0 g. or 28%. The chloroform-soluble fraction was recrystallized from dilute alcohol to yield 6.5 g., or 34% of white needles, which melted at 118–119.5°, and which gave no melting point depression when mixed with the methoxy lactone, (II) prepared from the acid.

β-(4-Acetoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (IV). The impure hydroxy lactone obtained as above was treated in the usual manner with acetic anhydride and fused sodium acetate. Upon pouring the deep red solution into ice-water a reddish liquid, which solidified upon stirring, separated. After repeated recrystallization from dilute methanol, long white needles which melted at 138.6–140.7° were obtained. This compound gave a positive Legal test.

Anal. Calc'd for $C_{12}H_{10}O_4$: C, 66.1; H, 4.6.
Found: C, 66.0; H, 4.9.

This acetate was hydrolyzed by warming for one minute with an equal volume of concentrated hydrochloric acid, and the product was recrystallized once from dilute alcohol. The pure hydroxy lactone formed white needles which melted at 260.5–263.6° and gave no melting point depression with the hydroxyphenyl lactone obtained as described below.

p-*Acetoxybenzoic acid* was prepared from *p*-hydroxybenzoic acid according to the method of Chattaway (10) who reports a 93% yield of material melting at 189–190°. We obtained a yield of 91% of material melting at 186.1°.

p-*Acetoxybenzoyl chloride* was prepared by heating the above acid with 3 cc. of thionyl chloride per gram of the acid for six hours at 50°. After removal of the excess thionyl chloride, using anhydrous benzene, the material was stored in sealed glass ampoules without further purification.

ω,4-Diacetoxyacetophenone. This substance was prepared from the acid chloride, by slowly adding a dry ether solution of the latter to an ethereal solution of excess diazomethane to form the diazomethyl ketone, which was then treated with glacial acetic acid. A 65% yield (based on the acid used) of crude yellow plates which melted at 93.2–94.6° was obtained. After repeated recrystallization from benzene, white diamond-shaped plates melting at 94.6–95.6° were obtained. Robertson and Robinson (11) report the melting point 98° for this compound prepared from ω-chloro-4-hydroxyacetophenone. The crude material is very unpleasant to work with as it causes the skin to sting and burn.

β-(4-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (III). A solution of 7.5 g. of the above ketone in 30 cc. of anhydrous benzene was added to 3.3 g. of 20-mesh zinc, and the mixture was heated to refluxing. A solution of 5.3 g. of freshly distilled ethyl bromoacetate in 10 cc. of anhydrous benzene was dropped in over a period of 15 min. After refluxing for another 30 min., the zinc and the walls of the flask had become coated with a yellow solid which was not dissolved by addition of fresh benzene and which stopped the reaction. After removing the benzene *in vacuo* the product was separated from the zinc by use of 20% hydrochloric acid. The decantate from the zinc contained suspended solid material which was warmed on the steam-bath for one minute with an equal volume of concentrated hydrochloric acid and then poured into ice-water. The precipitate thus obtained was recrystallized from 95% alcohol to yield 2.3 g. or 41% of white needles which melted at 262.5–263.5° in a sealed tube.

This material gave a strong Legal test and was proved, by mixed melting point, to be the same as that prepared as above.

Anal. Calc'd for $C_{10}H_8O_3$: C, 68.2; H, 4.6.
Found: C, 68.1; H, 4.8.

The methoxy lactone which was prepared by treating an acetone solution of the hydroxy lactone with diazomethane melted at 119–120° and proved to be identical with that prepared as above.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3; OCH_3, 16.3.
Found: C, 69.7; H, 5.4; OCH_3, 13.8.

m-*Acetoxybenzoic acid* was prepared from *m*-hydroxybenzoic acid according to the method of Chattaway (10). A 90% yield of material melting at 128.7–131.3° was obtained. Herzig and Titchatschek (12) report the acid as melting at 127–129°.

m-*Acetoxybenzoyl chloride* was prepared from the acid according to Hayashi (13) except for the fact that a heating period of 2.5 hrs. was found to be necessary instead of the 30 min. heating period given by him. The excess thionyl chloride was removed and the product was sealed in glass ampoules.

ω,3-Diacetoxyacetophenone was prepared by reaction between the acid chloride and diazomethane to yield the diazomethyl ketone, which was then heated for 2.5 hrs. on a boiling water-bath with glacial acetic acid. A 68% yield of a viscous yellow oil which boiled at 155–158° at 0.5 mm. was obtained. Hayashi (13) using a 20 min. heating period in a similar procedure, reports a 57% yield of a yellow oil which boiled at 189–197° at 14 mm.

β-(3-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide. The above ketone was condensed with ethyl bromoacetate in the same manner as before, except that alcohol was used to dissolve the gum which formed on the zinc. The resulting mixture was decanted from the excess zinc and concentrated *in vacuo* to yield a thick paste, which was then mixed with 100 cc. of 10% hydrochloric acid and heated on a boiling water-bath for 10 min. The clear red solution was poured, with stirring, into 250 cc. of ice-water, and the solid which separated was filtered off and washed with cold water. This crude product (34% yield) had a strong coumarin-like odor. After repeated recrystallization from methanol and washing with ether, a yield of 23% of odorless, slightly yellow, rectangular plates which melted at 187.5–188.5° (in a sealed tube) was obtained. The lactone was more soluble in the usual solvents than the para isomer. It gave a positive Legal test. An aqueous solution gave a positive ferric chloride test and also decolorized bromine water.

Anal. Calc'd for $C_{10}H_8O_3$: C, 68.2; H, 4.6.
Found: C, 68.5; H, 4.7.

β-(3-Methoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide was prepared in the same manner as was the para isomer. After three recrystallizations from dilute alcohol and two from water, it formed white needles which melted at 86.3–87.3°. The methoxy lactone gave a positive Legal test and a negative ferric chloride test.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3.
Found: C, 69.3; H, 5.4.

o-*Acetoxybenzoyl chloride* (*IX*) was prepared from *o*-acetoxybenzoic acid by the same procedure as was used in the preceding series.

ω-Diazo-2-acetoxyacetophenone (*X*) was prepared from the acid chloride in the usual manner and was not further purified. An attempt at hydrolysis, in which a dioxane solution of the diazomethyl ketone was heated at 50° with 10% sulfuric acid, yielded coumaranone (XI) (see later).

Attempted preparation of ω,2-diacetoxyacetophenone. When the above diazomethyl ketone was treated with glacial acetic acid according to the usual procedure, a dark red oil was obtained. Since this material could not be crystallized, it was distilled at 2 mm. A small portion distilled, crystallizing in the side arm of the flask, but the residue remained as a red tar which could not be identified. The distillate was recrystallized from isopropyl alcohol to form white needle-like plates which melted at 101–102° and was identified as coumaranone (XI), by mixed melting point. Clibbens and Nierenstein (8) obtained the same product by distillation of ω-chloro-2-acetoxyacetophenone and report the melting point 101–102°.

Anal. Calc'd for $C_8H_6O_2$: C, 71.6; H, 4.5.
Found: C, 71.5; H, 4.7.

In another attempt to form the diacetoxyacetophenone, the diazomethyl ketone was mixed with glacial acetic acid and was allowed to stand at room temperature for one week. As bubbles of gas were evolved when concentrated hydrochloric acid was added to a test portion, thus showing the presence of unreacted diazomethyl ketone, the reaction mixture

was then heated on a boiling water-bath for 1.5 hrs. The reaction mixture was worked up in the same manner as before to yield a red oil which did not crystallize when seeded with a sample of the coumaranone obtained previously. However, when this oil was washed with ether, a dark red solid was obtained which upon recrystallization from benzene formed orange needles which melted at 204–205°. This material was not further investigated.

Anal. Found: C, 67.6; H, 4.0.

Steam distillation of the ether washings yielded a small amount of coumaranone. The residue from the steam distillation was distilled to yield a yellow oil which boiled at 149–152° at 0.5 mm., and which quickly turned red upon standing. The bulk of the material remained in the flask in the form of a red tar. The distillate gave a positive ferric chloride test and dissolved in 10% aqueous sodium hydroxide with the formation of a dark red solution from which a red oil was obtained upon acidification with hydrochloric acid, but which could not be identified.

Other attempts, in which the diazomethyl ketone was treated with a saturated solution of fused sodium acetate in glacial acetic acid, produced similar results.

Methyl-o-methoxybenzoate was prepared by methylation of methyl salicylate with dimethyl sulfate and sodium hydroxide by a modification of the method of Sachs and Herold (14) which consisted of dropwise simultaneous addition to the methyl salicylate, with heating and stirring, of the sodium hydroxide solution and the dimethyl sulfate. A 71% yield of the ester, which boiled at 132–133° at 15 mm., was obtained. Sachs and Herold report a yield of 80–90% of material boiling at 252° at atmospheric pressure. When the Sachs and Herold procedure was attempted, the reaction invariably became violent and got out of hand.

o-*Methoxybenzoic acid* was prepared by alkaline hydrolysis of the above pure ester, or by hydrolysis of the crude reaction mixture. In the latter case, the procedure of Graebe (15) was used to separate it from salicylic acid by means of the calcium salt. The material melted at 100.6–102.5°. Cohen and Dudley (16) report the melting point 99–101°.

o-*Methoxybenzoyl chloride* was prepared from the acid according to the procedure of Fischer and Slimmer (17), and was sealed in glass ampoules after removal of the excess thionyl chloride.

ω-Diazo-2-methoxyacetophenone was prepared in the usual manner from the acid chloride. The yellow oil was used immediately without purification.

Reaction of ω-diazo-2-methoxyacetophenone with acetic acid. When acetic acid was mixed with the diazomethyl ketone at room temperature, a violent exothermic reaction immediately took place, and coumaranone crystallized from the reaction mixture. When this reaction mixture was worked up, only coumaranone was obtained.

When glacial acetic acid was added to an ether solution of the diazomethyl ketone, which was cooled in a cold water-bath, the reaction proceeded smoothly. After standing at room temperature for forty hours, a 75% yield of coumaranone was obtained.

ω,2-Dimethoxyacetophenone. o-Methoxyphenylmagnesium bromide was prepared from 100 g. of o-bromoanisole and magnesium according to the usual Grignard procedure. After refluxing the reaction mixture for one hour, it was cooled to room temperature, and a solution of 38.4 g. of methoxyacetonitrile in 200 cc. of sodium-dried ether was added with mechanical stirring over a period of one hour. At first a white solid separated, but soon a black gum formed which made stirring very difficult. However, upon stirring and refluxing for an additional 2 hrs. this gum disappeared leaving a creamy yellow mixture. The ether was then replaced with anhydrous benzene, and refluxing was continued for 2.5 hrs. The brown mixture was cooled, hydrolyzed with 10% sulfuric acid, and worked up in the usual manner, to give a yield of 52 g., or 54% of material which boiled at 149–152° at 10 mm. Pratt and Robinson (18) prepared this compound from o-methoxybenzoyl chloride and report a yield of 44% of material which boiled at 165° at 15 mm. The semicarbazone melted at 138.1–139.1°. Pratt and Robinson report the melting point 137° for this derivative.

Ethyl β-methoxymethyl-β-(2-methoxyphenyl)hydracrylate was prepared from the ketone by the same procedure used in the para series. The ester was obtained in 74% yield and

boiled at 127–128° at 0.2 mm. The colorless oil gradually became yellow upon standing. It gave a negative Legal test. Saponification by the usual procedure gave an oil which could not be crystallized.

β-(2-Methoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide. A solution of 21 g. of the above ester in 40 cc. of glacial acetic acid and 80 cc. of the acetic acid-hydrogen bromide mixture was heated at 110–120° for 30 min., and then worked up in the usual manner. After repeated recrystallization from benzene, a 51% yield of colorless, needle-like rectangular prisms which melted at 95.1–95.6° was obtained. This lactone gave a positive Legal test and a negative ferric chloride test. Neither an alcoholic solution nor an aqueous suspension of the lactone decolorized bromine water.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3.
Found: C, 69.2; H, 5.2.

Action of hydrogen bromide on β-(2-methoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide. Many attempts were made to split the ether in the above methoxy lactone by use of hydrobromic acid, of hydrogen bromide in glacial acetic acid, and of mixtures of these with one another or with glacial acetic acid, under various heating conditions, but in all cases a mixture of the starting material and an acidic substance which proved to be coumaronyl-3-acetic acid was obtained. After recrystallization from petroleum ether (Skellysolve B) the latter formed flattened white needles which melted at 89.2–91.2°. Titoff, Müller, and Reichstein (19) report the melting point 89–90°. The *amide* was prepared in the usual manner and was recrystallized from ether to yield long, flattened needles which melted at 190.6–191.1°. Reichstein and co-workers report the melting point 191° for this derivative.

Ethyl β-methoxymethyl-β-(2-methoxycyclohexyl)hydracrylate. A solution of 27 g. of ethyl β-(*o*-methoxyphenyl)-β-methoxymethylhydracrylate in 150 cc. of glass-distilled glacial acetic acid was shaken under 3 atm. pressure of hydrogen with 0.5 g. of platinum oxide. Absorption of hydrogen proceeded slowly and after 48 hrs. 0.5 g. of fresh catalyst was added. After about 60 hrs. absorption of hydrogen stopped after the calculated amount had been taken up. The reduction product was dissolved in ether and washed with sodium carbonate solution which removed a small amount of acidic materials. The neutral material was very carefully fractionally distilled under reduced pressure and a fraction of 15.4 g. of material boiling at 104–114° at 0.3 mm. followed by a second fraction of 7.9 g. boiling at 114–116° was collected. Redistillation of the second fraction yielded a colorless oil boiling at 122–123° at 1 mm. The analytical figures obtained with this material indicated that it was the desired ethyl β-methoxymethyl-β-(2-methoxycyclohexyl)hydracrylate.

Anal. Calc'd for $C_{14}H_{26}O_5$: C, 61.3; H, 9.5; Alkoxyl O, 17.5.
Found: C, 61.6; H, 9.4; Alkoxyl O, 15.1.

The lower-boiling fractions had higher carbon and lower hydrogen contents, indicating that some formation of hexahydrocoumaronyl derivatives by ester cleavage had taken place, an assumption which was supported by the lower alkoxyl oxygen content of these fractions. For example, a fraction boiling at 116–120° at 1 mm. gave the following figures:

Anal. Found: C, 63.4; H, 9.9; Alkoxyl O, 12.4.

Action of hydrochloric acid on ethyl β-methoxymethyl-β-(2-methoxycyclohexyl)hydracrylate. A solution of 3.8 g. of the above ester in 12 cc. of hydrochloric acid (sp. gr. 1.19) was refluxed for 3 hrs. After about 10 min. an oil separated. The cooled reaction mixture was extracted with chloroform, and the chloroform solution was washed successively with dilute sodium carbonate solution and water. After removal of the solvent a dark oil remained which contained chlorine and gave a strong Legal test. In order to replace the chlorine by hydroxyl, the oil was heated in a sealed tube at 120° with 30 cc. of water for 2 hrs. The reaction mixture was extracted with ether and the product still showed a faint Beilstein test for halogen and a strongly positive Legal test. It was distilled under reduced pressure and the fraction boiling at 185–195° at 0.1 mm. was collected as a nearly colorless oil. Analysis indicated that some dehydration of the nuclear hydroxyl group had occurred.

Anal. Calc'd for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7.
Calc'd for $C_{10}H_{12}O_2$: C, 73.2; H, 7.3.
Found: C, 68.4; H, 7.9.

When hydrobromic acid was used instead of hydrochloric acid for the above reaction, decomposition was more pronounced and an extremely small yield of product was obtained, which, however, gave a strong positive Legal test.

Methyl 2-methoxycyclohexane carboxylate. Methyl *o*-methoxybenzoate was dissolved in absolute methanol and hydrogenated in the presence of Raney Nickel, at 200° and 2000–2700 pounds per square inch pressure of hydrogen. Variation of the temperature or of the concentration of the solution did not appreciably alter the results, but the pressure must initially be high in order to get reaction. The catalyst was removed by centrifuging, and the reaction mixture was distilled, yielding 30% of material which boiled at 96.5–97° at 15 mm.

Anal. Calc'd for $C_9H_{16}O_3$: C, 62.8; H, 9.4.
Found: C, 62.8; H, 9.3.

The main product of the reaction was methyl cyclohexane carboxylate.

2-Methoxycyclohexane carboxylic acid. This acid was obtained by alkaline hydrolysis of the ester, in a yield of 83%, as a colorless viscous oil which boiled at 122–123° at 5 mm. It had an odor which resembled that of valeric acid.

Anal. Calc'd for $C_8H_{14}O_3$: C, 60.7; H, 8.9; OCH_3, 19.6.
Found: C, 60.9; H, 9.1; OCH_3, 19.8.

The *p*-toluidide was prepared in the usual manner, as a red oil which crystallized on addition of petroleum ether. After six recrystallizations from this solvent, it formed fine white needles which melted at 130.2–132.4°.

Anal. Calc'd for $C_{15}H_{21}NO_2$: C, 72.8; H, 8.6.
Found: C, 73.1; H, 8.7.

The mother liquors yielded a small amount of white needles which melted at 85–108°, and were probably a mixture of the *cis* and *trans* isomers. Further purification was not possible with the small amount of material available.

2-Methoxycyclohexane carboxylic acid chloride was prepared from the acid in the usual manner andwas sealed in glass ampoules without further purification.

ω-Diazo-2-methoxyhexahydroacetophenone was prepared from the above acid chloride according to the usual procedure and was obtained as a red oil which was used immediately without purification.

Attempted preparation of ω-acetoxy-2-methoxyhexahydroacetophenone. The diazomethyl ketone was treated with acetic acid, according to the usual procedure, and the red oil obtained was distilled three times to yield two colorless fractions. A yield of 4.8 g. of material which boiled at 88–90° at 10 mm., and of 1.5 g. of material which boiled at 93–105° at 10 mm. was obtained from 17.6 g. of the diazomethyl ketone. Analysis of both of these fractions indicated a mixture of hexahydrocoumaranone and ω-acetoxy-2-methoxyhexahydroacetophenone.

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 61.7; H, 8.5.
Calc'd for $C_8H_{12}O_2$: C, 68.5; H, 8.6.
Found: C, 67.0, 67.4; H, 8.8, 8.9.

Ethyl hexahydrosalicylate was prepared by high-pressure hydrogenation of an ethanol solution of methyl salicylate in the presence of Raney Nickel catalyst according to Connor and Adkins (20) who obtained material which boiled at 117–18° at 13 mm. We obtained material which boiled at 110–115° at 13 mm.

Hexahydrosalicylic acid. The above ester was shaken at room temperature with a slight excess of 10% aqueous sodium hydroxide solution for about 5 minutes. The resulting homogeneous solution was allowed to stand for 1.5 hrs. after which it was concentrated *in vacuo*, washed with ether, acidified with a slight excess of 10% hydrochloric acid, saturated with ammonium sulfate, and finally thoroughly extracted with ether. Removal of the ether gave a quantitative yield of a syrup which was crystallized with great difficulty. This material was apparently a mixture of *cis* and *trans* isomers, which caused difficulty in recrystallization, as it tended to separate as an oil from the solvents. After repeated recrystallization from dry ether and from ethyl acetate, two fractions of transparent prisms

were obtained. The larger fraction melted at 76–78°, and the other melted at 109–110°. Einhorn and Meyenburg (21), who prepared this acid from hexahydroanthranilic acid, report the melting point 111°, as do all other investigators who have made it with the exception of Böeseken and his co-workers (22), who state that they obtained a small amount of an acid which melted from 57–63° from the mother liquors of the 111° acid.

Anal. of the material which melted at 76–78°. Calc'd for $C_7H_{12}O_3$: C, 58.3; H, 8.4.
Found: C, 58.1; H, 8.2.

The *amide* was prepared in the usual manner from the ester and concentrated ammonium hydroxide. After several recrystallizations from acetone, it formed rectangular plates which melted at 113.7–114.7°.

Anal. Calc'd for $C_7H_{13}NO_2$: C, 58.7; H, 9.2.
Found: C, 58.8; H, 9.1.

2-Acetoxycyclohexane carboxylic acid. A crude sample of the above acid, melting at 51–91°, was dissolved in anhydrous ether and was gently refluxed for 1.5 hrs. with an excess of freshly distilled acetyl chloride. Distillation caused some decomposition, but a yield of 21% of a syrup which boiled at 132–135° at 4 mm. was obtained. This syrup crystallized after standing overnight, and after several recrystallizations from petroleum ether formed prisms which melted at 66.1–66.6°. When a sample of this material was mixed with a sample of the original acid, it liquified before it could be placed in a melting point tube. Easson and Pyman (23) describe the acetate as melting at 96–101°.

Anal. Calc'd for $C_9H_{14}O_4$: C, 58.1; H, 7.6.
Found: C, 58.1; H, 7.7.

Attempts at purification, without distillation, by seeding and recrystallization of the crude syrup were partially successful, but the process was very time consuming.

The p-*toluidide* was prepared in the usual manner, from the crude acid, by way of the acid chloride. Repeated recrystallization from petroleum ether gave two fractions; the larger fraction formed white needles which melted at 154–155.9°, and the smaller fraction formed white needles which melted at 124–143°.

Anal. of the first fraction. Calc'd for $C_{16}H_{21}NO_3$: C, 69.8; H, 7.7.
Found: C, 70.2; H, 8.0.

2-Acetoxycyclohexane carboxylic acid chloride was prepared in the usual manner by the action of thionyl chloride at room temperature upon crude acid. Distillation caused partial decomposition, but a yield of 30% of material which boiled at 100–107° at 4 mm. was obtained. Preparation of the *p*-toluidide gave a mixture which was identical with that obtained above.

ω-Diazo-2-acetoxyhexahydroacetophenone was prepared from the above acid chloride in the usual manner.

Attempted preparation of ω,2-diacetoxyhexahydroacetophenone. The diazomethyl ketone was treated with acetic acid in the usual manner, yielding a red oil. Distillation caused some decomposition, and the bulk of the material remained in the flask as a red tar, but a very small amount of a yellow liquid distilled at 80–120° at 0.4 mm. This material soon turned dark red upon standing. Further investigation of this substance was abandoned because of the extremely small yield.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

OBSERVATIONS ON THE EFFECT OF SOME SOLVENTS UPON THE ACYLATION OF PHENOL WITH HIGH MOLECULAR WEIGHT ACID CHLORIDES

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When phenol is acylated with caprylyl chloride in the presence of aluminum chloride, it has been recently shown (1) that the ratio of para- to ortho-hydroxy ketones produced is materially influenced by the solvent employed. In this previous work the solvents studied were carbon disulfide, nitrobenzene, tetrachloroethane, and a hydrocarbon (petroleum ether, b.p. 60–71°, Skellysolve B). The observation was made that carbon disulfide gave the lowest ratio of para- to ortho-hydroxycaprylophenone, while nitrobenzene decidedly favored the formation of the para isomer.

It seemed desirable to extend this work to include the influence of solvents during the acylation of phenol with acyl chlorides of higher molecular weight than caprylyl chloride. Previously, it has been shown (1, 2, 3, 4, 5) that the molecular proportion of aluminum chloride, the order of addition of the reactants, and the temperature are factors which influence the relative yield of isomers in both the rearrangement of phenyl esters and in the acylation of phenol. In order to obtain a direct comparison of the orienting effects of the several solvents studied in this work and to exclude other variables, a small excess of aluminum chloride over the amount required to form both the phenol-aluminum chloride and acyl chloride-aluminum chloride complexes was used. Three solvents have been investigated, namely: tetrachloroethane, carbon disulfide, and nitrobenzene. The even-numbered acyl chlorides from caprylyl chloride to stearoyl chloride inclusive were studied.

The results of this study, as summarized in Table I, show that when nitrobenzene is used as a solvent for these acylations in the presence of an excess of aluminum chloride the relative yield of para-hydroxy ketones to ortho-hydroxy ketones is much higher than when carbon disulfide is employed.

The length of the alkyl chain does not appear to exert a pronounced influence upon the relative yields of para- and ortho-hydroxy ketones. This is evidenced by the fact that the p/o ratios of the products are comparable over the entire range of acid chlorides.

Acylations in tetrachloroethane conducted with acyl halides of higher molecular weight than caprylyl chloride gave resinous products from which no ketones could be isolated. It has been previously shown (6) that good yields of both para- and ortho-hydroxy ketones can be obtained in the acylation of phenol with high molecular weight acyl chlorides when only one molecular equivalent of aluminum chloride is used and tetrachloroethane is employed as the solvent. Furthermore, it is known that when an excess of aluminum chloride is employed in acylations of phenol using caprylyl chloride the ratio of para- to ortho-hydroxy ketones produced is quite high. The observation, Table I, that acylations with

acyl chlorides of higher molecular weight than caprylyl chloride yield only resins when conducted in tetrachloroethane with an excess of aluminum chloride, indi-

TABLE I

EFFECT OF SOLVENTS UPON THE ACYLATION OF PHENOL IN THE PRESENCE OF EXCESS ALUMINUM CHLORIDE[a]

ACID CHLORIDE	SOLVENT									
	Tetrachlorethane[b]				Nitrobenzene[c]			Carbon Disulfide[d]		
	% Para		% Ortho	Ratio p/o	% Para	% Ortho	Ratio p/o	% Para	% Ortho	Ratio p/o
C_8	49.5		21.4	2.32	68.0	21.5	3.16	54.7	40.8	1.34
C_{10}		Resins			74.2	20.6	3.61	52.0	43.6	1.19
C_{12}		"			72.5	21.3	3.39	54.6	41.4	1.32
C_{14}		"			72.7	21.1	3.44	52.3	35.6	1.47
C_{16}		"			66.7	21.6	3.08	50.7	46.6	1.09
C_{18}		"			67.1	21.3	3.14	54.0	41.6	1.30

[a] 0.22 mole $AlCl_3$, 0.11 mole phenol and 0.1 mole RCOCl.
[b] 3 hrs. at 70°.
[c] 3 hrs. at 70°.
[d] 5.5 hrs. at 47°.

TABLE II

EFFECT OF ALUMINUM CHLORIDE UPON REAGENTS AND PRODUCTS IN THE ACYLATION OF PHENOL WITH LAUROYL CHLORIDE: TETRACHLOROETHANE 5 HRS. AT 50°

REACTANTS	THEORETICAL YIELD	YIELD, %
0.22 Mole $AlCl_3$ 0.11 Mole phenol 0.1 Mole lauroyl chloride 80 cc. Solvent	*o,p*-Hydroxylaurophenones 27.6 g.	Resins 70.7
0.22 Mole $AlCl_3$ 0.11 Mole phenol 60 cc. Solvent	Phenol 10.4 g.	Phenol 61.5 Resins 14.4
0.22 Mole $AlCl_3$ 0.1 Mole lauroyl chloride 60 cc. Solvent	Lauric acid 20.1 g.	Resins 64.2
0.08 Mole $AlCl_3$ 0.04 Mole *p*-hydroxylaurophenone 32 cc. Solvent	*p*-Hydroxy ketone 11.1 g.	Resins 84.7
0.0668 Mole $AlCl_3$ 0.0324 Mole *o*-hydroxylaurophenone	*o*-Hydroxy ketone 8.9 g.	Resins 78.6
0.22 Mole $AlCl_3$ 60 cc. Solvent	Solvent 58 cc.	Solvent 96.7

cates that this is not a satisfactory solvent for the preparation of high molecular weight para-hydroxy ketones.

The fact that only resinous products were obtained when acylations with higher molecular weight acid chlorides were conducted in tetrachloroethane under these conditions indicates either that one of the reactants is unstable or that the hydroxy ketones themselves undergo decomposition. It appeared that such reactions may also involve the solvent, since hydroxy ketones were obtained in high yields when carbon disulfide or nitrobenzene was used as the solvent. In order to investigate further the effect of tetrachloroethane upon these acylations, phenol, lauroyl chloride, and ortho- and para-hydroxylaurophenone were treated with excess aluminum chloride under conditions similar to those employed during the acylation reactions. The effect of aluminum chloride upon tetrachloroethane was also investigated. The results obtained are summarized in Table II and show that lauroyl chloride, *p*-hydroxylaurophenone and *o*-hydroxylaurophenone form resinous products when heated for five hours at 50° in the presence of two molecular equivalents of aluminum chloride in tetrachloroethane. Phenol is partially converted to resinous products by this treatment and tetrachloroethane is essentially unaffected.

The fact that neither of the hydroxylaurophenones is stable under these conditions is especially noteworthy. There appears to be no plausible explanation at this time why acylations with acyl chlorides higher than caprylyl chloride in this solvent with excess aluminum chloride yield only resinous products while smooth reactions are obtained with the lower acid chlorides. Hydroxycaprylophenones are stable in tetrachloroethane in the presence of an excess of aluminum chloride but hydroxylaurophenones undergo excessive decomposition.

EXPERIMENTAL

Acylation of phenol with lauroyl chloride in tetrachloroethane. Anhydrous aluminum chloride (29.3 g., 0.22 mole) was weighed into a dry, 200-cc., three-necked flask equipped with a mechanical stirrer, dropping-funnel, and thermometer. Tetrachloroethane (20 cc.) was then added, followed by phenol (10.4 g., 0.11 mole) dissolved in 50 cc. of tetrachloroethane. After the evolution of hydrogen chloride had subsided, lauroyl chloride (21.9 g., 0.1 mole) dissolved in 20 cc. of tetrachloroethane was added dropwise over a period of twenty-five minutes. The mixture was then heated for three hours at 70° with constant stirring, after which it was hydrolyzed by pouring into 200 cc. of cold water, and steam distilled to remove the solvent.

The product was cooled, transferred to a liter separatory funnel, ether added, and the aqueous layer removed. The ether layer was then extracted with two 100-cc. and two 40-cc. portions of 3% sodium hydroxide in a 10% solution of alcohol in water. The alkaline extract was acidified with hydrochloric acid, boiled to remove the alcohol and ether, and cooled. The oily product was dissolved in ether, placed in a Claisen flask and the ether removed by a water-bath. Vacuum distillation under 4 mm. pressure gave 7.8 g. of a viscous oil boiling up to 240°. The residue was a tar-like product which weighed 5.8 g.

The ether solution from the alkali extraction was dried with anhydrous sodium sulfate and the ether removed by evaporation. Distillation of the product under 4 mm. pressure gave an oily product (7.29 g.) and 1.69 g. of a tar-like residue.

p-Hydroxylaurophenone could not be identified in the alkali-soluble portion nor *o*-hydroxylaurophenone in the alkali-insoluble fraction.

Similar reactions were run using caprylyl, capryl, myristoyl, palmitoyl, and stearoyl chlorides. Resinous products were obtained in every case with the exception of the caprylyl chloride which gave 49.5% *p*-hydroxycaprylophenone (m.p. 62–63°, 2,4-dinitrophenylhydrazone m.p. 176–176.5°) and 21.4% of *o*-hydroxycaprylophenone (b.p. 115–120° at 1 mm., 2,4-dinitrophenylhydrazone m.p. 144.5–145°).

Acylation of phenol with lauroyl chloride in nitrobenzene. Anhydrous aluminum chloride (29.3 g., 0.22 mole) was mixed with 30 cc. of nitrobenzene, and phenol (10.4 g., 0.11 mole) dissolved in 30 cc. of nitrobenzene was added. Lauroyl chloride (21.9 g., 0.1 mole) dissolved in 30 cc. of nitrobenzene was then added dropwise. The reaction mixture was heated for three hours at 70°. The product was hydrolyzed, steam distilled, and the *o*- and *p*-hydroxylaurophenone separated as above described. This yielded 5.9 g. of *o*-hydroxylaurophenone (m.p. 42.5–43°, 2,4-dinitrophenylhydrazone m.p. 92–93°) and 20.0 g. of *p*-hydroxylaurophenone (m.p. 70–71°, 2,4-dinitrophenylhydrazone m.p. 147–148°.

Phenol was also acylated with caprylyl, capryl, myristoyl, palmitoyl, and stearoyl chlorides according to the above procedure. The yields are shown in Table I. The melting points of the hydroxy ketones and of their 2,4-dinitrophenylhydrazones agreed with those previously reported (6).

o-Hydroxycaprophenone and *p*-hydroxycaprophenone have not been previously described. The melting point of the former is 35.0–35.5° and of the latter 63.5–64.0°. The 2,4-dinitrophenylhydrazones melted at 111–112° and 148–148.5° respectively.

Anal. Calc'd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74.
Found: (ortho) C, 77.14; H, 10.03.
(para) C, 77.40; H, 9.75.

Acylation of phenol with lauroyl chloride in carbon disulfide. The acylation was conducted in a manner similar to that previously described with the exception that carbon disulfide was used as the solvent instead of nitrobenzene. The reaction was run for five and one-half hours at the reflux temperature of the carbon disulfide. Hydrolysis was accomplished by pouring into water followed by the addition of an equal volume of a mixture of alcohol and concentrated hydrochloric acid. The isomers were separated as described above.

Acylations were conducted in a similar manner with caprylyl, capryl, myristoyl, palmitoyl, and stearoyl chlorides. The melting points of the products agreed with those previously reported.

Effect of aluminum chloride upon phenol in tetrachloroethane. Phenol (10.4 g., 0.11 mole) in 60 cc. of freshly distilled tetrachloroethane was heated for five hours at 50° with anhydrous aluminum chloride (29.3 g., 0.22 mole). The product was hydrolyzed by pouring into water and the aqueous layer separated from the solvent layer. The former was acidified with hydrochloric acid and extracted four times with 50-cc. portions of ether. This ether solution was then dried with anhydrous sodium sulfate. The solvent layer was shaken with two 60-cc. portions of 5% aqueous sodium hydroxide solution and the alkaline extract acidified with hydrochloric acid and extracted with three 50-cc. portions of ether. This ether solution was then dried with anhydrous sodium sulfate and combined with the former ether extract. The ether was then removed and the product distilled at atmospheric pressure.

Effect of aluminum chloride upon lauroyl chloride in tetrachloroethane. Lauroyl chloride (21.9 g., 0.1 mole) was heated with anhydrous aluminum chloride (29.3 g., 0.22 mole) in 60 cc. of tetrachloroethane for five hours at 50°. The product was hydrolyzed and the solvent removed by steam distillation. This product was then dissolved in ether and the solution dried. Distillation at 6 mm. pressure gave only a resinous product, 12.9 g., 64.2%. No lauric acid was identified either in the distillate or residue.

Effect of aluminum chloride upon p*-hydroxylaurophenone.* *p*-Hydroxylaurophenone (11.1 g., 0.04 mole) was heated with anhydrous aluminum chloride (10.7 g., 0.08 mole) in 32 cc. of tetrachloroethane for five hours at 50°. After hydrolysis and steam distillation there was recovered 9.4 g., 84.7% of a resinous product from which no *p*-hydroxylaurophenone could be separated. A similar treatment of *o*-hydroxylaurophenone gave 78.0% of an oil from which no *o*-hydroxylaurophenone could be obtained.

Effect of aluminum chloride upon tetrachloroethane. Tetrachloroethane, 60 cc., was heated with 29.3 g. of anhydrous aluminum chloride for five hours at 50°. After hydrolysis and steam distillation, 58 cc. (96.7%) of the tetrachloroethane was recovered. Distillation gave only a trace of a brownish residue.

SUMMARY

1. Friedel-Crafts acylations of phenol have been conducted with even-numbered acyl halides from caprylyl to stearoyl chlorides inclusive in tetrachloroethane, nitrobenzene, and carbon disulfide in the presence of excess aluminum chloride, and the results compared.

2. Nitrobenzene exerts a much greater para-directing influence than carbon disulfide.

3. Acylations of phenol with acyl chlorides of higher molecular weight than caprylyl chloride in tetrachloroethane gave only resinous products.

4. The length of the alkyl chain does not exert an influence upon the ratio of para to ortho isomers obtained when phenol is acylated under the conditions described.

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

THE ACTION OF ALKALINE REAGENTS ON 1,4-DIHALO-1,4-DIBENZOYLBUTANES

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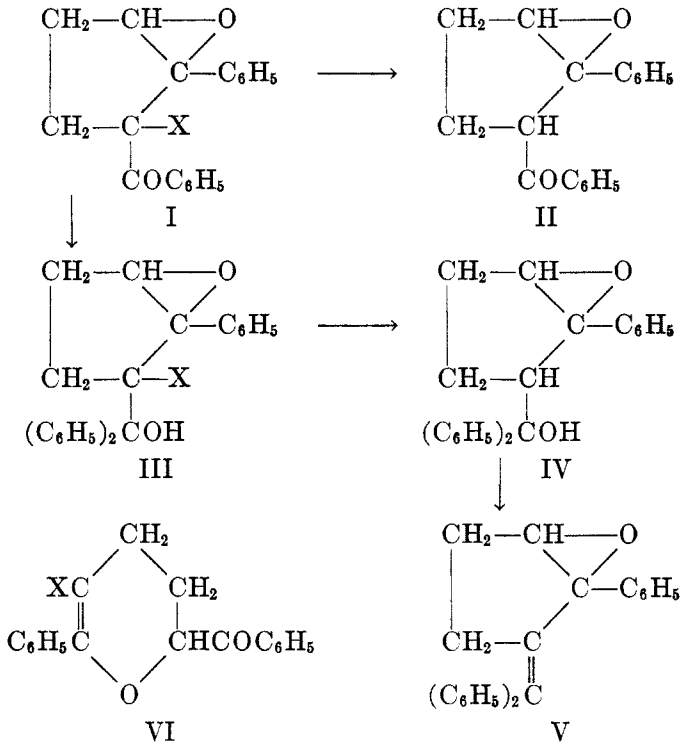
The bromo compound obtained by the action of sodium cyanide on 1,4-dibromo-1,4-dibenzoylbutane (1) has been identified by Kao (2) as 5-bromo-5-benzoyl-1-phenyl-1-cyclopentene oxide (I, X = Br). This structure is in accord with Kao's discovery that the bromo compound can be debrominated to give the known 5-benzoyl-1-phenyl-1-cyclopentene oxide (II) (3).



Our study of the bromo compound had yielded results similar to those of Kao. The bromo compound was prepared by the action of diethylamine on the dibromo diketone. Other alkaline reagents such as sodium cyanide and sodium acetate gave lower yields. We have also made the corresponding chloro compound by this method. The behavior of the chloro compound is similar to that of the bromo compound. The latter yields the cyclopentene oxide (II) when treated with zinc dust and sodium iodide in acetone. Treatment with hydroxylamine yields in each case an oxime. The bromo oxime was converted to the corresponding anilide.

Condensation with phenylmagnesium bromide gave in each instance the expected carbinol (III). The carbinols were dehalogenated by treatment with zinc in acetic acid. However, the halogen-free carbinol (IV) was obtained only from the chloro compound. The bromo compound gave a derivative whose composition corresponds to that of the dehydration product (V) of the carbinol. It is possible that in both IV and V the oxide ring may have rearranged to give the corresponding cyclopentanone.

An interesting transformation was observed when the chloro compound (I, X = Cl) was treated with zinc in acetic acid; 1,4-dibenzoylbutane was formed. The genetic relationship between this diketone and the oxide (II) is further obscured by the discovery that the former is converted partially to the oxide merely by the action of sodium methoxide. The oxide appears as a by-product in the synthesis of the isomeric phenylbenzoylcyclopentenes by the method of Bauer (4).

The most interesting property of the halogen compounds is their failure to give a precipitate when heated with alcoholic silver nitrate solution. For this reason an alternative formula, 2-phenyl-3-halo-6-benzoyl-5,6-dihydro-1,4-pyran (VI), was considered. It would account for the inertness of the halogen atoms. Objections to the structure are that the compounds are unaffected by reagents generally used to detect ethylenic linkages. Bromine in carbon tetrachloride, potassium permanganate in acetone, and hydrogen in the presence of platinum left the compound unchanged.

The inertness of the halogen atom in the cyclopentene oxide derivative (I) is in agreement with the known fact that in both phenacyl halides and β-halogen ethers (5) the halogen atoms are anomalously inert.

EXPERIMENTAL

5-Benzoyl-5-bromo-1-phenyl-1-cyclopentene oxide (*I, X = Br*). This compound was prepared in yields of 60% from 1,4-dibromo-1,4-dibenzoylbutane by the method described by Kao (2); m.p. 138–139° (from ethanol).

Anal. Calc'd for $C_{18}H_{15}BrO_2$: C, 63.0; H, 4.4; Br, 23.3
Found: C, 62.9; H, 4.5; Br, 23.3.

The *oxime*[1] (from ethanol) melted at 178–179°, with decomposition.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: C, 60.3; H, 4.5.
Found: C, 60.6; H, 4.5.

An unstable compound melting at 90–93°, with decomposition, was isolated from the mother liquor.

Treatment of the oxime with thionyl chloride in chloroform solution converted it to the *anilide*[1] which, after recrystallization from alcohol, melted at 172–173°, with decomposition.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: N, 3.9.
Found: N, 4.1.

Condensation of the bromocyclopentene oxide (*I, X = Br*) *with phenylmagnesium bromide.* A solution of phenylmagnesium bromide was prepared from 5.4 g. of bromobenzene and 1 g. of magnesium in 50 cc. of dry ether. A solution of 5.8 g. of the oxide in 225 cc. of absolute ether was added, with stirring, during one-half hour. Stirring and heating were continued for an hour and the mixture was decomposed with ice and hydrochloric acid. The carbinol (IV, X = Br) was recrystallized from ethanol; m.p. 127–129°, with decomposition.

Anal. Calc'd for $C_{24}H_{21}BrO_2$: C, 68.39; H, 5.03.
Found: C, 68.12; H, 5.10.

[1] This compound was made by Dr. G. E. Goheen.

Reduction of the carbinol (IV, X = Br). A mixture of 1 g. of the carbinol, 3 g. of zinc dust, and 90 cc. of glacial acetic acid was boiled for six hours, concentrated, and poured into water. The solution was neutralized and extracted with ether. From the ether solution was obtained a halogen-free product melting (from methanol) at 159–160°.

Anal. Calc'd for $C_{24}H_{20}O$: C, 88.88; H, 6.21.
Found: C, 88.57; H, 6.24.

1,4-Dichloro-1,4-dibenzoylbutane. Two hundred sixty-six grams of 1,4-dibenzoylbutane was dissolved in 2660 cc. of hot carbon tetrachloride. A stream of chlorine was passed into the solution at a moderate rate for twenty minutes; the solution became yellow. The carbon tetrachloride, hydrogen chloride, and excess chlorine were then removed by distillation under diminished pressure. The residue was collected on a filter and recrystallized from ethyl acetate. The yield was 200 g. of pure product, melting at 177–178°.

Anal. Calc'd for $C_{18}H_{16}Cl_2O_2$: Cl, 21.15.
Found: Cl, 21.04.

5-Benzoyl-5-chloro-1-phenyl-1-cyclopentene oxide (I, X = Cl). Four grams of 1,4-dichloro-1,4-dibenzoylbutane was refluxed with 17 g. of diethylamine and 100 cc. of dry benzene. During the course of the reaction, the mixture became dark red in color, but remained clear. It was then cooled, and 200 cc. of ether added. The ether soluton was washed with water to remove excess diethylamine. Evaporation of the solution left an oily, semi-crystalline residue, which yielded colorless crystals after two recrystallizations from methanol. Two and one-half grams of pure oxide was obtained; m.p. 131–132°.

Anal. Calc'd for $C_{18}H_{15}ClO_2$: C, 72.37; H, 5.03; Cl, 11.88.
Found: C, 72.19; H, 5.01; Cl, 11.95.

No precipitate was formed when the compound was boiled with alcoholic silver nitrate solution. The chlorocyclopentene oxide did not decolorize an acetone solution of potassium permanganate. It reacted with nitric acid and with ozone, but in neither case was it possible to isolate a crystalline product.

Oxime. The oxime (from alcohol) melted at 168–169°.

Anal. Calc'd for $C_{18}H_{16}ClNO_2$: N, 4.47.
Found: N, 4.59.

Reduction of the chlorocyclopentene oxide (I, X = Cl) with zinc and acetic acid. A solution of 1 g. of the oxide in 50 cc. of glacial acetic acid was brought to boiling and 2 g. of zinc dust was added. The mixture was refluxed, with stirring, for one hour and poured into 300 cc. of water. The resulting solution was neutralized and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and the solvent removed. Crystallization of the residue first from methanol, then from ethyl acetate, gave crystals of 1,4-dibenzoylbutane melting at 105–106°. The identification was confirmed by the mixed melting point method.

Condensation of the chlorocyclopentene oxide (I, X = Cl) with phenylmagnesium bromide. A solution of 5 g. of the oxide in 225 cc. of absolute ether was added during one and one-fourth hours to a refluxing solution of phenylmagnesium bromide made from 5.4 g. of bromobenzene and 1 g. of magnesium in 50 cc. of absolute ether. The mixture was stirred for one hour at room temperature and poured into a mixture of ice and hydrochloric acid. The ether layer yielded 4.45 g. of the carbinol (IV, X = Cl) melting at 167–170°. Recrystallization from ethanol gave crystals melting at 169.5–170.5°.

Anal. Calc'd for $C_{24}H_{21}ClO_2$: C, 76.47; H, 5.62; Cl, 9.41.
Found: C, 76.60; H, 5.53; Cl, 9.58.

The carbinol gave no precipitate when treated with hot alcoholic silver nitrate solution, and failed to react with hydroxylamine or phenylhydrazine.

The carbinol appeared to undergo *rearrangement* when treated with hydrogen chloride in ether. A solution of 1 g. in 175 cc. of dry ether was saturated with dry hydrogen chloride and allowed to stand for two and one-half hours. Removal of the solvent left a residue, which when crystallized from methanol melted at 79–80°.

Anal. Calc'd for $C_{24}H_{21}ClO_2$: C, 76.47; H, 5.62.
Found: C, 76.90; H, 5.59.

Reduction of the carbinol (IV, X = Cl). A mixture of 1 g. of the carbinol, 90 cc. of glacial acetic acid, and an excess of zinc dust was boiled for five hours, concentrated, and poured into water. The halogen-free carbinol, crystallized from methanol, melted at 112–113°.

Anal. Calc'd for $C_{24}H_{22}O_2$: C, 84.12; H, 6.48.
Found: C, 83.98; H, 6.47.

SUMMARY

Evidence is presented to support the cyclopentene oxide structure assigned by Kao to the bromo compound formed from 1,4-dibromo-1,4-dibenzoylbutane under the influence of alkaline reagents. A similar structure is proposed for a chloro compound obtained from 1,4-dichloro-1,4-dibenzoylbutane.

URBANA, ILL.

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

THE ADDITION OF METHYLMAGNESIUM IODIDE[1] TO *t*-BUTYL MESITYL DIKETONE

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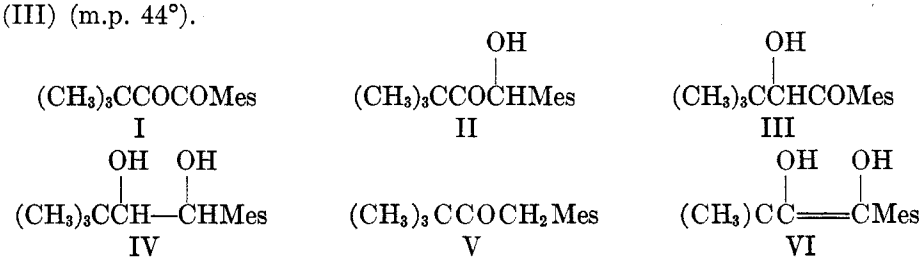
Many unsuccessful attempts have been made to bring about 1,2-addition of Grignard reagents to mesityl ketones (1). It seemed possible that this goal might be attained by operating on a diketone of the type MesCOCOR.[1] To test this idea we have prepared *t*-butyl mesityl diketone (I) and subjected it to the action of methylmagnesium iodide. It was to be expected that the enhanced reactivity characteristic of twinned carbonyl groups would favor the desired reaction.

SYNTHESIS OF THE DIKETONE

The diketone was made from mesitylpivalylcarbinol (II) by a modification of the procedure used to prepare *t*-butyl 3-nitromesityl diketone (2). It was found that the acyloin (II) could be oxidized to the diketone by the use of copper sulfate in pyridine.

An interesting observation was made in connection with the synthesis of the acyloin. When the condensation of *t*-butylglyoxal with mesitylene was carried out at a low temperature and over a long period of time, the chief product was not the known acyloin (m.p. 117–118°) but the isomer, *t*-butylmesitoylcarbinol (III) (m.p. 44°).



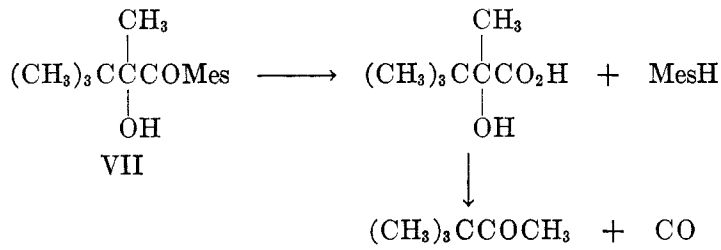
The new carbinol (III) was more soluble in alcohol than was its isomer. It formed an acetate when treated with acetic anhydride; oxidation converted it to the diketone (I); reduction transformed it to 1,2-*t*-butylmesitylethylene glycol (IV). The glycol yielded a diacetate when treated with acetic anhydride. Dehydration of the glycol with sulfuric acid produced mesityl pivalylmethane (V). This structure was assigned when it was found that the new ketone failed to respond to tests for hydroxyl or aldehyde groups, but formed a monoxime. Moreover, it did not liberate methane in contact with the methyl Grignard reagent. Finally, the low-melting acyloin (III) was found to rearrange under the influence of sodium ethoxide, to the high-melting isomer (II).

In this connection, it is interesting that hydrogenation of the diketone at low pressure yielded the corresponding enediol (VI); repeated tests with 2,6-dichlorobenzeneoneindophenol showed that the enediol persisted in solution for several hours. Isomerization to the high-melting acyloin (II) took place spontaneously. The latter was isolated in yields above 80%. None of the low-melting acyloin was detected.

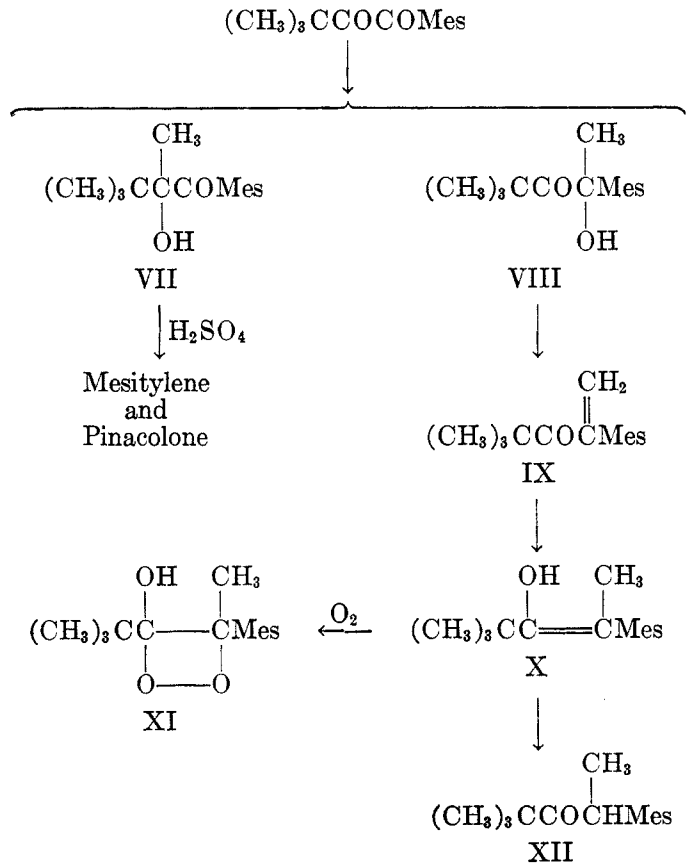
[1] Mes is used to represent the mesityl radical.

THE ADDITION OF METHYLMAGNESIUM IODIDE TO THE DIKETONE

The diketone reacted with methylmagnesium iodide in ether solution to yield two products, which proved to be the isomeric ketols formed by 1,2-addition of the reagent. The isomer which melted at 82° was identified as *t*-butylmesitoylmethylcarbinol (VII). This alcohol proved to be resistant to dehydrating agents. Heating with a mixture of concentrated sulfuric and glacial acetic acids, however, brought about cleavage of the molecule to mesitylene, pinacolone, and a gas, presumably carbon monoxide. These changes, which may be represented as follows, suffice to establish the structure of the ketol (VII).



The isomeric ketol (VIII), which melted at 105°, readily underwent dehydration yielding the vinyl ketone, IX.



This unsaturated ketone absorbed a mole of hydrogen in the presence of platinum to form the vinyl alcohol, X, which was converted by oxygen to the peroxide, XI. In attempts to isolate the vinyl alcohol, however, only the corresponding ketone (XII) was obtained.

These observations serve to demonstrate that methylmagnesium iodide reacts in the 1,2 manner with each of the carbonyl groups of *t*-butyl mesityl diketone, forming the corresponding ketols. Experiment showed also that pivalylmesitylene, the corresponding monoketone, was unaffected by methylmagnesium iodide. The formation of the ketol, mesitylmethylpivalylcarbinol (VIII) constitutes the first example of 1,2-addition of a Grignard reagent to a mesityl ketone.

EXPERIMENTAL[2]

t-Butylglyoxal. Pinacolone was oxidized with selenium dioxide to *t*-butylglyoxal, as was described previously (2). The yield of golden yellow liquid, b.p. 112–115°, was 48%.

Mesitylpivalylcarbinol and t-butylmesitoylcarbinol. An ice-cooled flask was charged with 160 cc. of mesitylene and 108 g. of anhydrous aluminum chloride. Stirring was begun, and 46 g. of freshly distilled *t*-butylglyoxal, dissolved in 40 cc. of mesitylene, was added over a period of forty-five minutes. Stirring was continued for one hour at 5°, and for an additional four hours at room temperature. After being allowed to stand overnight, the mass was poured on a mixture of 600 g. of ice and 200 cc. of concentrated hydrochloric acid. The mixture was diluted with 1 liter of water and 250 cc. of ether, stirred for thirty minutes, and filtered through a one-fourth inch layer of carbon. The organic layer was washed with water and dilute sodium bicarbonate and distilled under diminished pressure. The product, boiling at 125–130°/2 mm., weighed 30 g. It was recrystallized from ethanol; m.p. 117–118°. A mixed melting point with an authentic sample of mesitylpivalylcarbinol (II) showed no depression.

An identical run was made except that the reactants were stirred at 5° for nine hours. Subsequent decomposition in acid solution and distillation of the product yielded 40 g. of material boiling at 122–128°/2 mm. This corresponded to a yield of 43%. The substance did not crystallize from ethanol at room temperature. When it was dissolved in a small amount of the ethanol and cooled to *ca.* −80°, a solid precipitated. After three such recrystallizations, the *t*-butylmesitoylcarbinol (III) melted at 44°.

Anal. Calc'd for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40.
Found: C, 76.83; H, 9.53.

Four grams of *t*-butylmesitoylcarbinol was treated with 15 cc. of acetic anhydride and 10 cc. of pyridine at room temperature for twelve hours. The mixture was poured into water and the acetate, which separated as a white solid, was recrystallized from low-boiling petroleum ether. Its melting point was 68°.

Anal. Calc'd for $C_{17}H_{24}O_3$: C, 73.91; H, 8.69.
Found: C, 74.00; H, 8.58.

Isomerization of the acyloin. One-half gram of sodium was added to 10 cc. of absolute ethanol in a nitrogen-filled 3-necked flask. After the reaction was complete, a solution of 0.5 g. of *t*-butylmesitoylcarbinol in 10 cc. of absolute ethanol was added, and the solution was stirred for two hours at room temperature and for two hours at 75°. An atmosphere of nitrogen was maintained during the reaction period. The mixture was poured into 150 cc. of water, and the solid which separated was recrystallized from ethanol. The white, crystalline material melted at 117–118°, and the melting point in mixture with an authentic sample of mesitylpivalylcarbinol was not depressed.

When subjected to the treatment just described mesitylpivalylcarbinol was recovered unchanged.

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[2] Microanalyses by Miss Margaret McCarthy and Miss Theta Spoor.

t-*Butyl mesityl diketone.*[3] Twenty-three grams of mesitylpivalylcarbinol (or *t*-butylmesitoylcarbinol) was mixed with 50 g. of hydrated copper sulfate, 50 cc. of pyridine, and 20 cc. of water in a flask equipped with a stirrer and a condenser. The mixture was stirred and heated at 100° for three days. The yellow layer was separated and the aqueous layer was extracted with three 50-cc. portions of ether. The organic material was dried over anhydrous sodium sulfate and distilled. After the evaporation of the ether the diketone was distilled under reduced pressure. The yield of golden yellow oil was 19 g. or 83%; b.p. 115–118°/2 mm.; n_D^{20} 1.5068.

An *oxime* was prepared by mixing 1 g. of the diketone with 1 g. of hydroxylamine hydrochloride, 5 cc. of pyridine, and 5 cc. of absolute ethanol, and refluxing the solution overnight. The mixture was poured into 100 cc. of water and the solid which precipitated was recrystallized from a 4:1 methanol-water mixture. The oxime formed white crystals melting at 139°.

Anal. Calc'd for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50.
Found: C, 72.92; H, 8.52.

Reduction of t-*butyl mesityl diketone.* One gram of the diketone was dissolved in 30 cc. of ethanol. Fifty milligrams of platinum oxide was added and the mixture was treated with hydrogen for six hours at a pressure of two atmospheres. The colorless solution was filtered to remove the catalyst, and the solvent was evaporated rapidly under reduced pressure in an atmosphere of nitrogen. The solid residue, when recrystallized from ethanol, melted at 117–118°. A mixed melting point with mesitylpivalylcarbinol showed no depression.

Another sample of the diketone was reduced in a similar manner, and the resulting colorless solution was allowed to stand under an atmosphere of nitrogen. Samples were withdrawn from the flask at intervals and tested for the presence of an enediol with a solution of sodium 2,6-dichlorobenzeneoneindophenol. The solution continued to give a positive test for four or five hours, at the end of which time no enediol was present.

1,2-t-Butylmesitylethylene glycol (IV). A solution of 25 g. of *t*-butylmesitoylcarbinol in 150 cc. of ethanol was treated with hydrogen for eight hours in the presence of a copper chromite catalyst at 1500 pounds pressure and 175°. The ethanol was distilled under reduced pressure and the solid glycol was recrystallized from low-boiling petroleum ether. It weighed 23 g., constituting a 92% yield, and melted at 84–85°.

Anal. Calc'd for $C_{15}H_{24}O_2$: C, 76.27; H, 10.16.
Found: C, 76.12; H, 9.84.

The glycol formed a diacetate when treated with acetic anhydride and pyridine. After recrystallization from low-boiling petroleum ether it melted at 73–74°.

Anal. Calc'd for $C_{19}H_{28}O_4$: C, 71.25; H, 8.75.
Found: C, 71.08; H, 8.65.

Dehydration of 1,2-t-butylmesitylethylene glycol. A solution of 10 cc. of concentrated sulfuric acid in 15 cc. of water was added to 2 g. of the glycol, and the mixture was heated on the steam-cone for six hours. After the solution had cooled, it was diluted with 100 cc. of water and the solid which precipitated was recrystallized from methanol containing a small amount of water. The ketone (V) was obtained as white needles melting at 80–81°; yield 1.0 g.

Anal. Calc'd for $C_{15}H_{22}O$: C, 82.57; H, 10.09; mol. wt., 218.
Found: C, 82.57; H, 10.23; mol. wt. (ebullioscopic in chloroform) 214.

A Zerewitinoff determination showed no active hydrogen. When a 1-g. sample of the ketone was heated for twelve hours with 1 g. of hydroxylamine hydrochloride in ethanol and pyridine, a crystalline oxime was obtained. After crystallization from ethanol, it melted at 147°.

Anal. Calc'd for $C_{15}H_{22}NO$: C, 77.25; H, 9.87.
Found: C, 77.48; H, 9.76.

The reaction of t-*butyl mesityl diketone with methylmagnesium iodide.* A solution of 8.5 g. of methyl iodide in 15 cc. of anhydrous ether was added to 1.5 g. of magnesium turnings

[3] This compound was prepared by Dr. J. W. Corse.

in 15 cc. of dry ether at a rate sufficient to maintain a steady reflux of the solvent. After the mixture had been refluxed for an additional half hour, 8 g. of the diketone, dissolved in 15 cc. of dry ether, was added slowly. Refluxing was continued for four hours, the solution remaining nearly colorless. The reaction mixture was poured into 200 cc. of water containing 25 cc. of concentrated hydrochloric acid, and the ether layer was diluted, washed with a soution of sodium bicarbonate, and dried over anhydrous sodium sulfate. The semi-solid residue which remained after the ether was evaporated was dissolved in low-boiling petroleum ether. When the solution was chilled in a solid carbon dioxide bath the *t*-butyl-mesitoylmethylcarbinol (VII) precipitated as a white solid. It was recrystallized from the same solvent by intensive cooling and melted at 81–82°; yield 4 g.

Anal. Calc'd for $C_{16}H_{24}O_2$; C, 77.42; H, 9.68; mol. wt. 248.
Found: C, 77.31; H, 9.38; mol. wt. (ebullioscopic in chloroform) 249.

A Zerewitinoff determination showed one active hydrogen. Treatment with acetyl chloride and pyridine resulted in the formation of an acetate which, when recrystallized from low-boiling petroleum ether, melted at 77°.

Anal. Calc'd for $C_{18}H_{26}O_3$; C, 74.48; H, 8.96.
Found: C, 74.28; H, 8.65.

The mother liquors, after the isolation of the low-melting carbinol (VII), were allowed to evaporate at room temperature in contact with the air. The mesitylmethylpivalylcarbinol (VIII) formed large, cubic crystals. When washed free of the yellow diketone with the low-boiling petroleum ether, they weighed 1.5 g. and melted at 104–105°.

Anal. Calc'd for $C_{16}H_{24}O_2$: C, 77.42; H, 9.68; mol. wt., 248.
Found: C, 77.37; H, 9.57; mol. wt. (ebullioscopic in chloroform) 245.

A Zerewitinoff determination showed the presence of one active hydrogen. The material was recovered unchanged after treatment with acetic anhydride and pyridine.

Cleavage of t-*butylmesitoylmethylcarbinol* (*VII*). Three grams of the carbinol was dissolved in a mixture of 60 cc. of glacial acetic acid and 35 cc. of 60% (by volume) sulfuric acid, and the solution was heated on the steam-cone for five hours. The solution was poured into 200 cc. of water, the organic material was extracted with ether, and the solvent was evaporated. Distillation of the residue yielded two products. The lower-boiling compound was pinacolone (b.p. 100–110°). It was identified by the formation of a semicarbazone that melted at 154–156°. The other product was mesitylene which distilled at 55°/18 mm. It was identified by the formation of the dinitro derivative, which melted at 84–86°.

t-*Butyl* α-*mesitylvinyl ketone* (*IX*). Three grams of mesitylmethylpivalylcarbinol (VIII) was mixed with 30 cc. of 50% by volume sulfuric acid and heated for five hours on the steam-cone. The mixture was diluted with 100 cc. of water and extracted with ether. After the solvent was evaporated, the residue was distilled under diminished pressure. The pale yellow ketone (IX) boiled at 112°/3 mm.; n_D^{20} 1.5180; yield 2.5 g.

Anal. Calc'd for $C_{16}H_{22}O$: C, 83.47; H, 9.56.
Found: C, 83.71; H, 9.71.

Reduction of t-*butyl* α-*mesitylvinyl ketone*. A 0.5-g. sample of the vinyl ketone was dissolved in 20 cc. of ethanol, and 20 mg. of platinum oxide was added to the solution. The mixture was treated with hydrogen at atmospheric pressure for several hours after the calculated amount of gas had been absorbed. The resulting solution was filtered, and the solvent was evaporated. The mesitylmethylpivalylmethane (XII) was crystallized from a 5:2 methanol-water mixture; m.p. 86°.

Anal. Calc'd for $C_{16}H_{24}O$: C, 82.76; H, 10.34.
Found: C, 82.67; H, 10.21.

The ketone was recovered unchanged after treatment with acetic anhydride and pyridine.

The enol peroxide (*XI*). Another sample of the vinyl ketone was reduced in a similar manner, and immedately following the absorption of the calculated amount of hydrogen, a stream of air was passed through the solution for one hour. The solvent was distilled under reduced pressure and the residue was crystallized from methanol which contained a small amount of water. The crystalline peroxide melted at 106°.

Anal. Calc'd for $C_{16}H_{24}O_3$: C, 72.72; H, 9.09.
Found: C, 72.93; H, 9.20.

Treatment of pivalylmesitylene with methylmagnesium iodide. Pivalylmesitylene was prepared from pivalyl chloride and mesitylene (3). Twenty-one grams of the ketone was added to an excess of methylmagnesium iodide in a *n*-butyl ether solution. The mixture was refluxed, with stirring, for twelve hours and allowed to cool. It was poured on a mixture of 200 g. of ice and 25 cc. of concentrated hydrochloric acid, and the organic layer was washed free of acid, dried, and distilled. Distillation of the solvent left 17 g. of the original ketone; it boiled at 92–98°/2 mm.; n_D^{20} 1.5097. No other compound could be detected.

SUMMARY

The acyloin, *t*-butylmesitoylcarbinol (III), has been prepared by the condensation of *t*-butylglyoxal with mesitylene. When heated with sodium ethoxide it rearranged to the isomeric acyloin, mesitylpivalylcarbinol (II).

Oxidation of either acyloin with copper sulfate in pyridine has been shown to produce *t*-butyl mesityl diketone (I).

Hydrogenation of the diketone at low pressure yielded the corresponding enediol (VI), which rearranged spontaneously to the high-melting acyloin (II).

1,2-Addition of methylmagnesium iodide to each carbonyl group has been observed. This is the first recorded instance of 1,2-addition of a Grignard reagent to a mesityl ketone.

URBANA, ILL.

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[CONTRIBUTION FROM THE LABORATORIES OF SHELL DEVELOPMENT COMPANY]

THE PHOTO-ADDITION OF HYDROGEN SULFIDE TO OLEFINIC BONDS[1]

WILLIAM E. VAUGHAN AND FREDERICK F. RUST

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The photo-addition of hydrogen sulfide to olefinic bonds is so easily and quickly effected that it should find numerous applications in organic syntheses. Radiation of wave length sufficiently short to dissociate hydrogen sulfide (*ca.* 2800 Å.U.) seems to be the primary requisite for initiation of reaction. A quartz mercury arc as a radiation source and a quartz reaction vessel readily fulfill this requirement. However, Pyrex may be substituted for quartz if a small amount of a photo-sensitizer, such as acetone, which can be dissociated by longer wave length radiation, is added to the reaction mixture. In accordance with the rule proposed by Posner (10) concerning the addition of mercaptans to double bonds, the sulfhydryl group acts as does the mercapto group and adds to the carbon atom bonded to the greater number of hydrogen atoms. In the case of terminal olefinic bonds the only products are the primary mercaptan and the di-normal sulfide which is formed by combination of the mercaptan and the olefin. Although the rate of addition varies greatly from compound to compound, the reaction usually approaches completion at room temperatures in a relatively short time.

Although we have been unable to find references to a similar clean cut addition of hydrogen sulfide, certain work with mercaptans may be pertinent. Posner (10) observed the addition of certain mercaptans to the double bond of unsaturated ketones and proved that the reaction could be extended to olefins. In 1934, Burkhardt (2) suggested that the addition of thiophenol to styrene might proceed as a chain reaction. Jones and Reid (4) showed that peroxides are catalysts for such additions. Kharasch, Read, and Mayo (6) have shown that the additions of thioglycolic acid to styrene and isobutene take place in accordance with Posner's rule and suggest that this reaction and previously observed mercaptan additions are catalyzed by the presence of oxygen or peroxide, which generate chain-initiating RS radicals. They term such addition "abnormal," that is, contrary to an admittedly arbitrary extension of Markownikoff's Rule. Kaneko (5), in synthesizing $CH_3SCH_2CH_2CH_2OH$ by addition of methylmercaptan to allyl alcohol, indicates that daylight, in conjunction with mercury methylmercaptide and oxygen, greatly accelerates reaction, but that it is ineffective in the absence of the latter two materials.

The literature indicates that addition of hydrogen sulfide to double bonds takes place only under rather severe conditions. A number of workers have studied the reaction and have employed temperatures from 200° to 750°, various catalysts, and usually superatmospheric pressure. In general, the yields are relatively low and a complex mixture of isomers and by-products results. The

[1] Presented before the Division of Organic Chemistry of the American Chemical Society at its 103rd meeting, Memphis, Tennessee, April 20–23, 1942.

review by Mayo and Walling (8) is a concise summary of the field of hydrogen sulfide-olefin reactions.

MATERIALS AND TECHNIQUE

Hydrogen sulfide (Ohio Chemical) was collected in a liquid air-cooled trap, thoroughly degassed and distilled under vacuum from a trap cooled by solid carbon dioxide to one in liquid air. The 1-butene, propylene, diallyl, and vinyl chloride were the materials previously purified (12). Laboratory samples of diallyl ether and methyl acrylate were refractionated.

The techniques of both liquid- and gas-phase experiments were those described in the paper on the photo-addition of hydrogen bromide (12). Briefly, the reactants were distilled under a high vacuum into a bomb tube reactor (usually of quartz) which was sealed off and then exposed to radiation from a quartz mercury arc lamp. Selected temperatures were maintained by immersing the reactor in a transparent liquid bath contained in a larger quartz vessel.

DISCUSSION

Hydrogen sulfide shows continuous absorption beginning at *ca.* 2800 Å.U. and is photochemically decomposed with a quantum efficiency of the order of unity into hydrogen and sulfur. In the decomposition H atoms and HS radicals are formed (11). These particles can initiate a chain reaction in the following manners:

(a) $$H_2S \xrightarrow{h\nu} H + HS$$

(b) $$H + H_2C{=}CHR \longrightarrow H_3C\dot{C}HR$$

(c) $$H_3C\dot{C}HR + H_2S \longrightarrow H_3CCH_2R + HS$$

or (d) $$H + H_2S \longrightarrow H_2 + HS$$

Both (c) and (d) would also lead to the chain begun by the photo-generated HS radical:

(e) $$HS + H_2C{=}CHR \longrightarrow HSCH_2\dot{C}HR$$

(f) $$HSCH_2\dot{C}HR + H_2S \longrightarrow HSCH_2CH_2R + HS$$

The length of the chains precludes the ready detection of the saturated hydrocarbon or hydrogen formed in (c) and (d). Steps (e) and (f) are the chain-carrying steps and their length would be dependent upon processes of radical destruction which might occur in the system, as at walls or by recombination. The energetics of the various reactions, as roughly based upon bonding energies (9), are almost exactly the same as those involved in the analogous case of the photo-addition of hydrogen bromide to olefins.

With longer wave length radiation, the "abnormal" reaction can be sensitized by materials which are decomposed into radicals by such quanta. Thus, for example, acetone is dissociated at *ca.* 3200 Å.U. into CH_3 and $CH_3\dot{C}{=}O$; either

of these particles can remove an H atom from H_2S, giving an HS radical which can enter into the reaction (e).

EXPERIMENTAL

LIQUID-PHASE REACTION—SIMPLE OLEFINS

1-Butene (0.044 mole) and hydrogen sulfide (0.088 mole) sealed in a 10 mm. I.D. quartz tube were illuminated for four minutes at 0°C with the full radiation of a quartz mercury arc. After chilling in solid carbon dioxide the tube was opened, and the unreacted material evaporated off. The product (3.8 cc.) was shaken with a large excess of 10% sodium hydroxide solution and the supernatant liquid removed. This amounted to 0.5 cc. and had a refractive index n_D^{20} 1.4530. A sample of Eastman di-*n*-butyl sulfide (redistilled) gave n_D^{20} 1.4533; literature value (1), 1.4529. The alkaline solution was acidified with hydrochloric acid and the regenerated product analyzed by refractive index and boiling point: Found: n_D^{20} 1.4431; b.p. 98.0°. Redistilled Eastman *n*-butylmercaptan had a boiling range 98.0–98.2° and gave refractive indices *n*. 1.4426 and n_D^{25} 1.4400. Ellis and Reid (3) give n_D^{25} 1.4401 for *n*-butylmercaptan and 1.4338 for the secondary isomer. Approximately 80% of the 1-butene reacted during these four minutes and the product is apparently practically pure *n*-butylmercaptan (*ca.* 85%) and di-*n*-butyl sulfide (15%).

The same experiment was repeated at −78°. In this case, 40–45% of the butene reacted in four minutes. The product which contained *ca.* 5% sulfide was treated with sodium plumbite solution and the precipitate washed first with water, then with acetone, and dried. The mercaptan was regenerated with dilute hydrochloric acid and dried; its refractive index was n_D^{20} 1.4431.

Propylene and hydrogen sulfide in a sealed quartz tube combine quickly and smoothly when illuminated with the Uviarc lamp. More than 95% of the propylene was consumed when an equal volume mixture of the liquid reactants (6.5 cc. each) was irradiated for six minutes at 0°. The product was 65 wt.-% *n*-propylmercaptan and 35% di-*n*-propyl sulfide. The mercaptan boiled at 67.5° and had indices of n_D^{20} 1.4380 and n_D^{25} 1.4351. Ellis and Reid (3) give for the same constants 67.4–67.6° and n_D^{25} 1.4351, respectively. The sulfide had an index n_D^{20} 1.4480 and the boiling point 141.5°. The boiling point given in the literature is 141.5–142.5 (7) and the refractive index at 20°, 1.4481 (1).

The effectiveness of acetone in sensitizing the chain reaction is demonstrated by the following experiment: Two sealed Pyrex tubes, one containing 3.7 cc. each of propylene and hydrogen sulfide, and the other the same mixture plus an added 0.5 cc. of acetone, were illuminated at 0° for six minutes. In the first case, only 0.2 cc. of product was obtained, while in the second case, 75% of the propylene had reacted, giving 3.5 cc. of product, which was 80 wt.-% *n*-propylmercaptan and 20% di-*n*-propyl sulfide.

LIQUID PHASE—OTHER UNSATURATES

The photo-addition of hydrogen sulfide to the double bond offers a new method for preparing other interesting sulfur derivatives, *e.g.*, ethylene thiochlorohydrin is readily prepared from vinyl chloride.

$$H_2S + H_2C{=}CHCl \xrightarrow{h\nu} HSCH_2CH_2Cl$$

A secondary product is also readily formed which is extremely vesicant and is presumably β,β'-dichlorodiethyl sulfide.

$$ClCH_2CH_2SH + ClCH{=}CH_2 \xrightarrow{h\nu} (ClCH_2CH_2)_2S$$

Hydrogen sulfide (9 cc.) and vinyl chloride (10 cc.) in a quartz reactor were frozen in liquid air and the evacuated tube sealed off. The contents were illuminated by the quartz mercury arc for ten minutes at room temperature. Immediately on illumination, the tube contents boiled quietly; this ceased if the light was cut off, but began again upon irradia-

tion. After evaporating off the unreacted hydrogen sulfide and vinyl chloride, 10 cc. of vile smelling product remained. A micro-distillation of this material gave 4.5 cc. of product boiling at 93–108° which was analyzed for sulfur and chlorine:

Anal. Calc'd for C_2H_5ClS: Cl, 36.7; S, 33.2.
Found: Cl, 38.0; S, 31.3.

These results suggest that a small amount of vinyl chloride dimer may be present in the product. No sharply defined fractions boiling above this region were isolated. The yield based upon the amount of vinyl chloride reacting is 70–80%; somewhat more than half of this product is probably β,β'-dichlorodiethyl sulfide. Its characteristic delayed vesicant action was confirmed by exposing a small patch of skin on the forearm to the vapors for 15 minutes.

As in the case with 1-butene, photo-addition of hydrogen sulfide to vinyl chloride is slower at $-78°$. When an equal volume mixture of these compounds (9 cc. of each) was illuminated at the lower temperature for ten minutes, 4 cc. of product was left after distilling off the hydrogen sulfide and vinyl chloride. Chlorine and sulfur analyses of the product are as ollows:

Anal. Calc'd for $C_4H_6Cl_2S$: Cl, 45.2; S, 20.4.
Found: Cl, 39.6; S, 26.7.

Evidently, the product is a mixture of the sulfide and mercaptan (*cf.* theoretical chlorine-sulfur composition to the thiochlorohydrin).

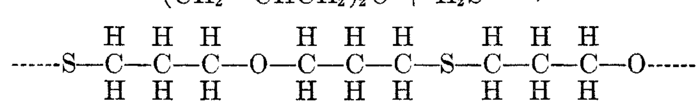
Hydrogen sulfide addition to the more highly substituted ethylenes, *e.g.*, 2-chlorobutene-2, is considerably slower. Four and five-tenths cubic centimeters of 2-chlorobutene-2 and 2.7 cc. of hydrogen sulfide were sealed off in the quartz reactor and illuminated with the quartz mercuy arc for ten minutes at $-78°$. After evaporating and distilling off the unreacted materials, about 0.5 cc. of crude product remained. The admittedly impure material was analyzed for sulfur and hydrolyzable chlorine; the latter value was determined by potentiometric titration both in sodium acetate and in acid solution.

Found: Sulfur–19.0, 19.8%; 0.59, 0.62 eq./100 g.
Hydrolyzable chlorine, in sodium acetate solution; 0.56 eq./100 g.
Hydrolyzable chlorine, in acid solution; 0.57 eq./100 g.

It seems improbable that chlorine would have been retained in the molecule if the —SH group had added to the $-\overset{\overset{\displaystyle Cl}{|}}{C}=$ side of the double bond, and the near equality of the hydrolyzable chlorine and sulfur content speaks for the formation of the thiochlorohydrin.

Following the same technique, hydrogen sulfide is easily added to diallyl or diallyl ether to give high molecular weight compounds. Thus for diallyl ether:

$$(CH_2{=}CHCH_2)_2O + H_2S \xrightarrow{h\nu}$$



By treating diallyl with hydrogen sulfide at 0°, a liquid was obtained which contained 30.9% total sulfur and 16.3% mercaptan sulfur; its average molecular weight was 210. Product from the reaction of diallyl ether with hydrogen sulfide had a molecular weight of 285 and contained 25.9% total sulfur.

Methyl acrylate and allyl alcohol reacted with hydrogen sulfide with difficulty at 0°; a small amount of product, which was precipitated with Pb^{++} and Ag^{+} ions, was obtained in each case. Because of the small quantities involved, no analyses were attempted.

GAS-PHASE REACTION

The gas-phase photo-addition of hydrogen sulfide to 1-butene is slow. When 99.2 mm. of 1-butene and 201.5 mm. of hydrogen sulfide in a one-liter Pyrex bulb were illuminated for two hours by the quartz mercury arc, there was no pressure change. Acetone (19.5 mm.)

was then added to sensitize reaction. After four hours, the pressure decreased 20 mm. The product was washed free of acetone and a refractive index taken.

Product n_D^{20}	1.4487
n-C_4H_9SH	1.4426
$(n$-$C_4H_9)_2S$	1.4533

Pressure decrease was somewhat more rapid when the reaction of the same proportions of gases was carried out in a quartz vessel. It amounted to 18 mm. in 25 minutes (initial pressure 304 mm.), and 111 mm. in three hours. Product formed in the small quartz vessel was insufficient for analysis, but a portion of it seemed to be sulfur dust from the photolysis of hydrogen sulfide. Hydrogen was also present.

SUMMARY

1. Short wave length ultra-violet radiation readily promotes the addition of hydrogen sulfide to olefins to form mercaptans and sulfides.

2. Light of wave length transmittible by Pyrex is effective in initiating reaction if a small amount of photo-dissociable material such as acetone is present.

3. The sulfur of the sulfhydryl or mercapto group adds exclusively to the carbon atom of the double bond having the larger number of hydrogen atoms.

4. Hydrogen sulfide and olefin combine slowly in the gas phase under the influence of ultra-violet radiation.

5. The mechanism is one of a free radical chain and is dependent upon the preliminary dissociation of hydrogen sulfide.

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THE PHOTO-ADDITION OF HYDROGEN BROMIDE TO OLEFINIC BONDS[1]

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Probably the most important generalization regarding the reaction of hydrogen halides with olefinic bonds is that of Markownikoff (1870) (14, 15). Chemical literature abounds with papers dealing with this subject of directed addition and in many of the cases involving hydrogen bromide[2] the early results have been contradictory and confusing. Most of this uncertainty has been removed by the extensive studies on liquid-phase systems by Kharasch, Mayo, and their co-workers, who have shown that the presence of oxygen is a determining factor. Thus, when air, oxygen, or peroxides are absent (and ofttimes in the presence of anti-oxidants), hydrogen bromide and olefinic compounds react substantially in accord with the Rule; that is, the halogen combines with the carbon atom with the fewer hydrogen atoms. This is termed the "normal" reaction. However, if oxygen or peroxides are present, considerable amounts of the "abnormal" addition product result; that is, the bromine becomes attached to the carbon atom bonded to the greater number of hydrogen atoms, contrary to the Rule.[3] These results have been confirmed and amplified by other investigators.

Excellent reviews of the literature on this phenomenon, the "peroxide effect," have appeared recently (16, 21, 22, 23). Suffice it to say for the purposes of the present paper that it seems to be rather generally accepted that the "normal" reaction occurs as a molecular addition process, possibly involving ions, usually at walls, in solution or on catalysts. On the other hand, the "abnormal" reaction is thought to be a chain process involving bromine atoms; Kharasch, Mayo, and their co-workers postulate their origin from interaction of oxygen and/or peroxide with hydrogen bromide. The halogen atom so generated adds exclusively to the carbon with the larger number of hydrogen atoms and the radical thus formed reacts with hydrogen bromide to form a stable molecule and a bromine atom; the latter continues the chain. Several exceptions to this view have appeared (5, 17, 18, 25, 26).

In the following we wish to report observations which confirm the bromine atom chain mechanism for "abnormal" addition of hydrogen bromide. Further, the reaction has now been clearly extended to the vapor phase (see 16, page 365). Also, the important effect of light upon the process is discussed and it is shown that oxygen, peroxides, and certain metals are not as peculiar in their activity

[1] Presented before the Division of Organic Chemistry of the American Chemical Society at its 103rd meeting, Memphis Tennessee, April 20–23, 1942.

[2] Hydrogen chloride and hydrogen iodide add to olefinic bonds according to the generalization.

[3] This finding was indicated by Bauer (2) in 1922 in a patent which states that in the presence of oxygen, acetylene and hydrogen bromide give 90% of 1,2-dibromoethane; the second molecule of the halide reacts contrary to the Rule, which as originally framed covers halo-olefins.

as has been hitherto supposed (see 16, page 377). Other substances and conditions can lead to quantitative yields of "abnormal" bromide in fractions of the times previously reported.

MATERIALS AND TECHNIQUE

Propylene and isobutene, obtained by dehydration of isopropyl and tertiary butyl alcohols with sulfuric acid, were purified by careful fractionation. 1-Butene was prepared by dehydration of normal butyl alcohol over activated alumina at 375–400° and was fractionated in a 44-plate column (purity better than 95%). The ethylene (Ohio Chemical Company) and vinyl chloride (Dow) were used without further purification. Allyl bromide (Eastman) was redistilled (71.0–71.5°). Diallyl was synthesized by the reaction of allyl chloride and magnesium in ether; the product boiled at 58.8–58.9° (uncorrected). Hydrogen bromide was prepared by direct combination of the elements in accordance with the method of Ruhoff, Burnett, and Reid (20) and special care was taken to remove traces of bromine by passing the gas over active copper in the presence of excess hydrogen. The product was water-white. In every case the unsaturates and the hydrogen bromide were condensed with solid carbon dioxide or liquid air and degassed by repeated distillation under high vacuum obtained with a mercury vapor-pump in conjunction with an oil-pump. Mercury vapor was excluded from the reaction system by two liquid air-cooled traps. In all experiments the entire system was subjected to prolonged evacuation at pressures of *ca.* 10^{-5} mm. The propylene, 1-butene, isobutene, and hydrogen bromide were distilled from a CO_2-cooled trap into one cooled with liquid air. In certain cases where still greater certainty of the absence of oxygen was desired, hexaphenylethane[4] was dissolved in the reagents before they were distilled into the reactor. Ethylene was stored as a gas in a large Pyrex bulb and the remaining materials were condensed and stored in solid carbon dioxide-cooled traps which were connected with the vacuum system.

In the liquid-phase experiments the reactants were distilled through the previously evacuated apparatus and condensed in the quartz reaction tube, (1.4 × 29 cm.). With the reactants frozen out with liquid air and the system under high vacuum the quartz tube was sealed off. The reactor was then transferred to a large clear quartz test tube (3.5 × 30 cm.) filled with a CO_2-isopropyl alcohol mixture or ice water, depending upon the experimental conditions desired, and irradiated by a General Electric Laboratory Uviarc about 20 cm. distant. After completion of reaction, the mixture was cooled in solid CO_2-alcohol mixture, opened, and any volatile material carefully evaporated. After suitable treatment, analyses were made by refractive index and boiling point, and the values determined were compared with those found in usual sources or with those of the Kharasch group.

The apparatus for gas-phase work is illustrated in Figure 1. In these experiments, the reactants were admitted to a water-thermostated (25°), evacuated Pyrex bulb with a small appendage on the bottom in which the product could be condensed by liquid air and removed by breaking the connection with the large flask. The bulb was connected to a quartz spiral manometer (3) which is used as a null point instrument, *i.e.*, when the fixed and movable pointers are brought into coincidence, the pressure as measured on a mercury manometer connected to the external jacket of the gauge equals the pressure in the reactor.

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[4] Hexaphenylethane was prepared by reducing recrystallized triphenyl-chloromethane, according to the method of Conant, Small, and Taylor (4). The solid triphenylmethyl was separated from the reaction mixture by filtration, washed with boiled distilled water, and dried under vacuum. This material was then dissolved in freshly distilled allyl chloride (any other low-boiling solvent would be satisfactory) and run into an evacuated receiver. The solvent was then evaporated by pumping on the system and the evacuated receiver was closed off and transferred to the high vacuum system. Here any remaining solvent could be pumped off and the purified olefins distilled into this receiver.

In actual practice a small correction is necessary because of the difficulty of constructing a gauge with pointers in exact coincidence at the point of precise equality of pressure. A small viewing-telescope for following the deflections of the pointer completed the set-up. A Bourdon-type gauge in the vacuum line connecting the storage vessels to the reaction

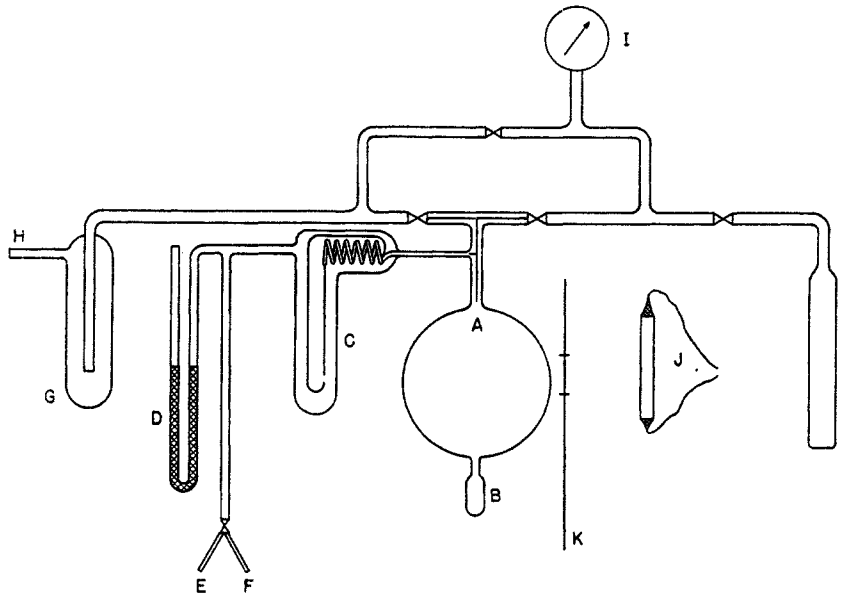

FIG. 1. APPARATUS FOR GAS-PHASE PHOTO-HYDROBROMINATIONS

A. Reaction flask (thermostated at 25°).
B. Trap for product collection.
C. Quartz spiral manometer.
D. Mercury manometer with vernier reading scale.
E. To vacuum.
F. To atmospheric pressure.
G. Liquid air-cooled trap.
H. To McLeod gauge, mercury vapor-pump and oil-pump.
I. Vacuum gauge on by-pass line.
J. Quartz mercury arc lamp.
K. Shield with diaphragm.
L. Reactant storage trap (one of several on a manifold).

system vastly simplified work when it was necessary to distill and degas materials whose vapor pressures at ordinary temperatures are far above one atmosphere.

DISCUSSION

The bromide atom theory of the "abnormal" addition has heretofore depended almost entirely[5] upon the evidence of oxygen, peroxides, or certain finely divided metals as the generating source of the atoms. Additional support would be adduced if other sources could be used.

Photolytic dissociation of hydrogen bromide occurs at wave lengths as long

[5] Of course, the action of "antioxidants" as inhibitors is further evidence for chains.

as *ca.* 2900 Å.U. (19) (which is about the lower limit of transmission of Pyrex) with a quantum efficiency of two; the primary step is the formation of a normal hydrogen and a normal bromine atom. As will be brought out, we have employed this process in so efficient a manner to produce "abnormal" bromides that the method suggests itself as one for practical syntheses. Likewise, other photo-dissociable materials can give rise to radicals which can act efficiently as chain initiators.

In previous work the treatment of the effect of radiation has been rather inconclusive [see (16), pages 378–86]. Investigators seemed to have confined their attention to sources of visible and near ultra-violet radiations and have not used equipment which transmits appreciably below *ca.* 2900 Å.U. The effects observed are probably in most instances consequences of photo-reactions involving peroxides or other co-present sensitizers[6] rather than of a primary effect upon the hydrogen bromide or the olefin, which do not absorb light of the frequencies used. We have found that wave length is a determining factor for the reaction, especially in the absence of sensitizers.

Before passing to the Results, the peculiar specificity of the attack of a normal (in the spectroscopic sense) bromine atom on the carbon atom of a double bond to give rise to the "abnormal" product (in the Markownikoff sense) justifies a brief comment. The schematic representation of reacting electronic structures (7) formally portrays the result, but is not wholly satisfying. A knowledge of the energy levels of olefinic bonds and of the relative stability of isomeric free radicals, unfortunately at present almost virgin fields, probably would shed much light on this intriguing process.

RESULTS

Liquid-phase experiments. Table I summarizes the liquid-phase experiments.

In order to demonstrate the effectiveness of the photochemical process, conditions have been selected which seem most unfavorable for the intervention of a "peroxide effect." Kharasch and Hinckley (9) report that the "normal" addition of hydrogen bromide to 1-butene is unaltered by the presence of air or solvents, conditions which ordinarily favor the "abnormal" reaction. Therefore, low temperature (−78°), a recalcitrant, carefully purified olefin (1-butene), and a high concentration of reagents (no solvents) were chosen as conditions most unfavorable for the manifestation of a "peroxide effect." As a further assurance that oxygen would not be present, the 1-butene was distilled under high vacuum from one storage bulb containing triphenylmethyl (hexaphenylethane) to a second evacuated bulb before the final distillation into the reaction tube. Illumination at −78° of an equimolar mixture (0.043 moles of each) in the quartz tube by the quartz mercury arc *effected a 99+ % reaction within*

[6] This is concurred in by Kharasch (12), who in an early publication stated, "These factors (solvents, temperature, and light) have no effect by themselves, but only an indirect effect through their action on peroxides." Further (11), "All the factors (including now the light effect) which influence the addition of hydrogen bromide to allyl bromide exert their influence only through their effects on the minute but significant quantities of peroxides or oxygen present in the materials."

30 seconds. The product boiled at 101.1° and had the refractive index, n_D^{20} 1.4397. The literature gives for *n*-butyl bromide, b.p. 101.6° and n_D^{20} 1.4398. This experiment could be successfully duplicated. Even in the presence of thiocresol (1.0 mole-%), one of the more effective inhibitors of "abnormal" addition (16, pp. 369–372), reaction was 60–70% complete within 30 seconds at −78°, and the product was *n*-butyl bromide.

Allyl bromide is somewhat less reactive than 1-butene. The same care was taken to exclude oxygen. Reaction was virtually complete after five minutes although only about 60% of the material reacted in one minute. However almost no combination had occurred after 5 minutes in the presence of 0.6 mole-% thiocresol. The product was analyzed according to the method of Kharasch and Mayo (11) which involves removal of excess allyl bromide with dimethylaniline (reaction time 24 hours) and subsequent removal of the quaternary compound with 6 *N* H_2SO_4. The dibromide formed boiled at 166.0° and had n_D^{20} 1.5230. For 1,3-dibromo propane in the literature, one finds n_D^{20} 1.5232 and b.p. 167°.

Oxygen-free propylene and hydrogen bromide combined so rapidly upon illumination even at −78° that in one experiment there was slight carbonization in the gas-phase tip of the quartz tube. Such violence is indicative of very long chains with consequent virtually instantaneous evolution of the heat of reaction. The product was pure *n*-propyl bromide, n_D^{20} 1.4339 and b.p. 69.8–71.0°. Earlier work, using peroxides as catalysts (12), employed times of the order of hours to obtain yields of 87% *n*-propyl bromide.

Diallyl (4 cc.) and hydrogen bromide (3.2 cc.) react practically completely in one minute at −78° to give hexamethylene dibromide; n_D^{20} product 1.5037; Eastman hexamethylene dibromide (redistilled), 1.5038.

Pyrex glass is able to transmit a sufficient amount of short wave length radiation to bring about rapid liquid-phase combination of propylene and hydrogen bromide. The product obtained by illumination with an unshielded quartz-mercury arc of 0.3 moles hydrogen bromide and 0.62 moles propylene for *ca.* one minute had n_D^{20} 1.4340, which indicates pure *n*-propyl bromide. This rapid rate in Pyrex is further evidence of very long chains.

Gas-phase experiments. The only previous references to gas-phase "abnormal" additions are to be found in the patents of W. Bauer (1, 2), who observed the formation of 1,2-dibromoethane from acetylene and hydrogen bromide under the influence both of light and oxygen. However, these experiments are not clearly defined, as Bauer fails to specify the transmission limits of his glass vessels, and further, the results are complicated by the presence of a liquid phase. During the present investigation, gas-phase photo-addition has been effected with ethylene, propylene, 1-butene, isobutene, and vinyl chloride. In every case where a distinction could be made, the product has been almost entirely the so-called "abnormal" compound. The results of these experiments are presented in Table II. In quartz vessels photo-hydrobromination proceeds so rapidly that it is almost impossible to follow the rate of pressure decrease (see Fig. 3). In Pyrex the gas-phase rate can be observed.

Propylene (*ca.* 100 mm.), pretreated in the vacuum system by distillation and degassing, was admitted to the Pyrex reaction bulb and was followed by an equivalent amount of hydrogen bromide. These proportions were selected so that no liquid phase would be formed during the experiment. No reaction took place until the reactor was illuminated with the quartz mercury arc. A mixture of propylene and hydrogen bromide (100 mm. each) stood in the dark at 25° for 64 hours without pressure change.[7] An induction period was found in some runs. In others the reaction began immediately; in these a slight, short pressure *rise*, probably Draper effect, was observable. Figure 2 illustrates the course of a typical run in a thin-walled Pyrex bulb, which transmits a minor amount of

TABLE I

PHOTO-HYDROBROMINATIONS IN LIQUID PHASE AT −78°C. IN QUARTZ

COMPOUND	TIME	% REACTED	n_D^{20} PRODUCT	PRODUCT AND REMARKS
Propylene	<30 sec.	99+	1.4339	*n*-Propyl bromide[a]; b. range 69.8–71.0°
Propylene in Pyrex	<1 min.	[e]	1.4340	*n*-Propyl bromide
1-Butene	<30 sec.	99+	1.4397	*n*-Butyl bromide[b]; b.p. 101.01°
1-Butene + 1 mole-% thiocresol	<30 sec.	60–70	1.4398	*n*-Butyl bromide
Allyl bromide	5 min.	95–100	1.5230	1,3-Dibromopropane[c] b.p. 166.0°
Allyl bromide	1 min.	60	1.5228	1,3-Dibromopropane
Allyl bromide + 0.6 mole-% thiocresol	5 min.	0(?)	—	Apparently no reaction
Diallyl	1 min.	95–100	1.5037	1,6-Dibromohexane[d]

[a] *n*-Propyl bromide, 1.43414 (6), 70.9° (6); isopropyl bromide, 1.42508 (6), 59.6° (6).

[b] *n*-Butyl bromide, 1.4395 (9), 1.4398 (6), 101.6° (6); *sec*-butyl bromide, 1.4369 (9), 91.3° (6).

[c] 1,3-Dibromopropane, 1.5232 (20), 167° (6); 1,2-dibromopropane, 1.5194 (11), 141.6° (6).

[d] Eastman hexamethylene dibromide, redistilled, 1.5038.

[e] This was the initial experiment and the reaction tube was closed with a stopcock; reaction was so violent that pressure increase blew out the plug of the cock; due to loss of material no "% reacted" can be given.

effective radiation. The results were not exactly reproducible because the rate of the reaction is dependent upon a number of variables, such as light intensity and the condition of the Pyrex surface. Reasonable consistence was obtained, however, by placing the quartz mercury arc in precisely the same position each time. The arc was operated for one-half hour before any experiment so that it might come to an equilibrium state. Before most runs the reactor was cleaned with hot sulfuric-nitric acid mixture and washed very thoroughly with distilled water. No attempt was made to measure quantum yields, although this would be an interesting study.

[7] Professor Kistiakowsky has informed us that he has observed similar non-reactivity of this gaseous mixture at even higher temperatures.

Ethylene and 1-butene hydrobrominate at about the same rate as propylene, while vinyl chloride is somewhat less reactive. Isobutene is easily the most reactive of the olefins studied. When this compound and hydrogen bromide were left in the dark for 18 hours, the product was almost pure tertiary butyl bromide (probably largely as a result of combination at the walls), but principally isobutyl bromide if the mixture was illuminated. The proportion of the "abnormal" product was increased from 86% to 91% when a small enough quantity of reactants was used to prevent formation of a liquid phase. The "normal" reaction apparently proceeds more readily when a liquid phase is present.

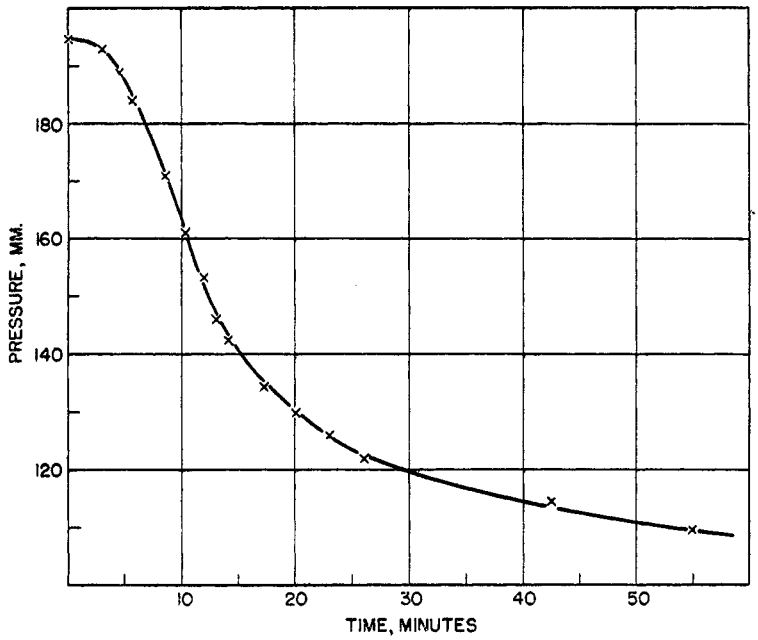

FIG. 2. GAS-PHASE PHOTO-ADDITION OF HYDROGEN BROMIDE TO PROPYLENE; 25°C. 98.5 MM. C_3H_6; 95.6 MM. HBR.

Effect of light wave length. If light of a wave length short enough to dissociate hydrogen bromide is transmitted to the gaseous reaction mixture, combination is greatly accelerated. Pyrex glass does transmit such radiation (a spectrographic test with an iron arc shows that Pyrex transmits faintly down to 2800 Å.U.) but so poorly that without the intervention of some other free radical source the chain process is slow. However, a quartz reactor fulfills the necessary requirements with regard to transparency to ultra-violet. Figure 3 shows graphically the course of reaction in a quartz vessel before and after a shielding Pyrex container was removed. As above, illumination was supplied with the quartz mercury arc and *ca.* 100 mm. each of propylene and hydrogen bromide were the reactants.

The ineffectiveness of long wave lengths was also demonstrated by passing

radiation from the quartz mercury arc through various Wratten light-filters fitted into one of the walls of an otherwise light-tight shield surrounding a quartz reactor. Figure 4 is a time-pressure curve depicting the changes brought about by the various wave lengths. The transmission ranges of the filters were determined spectrographically using an iron arc as a convenient source. Wratten No. 75 transmitted only above 4700 Å.U., No. 2A above 4100 Å.U. and No. 1 above 3500 Å.U. Filter No. 1 apparently suffered some breakdown; a test after the experimental work showed this filter to be transmitting very slightly in the critical 2800–2900 Å.U. region. This may account for the 0.7 mm. pressure drop observed in this particular case. This evidence, we believe, strongly supports

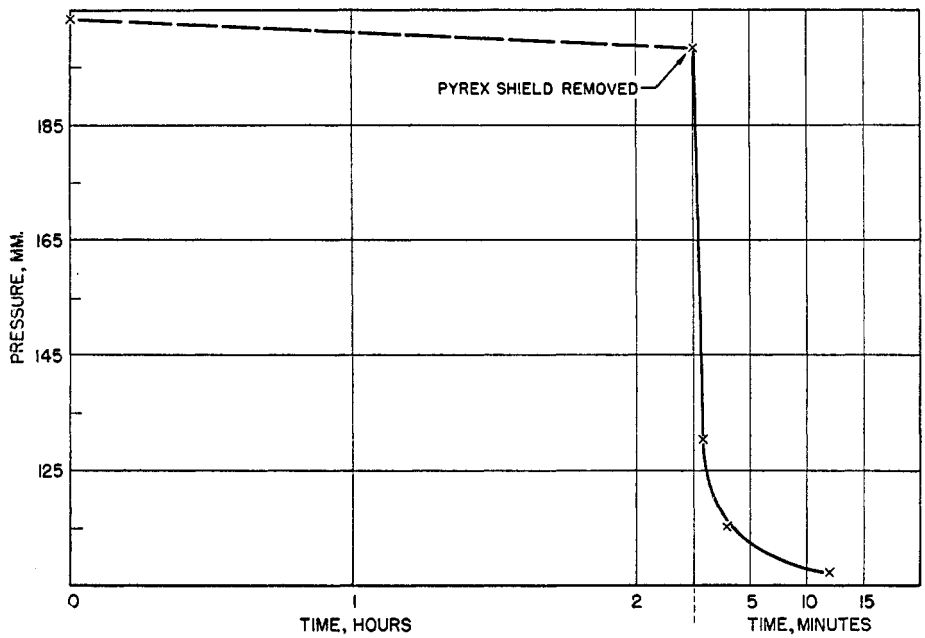

FIG. 3. EFFECT OF WAVE LENGTH ON THE VAPOR-PHASE HYDROBROMINATION OF PROPYLENE 102.9 MM. C_3H_6; 99.8 MM. HBr QUARTZ REACTOR

the contention that in the absence of sensitizers, such as peroxides or acetone, the photo-hydrobromination can only be initiated by dissociation of hydrogen bromide with light of sufficiently short wave length.

Catalysts and inhibitors. The effect of peroxides in catalyzing "abnormal" addition and the stimulating action of light when used in conjunction with such catalysts has been amply demonstrated by Kharasch, Mayo, and their coworkers. There is no need to believe, however, that such action is peculiar to peroxides. Very small amounts of acetone, acetaldehyde, tetraethyllead, bromine, and probably many other photo-dissociable materials are highly effective in sensitizing the "abnormal" addition of hydrogen bromide.

Acetone is photochemically decomposed at *ca.* 3100 Å.U. and methyl radicals

result (19, p. 234 ff.). Such radicals can react with hydrogen bromide to yield bromine atoms by which the chain is started. The action of acetone (5 mm., 2.5 mole-%) upon an illuminated mixture of propylene (102.7 mm.) and hydrogen bromide (102.3 mm.) is shown in Figure 5. Inclusion of 0.85% and 9.0% acetone[8] with the reactants caused reaction of 60% and 85% respectively in five minutes, and the product was *n*-propyl bromide.

Acetaldehyde is similaraly effective under essentially the same conditions. The pressure decrease in an illuminated propylene-hydrogen bromide mixture (101.6 + 100.7 mm., respectively) was 9 mm. in 25 minutes, but following the admission of 6.9 mm. of acetaldehyde the pressure dropped 60 mm. in the next

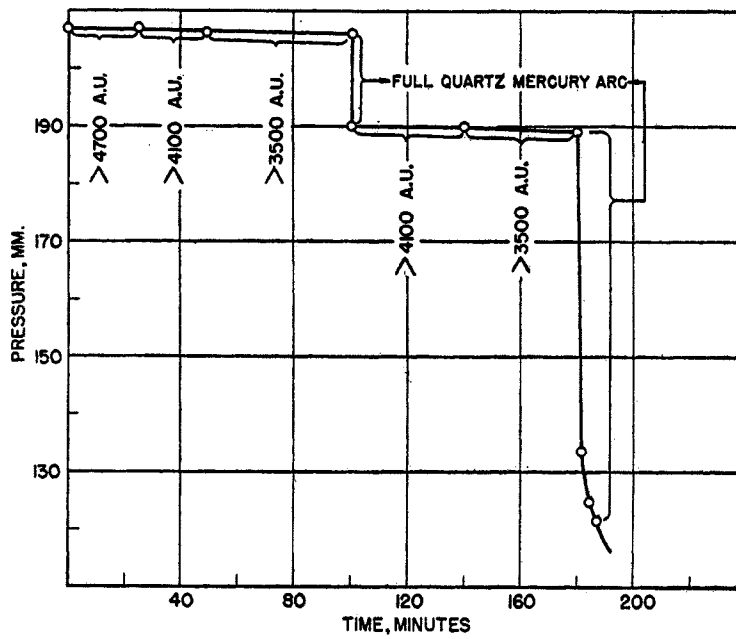

FIG. 4. EFFECT OF WAVE LENGTH ON THE VAPOR-PHASE HYDROBROMINATION OF PROPYLENE
104.8 MM. C_3H_6; 102.0 MM. HBr QUARTZ REACTOR

2.6 minutes and continued on toward completion (Figure 5). Dissolved triphenylmethyl was kept in the storage vessels for both the acetone and acetaldehyde to ensure the complete absence of oxygen. With acetone, results were checked with material having none of the dissolved free radical.

Photo-hydrobromination is effectively promoted by minute amounts of tetraethyllead, which has a long wave length absorption limit of 3500 Å.U. (13),

[8] When large amounts of acetone are present, a somewhat unstable condensation product is formed—the hydrobromide of mesityl oxide—which is not, however, dependent upon illumination for its formation. The compound evolves hydrogen bromide easily on heating and gives a copious precipitate of silver bromide with aqueous 5% silver nitrate. A bromine analysis gave 42.8% and 42.5% Br; calc'd for $CH_3COCH_2(CH_3)_2Br$, 44.6% Br.

and which is readily photochemically decomposed into lead and ethyl radicals. The relative effectiveness of 0.02 mole-% and 0.18 mole-% tetraethyllead in the illuminated mixture is shown in Figure 6. The dependency of this transformation on the lead alkyl is further shown by the noteworthy falling off of the reaction rate long before the principal reactants have been consumed.

Chains initiated by bromine do involve copresent hydrogen bromide, although with the particular concentrations of reagents used, more dibromide than monobromide was formed. In the most conclusive experiment 16.8 mm. bromine, 97.9 mm. hydrogen bromide, and 101.9 mm. propylene were added in that order.

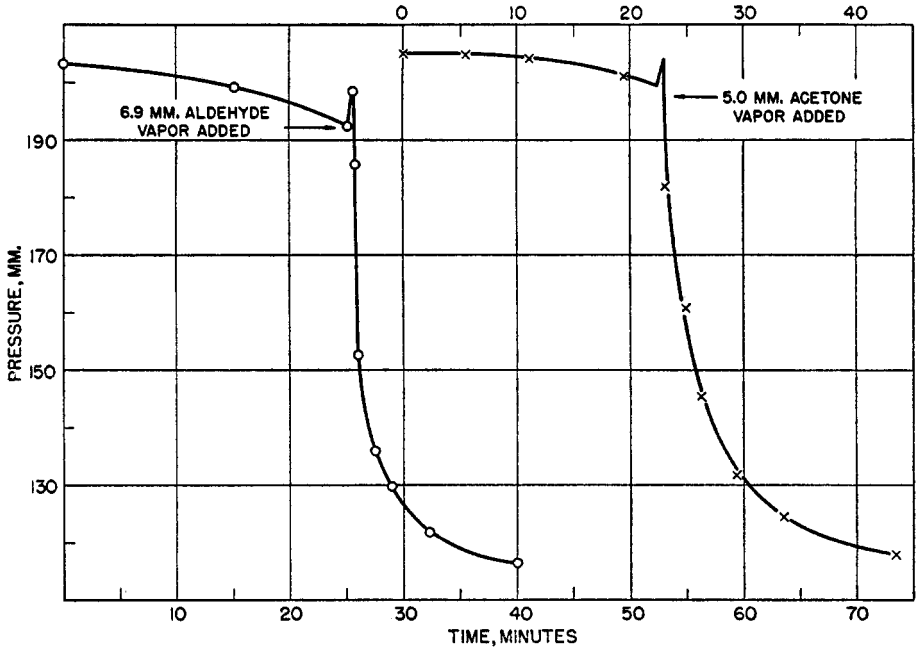

FIG. 5. PHOTO-ADDITION OF HYDROGEN BROMIDE TO PROPYLENE. CATALYSIS BY ACETONE AND ACETALDEHYDE

102.7 mm. C_3H_6; 102.3 mm. HBr; 5.0 mm. acetone
101.6 mm. C_3H_6; 100.7 mm. HBr; 6.9 mm. acetaldehyde

There was an almost instantaneous pressure drop of 47.5 mm. despite the fact that the reactor was illuminated solely by diffuse light. Even if all the bromine had added to propylene and all the resulting dibromide had condensed, only 33.6 mm. of the pressure decrease would be accounted for. Therefore at least 14 mm. of propyl bromide was formed. A related observation has been made by Smith (24), who reported that intermittent additions of bromine caused the abnormal addition of hydrogen bromide to undecenoic acid in carbon tetrachloride solution.

Kharasch, Mayo, and their co-workers have given numerous conclusive instances of the inhibiting power of so-called anti-oxidants, but whether inhibi-

tion is a result of the destruction of the chain-initiating peroxides or actual chain termination has been a subject of considerable speculation. For this reason the finding that methyl iodide and iodine are powerful retardants of the gas-phase photochemical process, although they certainly are no anti-oxidants, seems to be evidence in favor of the latter postulate. A mixture of propylene (102.2 mm.) and hydrogen bromide (101.2 mm.) in the Pyrex vessel was illuminated by the quartz-mercury arc for 25 minutes. At the end of this time the pressure had decreased 5.3 mm. In the 107 minutes following the addition of 12.1 mm. methyl iodide the pressure dropped only 8.1 mm.; in fact, during the last 92

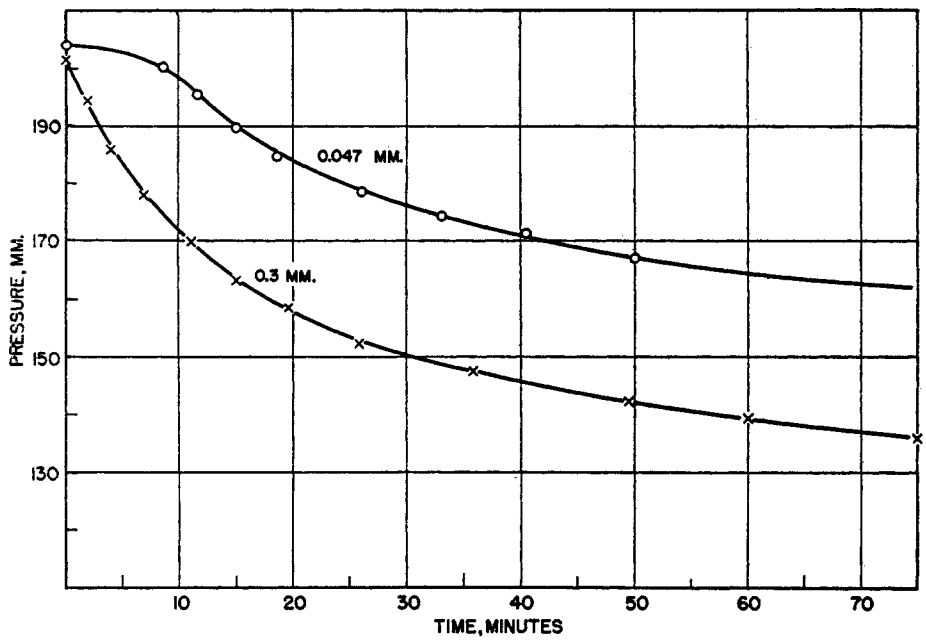

FIG. 6. PHOTO-ADDITION OF HYDROGEN BROMIDE TO PROPYLENE. CATALYSIS BY TETRAETHYLLEAD

102.8 mm. C_3H_6; 102.2 mm. HBr; 0.047 mm. $Pb(C_2H_5)_4$
102.4 mm. C_3H_6; 101.7 mm. HBr; 0.3 mm. $Pb(C_2H_5)_4$

minutes the decrease was only 4.8 mm. Further illumination of this same mixture for one-half hour after standing in the dark overnight did not bring about any observable reaction. When acetone (6.3 mm.) was added to the mixture the pressure decreased only 17 mm. in 126 minutes; in the absence of methyl iodide this quantity of acetone would have caused virtually complete reaction in far less time.

Iodine is an even more powerful retardant. Under the same conditions as above, reaction was completely suppressed by 0.15% iodine for more than 90 minutes. Acetone, in the presence of this small amount of iodine, catalyzed the reaction very slowly at first, but more rapidly later. This increasing rate prob-

TABLE II

PHOTO-HYDROBROMINATION IN VAPOR PHASE AT 25°C. IN PYREX

COMPOUND	INITIAL PRESSURES, MM.		ADDED MATERIALS	n_D^{20} PRODUCT	PRODUCT AND REMARKS
	p olefin	p HBr			
Ethylene	100.7	102.6	—	—	Ethyl bromide[a]
	100.0	366.9	—	—	" "
	286.9	100.7	—	—	" "
Propylene	101.8	99.7	—	1.4341	*n*-Propyl bromide[b]
	100.4	288.3	—	1.4339	" "
	216.0	109.6	—	1.4339	" "
	246.8	255.1	—	1.4341	" " [c]
	102.7	102.3	Acetone 1.7 mm.	1.4340	" " see text
	102.8	102.5	" 5.0 mm.	—	" " " "
	99.7	99.3	" 19.6 mm.	1.4337	" " " "
	101.6	100.7	Acetaldehyde 6.9 mm.	—	" " " "
	102.4	101.7	$Pb(C_2H_5)_4$ 0.047 mm.	—	" " " "
	102.9	99.6	" 0.3 mm.	1.4340	" " " "
	101.9	97.9	Bromine 16.8 mm.	—	See text
	103.4	101.5	Oxygen <1 mm.	1.4337	*n*-Propyl bromide; b.p. 71.6°[d]
	101.1	106.6	" 15.4 mm.	—	*n*-Propyl bromide; see text
	101.1	106.6	"Dark" reaction	none	None in 64 hrs.; see text
1-Butene	101.3	101.0	—	1.4393	*n*-Butyl bromide[e]
Isobutene	51.4	50.5	—	1.4348	Isobutyl bromide[f]
	199.7	201.1	—	1.4344	" " [g]
	198.2	199.7	"Dark" reaction	1.4282	*t*-Butyl bromide; see text
	99.6	97.8	Acetone 16.7 mm.	1.4352	Isobutyl bromide[h]
Vinyl chloride	102.9	102.1	—	1.4900	1-Chloro-2-bromoethane[i]

[a] These runs with ethylene and several with propylene were made in an attempt to derive a rate expression. Although they proceeded smoothly, rates were not reproducible from run to run. The data of certain individual gas-phase runs indicated a rough proportionality of the rate to the product of the hydrogen bromide and olefin concentrations. However, in view of the uncontrolled variables in the experiments (light intensity, influence of surface, rate of diffusion into the illuminated zone, etc.), this aspect was not pursued at length.

[b] *n*-Propyl bromide, 1.43414 (6); isopropyl bromide, 1.42508 (6).

[c] Due to the higher initial pressures, condensation of product occurred during this experiment.

[d] *n*-Propyl bromide, 70.9° (6); isopropyl bromide, 59.6° (6).

[e] *n*-Butyl bromide, 1.4295 (9), 1.4398 (6); *sec*-butyl bromide, 1.4369 (9). Condensation occurred during this run. Due to the uncertainty in the index of pure *n*-butyl bromide, the purity of the product cannot be stated accurately.

[f] Isobutyl bromide, 1.4355 (10); *t*-butyl bromide, 1.4276 (10). 1.4348 Corresponds to 91% isobutyl bromide.

[g] 1.4344 Corresponds to 86% isobutyl bromide.

[h] 1.4352 Corresponds to 96% isobutyl bromide.

[i] 1-Chloro-2-bromoethane, 1.4908 (8); 1-chloro-1-bromoethane, 1.4660 (8).

ably parallels the gradual clean-up of the free iodine by radicals liberated by the photolysis of acetone. The mechanism of chain termination is postulated as follows:

$$R + I_2 \rightarrow RI + I$$

The iodine atoms probably recombine much more readily than they react with olefin to continue the chain. In fact, the inability to find a free radical chain addition of hydrogen iodide to olefins and certain thermodynamic considerations suggest that the association

$$RCH{=}CH_2 + I \rightarrow \overset{|}{R}\overset{|}{C}H{-}CH_2I$$

is a relatively infrequent process.

Effect of oxygen. Oxygen has been shown by previous work to be an effective catalyst for the "abnormal" addition of hydrogen bromide to olefins in the liquid phase. In the gas phase the inclusion of a small amount of oxygen in an illuminated mixture also catalyzed the combination. In the presence of a large amount of oxygen, however, the rate of reaction is much slower, and other products appear. The reactions in mixtures of olefin, oxygen, and hydrogen bromide will be discussed in a forthcoming paper.

SUMMARY

1. "Abnormal" addition of hydrogen bromide to olefinic bonds has been effected photochemically in both liquid and vapor phase without the intervention of oxygen or peroxides.

In the liquid phase, quantitiative conversions can be obtained so rapidly that the method suggests itself for practical syntheses. Sufficiently short wave length radiation is the principal requirement.

Heretofore no clear-cut case of "abnormal" addition in the vapor phase has been observed.

2. It has been shown that certain photo-dissociable materials are able to sensitize the "abnormal" addition even when radiation is used which is not absorbed by the hydrogen bromide or the olefinic substance. Some examples of such materials are aldehydes, ketones, and metal alkyls.

3. Certain materials, such as methyl iodide and iodine, are powerful inhibitors of the gas-phase process.

4. All of the evidence substantiates previous conclusions that the mechanism of the "abnormal" addition is a chain reaction involving bromine atoms and free radicals.

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[CONTRIBUTION FROM THE LABORATORIES OF SHELL DEVELOPMENT COMPANY]

THE OLEFIN-OXYGEN-HYDROGEN BROMIDE PHOTO-REACTION[1]

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Received July 1, 1942

Oxygen has been shown by Kharasch, Mayo, and their co-workers (5) to be an effective catalyst for the "abnormal" or chain addition of hydrogen bromide to olefins. However, oxygen is also known to retard chlorination and bromination chains (10) which, in common with "abnormal" hydrobromination, involve halogen atoms and alkyl radicals. The recent demonstration (11) that this latter reaction can occur in the vapor phase permits the investigation of the effect of larger concentrations of oxygen than has heretofore been possible. In agreement with expectations, we have found that high concentrations of oxygen do inhibit photo-hydrobromination.

Of particular interest is the ultimate fate of the oxygen. Urushibara and Simamura (9) and Simamura (8), who have investigated the liquid-phase interaction of oxygen, hydrogen bromide, and allyl bromide, state that water, 1,3-dibromopropane, 1,2,3-tribromopropane, and an unidentified peroxide are products of the reaction. This last compound they assume to be the peroxide obtained by Bockemüller and Pfeuffer (2) from the bromination of allyl bromide in an atmosphere of oxygen, namely bis-1,3-dibromoisopropyl peroxide. Offhand, it seems rather unexpected that such peroxidic constituents would persist for long in an atmosphere of hydrogen bromide.

In actuality, bromoacetone, which we have identified in the C_3H_6-HBr-O_2 reaction product, simulates peroxides in its ability to oxidize acidified potassium iodide, ferrous ion, and numerous other reagents ordinarily used for peroxide identification. No positive evidence of peroxidic compounds was obtained. In agreement with earlier work, bromine addition products were found, and another product, bromohydrin, is a major constituent when oxygen is in excess. The complex reaction mixture is probably best explained by assuming an initial photo-oxidation of hydrogen bromide analogous to that suggested by Cook and Bates (3) for hydrogen iodide. Bromine atoms produced by photolysis lead to some "abnormal" hydrobromination. This is accompanied by the formation of bromohydrin and dibromide from olefin and the products of the hydrogen bromide oxidation—bromine and water. In the case of propylene, subsequent oxidation of the bromohydrin by bromine is most likely responsible for the bromo ketone. It has been found that this latter compound is an unusually effective catalyst for the "abnormal" addition of hydrogen bromide to olefins.

MATERIALS AND TECHNIQUE

The materials, apparatus, and technique were the same as described previously (11). In brief, hydrogen bromide was prepared by combination of the elements and purified by

[1] Presented before the Division of Organic Chemistry of the American Chemical Society at its 103rd meeting, Memphis, Tennessee, April 20–23, 1942.

repeated distillation at low temperatures and high vacuum. Ethylene and propylene were similarly purified. Oxygen was passed through a liquid air-cooled trap and used without further treatment.

A three-liter Pyrex flask, fitted with a quartz window (5 cm. dia.) served as the reactor, and the pressure changes during illumination with the General Electric Company Laboratory Uviarc were followed by means of a quartz spiral manometer used as a null point instrument. The bulk of the product condensed out and collected in a small appendix on the bottom of the reactor. The vapor-phase product and unconsumed oxygen were passed through a liquid air-cooled trap and the condensate added to the material in the appendix. Analysis was difficult because of the small amounts with which one had to work.

RESULTS AND DISCUSSION

Ethylene. In Figure 1 is shown the course of the pressure change in an illuminated mixture of *ca.* 200 mm. each of hydrogen bromide, oxygen, and ethylene. It is seen that reaction is much slower than that occurring in the vapor phase in the absence of oxygen (compare with Figure 3 of Reference 11), reaching a point of essentially constant pressure only after 3.5 hours compared to 10 minutes.

Approximately 8.5 cc. of a two-phase product containing water was collected from five such runs. The water-extractable fraction amounted to *ca.* 4.0 cc. and an insoluble portion to *ca.* 4.5 cc.

The water extract was distilled and the resulting constant-boiling mixture (99.0–99.5°) saturated with sodium sulfate, yielding a heavy oil. A second distillation removed dissolved water from the oil. The 3,5-dinitrobenzoate derivative was then prepared and recrystallized from an alcohol-water solution. Its melting point was 81–82°. The same derivative of ethylene bromohydrin (Eastman Kodak, redistilled) and a mixture of the known and unknown esters also melted in the same range. Ethylene bromohydrin is therefore one product of the reaction.

The water-insoluble material was distilled in microcolumn. A few drops of low-boiling liquid were obtained which had the index n_D^{20}1.4240. Ethyl bromide has the index n_D^{20}1.4239 (4). The major fraction (*ca.* 4 cc.) boiled at 130.4° and had the index n_D^{20}1.5375. The literature (4) gives for the boiling point of ethylene dibromide 131.6° and n_D^{20}1.5379. A test for aldehyde was easily obtained with Schiff's reagent, although indications were that the amount was very small. It might possibly have formed by decomposition of the bromohydrin. Acidified potassium iodide solution and ferrous sulfate-ammonium isothiocyanate solution were both very slowly oxidized by the product. Peroxide, if actually present, must have been in very small amount. Test with still another peroxide reagent, vanadic acid, was also negative. In this connection it should be mentioned that we found vanadic acid reagent (6) to be the only peroxide indicator which is not affected by bromo ketone.[2]

[2] The Japanese workers (8, 9) based their conclusion of the presence of peroxide in the hydrogen bromide-oxygen-allyl bromide reaction product solely on the liberation of iodine from acidic potassium iodide solution. With Dr. B. Barnett we have attempted to duplicate the liquid-phase experiments of these workers. Ketonic material (presumably *sym*-dibromoacetone and its hydrolysis product) has been positively identified. While this material is capable of reaction with potassium iodide, vanadic acid reagent is unaffected by it.

Propylene. When propylene was substituted for ethylene in the olefin-oxygen-hydrogen bromide mixture, the photo-reaction was complete in fifty minutes as compared with three and one-half hours in the case of ethylene (see Figure 1). However, oxygen does inhibit the "abnormal" addition reaction which in the absence of oxygen occurs in approximately ten minutes.

The water-containing, two-phase product was extremely lachrymal. This material, which presumably consisted in part of CH_3COCH_2Br, gave a bromine-containing precipitate with 2,4-dinitrophenylhydrazine, and its hydrolysis pro-

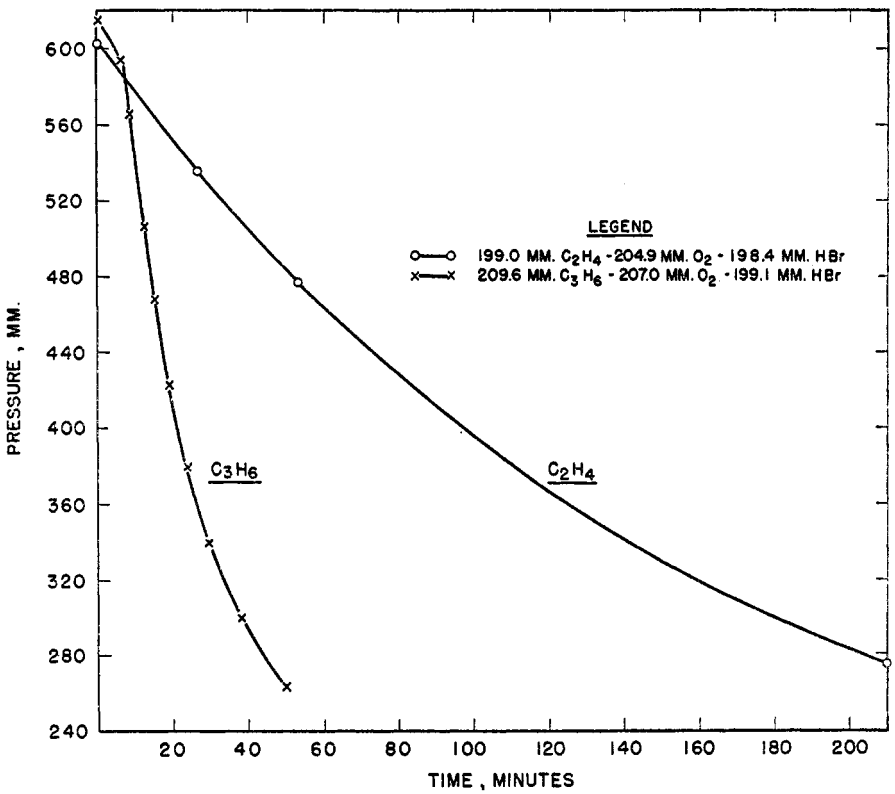


FIG. 1. PHOTO-REACTION OF OLEFIN-OXYGEN-HYDROGEN BROMIDE
(Full quartz mercury arc radiation)

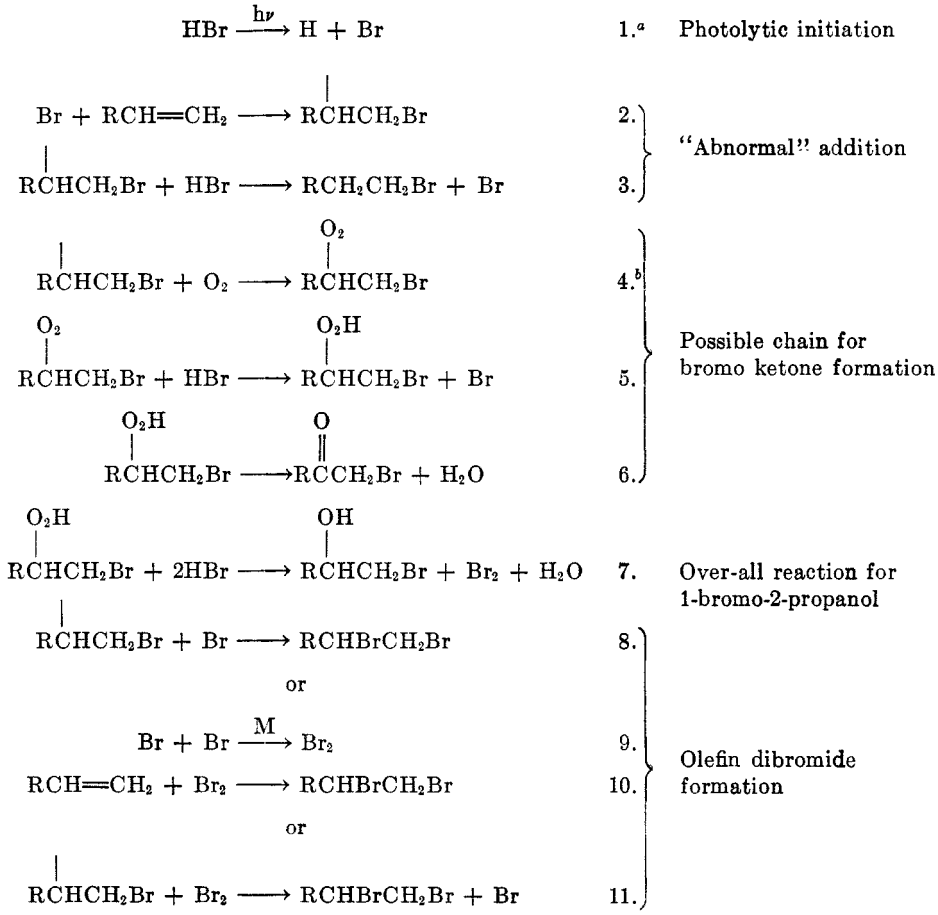
duct (presumably CH_3COCH_2OH) reduced both ammoniacal silver nitrate and Fehling's solution in the cold. There was no positive test for aldehyde. Both acidified potassium iodide and ferrous sulfate-ammonium isothiocyanate mixture were oxidized by the product. However, vanadic acid solution, which readily gives a red color with ether peroxides, gave no test. The behavior of a sample of prepared bromoacetone toward these peroxide reagents was in agreement with the responses of the product.

A portion of the reaction mixture was extracted with water, and the aqueous solution, to which was added hydroxylamine to remove bromoacetone, was

distilled. A sweet smelling oil which separated when the distillate was saturated with sodium sulfate, after drying contained 57.0% bromine (theory for propylenebromohydrin: 57.5%).

The water-insoluble portion of the product was distilled in a microcolumn, and a first fraction obtained which had the boiling point 69.7° [*n*-propyl bromide b.p. 70.9° (4)]. The higher-boiling material contained not only propylene dibromide but also high molecular weight compounds which seemed to be condensation products of bromoacetone. This fraction was washed three times with 10% sodium hydroxide solution, then with water, dried and distilled. The material so obtained contained 77.9% bromine and had the boiling point 142.0° [theory for propylene dibromide: 79.2% Br and b.p. 141.6° (4)].

There is a possibility that the bromohydrin and the bromoacetone might have a common origin in an unstable peroxide formed by interaction of the 1-bromoisopropyl radical and oxygen in accordance with a chain mechanism such as the following:



[a] Of course, the H atom could also act as a chain initiator.
[b] Reaction 4 possibly leads to chain termination; see text.

If the bromohydrination of propylene were entirely analogous to liquid-phase chlorohydrination, one should find two isomeric products, 1-bromo-2-propanol and 2-bromo-1-propanol, while if the foregoing free radical chain were operative, only 1-bromo-2-propanol would be found (Reactions 6 and 7). Unfortunately, no distinction between these alternative mechanisms is possible, because only 1-bromo-2-propanol is formed during liquid-phase bromohydrination. Purified product from the addition of hydrogen bromide to propylene oxide and from the interaction of propylene and bromine water had almost identical refractive indices, n_D^{20}1.4768 and 1.4767 respectively.

Certain facts, however, favor the belief that, with the exception of the small amount of "abnormal" addition (Reactions 2 and 3), the olefin reacts primarily with the products of the hydrogen bromide photo-oxidation, namely, bromine and water, yielding bromohydrin. The presence of bromoacetone is readily explained by the oxidation of the bromohydrin by bromine. This idea receives support from the fact that when propylene is bubbled into bromide water, some bromoacetone is formed.

The foregoing evidence would indicate that the rate of formation of monobromides (ethyl bromide and *n*-propyl bromide), presumably formed *via* a chain mechanism, is greatly reduced by the presence of a large amount of oxygen. The inhibiting reaction is probably of the type

$$R + O_2 \rightarrow RO_2$$

wherein R represents a radical. The fact that under identical conditions the propylene-oxygen-hydrogen bromide reaction is faster than the corresponding change with ethylene, demonstrates the effectiveness of bromoacetone as a catalyst (see the following section). When ethylene is involved there is no opportunity for the generation of such a catalytic compound.

Catalysis of "abnormal" hydrobromination by bromoacetone. Since the generation of bromine atoms (for example, by interaction of hydrogen bromide and oxygen, or by photolytic dissociation of the halide) is the source of reaction centers, the use of bromo ketone suggest itself as another interesting mode for catalyzing "abnormal" addition. Minute amounts of bromine released in accord with the equilibrium (1):

$$CH_3COCH_2Br + HBr \leftrightarrows CH_3COCH_3 + Br_2$$

should supply new centers for chain initiation. To test this theory, bromoacetone was prepared according to the directions given in Organic Syntheses (7). The product was vacuum distilled, transferred to storage vessels, and carefully degassed on the high vacuum line. Propylene (3.4 cc.), hydrogen bromide (1.9 cc.), and bromoacetone (0.2 cc.) were distilled into a Pyrex bomb tube at $-78°$ and sealed off in the absence of air. The tube was shrouded from even diffuse light and after ten minutes, during which time the contents warmed from liquid air temperature, the tube was cooled in solid carbon dioxide and the product removed. After washing with dilute caustic and water, the material was dried and distilled. A quantitative yield of pure *n*-propyl bromide was obtained (n_D^{20}, found, 1.4340; theory, 1.4341).

The same procedure was followed with butene-1 (4.4 cc.), hydrogen bromide (3.2 cc.), and bromoacetone (0.1 cc.), except that the total reaction time was reduced to five minutes. Again the yield was quantitative and apparently the product was pure *n*-butyl bromide (n_D^{20}, found, 1.4400; theory, 1.4398).

As a check on the foregoing experiments, the same procedure was again followed with respect to a mixture of acetone (0.3 cc.), propylene (3.8 cc.), and hydrogen bromide (2.1 cc.), except that the reaction time was lengthened to two hours. In this case only isopropyl bromide was formed (n_D^{20}, found, 1.4252; theory, 1.4251). These results demonstrate conclusively that bromoacetone can provide initial centers for the "abnormal addition" of hydrogen bromide.

SUMMARY

1. The presence of large concentrations of oxygen inhibits the photo-reaction of hydrogen bromide and olefins (ethylene and propylene).

2. The products of these retarded reactions include the *n*-monobromide, dibromide, bromohydrin, and water. In the case of propylene, bromoacetone is also formed. No peroxidic compounds were found.

3. Bromoacetone (and by analogy any α-bromo ketone) acts as a powerful catalyst for the "abnormal" addition of hydrogen bromide to olefins, even in the dark.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

A HOFMANN TYPE REARRANGEMENT IN LIQUID AMMONIA[1]

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Potassium amide and potassium nitrate dissolved in liquid ammonia at room temperatures react with 2-phenylquinoline-4-carboxylic acid (cinchophen) to give 2-phenylindole in good yield (1). During this rather peculiar reaction, the ring is opened, two carbon atoms are lost, and the indole derivative then formed by ring closure. In an attempt by us to extend this reaction to derivatives of cinchophen, it was found that the corresponding amide (2-phenylquinoline-4-carbonamide) rather unexpectedly reacted with potassium amide and potassium nitrate in liquid ammonia to give 4-amino-2-phenylquinoline in yields of 90–98%, together with a corresponding amount of potassium nitrite and potassium cyanate. It is with this reaction that the present paper is concerned.

Excellent yields of 4-amino-2-phenylquinoline and potassium cyanate may also be obtained by shaking 2-phenylquinoline-4-carbonamide with an excess of potassium amide in the presence of mercury. A dilute potassium amalgam is formed at the same time. Potassium nitrate or mercury are both highly desirable in the above reactions, since in their absence the yield of product drops to about 40%.

Homologs of 4-amino-2-phenylquinoline were formed in fair amount by the action of potassium amide and potassium nitrate on 6-methyl-2-phenylquinoline-4-carbonamide and 2-phenylbenzoquinoline-4-carbonamide (2-phenyl-β-naphthocinchoninamide). Benzamide, phenylacetamide, stearamide, and 2-*n*-propyl-2-phenyl-4-methylpentane amide are not converted in this manner to the corresponding amine. The only other amide found to undergo this type of reaction was *o*-benzoylbenzamide, from which *o*-aminobenzophenone was obtained in 20% yield.

2-β-Naphthylquinoline-4-carbonamide, 2-*p*-tolylquinoline-4-carbonamide, and 2-*p*-methoxyphenylquinoline-4-carbonamide all react readily with potassium amide and potassium nitrate in liquid ammonia, but without the formation of definite products.

Potassium amide and potassium nitrate react with 9-phenyl-9-fluorylamine in liquid ammonia to give 9-aminophenanthridine, while triphenylmethylamine is changed under similar conditions to benzamide. The latter appears to result from the hydrolysis of primarily formed benzamidine (ammonobenzoic acid). Both of these reactions may be interpreted as Stieglitz rearrangements (2, 3).

Quinoline-4-carbonamide (cinchoninamide) reacts with potassium amide and potassium nitrate, in accordance with an earlier type of reaction (4), to form 2-aminoquinoline-4-carbonamide instead of the anticipated 4-aminoquinoline.

[1] From the Doctorate Thesis of H. C. White, Stanford University, 1940.

MECHANISM OF THE REACTIONS

The most obvious mechanism is one involving the direct replacement of the carbonamide group, $CONH_2$, by an amine group in accordance with the equations,

1. $RCONH_2 + 2KNH_2 \rightarrow RNHK + HCONHK + NH_3$

Hydrolysis of the potassium salts on the right hand side of the equation above will give an amine, RNH_2, and formamide. The failure to isolate the latter is understandable in view of the known reaction (5),

2. $HCONHK + (KNH_2) \rightarrow KNCO + H_2 + (KNH_2)$

which occurs only in the presence of potassium amide. Perhaps with potassium nitrate the decomposition might follow the equation,

3. $HCONHK + KNO_3 + KNH_2 \rightarrow KNO_2 + KOH + NH_3 + KCNO$

Reaction 3 was however ruled out, because excess potassium amide reacts with potassium nitrate and formamide in liquid ammonia to yield hydrogen in almost theoretical quantity. Hydrogen is not a product of the reaction between potassium amide, potassium nitrate, and 2-phenylquinoline-4-carbonamide, in which 2-phenyl-4-aminoquinoline and potassium nitrite are formed to the exclusion of reduced quinoline derivatives. Accordingly, the entire mechanism above can be ruled out.

It is more probable that the reaction proceeds by a mechanism having some formal similarity to the Hofmann rearrangement of acid amides to amines, and also to the formation of 2-aminoquinoline from quinoline with potassium amide and potassium nitrate in liquid ammonia (6). The following equations are proposed.

4. $RCONH_2 + KNH_2 \rightarrow RCONHK + NH_3$
5. $RCONH_2 + KNH_2 \rightleftarrows RCONK_2 + NH_3$

The anion of $RCONK_2$ is $RCON^{=}$

6. $RCON^{=} + NO_3^{-} + NH_3 \rightarrow RNCO + NO_2^{-} + NH_2^{-} + OH^{-}$

or $RCON^{=} + xHg \rightarrow RNCO + Hg_x^{=}$

7. $2KNH_2 + RNCO \rightarrow RNHK + KNCO + NH_3$

The over-all reactions are therefore,

8. $RCONH_2 + 3KNH_2 + KNO_3 \rightarrow RNHK + KNCO + KNO_2 + KOH + 2NH_3$
9. $RCONH_2 + 4KNH_2 + xHg \rightarrow RNHK + KNCO + K_2Hg_x + 3NH_3$

Equation 5 represents the formation of the dipotassium salt of the acid amide as reversible, since most acid amides of the type $RCONH_2$ are known only to form stable monopotassium salts (7). It is known that three or more equivalents of potassium amide are necessary for a good yield in the reaction expressed by equation 8, and it is logical to assume that one of its functions is to produce the doubly charged anion, $RCON^{=}$, of equation 5. The removal of the two negative charges and the formation of the isocyanic ester, RNCO, is doubtless a continuous process, as Wallis and Moyer (8) have suggested to be the case in the true Hofmann rearrangement. It is highly improbable that the monovalent nitrogen intermediate of Stieglitz, RCON, is formed at any stage of the reaction.

Attempts to isolate the intermediate 2-phenylquinoline-4-isocyanic ester (an aquo-ammono ester) in the reaction between potassium amide, potassium nitrate,

and 2-phenylquinoline-4-carbonamide have proved fruitless. The ester, formed by other means, reacts much more slowly with potassium amide and potassium nitrate than does 2-phenylquinoline-4-carbonamide, suggesting either that the latter reaction is a continuous process in which the aquo-ammono ester does not appear as such, or else the ester is much more easily saponified immediately after it is formed.

Phenylisocyanate reacts with liquid ammonia to form monophenylurea, as expected, since the same well known reaction occurs with gaseous ammonia. Both phenylisocyanate and α-naphthylisocyanate react with a liquid ammonia solution of potassium amide to give both the mono- and the di-substituted urea. The latter is presumably formed by the following series of reactions,

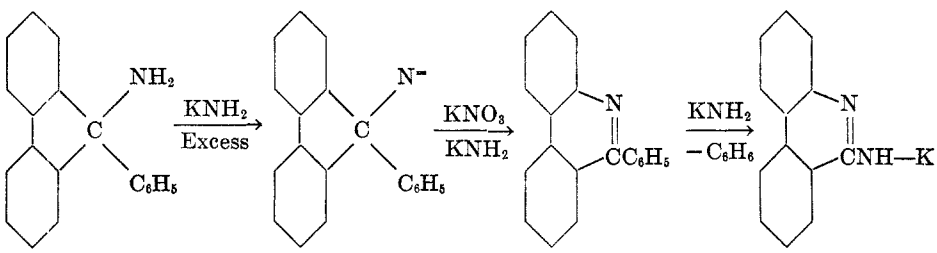
10. $RNCO + 2KNH_2 \rightarrow RNHK + KNCO + NH_3$
11. $RNHK + RNCO \rightarrow (RNK)CO(NHR) \xrightarrow{H_2O} (RNH)_2CO.$

In support of equation 11, it was found that potassium α-naphthylamide reacts with a liquid ammonia solution of α-naphthylisocyanate to form both mono- and di-α-naphthylurea, the former probably the result of a reaction with liquid ammonia alone. There is accordingly some basis for saying that the amine of equations 8 and 9 can be formed by the reaction of equation 7, but it is necessary to make the plausible assumption that the potassium salt of the amine does not readily add to these comparatively unreactive isocyanates to form substituted ureas.

4-Amino-2-phenylquinoline is formed in about 20% yield by the action of potassium amide and potassium nitrate on 2-phenylquinoline-4-carbondimethylamide and in 70% yield from the monomethylamide, probably because these compounds, mixed aquo-ammono esters, are saponified by the potassium amide to dimethylamine, or monomethylamine, and 2-phenylquinoline-4-carbonamide.

The reason for the failure of some 2-substituted quinoline-4-carbonamides to undergo this type of reaction is unknown. Apparently side reactions that lead to the formation of tars and resins predominate over the ones expressed by equations 4–9. Since the two open-chain acid amides failed to react at all with potassium amide and potassium nitrate, it seems that some type of activation of the $CONH_2$ group is necessary, as by C=O or C=N in the ortho or para position with respect to $CONH_2$.

9-Aminophenanthridine (as a potassium salt) is possibly formed from 9-phenyl-9-fluorylamine in accordance with the equations,



The mechanism therefore resembles that suggested by Pinck and Hilbert (2) for the conversion of 9-phenyl-9-fluorylamine to 9-phenylphenanthridine out-

side of liquid ammonia, in the same way that the reactions of equations 4–9 resemble the Hofmann rearrangement. Since potassium amide reacts with 9-phenylphenanthridine to form 9-aminophenanthridine (9), the latter product is the only one isolated in the liquid ammonia reaction.

The conversion of triphenylmethylamine to benzamide by the action of potassium amide and potassium nitrate may possibly follow the equations,

12. $(C_6H_5)_3CNH_2 + KNH_2 + KNO_3 \rightarrow (C_6H_5)_2C{=}NC_6H_5 + KOH + NH_3 + KNO_2$

13. $(C_6H_5)_2C{=}NC_6H_5 + 2KNH_2 \rightarrow C_6H_5NHK + C_6H_5C(NH)(NHK) + C_6H_6$

14. $C_6H_5C(NH)NHK \xrightarrow{H_2O} KOH + C_6H_5C(NH)NH_2 \xrightarrow{H_2O} C_6H_5CONH_2$

In support of this mechanism, it was found that benzophenone anil when heated with potassium amide and potassium nitrate in liquid ammonia gave, after hydrolysis and steam distillation, aniline and benzoic acid in fair yield. The benzoic acid represents the last step in the hydrolysis of benzamidine. Equation 13 recalls the similar scission of benzophenone by heated sodium amide, to benzene and potassium benzamide, or by heated potassium hydroxide to benzene and potassium benzoate (10). Benzophenone anil is an ammono ketone-ether (11).

EXPERIMENTAL PART

Preparation of Acid Amides

With the exception of 2-phenylquinoline-4-carbonamide, none of the compounds below have been described in the literature.

2-Phenylquinoline-4-carbonamide.[2] Isatin (22.1 g., 0.15 mole), ammonium chloride (16 g., 0.30 mole), concentrated aqueous ammonia (180 cc.), and acetophenone (20 g., 0.17 mole) were gently refluxed for fifty minutes with good mechanical stirring. After cooling, the precipitate was collected and recrystallized from alcohol; yield, 18.5 g., or 49.7%; m.p. 195–197°.

Anal. Calc'd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.29.
Found: C, 77.70; H, 4.72; N, 11.50.

The product was found by mixed melting point determinations to be identical with the 2-phenylquinoline-4-carbonamide previously prepared (12).

2-β-Naphthylquinoline-4-carbonamide. 2-β-Naphthylquinoline-4-carboxylic acid (7 g., Ref. 14) was refluxed for thirty minutes (water-bath) with thionyl chloride (50 cc.). The excess thionyl chloride was distilled off, first at atmospheric pressure, and then under a partial vacuum. One hundred cubic centimeters of concentrated ammonia water was added and the mixture allowed to stand for one hour. The tan reaction product was twice crystallized from dil. alcohol; yield, 5.5 g. of colorless crystals, m.p. 250.5–251.0°, uncorr.

Anal. Calc'd for $C_{20}H_{14}N_2O$: C, 80.50; H, 4.69; N, 9.40.
Found: C, 80.43; H, 4.53; N, 9.42.

Other acid chlorides were prepared in the same manner from 7–8 g.of the carboxylic acid and 50 cc. of thionyl chloride, and converted to the amide by the action of ammonia water (100 cc.).

2-p-Methoxyphenylquinoline-4-carbonamide. The product after crystallizaion from cellosolve (ethylene glycol monoethyl ether) melted at 245–246°, uncorr.; yield, 9 g. from 12 g. of 2-*p*-methoxyphenylquinoline-4-carboxylic acid (15) and 85 g. of thionyl chloride.

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[2] This preparation was first worked out by Dreisbach in these laboratories (13).

Anal. Calc'd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07.
Found: C, 73.18; H, 5.02.

2-Phenylbenzo[h]quinoline-4-carbonamide (16). The crude amide, crystallized from dilute cellosolve, melted at 268–269° uncorr.; yield, 67%.

Anal. Calc'd for $C_{20}H_{14}N_2O$: C, 80.54, H, 4.69; N, 9.43.
Found: C, 80.74; H, 4.73; N, 9.42.

2-p-Xenylquinoline-4-carboxylic acid and its amide. *p*-Phenylacetophenone (10 grams) and isatin (9 grams) were refluxed in 100 cc. of 33% potassium hydroxide solution with mechanical stirring for five hours. To the cooled mixture of solid and solution, an excess of dilute acetic acid was added, forming a bulky yellow precipitate. This was collected, washed, and crystallized twice from cellosolve; it then melted at 292–293°, uncorr. The yield was 11 g. Analytical figures for hydrogen and nitrogen were close to the theoretical, but carbon was for some reason low, in all analyses.

Anal. Calc'd for $C_{22}H_{15}NO_2$: C, 81.23; H, 4.65; N, 4.31.
Found: C, 80.23, 79.90, 79.77, 80.03; H, 4.60, 4.60, 4.54, 4.61; N, 4.34.

The acid chloride, prepared in the usual way with thionyl chloride, was converted by treatment with conc'd ammonium hydroxide to the amide, which was twice crystallized from cellosolve. The yield was 4 g. from 8 g. of the acid; m.p. 245.5–246°, uncorr.

Anal. Calc'd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.93.
Found: C, 81.33; H, 4.73.

3-Phenylbenzo[f]quinoline-1-carbonamide. The amide, crystallized from alcohol using Norit, melted at 239–240°, uncorr.; yield, 81%.

Anal. Calc'd for $C_{20}H_{14}N_2O$: C, 80.54; H, 4.69; N, 9.43.
Found: C, 80.37; H, 4.82; N, 9.30.

Reactions in liquid ammonia. General procedure. Reactions in two-legged glass ammonia tubes were carried out in a previously described manner (17). A liquid ammonia solution of potassium amide, prepared in one leg from metallic potassium with an iron oxide catalyst, was added to an ammonia solution or suspension of potassium nitrate and the acid amide in the other leg. Strongly colored solutions resulted. After evaporation of ammonia, the reaction products were treated in the tube with benzene and alcohol to destroy reactive potassium salts, water was added and the first two solvents evaporated. The solid was filtered and crystallized from an appropriate solvent.

2-Phenylquinoline-4-carbonamide and potassium amide. In a straight tube (18) was prepared the potassium amide from 1.17 g. (30 milliatoms) of potassium with an iron wire catalyst. After cooling and removing the catalyst, 2.48 g. (10.0 millimoles) of 2-phenylquinoline-4-carbonamide was introduced, the tube sealed, and allowed to stand at room temperatures for 23 days. The solution at various stages was colored green, reddish-brown, and greenish-brown. Gases obtained during the reaction were insignificant (H_2, 0.4 cc.; N_2, 1.1 cc., standard conditions). The ammonia solution of the reaction product (at −78°) was poured into a beaker, and excess ammonium chloride added to destroy potassium amide. After evaporation of solvent, the solid was washed with water and the dried residue then extracted with hot benzene, the extracts concentrated and cooled to obtain 2-phenyl-4-aminoquinoline. The yield was 0.932 g., m.p. 163.0–170.0°, uncorr., or 43.4%. It was identified after recrystallization as 2-phenyl-4-aminoquinoline (m.p. 163–164°) by mixed melting point determinations. A small amount (0.15 g., m.p. 264–275°) of benzene-insoluble material was also isolated.

2-Phenylquinoline-4-carbonamide, potassium amide, and potassium nitrate. (a) 2-Phenylquinoline-4-carbonamide (1.695 g., 6.82 millimoles), potassium nitrate (1.20 g., 11.9 millimoles), and the potassium amide from 1.20 g. (28.1 milliatoms) of potassium reacted for one day at room temperatures in a two-legged reaction tube, as in the general procedure; yield, 1.342 g., or 89.6%, m.p. 162.5–163.5°, uncorr. In other experiments, yields up to 98% (m.p. 162.5–164°) were obtained. The melting point when the compound was mixed with known 2-phenyl-4-aminoquinoline (19) was 163.5–164.5°, showing their identity.

(b) The above experiment was repeated with an iron wire catalyst for making the potassium amide, since iron oxide catalyzes the formation of potassium nitrite from potassium

nitrate (20). The reaction product was hydrolyzed in the tube with water vapor (21), then treated with water (after breaking open the tube) and the solid collected on a filter. The yield was 1.420 g. or 94.9%. The aqueous filtrate was diluted to 50 cc. and nitrite (22) and cyanate determined on aliquot portions.

One-tenth aliquot gave 14.24 cc. N_2, standard conditions, or 93.2% on the basis of equation 8.

One-half aliquot was treated with excess silver nitrate in very dilute nitric acid, and then with 10 cc. of conc'd sodium nitrite to dissolve possible silver nitrite in the precipitate. The washed silver cyanate collected on a Gooch filter weighed 0.446 g. (88.3%).

(c) In a two-legged tube, 1.63 g. of 2-phenylquinoline-4-carbonamide (6.56 millimoles) reacted with 1.05 g. (10.4 millimoles) of potassium nitrate and the potassium amide from 1.02 g. of potassium (26.1 milliatoms) for 9 days. The solvent was evaporated and the reaction mixture hydrolyzed with benzene and alcohol, and then worked over in the usual way. The yield of 2-phenyl-4-aminoquinoline was 1.394 g., (6.43 millimoles or 97.9%), m.p. 163–164.5°.

(d) In a repetition of reaction (a) at −33° (five hours, round-bottomed flask), 83% of the 2-phenylquinoline-4-carbonamide was recovered unchanged.

(e) In a steel autoclave (22), 128 millimoles of potassium amide reacted for five hours (at 55°) with 60.4 millimoles of 2-phenylquinoline-4-carbonamide and 99 millimoles of potassium nitrate. Considerable resinous material was formed, together with 6.7 g. of solid, m.p. 137–142°, after several crystallizations from alcohol. No pure reaction product was isolated.

(f) *2-Phenylquinoline-4-carbonamide and barium amide.* The chief isolable product is 2-phenylquinoline. Details of this peculiar reaction are reserved for a future article.

2-Phenylquinoline-4-carbonamide, potassium amide, and mercury. In a two-legged glass tube (23) the potassium amide from 1.1 g. (28.2 milliatoms) of potassium was rocked for two days at room temperatures with 1.695 g. (6.82 millimoles) of 2-phenylquinoline-4-carbonamide and 3 cc. of purified mercury. At the end of the reaction, the mercury was well washed with ammonia. Negligible amounts of water-insoluble gases were formed (0.3 cc. H_2, 0.3 cc. N_2). Thirteen and two-tenths milliatoms of potassium was found in the mercury, or 96.8% (equation 9). The yield of 2-phenyl-4-aminoquinoline was 1.401 g. (92.7%).

To the aqueous filtrate of the above, made barely acid with dil. nitric acid, was added excess silver nitrate solution; AgCNO, 0.9180 g. or 90%, AgCl from the AgCNO, 0.8740 g. as against a theoretical 0.8770 g.

2-Phenyl-6-methylquinoline-4-carbonamide, potassium amide, and potassium nitrate. The acid amide (1.20 g., 4.57 millimoles), potassium amide (19.2 millimoles from 0.75 g. of potassium), and potassium nitrate (0.90 g., 7.9 millimoles) reacted for four days at room temperatures.

The tarry precipitate left after evaporation of the benzene-alcohol was freed from water and extracted with petroleum ether. The reddish-brown solid, m.p. 150–160°, that remained was twice crystallized from dilute alcohol with the addition of Norit. It then melted at 184–185°. 2-Phenyl-4-amino-6-methylquinoline melts at 188–189° (24).

2-Phenylbenzo[h]quinoline-4-carbonamide, potassium amide, and potassium nitrate. The acid amide (1.31 g., 4.35 millimoles), potassium amide (17.9 millimoles from 0.70 g. potassium), and potassium nitrate (7.9 millimoles) reacted for three days at room temperatures. The yield of 2-phenyl-4-aminobenzo[h]quinoline (m.p. 162.5–163°) was 0.60 g., or 54%. It was crystallized from alcohol with the use of Norit.

Anal. Calc'd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.20; N, 10.37.
Found: C, 84.20; H, 5.54; N, 10.50.

2-Phenylquinoline-4-carbonmethylamide, potassium amide, and potassium nitrate. The methylamide was prepared by the action of methylamine on the acid chloride of 2-phenylquinoline-4-carboxylic acid. Five millimoles, reacting for four days (20°) with 20.5 millimoles of potassium amide and 8.9 millimoles of potassium nitrate, yielded 0.264 g. (78.5%) of 2-phenyl-4-aminoquinoline (m.p. 162–163° uncorr.).

2-Phenylquinoline-4-carbondimethylamide, potassium amide, and potassium nitrate. The dimethylamide was prepared from the acid chloride of cinchophen and dimethylamine. Five millimoles reacted for two days (20°) with 20 millimoles of potassium amide and 9 millimoles of potassium nitrate. The yield of 2-phenyl-4-aminoquinoline (m.p. 160–162°) was 0.243 g., or 23.3%.

o-Benzoylbenzamide, potassium amide, and potassium nitrate. *o*-Benzoylbenzamide, (1.059 g., 4.71 millimoles) (25) potassium amide (19.2 millimoles), and potassium nitrate (0.80 g., 7.9 millimoles) reacted for six days at 20° in a two-legged tube.

The hydrolysate, freed from benzene and alcohol, was concentrated to about 25 cc. and an excess of dilute hydrochloric acid added. The crystals that separated after standing overnight were added to aqueous sodium hydroxide. The yield of slowly forming yellow crystals was 0.23 g. (20%), m.p. 105–107°. Fifty-one per cent of the theoretical quantity of nitrite was formed (equation 8). *o*-Aminobenzophenone melts at 105° (26). In a repetition of this experiment at −33° (six hours), only a trace of *o*-aminobenzophenone was isolated.

Other Acid Amides with Potassium Amide and Potassium Nitrate

Under the conditions of the preceding experiments (general method), 2-*p*-tolylquinoline-4-carbonamide, 2-*β*-naphthylquinoline-4-carbonamide, 2-*p*-xenylquinoline-4-carbonamide, and 2-*p*-methoxyphenylquinoline-4-carbonamide were converted to tar. Benzamide did not react with four equivalents of potassium amide and two equivalents of potassium nitrate in liquid ammonia at room temperatures during three weeks. Phenylacetamide dissolves in excess potassium amide with a deep red color, indicating possibily that a dipotassium salt, $C_6H_5CHKCONHK$, is formed. Under the usual conditions, with the addition of potassium nitrate, no appreciable reaction had occurred within one week (74% of the phenylacetamide was recovered and no nitrite was formed). Stearamide (6.82 millimoles), potassium amide (23 millimoles) and potassium nitrate (9.9 millimoles) did not react at all in liquid ammonia at 90° (18 hours). 2-*n*-Propyl-2-phenyl-4-methylpentanamide (27) failed to react in three days at 20° with excess potassium amide and potassium nitrate. It was hoped that an optically active amine would be formed.

In all of the above cases, failure to observe a reaction signifies that nothing occurred beyond the formation of a potassium salt, such as RCONHK, from which the acid amide was regenerated on hydrolysis.

Quinoline-4-carbonamide, potassium amide, and potassium nitrate. Quinoline-4-carbonamide[3] (0.30 g., 1.74 millimoles), potassium nitrate (0.30 g., 3.0 millimoles) reacted for two days in a two-legged reaction tube with the potassium amide from 0.30 g. (7.7 millimoles) of potassium (iron wire catalyst). The product, crystallized from water, had the composition of 2-aminoquinoline-4-carbonamide; yield, 0.175 g. (54%), m.p. 218–218.5°, uncorr.; picrate, m.p. 278–280°, uncorr., decomp. Six hundred fourteen thousandths of a mole of nitrite were formed per mole of quinolinecarbonamide.

Anal. Calc'd for $C_{10}H_9N_3O$: C, 64.09; H, 4.85.
Found: C, 63.89; H, 4.99.

One gram was refluxed with dilute hydrochloric acid (about 10%) for one hour, then dil. sodium hydroxide was added to neutrality. The resulting precipitate was filtered cold and washed. The yield was 0.80 g.; m.p. 349–353°, uncorr., depending upon the rate of heating. These properties are those of 2-aminoquinoline-4-carboxylic acid (29).

The Action of Potassium Amide and Liquid Ammonia on Isocyanates

2-Phenylquinoline-4-isocyanic ester, potassium amide, and potassium nitrate. 2-Phenylquinoline-4-isocyanic ester (30) (m.p. 230–231°, uncorr.; 0.71 g. or 2.85 millimoles), potas-

[3] Prepared from cinchoninic acid chloride and aqueous ammonia. The physical properties are the same as those described by Wenzel (28), who prepared the substance by another method.

sium nitrate (0.4 g., 4.0 millimoles), and the potassium amide from 0.35 g. of potassium (9.0 milliatoms) reacted for two days at room temperatures in a two-legged tube. Most of the isocyanate (77%) was recovered from the hydrolysate of the reaction mixture.

In another experiment, five equivalents of potassium amide reacted with 1.23 g. of the isocyanic ester and one equivalent of potassium nitrate for 36 hours at room temperatures. The hydrolyzed product, when crystallized from alcohol, gave 0.75 g. (62%) of the original isocyanic ester, and 0.22 g. (20%) of 2-phenyl-4-aminoquinoline, m.p. 161–162° uncorr.

2-Phenyl-6-methylquinolyl-4-isocyanic ester. This was prepared through the acid azide by the method of John (31) but melted at 246–247°, instead of the reported 214°, even though the melting points of the intermediate hydrazide and acid azide agreed with the values of John.

Anal. Calc'd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65.
Found: C, 78.15; H, 4.85.
Mol. wt. (Rast): Calc'd, 260; found, 267.

When refluxed for ten hours with 33% alcoholic potassium hydroxide, 2-phenyl-4-amino-6-methylquinoline was formed (0.6 g. from 1.0 g. isocyanate); m.p. 188.5–189.3°, uncorr.; picrate, m.p. 206–207° (John reports 208°). The substance in hand therefore had the properties of the isocyanic ester, in spite of the different melting point of John (a misprint?).

2-Phenyl-6-methylquinolyl-4-isocyanic ester (1.23 g.), potassium nitrate (1.0 g.), and the potassium amide from 0.9 g. of potassium (0.02 g. Fe_2O_3 catalyst) reacted for two days in a two-legged tube at room temperatures. One and five hundredths grams of the isocyanic ester was recovered unchanged from the hydrolysate.

Phenylisocyanate and potassium amide. (a) Fifty cubic centimeters of liquid ammonia was added to 4.5 g. of phenylisocyanate in a 200-cc. round-bottomed flask, forming a colorless solution. After the ammonia had evaporated (about four hours) there was left an almost solid colorless residue, which was crystallized from alcohol. The yield was 4.5 g., m.p. 144–145°, uncorr. (87.5%). It was identified as phenylurea by a mixed melting point.

(b) Five grams of phenylisocyanate was added to a liquid ammonia solution (75 cc.) of the potassium amide prepared from 2 g. of potassium with an iron oxide catalyst. A vigorous reaction took place with the formation of a voluminous light purple precipitate. After the ammonia had evaporated (about four hours), the solid was treated with benzene-alcohol mixture, boiled with Norit, and filtered. Colorless crystals (3.7 g.) of sym. diphenylurea, m.p. 233–234°, were obtained and identified by the melting point of a mixture with authentic material. Varying amounts of monophenylurea were also obtained. Under the same conditions, monophenylurea reacted with potassium amide only to form a salt, and not to form diphenylurea.

α-Naphthylisocyanate and potassium amide. Four grams of α-naphthylisocyanate was added to a liquid ammonia solution of the potassium amide from 1.0 g. of potassium in 75 cc. of liquid ammonia at −33°. A copious yellow precipitate formed. An excess of ammonium chloride (1.5 g.) was added after five minutes. The reaction product remaining after evaporation of the ammonia was fractionally crystallized from alcohol, thereby yielding 2.1 g. (48%) of α-naphthylurea (m.p. 211–212° uncorr.) and 1.4 g. (38%) of di-α-naphthylurea (m.p. 283–285°, uncorr.). Identification was by mixed melting point.

Potassium α-naphthylamide and α-naphthylisocyanate. Potassium amide was prepared from a liquid ammonia solution of 2 g. of potassium in the presence of an iron wire catalyst, in an Erlenmeyer flask. To this was added 4 g. of α-naphthylamine, to form potassium α-naphthylamide, whose liquid ammonia solution was orange-red in color. Four grams of α-naphthylisocyanate was slowly introduced, resulting in the formation of a yellow solution and a yellow precipitate. The reaction was stopped after ten minutes by the addition of 3 g. of ammonium chloride. The precipitate remaining after the evaporation of the solvent ammonia was treated with water, filtered, and dissolved in hot alcohol. Addition of conc'd hydrochloric acid gave a precipitate of α-naphthylamine hydrochloride (1.5 g., or 30%). From the filtrate, two fractions were obtained by concentration: α-naphthylurea, 2.4 g., 55%, melting at 210–212°, and di-α-naphthylurea, 2.8 g., or 38%, melting at 282–284°.

Formamide, potassium amide, and potassium nitrate. In a two-legged reaction tube, the potassium amide from 0.75 g. (19 milliatoms) of potassium (iron wire catalyst) was added to a liquid ammonia solution of 0.384 g. (8.53 millimoles) of formamide and 1.10 g. (11 millimoles) of potassium nitrate. Gases were collected at irregular intervals for 18 hours, but little or none was obtained after the first three hours (32). There was obtained 176.6 cc. of gas, standard conditions, consisting of H_2, 97.5%; yield 90%. Small losses of gas always occur when two-legged reaction tubes with stopcock are used, as in the present case.

Pinck and Hilbert type rearrangement. 9-Amino-9-phenylfluorene (1.47 g., 5.00 millimoles), potassium nitrate (0.80 g., 7.9 millimoles), and the potassium amide from 1.0 g. (25.6 milliatoms) of potassium (iron wire catalyst) reacted for two days in a liquid ammonia reaction tube at room temperatures. The product, crystallized from alcohol, proved to be 9-aminophenanthridine, m.p. 190–190.5°, uncorr. The mixed melting point with 9-aminophenanthridine prepared by the action of potassium amide on 9-phenylphenanthridine (9) was the same. The yield was 0.689 g., or 61%. Potassium nitrite was also a reaction product.

Stieglitz type rearrangement. Triphenylmethylamine was not appreciably attacked by potassium amide and potassium nitrate in liquid ammonia at room temperatures; accordingly, it was necessary to apply heat.

Triphenylmethylamine (1.003 g., 3.84 millimoles), potassium nitrate (0.75 g., 7.4 millimoles), and the potassium amide from 0.70 g. (18 milliatoms) of potassium (with 0.02 g. of iron oxide as a catalyst) were rocked in a steel bomb (33)[4] for fourteen hours at 80°. The product was treated with alcohol-benzene mixture, then with water, and the first two solvents evaporated. Benzamide (0.202 g., crude or 43%) was obtained by concentrating and cooling the aqueous solution. The recrystallized material was identified as benzamide by its melting point alone and in mixture with authentic benzamide.

SUMMARY

1. 2-Phenylquinoline-4-carbonamide is converted in about 40–50% yields to 2-phenyl-4-aminoquinoline by reaction with potassium amide in liquid ammonia. Almost quantitative yields are obtained in the presence of potassium nitrate or of mercury.

2. Only a few of the homologs of 2-phenylquinoline-4-carbonamide behave similarly. Open-chain acid amides studied failed to react. The amide of *o*-benzoylbenzoic acid is converted in poor yield to *o*-aminobenzophenone by potassium amide and potassium nitrate. It is thus apparent that a reaction of the above type occurs only if the $-CONH_2$ group is activated by C=O or C=N at a favorable position in the molecule.

3. The direct replacement of the $-CONH_2$ group by $-NH_2$ is very improbable.

4. A more probable mechanism is the following: $RCONH_2$ (2-phenylquinoline-4-carbonamide, etc.) reacts with potassium amide reversibly to form some of the ion, $RCON^-$. This loses two electrons to potassium nitrate or to mercury to give the rearranged product, RNCO, which excess potassium amide converts to RNHK and KNCO. The over-all reactions are

$$RCONH_2 + 3KNH_2 + KNO_3 \rightarrow RNHK + KNCO + 2NH_3 + KOH + KNO_2$$

$$RCONH_2 + 4KNH_2 + xHg \rightarrow RNHK + KNCO + K_2Hg_x + 3NH_3$$

[4] A sealed glass tube was enclosed in a steel bomb tube containing liquid ammonia to counterbalance the internal pressure.

2-Phenylquinoline-4-isocyanic ester and 2-phenyl-6-methylquinolyl-4-isocyanic ester react more slowly with potassium amide to form the corresponding amine than this latter is produced in accordance with the equations above from quinoline-4-carbonamide derivatives. Isocyanate is, therefore, either not a true intermediate in the reactions, or it is much more readily saponified by potassium amide immediately after its formation.

5. Phenyl- and naphthyl-isocyanates react with liquid ammonia at $-33°$ to form monosubstituted ureas, but disubstituted ureas are also formed in the presence of potassium amide. This can be interpreted as involving the intermediate formation of a salt of a primary amine, *e.g.*, C_6H_5NHK, which adds to the isocyanate to form the disubstituted urea. Accordingly, the assumption of the formation of the isocyanic ester (paragraph 4 of summary) receives some support.

6. 9-Phenyl-9-fluorylamine reacts with potassium amide and potassium nitrate to form 9-aminophenanthridine by a method related to the Pinck-Hilbert modification of the Stieglitz rearrangement. The expected primary product, 9-phenylphenanthridine, has been converted by potassium amide to 9-aminophenanthridine.

7. Potassium amide and potassium nitrate react with triphenylmethylamine to form benzamide. It is assumed that a Stieglitz-type rearrangement takes place with the formation of benzophenone anil, which is cleaved by potassium amide to potassium benzamidine. The latter is hydrolyzed to benzamide.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF GEORGIA]

SOME HYDROXYLAMINE DERIVATIVES OF ANTHRANILIC ACID[1]

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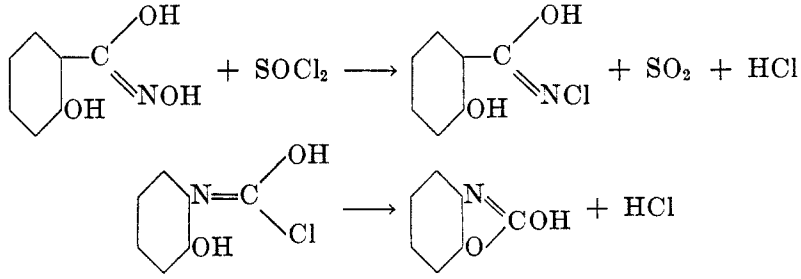
INTRODUCTION

The term hydroxamic acid is given to the mono-acyl derivatives of hydroxylamine and indicates most readily a compound with the hydroxylamide structure. Even though the term hydroxamic acid is used commonly to denote all the mono-acyl derivatives of hydroxylamine, there is a tautomeric hydroximic acid with a hydroxylimide structure.

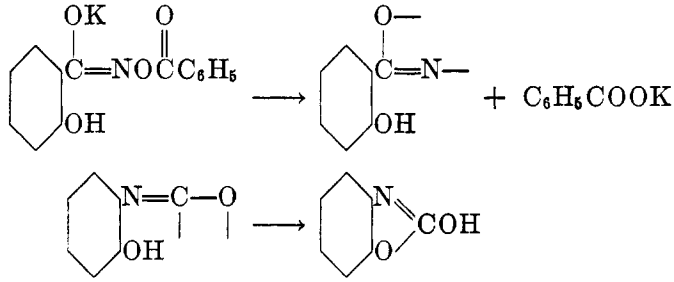
W. Lossen (1) tried to establish the true structural formula of the hydroxamic acids and finally came to the conclusion that each of the hydrogen atoms in hydroxylamine has a different substitution value, or else the constitution of the base changes when its hydrogen atoms are replaced by radicals, so that each of the three nitrogen valencies acts in a different manner. He supposed that the mono-acyl hydroxylamines had the structure known as the hydroximic and not the hydroxamic acid. There is no definite proof of the true structure, since no desmotropes have been found and each acid reacts as if it had both structures. Since the time of Lossen many hydroxamic acids have been prepared for the primary purpose of studying their rearrangement. This rearrangement is brought about by heating the sodium or potassium salt of the benzoyl or acetyl ester of the hydroxamic acid in water. Practically all of the hydroxamic esters prepared so far have been found to rearrange in the presence of water to form symmetrically disubstituted ureas, organic acids, and carbon dioxide.

The effect of substituted groups upon the rearrangement of benzhydroxamic acid has been studied by several investigators in the past. Marquis (2) found that salicylhydroxamic acid formed an oxycarbonil when treated with thionyl chloride. He believed that this was the product of a true Beckmann rearrangement and postulated the reaction as follows:

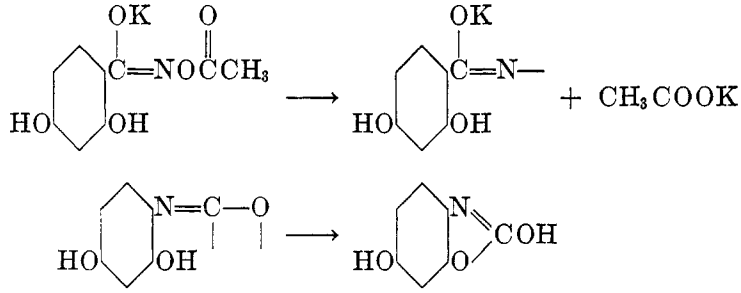


[1] This paper is based upon a thesis presented by Burrell L. Wood, Jr., to the Graduate

Scott and Mote (3) found that the potassium salt of the benzoyl ester of salicylhydroxamic acid rearranged to form the oxycarbonil as obtained by Marquis from salicylhydroxamic acid itself. This reaction can be shown as follows:



Scott and Kearse (4) found that the potassium salt of the acetyl ester of 2,4-dihydroxybenzhydroxamic acid rearranged to form an oxycarbonil rather than the disubstituted urea. This was entirely in accord with the results obtained by Scott and Mote with salicylhydroxamic acid. This reaction can be shown by the following equations:



The present investigation was undertaken in order to study the effect of an ortho substituted amine group on the rearrangement of benzhydroxamic acid. For this study 2-aminobenzhydroxamic acid was selected.

DISCUSSION OF RESULTS

I

2-Aminobenzhydroxamic acid as described by Meyer and Bellman (5) was prepared from isatoic acid anhydride. The product obtained corresponded in every respect to their product. The benzoyl derivative of this compound was prepared by treatment with benzoic acid anhydride. The potassium salt of the benzoyl derivative was found to rearrange when heated in water to form N-phenyl-N′-(2-carboxyphenyl)urea and 3-phenyl-2,4-dioxotetrahydroquinazoline.

The formation of these rearrangement products cannot be explained if the above acid is assumed to be the true hydroxamic acid. If the acid above were the true hydroxamic acid and the salt were the potassium salt of the O-benzoyl

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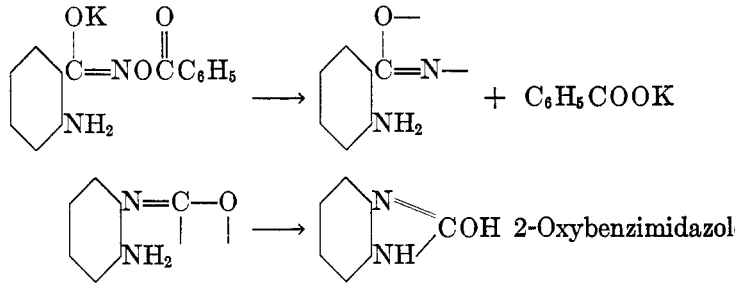
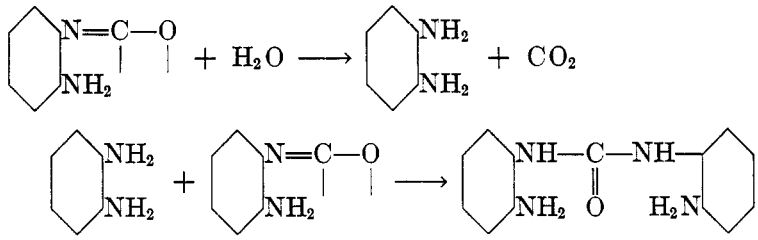
ester of 2-aminobenzhydroxamic acid, the rearrangement products expected would be as follows:

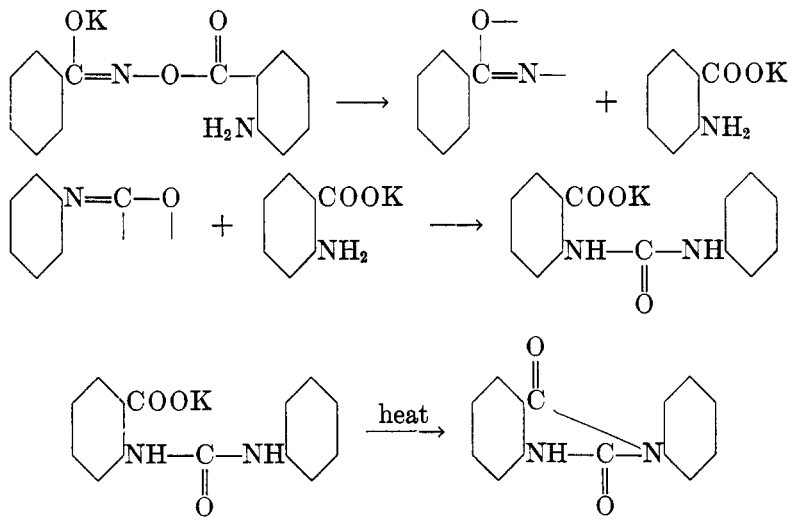


or

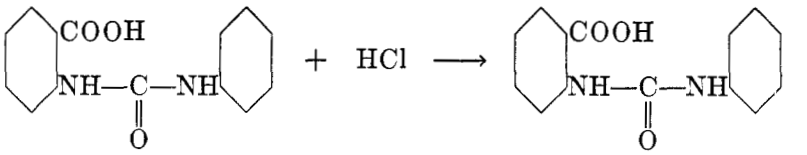


N,N′-bis-(2-aminophenyl)urea

Since the expected rearrangement products were not obtained, the following reactions are postulated to explain the course of the rearrangement. The salt in this case is assumed to be the potassium salt of the O-(2-aminobenzoyl) ester of benzhydroxamic acid.

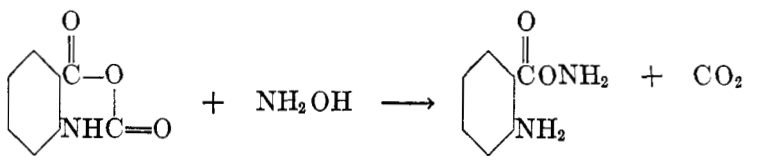


3-Phenyl-2,4-dioxotetrahydroquinazoline



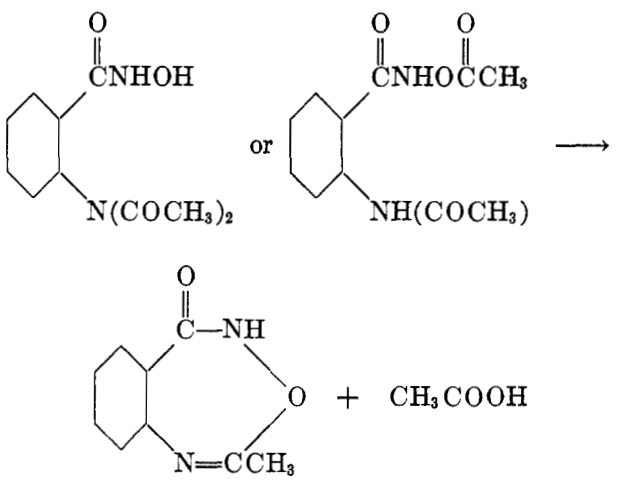
N-phenyl-N′-(2-carboxyphenyl)urea

This postulation assumes that the 2-aminobenzhydroxamic acid prepared from isatoic acid anhydride is an O-acyl hydroxylamine rather than an N-acyl hydroxylamine. The equation for its preparation can be shown as follows:



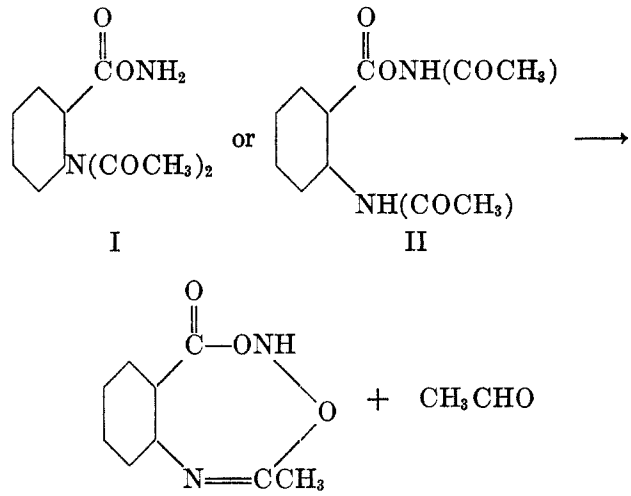
This structure explains why this compound does not give a test for hydroxamic acids with ferric chloride, since there are no acidic hydrogen atoms present. This also explains why Pope (6) was unable to prepare the benzoyl derivative by the modified Schotten-Baumann method.

This structure can be used to explain why Meisenheimer and Diedrich (7) were unable to form a cyclic compound by splitting off acetic acid from the diacetyl derivative of this compound. If this were the true hydroxamic acid, this cyclization might take place as follows:



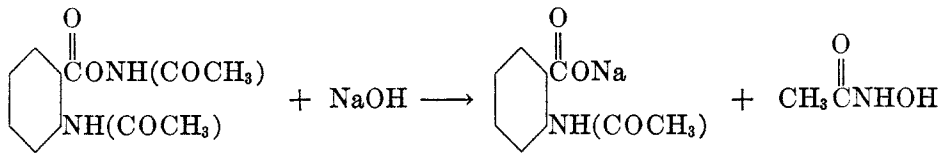
If this compound has the O-acyl structure, it can be easily seen why cyclization cannot take place. Such cyclization would involve the splitting off of a

molecule of acetaldehyde which would be extremely unusual. The equation could be shown as follows:



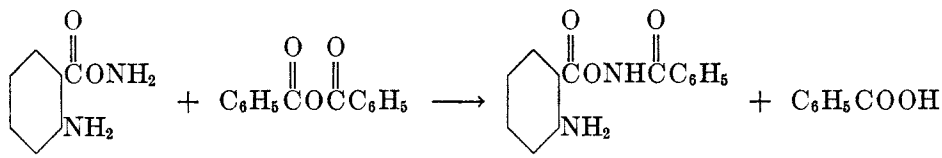
I II

Structure II seems to be the correct structure for the diacetyl derivative, since upon treatment with dilute sodium hydroxide the compound gave a test for hydroxamic acids with ferric chloride. This would seem to indicate that acethydroxamic acid had been formed by hydrolysis. Meisenheimer and Diedrich (7) found that upon treatment with dilute sodium hydroxide acetanthranilic acid was split off. This can be explained as a normal hydrolysis if structure II is assumed.

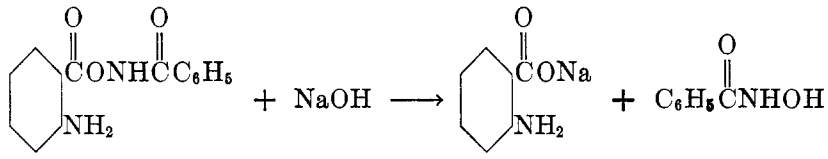


Acethydroxamic acid

The preparation of the benzoyl derivative of this compound can be shown by the following equation:



It was found that treatment of the benzoyl derivative with dilute sodium hydroxide gave a solution that gave a test for hydroxamic acids with ferric chloride. This would seem to indicate that benzhydroxamic acid had been hydrolyzed off. The equation for the hydrolysis can be shown as follows:



Benzhydroxamic acid

This hydrolyzed solution also gave a grass-green precipitate with cupric acetate.

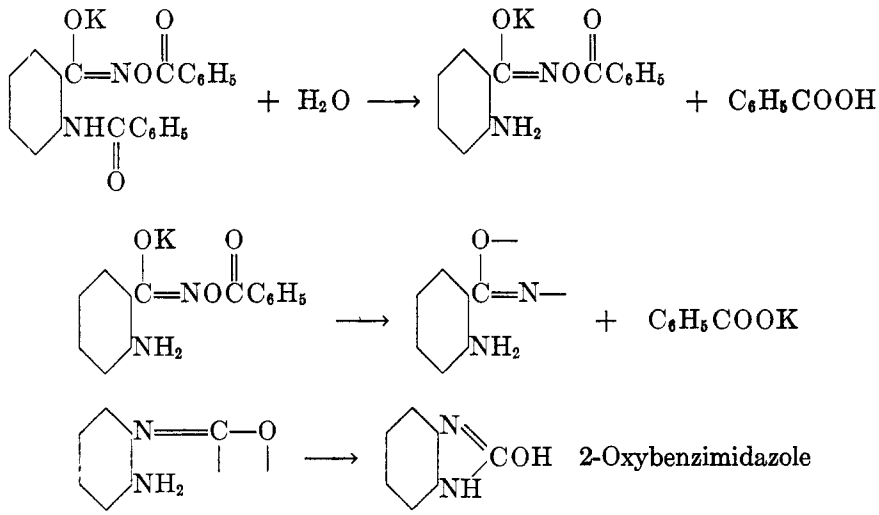
Upon checking the literature, no O-mono-acyl derivatives of hydroxylamine were found. This structure was suggested by Lossen (8) as a probable structure for the hydroxamic acids and called by him the oxylamide structure. All the so-called dihydroxamic acids or hydroxamic esters may be considered as derivatives of O-acyl hydroxylamines. This would indicate the possibility of the existence of the O-acyl hydroxylamines.

The compound prepared from isatoic acid anhydride decomposed readily in moist air and slowly when kept in a desiccator. This is a further indication that the compound has an O-acyl structure (see below).

II

2-Aminobenzhydroxamic acid was prepared by the action of hydroxylamine on methyl anthranilate. This compound differs markedly from the 2-aminobenzhydroxamic acid described by Meyer and Bellman (5), in that it has a melting point 67° higher, and it gives the usual color reaction of hydroxamic acids with ferric chloride; it gives a green salt with copper acetate; it has been kept for several months without appreciable decomposition, and it shows the general chemical properties of hydroxamic acids.

The dibenzoyl derivative was prepared and its potassium salt rearranged when heated in water to form 2-oxybenzimidazole. The course of this reaction can be shown as follows:



2-Oxybenzimidazole

This is the product of a normal rearrangement of such a hydroxamic acid according to the hypothesis of Scott and Kearse (4) and indicates that the compound prepared from methyl anthranilate is the N-acyl hydroxylamine.

EXPERIMENTAL

A. *Isatoic acid anhydride* was prepared by the method of Erdmann (9).

B. *O-(2-Aminobenzoyl)hydroxylamine* was prepared according to the method of Meyer and Bellman (5). This compound was found to decompose readily in moist air and slowly when kept in a desiccator. It was found to be very soluble in ethyl acetate, soluble in acetone and ether, and slightly soluble in water. It did not give a test for hydroxamic acids with ferric chloride. When it was dissolved in dilute alkali and heated or allowed to stand overnight, a solution was formed that gave a test for hydroxamic acids with ferric chloride. The yield was 60%.

Anal. Calc'd for $C_7H_8N_2O_2$: N, 18.46. Found: N, 18.42.

This analysis was run by Pope (6).

C. *Benzoyl derivative of O-(2-aminobenzoyl)hydroxylamine* was prepared by the method given by Pope (6). Eleven and three-tenths grams of benzoic anhydride was mixed with 7.6 grams of O-(2-aminobenzoyl)hydroxylamine. The solid mixture softened as heat was produced spontaneously. When the mixture began to harden, it was warmed on a hot plate for fifteen minutes at about 70°. After the reacted mass had cooled, it was ground in a mortar and extracted with boiling ligroin to remove benzoic acid and benzoic anhydride. The residue was recrystallized from a mixture of alcohol and ligroin. The benzoyl derivative was obtained as white needles which melted at 157°.

This compound did not give a ferric chloride test, but when it was dissolved in excess sodium hydroxide and warmed for fifteen minutes, the resulting solution gave a hydroxamic test with ferric chloride and a grass-green precipitate with cupric acetate. (The copper salt was dried and suspended in dry ether, and hydrogen sulfide was passed through the solution. This freed the hydroxamic acid but not enough of the pure acid was obtained to determine its melting point.)

Anal. Calc'd for $C_{14}H_{12}N_2O_3$: N, 10.93. Found: N, 11.04.

This analysis was run by Pope (6).

D. *Potassium Salt of C.* Two and fifty-six hundredths grams of the benzoyl derivative of O-(2-aminobenzoyl)hydroxylamine was dissolved in 75 ml. of butyl alcohol. To this solution was added 20 ml. of butyl alcohol containing 0.391 g. of potassium. Upon stirring, a white solid began to settle out. This was filtered and washed with butyl alcohol. The potassium salt thus formed was dried overnight in a desiccator.

Rearrangement of D. This potassium salt was dissolved in the minimum of water and warmed on a hot plate. After the solution had been heated for a few minutes a white compound began to precipitate. The solution was cooled and filtered by suction. The precipitate was recrystallized from ethyl alcohol and melted at 280°. The analysis of this compound as made by Pope (6) indicates that it is 3-phenyl-2,4-dioxotetrahydroquinazoline.

Anal. Calc'd for $C_{14}H_{10}N_2O_2$: N, 11.76. Found: N, 11.35.

3-Phenyl-2,4-dioxotetrahydroquinazoline was prepared by Paal (10), from N-phenyl-N'-(2-carboxyphenyl)urea by boiling in dilute ammonia. Kunckell (11) reported the melting point as 280°.

When the filtrate from the above rearrangement product was acidified with hydrochloric acid, a white precipitate settled out. This was filtered and recrystallized from a mixture of acetone and ligroin. The melting point was 180° [Pope (6) 182°]. The analysis of this compound as made by Pope (6) indicates that it is N-phenyl-N'-(2-carboxyphenyl)urea.

Anal. Calc'd for $C_{14}H_{12}N_2O_3$: N, 10.93. Found: N, 10.32.

N-phenyl-N'-(2-carboxyphenyl)urea was prepared from sodium anthranilate and phenyl isocyanate in accordance with the work of Paal (10). He reported its melting point as 181°. A mixed melting point of these two products was 181–182°.

E. *2-Aminobenzhydroxamic acid* was prepared by the method given by Pope (6). To a cooled solution of 48 g. of sodium hydroxide in 300 ml. of water was added slowly with stirring 41.6 g. of hydroxylamine hydrochloride. To this solution was added 45.2 g. of methyl anthranilate and enough methyl alcohol to bring it into solution. This solution was allowed to stand for three days at room temperature. It then gave a good test for hydroxamic acids with ferric chloride. The solution was distilled under reduced pressure until the sodium salt of the hydroxamic acid was precipitated, leaving about 100 ml. of the mother liquor in the flask. The salt was filtered by suction and washed with ether. The filtrate was made acid with hydrochloric acid and the free hydroxamic acid was precipitated. The crude product was recrystallized from ether by use of a Soxhlet extractor. It was light brown in color and had the melting point 149°. The yield of the sodium salt and the free hydroxamic acid recovered from the mother liquor was 70%.

This compound gives a good test for hydroxamic acids with ferric chloride. It is fairly stable up to 140° and was kept for three months at room temperature without noticeable decomposition. It is soluble in ethyl acetate, slightly soluble in ether and almost insoluble in ligroin.

Anal. Calc'd for $C_7H_8N_2O_2$: N, 18.46. Found: N, 18.24.

Rearrangement of the sodium salt of 2-aminobenzhydroxamic acid. The dry sodium salt was heated until evidences of sublimation were noted. The residue was extracted with dilute potassium hydroxide and filtered into dilute hydrochloric acid. The precipitate formed was filtered and recrystallized from alcohol. It melted at 302–303°. 2-Oxybenzimidazole was made according to the method described by Kyn (12). A mixed melting point of the two compounds was 302–303°.

F. *Dibenzoyl derivative of 2-aminobenzhydroxamic acid* was prepared by adding 10 g. of the sodium salt of 2-aminobenzhydroxamic acid to 8 g. of benzoyl chloride dissolved in 50 ml. of dioxane. This was shaken thoroughly for thirty minutes and filtered to remove the precipitated sodium chloride. The crude benzoyl derivative was obtained by evaporating the dioxane solution to dryness. The residue was recrystallized from ethyl acetate and had the melting point 169°. This compound did not give a ferric chloride test for hydroxamic acids.

Anal. Calc'd for $C_{21}H_{16}N_2O_4$: N, 7.78. Found: N, 7.66.

G. *Potassium salt of F.* Two and fifty-six hundredths grams of the dibenzoyl derivative of 2-aminobenzhydroxamic acid was suspended in 50 ml. of butyl alcohol containing 0.391 g. of potassium. This was stirred for fifteen minutes and the solid dissolved. The potassium salt was obtained by allowing the butyl alcohol to evaporate. The crude salt was dried and washed with ether. It was then dried overnight in a desiccator.

Rearrangement of G. This potassium salt was added to 100 ml. of boiling water. After boiling for fifteen minutes, a white precipitate began to settle out. The solution was cooled and filtered. The precipitate was dissolved in dilute potassium hydroxide and filtered into dilute hydrochloric acid. The precipitate was filtered and recrystallized from alcohol. Its melting point was 298°. A mixed melting point with 2-oxybenzimidazole was 300°. 2-Oxybenzimidazole, prepared by the method of Kyn (12), melted at 302°. This indicates that the rearrangement product was 2-oxybenzimidazole.

SUMMARY

1. The 2-aminobenzhydroxamic acid reported by Meyer and Bellman (5) was prepared and shown to be O-(2-aminobenzoyl)hydroxylamine.

2. The compound prepared from methyl anthranilate and hydroxylamine was found to be the true 2-aminobenzhydroxamic acid.

3. The potassium salt of the dibenzoyl derivative of 2-aminobenzhydroxamic acid was found to rearrange to form 2-oxybenzimidazole rather than a *sym.*-disubstituted urea.

4. The sodium salt of 2-aminobenzhydroxamic acid formed 2-oxybenzimidazole upon heating.

ATHENS, GA.

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

THE DIALKYLATION OF NAPHTHALENE. 1, 4-DICYCLOHEXYLNAPHTHALENE

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Although many dialkylated derivatives of naphthalene have been reported from Friedel-Crafts type alkylations, many of the products have not been separated into pure chemical components, and even for those few dialkylnaphthalenes which have been isolated as pure crystalline compounds, the structure has in no case been established.

The dialkylnaphthalenes most readily obtained in crystalline form are the di-*t*-butyl derivatives (1, 2). Fractional distillation of the product from the reaction of naphthalene with *t*-butyl or isobutyl chloride and aluminum chloride (1, 2) or with *t*-butyl alcohol and boron fluoride (3) or hydrogen fluoride (4, 5)[1] gave solid mixtures of di-*t*-butylnaphthalenes. This mixture contained varying proportions of an isomer (I) which crystallized as stout, flat needles melting at 145–146°, and which could be converted to the corresponding quinone by chromic oxide in acetic acid (2), but could not be converted into a picrate. The residue remaining after separation of this high-melting isomer gave a beautifully crystalline picrate, m.p. 156–156.5°. This picrate, which was not previously analyzed successfully (2), has now been shown to be composed of three moles of hydrocarbon and two of picric acid. Furthermore, the hydrocarbon recovered from the purified picrate, which crystallized from alcohol as fine, cottony needles melting unsharply at 80–82°, has been shown to be a mixture of two isomers. Careful fractional recrystallization from alcohol or acetic acid yielded fine needles (II) melting sharply at 103–104°. A mixture of this substance (2 parts) with the higher-melting isomer (I) (1 part) melted at 80–82° and was identical with the material recovered from the picrate. Evidently the picrate contains one molecule of I, two molecules of II and two of picric acid.

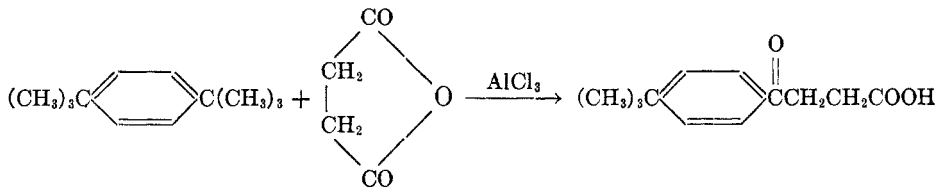
$$\underset{\text{m.p. } 146^\circ}{\underset{\text{I}}{C_{10}H_6(C_4H_9)_2}} + \underset{\text{m.p. } 104^\circ}{\underset{\text{II}}{2C_{10}H_6(C_4H_9)_2}} \longrightarrow \underset{\text{m.p. } 80\text{–}82^\circ}{\text{mixture}} \xrightarrow[NH_4OH]{2C_6H_3N_3O_7} \underset{\text{m.p. } 156\text{–}156.5^\circ}{\text{Picrate } (3C_{18}H_{24} + 2C_6H_3H_3O_7)}$$

All attempts to establish the structure of these two hydrocarbons by degradation have failed. Oxidation with dilute nitric acid gave no naphthalic acids. Oxidation of either isomer I or II with mercuric sulfate and sulfuric acid yielded

[1] Tsukervanik and Terent'eva (5), using *t*-butyl alcohol and aluminum chloride, report a di-*t*-butylnaphthalene, m.p. 132°, picrate, m.p. 99°, which differs from any product isolated by any other procedure.

small amounts of phthalic anhydride. This evidence may not signify the presence of both alkyl groups in one ring, however, since the sulfuric acid may have catalyzed the elimination of a *t*-butyl group during the oxidation (6).

A synthetic approach also failed, since the reaction of *p*-di-*t*-butylbenzene with succinic or maleic anhydrides was found to result in almost complete elimination of one *t*-butyl group, the principal product from the two reactions consisting principally of *p*-*t*-butylbenzoylpropionic and acrylic acids, respectively.



A similar elimination of a *t*-butyl group of *p*-di-*t*-butylbenzene has been previously observed for acetylation by Koch and Steinbrink (7).

From the alkylation of naphthalene with cyclohexanol and aluminum chloride, Bodroux (8) obtained a crystalline dicyclohexylnaphthalene, m.p. 151°, as well as a liquid isomer. Using cyclohexene as the alkylating agent, Pokrovskaya and Stepantseva (9) obtained similar products. The crystalline isomer was dehydrogenated to a diphenylnaphthalene (9), m.p. 230°, melting much higher than any previously reported diphenylnaphthalene.

By alkylation of naphthalene with cyclohexanol and boron fluoride, we have obtained a new crystalline dicyclohexylnaphthalene, m.p. 83°, accompanied by an isomeric liquid. Dehydrogenation of the new crystalline isomer by heating with selenium gave 1,4-diphenylnaphthalene, m.p. 132–133°, identical with an authentic specimen.

Similar dehydrogenation of the liquid material yielded only traces of a crystalline product, which melted at 231° and is evidently identical with the diphenylnaphthalene of unknown structure obtained by Pokrovskaya and Stepantseva (9). It was undoubtedly formed from traces of the high-melting (151°) isomer present in the liquid in amounts too small to isolate.

It thus appears that the alkylation of naphthalene with cyclohexanol yields at least three isomeric dicyclohexylnaphthalenes. The crystalline isomer melting at 83°, isolated from the boron fluoride-catalyzed reaction, has been definitely identified as 1,4-dicyclohexylnaphthalene.

The most likely structure for the crystalline isomer melting at 151° is that of 2,6-dicyclohexylnaphthalene. The liquid material is an isomer (or isomers) as yet unidentified.

EXPERIMENTAL[2]

Di-t-butylnaphthalenes. The reaction of naphthalene (118 g.) with two moles of *t*-butyl chloride in 100 cc. of carbon disulfide proceeded vigorously on the addition of 8 g. of alu-

[2] Analyses by Charles W. Beazley, L. G. Fauble, Mary Kreger, and Margaret McCarthy.

minum chloride with stirring. Hydrolysis and distillation yielded a solid mixture of di-*t*-butylnaphthalenes (88–95%), boiling at about 200° (20 mm.). Approximately 10% of this mixture could be obtained as stout, flat needles by careful fractional recrystallization from methyl or ethyl alcohol, m.p. 145–146°. The residue formed fine, cottony needles melting unsharply at about 80–82°. This latter material formed a picrate crystallizing from alcohol as lustrous, orange needles, m.p. 156–156.5°, for which the analytical data indicate the formula $(C_{18}H_{24})_3(C_6H_3O_7N_3)_2$.

Anal. Calc'd for $C_{66}H_{78}N_6O_{14}$: C, 67.18; H, 6.67; N, 7.13.
Found: C, 67.09; H, 6.71; N, 7.20.

Decomposition of the picrate regenerated the hydrocarbon as fine needles, m.p. 80–82°. Careful recrystallization of this substance from acetic acid or alcohol yielded needles melting sharply at 103–104°. A mixture of this compound (2 parts) and the higher-melting isomer (1 part) melted at 80–82° and was identical with the material recovered from the picrate.

The higher-melting isomer was readily converted to the corresponding *quinone*, m.p. 83–83.5° (2), but all attempts to prepare a quinone from the lower-melting isomer or the low-melting mixture by oxidation with chromic acid in acetic acid have yielded red oils from which no crystalline material could be isolated.

Reductive acetylation of the oily oxidation product by heating with zinc dust in acetic anhydride gave an oil from which a small amount of white needles, m.p. 139–140°, was obtained by recrystallization from alcohol. These needles are evidently the *diacetate* of the hydroquinone derived from the high-melting hydrocarbon.

Anal. Calc'd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92.
Found: C, 73.76, 74.44; H, 7.78, 8.00.

Oxidation of either di-*t*-butylnaphthalene with mercuric sulfate in concentrated sulfuric acid yielded only phthalic acid. Either the *t*-butyl groups are on the same ring or, very probably, the sulfuric acid caused dealkylation (6).

p-*Di-t-butylbenzene and succinic anhydride* in carbon disulfide solution were treated with an equivalent amount of aluminum chloride at −15° for twelve hours. Hydrolysis, followed by extraction with sodium bicarbonate yielded a large amount of acid. This material was almost entirely *p-t*-butylbenzoylpropionic acid, m.p. 126° (2), identified further by permanganate oxidation to *p-t*-butylbenzoic acid, m.p. 162° (2). By careful fractional crystallization from methanol, a small portion (3.5%) of the crude product was isolated as colorless tetragonal crystals, m.p. 176–177°. This acid was isolated more readily by converting the crude acid mixture to its benzylthiuronium salt with a limited quantity of benzylthiuronium chloride (10). The salt, m.p. 142–143°, was decomposed by dissolving in hot acetic acid; the free acid crystallized on cooling. This acid had the proper neutral equivalent for a di-*t*-butylbenzoylpropionic acid but the analysis indicated two too few hydrogen atoms. The product gave a negative test for unsaturation with bromine and with permanganate.

Anal. Calc'd for $C_{18}H_{26}O_3$: C, 74.43; H, 9.03; N.E., 290.
Calc'd for $C_{18}H_{24}O_3$: C, 74.95; H, 8.39; N. E., 288.
Found: C, 74.96; 74.98, 75.03; H, 8.29, 8.30, 8.58; N. E., 286, 284, 288.

Oxidation with permanganate (11) has yielded two crystalline oxidation products. One, lustrous pearly plates, m.p. 194–196°, is apparently the normal oxidation product, since the analysis and neutral equivalent indicated a product with two less hydrogen atoms than di-*t*-butylbenzoic acid.

Anal. Calc'd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47; N. E., 234.
Calc'd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; N. E., 232.
Found: C, 77.53; H, 8.69; N. E., 231.

A second oxidation product, m.p. 217–218°, had the same neutral equivalent (233) but contained 71.41% carbon and 7.33% hydrogen.

p-*Di-t-butylbenzene and maleic anhydride* were condensed by the same procedure as that used for succinic anhydride. The only product which could be isolated was p-t-*butyl-*

benzoylacrylic acid, which crystallized from benzene-ligroin as yellow-green plates, m.p. 123°, or yellow-green needles, m.p. 128°.

Anal. Calc'd for $C_{14}H_{16}O_3$: C, 72.38; H, 6.93; N. E., 232.
Found (123°): C, 72.44; H, 7.09; N. E., 231.
Found (128°): C, 72.21; H, 7.06; N. E., 233.

Both forms gave positive tests for unsaturation with bromine and with permanganate, and yielded *p-t*-butylbenzoic acid on oxidation.

Dicyclohexylnaphthalene. Boron fluoride was found to be a much more convenient catalyst for alkylation of naphthalene with alcohols (3) than aluminum chloride. The reaction is carried out very simply by passing boron fluoride through a suspension of naphthalene in alcohol at room temperature. In several reactions cooled to 0° there was no apparent reaction for half an hour or so and then the reaction proceeded so vigorously that all stoppers were blown out of the apparatus and a considerable portion of the reaction mixture was lost. Apparently, when the alkylation mixture is cooled, the boron fluoride dissolves without reacting and then suddenly, all the dissolved catalyst reacts at once, whereas, at room temperature, the reaction proceeds smoothly as the boron fluoride is passed into the mixture.

To prepare dicyclohexylnaphthalenes, 128 g. (1 mole) of naphthalene was suspended in 220 g. (2.1 moles) of cyclohexanol in a 1-liter flask. Boron fluoride was passed in rapidly for thirty minutes; the mixture was allowed to warm up from the heat of reaction. The dark red reaction mixture separated into two layers and, after standing for one day at room temperature, it was washed with dilute alkali and water; 300 cc. of benzene was added to facilitate the washing process. The pale tan benzene solution was dried and distilled. The dicyclohexylnaphthalene fraction, 55 g. (19%), b.p. 240–260° (6 mm.), was a pale yellow oil. The oil was dissolved in the minimum amount of ligroin and cooled in a solid carbon dioxide-alcohol bath to induce crystallization. After three weeks at 0°, 7 g. of crystalline material had separated. Recrystallization from ligroin and from alcohol yielded *1,4-dicyclohexylnaphthalene*, m.p. 83–83.5°.

Anal. Calc'd for $C_{22}H_{28}$: C, 90.35; H, 9.65.
Found: C, 90.15; H, 9.61.

Dehydrogenation. The position of the dicyclohexyl groups was demonstrated by dehydrogenation of 7 g. of the hydrocarbon with 14 g. of selenium at 350° for sixty hours. Distillation of the product, followed by recrystallization from alcohol, gave a substantial yield of *1,4-diphenylnaphthalene*, clusters of needles, m.p. 132–133°. The identity was checked by a mixed melting point determination with an authentic specimen.

The liquid dicyclohexylnaphthalene mixture recovered from the first crystallization of the 1,4-isomer was subjected to the same treatment with selenium. Only a minute amount of diphenylnaphthalene was recovered; it crystallized from alcohol as shiny plates, m.p. 231°. It is evidently identical with the diphenylnaphthalene Pokrovskaya and Stepantseva (9) obtained by dehydrogenation of the dicyclohexylnaphthalene melting at 151°. In view of the high melting point of these two compounds, in comparison with isomers of known structure, it seems highly probable that the phenyl and cyclohexyl groups are in the 2,6-position.

SUMMARY

A new di-*t*-butylnaphthalene, m.p. 104°, has been isolated from the mixture formed by the alkylation of naphthalene. The dialkylated material melting at about 80–82° has been shown to be a mixture of two parts of this new isomer and one part of the isomer melting at 146°. These two isomers form a mixed picrate composed of one mole of the high-melting (146°) di-*t*-butylnaphthalene, two of the low-melting (104°) isomer and two of picric acid.

The principal product of the reaction of *p*-di-*t*-butylbenzene with succinic

anhydride was *p-t*-butylbenzoylpropionic acid, accompanied by small amounts of a saturated acid of unknown structure containing two less hydrogen atoms than di-*t*-butylbenzoylpropionic acid.

From the boron fluoride-catalyzed alkylation of naphthalene with cyclohexanol a new crystalline dicyclohexylnaphthalene, m.p. 83–83.5°, has been isolated. Since dehydrogenation yielded 1,4-diphenylnaphthalene, this compound must be 1,4-dicyclohexylnaphthalene.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

REARRANGEMENT OF PHENYL CAPRYLATE WITH FERRIC CHLORIDE, TITANIUM TETRACHLORIDE, STANNIC CHLORIDE, AND ZINC CHLORIDE

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When phenyl caprylate is rearranged in the presence of aluminum chloride it has been shown (1) that the ratio of para- to ortho-hydroxy ketones obtained is influenced by the amount of catalyst employed. Although metallic halides, other than aluminum chloride, have been somewhat extensively investigated as acylation catalysts very little work has been reported with regard to the effect of such catalysts upon the rearrangement of phenyl esters. Eijkman (2) studied the rearrangement of substituted phenyl esters in the presence of ferric and zinc chlorides. The rearrangement of phloroglucinol triacetate in the presence of ferric chloride and also of zinc chloride has been reported by Heller (3, 4). These catalysts were considered only slightly less active than aluminum chloride. Huber and Brunner (5) obtained a 25% yield of *p*-hydroxyacetophenone by the action of ferric chloride upon phenyl acetate, and a 16% yield of *p*-hydroxyisobutyrophenone from phenyl isobutyrate. They also reported a 28% yield of *p*-hydroxybenzophenone together with a small amount of *o*-hydroxybenzophenone by the action of ferric chloride upon phenyl benzoate. Sekera (6) has studied the transformation of aryl esters of carboxylic acids to hydroxyaryl ketones by the use of ferric chloride and also of zinc chloride, and considered neither as effective as aluminum chloride.

This previous work has indicated that both ferric and zinc chlorides produce less ester rearrangement than aluminum chloride. The quite recent work of Dermer and co-workers (7, 8) upon the acylation of toluene with acetyl chloride in the presence of various metallic halides has essentially confirmed the order of catalytic activity in acylation reactions as given by Calloway (9). The conclusions were that ferric chloride, titanium tetrachloride, stannic chloride, and zinc chloride are materially less active than aluminum chloride. Although these conclusions were drawn from acylation experiments, it seems likely that they would also apply to ester rearrangements. Since we have previously studied (1, 10) the rearrangement of phenyl caprylate with aluminum chloride under a variety of conditions, it appeared of interest to investigate this rearrangement further using several other metallic halides. Ferric chloride, titanium tetrachloride, stannic chloride, and zinc chloride were selected as the halides to be used in this investigation. The rearrangement of phenyl caprylate with various molecular ratios of these halides has, therefore, been studied and the results compared with those previously obtained with aluminum chloride under similar conditions.

Ferric chloride is a very active catalyst for the rearrangement of phenyl caprylate as can be seen from the data in Table I. For this particular rearrangement the activity of ferric chloride appears to be comparable to that of aluminum chloride.

Compared to aluminum chloride, ferric chloride gives a decidedly greater ratio of para- to ortho-hydroxy ketones for the same percentage of ester conversion. One very significant difference between ferric chloride and aluminum chloride is that when ferric chloride is used as the catalyst the p/o ratio of the product is less the greater the molecular amount of catalyst employed, while with aluminum chloride the reverse was found to be true (10). The reason for this is not apparent at the present time. In drawing conclusions from any comparisons of this nature it is necessary to establish the absence of any rearrangement of the products under the experimental conditions employed in the ester rearrangement. When ortho-hydroxycaprylophenone was heated for six hours at 70° in the presence of a molecular ratio of ferric chloride, an 84.5% recovery of the hydroxy ketone was obtained and no para isomer was found. A recovery of 94.5%

TABLE I

REARRANGEMENT OF PHENYL CAPRYLATE BY FERRIC CHLORIDE: SOLVENT, TETRACHLOROETHANE

MOLECULAR RATIOS	TIME, AND TEMP., °C	% PARA	% ORTHO	% ESTER	RATIO P/O	REMARKS
Ester 1 $FeCl_3$ 0.5	6 hrs. 70	45.9	12.5	24.3	3.67	8.7% ortho residue
Ester 1 $FeCl_3$ 1	6 hrs. 70	52.3	18.6	9.1	2.81	15.0% ortho residue
Ester 1 $FeCl_3$ 1.3	6 hrs. 70	55.9	23.5	6.5	2.38	5.5% ortho residue
Ester 1 $FeCl_3$ 2	6 hrs. 70	44.5	28.7	6.7	1.55	3.2% ortho residue
Ester 1 $FeCl_3$ 2	3 days 40	57.7	27.4	4.4	2.10	4.1% ortho residue 4.2% para residue

of the para-hydroxy ketone was encountered under similar conditions. It is, therefore, apparent that these hydroxy ketones did not undergo rearrangement in our experiments.

That titanium tetrachloride is not as effective in promoting the rearrangement of phenyl caprylate as ferric chloride is apparent from a comparison of the results in Tables II and III with those in Table I. Several other significant differences between the action of these two catalysts are worthy of comment. The p/o ratio is much less when titanium tetrachloride is employed than when ferric chloride is used. Substantial amounts of caprylic acid and *p*-caprylylphenyl caprylate are present in the reaction products when titanium chloride is employed whereas these substances were not observed in rearrangements with ferric chloride. In similar rearrangements using aluminum chloride (1) caprylic acid was found to be one of the reaction products when less than molecular amounts of aluminum chloride were used or when aluminum chloride complexes were em-

ployed to effect the rearrangement. Its presence was ascribed to the slow rate of acylation of aluminum chloride complexes. *p*-Caprylylphenyl caprylate has been previously shown (1) to be one of the intermediate products in the rearrangement of phenyl caprylate with aluminum chloride and its presence is indicative of incomplete acylation.

TABLE II

REARRANGEMENT OF PHENYL CAPRYLATE BY TITANIUM TETRACHLORIDE: SOLVENT, TETRACHLOROETHANE

MOLECULAR RATIO	TIME, AND TEMP. °C.	% PARA	% ORTHO	% ESTER	% ORTHO	REMARKS
Ester 1 $TiCl_4$ 1	1.5 hrs. 30	0.9	18.7	57.6	0.05	2.7% *p*-Caprylylphenyl caprylate 3.2% caprylic acid.
Ester 1 $TiCl_4$ 1	3 hrs. 70	13.5	11.5	44.6	1.17	8.2% *p*-Caprylylphenyl caprylate 10.0% caprylic acid.
Ester 1 $TiCl_4$ 1	3 hrs. 100	22.7	36.6	7.0	0.62	7.7% *p*-Caprylylphenyl caprylate 6.2% caprylic acid.
Ester 1 $TiCl_4$ 1	6 hrs. 70	19.1	22.1	19.7	0.86	10.0% *p*-Caprylylphenyl caprylate 5.2% caprylic acid.
Ester 1 $TiCl_4$ 2	2 hrs. 30	0.9	4.1	79.1	0.22	1.8% *p*-Caprylylphenyl caprylate 5.5% caprylic acid.

TABLE III

REARRANGEMENT OF PHENYL CAPRYLATE BY TITANIUM TETRACHLORIDE: SOLVENT, NITROBENZENE

MOLECULAR RATIO	TIME, AND TEMP. °C.	% PARA	% ORTHO	% ESTER	RATIO P/O	REMARKS
Ester 1 $TiCl_4$ 0.5	6 hrs. 70	29.5	11.6	19.3	2.54	5.4% Caprylic acid.
Ester 1 $TiCl_4$ 1	6 hrs. 70	35.0	18.4	2.0	1.90	17.4% Caprylic acid.
Ester 1 $TiCl_4$ 1.3	6 hrs. 70	29.5	26.3	1.9	1.12	10.5% Caprylic acid.

When nitrobenzene is employed as the solvent (Table III) the p/o ratio is decidedly greater than when tetrachloroethane is used. This is in agreement with previous observations (1) with aluminum chloride. The decrease in the value of p/o with increased amounts of titanium tetrachloride was also observed with ferric chloride.

When carbon disulfide was employed as the solvent, 2.3% of *p*-hydroxycapry-

lophenone and 0.9% of the ortho isomer were obtained after six hours at 30° in the presence of titanium tetrachloride. Since 85.4% of the ester was recovered unchanged, it is evident that this reaction does not proceed as rapidly as in either tetrachloroethane or nitrobenzene.

In order to exclude the possibility of a rearrangement of the hydroxy ketones themselves in the presence of titanium tetrachloride *o*-hydroxycaprylophenone and *p*-hydroxycaprylophenone were treated with one molecular equivalent of titanium tetrachloride in nitrobenzene for six hours at 70°. The recovery of the former was 91.4% and of the latter 94.5%, thus showing the absence of rearrangement.

Stannic chloride is a much weaker catalyst than either ferric chloride or titanium tetrachloride for the rearrangement of phenyl caprylate as shown by the results in Table IV. In spite of the higher temperatures employed, the yield of ortho- and para-hydroxy ketones is quite small and a large proportion of the

TABLE IV

REARRANGEMENT OF PHENYL CAPRYLATE BY STANNIC CHLORIDE: SOLVENT, TETRACHLOROETHANE

MOLECULAR RATIO	TIME, AND TEMP. °C.	% PARA	% ORTHO	% ESTER	REMARKS
Ester 1 $SnCl_4$ 0.5	7 hrs. 150	1.8	6.9	70.8	5.0% *p*-Caprylylphenyl caprylate.
Ester 1 $SnCl_4$ 1	7 hrs. 150	1.8	6.7	71.5	2.7% *p*-Caprylylphenyl caprylate.
Ester 1 $SnCl_4$ 2	7 hrs. 150	4.5	6.3	70.1	5.0% *p*-Caprylylphenyl caprylate.

original ester is recovered unchanged. The presence of significant amounts of *p*-caprylylphenyl caprylate in the reaction products is noteworthy.

Runs made with phenyl caprylate and zinc chloride in both tetrachloroethane and nitrobenzene under conditions varying from six hours at 100° to twenty-four hours at 160°, showed this catalyst to be much less effective than stannic chloride. In all cases the phenyl caprylate was recovered essentially unchanged, showing that zinc chloride is only very slightly catalytic under these conditions. The order of activity of the catalysts investigated is, therefore: $FeCl_3 > TiCl_4 > SnCl_4 > ZnCl_2$.

EXPERIMENTAL

The following procedures are typical examples of runs reported in this article.

Fries rearrangement of phenyl caprylate with ferric chloride. Anhydrous ferric chloride (16.2 g., 0.1 mole) was placed in a 200-cc. three-necked flask equipped with a mechanical stirrer, thermometer, and dropping-funnel. Tetrachloroethane (25 cc.) was then added, and phenyl caprylate (22 g., 0.1 mole) dissolved in 25 cc. of tetrachloroethane was admitted through the dropping-funnel (10 min.). The dropping-funnel was then replaced by a condenser and the reaction mixture heated for six hours at 70°. It was allowed to cool

and hydrolyzed by pouring into 200 cc. of 5% hydrochloric acid. The tetrachloroethane was removed by steam distillation, the product cooled and extracted with ether. The ether solution was dried over anhydrous sodium sulfate. Unless this solution is dried, emulsions are obtained upon extraction of the para isomer. The ether solution was then extracted with four 25-cc. portions of 3% sodium hydroxide. The ether solution was then washed with water and these washings added to the alkaline extract.

The alkaline extract was acidified with hydrochloric acid, the excess ether removed by boiling, and the mixture cooled in order to solidify the *p*-hydroxy ketone. The mixture was then filtered and the product air dried. This product was weighed, recrystallized from petroleum ether, and identified as *p*-hydroxycaprylophenone by mixed melting point (yield 11.5 g., 52.3%).

The ether extract was dried with anhydrous sodium sulfate, filtered, and the ether removed in a Claisen flask in a water-bath. The product was distilled under reduced pressure and that boiling below 165° was retained. The percentage of phenyl caprylate in the mixture was then determined as previously described (10) (yields: 2.0 g. phenyl caprylate, 9.1%; 4.1 g. *o*-hydroxycaprylophenone, 18.6%).

Fries rearrangement of phenyl caprylate with titanium tetrachloride. Phenyl caprylate (22 g., 0.1 mole) was weighed into a 200-cc. three-necked flask and 25 cc. of tetrachloroethane added. Freshly distilled titanium tetrachloride (19.0 g., 0.1 mole) dissolved in 25 cc. of tetrachloroethane was added dropwise over a period of fifteen minutes. The reaction mixture was heated for six hours at 70°, after which it was cooled and hydrolyzed as previously described. The tetrachloroethane solution was washed several times with 5% hydrochloric acid in order to remove titanium salts. The omission of this step leads to the formation of emulsions during the separation of the isomers. The tetrachloroethane was removed by steam distillation and the separation and identification of the isomers carried out as previously described.

In the distillation of the *o*-hydroxy ketone-ester fraction a product boiling above 165° was obtained which, after purification, was identified as *p*-caprylylphenyl caprylate. Identification was made by mixed melting point. Caprylic acid in the para fraction was determined by titration. The yields were as follows: *p*-hydroxycaprylophenone, 4.2 g., 19.1%; *o*-hydroxycaprylophenone, 4.9 g., 22.3%; *p*-caprylylphenyl caprylate, 2.2 g., 10%; caprylic acid, 1.5 g., 6.8%.

Fries rearrangements of phenyl caprylate in the presence of stannic chloride and of zinc chloride. These arrangements and the separation of the products were conducted in a manner similar to that described above. When stannic chloride is employed it is advisable to remove the tin salts by washing with hydrochloric acid prior to steam distillation of the solvent. Failure to do this results in the formation of emulsions from which the product separates with great difficulty.

Attempted rearrangement of p-*hydroxycaprylophenone.* *p*-Hydroxycaprylophenone (22.0 g., 0.1 mole) was dissolved in 25 cc. of tetrachloroethane, and ferric chloride (16.2 g., 0.1 mole) added. The mixture was heated for six hours at 70° and steam distilled to remove the tetrachloroethane; alkaline extraction of the product gave 20.6 g., 94.5%, of *p*-hydroxycaprylophenone. No *o*-hydroxycaprylophenone was present.

Under similar conditions *o*-hydroxycaprylophenone was recovered unchanged (18.6 g., 84.5%).

Similar reactions using titanium tetrachloride as the catalyst and nitrobenzene as the solvent resulted in a recovery of 20.8 g., 94.5%, of *p*-hydroxycaprylophenone and 20.1 g., 91.4%, of *o*-hydroxycaprylophenone.

SUMMARY

1. A study of the rearrangement of phenyl caprylate in the presence of ferric chloride, titanium tetrachloride, stannic chloride, and zinc chloride has been made.

2. The activity of ferric chloride is comparable to that of aluminum chloride for this rearrangement; titanium tetrachloride is appreciably less active and both stannic and zinc chlorides are only weakly catalytic.

3. Ferric chloride produces a much higher ratio of para-hydroxy ketones to ortho-hydroxy ketones than aluminum chloride or titanium tetrachloride.

4. Caprylic acid and *p*-caprylylphenyl caprylate are among the products formed during the rearrangement of phenyl caprylate with either titanium tetrachloride or stannic chloride.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

STUDIES IN SILICO-ORGANIC COMPOUNDS. IV.

THE ACTION OF ORGANIC ACID HALIDES AND OF HYDROHALOGEN ACIDS ON SILICO-ORTHOESTERS[1]

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It was the primary purpose of this investigation to study the action of organic acid halides on silico-orthoesters. Interest in this problem was first aroused when it was discovered that most of the fundamental work herein was carried out long ago and in some cases had not been reported as completely as might have been expected. As the work developed it soon became apparent that data should be at hand concerning the action of dry hydrohalogen acids on silico-orthoesters.

Friedel and Crafts (1) in 1866, reported the discovery of a reaction between acetyl chloride and ethyl orthosilicate.

I. $$Si(OC_2H_5)_4 + CH_3COCl = ClSi(OC_2H_5)_3 + CH_3COOC_2H_5$$

These investigators prepared the same product, triethoxysilicon chloride, by another method, namely the action of phosphorus pentachloride on ethyl orthosilicate. The work was continued by Friedel and Ladenburg (2, 3), not only making use of ethyl orthosilicate but ethyl ethane orthosiliconate as well. The silicon compound present after the reaction was completed was not isolated in the second case, but its hydrolysis product gave a satisfactory analysis for ethane siliconic acid. The reaction product could have been $C_2H_5Si(OC_2H_5)_3$, $C_2H_5SiCl_3$, or compounds with varying numbers of ethoxyl groups and chlorines. Ethyl acetate was also isolated.

Ladenburg (4) reported two years later on the reaction between benzoyl chloride and ethyl ethane orthosiliconate in which ethyl benzoate and $C_2H_5Si(OC_2H_5)_2Cl$ were formed.

Analogous reactions exist in the chemistry of the carbon series of orthoformates (5).

To date, work carried out on the action of hydrohalogen acids on silico-orthoesters has been confined to reactions in the field of hydrolysis (4, 6). The closest analogies which could be found lie in the field of the carbon orthoformates (7, 8).

II. $$HC(OC_2H_5)_3 + HCl = C_2H_5Cl + HCOOC_2H_5 + C_2H_5OH$$

III. $$HC(OC_3H_7)_3 + 2HBr = 2C_3H_7Br + HCOOH + C_3H_7OH$$

IV. $$HC(OC_2H_5)_3 + 3HI = 3C_2H_5I + HCOOH + HOH$$

[1] Abstract of a thesis presented by the second author in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DISCUSSION

Acetyl chloride has been found to react with ethyl orthosilicate in the molar ratio of one to one at 135° with the production of a ninety per cent yield of triethoxysilicon chloride (Equation I). Two moles of acetyl chloride react with one of ethyl orthosilicate in a sealed tube at 185° giving a fair yield of impure diethoxysilicon dichloride. When treated in the same manner, with five moles of chloride to one of orthoester, a slight amount of ethoxysilicon trichloride was formed. Two other runs were made, in a steel bomb, at 200° the molar proportions being two of chloride to one of orthoester in one case and one to one in the other. Only ethyl acetate could be identified from either run. Dry, spongy, siliceous polymers were found after distillation of ethyl acetate. Butyl orthosilicate reacted at 185° in a sealed tube with an equimolar amount of acetyl chloride to form tributoxysilicon chloride.

Equimolar amounts of ethyl orthosilicate and benzoyl chloride were heated together for five hours just at the boiling point of the mixture. Considerable darkening took place and distillation revealed the formation of a seventy per cent yield of triethoxysilicon chloride along with an eighty-eight per cent yield of ethyl benzoate. As a means of identification the product from this run (No. 7, Table I) was treated with butyl alcohol, producing butyl triethyl orthosilicate.

V. $$C_4H_9OH + ClSi(OC_2H_5)_3 = HCl + C_4H_9OSi(OC_2H_5)_3$$

Repeating the run, using four molar times the amount of benzoyl chloride did not give a product capable of identification.

Polyalkoxysilicon acylates have already been prepared (9). It seemed of interest to study the reaction of one or two of these compounds with an acyl halide to determine the course of the reaction. It was not known whether the halogen atom of the halide would attach to silicon with the formation of an organic acid anhydride or to the acyl radical forming a different acyl halide. Accordingly, triethoxysilicyl acetate and acetyl chloride were allowed to react, in the molar ratio of one to two, at about 40° for three hours. No reaction took place. Equimolar amounts were then heated in a sealed tube at 185° for five hours. Distillation of this product gave no compounds capable of identification although some reaction had taken place. The same may be said of the attempted reaction between triethoxysilicyl propionate and acetyl chloride, in equimolar amounts at 185° in a sealed tube for ninety minutes.

In all the above described reactions, varying quantities of polymerized siliceous material were formed.

A study of the action of acid bromides on silico-orthoesters developed rather unusual features. Acetyl bromide was found to react with ethyl orthosilicate in equimolar proportions when heated for two hours at 185°, with the production of no homogeneous silicon-containing material. Ethyl bromide was formed in twenty per cent yield and ethyl acetate, eighty per cent. A slowly rising boiling point of the remainder of the material indicated that polymerization had taken place. All of these fractions showed positive tests for bromine but this

was not surprising, since hydrogen bromide was given off during distillation. In exactly the same manner, benzoyl bromide reacted with ethyl orthosilicate, giving rise to a twenty-six per cent yield of ethyl bromide and sixty-eight per cent yield of ethyl benzoate. Acetyl bromide was found to react with butyl orthosilicate to produce butyl bromide but butyl acetate could not be separated from the remainder of the material in condition pure enough for accurate determination, although there was evidence for its existence. The run was made under exactly the same conditions as those described above, save that the heating was limited to one hour. A small amount of a compound was isolated, however, which gave the correct bromine analysis for tributoxysilicon bromide. As will be explained under Conclusions, it was thought that an ether might be

TABLE I

RUN	REACTANTS	CONDITIONS	PRODUCTS
1	$Si(OC_2H_5)_4 + CH_3COCl$	120 min, 135°	$ClSi(OC_2H_5)_3$
2	$Si(OC_2H_5)_4 + 2CH_3COCl$	60 min, 185° (sealed tube)	$Cl_2Si(OC_2H_5)_2$
3	$Si(OC_2H_5)_4 + 5CH_3COCl$	60 min, 185° (sealed tube)	$Cl_3Si(OC_2H_5)$
4	$Si(OC_2H_5)_4 + 2CH_3COCl$	60 min, 200° (bomb)	polymers
5	$Si(OC_2H_5)_4 + CH_3COCl$	60 min, 200° (bomb)	polymers
6	$Si(OC_4H_9)_4 + CH_3COCl$	60 min, 185° (sealed tube)	$ClSi(OC_4H_9)_3$
7	$Si(OC_2H_5)_4 + C_6H_5COCl$	300 min, b.p.	$ClSi(OC_2H_5)_3$
8	$Si(OC_2H_5)_4 + 4C_6H_5COCl$	120 min, b.p.	unidentifiable
9	$CH_3COOSi(OC_2H_5)_3 + 2CH_3COCl$	180 min, 40°	no reaction
10	$CH_3COOSi(OC_2H_5)_3 + CH_3COCl$	300 min, 180° (sealed tube)	unidentifiable
11	$C_2H_5COOSi(OC_2H_5)_3 + CH_3COCl$	90 min, 185° (sealed tube)	unidentifiable

TABLE II

RUN	REACTANTS	CONDITIONS	RESULTS
12	$Si(OC_2H_5)_4 + CH_3COBr$	120 min, 185° (sealed tube)	$C_2H_5Br + CH_3COOC_2H_5$
13	$Si(OC_2H_5)_4 + C_6H_5COBr$	120 min, 185° (sealed tube)	$C_2H_5Br + C_6H_5COOC_2H_5$
14	$Si(OC_4H_9)_4 + CH_3COBr$	60 min, 185° (sealed tube)	$C_4H_9Br + CH_3COOC_4H_9$ $BrSi(OC_4H_9)_3$(?)

the intermediate in some of these reactions. Consequently, one run was carried out as was No. 2, save that dibutyl ether was added to the reactants. The results were the same as would have been expected had no ether been present. Analogous results were obtained when a mixture of dibutyl ether, ethyl orthosilicate and benzoyl bromide was heated in a sealed tube. Acetyl chloride did not react with dibutyl ether in the absence of the orthosilicate.

Because of the evolution of hydrogen bromide from some of the reaction mixtures on distillation, it was thought desirable to investigate the action of dry hydrohalides on ethyl and butyl orthosilicates.

Thoroughly dried hydrogen chloride was passed through ethyl orthosilicate at room temperature. An ice and salt-bath in series, after the reaction chamber, did not condense anything. At one time the reaction flask warmed up slightly.

An estimated three per cent yield of ethyl alcohol resulted on distillation of the products, two-thirds of the orthoester was recovered and the remainder consisted of polymerized silicon compounds. Repeating the procedure, using a solid carbon dioxide trap instead of ice and salt, gave no different results. In a third run, 25 cc. of a saturated solution of dry hydrogen chloride in ethyl orthosilicate was sealed in a tube and heated to 185° for one hour. On distillation, excess hydrogen chloride was caught in sodium hydroxide, and in addition, about 7 cc. was condensed in the CO_2 trap, probably ethyl chloride.

When dry hydrogen chloride was bubbled through butyl orthosilicate no evidence of a reaction could be detected, nor could any products be isolated even after heating in a sealed tube as before.

There was a much more pronounced heat effect when dry hydrogen bromide was bubbled through ethyl orthosilicate, the temperature rising as high as 50–60° at times, this increase varying as the flow of gas. A small amount of ethyl bromide and of ethyl alcohol was isolated in a trap of ice and salt. When

TABLE III

RUN	REACTANTS	CONDITION	RESULTS
15	$Si(OC_2H_5)_4 + xHCl$[a]	room temperature	C_2H_5Cl (?)
16	$Si(OC_2H_5)_4 + xHCl$	room temperature	C_2H_5Cl (?)
17	$Si(OC_2H_5)_4 + xHCl$	60 min, 185° (sealed tube)	C_2H_5Cl (?)
18	$Si(OC_4H_9)_4 + xHCl$	room temperature	?
19	$Si(OC_4H_9)_4 + xHCl$	60 min, 185° (sealed tube)	?
20	$Si(OC_2H_5)_4 + xHBr$	room temperature	C_2H_5Br
21	$Si(OC_4H_9)_4 + xHBr$	room temperature	$C_4H_9Br + C_4H_9OH$
22	$Si(OC_2H_5)_4 + xHI$	room temperature	$C_2H_5I + C_2H_5OH$
23	$Si(OC_4H_9)_4 + xHI$	room temperature	$C_4H_9I + C_4H_9OH$

[a] x denotes undetermined amounts.

treated in the same manner, butyl orthosilicate yielded less than two per cent of butyl alcohol and about twenty per cent of butyl bromide.

Ethyl orthosilicate reacted in the same manner with dry hydrogen iodide to form much ethyl alcohol and ethyl iodide. Accurate determinations of percentage yields were not feasible owing to the difficulty of quantitative separation of alcohol and iodide. Butyl orthosilicate reacted thus, to form butyl alcohol and butyl iodide.

EXPERIMENTAL PART

Ethyl orthosilicate used in this work was obtained from the Carbide and Carbon Chemicals Corporation, freshly distilled. Acetyl chloride, acetyl bromide, benzoyl chloride and benzoyl bromide were purchased from the Eastman Kodak Company, or were of a comparable grade. Butyl orthosilicate was prepared by the action of butyl alcohol on silicon tetrachloride and fractionation of the products. Hydrogen chloride was prepared from concentrated hydrochloric acid and concentrated sulfuric acid, then passed over phosphorus pentoxide before being allowed to enter the reaction chamber. Hydrogen bromide was prepared by the interaction of water, bromine and red phosphorus. It was dried by passage through tubes of calcium chloride and phosphorus pentoxide. Hydrogen iodide was pre-

pared by the action of water on red phosphorus and a large excess of iodine, then dried by passage over phosphorus pentoxide.

Triethoxysilicyl acetate was prepared by the action of acetic anhydride on ethyl orthosilicate (9). Triethoxysilicyl propionate was prepared in like manner, by the action of propionic anhydride on ethyl orthosilicate (9).

Butyl triethyl orthosilicate was prepared in Run 7, Table I, by the action of butyl alcohol on triethoxysilicon chloride, b.p. 88–90° (16 mm.), n_D^{20} 1.3945, literature b.p. 82.5° (15 mm.), n_D^{20} 1.395 (9). These data were checked by another preparation from butyl alcohol and ethyl orthosilicate, b.p. 87° (14 mm.), n_D^{20} 1.3925. In the course of the latter run diethyl dibutyl orthosilicate was formed, b.p. 105–107° (14 mm.), n_D^{20} 1.4010.

Triethoxysilicon chloride was identified, b.p. 156–157° (744 mm.), Run 1, Table I, 154–159°, Run 7, Table I, Cl found 16.6, theory 17.9, Run 1, Table I.

Diethoxysilicon dichloride was identified b.p 135–137° (748 mm.), Cl found 36.2, theory 37.5; Si found 15.6, theory 14.8, Run 2, Table I.

Tributoxysilicon chloride was identified b.p. 84–85° (1 mm.), Cl found 12.50, theory 12.55; Si found 20.0, theory 21.3, Run 6, Table I.

Tributoxysilicon bromide was identified, Br found 23.4, theory 24.9, Run 14, Table II.

Other compounds isolated in the course of the work were identified in the same general manner, by the determination of their simple physical constants.

CONCLUSIONS

It has been shown that the reaction of an organic acid chloride on ethyl or butyl orthosilicate results in the formation of the expected trialkoxysilicon chloride. When the relative amount of acid chloride is increased, the corresponding dialkoxysilicon dichloride is formed. Optimum conditions seem to include heating, preferably in a sealed tube. The formation of alkyl bromide when acetyl or benzoyl bromide is used complicates any concept of reaction mechanism.

With the alkyl bromides it was at first thought possible that the orthosilicate decomposed under the influence of the acid halide to a metasilicate and an ether

VI. $$SiO(OC_2H_5)_4 = OSi(OC_2H_5)_2 + C_2H_5OC_2H_5$$

and that the ether then reacted with the acid halide. But separate runs carried out in the presence of dibutyl ether failed to produce any evidence in favor of a reaction of this type. At the present time it seems improbable to suspect a direct splitting off of ethyl from ethyl orthosilicate—no evidence exists which could be accepted as proof of this type of orthoester decomposition. A break between ethyl and oxygen might be slightly more probable if the halogen were already attached to silicon, as for example:

VII. $$BrSi(OC_2H_5)_3 = C_2H_5Br + OSi(OC_2H_5)_2,$$

but there is no proof for this mechanism either. The facts are, however, that both alkyl bromide and alkyl acetate, or benzoate, were formed when acid bromide reacted with silico-orthoester.

The action of dry hydrohalogen acids on silico-orthoesters bears out the general concept of the relative reactivities of these acids in organic media, namely that hydriodic acid is the most reactive of the three, hydrobromic second, and hydrochloric acid least. Qualitatively, the relative amounts of halide isolated

check with this fact. Although no proof exists, a mechanism might be assumed providing for the formation, first, of alcohol, which then would be expected to react with dry hydrohalogen acid

VIII. $$Si(OC_2H_5)_4 + HI = ISi(OC_2H_5)_3 + C_2H_5OH$$

IX. $$C_2H_5OH + HI = HOH + C_2H_5I$$

X. $$HOH + ISi(OC_2H_5)_3 = HI + C_2H_5OH + OSi(OC_2H_5)_2$$

Polymerized silicon compounds could easily form by silicon-ether formation as soon as hydroxyl groups appear attached to silicon. These polymers were always obtained.

SUMMARY

1. The action of acetyl chloride on ethyl orthosilicate, butyl orthosilicate, triethoxysilicyl acetate, and triethoxysilicyl propionate has been investigated within restricted sets of conditions. Benzoyl chloride has been found to react with ethyl orthosilicate at the boiling point of the mixture.

2. Acetyl bromide has been found to react with ethyl and butyl orthosilicates, and benzoyl bromide with the former orthoester. The results are somewhat different as contrasted with those found in the case noted under '1.'

3. Dry hydrohalogen acids react with ethyl orthosilicates with results which could be explained on the assumption of the alcohol as intermediate. Dry hydrobromic and hydriodic acids were found to react with ethyl orthobutyrate. No definite proof is submitted as to the mechanism, however.

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A SEMIQUANTITATIVE EXTENSION OF THE ELECTRONIC THEORY OF THE ENGLISH SCHOOL

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Of the many attempts to apply the electron theory to problems of organic reactivity, the most successful and hence the most widely used is the one developed chiefly by the English school of organic chemists (1). According to this theory all chemical reactions are considered to be generalized oxidation-reduction reactions in the sense that a necessary condition for reaction is the bringing together of an electron-rich center of sufficiently low electronegativity and an electron-poor center of sufficiently high electronegativity; or one may say that no reaction can possibly occur unless the nucleophilic centers and the electrophilic centers have, respectively, sufficiently high nucleophilic and electrophilic reaction tendencies (2). It is also considered that in all slow reactions the rate-controlling step consists of the union of the most strongly electrophilic with the most strongly nucleophilic center unless such a union can be classified as a "neutralization" in the generalized sense of G. N. Lewis (3), in which event it involves no activation energy. Finally, substituents may alter the speed of a reaction by altering the electron density at the reaction site by five different modes of electron displacement: the I_s, I_d, E, M, and D effects (1).

The weakness of the English theory lies in the fact that it is a qualitative theory and thus is not only unable to predict which of the various opposing electron-displacement effects is the largest but is also unable to predict the effect of substituents on a reaction whose mechanism is not known or, alternatively, whose membership in class A or class B (4) has not been established by actual experiment. The desirability of an extension of the theory in a more quantitative direction is obvious.

The purpose of this paper is to consider the possibility of making *a priori* estimates of reaction mechanism by a semiquantitative extension of Lapworth's ideas on nucleophilic and electrophilic reaction tendencies. Such a method could also be used to predict the relative speeds of sufficiently similar reactions involving unsubstituted compounds. No attempt will be made here to discuss the sister-problem of establishing more quantitative methods for dealing with the five electron displacement effects.

The problem whose solution we seek has already been developed extensively under the title of the transition state theory or, as it is sometimes called, the theory of absolute reaction rates (5). However, the mathematical complexities of this theory are discouraging to the average organic chemist, who needs some simpler method of attack. Such a simplified method will now be outlined, but the organic chemists for whom it is developed must remember that simplification is usually achieved only through a compensating loss of accuracy.

According to the Lapworth theory, adopted by the English school, nucleo-

philic and electrophilic reaction tendencies of atoms in molecules are to be judged by their tendencies to form covalencies. Just how these tendencies are to be measured was apparently never definitely decided, nor were they ever quantitatively defined. Sometimes they are measured in terms of ionization constants or reduction potentials, sometimes by electronegativity differences deduced from the periodic table, sometimes by observing the speed of a reaction, etc. It seems to the author, however, that they could logically be defined as the ΔF or ΔH of covalency formation between two neutral radicals or atoms, when a "non-ionic mechanism" is concerned, or between two ions when the

TABLE I

IONIZATION ENERGIES (7)

ATOM	KCAL./MOLE	ATOM	KCAL/MOLE
H	311.8	P	251.2
C	258.5	S	237.4
N	333.7	Cl	298.5
O	312.3	Br	272.0
F	399.7	I	244.3

TABLE II

ELECTRON AFFINITIES OF ATOMS[a]

ATOM	KCAL./MOLE	ATOM	KCAL./MOLE
H	17.5	P	3.4
C	31.6	S	47.5
N	0.9	Cl	85.3
O	87.6	Br	81.5[b]
F	91.2	I	72.6[c]

[a] Unless otherwise designated, these values were taken from reference (8). The factor 23.05 was used to convert electron-volts into kcal./mole.

[b] This is the value of Mayer and Helmholz (9). Glockler and Calvin (10) report 88 ± 3.4 kcal. while Piccardi (11) reports 86.7 kcal.

[c] See Mayer (12).

mechanism is "ionic." Only examples of the latter mechanism will be considered in this paper.

Since tables of bond energies ($-\Delta H$) are in existence, while no corresponding values exist for the free energies of bond formation, it will be convenient to measure "tendencies for covalency formation" by means of the values of ΔH for the formation of normal covalent bonds from their gaseous ions. Such a table (see Table III) can easily be constructed by combining data on bond energies (6), electron affinities (Table II), and ionization potentials (Table I). This is illustrated by the following calculation.

$C^+ + e \rightarrow C$	(ioniz. pot.)	$\Delta H = -258.5$ kcal.
$Cl^- \rightarrow Cl + e$	(electron aff.)	$\Delta H = 85.3$
$C + Cl \rightarrow C{-}Cl$	(bond energy)	$\Delta H = -66.5$
$C^+ + Cl^- \rightarrow C{-}Cl$		$\Delta H_{C^+ Cl^-} = -239.7$ kcal.

By means of Table III it is easy to see, for example, that C^- is more nucleophilic than O^-. This is shown by the following figures:

X^+	ΔH_{C-X^+}	ΔH_{O-X^+}
H^+	−367 kcal.	−334 kcal.
C^+	−285	−241
Cl^+	−270	−260
O^+	−350	−259

But we cannot make the comparison for two ions bearing opposite charges because the two cannot be combined separately with the same reference ion. Moreover, it sometimes happens that more than one bond needs to be considered in order to predict the more probable reaction path. All in all, it would seem best to judge the most probable reaction path by comparing the summation of ΔH for all bonds made and broken in the rate-controlling step. If this sum-

TABLE III

HEAT EFFECTS IN THE GAS PHASE FORMATION OF BONDS FROM IONS IN KCAL./MOLE

BOND	IONS	$\Delta H_{A^+ B^-}$	BOND	IONS	$\Delta H_{A^+ B^-}$
H—C	H^+, C^-	−367.5	C—I	C^+, I^-	−231.4
H—N	H^+, N^-	−394.6	C—I	C^-, I^+	−258.2
H—O	H^+, O^-	−334.4	N—Cl	N^-, Cl^+	−336.0
H—Cl	H^+, Cl^-	−329.2	N—Cl	N^+, Cl^-	−286.8
H—Br	H^+, Br^-	−317.6	O—Cl	O^-, Cl^+	−260.2
H—I	H^+, I^-	−310.6	Cl—Cl	Cl^+, Cl^-	−271.0
C—C	C^+, C^-	−285.5	Br—Br	Br^+, Br^-	−236.6
C—N	C^+, N^-	−306.2	I—I	I^+, I^-	−207.9
C—O	C^+, O^-	−240.9	C=C	C^+—C^-	(−268.3)
C—O	C^-, O^+	−350.7	C=N	C^+—N^-	+2.3
C—Cl	C^+, Cl^-	−239.7	C=O	C^+—O^-	(−249.9)
C—Cl	C^-, Cl^+	−333.4	P—Cl	P^+, Cl^-	−228.7
C—Br	C^+, Br^-	−231.0	P—Cl	P^-, Cl^+	−357.9
C—Br	C^-, Br^+	−294.4	P—H	P^-, H^+	−371.4

mation were made correctly, taking into account the interaction between the bonds involved, the value of ΔH finally obtained should be the heat of activation[1] ($\Delta H^\ddagger$). Such calculations can be made with fair accuracy for simple compounds on the basis of the theory of absolute reaction rates. However, it is the purpose of this paper to show that, if these interactions are neglected and a simple summation is made of the ΔH values for the bonds made and broken, the results give a reasonably safe guide for comparing reactions involving unsubstituted, unconjugated compounds and hence form a semiquantitative extension of the electronic theory of the English school. Thus for the reactions

$$A + BC \rightleftharpoons A \cdots B \cdots C \rightarrow A—B + C$$

and

$$D—E + F—G \rightleftharpoons D \cdots E \cdots F \cdots G \rightarrow D + E—F + G$$

[1] Note that such a summation for all bonds made and broken in the entire reaction (not merely in the rate-controlling step) would give the value of ΔH for the reaction (not $\Delta H\ddagger$).

we could define the quantity $\Delta H_1^{\ddagger}$ by the respective equations:

$$\Delta H_1^{\ddagger} = \Delta H_{AB} - \Delta H_{BC}$$

and

$$\Delta H_1^{\ddagger} = \Delta H_{EF} - \Delta H_{DE} - \Delta H_{FG}$$

where ΔH_{AB} represents the change in heat content attending the formation of the bond A—B in the gaseous molecule AB from the gaseous ions A^+ and B^- or A^- and B^+, etc. Which pair of ions is involved in a given case may be indicated by the alternative symbols $\Delta H_{A^+B^-}$ or $\Delta H_{A^-B^+}$. Such a calculation assumes that all of the energy of the bond being formed finds its way into the bonds being broken and that all of the bonds concerned are completely formed or completely broken. Neither assumption is correct. However, Ri and Eyring (13) state that in general, bonds being made or broken in a critical complex are about ten per cent longer than normal bonds. This indicates that there is at least a uniformity in this regard, and that the proposed summation of heat effects should, roughly speaking, do equal violence to the calculated values of $\Delta H^{\ddagger}$ for different reactions, if they are not too different, thus giving the same sequence of $\Delta H_1^{\ddagger}$ values as would obtain for the true values of $\Delta H^{\ddagger}$. Of course the relative probabilities of the two reactions are not determined by the relative heats of activation, but by the relative free energies of activation ($\Delta F^{\ddagger}$). Thus the sequence of values of $\Delta H_1^{\ddagger}$ may not parallel the sequence of probabilities unless the entropy terms ($\Delta S^{\ddagger}$) are either small or equal. The latter is apt to be the case when the reactions are similar, *i.e.*, when they involve the same number of reactant and product molecules of about the same complexity, and when their transition states, as pictured above, involve the same number of dotted line bonds.

Since the proposed method aims at nothing more profound than establishing a sequence of the relative probabilities of different conceivable rate-controlling steps, the calculations will be still further simplified by omitting from consideration all of the ΔH terms for bonds which would occur in both or all of the reactions being considered, and which would accordingly cancel out when the final comparison is made. The resultant values of ΔH will be referred to as "comparative heats of activation" ($\Delta H_{com}^{\ddagger}$). The remainder of this paper will be devoted to examples showing how these simply calculated values of $\Delta H_1^{\ddagger}$ and $\Delta H_{com}^{\ddagger}$, involving no kinetic data, can be used to determine: (a) the mechanism of a reaction, and (b) the relative speeds of reactions of the same type.

A. *The addition of halogens to ethylene.* In order to make an *a priori* determination of the mechanism of any reaction, it is convenient to start by formulating the different rate-controlling steps which conceivably could occur. In this case there are four:

I. An electrophilic attack by the halogen molecule [polarized by the glass walls of the reaction vessel (14)] on the carbon atom of the ethylene molecule:

$$H_2C{=}CH_2 + Cl_2 \rightleftharpoons \underset{\substack{\\ Cl^+{-}Cl^-}}{H_2\overset{-}{C}{=}\overset{+}{C}H_2} \rightarrow H_2CCl\cdot\overset{+}{C}H_2 + Cl^-$$

transition state

Here the transition state is represented as involving the simultaneous formation of a $C^-—Cl^+$ bond and the rupture of the $Cl^-—Cl^+$ bond and one-half of the double bond, *i.e.*, it is represented as a typical displacement reaction (15).

II. A nucleophilic attack by halogen on carbon:

$$H_2C{=}CH_2 + Cl_2 \rightleftharpoons H_2\overset{+}{C}{=}\overset{-}{C}H_2 \rightarrow CH_2Cl\cdot\overset{-}{C}H_2 + Cl^+$$
$$\qquad\qquad\qquad\qquad\quad \vdots$$
$$\qquad\qquad\qquad\qquad\quad Cl^-\cdots Cl^+$$

III. A nucleophilic attack by halogen on hydrogen, leading to substitution:

$$H_2C{=}CH_2 + Cl_2 \rightleftharpoons H_2C{=}\overset{H}{C}{}^-\cdots H^+\cdots Cl^-\cdots Cl^+ \rightarrow$$
$$H_2C{=}\overset{-}{C}H + HCl + Cl^+$$

IV. A nucleophilic attack by halogen on carbon, leading to substitution:

$$H_2C{=}CH_2 + Cl_2 \rightleftharpoons H_2C{=}\overset{H}{C}{}^-\cdots H^+ \rightarrow H_2C{=}CHCl + H^+ + Cl^-$$
$$\qquad\qquad\qquad\qquad\quad \vdots$$
$$\qquad\qquad\qquad\qquad\quad Cl^+\cdots Cl^-$$

On the basis of these equations we may now easily calculate the values of $\Delta H^{\ddagger}$.

$$(\Delta H^{\ddagger})_I = \Delta H_{C\text{-}Cl^+} - \Delta H_{C^+=C^-} - \Delta H_{Cl\text{-}Cl^+} = -333 + 268 + 271 = 206 \text{ kcal.}$$

$$(\Delta H^{\ddagger})_{II} = \Delta H_{C^+Cl^-} - \Delta H_{C^-=C^+} - \Delta H_{Cl\text{-}Cl^+} = -240 + 268 + 271 = 299$$

$$(\Delta H^{\ddagger})_{III} = \Delta H_{H^+Cl^-} - \Delta H_{C\text{-}H^+} - \Delta H_{Cl\text{-}Cl^+} = -329 + 367 + 271 = 309$$

$$(\Delta H^{\ddagger})_{IV} = \Delta H_{C\text{-}Cl^+} - \Delta H_{C\text{-}H^+} - \Delta H_{Cl\text{-}Cl^+} = -333 + 367 + 271 = 305$$

Since $(\Delta H^{\ddagger})_I$ has the smallest value, it is apparent that: (a) I represents the most probable mechanism; (b) the reaction will lead to addition in preference to substitution (at least if substitution involves an ionic mechanism, which it probably does not); and (c) ethylene is the nucleophilic reagent in this reaction, which may accordingly be placed in class A of the Ingold-Rothstein classification, *i.e.*, electron-releasing substituents in the ethylene molecule should facilitate the reaction. Similar calculations for the addition of bromine or iodine lead to the same conclusion, which is in complete accord with the known facts.

The next check on our rough method of calculation will be to see if it is capable of predicting the well established order of velocities of halogen addition to olefins, *viz.*, $Cl_2 > Br_2 > I_2$. For these reactions we have, from consideration of Eq. I:

For Cl_2: $\Delta H^{\ddagger}_{com} = \Delta H_{C\text{-}Cl^+} - \Delta H_{Cl\text{-}Cl^+} = -333 + 271 = -62$ kcal.

For Br_2: $\Delta H^{\ddagger}_{com} = \Delta H_{C\text{-}Br^+} - \Delta H_{Br\text{-}Br^+} = -294 + 236 = -58$ kcal.

For I_2: $\Delta H^{\ddagger}_{com} = \Delta H_{C\text{-}I^+} - \Delta H_{I\text{-}I^+} = -258 + 207 = -51$ kcal.

These figures give the correct order of velocities. It is unfortunate, however, that the value of the electron affinity of bromine is in grave doubt (9).

B. *The addition of hydrogen halides to olefins.* First it must be determined

whether the rate-controlling step is an electrophilic attack by hydrogen ion, or a nucleophilic attack by halide ion, on the carbon atom of the olefin.

I. $R_2C{=}CR_2 + HX \rightarrow R_2C(H{-}X){-}CR_2$

II. $R_2C{=}CR_2 + HX \rightarrow R_2C(X{-}H){-}CR_2$

$$(\Delta H^{\ddagger})_I = \Delta H_{C^-H^+} - \Delta H_{H^+X^-} - \Delta H_{C^-=C^+}$$

$$(\Delta H^{\ddagger})_{II} = \Delta H_{C^+X^-} - \Delta H_{H^+X^-} - \Delta H_{C^-=C^+}$$

Therefore, for any given halogen hydride:

$$(\Delta H_{com})_I = \Delta H_{C^-H^+} = -367.5 \text{ kcal.}$$

$$(\Delta H_{com})_{II} = \Delta H_{C^+X^-} = \begin{cases} -239.7 \text{ for HCl} \\ -231.0 \text{ for HBr} \\ -231.4 \text{ for HI} \end{cases}$$

It is concluded, therefore, that reaction I represents the rate-controlling step. The next problem is to make a comparison of the relative speeds of addition of the different hydrogen halides. It is evident from the above that $\Delta H^{\ddagger}_{com} = -\Delta H_{H^+X^-}$ for this purpose.

For HCl: $\Delta H^{\ddagger}_{com} = -\Delta H_{H^+Cl^-} = 329.2$ kcal.
For HBr: $\Delta H^{\ddagger}_{com} = -\Delta H_{H^+Br^-} = 317.6$
For HI: $\Delta H^{\ddagger}_{com} = -\Delta H_{H^+I^-} = 310.6$

The predicted order of velocity (neglecting entropy factors) thus turns out to be: HI > HBr > HCl, which is in complete accord with the well known facts.

C. *The hydrolysis of the chlorides of nitrogen and phosphorus.* The hydrolysis of NCl_3 yields HOCl while that of PCl_3 yields HCl. This perplexing difference in behavior between two sister elements has been a standing challenge to theorists, and it is interesting to discover to what extent our method of calculation is able to meet the challenge.

We may simplify the problem by making the calculations on the basis of pure water as the reactant. Then, since the concentrations of H_3O^+ and OH^- ions are very low, we may assume water as the most probable attacking reagent. Now regardless of whether the attack is made by hydrogen or oxygen atoms of water, the H—OH bond must become ruptured, and hence this energy factor will cancel out. We may then consider H^+ and OH^- as the attacking reagents for purposes of comparison.

There are four possible modes of attack, since there are two possible attacking ions and two possible points of attack. These four possibilities may be formulated as follows, using X to represent either P or N.

I. $XCl_3 + H^+ \rightleftharpoons H \cdots XCl_2 \cdots Cl \rightarrow HXCl_2 + Cl^+$

II. $XCl_3 + H^+ \rightleftharpoons Cl_2X \cdots Cl \cdots H \rightarrow Cl_2X^+ + HCl$

III. $$XCl_3 + OH^- \rightleftharpoons Cl_2X \cdots Cl \rightarrow Cl_2XOH + Cl^-$$
$$\vdots$$
$$OH$$

IV. $$XCl_3 + OH^- \rightleftharpoons Cl_2X \cdots Cl \cdots OH \rightarrow Cl_2X^- + HOCl$$

The calculations of the corresponding values of $\Delta H^{\ddagger}_{com}$ may now easily be made. If X is taken to be phosphorus, then:

$$(\Delta H^{\ddagger}_{com})_I = \Delta H_{H^+P^-} - \Delta H_{P-Cl^+} = -13.5 \text{ kcal.}$$

$$(\Delta H^{\ddagger}_{com})_{II} = \Delta H_{H^+Cl^-} - \Delta H_{P^+Cl^-} = -100.5 \text{ kcal.}$$

$$(\Delta H^{\ddagger}_{com})_{III} \text{ Data unavailable}$$

$$(\Delta H^{\ddagger}_{com})_{IV} = \Delta H_{O^-Cl^+} - \Delta H_{P-Cl^+} = 97.7 \text{ kcal.}$$

The relative probabilities of the three mechanisms for which data are available turns out to be II > I > IV. If we may assume that all three chlorine atoms are removed by the same mechanism, we are thus led to the result that PCl_3 should yield HCl and H_3PO_3 on hydrolysis.

If the corresponding calculations are made for NCl_3, the values of $\Delta H^{\ddagger}_{com}$ for cases I, II, and IV are found respectively to be −58.6, −43.4, and +76.8 kcal. Thus mechanism I is most probable in this case, and we would predict that NCl_3 would yield HOCl and NH_3 on hydrolysis.

Our assumption that all three chlorine atoms are removed by the same mechanism is justified by qualitative considerations. Thus, if the first chlorine atom is replaced by hydrogen, the lone pair of the resulting $HXCl_2$ is all the more available for coordination with another proton (mechanism I), and XH_3 will ultimately result. But if mechanism II results in the replacement of Cl^- by OH^-, the resultant $HOXCl_2$ will be only slightly more basic than XCl_3, since the $-I_s$ effect of hydroxyl is only slightly less than that of chlorine. In view of the large difference in $\Delta H^{\ddagger}_{com}$ (−13.5 compared to −100.5 kcal.) which is found between mechanisms I and II in this case, it is hardly likely that this slight alteration would cause an inversion of mechanism in the second or third step.

D. *The hydrolysis of alkyl halides.* A very large amount of experimental work has been done in an effort to establish the mechanism of the hydrolysis of alkyl halides. Due chiefly to the work of Hughes, Ingold, and their collaborators (16), it now appears that methyl and ethyl halides show a strong tendency to hydrolyze by a bimolecular mechanism involving a nucleophilic attack by hydroxyl ion on carbon, while tertiary butyl halides tend to hydrolyze by a unimolecular mechanism involving the solvolytic production of carbonium ions. Isopropyl halides occupy an intermediate position, usually involving a mechanism compounded of sizeable proportions of both the unimolecular and bimolecular reactions. The mechanism obtaining in any case is, however, decidedly dependent on conditions, and it has been observed that increasing alkalinity of solution favors the bimolecular reaction (17), while increasing acidity seems to favor the unimolecular mechanism. Thus, although the normal mode of reaction of primary alkyl halides is bimolecular, it was found (18) that the hydrolysis

of *n*-butyl bromide in formic acid containing a small proportion of water is mainly unimolecular.

It is hardly to be expected that our crude method could be a completely reliable guide in a border line case like the hydrolysis of alkyl halides, but its general implications are reliable as shown by the following calculations.

The three following mechanisms are conceivable if the hydrolysis takes place in basic solutions, in which, of course, the hydronium ion concentration is very low.

I. A nucleophilic attack by hydroxyl ion on carbon.

$$CH_3X + OH^- \cdot Aq \rightleftharpoons HO \cdots CH_3 \cdots X + Aq \rightarrow CH_3OH + X^- + Aq$$

Aq stands for water of hydration, which is presumably lost on entering the transition state.

II. An electrophilic attack by hydrogen on halogen.

$$CH_3X + HOH \rightleftharpoons H_3C \cdots X \cdots H \cdots OH \rightarrow CH_3^+ + HX + OH^-$$

III. An electrophilic attack by hydrogen on carbon.

$$CH_3X + HOH \rightleftharpoons HO \cdots H \cdots CH_3 \cdots X \rightarrow OH^- + CH_4 + X^+$$

The corresponding values of $\Delta H^{\ddagger}$ may now be calculated for the case where X = Cl.

$$(\Delta H^{\ddagger})_I = \Delta H_{C^+O^-} - \Delta H_{C^+Cl^-} - \Delta H_{Aq\cdot OH^-} = -\Delta H_{Aq\cdot OH^-} - 1 \text{ kcal.}$$

$$(\Delta H^{\ddagger})_{II} = \Delta H_{H^+Cl^-} - \Delta H_{C^+Cl^-} - \Delta H_{H^+O^-} = 145 \text{ kcal.}$$

$$(\Delta H^{\ddagger})_{III} = \Delta H_{C^-H^+} - \Delta H_{H^+O^-} - \Delta H_{C^-Cl^+} = 300 \text{ kcal.}$$

Obviously, there is no chance of a hydrocarbon being formed (III). The value for the heat of hydration of the hydroxyl ion is not known, but it could hardly be much more than 100 kcal., since the corresponding value for chloride ion is 92.1 kcal. (19). Thus, mechanism I is clearly favored, which is in accord with experiment.

Having thus established the mechanism, we may now calculate $\Delta H^{\ddagger}_{com}$ for RCl and RBr. Taking $\Delta H^{\ddagger}_{com} = \Delta H_{C^+X^-}$, we get the values 239 and 231 kcal. for chlorides and bromides, respectively. The experimental activation energies for the hydrolysis of ethyl chloride and bromide fall in the same order, *viz.*, 23 and 21 kcal., respectively (20).

If the hydrolysis is carried out in an acid solution, the above three mechanisms become respectively:

I. $$CH_3X + HOH \rightleftharpoons \begin{matrix} H_3C & - & OH \\ | & & | \\ X & & H \end{matrix} \rightarrow CH_3OH + H^+ + X^-$$

II. $$CH_3X + Aq\cdot H^+ \rightleftharpoons H_3C{-}X{-}H^+ + Aq \rightarrow CH_3^+ + HX + Aq$$

III. $$CH_3X + Aq\cdot H^+ \; H_3C\overset{H^+}{\cdots}X + Aq \rightarrow CH_4 + X^+ + Aq$$

$$(\Delta H^{\ddagger})_I = \Delta H_{C^+O^-} - \Delta H_{C^+Cl^-} - \Delta H_{H^+O^-} = 333 \text{ kcal.}$$

$$(\Delta H^{\ddagger})_{II} = \Delta H_{H^+Cl^-} - \Delta H_{C^+Cl^-} - \Delta H_{Aq\cdot H^+} = 164 \text{ kcal. (19)}$$

$$(\Delta H^{\ddagger})_{III} = \Delta H_{H^+C^-} - \Delta H_{C^-Cl^+} - \Delta H_{Aq\cdot H^+} = 219 \text{ kcal. (19)}$$

These figures show mechanism II to be the favored mechanism. This is at least in accord with the trend experimentally observed in acid solutions.

E. *Cyanhydrin formation with aldehydes.* Calculations will now be made to determine whether this reaction is favored by basic or acidic solutions, and whether the aldehyde exhibits electrophilic or nucleophilic properties.

In an acid solution, either HCN or H_3O^+ could be the attacking reagent. Of these two, H_3O^+ is favored, because it would call the electromeric effect of the carbonyl group into play more strongly than would the uncharged HCN; moreover, H_3O^+ is the stronger acid, and hence would lose its proton more easily. In a basic solution the attack would be more apt to be made by CN^- or OH^- ions, because of their high concentrations, and to other factors which the calculations below will make clear. Accordingly, there are three possible rate controlling steps to be considered.

I. $$CH_3CHO + H_3O^+ \rightleftharpoons CH_3\overset{H}{C}{=}O\cdots H^+\cdots OH_2$$

II. $$CH_3CHO + CN^-(Aq) \rightleftharpoons CH_3\overset{CN^-}{\overset{H}{C}}{=}O + Aq$$

III. $$CH_3CHO + OH^-(Aq) \rightleftharpoons CH_3\overset{OH^-}{\overset{H}{C}}{=}O + Aq$$

In calculating the corresponding values of $\Delta H^{\ddagger}_{com}$, $\Delta H_{C^+=O^-}$ may be omitted since it is common to all three. Thus we may write:

$$(\Delta H^{\ddagger}_{com})_I = \Delta H_{O-H^+} - \Delta H_{Aq\cdot H^+} = -334 + 253 = -81 \text{ kcal.}$$

$$(\Delta H^{\ddagger}_{com})_{II} = \Delta H_{C^+CN^-} - \Delta H_{Aq\cdot CN^-} = -285 - 75 = -360 \text{ kcal.}^2$$

$$(\Delta H^{\ddagger}_{com})_{III} = \Delta H_{C^+O^-} - \Delta H_{Aq\cdot OH^-} = -241 - \Delta H_{Aq\cdot OH^-}$$

Since the value of $\Delta H_{Aq\cdot OH^-}$ is not known, the calculations do not make clear whether the hydroxyl or cyanide ion will lead the attack, but the use of any reasonable value for $\Delta H_{Aq\cdot OH^-}$ at least clearly establishes the electrophilic char-

[2] Bichowsky and Rossini (21) give the value of Qf for $CN^-(Aq)$ as -34.9 kcal.mole^{-1}. The conversion of this value to the basis used by Rice (19) for the heats of hydration of ions gives: $\Delta H_{Aq\cdot CN^-} = 74.7$ kcal.mole.$^{-1}$.

acter of the aldehyde in basic solutions, (*i.e.*, either II or III is more probable than I), and indicates that more facile addition is to be expected in basic than in acidic solutions, all of which is in accord with experiment (22). If our previous guess that $-\Delta H_{Aq\cdot OH^-}$ is of the order of magnitude of -100 kcal., then $\Delta H^{\ddagger}_{com}$ = *ca.* $-$ 141 kcal. for III, and the CN^- ion is indicated as the attacking ion.

F. *Reactions of ethers with halogen hydrides, etc.* Three possible mechanisms may be considered.

I. An electrophilic attack by H on oxygen.

$$CH_3OCH_3 + HX \rightleftharpoons CH_3O(H{-}X){-}CH_3 \rightarrow CH_3OH + X^- + CH_3^+$$

II. An electrophilic attack by H on C.

$$CH_3OCH_3 + HX \rightleftharpoons X \cdots H \cdots CH_3 \cdots OCH_3 \rightarrow CH_4 + X^- + OCH_3^+$$

III. A nucleophilic attack by X on C.

$$CH_3OCH_3 + HX \rightleftharpoons H_3C(X{-}H){-}OCH_3 \rightarrow CH_3X + H^+ + OCH_3^-$$

The most probable mechanism may now be predicted by calculating the corresponding values of $\Delta H^{\ddagger}$ for the case in which HX is HI.

$$(\Delta H^{\ddagger})_I = \Delta H_{H^+O^-} - \Delta H_{C^+O^-} - \Delta H_{H^+I^-} = 218 \text{ kcal.}$$

$$(\Delta H^{\ddagger})_{II} = \Delta H_{H^+C^-} - \Delta H_{C-O^+} - \Delta H_{H^+I^-} = 295$$

$$(\Delta H^{\ddagger})_{III} = \Delta H_{C^+I^-} - \Delta H_{C^+O^-} - \Delta H_{H^+I^-} = 321$$

Similar calculations made for HBr and HCl show that in all cases mechanism I is the most probable. Incidentally, the calculations make it amply clear why the reaction cannot lead to the formation of a hydrocarbon and an alkyl hypochlorite (II).

The next step is to decide which of the halogen hydrides should be most reactive. For this purpose we may calculate $\Delta H^{\ddagger}_{com} = -\Delta H_{H^+X^-}$. We thus get the following values for $\Delta H^{\ddagger}_{com}$: 311 for HI, 318 for HBr, 329 for HCl, 334 for H_2O, and 334 for HOR. It is thus predicted that HI is the most reactive, which is in accord with experience, although concentrated aqueous solutions are used experimentally, while our calculations were made for the gas-phase reaction. It is well known that ethers are practically unreactive with water and alcohols at room temperature. Furthermore, the hydrolysis is said to be accelerated by hydrogen ions and not by hydroxyl ions, which is in accord with the nucleophilic properties established for the ethers by our rough calculations.

G. *Reactions of alcohols with halogen hydrides.* The formulation of this reaction is exactly like the preceding, and the calculated values are the same. This means that the predicted order of reactivity is HI > HBr > HCl, which is in accord with common knowledge of the reactions involving the anhydrous gases.

In accord with the nucleophilic properties of the alcohols in these reactions, it would be predicted that an increase in the basicity of the oxygen atom would aid the reaction, and hence that the order of reactivity should be tertiary > secondary > primary, which is in accord with common knowledge.

CONCLUDING REMARKS

Many chemists believe that the natural complexity of organic compounds must of necessity introduce such insuperable mathematical difficulties that organic chemists need expect no practical aid from physical chemistry in predicting the paths which are pursued by organic reactions. Perhaps they are right, but the above discussion gives one the right to hope, at least, that simple considerations of the energy involved in making and breaking valence bonds will prove to be a step forward. Unfortunately, the simplifications employed above were not rigorously justified, but they do seem to follow logically from Lapworth's theory of electrophilic and nucleophilic reaction tendencies, and hence at least may be said to constitute a semiquantitative extension of that theory. It is also unfortunate that it was necessary to use the ΔH rather than the ΔF of bond formation as a measure of the tendency to form covalencies, since the former can only lead to estimations of activation energy, while the latter would lead to estimations of reaction velocity. Moreover, the vagaries of solvation make it difficult to apply the theory with confidence to reactions in solution. Nevertheless, the success enjoyed in all of the examples thus far investigated justifies the tentative conclusion that this simple method is a safe guide if applied to the comparison of sufficiently similar reactions of the "ionic" type which are not complicated by mesomeric effects or polar substituents. These limitations make the method chiefly of use in predicting the mechanism and hence the reaction path followed by unsubstituted reactants. With these facts established one may usually proceed safely by applying the customary methods of the English school to predict the effects of substituents.

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THE SOLUBILITIES OF THE NORMAL SATURATED FATTY ACIDS

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The solubilities of the lower members of the normal saturated fatty acid series in a wide variety of solvents have long been known with considerable accuracy, and complete phase diagrams with most of the ordinary solvents have been constructed. While extensive data have been reported for various derivatives of the higher acids, such as the soaps and esters, the solubilities of the acids themselves, from caproic acid upward in the series, have been determined in relatively few solvents and considerable disagreement exists among the recorded values. Seidell (1), Brown (2), and Lewkowitsch (3) have compiled some of the solubility data for the saturated acids, and, in addition, the literature contains many references to the solubility of certain acids in specific solvents. No solubility data have as yet been available for several of the acids.

Since a wide variety of experimental procedures, such as surface studies, extraction, and fractional crystallization, require accurate solubility data, determination of the solubilities of the higher acids in common solvents is of appreciable value. This paper presents a comprehensive study of the solubilities of the normal saturated fatty acids, from caproic to stearic acid, inclusive, in water, ethanol, acetone, 2-butanone, benzene, and glacial acetic acid from 0° (slightly below in several cases) to the boiling points of the solvents, except in the case of water and of glacial acetic acid.

In connection with the investigation of the solubility, a study of the state of the acids in solution can readily be made by calculation of the apparent molecular weight from the depression of the freezing point of the solvent by addition of known amounts of acid. Numerous recent papers have reported association of the fatty acids in benzene (4), cyclohexane (5), quinoline (6), and in pyridine (7). This paper presents a further consideration of this problem with a discussion of the apparent association of the fatty acids in benzene and in glacial acetic acid.

EXPERIMENTAL

The acids employed in this investigation were of the same lots as were used in recent studies in this laboratory, and their preparations have been reported (8, 9). The freezing points of these acids are listed in Table I.

The water used was freshly distilled conductivity water. The ethanol was commercial "absolute" (99.4% by weight). The various dilutions which were used were determined by measurement of the density at each dilution and interpolation of these values with known densities at given concentrations (10). The acetone was redistilled from potassium permanganate as was the 2-butanone. The benzene was Baker C.P. thiophene-free grade and was dried over sodium wire. The glacial acetic acid was U. S. P., 99.5%.

The solubility of the fatty acids in water was determined by shaking flasks containing acid-water samples in a constant temperature bath for 2–4 days. The desired temperatures were arrved at from higher and from lower temperatures in order to assure that equilibrium had been attained. Solution was removed from the flasks by means of a small, fine sintered Pyrex glass filter sealed in a glass tube. The solutions were titrated with standardized

$Ba(OH)_2$ using phenolphthalein as the indicator, The less soluble samples, from lauric acid upwards in the series, were titrated conductimetrically with the conductivity apparatus described elsewhere (11). A microburette was used to measure the amounts of $Ba(OH)_2$.

The solubilities of the fatty acids in the organic solvents were determined in sealed tubes by the method and with the apparatus previously described (8, 12, 13).

TABLE I

FREEZING POINTS OF PURIFIED FATTY ACIDS

ACID	NO. OF C ATOMS	F.P., °C.	ACID	NO. OF C ATOMS	F.P., °C.
Caproic	6	−3.24	Tridecylic	13	41.76
Heptylic	7	−6.26	Myristic	14	53.78
Caprylic	8	16.30	Pentadecylic	15	52.49
Nonylic	9	12.24	Palmitic	16	62.41
Capric	10	30.92	Heptadecylic	17	60.94
Undecylic	11	28.13	Stearic	18	69.20
Lauric	12	43.86			

TABLE II

SOLUBILITIES OF THE FATTY ACIDS IN WATER

NO. OF C ATOMS	G. ACID PER 100 G. H_2O				
	0.0°	20.0°	30.0°	45.0°	60.0°
6[a]	0.864	0.968	1.019	1.095	1.171
7[b]	.190	.244	0.271	0.311	0.353
8[c]	.044	.068	.079	.095	.113
9	.014	.026	.032	.041	.051
10[d]	.0095	.015	.018	.023	.027
11	.0063	.0093	.011	.013	.015
12	.0037	.0055	.0063	.0075	.0087
13	.0021	.0033	.0038	.0044	.0054
14	.0013	.0020	.0024	.0029	.0034
15	.00076	.0012	.0014	.0017	.0020
16	.00046	.00072	.00083	.0010	.0012
17	.00028	.00042	.00055	.00069	.00081
18[e]	.00018	.00029	.00034	.00042	.00050

[a] 0.882 g. per 100 g. H_2O at 15° (3), 1.08 at 20° (14);
[b] 0.22 at 15° (14), 0.241 at 15° (15);
[c] 0.079 at 15° (3), 0.25 at 100° (3);
[d] 0.1 at 100° (3);
[e] 0.034 at 25° (16), 0.0033 at 25° (17), 0.1 at 37° (18), 0.0165 at 50° (17).

The depression of the freezing points of benzene and of glacial acetic acid by the addition of known amounts of fatty acids was determined using 25-g. portions of solvent. A Beckmann thermometer which had been calibrated by the National Bureau of Standards was employed.

RESULTS

Solubilities in water. The solubilities of the normal saturated fatty acids in water are listed in Table II.

The reproducibility of the results presented are shown by the following examples: for caprylic acid at 20.0° the experimental results gave a value of 0.068 ± 0.002 g. acid per 100 g. water, an average of 7 separate determinations; for lauric acid at 45.0°, 0.0075 ± 0.0005 g. for 6 determinations; and for heptadecylic acid at 30.0°, 0.00055 ± 0.00003 g. for 8 determinations. The values for the other acids at a given temperature are of similar reproducibility for averages of 3 to 8 separate determinations of each acid at each temperature.

With these values for the solubilities of the fatty acids in water and those previously reported (8) for the solubility of water in the fatty acids, the phase diagrams of the acids can now be fairly completely constructed.

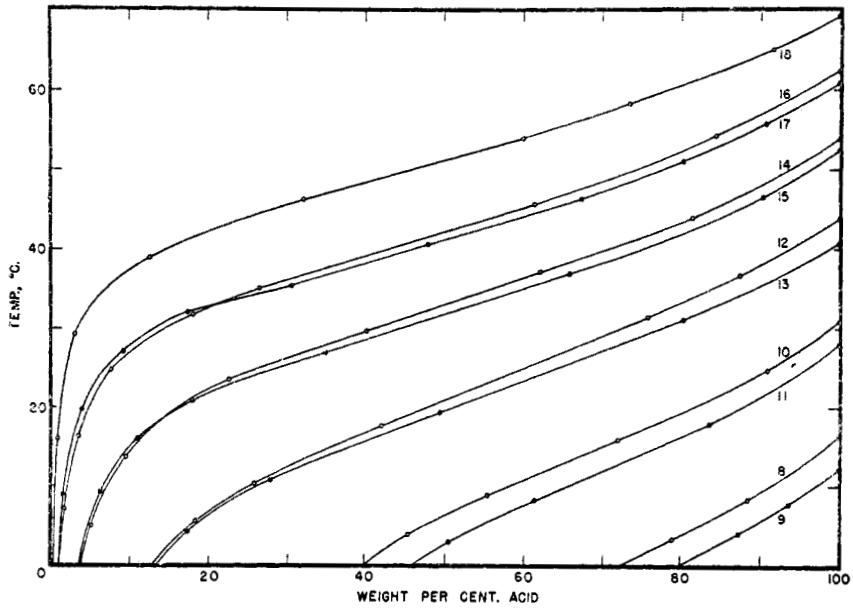

FIG. 1. SOLUBILITIES OF THE FATTY ACIDS IN 95.0% ETHANOL (BY WEIGHT)

The numbers on the curves refer to the number of carbon atoms in the acid molecule

Solubilities in ethanol. The solubilities of the fatty acids in ethanol were determined rapidly, and with the minimum of heating to high temperatures in order to reduce the possibility of esterification. The results are listed in Table III, and are shown graphically[1] for 95.0% ethanol in Fig. 1.

Comparison of the values in Table III with those previously recorded in the literature shows relatively good agreement among a number of the values. In general, the agreement is much better at lower temperatures than at higher temperatures. Some of these reportedly higher solubilities were investigated by

[1] In the figures in this report, the solubilities are shown in terms of weight percentage rather than in terms of g. per 100 g. of solvent because of the more convenient scale for diagrammatic presentation.

preparing a number of samples at the recorded values. Upon cooling, most of the samples crystallized before the reported temperature was reached. Crystal-

TABLE III

SOLUBILITIES OF THE FATTY ACIDS IN ETHANOL

% ETHANOL (BY WEIGHT)	NO. OF C ATOMS	G. ACID PER 100 G. SOLVENT						
		0°	10°	20°	30°	40°	50°	60°
99.4	12[a]	20.4	41.6	105	292	1540	∞	∞
	14[b]	7.07	9.77	23.9	84.7	263	1560	∞
	16[c]	1.89	3.20	7.21	23.9	94.2	320	2600
	17[d]	2.04	2.98	6.62	22.2	110	388	8230
	18[e]	0.42	1.09	2.25	5.42	22.7	105	400
95.0	8	262	1035	∞	∞	∞	∞	∞
	9	393	3230	∞	∞	∞	∞	∞
	10	60.6	93.5	440	8980	∞	∞	∞
	11	85.2	190	706	∞	∞	∞	∞
	12[f]	15.2	34.0	91.2	260	1410	∞	∞
	13	15.5	34.5	104	336	6560	∞	∞
	14	3.86	7.64	18.9	68.7	238	1485	∞
	15	3.82	7.18	19.5	78.5	295	2460	∞
	16[g]	0.85	2.10	4.93	16.7	73.4	287	2280
	17	1.03	1.68	4.17	15.3	84.2	344	6560
	18[h]	0.24	0.65	1.13	3.42	17.1	83.9	365
91.1	16[i]	0.76	1.94	4.60	15.3	...	...	...
	18[j]	0.13	0.35	0.66	2.30	13.5	68.7	...
80.8	18	*ca.* 0.06	0.10	0.20	0.81	3.20	50.8	238

[a] 20.5 at 0° (19), 25.8 at 0° (20), 45.6 at 8° (20), 61.2 at 12° (20), 92.1 at 16.5° (20), 57.3 at 21° (19).

[b] 7.14 at 0° (19), 31 at 21° (19).

[c] 2 at 0° (19), 1.93 at 0° (20), 1.45 at 0° (21), 2.0 at 5° (21), 4.0 at 10° (21), 3.5 at 10° (22), 6.5 at 15° (21), 6.86 at 17° (20), 9.9 at 20° (21), 11.6 at 20° (22), 10.1 at 21° (19), 16.8 at 25° (21), 11.0 at 25° (23), 29.0 at 28° (21), 81.0 at 36° (21), 41.3 at 40° (22).

[d] 1.53 at 0° (21), 2.42 at 5.4° (21), 4.12 at 10° (21), 6.72 at 15° (21), 13.4 at 21° (21), 32.14 at 28° (21).

[e] 0.37 at 0° (21), 0.51 at 5° (21), 1.10 at 10° (21), 0.90 at 10° (22), 1.6 at 15° (21), 2.5 at 20° (21), 4.9 at 25° (21), 8.30 at 25° (16), 6.0 at 28° (21), 20.0 at 36° (21), 17.9 at 40° (22).

[f] 35.0 at 8° (20), 45.2 at 12° (20), 69.7 at 16.5° (20).

[g] 2.21 at 8° (20), 2.72 at 12° (20), 5.90 at 20° (20), (94.0% ethanol) 0.70 at 0° (24).

[h] 5.55 at 25° (16), (94.6% ethanol) 0.1515 at 0° (25), (94.4%) 0.188 at 0° (26), (94.0%) 0.15 at 0° (24).

[i] (87.6% ethanol) 0.451 at 0° (27).

[j] (91.6% ethanol) 0.112 at 0° (3), (91.53%) 0.136 at 0° (28), 0.481 at 10° (28), 2.23 at 25° (29), (90%) 3.30 at 25° (16), (87.6%) 0.89 at 0° (27), (86.16%) 0.073 at 0° (28), 0.278 at 10° (28).

lization of the other samples was induced by seeding. This behavior of undercooling and supersaturation, indicating the necessity of maintaining equilibrium

conditions, has been discussed by Emerson (25) with regard to the solubility of stearic acid in ethanol at 0°.

Some of the divergent solubilities which are recorded may indicate contamination of a given acid by its homologs. Investigation of the solubilities of binary mixtures of the acids shows that their values fall between those of the pure components. A mixture containing 5% palmitic and 95% stearic acids dissolves in twice its weight of 95% ethanol at about 1.5° lower than does an equal concentration of pure stearic acid in 95% ethanol.

TABLE IV

SOLUBILITIES OF THE FATTY ACIDS IN ACETONE

NO. OF C ATOMS	G. ACID PER 100 G. ACETONE					
	0°	10°	20°	30°	40°	56.5°
8	221	975	∞	∞	∞	∞
9	356	3740	∞	∞	∞	∞
10	45.3	112	407	4660	∞	∞
11	50.2	149	706	∞	∞	∞
12	8.95	21.9	60.5	218	1590	∞
13	7.52	20.2	78.6	316	8230	∞
14	2.75	6.50	15.9	42.5	149	∞
15	2.20	5.27	13.8	49.3	183	∞
16	0.60	1.94	5.38	15.6	58.0	880
17	0.40	1.50	4.28	14.6	67.5	1330
18[a]	0.21	0.80	1.54	4.93	17.0	220

[a] 4.96 at 25° (16).

TABLE V

SOLUBILITIES OF THE FATTY ACIDS IN 2-BUTANONE

NO. OF C ATOMS	G. ACID PER 100 G. 2-BUTANONE						
	0°	10°	20°	30°	40°	50°	60°
10	42.4	100	318	7040	∞	∞	∞
11	47.9	139	521	∞	∞	∞	∞
12	11.5	24.7	64.7	202	1825	∞	∞
13	11.9	29.5	95.0	315	8230	∞	∞
14	4.28	8.46	18.5	54.3	189	1230	∞
15	4.28	8.70	20.2	70.4	257	2530	∞
16	0.90	3.09	8.57	20.6	66.1	228	2390
17	0.71	2.88	7.41	20.3	77.7	288	6560
18	0.25	1.01	2.99	8.34	24.8	84.7	344

Solubilities in acetone and 2-butanone. The solubilities of the fatty acids in acetone and in 2-butanone are listed in Tables IV and V, respectively, and are shown graphically in Figs. 2 and 3.

As in the case of the acids in ethanol, the curves for acetone and 2-butanone

are also paired. The acids of higher molecular weight are the more soluble of each pair, with certain obvious exceptions. All of the acids investigated are more

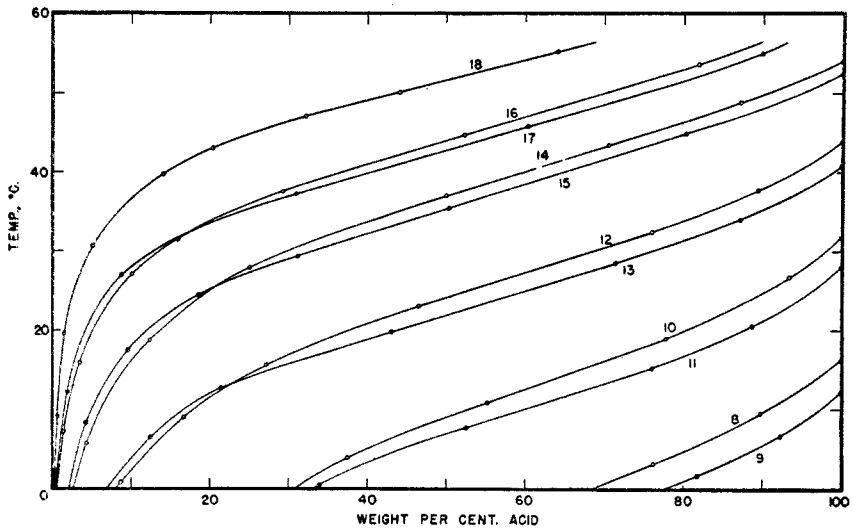

FIG. 2. SOLUBILITIES OF THE FATTY ACIDS IN ACETONE

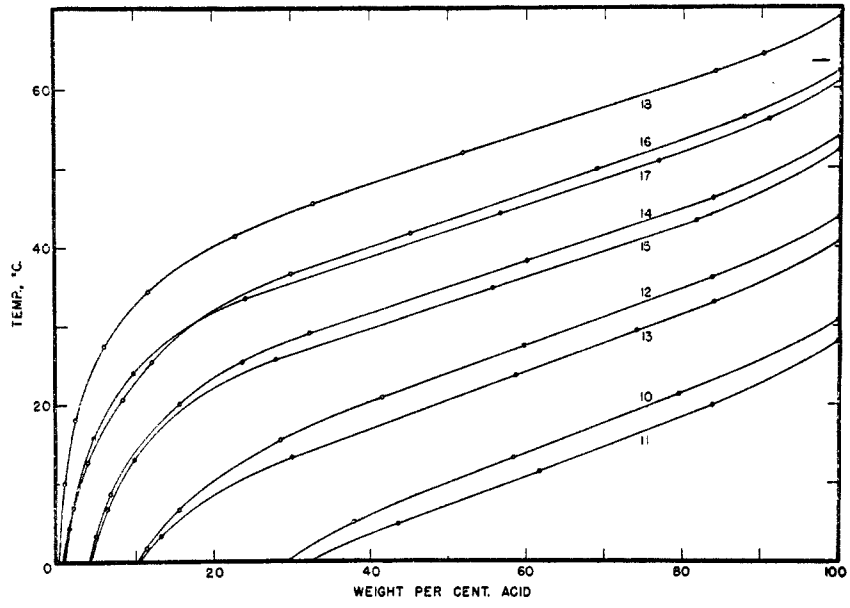

FIG. 3. SOLUBILITIES OF THE FATTY ACIDS IN 2-BUTANONE

soluble in 2-butanone at a given temperature than in acetone at the same temperature, except capric and undecylic acids, which are more soluble in acetone.

TABLE VI

SOLUBILITIES OF THE FATTY ACIDS IN BENZENE[a]

NO. OF C ATOMS	G. ACID PER 100 G. BENZENE					
	10°	20°	30°	40°	50°	60°
8	770	∞	∞	∞	∞	∞
9	2680	∞	∞	∞	∞	∞
10	145	398	8230	∞	∞	∞
11	208	663	∞	∞	∞	∞
12[b]	32.3	93.6	260	1390	∞	∞
13	42.4	117	354	7600	∞	∞
14	6.95	29.2	87.4	239	1290	∞
15	8.84	36.2	103	295	2280	∞
16	1.04	7.30	34.8	105	306	2170
17	1.52	9.23	42.1	121	369	5450
18[c]	0.24	2.46	12.4	51.0	145	468

[a] Powney and Addison (31) investigated the solubilities of several acids (caprylic, lauric, myristic, palmitic, and stearic) in benzene, but, unfortunately, no values were tabulated, and the solubilities cannot be read accurately from their small diagrams.

[b] 186 at 25° (30), ∞ at 40° (30);

[c] 22 at 23° (3).

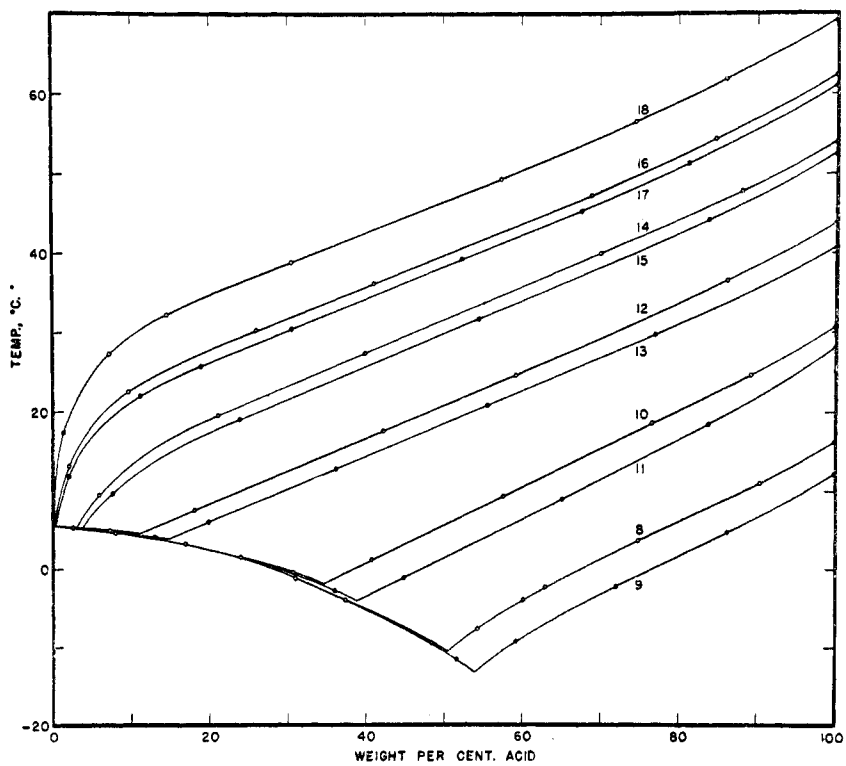

FIG 4. LIQUIDUS CURVES FOR THE FATTY ACID SYSTEMS WITH ANHYDROUS BENZENE

Solubilities in benzene. The solubilities of the fatty acids in benzene are listed in Table VI and the liquidus curves of the systems are shown in Fig. 4.

TABLE VII

SOLUBILITIES OF THE FATTY ACIDS IN GLACIAL ACETIC ACID

NO. OF C ATOMS	G. ACID PER 100 G. GLACIAL ACETIC ACID				
	20°	30°	40°	50°	60°
10	567	8230	∞	∞	∞
11	800	∞	∞	∞	∞
12	81.8	297	1480	∞	∞
13	96.8	395	8230	∞	∞
14	10.2	51.1	289	1410	∞
15	8.76	62.0	350	2600	∞
16	2.14	8.11	51.7	313	2280
17	1.27	6.52	61.0	384	6560
18	0.12	1.68	7.58	74.8	485

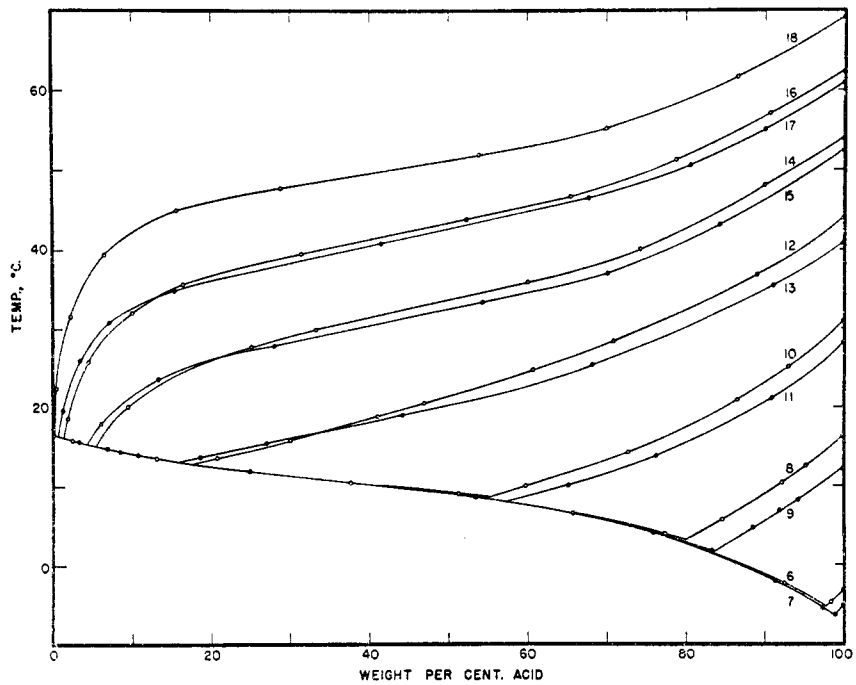

FIG. 5. LIQUIDUS CURVES FOR THE FATTY ACID SYSTEMS WITH GLACIAL ACETIC ACID

Again pairing of adjacent homologs occurs. It is of interest that in this case no pairs of curves intersect, as with the preceding solvents discussed. Each of the acids forms a eutectic with benzene, these eutectics occurring at the following concentrations and melting at the following temperatures: C_8 at 50.4% and

$-10.5°$; C_9, 54.0% and $-13.1°$; C_{10}, 34.5% and $-2.0°$; C_{11}, 38.9% and $-4.0°$; C_{12}, 11.2% and 4.5°; C_{13}, 14.6% and 3.7°; C_{14}, 2.88% and 5.20°; C_{15}, 3.65% and 5.15°; C_{16}, 0.19% and 5.40°; C_{17}, 0.42% and 5.35°; and C_{18}, 0.015% and 5.50°; These values agree reasonably with those of Powney and Addison (31).

Calculations from the freezing point data show that at the freezing point of benzene, the ratio of apparent to true molecular weight (M/M_0) for caprylic acid approaches a value of 2 at about 0.5 molal, indicating association in solution. In solutions of lauric acid in benzene, the values of M/M_0 approach 2 at 0.3 molal. Investigations at higher temperatures by other methods (4) indicate that the values of M/M_0 for the fatty acids in benzene approach limits somewhat less than 2, and their limiting value is approached in relatively higher concentrations.

Solubilities in glacial acetic acid. The solubilities of the fatty acids in glacial acetic acid are listed in Table VII, and the liquidus curves of the systems are shown in Fig. 5.

Again pairing occurs, with the acid of higher molecular weight being, in general, the more soluble of a given pair. Each of the acids forms a eutectic with glacial acetic acid, these eutectics having a composition and melting point as follows: C_6, 97.7% and $-5.4°$; C_7, 98.8% and $-6.5°$; C_8, 80.0% and 3.1°; C_9, 83.6% and 1.6°; C_{10}, 55.1% and 8.6°; C_{11}, 57.5% and 8.0°; C_{12}, 17.3% and 12.8°; C_{13}, 15.9% and 13.1°; C_{14}, 5.3% and 15.18°; C_{15}, 4.3% and 15.40°; C_{16}, 1.23% and 16.17°; C_{17}, 0.58% and 16.34°; and C_{18}, 0.03% and 16.48°.

Calculations from the freezing point data indicate that the values of M/M_0 of lauric acid in acetic acid approach 1.65 at about 0.2 molal. Thus, as in the case of benzene solutions of the acids, there appears to be some formation of double molecules of the fatty acids in glacial acetic acid.

SUMMARY

The solubilities of the normal saturated fatty acids from caproic to stearic, inclusive, have been determined in water, ethanol, acetone, 2-butanone, benzene, and glacial acetic acid.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

ALSTONIA ALKALOIDS. I. DEGRADATION OF ALSTONINE TO β-CARBOLINE BASES AND THE REDUCTION OF TETRAHYDROALSTONINE WITH SODIUM AND BUTYL ALCOHOL

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The bark of various species of *Alstonia* has enjoyed a local reputation as a febrifuge in the treatment of malaria for a number of years in China and the Pacific Islands. Studies on the total alkaloids isolated from the bark of two varieties, *Alstonia constricta* and *Alstonia scholaris* (1) led to the conclusion that perhaps a slight action on birds infected with *Plasmodium inconstans* was present in both cases, with the alkaloids of the latter being somewhat more potent than those of the former. Furthermore, similar studies on individual alkaloids isolated from certain species (1, 2) have failed to substantiate the purported action attributed to the barks. However, since it has been a somewhat common experience that native remedies in the past occasionally have a sound basis for use, and since knowledge of the chemistry of these alkaloids is scanty, it appeared worth while to undertake a new investigation of the latter subject. At the same time the question of isolation and characterization of alkaloids hitherto not well described, has been studied (3). From results obtained so far on the latter phase of the work, it appears that the alkaloidal constituents of *Alstonia constricta* are unusually susceptible to atmospheric oxidation, and that the observed pharmacological action of total alkaloid fractions or of individual constituents thereof, may not be representative of the action of freshly prepared infusions of the bark. Furthermore, it was felt that elucidation of the structure of the constituent alkaloids might suggest new approaches to the preparation of antimalarial agents by modification of the molecules.

In the present communication we wish to present the results of certain phases of the study of alstonine obtained from *Alstonia constricta*. The bark used was purchased on the open market and was identified as that of *Alstonia constricta*, F. Muell. by Dr. Heber W. Youngken, of Boston, Mass. Alstonine was isolated in the earlier work according to Sharp (2a) and later by a procedure developed in these laboratories (3).

The early investigations on this alkaloid have been adequately reviewed by Sharp, who, at the same time, investigated several of its reactions (2a, 4). The formula, $C_{21}H_{20}N_2O_3$, was accepted for the base, on the basis of analyses of various salts, although for the nitrate, hydrochloride, and acid sulfate, the figures obtained agreed better with the formula, $C_{22}H_{22}N_2O_3$. The free base could not be obtained crystalline, although hydrates of the base were described as crystalline. The presence of one methoxyl group in the form of a methyl ester, one basic tertiary nitrogen atom, and one apparently inert nitrogen atom, was noted. Alstonine does not contain an N-alkyl group, and neither phenolic nor alcoholic hydroxyl groups. On catalytic reduction with platinum oxide, tetrahydroal-

stonine was formed, although it was reported that salts of the base were not reduced under similar conditions. The methyl ester group of tetrahydroalstonine was described as being very resistant to alkaline hydrolysis, suggesting a quaternary carbomethoxy group. Tetrahydroalstonine is unaffected by acetic anhydride, benzoyl chloride, and semicarbazide, as is alstonine, and is little affected by hydrobromic acid. Sharp also noted the formation of a dibromide by substitution when alstonine sulfate was treated with bromine water. At the same

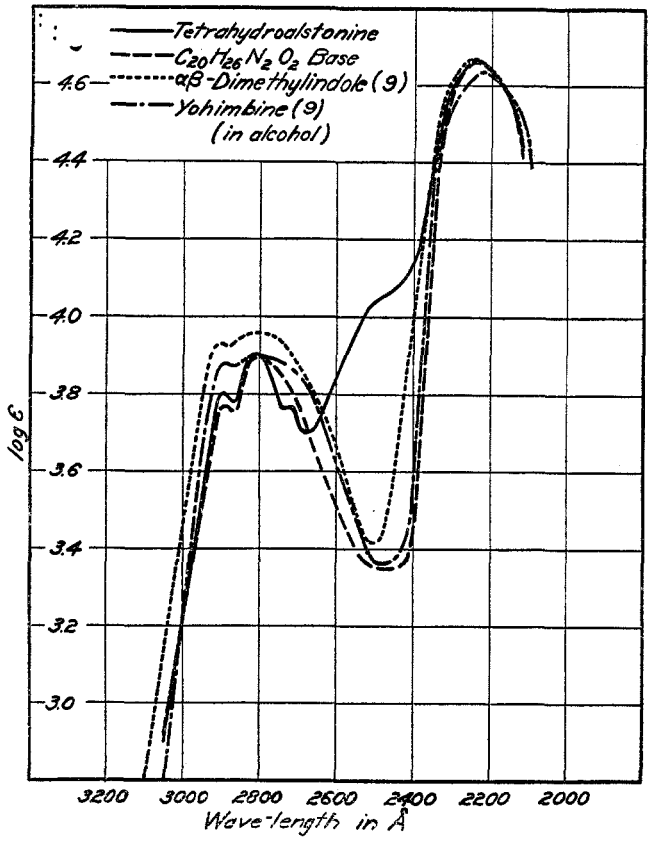


FIGURE 1

time an oxygen atom was introduced. No clue to the structure of this substance was obtained by a study of its catalytic reduction. However, when alstonine was oxidized with permanganate, oxalic acid and N-oxalylanthranilic acid were obtained, from which Sharp concluded that either an indole or quinoline nucleus was present in the alkaloid. On selenium dehydrogenation, a base, alstyrine, to which the formula, $C_{19}H_{22}N_2$ or $C_{18}H_{20}N_2$, was assigned, was obtained. Finally, attempted exhaustive methylation, by a variety of procedures, of alstonine, tetrahydroalstonine, and alstyrine did not result in elimination of nitrogen, although poorly defined products of an indole-like nature were obtained from the latter.

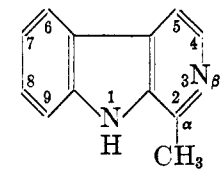
At the start of the present work, a clue to the presence of a tetrahydro-β-carboline ring system in tetrahydroalstonine was furnished by the observation that this base gave a color similar to that obtained with yohimbine in the Adamkiewicz test, as modified by Harvey, Miller, and Robson (5), who noted development of a similar color with other tetrahydro-β-carbolines. The color developed at the interface of a solution of the compound in glacial acetic acid plus half a drop of 10% ferric chloride solution, layered on concentrated sulfuric acid, was taken as the test. Tetrahydroalstonine and yohimbine both showed an original blue to violet color which changed through green to a final yellow green. It is interesting that salts of alstonine give only a yellow color. Likewise the ultra-violet absorption curve for yohimbine and tetrahydroalstonine showed similarity except for the inflection point at about 2500 Å displayed by the latter (Fig. 1). The presence of a β-carboline ring system in tetrahydroalstonine and alstonine was definitely confirmed by the nature of the products formed on various degradations of both substances.

When alstonine was fused with potassium hydroxide, no volatile amine was noted, and from the fusion mixture, harman (I) was isolated. No significant amount of neutral product was formed, and while a considerable acid fraction was found, it has not been possible to isolate any pure substance from this at present.

On the other hand, when tetrahydroalstonine was similarly fused with potassium hydroxide, several products were isolated. Harman (I), as well as norharman (II), was found in the basic fraction. In addition to these bases, three other bases have been isolated, but with the amounts available it has not been possible to identify them at present, although tentative empirical formulas are suggested. The separation of the above five bases was achieved by chromatographic adsorption on aluminum oxide, as described in detail in the experimental part. The first of the three unidentified bases, Base A, is assigned the formula, $C_{17}H_{16}N_2$, on the basis of analyses of the free base and its picrate. In alcoholic hydrochloric acid solution it shows a strong blue fluorescence and it is probably a substituted β-carboline. Base B is assigned the tentative formula, $C_{16}H_{16}N_2$, or $C_{16}H_{18}N_2$, on the basis of analysis of its picrate. It likewise showed a blue fluorescence in hydrochloric acid solution, as did Base C, to which is assigned the tentative formula, $C_{17}H_{18}N_2$, on the basis of analysis of its picrate. From the acidic products of the fusion, indole-α-carboxylic acid (III) was isolated. No pure substance could be isolated from the neutral fraction, although the general behavior of this part suggested the presence of indole derivatives.

Thermal decomposition of alstonine likewise resulted in the formation of a variety of bases, all apparently derived from β-carboline, although none of them has been definitely identified. The bases were separated by fractional crystallization of their picrates. The picrate of one of these substances (Base D) is characterized by its extreme insolubility in alcohol, and was easily isolated, although in small amounts. The picrate furnished analytical figures corresponding to those required for the picrate of a base of formula, $C_{17}H_{18}N_2$. However, this picrate melts some 50° higher than the picrate of the above Base C, and the

crystalline form of the two is different. The two bases, therefore, can be considered isomeric. The most soluble of the three picrates furnished analytical figures agreeing with those required for the picrate of a base of composition, $C_{18}H_{20}N_2$, or $C_{19}H_{22}N_2$ (Base E). The two suggested formulas are the same as those put forward by Sharp (4) for alstyrine. However, identity of Base E with alstyrine is unlikely since the picrates differ both in melting point and crystalline form. The third base (Base F) was formed in relatively larger quantities. It is



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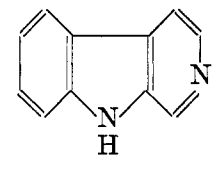

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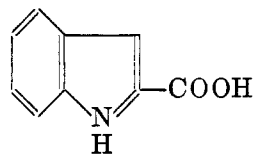

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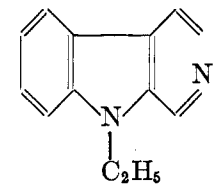

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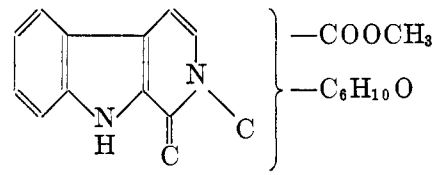

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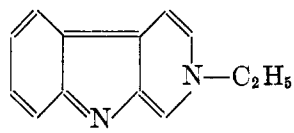

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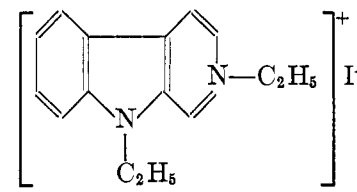

VII

assigned the formula, $C_{13}H_{12}N_2$, on the basis of analysis of the free base, its picrate, and methiodide. The hydrochloride exhibits a strong blue fluorescence in water or alcohol solution. The ultra-violet absorption curve for Base F shows close similarity to that for 2-ethyl-β-carboline (Fig. 2), from which it may be concluded that a β-carboline structure is present. Of the β-carboline derivatives of empirical formula corresponding to Base F, 2-ethyl-β-carboline (6), 1,2-dimethyl-β-carboline (6), and 2,3-dimethyl-β-carboline (7) are known and are not identical with Base F. Since an N-alkyl determination indicated the possible presence of an N-ethyl group, 1-ethyl-β-carboline (IV) was synthesized by a

combination of the procedures of Manske (8) and Späth and Lederer (6) for the preparation of the corresponding methyl derivative, and was not identical with Base F. Likewise 3-ethyl-β-isocarboline (VI) was prepared and was not identical with Base F.

When alstonine was distilled with zinc dust, the only product isolated was a base presumably identical with Base F, although this identification is not unequivocal.

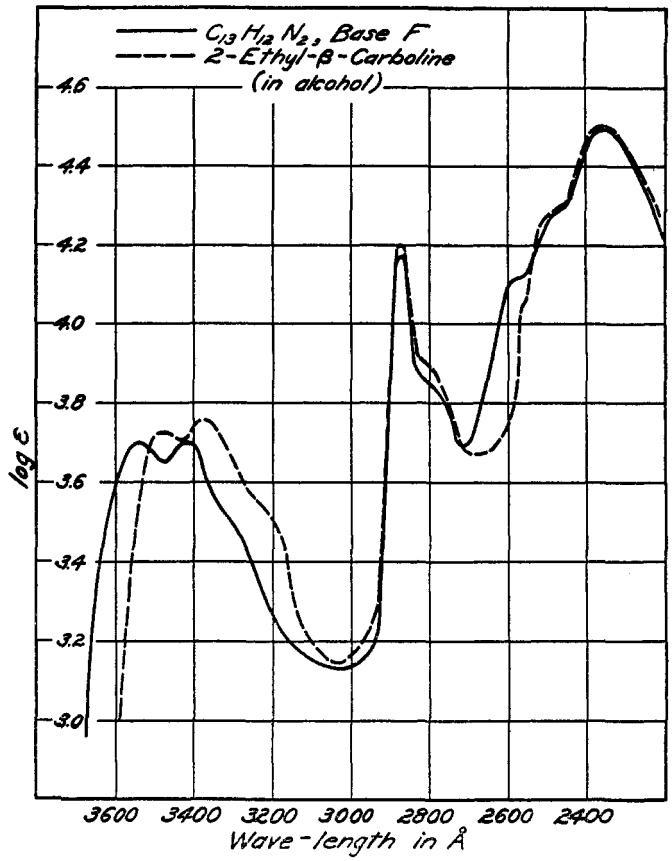

FIGURE 2

We have also investigated the reduction of tetrahydroalstonine with sodium and butyl alcohol. In the preparation of tetrahydroalstonine, our results agree with those of Sharp, in that while alstonine itself in methanol solution readily absorbs two moles of hydrogen in the presence of platinum oxide catalyst, alstonine hydrochloride in methanol and alstonine in acetic acid solution are not reduced with the same catalyst. Further, a methanol solution of alstonine is not reduced in the presence of palladium black. When tetrahydroalstonine was further reduced with sodium and butyl alcohol, the methyl ester group was re-

duced to a primary alcohol and an additional mole of hydrogen was introduced into the molecule. The reduction product, for which we suggest the name hexahydroalstonol, has the empirical formula, $C_{20}H_{26}N_2O_2$. The newly formed primary alcoholic hydroxyl group can be easily acetylated, which contrasts with the reported difficult hydrolysis of the ester group in tetrahydroalstonine. While the ultra-violet absorption curve for the new base clearly indicates that it is an α,β-disubstituted indole (Fig. 1), the relationship of tetrahydroalstonine to its reduction product is not so clear. Likewise, the point of addition of the two additional hydrogens is not clear. The two hydrogens in question can conceivably have been taken up by the reduction of a double bond conjugated with either the carbomethoxy group or indole system of tetrahydroalstonine, by the reduction of a $\rangle C{=}O$ or $\rangle C{=}N-$ group, or by the cleavage of an allyl ether type of linkage. It seems unlikely that a double bond occurs in conjugation with the carbomethoxy group; if this were so, such a double bond should have been reduced in the formation of tetrahydroalstonine. Whether a similar argument applies to a double bond conjugated with the indole system must be left open for the present, although the disappearance of the inflection point at 2500 Å in the absorption curve of tetrahydroalstonine on passing to hexahydroalstonol suggests that some sort of conjugation has been attacked. If a $\rangle C{=}O$, $\rangle C{=}N$ or allyl ether had been reduced, an acylatable group should have resulted and acetylation of hexahydroalstonol, under the strong conditions employed, should have resulted in the formation of a diacetate.

At this point it may be profitable to summarize the information at present at hand concerning the structure of alstonine. From the results here obtained the partial formula V appears to be justified. Results of Zerewitinoff active hydrogen determinations indicate the presence of one active hydrogen which is accounted for by the indole hydrogen and failure to detect any hydroxyl groups either by ourselves or Sharp (4). The tertiary nature of the pyridine nitrogen of the β-carboline system is indicated by the failure of both alstonine and tetrahydroalstonine to show reactions characteristic of both primary and secondary amines. Furthermore, the number of active hydrogens is the same in both alstonine and tetrahydroalstonine, indicating that the basic nitrogen function does not undergo any change on catalytic reduction. The presence of two double bonds closely adjacent to the indole nucleus is indicated by the easy formation of tetrahydroalstonine, although some tautomeric shift of these double bonds must occur when the salts of the base are formed because of the failure of the latter to undergo catalytic reduction. Alstonine hydrochloride absorbs ultraviolet light of longer wave length than any of the related compounds with which it is compared in Fig. 3. It may be concluded that alstonine hydrochloride possesses greater conjugation than lysergic acid, where one double bond is conjugated with the benzene ring, and also greater conjugation than 2-ethyl-β-carboline hydrochloride and harmol, where the additional unsaturation lies in the pyridine ring fused to the α- and β-carbons of indole. Since there is a difference

in the absorption curves of 2-ethyl-β-carboline and its hydrochloride (*cf.* Figs. 2 and 3), there is most likely a difference between the absorption curve of alstonine and that of its hydrochloride. The absorption spectrum of alstonine itself could not be measured because of the instability of the free base, but the probability of the difference in spectra is borne out by the visible difference in the color of alstonine and of its salts; the former is a deeper orange, both as a solid and in solution. The nature of the third oxygen atom remains unknown. Furthermore, the exact location of the double bond external to the indole nucleus in

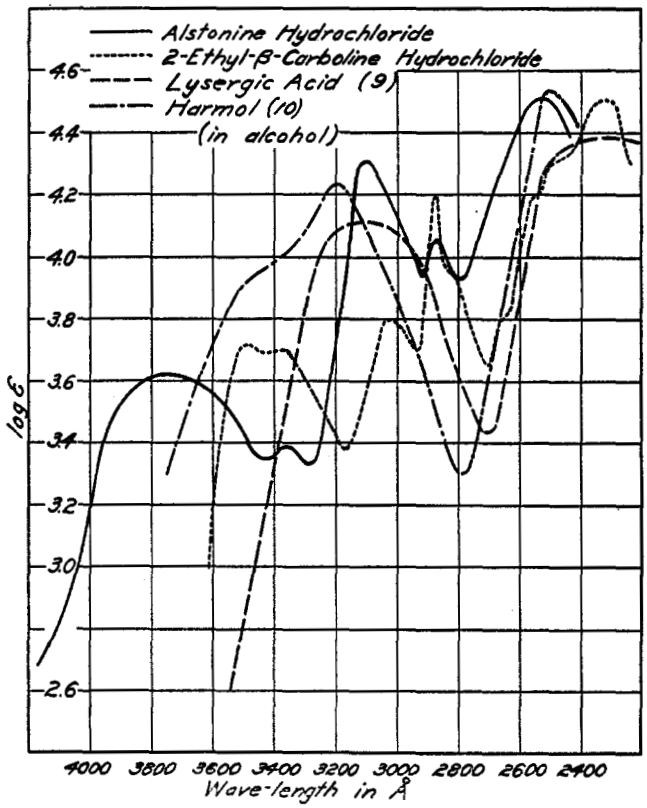

FIGURE 3

tetrahydroalstonine must be left open for the present. It is also now possible to formulate the entire ring structure of alstonine as either a tetracyclic or pentacyclic system, depending on the nature of the oxygen atom not accounted for.

Through the kind cooperation of Dr. John Maier of the Rockefeller Foundation, pharmacological tests were performed and it was found that alstonine is inactive in doses of 35 mg. per day in birds infected with avian malaria.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Alstonine was originally obtained from the dry, powdered *Alstonia constricta* bark, according to the method of Sharp (2a), but later according to a modification developed in

this laboratory (3). Salts were prepared for identification purposes and in order to establish definitely the empirical formula which was left in some doubt from the analyses obtained by Sharp for the hydrochloride, nitrate, and acid sulfate.

Alstonine sulfate (*dihydrate*) crystallized as yellow prisms from absolute alcohol, melted at 195–196°, and foamed at 208°; $[\alpha]_D^{25}$ 127° ± 2° (c = 0.492 in water); $[\alpha_M]_D^{25}$ 527°.

Anal. Calc'd for $(C_{21}H_{20}N_2O_3)_2H_2SO_4 \cdot 2H_2O$: C, 60.7; H, 5.6; N, 6.7; S, 3.9.
Found: C, 60.4; H, 5.9; N, 6.4; S, 4.0.

Alstonine sulfate (*tetrahydrate*) formed nearly colorless needles from absolute alcohol-ethyl acetate and melted at 203–204°; $[\alpha]_D^{25}$ 120° ± 2° (c = 0.548 in water); $[\alpha_M]_D^{25}$ 520°.

Anal. Calc'd for $(C_{21}H_{20}N_2O_3)_2H_2SO_4 \cdot 4H_2O$: C, 58.2; H, 5.8; N, 6.4.
Found: C, 58.6; H, 5.6; N, 6.3.

Alstonine acid sulfate crystallized as yellow rosettes of prisms from absolute alcohol and melted at 243–244° with decomposition; $[\alpha]_D^{25}$ 120° ± 2° (c = 0.588 in water); $[\alpha_M]_D^{25}$ 535°. Sharp reports the melting point 246–248° with decomposition and $[\alpha]_D$ 113.1° in water.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot H_2SO_4$: C, 56.5; H, 5.0.
Found: C, 56.8; H, 5.0.

Alstonine chloroplatinate formed small orange-yellow prisms from absolute alcohol which melted at 220–221° with decomposition.

Anal. Calc'd for $(C_{21}H_{20}N_2O_3)_2 \cdot H_2PtCl_6 \cdot H_2O$: C, 44.8; H, 4.0; Pt, 17.3.
Found: C, 44.5; H, 4.3; Pt, 17.2.

Alstonine hydrochloride crystallized as nearly colorless plates from absolute alcohol-ethyl acetate and melted at 278–279° with decomposition; $[\alpha]_D^{25}$ 141° ± 2° (c = 0.422 in water); $[\alpha_M]_D^{25}$ 545°. Sharp reports the decomposition melting point 286° and $[\alpha]_D$ 131.9° in water. Neutralization equivalent of alstonine hydrochloride: calc'd: 385; found: 391.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot HCl$: C, 65.5; H, 5.5.
Found: C, 65.5; H, 5.6.

Alstonine nitrate formed stout yellow monoclinic prisms from absolute alcohol and melted at 252–254° with decomposition. Sharp reports the melting point 262–263°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot HNO_3$: C, 61.3; H, 5.2.
Found: C, 61.2; H, 5.3.

Alstonine hydriodide formed pale yellow plates from absolute alcohol and melted at 270° with decomposition. Sharp reports 291°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot HI$: C, 52.9; H, 4.5.
Found: C, 53.1; H, 4.6.

Alstonine perchlorate crystallized as stout yellow prisms from absolute alcohol and melted at 239–240°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot HClO_4$: C, 56.2; H, 4.7.
Found: C, 56.3; H, 4.9.

Tetrahydroalstonine was obtained on reduction of alstonine in absolute methyl alcohol with platinum oxide but not with palladium. No tetrahydroalstonine was obtained on attempted reduction of alstonine salts or of alstonine in acetic acid solution with platinum oxide. The substance formed colorless plates from 90% alcohol and melted at 230–231°; $[\alpha]_D^{30}$ −110° ± 2° (c = 0.672 in chloroform), $[\alpha]_D^{27}$ −88° ± 2° (c = 0.412 in pyridine). Sharp (4) reports the substance as melting at 230–231° and showing $[\alpha]_D$ −107.0° in chloroform. Molecular weight by the Rast method in camphor: calc'd: 352; found: 354.

Fusion of alstonine with potassium hydroxide. An intimate mixture of 10 g. of alstonine hydrochloride and 75 g. of finely-ground potassium hydroxide was placed in a nickel crucible and fused for 1 hr. at 300–350° under a slow stream of nitrogen, with continual stirring. When cold, the melt was dissolved in water and exhaustively extracted with ether. The ether extract contained basic and neutral fractions and was subsequently extracted ten times with 2 *N* hydrochloric acid, after which the ether layer was washed with water. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness, leaving a negligible amount of impure neutral material. The combined hydrochloric acid extracts, containing basic compounds as their hydrochloride salts, were made strongly alkaline with sodium hydroxide solution and extracted with ether. The total

ether extract was dried and the solvent removed, leaving 2.2 g. of impure brownish crystals. These were dissolved in 250 cc. of dry benzene and chromatographed on 35 g. of aluminum oxide (Brockmann). The column was eluted exhaustively with dry benzene, and the total benzene eluate was evaporated to dryness, yielding 1.5 g. of white crystals. These were recrystallized five times from benzene; they appeared to have different crystal habits, separating out both as needles and as small regular prisms. The prisms are evidently the more stable form, since the needles, on standing a sufficient length of time either at room temperature or at 0°, reverted to the prismatic form. Both forms melted at 239–241°. The analytical figures, as well as physical properties, correspond to those of harman (11).

Anal. Calc'd for $C_{12}H_{10}N_2$: C, 79.1; H, 5.5; N, 15.4.
Found: C, 79.2; H, 5.7; N, 15.4.

Accordingly, *harman* (2-methyl-β-carboline) was prepared by the method of Kermack, Perkin, and Robinson (11), who did not note the occurrence of the two crystalline forms. Our synthetic material crystallized both as needles and prisms and was exactly similar in properties to the base (I) obtained from alstonine. It melted at 239–241° and the melting point of mixtures of varying percentage composition of the two specimens showed no depression.

For further identification the *picrate*, melting at 257–258° with decomposition after recrystallization from alcohol, the *chloraurate*, melting at 229.5–230° with decomposition after recrystallization from dilute alcohol acidulated with hydrochloric acid, and the *benzal derivative* (11) melting at 204–205°, after recrystallization from dilute alcohol, were prepared from material from both sources. All pairs of these derivatives were identical and showed no depression of melting point when mixed.

While other bases were formed in this reaction, we have been unable to isolate any chemical individual as yet. Likewise, no pure substance has been obtained from the acidic fraction.

Fusion of tetrahydroalstonine with potassium hydroxide. A mixture of 5 g. of pure tetrahydroalstonine and 75 g. of potassium hydroxide was fused in a nickel crucible, under a stream of nitrogen, for one hour above 310°. When cold, the melt was dissolved in water and exhaustively extracted with ether. The ether solution was extracted ten times with 1 *N* hydrochloric acid, and then washed with water, leaving the neutral compounds in the ether. The total acid extract was then made strongly alkaline with sodium hydroxide and extracted with ether. The ethereal solution was dried and the solvent removed, leaving about 500 mg. of basic material, which was distilled *in vacuo* at 140–200° bath temperature and 0.1 to 0.15 mm. The distillate was dissolved in benzene (*ca.* 350 mg. in 175 cc. of dry benzene) and chromatographed on aluminum oxide (Brockmann).

The column was eluted exhaustively with benzene, the benzene removed at atmospheric pressure, and the oily residue kept at 0° for several days. Upon standing, the residue partially crystallized. The crystals were separated mechanically from the oily upper layer and recrystallized twice from ligroin, b.p. 77–116° (Skellysolve D). After two more recrystallizations from petroleum ether, b.p. 60–71° (Skellysolve B), rosettes of needles were obtained (15 mg.), melting at 171.5–172.5°.

Anal. Calc'd for $C_{17}H_{16}N_2$: C, 82.2; H, 6.5.; N, 11.3.
Found: C, 82.4; H, 6.4; N, 11.4.

The *picrate* was prepared in alcohol and recrystallized five times from 90% alcohol, in which it is sparingly soluble. It formed yellow rhombic prisms melting, with decomposition, above 267°.

Anal. Calc'd for $C_{17}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 57.9; H, 4.0.
Found: C, 58.3; H, 3.8.

The free base (Base A) gives no color with vanillin-hydrochloric acid solution, nor with Ehrlich's reagent. In alcoholic hydrochloric acid solution, it exhibits a strong blue fluorescence. It is probably a substituted β-carboline.

The oily portion of the residue obtained above from the benzene eluate did not crystallize

on long standing at 0°; therefore, the oil was dissolved in absolute alcohol and the basic picrates were precipitated by addition of a saturated picric acid solution in absolute alcohol. The insoluble yellow picrates obtained were once recrystallized from aqueous alcohol and then fractionally crystallized from the same solvent. This was done by taking up the picrates in about 100 cc. of hot 90% alcohol. The material which remained insoluble was in turn recrystallized from a large volume of aqueous alcohol, from which monoclinic rods separated on cooling. These were recrystallized three times from aqueous alcohol and yielded 10 mg. of yellow monoclinic rods which melted at 261°, with decomposition and foaming.

Anal. Calc'd for $C_{16}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 56.8; H, 4.1; N, 15.1.
Calc'd for $C_{16}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 56.5; H, 4.5; N, 15.0.
Found: C, 56.6; H, 4.4; N, 15.1.

It is not possible to decide the empirical formula of this substance (Base B) merely on the basis of the analysis of the picrate alone, although $C_{16}H_{18}N_2$ is favored.

The more soluble of the picrates was obtained crystalline upon concentration and cooling of the original 90% alcoholic solution, after previous filtration from the insoluble picrate. The more soluble picrate was then recrystallized five times from absolute alcohol, yielding 15 mg. of long yellow needles which melted with decomposition at 203.5–205.5°.

Anal. Calc'd for $C_{17}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 57.6; H, 4.4; N, 14.6.
Found: C, 57.6; H, 4.6; N, 14.6.

The empirical formula for this base (Base C) is probably $C_{17}H_{18}N_2$; it is certainly not identical with Base A, of empirical formula, $C_{17}H_{16}N_2$, since their picrates have different crystalline forms and different melting points.

The aluminum oxide column, after benzene elution, was eluted with dry ether. The ethereal solution was evaporated to dryness, leaving 100 mg. of impure crystals. These were recrystallized three times from benzene, giving needles and prisms, with the latter as the stable form, melting at 238–240°. A mixed melting point with an authentic sample of harman was 238–241°, thus proving its identity with *harman* (I). It should be noted that harman is obtained in much smaller yield (100 mg. from 5 g.) from potassium hydroxide fusion of tetrahydroalstonine than from similar fusion of alstonine itself (1.5 g. from 10 g.).

Following ether elution, the aluminum oxide column was eluted with acetone, and 10 mg. of solid crystalline material was obtained upon evaporation of the acetone solution to dryness. After five recrystallizations from benzene, the substance formed white needles (approximately 2 mg.) which melted at 195.5°.

The *picrate* of the above base was made in alcohol solution from the mother liquor obtained above. It was recrystallized, with decolorizing carbon, from alcohol. After eight more recrystallizations from alcohol, golden yellow needles were obtained which melted at 262–263°, with decomposition. The amount of material was insufficient for analysis. However, the melting point of the base was suggestive of that of norharman (II). Therefore, the latter was prepared according to Kermack, Perkin, and Robinson (11), and melted at 196°. The melting point of mixtures of the base in question and norharman was not depressed. Similarly synthetic norharman picrate melted at 261–263° with decomposition and showed no depression of melting point when mixed with the picrate of the above base which is, therefore, *norharman* (β-carboline).

The original potassium hydroxide solution, following fusion, solution, and ether extraction, was made acid to *p*H 3 with hydrochloric acid and thoroughly extracted with ether. The ethereal solution was then extracted in turn with water, 5% sodium bicarbonate, 5% sodium carbonate, and finally with 10% sodium hydroxide solution. Each of the aqueous extracts obtained was subsequently acidified with hydrochloric acid and extracted with ether. Each ether solution was dried and the solvent removed. The ethereal solution obtained from the water-soluble fraction had the odor of a low molecular weight fatty acid, but the residue remaining after removal of the ether underwent decomposition, leaving a dark, oily, intractable tar. The carbonate and hydroxide fractions did not yield any appreciable residues upon evaporation of their respective ether extracts. Upon evaporation of

the ether solution obtained from the bicarbonate fraction, a brown oil remained which was distilled in a vacuum-sublimation apparatus. Two fractions were obtained: (a) 110–170° bath temperature and 0.2 mm.; (b) above 170° bath temperature and 0.2 mm. Decarboxylation took place during the distillation. Fraction (a) was redistilled at the same bath temperature and pressure, and the distillate was recrystallized, with decolorization, from benzene. After five recrystallizations from benzene, 55 mg. of colorless plates was obtained, melting at 205.5–206°.

Anal. Calc'd for $C_9H_7NO_2$: C, 67.0; H, 4.3; N, 8.7.
Found: C, 67.0; H, 4.4; N, 8.7.

The compound gave no color with vanillin-hydrochloric acid reagent and no color with Ehrlich's reagent, indicating that, if it is an indole derivative, it has not a free α-position. The compound was insoluble in cold water, but readily soluble in cold, dilute alkali. It gave a red-brown color with ferric chloride solution. The empirical formula of the acid, its melting point, and crystalline form, together with its chemical properties, suggested its identity with *indole-α-carboxylic acid* (III). Ciamician and Zatti (12) described this acid as separating from benzene as platelets, melting at 203–204° and giving a red-brown color with ferric chloride solution. They also describe the methyl ester as needles melting at 151–152°.

The *methyl ester* of the acid obtained above was prepared according to Ciamician and Zatti, using methyl alcohol saturated with hydrogen chloride. It was recrystallized twice from benzene, from which it was obtained as needles which melted at 150–151.5°. Since the melting point of this methyl ester corresponds to that for methyl indole-α-carboxylate, and since the melting point of the compound in question corresponds to that for indole-α-carboxylic acid, the identity of the acid obtained above may be considered established.

Thermal decomposition of alstonine. Alstonine was freshly prepared from 4 g. of alstonine hydrochloride and the calculated amount of potassium hydroxide. The free alstonine formed (*ca.* 3.6 g.) was dried and heated rapidly in a sublimation apparatus to 300° sand-bath temperature, then kept at 310–330° bath temperature for 1 hr. The sublimate was dissolved in ether and the solution was extracted five times with 10% hydrochloric acid. The ethereal solution was then washed with water, dried, and evaporated to dryness. The neutral residue, in alcoholic solution, gave a blue-violet color with Ehrlich's reagent reminiscent of β-substituted indoles such as skatole. No attempt was made to purify this small amount of neutral material pending accumulation of larger amounts.

The combined hydrochloric acid extracts were made alkaline with sodium hydroxide, extracted with ether, and the ethereal solution was dried and evaporated to dryness. The residue was distilled over a wide temperature range *in vacuo* and then redistilled at 120–170° bath temperature and 0.15 mm. pressure. The sticky orange distillate was dissolved in alcohol and treated with a saturated alcoholic solution of picric acid, yielding a copious yellow precipitate. The precipitated picrates were separated by fractional crystallization, following the course of the separation by means of melting points and microscopic examination of the crystals obtained at each crystallization. The picrates were digested in about 250 cc. of hot absolute alcohol; that which remained undissolved was filtered off and recrystallized twice from a large volume of absolute alcohol and then twice from 95% alcohol, in which it was more soluble. Yellow monoclinic prisms were obtained, melting, with decomposition, at 254–256° (picrate of Base D).

Anal. Calc'd for $C_{17}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 57.6; H, 4.4; N, 14.6.
Found: C, 57.4; H, 4.5; N, 14.8.

This picrate is not identical with the picrate of Base C, which has the same empirical formula on the basis of analysis: the melting-decomposition points of the picrates are 50° apart.

The picrates which dissolved originally in the hot absolute alcohol (above) were further separated into two fractions: a more insoluble picrate, separating as very small, fine needles, and a more soluble picrate, obtained on concentration of the mother liquors, which separated as long, slender needles. The latter, or more soluble picrate, was recrystallized several

times from absolute alcohol and formed long yellow needles which melted at 193.5–195° (picrate of Base E).

Anal. Calc'd for $C_{18}H_{20}N_2 \cdot C_6H_3N_3O_7$: C, 58.5; H, 4.7; N, 14.2.
Calc'd for $C_{19}H_{22}N_2 \cdot C_6H_3N_3O_7$: C, 59.1; H, 5.0; N, 13.8.
Found: C, 58.7; H, 4.9; N, 13.9.

The less soluble picrate, which separated as very small, fine needles, was recrystallized several times from absolute alcohol and twice from 80% alcohol. The clusters of yellow needles melted, with decomposition, at 261–262.5° (picrate of Base F).

Anal. Calc'd for $C_{13}H_{12}N_2 \cdot C_6H_3N_3O_7$: C, 53.7; H, 3.6; N, 16.5.
Found: C, 53.9; H, 3.8; N, 16.7.

The *free base* (Base F) was prepared by dissolving the picrate in a large amount of water, in which it is sparingly soluble. The resulting solution was made strongly acid with conc'd hydrochloric acid and the picric acid was removed by exhaustive extraction with ether. The aqueous solution, which exhibited a strong blue fluorescence, was rendered strongly alkaline with sodium hydroxide and extracted with ether. The total ether extract was dried and the solvent removed, leaving a brownish-yellow oil. This was taken up in ligroin (Skellysolve D) plus just sufficient benzene to dissolve it at the boiling temperature. On cooling, some oily material settled out; this was centrifuged down, the supernatant liquor was poured off and concentrated. After standing 1 week in the ice-box, crystals formed, which were recrystallized from ligroin plus the minimum quantity of benzene. Fifteen milligrams of long white, rectangular rods were obtained, melting at 79–81°. The compound gave no color with Ehrlich's reagent or with vanillin-hydrochloric acid reagent.

Anal. Calc'd for $C_{13}H_{12}N_2$: C, 79.6; H, 6.2.
Found: C, 79.5; H, 6.4.

The *hydrochloride* of the $C_{13}H_{12}N_2$ base separated in clusters of fine white needles from alcohol, turning brown at 227° and undergoing final decomposition and liquefaction at about 275°. The hydrochloride is hygroscopic; it exhibits a strong blue fluorescence in water or alcohol solution.

The *methiodide* of Base F was prepared by refluxing the base in benzene solution with excess methyl iodide. Recrystallized from absolute alcohol, it separated as fine, pale yellow needles, melting, with decomposition, at 283–284°. The methiodide also exhibits a blue fluorescence in solution. Considerable difficulty was encountered in burning the methiodide on analysis, so that the figures left something to be desired.

Anal. Calc'd for $C_{14}H_{15}IN_2$: C, 49.7; H, 4.5.
Found: C, 49.1; H, 4.5.

Since the empirical formula of Base F corresponded to an ethyl-, or dimethyl-β-carboline, and since the fluorescence, absorption spectrum, and other general properties of the base showed close similarity to a carboline, 1-ethyl-β-carboline (IV) was prepared on the basis of an experimentally determined value of 3.5% of N-alkyl groups (calculated as ethyl) found with the picrate of Base F.[1]

N-nitrosoethylaniline. The method for N-nitrosomethylaniline described in "Organic Syntheses" (13) was employed, starting with 242 g. (2 moles) of ethylaniline and using proportionate amounts of the other reagents. A 270 g. or 90% yield of N-nitrosoethylaniline was obtained as a light yellow liquid, boiling at 125–126° at 17 mm. Schmidt (14) describes boiling points of 119.5–120° at 15 mm. and 133° at 19 mm.

α-Ethyl-α-phenylhydrazine. The method for α-methyl-α-phenylhydrazine described in "Organic Syntheses" (15) was employed, starting with 270 g. (1.8 moles) of N-nitrosoethylaniline and using proportionate amounts of the other reagents. The product was twice fractionally distilled, and two main fractions were obtained: (a) 59.0 g. boiling at 102–110° at 13.5 mm., n_D^{26} 1.5567; (b) 121.0 g. (49% yield) boiling at 114–116° at 13.5 mm., n_D^{26} 1.5642. The boiling point under vacuum has not been recorded previously; the boiling point of α-methyl-α-phenylhydrazine, obtained by this method in 52–56% yield, is 106–109° at 13 mm.

[1] N-Alkyl determination by Mr. D. Rigakos, Rockefeller Institute.

Benzaldehyde α-ethyl-α-phenylhydrazone was prepared from fraction (b) and pure benzaldehyde, and after two recrystallizations from water-alcohol, the compound melted at 49°. Michaelis and Phillips (16) report the melting point 49° for the α-ethyl-α-phenylhydrazone of benzaldehyde. Fraction (b) was used in subsequent reactions.

Diethylacetal of γ-aminobutyraldehyde. This compound was prepared in good yield according to the method of Manske (8), starting with acrolein, hydrobrominating this to give the diethylacetal of β-bromopropionaldehyde, then replacing the bromine with the cyano group, and finally reducing the diethylacetal of β-cyanopropionaldehyde (n_D^{25} 1.4162) with sodium and alcohol to yield the diethylacetal of γ-aminobutyraldehyde, boiling at 85° at 11 mm., n_D^{25} 1.4266. Manske reports the boiling point 84° at 11 mm.

1-Ethyltryptamine. This was made according to the method employed by Manske for the preparation of tryptamine. A mixture of 40 g. (0.25 mole) of the above acetal and 35 g. (0.26 mole) of α-ethyl-α-phenylhydrazine contained in a 500-cc. round-bottom flask, was treated with 34 g. (0.25 mole) of finely powdered, freshly fused zinc chloride. The mixture was heated together, finally under reflux, until the end of the vigorous exothermic reaction. The product, upon cooling, was dissolved in acetic acid (30 g. of glacial acetic acid and 50 g. of water). Three hundred cubic centimeters of water was added and the zinc was precipitated by a stream of hydrogen sulfide. After filtration, the filtrate was made alkaline with sodium hydroxide and extracted with ether. The ethereal solution was dried, the solvent removed, and the residue distilled *in vacuo*, with fractionation, giving the following fractions: fraction (a) 9.1 g. boiling below 165° at 2 mm.; fraction (b) 18.0 g. (38% yield) boiling at 165–175° and 2 mm. Fraction (b), on redistillation, boiled at 170–171° and 2 mm., giving a pale yellow liquid; n_D^{26} 1.5821.

Anal. Calc'd for $C_{12}H_{16}N_2$: C, 76.5; H, 8.6; N, 14.9.
Found: C, 76.5; H, 8.6; N, 14.9.

The *phthalimide* was prepared according to the method of Manske for the same derivative of 1-methyltryptamine. It formed long, monoclinic needles from absolute alcohol and melted at 149–150°.

Anal. Calc'd for $C_{20}H_{18}N_2O_2$: C, 75.5; H, 5.7.
Found: C, 75.3; H, 5.8.

The *picrate* of 1-ethyltryptamine was made in alcohol solution and recrystallized from absolute alcohol as stout, orange, monoclinic prisms, melting at 178.5–180.5°.

Anal. Calc'd for $C_{18}H_{19}N_5O_7$: C, 51.8; H, 4.6.
Found: C, 52.0; H, 4.7.

1-Ethyl-2,3,4,5-tetrahydro-β-carboline. The method of preparation was analogous to that used by Späth and Lederer (6) for the preparation of the 1-methyl compound. A solution of 4 g. of 1-ethyltryptamine in 250 cc. of dilute sulfuric acid (2 cc. of conc'd sulfuric acid in 250 cc.), after addition of 5 cc. of 40% formalin, was warmed at 70° for 1 min. The solution was cooled, made alkaline, and extracted with ether, the ether evaporated, and the residue refluxed 45 min. with 2 liters of sulfuric acid (2:250). The resulting solution was cooled, made alkaline, and extracted with ether. The residual yellow oil, after removal of the ether, was dissolved in alcohol. To the alcoholic solution was added picric acid in alcohol solution and the orange picrate thus obtained was recrystallized from alcohol, with decolorizing carbon. The total yield of *1-ethyl-2,3,4,5-tetrahydro-β-carboline picrate* was 7.5 g. or 82%. The orange monoclinic prisms melted at 224–225°.

Anal. Calc'd for $C_{19}H_{19}N_5O_7$: C, 53.2; H, 4.5.
Found: C, 53.6; H, 4.7.

Two grams of the picrate was decomposed by the addition of strong hydrochloric acid to a water suspension which was stirred with benzene on a steam-bath. The benzene layer was removed and a fresh portion of benzene added, this process being repeated until the extraction of picric acid was complete. The acidic solution was then made alkaline with sodium hydroxide and extracted with ether. The ethereal solution was dried and the ether removed, leaving a clear yellow oil which was distilled *in vacuo* at 140–170° bath temperature and 0.2 mm. pressure. The free base could not be obtained crystalline and an analysis was not attempted on the light yellow oil.

The p-*nitrobenzamide* of the secondary amine was made by refluxing 100 mg. of the oil and 100 mg. of pure *p*-nitrobenzoyl chloride for 1 hr. in benzene solution. Benzene and unreacted acid chloride and acid were removed, and the residual crystalline material was recrystallized three times from alcohol, from which the *p*-nitrobenzamide separated as pale yellow, diamond-shaped crystals, melting at 146–148°.

Anal. Calc'd for $C_{20}H_{19}N_3O_3$: C, 68.8; H, 5.5.
Found: C, 68.9; H, 5.6.

1-Ethyl-β-carboline (*IV*). This was prepared by dehydrogenation of the tetrahydrocarboline according to the method employed by Späth and Lederer (6) for making 1-methyl-β-carboline. Six hundred seventy milligrams of 1-ethyl-2,3,4,5-tetrahydro-β-carboline was heated at 160–170°for 45 min. with 1.5 g. of palladium black (one-third of this quantity also gives a good yield). On distillation at 130–160° bath temperature and redistillation at 130–140° bath temperature and 0.2 mm. pressure, a straw-yellow oil was obtained. When this oil was taken up in petroleum ether (Skellysolve B) and the minimum quantity of benzene necessary for solution, crystals formed very slowly on long standing. The colorless regular prisms melted at 41–42° after two slow recrystallizations from benzene-petroleum ether.

Anal. Calc'd for $C_{13}H_{12}N_2$: C, 79.6; H, 6.2; N, 14.3.
Found: C, 79.2; H, 6.2; N, 14.4.

The *picrate* of 1-ethyl-β-carboline was made in alcohol solution and recrystallized three times from alcohol, in which it is but slightly soluble, giving long, golden-yellow needles, melting at 227–228°.

Anal. Calc'd for $C_{19}H_{15}N_5O_7$: C, 53.7; H, 3.6.
Found: C, 54.0; H, 3.8.

The *methiodide* was made by refluxing the free base with excess methyl iodide in benzene. It separated from absolute alcohol as pale yellow needles, melting at 293–295°.

Anal. Calc'd for $C_{14}H_{15}IN_2$: C, 49.7; H, 4.5.
Found: C, 49.9; H, 4.8.

1-Ethyl-β-carboline (IV) is not, therefore, identical with Base F, since the melting points of the free bases, picrates, and methiodides are not the same.

In addition, the other possible N-ethyl-β-carboline, namely *3-ethyl-β-isocarboline* (*VI*), was synthesized for comparison with Base F.

Norharman ethiodide was prepared by refluxing 400 mg. of norharman in dry benzene with excess ethyl iodide. The insoluble ethiodide was recrystallized from absolute alcohol, from which it separated as pale yellow needles melting at 198–199°.

3-Ethyl-β-isocarboline (*VI*). This was prepared according to the method of Fischer (19) and Perkin and Robinson (20) for making methylharmine and methylnorharmine. A water solution of 600 mg. of norharman ethiodide was treated with excess sodium hydroxide solution. The yellow crystalline precipitate was recrystallized twice from water, from which it separated slowly as yellow plates; these softened and bubbled on slow heating, with final melting taking place at 176.5–178.5°. The material was dried *in vacuo* over phosphorus pentoxide for 12 hrs. at room temperature, then for 5 hrs. at 100°. The partially dehydrated sample was taken up in boiling toluene and boiled down to small volume. A further portion of dry toluene was added and the solution boiled down again. This process was repeated several times. Upon cooling of the conc'd toluene solution, flocculent yellow needles separated which were recrystallized once from dry toluene and twice from dry benzene. The yellow, hygroscopic needles melted at 176.5–178.5° (VI).

Anal. Calc'd for $C_{13}H_{12}N_2$: C, 79.6; H, 6.2.
Found: C, 79.6; H, 6.3.

3-Ethyl-β-isocarboline ethiodide (*VII*). The ethiodide was prepared by refluxing 3-ethyl-β-isocarboline in dry benzene with excess ethyl iodide. The precipitated ethiodide crystallized from absolute alcohol as very pale yellow needles which melted at 213.5–215°.

Anal. Calc'd for $C_{13}H_{12}N_2 \cdot C_2H_5I$: C, 51.1; H, 4.9.
Found: C, 50.9; H, 5.0.

The *ethiodide* of *1-ethyl-β-carboline* (*IV*), which was prepared in a similar manner, like-

wise separated from absolute alcohol as very pale yellow needles melting at 213.5–215°. As would be expected (21), this ethiodide proved identical in every way with VII, and mixed melting points of the ethiodides prepared by the two methods showed no depression.

2-Ethyl-β-carboline was prepared by heating 500 mg. of tryptophan in dilute sulfuric acid with 15 cc. of 12% propionaldehyde solution, followed by oxidation with potassium dichromate; the method was exactly like that employed by Kermack, Perkin, and Robinson (11) for the preparation of the next lower homolog, 2-methyl-β-carboline, or harman. The compound separated from benzene as prisms and melted at 193–195°, as reported by Späth and Lederer (6) for the same compound prepared by a different method.

Zinc dust distillation of alstonine. This reaction was carried out both in an atmosphere of hydrogen and under normal atmospheric conditions, with no appreciable difference in the final result. For the distillation in a stream of hydrogen, the apparatus used was similar to that described by Jacobs and Craig (17); for distillation in air, a wide knee-tube was used. A mixture of 2 g. of alstonine and 50 g. of zinc dust was heated in a sand-bath for 1 hr. at 300-350°, after raising the temperature rapidly to this region. The distillate was dissolved in ether, extracted with 10% hydrochloric acid, and then the ethereal solution was washed with water. The neutral material obtained on evaporation of the ether gave a blue color with Ehrlich's reagent. The color was similar to that shown by β-alkyl indoles. However, no chemical individual could be isolated from this fraction. The hydrochloric acid solution was made alkaline and extracted with ether. The ether was removed and the residue was twice distilled *in vacuo* at 140–180° bath temperature and 0.2 mm. The distillate was dissolved in benzene (300 mg. in 50 cc.) and chromatographed on 6 g. of aluminum oxide (Brockmann). Three main rings were obtained, which were developed and eluted with benzene. No pure chemical individual could be obtained from the first and third zones, nor could any crystalline picrate be obtained from their solutions. The benzene eluate of the second zone was treated with dry picric acid in benzene, and a crystalline picrate was obtained. This was filtered off and recrystallized many times from alcohol, from which it finally separated as clusters of fine yellow needles, melting with decomposition at 261–263°. A mixed melting-decomposition point with the picrate of Base F showed no depression.

Reduction of tetrahydroalstonine with sodium and butyl alcohol. Hexahydroalstonol. To 100 cc. of boiling *n*-butyl alcohol was added 2 g. of tetrahydroalstonine; when solution was complete 8 g. of sodium was added quickly in small portions. The solution became slightly yellow, and when all the sodium had dissolved, the solution was cooled rapidly and poured quickly into 5% hydrochloric acid. If allowed to cool slowly, the solution turned red, but this color change, with the subsequent difficulty in obtaining a pure, colorless product, could be circumvented by rapid cooling. The resulting acidic mixture was steam-distilled to free it from butyl alcohol. The yellow solution remaining in the distilling flask was made strongly basic with sodium hydroxide solution and extracted with chloroform. The total chloroform extract was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The yellow crystalline residue was recrystallized three times from 90% alcohol, and yielded 800 mg. of material; this was recrystallized from absoute alcohol, from which it separated as tiny, well-formed prisms which melted at 282–284° with decomposition. It showed $[\alpha]_D^{27}$ −78° ± 3° (c = 0.338 in pyridine) as compared with $[\alpha]_D^{27}$ −88° ± 2° for tetrahydroalstonine in pyridine.

Anal. Calc'd for $C_{20}H_{26}N_2O_2$: C, 73.6; H, 8.0; N, 8.6.
Found: C, 73.3, 73.5; H, 8.0, 8.1; N, 8.8.

The *picrate* was prepared in alcohol and after three recrystallizations from alcohol, formed small, stout yellow prisms which melted at 237–238° with decomposition.

Anal. Calc'd for $C_{20}H_{26}N_2O_2 \cdot C_6H_3N_3O_7$: C, 56.2; H, 5.3; N, 12.6.
Found: C, 55.9; H, 5.2; N, 12.5.

The above $C_{20}H_{26}N_2O_2$ compound could not be obtained from the reduction of alstonine itself with sodium and butyl alcohol; as a matter of fact, no crystalline product could be obtained from this reaction.

The acetate was prepared by refluxing the free base with acetic anhydride for 1 hr. and

also by warming it with pyridine and acetic anhydride; however, the optimum conditions were the following: 50 mg. of base was dissolved in 5 cc. of anhydrous pyridine and 0.4 cc. of redistilled acetic anhydride was added. The solution was allowed to stand 5 days at 25°, well-stoppered and in the absence of light. To the straw-yellow solution was added 3 cc. of methyl alcohol and the solution was evaporated to dryness *in vacuo*. This process was repeated several times with methyl alcohol and finally with water. The crystalline residue was decolorized with charcoal in alcoholic solution and recrystallized five times from absolute alcohol, yielding colorless crystals, mainly in the form of tetragonal bipyramids, which melted at 95–96°.

Anal. Calc'd for $C_{24}H_{30}N_2O_4$: C, 70.2; H, 7.4; N, 6.8.
Calc'd for $C_{22}H_{28}N_2O_3$: C, 71.7; H, 7.7; N, 7.6.
Found: C, 71.4; H, 7.6; N, 7.6.

The *picrate of acetylhexahydroalstonol* was prepared in alcohol solution, from which it separated after boiling and long standing. It formed small yellow plates after five recrystallizations from alcohol, and melted, with decomposition, at 223–224.5°.

Anal. Calc'd for $C_{24}H_{30}N_2O_4 \cdot C_6H_3N_3O_7$: N, 10.9.
Calc'd for $C_{22}H_{28}N_2O_3 \cdot C_6H_3N_3O_7$: N, 11.7.
Found: N, 11.9.

The Zerewitinoff determinations were carried out in dry pyridine in an atmosphere of dry nitrogen (18).

TABLE I

ZEREWITINOFF ACTIVE HYDROGEN DETERMINATION

SUBSTANCE	MOLES CH_4 PER MOLECULE
Yohimbine hydrochloride	3.2
Tetrahydroalstonine	1.28
Alstonine hydrochloride	2.3
Alstonine acid sulfate	3.2

The ultra violet absorption spectra measurements were done with a Hilger rotating sector quartz spectrophotometer using Eastman Process plates.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. The formula of alstonine has been definitely checked as $C_{21}H_{20}N_2O_3$.

2. From the products of alkali fusion of alstonine and tetrahydroalstonine, harman, norharman, indole-α-carboxylic acid, and three bases of undetermined structure, probably β-carboline derivatives, have been obtained.

3. Thermal decomposition of alstonine leads to the formation of three bases of undetermined structure, but which are apparently β-carboline derivatives.

4. Reduction of tetrahydroalstonine with sodium and butyl alcohol leads to a new base, hexahydroalstonol, $C_{20}H_{26}N_2O_2$, the absorption curve for which is identical with that of yohimbine and α,β-dimethylindole.

5. 1-Ethyl-β-carboline and 3-ethyl-β-isocarboline have been prepared.

6. A partial structure for alstonine is discussed.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

ALSTONIA ALKALOIDS. II. A NEW ALKALOID, ALSTONILINE, FROM *A. CONSTRICTA*

W. LINCOLN HAWKINS[1] AND ROBERT C. ELDERFIELD

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In a previous communication (1) attention has been called to the fact that infusions of various species of *Alstonia* are reported to function as febrifuges in the treatment of malaria. Studies on the antimalarial activity of various isolated alkaloids have shown, however, that these bases are inactive, or only slightly active, on birds infected with *Plasmodium inconstans* (2, 3, 4). It has also been pointed out (1) that possible oxidative changes may occur during isolation of the alkaloids with resultant loss in physiological activity. In the present investigation, a new alkaloid, alstoniline, has been isolated from *A. constricta* and has been found to be unusually susceptible to atmospheric oxidation. Probably because of its susceptibility to oxygen, alstoniline has not been isolated in previous investigations of *A. constricta* (3, 5). In the form in which it exists in crude alcoholic extracts, alstoniline is readily oxidized yielding a crystalline oxidation product. This oxidation probably takes place during concentration of the extracts as described by Sharp (3), the product then being dispersed through the various larger alkaloid fractions.

In the present investigation, crude extracts of the bark were first acidified with hydrochloric or sulfuric acids and the resultant salts of alstoniline were found to be somewhat more stable to oxidation. By concentrating the acidified extracts in an atmosphere of nitrogen, the salts were obtained, together with large amounts of resinous material, as insoluble precipitates. From these crude precipitates, alstoniline hydrochloride or sulfate was recovered by aqueous extraction. Both of the salts are characterized by their intense red color and by their slight solubility in water and organic solvents.

Alstoniline is a minor alkaloid of *A. constricta*, amounting to 0.02–0.05% of the bark. From a study of the crystalline base and several of its derivatives, the formula, $C_{22}H_{18}N_2O_3$, has been established for alstoniline. The base also exists, however, as a crystalline monohydrate, $C_{22}H_{18}N_2O_3 \cdot H_2O$. Derivatives of alstoniline fall into two groups, depending on whether or not this molecule of water is present. Alstoniline monohydrate is obtained on neutralization of the hydrochloride, which contains a molecule of water of crystallization, whereas the anhydrous form of the base results from neutralization of the sulfate which is not hydrated. All derivatives of alstoniline monohydrate contain a molecule of water, but derivatives of the anhydrous base may or may not be associated with water. These various relationships are summarized in Figure 1. Apparently the monohydrate exists in the original extracts since the anhydrous base is converted into it on recrystallization from 95% alcohol. The conversion to the monohydrate may also be accomplished by preparing the hydrochloride

[1] National Research Council Fellow in Chemistry, 1941–42.

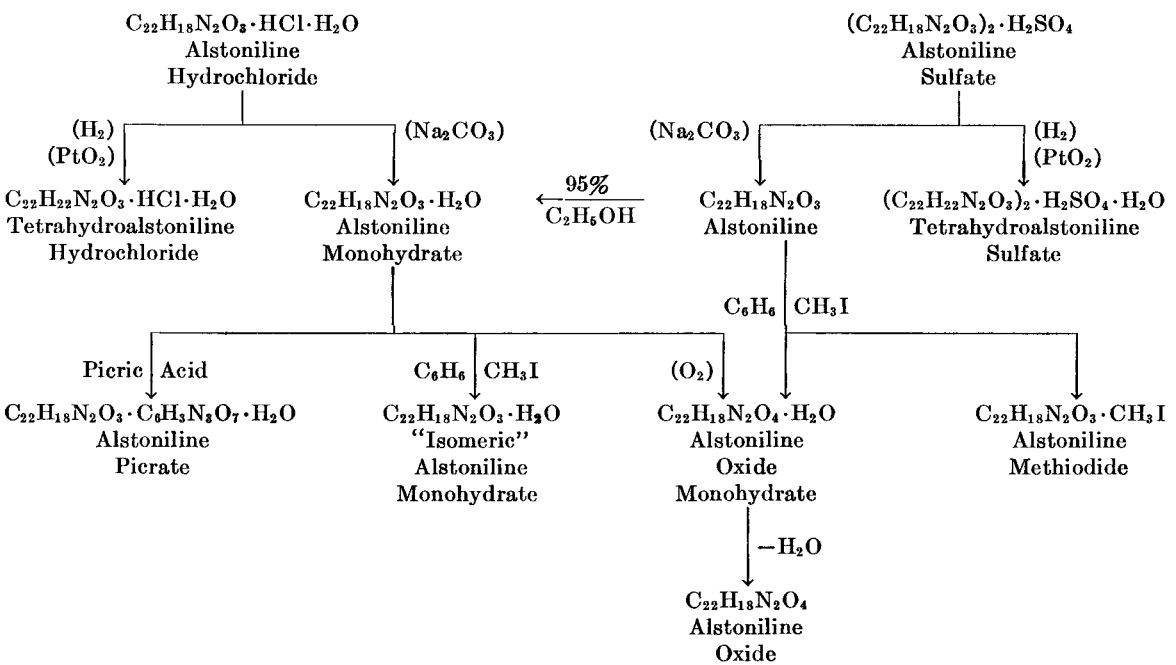
$C_{22}H_{18}N_2O_3 \cdot HCl \cdot H_2O$
Alstoniline
Hydrochloride
(H_2)
(PtO_2)
(Na_2CO_3)
$C_{22}H_{22}N_2O_3 \cdot HCl \cdot H_2O$
Tetrahydroalstoniline
Hydrochloride
$C_{22}H_{18}N_2O_3 \cdot H_2O$
Alstoniline
Monohydrate
95%
C_2H_5OH
$(C_{22}H_{18}N_2O_3)_2 \cdot H_2SO_4$
Alstoniline
Sulfate
(Na_2CO_3)
(H_2)
(PtO_2)
$C_{22}H_{18}N_2O_3$
Alstoniline
$(C_{22}H_{22}N_2O_3)_2 \cdot H_2SO_4 \cdot H_2O$
Tetrahydroalstoniline
Sulfate
C_6H_6
CH_3I
Picric Acid
C_6H_6
CH_3I
(O_2)
$C_{22}H_{18}N_2O_3 \cdot C_6H_3N_3O_7 \cdot H_2O$
Alstoniline
Picrate
$C_{22}H_{18}N_2O_3 \cdot H_2O$
"Isomeric"
Alstoniline
Monohydrate
$C_{22}H_{18}N_2O_4 \cdot H_2O$
Alstoniline
Oxide
Monohydrate
$C_{22}H_{18}N_2O_3 \cdot CH_3I$
Alstoniline
Methiodide
$-H_2O$
$C_{22}H_{18}N_2O_4$
Alstoniline
Oxide

FIGURE 1

from anhydrous alstoniline, under conditions used in extraction of the bark. The base liberated on neutralization of this salt is alstoniline monohydrate. Similarity between the ultra-violet absorption curves (Fig. 2) of alstoniline and alstoniline monohydrate indicates that hydration does not involve a basic change in the arrangement of double bonds of the two substances.

The behavior of alstoniline monohydrate under conditions of atmospheric oxidation is noteworthy. When alcoholic solutions of the base were aerated for several hours, one atom of oxygen was absorbed and a crystalline oxidation

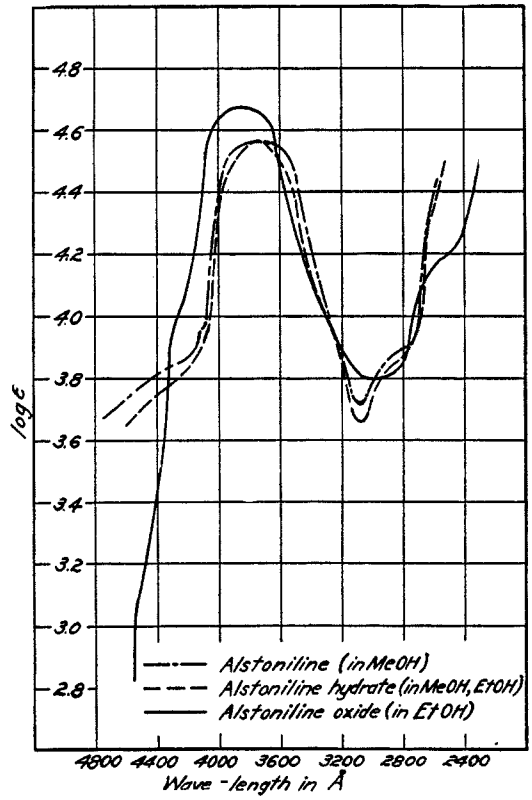

FIGURE 2

product, $C_{22}H_{18}N_2O_4 \cdot H_2O$, was formed. Pending definite elucidation of the mode of formation of this substance, we suggest that it be designated alstoniline oxide. More striking is the behavior of alstoniline monohydrate on catalytic reduction with platinum oxide. Two moles of hydrogen were absorbed during the reduction, and the color of the solution changed from a deep orange-red to a strongly fluorescent yellow. However, during exposure to air in working up the product, the hydrogen taken up during the reduction was lost, an atom of oxygen was absorbed and the above alstoniline oxide monohydrate resulted. Such a change during recrystallization of the product was indicated by varia-

tion in the melting point, which remained constant during several crystallizations and then rose as much as twenty degrees on a subsequent recrystallization. Likewise, analyses of the product at various stages of purification showed a carbon content ranging progressively from that of the expected reduction product to that of alstoniline oxide monohydrate. Attempts to isolate the reduced base by recrystallization under nitrogen were unsuccessful. However, in contrast to the behavior of the free base, alstoniline hydrochloride absorbed two moles of hydrogen on catalytic reduction and alstoniline sulfate absorbed four moles. Moreover, the products of the reduction of the salts were stable to atmospheric oxidation. At present no explanation of the nature of the unsaturated system which is responsible for the reversible reduction of alstoniline hydrate, and for the apparently irreversible reduction of its salts, suggest itself.

The ease with which reduced alstoniline underwent oxidation suggested that possibly the base might have undergone isomerism under the conditions of the reduction, although no isomeric base could be isolated. However, in one experiment, a second form of alstoniline monohydrate was obtained in small amounts, when the preparation of a methiodide was attempted in benzene solution. This melted at 189–190° as contrasted with the usually observed melting point of 356° for alstoniline monohydrate. The second form underwent atmospheric oxidation in the solid state, and more rapidly in solution, yielding alstoniline oxide. Unfortunately we have been unable to work out an exact procedure for obtaining this substance with the amount of material at present available. In subsequent experiments, despite the use of precautions to exclude oxygen, only alstoniline oxide was obtained.

All derivatives of alstoniline which were examined were found to be optically inactive. Alstoniline monohydrate gave a negative result with Ehrlich's reagent. In the Adamkiewicz reaction as modified by Harvey, Miller, and Robson (6), tetrahydroalstoniline sulfate gave a color change from blue to olive green, similar to that observed with tetrahydroalstonine. Inasmuch as this reaction is considered indicative of a tetrahydro-β-carboline ring system, alstoniline probably contains this nucleus. Alstoniline monohydrate gave an entirely different color series with this reagent. The presence of two methoxyl groups in alstoniline oxide was indicated by analysis.

Physiological examination of *A. constricta* and its alkaloid fractions was made possible through the kindness of Dr. John Maier of the Rockefeller Foundation. Finely ground *A. constricta* bark was found to be inactive in dosages of 150 mg. per day in birds infected with avian malaria. The total alkaloid fraction, obtained by Sharp's procedure (3), and which presumably contained alstoniline as the oxide, was inactive in dosages of 60 to 120 mgm. per day both as the free bases and as the hydrochlorides. This sample also showed no activity toward sporozoite transmitted infections in dosages of 90 mg. per day. The free bases from fractions II and III (see Experimental) were found to be inactive in dosages of 30 mg. per day in avian malaria. The possiblity that alstoniline, in its unoxidized form, may be active, is now under consideration.

EXPERIMENTAL

All melting points have been corrected for stem exposure. Those designated as "B" were taken in a copper melting point block.

Extraction of Alstonia constricta *bark.* *Alstonia constricta* bark[2] (30 lbs.), ground to 60 mesh in a ball mill, was moistened with sufficient 95% alcohol to cover the bark. After standing at room temperature for two days with occasional stirring, the moist bark was pressed in an hydraulic press. The alcoholic extracts from six such treatments were combined and acidified with hydrochloric acid [27 cc. of hydrochloric acid (1.19) and 73 cc. of water]. This acidified solution was then concentrated to approximately three liters at reduced pressure, in an atmosphere of nitrogen. During the concentration, a semi-crystalline solid separated and this precipitate (Fraction I) was filtered off and dried. The yield was 16 g.

The filtrate, after removal of Fraction I, was taken to dryness at reduced pressure and in an atmosphere of nitrogen. The dark, gummy residue was extracted with 0.5% hydrochloric acid (3.5 liters) and this extract was filtered and then diluted with an equal volume of water. The acid extract, in five portions, was adjusted to *p*H 10 with dilute sodium hydroxide solution and the free alkaloids were exhaustively extracted with chloroform. The combined chloroform extracts were then shaken out several times with 0.5% hydrochloric acid. This purification through the free bases was repeated, and the final acid extract was partially neutralized (*p*H 5) with sodium carbonate, and then taken to dryness at reduced pressure under nitrogen. The residue was extracted with absolute alcohol (60 cc.) and this solution was kept at 0° for several days. Crystalline alstonine hydrochloride separated out slowly. The total yield was 70.0 g. or 0.51% of the bark.

The filtrate from the alstonine hydrochloride crystallization was taken to dryness under vacuum in an atmosphere of nitrogen. The glassy, brown residue was dissolved in water and the *p*H of the solution was adjusted to 7.0–7.5 by addition of aqueous sodium bicarbonate. The liberated alkaloid fraction was exhaustively extracted with chloroform and the combined chloroform extracts were shaken out several times with 0.5 *N* hydrochloric acid. The acid extract was partially neutralized (*p*H 5) and taken to dryness at reduced pressure in an atmosphere of nitrogen. The residue was extracted with alcohol and this solvent was then allowed to evaporate off at atmospheric pressure leaving an amorphous residue (Fraction II). The total yield was 19.0 g. or 0.14% of the bark.

The aqueous solution, after extraction of Fraction II, was adjusted to *p*H 8.0–8.5 with aqueous sodium carbonate. The alkaloid fraction was extracted with chloroform and back extracted with 0.5 *N* hydrochloric acid as above. The partially neutralized acid extract (*p*H 5) was evaporated to dryness at reduced pressure in an atmosphere of nitrogen, and the residue was taken up in absolute alcohol (25 cc.). Alstonine hydrochloride crystallized from this solution on addition of an equal volume of ethyl acetate. The total yield was 13.5 g. or 0.10% of the bark, and the over-all yield of alstonine hydrochloride was 0.61% of the bark.

The aqueous solution, from which alstonine hydrochloride had been extracted, was adjusted to *p*H 10 with dilute aqueous sodium hydroxide, and the alkaloid fraction was extracted with chloroform and back extracted with 0.5 *N* hydrochloric acid. Evaporation of the partially neutralized acid extract (*p*H 5) at reduced pressure under nitrogen left a glassy residue which was extracted with alcohol to remove inorganic impurities. An amorphous residue was left on evaporation of the alcohol, and pulverized to a brown powder (Fraction III). The total yield was 7.0 g. or 0.05% of the bark.

Although some tar was formed during this fractionation, the amount was considerably less than that resulting from the use of Sharp's isolation procedure (3).

Isolation of alstoniline hydrochloride and sulfate. Fraction I (3.0 g.) from the preceding

[2] Identified as *A. constricta* F. Muell. by Dr. Heber Youngken of Boston, Mass.

fractionation was treated with boiling water (1200 cc.). A large amount of insoluble residue was removed by filtration and sodium sulfate was added to the filtrate. Alstoniline hydrochloride separated out as a reddish-brown, amorphous solid. The hydrochloride crystallized from methanol as fine, red needles decomposing over a wide range without melting. The yield was 0.5 g. or 0.02% of the bark.

Anal. Calc'd for $C_{22}H_{18}N_2O_3 \cdot HCl \cdot H_2O$: C, 64.0; H, 5.1; N, 6.8.
Found: C, 64.4; H, 5.0; N, 7.0.

Extractions carried out on a one-kilogram scale, in which the bark was vigorously shaken with alcohol for 24-hr. periods, resulted in yields of alstoniline hydrochloride as high as 0.05% of the bark.

Crude alstoniline sulfate was obtained from a similar extraction of *A. constricta* bark (30 lbs.) in which the alcoholic extract was neutralized with an equivalent amount of sulfuric acid. The yield was 14 g. Extraction of this crude product (3.0 g.) with boiling water (1200 cc.) yielded alstoniline sulfate (0.5 g.). The sulfate crystallized from both methanol and ethanol as fine, red needles which melted at 260–264° with decomposition (B).

Anal. Calc'd for $(C_{22}H_{18}N_2O_3)_2 \cdot H_2SO_4$: C, 64.8; H, 4.7; N, 6.9.
Found: C, 65.0; H, 4.8; N, 7.0.

Preparation of alstoniline monohydrate. Alstoniline hydrochloride (0.5 g.) was dissolved in boiling water (100 cc.) and the solution was filtered and cooled. On neutralization with sodium carbonate, the free base separated as a brown, amorphous powder. The yield was 0.4 g. Alstoniline monohydrate, which is only slightly soluble in dilute methanol and ethanol, can be crystallized from either of these solvents by concentrating highly dilute solutions of the base to approximately one-fifth of the original volume and then cooling. On repeated recrystallization from dilute ethanol, alstoniline monohydrate was obtained as fine, yellowish-brown needles decomposing sharply at 356° (B).

Anal. Calc'd for $C_{22}H_{18}N_2O_3 \cdot H_2O$: C, 70.2; H, 5.3.
Found: C, 69.8; H, 5.1.

A *picrate*, prepared from the base monohydrate, crystallized from methanol as red needles decomposing sharply at 294° (B).

Anal. Calc'd for $C_{22}H_{18}N_2O_3 \cdot C_6H_3N_3O_7 \cdot H_2O$: C, 55.5; H, 3.8.
Found: 55.5; H, 3.9.

In an attempt to form a methiodide of alstoniline monohydrate by heating the base (0.1 g.) in benzene (700 cc.) with a large excess of methyl iodide (10 g.) at 60° for seven hours, a base monohydrate giving analytical figures corresponding to alstoniline monohydrate was obtained in 33% yield. The alstoniline monohydrate, which did not dissolve, was removed by filtration, and the filtrate was taken to dryness at reduced pressure. The new base crystallized from dilute alcohol as shiny yellow needles which melted at 189–190°.

Anal. Calc'd for $C_{22}H_{18}N_2O_3 \cdot H_2O$: C, 70.2; H, 5.3.
Found: C, 70.0; H, 5.2.

A small amount of material, containing halogen, separated out during this reaction. Several attempts to repeat this were made, but without success.

The new base proved to be unstable, oxidizing rapidly in the presence of air, both in solution and in the solid form. The product of this oxidation, alstoniline oxide, crystallized from absolute ethanol in two crystalline forms, large yellow rosettes and stout orange needles which were shown by mixed melting point to be the same substance. Both forms melted at 212.5–213.5° and the oxide was identical with that obtained as described below.

Anal. Calc'd for $C_{22}H_{18}N_2O_4 \cdot H_2O$: C, 67.4; H, 5.2; N, 7.1; 2 OCH_3, 15.8; Mol. Wt. 392.
Found: C, 67.5; H, 5.2; N, 7.4; OCH_3 14.4; Mol. Wt., 383.

Alstoniline oxide. Alstoniline monohydrate was aerated in 95% alcoholic solution to yield the oxide monohydrate, which melted at 212–213° and was identical with the substance obtained above.

Anal. Found: C, 67.8; H, 5.2.

The molecule of water of crystallization was removed by prolonged drying over phos-

phoric anhydride at 110°, the anhydrous base melting at 219–221.5°. The water lost was 4.3%. Calc'd for a monohydrate: 4.6%.

Anal. Calc'd for $C_{22}H_{18}N_2O_4$: C, 70.6; H, 4.9.
Found: C, 70.2; H, 5.3.

Preparation of anhydrous alstoniline. Alstoniline sulfate (0.5 g.) was dissolved in hot water (100 cc.) and the resultant solution was filtered. This solution was allowed to cool to incipient crystallization and then neutralized with sodium carbonate and cooled rapidly to room temperature. The anhydrous base, which separated out as a brown, amorphous powder, crystallized from methanol, on concentrating dilute solutions of the base, as fine, yellow-brown needles decomposing sharply at 372° (B). The yield was 0.4 g. Traces of inorganic material, present in this sample, were extremely difficult to remove.

Anal. Calc'd for $C_{22}H_{18}N_2O_3$: C, 73.7; H, 5.1.
Found: C, 73.1; H, 5.0.

On heating the anhydrous base (0.1 g.) in benzene (500 cc.) with a large excess of methyl iodide (10 g.) at 60° for seven hours, an insoluble methiodide was formed in 33% yield. The principal product of the reaction was alstoniline oxide as determined by a mixed melting point. The methiodide, which crystallized from dilute methanol as orange-red needles, decomposed over a wide range without melting.

Anal. Calc'd for $C_{22}H_{18}N_2O_3 \cdot CH_3I$: C, 55.2; H, 4.2.
Found: C, 55.2; H, 4.2.

The anhydrous base formed a picrate which was different from that obtained from alstoniline monohydrate. The picrate of the anhydrous base decomposed explosively above 350° and could not be purified for analysis, apparently due to a gradual decomposition during recrystallization (absolute methanol).

Conversion of anhydrous alstoniline to the monohydrate. Alstoniline (0.08 g.) was dissolved in 95% alcohol (400 cc.) containing 10% water, this concentration being approximately equivalent to that existing in an actual extraction of *Alstonia constricta* bark, and the added water compensating for the moisture content of the bark. The solution was filtered and hydrochloric acid [1 cc. of hydrochloric acid (1.19) and 4 cc. of water] was added to the filtrate. The reaction mixture, which turned red on acidification, was allowed to stand at room temperature for 96 hrs. The free base was then liberated by neutralizing with sodium carbonate, and the brown, amorphous precipitate (0.04 g.) crystallized from dilute alcohol as yellow-brown needles, decomposing sharply at 356° (B).

Anal. Calc'd for $C_{22}H_{18}N_2O_3 \cdot H_2O$: C, 70.2; H, 5.2.
Found: C, 69.9; H, 5.1.

This conversion also took place when the anhydrous base was simply recrystallized from 95% alcohol, but did not occur in methanol or aqueous solutions.

Reduction of alstoniline hydrochloride. Alstoniline hydrochloride (0.1342 g.) was dissolved in absolute methanol (200 cc.) and reduced over platinum oxide (0.07 g.). At first the orange-red solution turned yellow and exhibited a strong fluorescence. Hydrogen uptake was complete at this point, the sample absorbing 2.0 moles in 10 min. The catalyst was removed by filtration and the filtrate was taken to dryness at reduced pressure in an atmosphere of nitrogen, leaving a red, amorphous residue. This product crystallized from absolute alcohol yielding pale yellow, micro-crystals which melted at 231–232° with decomposition.

Anal. Calc'd for $C_{22}H_{18}N_2O_3 \cdot HCl \cdot H_2O$: C, 63.4; H, 6.0; N, 6.7.
Found: C, 63.3; H, 5.7; N, 6.4.

Reduction of alstoniline sulfate. Alstoniline sulfate (0.0918 g.) was dissolved in absolute methanol (175 cc.) and reduced over platinum oxide (0.06 g.). The orange-red solution gradually turned yellow during the first ten minutes, exhibiting strong fluorescence at this point. During the next sixty minutes, the fluorescence disappeared, leaving a pale yellow solution. Reduction was complete in three hours with a hydrogen uptake of 4.04 moles. The catalyst was removed by filtration and the filtrate was taken to dryness at reduced

pressure under nitrogen. The red, amorphous residue crystallized from dilute alcohol and was recrystallized from absolute methanol, yielding pale yellow, micro-crystals which melted at 233–234° with decomposition.

Anal. Calc'd for $(C_{22}H_{16}N_2O_3)_2H_2SO_4 \cdot H_2O$: C, 62.8; H, 5.8; N, 6.7.
Found: C, 62.6; H, 5.7; N, 6.5.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. A new crystalline base, alstoniline, has been isolated from *Alstonia constricta* bark.

2. Reactions of alstoniline have established the susceptibility of this alkaloid to atmospheric oxidation.

3. *Alstonia constricta* and several of its alkaloid fractions have been found to be inactive in avian malaria.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OKLAHOMA AGRICULTURAL AND MECHANICAL COLLEGE]

ARYLAMINE SALTS AS DERIVATIVES FOR IDENTIFYING AROMATIC SULFONIC ACIDS

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It has been suggested repeatedly that arylamine sulfonates be used in identifying the sulfonic acids and their salts; for literature see Chambers and Watt (1) and others (2, 3, 4, 5, 6). Systematic investigation of their value for a wide variety of sulfonic acids, however, does not appear to have been made; much work has dealt with arylamine salts of the dye intermediates only, and then with a view as much toward separation as to characterization. The converse idea of using sulfonates as identifying derivatives of aromatic amines has been considered (2, 7, 8, 9).

Several authors have commented on the lack of agreement in the literature upon the melting points of these derivatives; this diversity, itself a bad sign, has hitherto been ascribed to insufficient drying (6, 9, 10). Only Fieser (6) has explicitly mentioned the undesirable sintering which precedes the melting of so many of these salts, although a few papers imply it by giving some melting points as wide ranges. This behavior has now been found to persist after exhaustive recrystallization and drying, with either slow or rapid heating, and with or without a sealed capillary tube. Reproducibility, as well as reasonable agreement with the best literature values, can be attained by disregarding sintering and calling the melting point the interval between the temperature at which liquid is just visible and that at which the droplets flow down the capillary.

Tables I, II, and III represent compilations of melting point data on the aniline, *o*-toluidine, and *p*-toluidine salts of aromatic sulfonic acids, including both literature values and those obtained in this work. The rather lengthy results of the literature search are recorded here because only a few of the values are in Beilstein or any other survey. When various melting points for the same compound have been reported, only the "best" value (almost always the most recent) is used, but all references are cited. No notice is given to papers reporting preparation but not melting points of amine salts.

It may be admitted at once that some of the melting points tabulated are inconveniently high and blurred by decomposition. Moreover, the values for isomers and for homologs and other structurally related compounds often do not vary sufficiently to ensure differentiation. Aromatic aminosulfonic acids can not be converted to useful arylamine salts without previously subjecting them to acetylation (3, 11) or the Sandmeyer introduction of chlorine (5). The latter has recently been similarly employed to make possible the identification of such amino sulfonic acids in the form of the sulfonamides or sulfonanilides (13).

On the other hand, most of these salts are exceptionally easy to prepare and recrystallize; none of those made in the present work showed any tendency to

TABLE I

ANILINE SALTS OF AROMATIC SULFONIC ACIDS

M.P., °C	SULFONIC ACID
159–161 d	*o*-carbamidobenzene- (17)
165	*o*-sulfobenzoic (18)
170	*p*-phenol- (18)
170–171	6-carbamido-*m*-toluene- (17)
183	naphthalene-1- (2)
183–185	*p*-bromophenylcarbamide - *o* - (17, 19)
186–187	1-naphthol-4- (3)
187	*p* - chlorophenylcarbamide - *o* - (19)
190 d	4 - isopropylnaphthalene - 1 -
191.5	2-amino-5-iodobenzene- (17)
192	*p* - sulfocinnamic acid dibromide (18)
201.9	1-nitronaphthalene-2- (21)
206.5	diphenylamine-4- (22)
206–207	*m*-chlorobenzene- (5)
207	2-nitro-4-chlorobenzene- (23)
208–209	*o*-sulfocinnamic (mono salt) (24)
209–210 d	2-isopropylnaphthalene-1- (20)
210	2-amino-5-chlorobenzene- (17)
180–210 d	*o*-aminobenzene- (17)
209–211	5-methylnaphthalene-2- (25)
d 212	*p*-bromophenylbiuret-*o*- (17)
212–213	*p*-iodophenylbiuret-*o*- (17)
214	2-amino-5-bromobenzene- (17)
215	acetophenone phenylhydrazone-*p*- (26)
215–220	cinnamaldehyde phenylhydrazone-*p*- (26)
218	*o*-toluene- (15)
221	benzaldehyde phenylhydrazone-*p*- (26)
221	anisaldehyde phenylhydrazone-*p*- (26)
221–222	1-benzyl - 4 - benzoylnaphthalene-5- (27)
222	*m*-nitrobenzene- (8)
222–223[a]	*p*-chlorobenzene- (5)
224 d	*p*-phenetole- (18)
224–226	*m*-sulfobenzoic (mono salt) (28)
d 226–229	8-nitronaphthalene-1- (18, 29)
229	2-nitrotoluene-4- (18, 30)
229–230.5[a]	2-chlorotoluene-5-
231–232	acetylnaphthionic (3)
235	1-benzoylnaphthalene - 5 - (27, 31)
234–236[a]	2-bromotoluene-5-
d 236–237	2-amino-5-nitrobenzene- (17)
237–238[a]	*p*-bromobenzene-
238	*p*-toluene- (18, 15, 7, 32, 33, 9)
238 d	*m*-sulfocinnamic (mono salt) (23)
237–239[a]	2-iodotoluene-5-
239	diphenylamine-4,4′-di- (22)
240	2-naphthol-8- (35)
240	benzene- (18, 7, 36)
237–241 d	6-amino-*m*-toluene- (17)
241–242	2-naphthol-3- (36)
246–248 d[a]	2-chloro-3-nitrotoluene-5-
247–249	6-carbamido-*m*-toluene- (17)
249	salicylaldehyde phenylhydrazone-*p*- (26)
248–250	8-methylnaphthalene-2- (37)
249–250[a]	*p*-*t*-butylbenzene-
250	*m*-sulfobenzamide (28)
250–251[a]	*p*-ethylbenzene-
251–252	naphthalene-2,7-di- (38)
252–253	1,8 - dibenzylnaphthalene - 4 - (39)
254	2-naphthol-3,6-di- (35)
254–255[a,b]	3,4-dichlorobenzene-
256	acetyl - 2 - naphthylamine-6- (11)
256–257	3-bromoacenaphthene-β- (40)
256–258[a]	*p*-phenoxybenzene-
256–259[a]	3-nitro-4-bromobenzene-
d 255–260[a]	4-(*p*-nitrophenoxy) benzene-
d 260	5-nitronaphthalene-2- (18)
260–261	3-bromoacenaphthene-α- (40)
259–262 d[a]	2,4-dinitrobenzene-
262–263[a]	2,5-dichlorobenzene-
264	2-naphthol-6- (35)
d 265	5-nitronaphthalene-1- (18)
269[a]	naphthalene-2- (15, 2)
269–271 d[a]	4-nitrotoluene-2- (30)
273	acetyl-1-naphthylamine-8- (11)
d 273–274	3-iodo-5-sulfosalicylic (41)
284	anthraquinone-1- (42, 16)
298–299 d	naphthalene-1,6-di- (4)
300 d	1,8 - dihydroxynaphthalene-3,6-di- (12)
309	anthraquinone-2- (42, 16)
312 d	1-naphthylamine - 3,6,8 - tri- (12)

[a] Value established or confirmed in this work.

[b] Monohydrate when air-dried.

TABLE I—*Continued*

M.P. °C	SULFONIC ACID		
d 340	1-amino - 8 - naphthol-3,6-di- (12)	>345	naphthalene-2,6-di- (38)
344 d	acetyl-1-naphthylamine-5- (11)	d > 200	2-chloro-5-nitrobenzene- (18)
>300	2-naphthol-6,8-di- (35)	d > 200	3-sulfo - 4 - bromobenzoic (mono salt) (18)
>330 d[a]	biphenyl-4,4′-di-	d	naphthalene-1,5-di- (16, 4)

TABLE II

o-TOLUIDINE SALTS OF AROMATIC SULFONIC ACIDS

M.P. °C	SULFONIC ACID		
127.5	*o*-sulfobenzoic (43)	230 d	cinnamaldehyde phenylhydrazone-*p*- (26)
162.5–164[a]	*p*-chlorobenzene-	234–235	*o*-sulfocinnamic (mono salt) (24)
170–172[a]	3,4-dichlorobenzene	235–237 d[a]	2-chloro-3-nitrotoluene-5-
173.5–175[a]	2-chlorotoluene-5-	237	naphthalene-1- (2)
176	benzene- (43, 7)	238	naphthalene-2,7-di- (38)
178–180[a]	2-bromotoluene-5-	242	2-naphthol-8- (35)
182–183.5[a]	*p*-bromobenzene-	245–246.5 d[a]	2,4-dinitrobenzene-
190[a]	*p*-toluene (43, 9)	250–251[a]	2,5-dichlorobenzene-
190.5–191.5[a]	2-iodotoluene-5-	253–254[a]	*p*-*t*-butylbenzene-
192	*p*-phenol (43)	257	2-naphthol-3,6-di- (35)
192–193[a]	*p*-ethylbenzene-	256–258 d[a]	4-nitrotoluene-2- (30)
193	*m*-nitrobenzene- (8)	259	acetyl -1- naphthylamine -5- (11)
196[b]	cinnamaldehyde phenylhydrazone-*p*- (26)	260–261	acetylnaphthionic (3)
198	acetyl - 1 - naphthylamine-8- (11)	262	acetyl -2- naphthylamine -6- (11)
199–200[a]	3-nitro-4-bromobenzene-	270–271	2-naphthol-6,8-di- (35)
202	2-nitrotoluene-4- (30)	290 d	1,8-dihydroxynaphthalene -3, 6-di- (12)
205.5–207[a]	*p*-phenoxybenzene-	303–304	1-naphthol-4- (3)
208	2-naphthol-6- (35)	304 d	1- naphthylamine -3,6,8 -tri- (12)
213 d	benzaldehyde phenylhydrazone-*p*- (26)	d 320	1-amino -8- naphthol -3,6- di- (12)
213[a]	naphthalene-2- (2)	323–324 d	naphthalene-1,6-di- (4)
214	diisopropylnaphthalene - 1 - (20)	338 d	naphthalene-2,6-di- (38)
219	salicylaldehyde phenylhydrazone-*p*- (26)	338–339 d	naphthalene-1,5-di- (4)
226–228[a]	*p*-(4-nitrophenoxy)benzene-	>330 d[a b]	biphenyl-4,4′-di-

[a] Value established or confirmed in this work.
[b] Monohydrate when air-dried.

form an oil. Since almost none are hydrated, there is no difficulty in drying them to constant composition and melting point. Moreover, those not containing hydroxyl or amino groups have sharp neutralization equivalents; this alone would make them useful for finding the equivalent weight of an unknown sulfonic acid, given the metallic salt of such acid. A table of equivalent weights found for the new compounds here reported has seemed unnecessary; it may merely be stated that upon titration each gave a molecular weight value within

one per cent of the theoretical value. Only three proved to contain water of crystallization, each of these being a monohydrate. Drying them overnight

TABLE III

p-TOLUIDINE SALTS OF AROMATIC SULFONIC ACIDS

M.P. °C	SULFONIC ACID
139–140	4-*n*-hexylphenol-2- (44)
141–143	4-*n*-propylphenol-2- (44)
147–149	4-*n*-amylphenol-2- (44)
149–150	4-*n*-butylphenol-2- (44)
181	naphthalene-1- (2)
d 182	3,4 - dihydroxyphenanthrene-1- (45)
191–192	2,4-dimethoxybenzene- (46)
196	1-naphthol-4- (3)
197	*o*-sulfobenzoic (47)
198	*p*-toluene- (15, 9, 13)
199–200	*m*-chlorobenzene- (5)
202	*p*-phenol- (47)
203–204	*o*-toluene- (15)
204–205	2-methyl -4- methoxybenzene (48)
204–206[a,b]	3,4-dichlorobenzene-
205	benzene- (7)
207	acetyl-1-naphthylamine-8- (11)
208–209[a]	*p*-ethylbenzene-
208–210[a]	*p*-chlorobenzene- (5)
214–215	2-nitrotoluene-4- (30)
215–216.5[a]	*p*-bromobenzene-
218–220[a]	2-chlorotoluene-5-
221[a]	naphthalene-2- (2, 14)
220–222[a]	2-iodotoluene-5-
222	*m*-nitrobenzene- (8)
222	phenanthrene-3- (6, 49)
222–223[a]	2-bromotoluene-5-
222–223.5[a]	*p*-phenoxybenzene- (50)
223	cinnamaldehyde phenylhydrazone-*p*- (26)
226	benzaldehyde phenylhydrazone-*p*- (26)
226	salicylaldehyde phenylhydrazone-*p*- (26)
225–227[b]	*o*-sulfocinnamic (mono salt) (24)
229–230	*m*-sulfocinnamic (mono salt) (34, 24)
232	2-naphthol-8- (35)
232–233	acetylnaphthionic (3)
233–234	retene-6- (51)
235	phenanthrene-4- (6)
235–236 d[a]	3-nitro-4-bromobenzene-
238–240 d[a]	2-chloro-3-nitrotoluene-5-
243	acetyl-2-naphthylamine-6- (11)
245–247 d[a]	2,4-dinitrobenzene-
245–247	*p*- (4- bromophenoxy)benzene- (50)
247–248[a]	2,5-dichlorobenzene-
248	2-naphthol-6- (35)
247–249 d[a]	azobenzene-4- (52)
248–249 d	4,7- dimethylhydrindene -5- (53)
250	2-naphthol-3,6-di- (35)
251	3,5-dinitro-*p*-toluene- (15)
254–255[a]	*p*-*t*-butylbenzene- (14)
255	acetyl-1-naphthylamine-5- (11)
256–257 d[a]	4-nitrotoluene-2- (30)
266–267	*p*-(4- sulfophenoxy)benzoic (54)
267	phenanthrene-1- (6)
277 d	toluene-2,4-di- (15)
288–289	*p*- (4- sulfophenyl)benzoic (54)
291	phenanthrene-2- (6, 49)
292 d	1- naphthylamine- 3,6,8-tri- (11)
294	2-naphthol-6,8-di- (35)
299	naphthalene-2,7-di- (38)
308 d	1,8 - dihydroxynaphthalene-3,6-di- (12)
308	anthraquinone-2- (16)
314–315 d	naphthalene-1,6-di- (4)
318–320 d	6-nitroacridone-2- (55)
332 d	naphthalene-1,5-di- (4)
d 335	1-amino -8- naphthol-3,6-di- (11)
>300	*p*-aminobenzene- (15, but *cf.* 3)
>330 d	biphenyl-4,4′-di-
>360 d	naphthalene-2,6-di- (38)
	1,2- phenanthraquinone -4-(56)

[a] Value established or confirmed in this work.

[b] Monohydrate when air-dried.

at 110° removed the water, which, however, when present, did not interfere with melting point determinations if heating was gradual (*cf.* 10). The ease of regeneration of an alkali sulfonate by neutralizing the amine salt and evaporat-

ing to dryness makes it possible to prepare several derivatives consecutively from the same sample of unknown material.

For the sulfonates of individual acids giving lower-melting salts the usual order of melting points is *o*-toluidine < *p*-toluidine < aniline, but no such order is apparent for the higher-melting salts. There seems to be no good reason to recommend any one of the three types as better than the others for identifications.

EXPERIMENTAL

The procedure used in preparing the salts was almost exactly that of Fieser (6, 10, 14), and it will therefore be only summarized. The alkali sulfonate, a slight excess of freshly distilled amine, hydrochloric acid, and water were heated together to cause solution. Then charcoal was added, the solution was filtered and chilled, and the salt was recrystallized to constant melting point (2–4 recrystallizations) from 1% acetic acid to minimize hydrolysis.

After thorough air-drying, weighed portions of the salts were titrated with 0.1 *N* alkali by the usual procedure (*cf.* 15, 16). Melting points were determined in a mechanically stirred bath with a calibrated thermometer, corrected for stem exposure.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF SCHERING CORPORATION]

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY AND AQUEOUS ALKALI

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PART I. THE CARBONYL GROUP

Since the report by Whitman, Wintersteiner, and Schwenk (1) on the reduction of estrone to a mixture of alpha- and beta-estradiol by a nickel-aluminum (Raney) alloy in alkaline solution there has appeared in the literature, as far as we could determine, but one instance (2) of the use of this reduction method. During the course of other investigations, we have had the opportunity to study further the reducing action of this alloy. This first paper represents the results we have obtained with compounds containing the carbonyl group.

Compounds of this type usually take up hydrogen quite easily when treated with nascent hydrogen, or with hydrogen in the presence of a catalyst, to give the corresponding alcohols. Occasionally, even reduction to the hydrocarbon has been observed. A more general method of obtaining the hydrocarbon is by the Clemmensen reduction, which, however, has not always given satisfactory results (3, 4). Alternative methods for accomplishing the transformation of carbonyl compounds to the hydrocarbons are the Wolff-Kishner reduction and catalytic hydrogenation.

We have found that with many carbonyl compounds our reduction method gives results comparable to those obtainable by the Clemmensen reduction. However, unlike the Clemmensen reduction, our reduction method is not specific, in that it converts carbonyl compounds to either the corresponding carbinol or the hydrocarbon, the extent of the reduction depending solely on the structure of the carbonyl compound. Carbonyl compounds of the general formula I

$$\underset{\text{I}}{C_6H_5C{=}OR} \qquad \underset{\text{II}}{C_6H_5(CH_2)_xC{=}OR'}$$

$$R = \text{H, alkyl or aryl;} \qquad R' = \text{H or alkyl}$$

yield the hydrocarbon, whereas carbonyl compounds of the general formula II yield the carbinol.

It is apparently necessary that the carbonyl group be directly attached to an aromatic carbon atom, formula I, forming a conjugated system, in order to obtain reduction of the carbonyl group to the hydrocarbon. However, when the carbonyl group, even as part of a conjugated system, is not directly attached to an aromatic carbon atom, formula II, the reduction of the carbonyl group proceeds only as far as the alcohol. Thus, while benzaldehyde gives toluene, and acetophenone gives ethylbenzene, cinnamic aldehyde and salicylacetone are only reduced to hydrocinnamyl alcohol and 4-(*o*-hydroxyphenyl)butanol-2, respectively.

As in the Clemmensen reduction, benzyl alcohol and *p*-hydroxybenzyl alcohol

are reduced to toluene and *p*-cresol, respectively. Other functional groups in addition to the carbonyl group, such as the nitro group, which is reduced to the amine, may be reduced as usual without interfering with the reduction of the carbonyl group.

With compounds soluble in alkali, the reduction proceeds smoothly to the desired product in good yield (70–90%). Difficulties are encountered with most of the carbonyl compounds which are insoluble in alkali. They are either not reduced or yield intermediate reduction products. However, we have found that the reduction of a great majority of these insoluble compounds proceeds satisfactorily to the hydrocarbon or the alcohol in the presence of a suitable solvent such as alcohol and/or toluene. For example, benzil without solvent gives a mixture of intermediate reduction products, whereas with alcohol as solvent dibenzyl was obtained exclusively.

We have also encountered several interesting examples of alkali-insoluble compounds which yield different reduction products with different solvents. Anisil, which was not reduced without solvent, gave in the presence of toluene anisoin as the only reduction product, and with toluene and alcohol as solvent hydroanisoin was obtained. However, in none of these experiments did we obtain any 4,4′-dimethoxydibenzyl. Dibenzalacetone also proved an interesting example of the effect of solubility on the course of the reduction. With no solvent or with alcohol as solvent, dibenzalacetone was recovered unchanged. With toluene as solvent, the only product obtained, besides some unchanged dibenzalacetone, was 1,5,6,10-tetraphenyl-3,8-diketodecadien-2,9 (5). Notwithstanding the fact that this compound contains four potentially reducible groups, attempts to reduce it further were unsuccessful.

The procedure employed for these reductions is essentially that described for the preparation of Raney's nickel hydrogenation catalyst (6). The nickel-aluminum alloy is added gradually to an alkaline solution of the carbonyl compound, and the reduction proceeds with the liberation of the hydrogen from the alloy. It appears possible that the reduction is due to the liberation of hydrogen which is then activated by the presence of the nickel catalyst, because we have been able to obtain reduction of the carbonyl group by using aluminum in conjunction with the previously prepared nickel catalyst. In these cases, if the nickel catalyst is omitted and only aluminum used, either no reduction occurs or amorphous products are obtained from which we could not isolate any pure substances. Although we have obtained, with most of the carbonyl compounds which we have studied, identical results in the reductions with either the nickel-aluminum alloy or the aluminum-nickel catalyst combination, we have found that some of the carbonyl compounds, especially those insoluble in alkali, require with the latter reducing agent excessive amounts of aluminum for complete reduction. In Table I are listed the carbonyl compounds and several alcohols which we have reduced by this method.

EXPERIMENTAL

General procedure. The procedure employed is essentially that previously described (1) with the following modifications. Ten grams of the compound is dissolved in 300 ml.

of 10% sodium hydroxide, heated to 90°, and 30 g. of Raney's nickel-aluminum alloy is added in small portions with stirring. The reaction mixture is stirred for an additional hour, the temperature being maintained at 90°. The original volume is maintained by the addition of water. A few drops of octyl alcohol are added occasionally to prevent any excessive foaming. Although this treatment is usually sufficient to complete the reduction

TABLE I

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY

COMPOUND	REDUCTION PRODUCT	YIELD[a], %
Benzyl alcohol[b]	Toluene	70
o-Hydroxybenzyl alcohol	*o*-Cresol	85
Benzaldehyde	Toluene	60
Salicylaldehyde[b]	*o*-Cresol	75
p-Hydroxybenzaldehyde	*p*-Cresol	80
Cinnamic aldehyde[c]	Hydrocinnamyl alcohol	50
Acetophenone[c]	Ethylbenzene	70
m-Nitroacetophenone[c]	*m*-Aminoethylbenzene	76
p-Hydroxyacetophenone	*p*-Ethylphenol	72
p-Hydroxypropiophenone	*p*-Hydroxypropylbenzene	78
p-Hydroxybenzophenone[b]	*p*-Hydroxydiphenylmethane	90
2-Methylcyclohexanone[c]	2-Methylcyclohexanol	80
Dibenzyl ketone[c]	Dibenzyl carbinol[d]	70
Salicylacetone[b]	4-(*o*-Hydroxyphenyl)butanol-2	85
p-Hydroxybenzalacetophenone	*p*-Hydroxydiphenylpropane[e]	50
Dibenzalacetone[f]	1,5,6,10-Tetraphenyl-3,8-diketo-decadien-2,9[g]	50
Desoxybenzoin[c]	Dibenzyl[h]	70
Benzoin[c]	Dibenzyl[h]	50
Benzil[c]	Dibenzyl + desoxybenzoin[i]	
Anisil[f]	Anisoin	80
Anisil[j]	Hydroanisoin	80
β-(*m*-Methoxybenzoyl)-α-anisylpropionic acid[k]	γ-(*m*-Methoxyphenyl)-α-anisylbutyric acid[k]	15

[a] The yields are based on the reduction of 10 g. of the carbonyl compound. [b] Also reduced with the aluminum-nickel catalyst combination. [c] 25 cc. of alcohol used as solvent. [d] Prepared *p*-nitrobenzoate, m.p. 80–81°; Calc'd. for $C_{22}H_{19}O_4N$:C, 73.10; H, 5.30. Found: C, 73.19; H, 5.70. [e] Also prepared by J. v. Braun and H. Deutsch, *Ber.*, **45,** 2187 (1912), b.p., 205–210°/13 mm. The 1-(*p*-phenoxyacetic acid)-3-phenyl propane, m.p. 92–93°; Calc'd for $C_{17}H_{18}O_3$: C, 75.51; H, 6.72. Found: C, 75.25; H, 6.62. [f] 25 cc. of toluene used as solvent. [g] Also prepared by Borsche and J. Wollemann, *Ber.*, **45,** 3719 (1912) Calc'd for $C_{34}H_{30}O_2$: C, 86.82; H, 6.06. Found: C, 86.57; H, 6.40%. [h] 4,4'-Dinitro derivative m.p. 179–180°, *J. Am. Chem. Soc.*, **52,** 5041 (1930). [i] Additional 10 g. alloy yielded dibenzyl exclusively. [j] 25 cc. of alcohol and 25 cc. of toluene used as solvent. [k] Prepared by Robinson, *et al*, *Proc. Roy. Soc.*, **B127,** 164 (1939).

further heating of the reaction mixture with the addition of 5 g. of alloy and 50 ml. of 10% sodium hydroxide gave indications of an increased yield, especially with the alkali-insoluble compounds. The hot solution was filtered and the residue was washed thoroughly with water in such a manner that it was always covered with fluid. If the nickel residue is allowed to become dry it will ignite. The filtrate was cooled and acidified to Congo red paper with concentrated hydrochloric acid. It is desirable to effect the acidification by

adding the alkaline solution to the hydrochloric acid with stirring. If the acidification is carried out in the reverse order, aluminum salts usually precipitate out and it is then necessary to heat the solution in order to redissolve the salts. The reduction product was isolated either by filtration or by extraction of the acidified solution. For the alkali-insoluble compounds the reductions were carried out in a one-liter flask equipped with an adapter and reflux condenser. During the addition of the alloy the reaction mixture was shaken frequently. With several compounds, toluene was added in sufficient quantity to retain the compound in a uniform surface layer (3). Other compounds were reduced in the presence of an amount of alcohol sufficient to keep them in solution. The reduction product was isolated either by steam distillation or extraction of the alkaline solution.

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SUMMARY

1. The use of a nickel-aluminum alloy (Raney's) in aqueous alkali for the reduction of carbonyl compounds is described.

2. Carbonyl compounds of the general formula $C_6H_5C{=}OR$ where R is hydrogen, alkyl, or aryl yield the corresponding hydrocarbon.

3. Carbonyl compounds of the general formula $C_6H_5(CH_2)_xC{=}OR$ or $C_6H_5CH{=}CH(CH_2)_xC{=}OR$ where R is hydrogen or alkyl yield the corresponding alcohol.

4. The reduction of alkali-soluble carbonyl compounds proceeds smoothly in good yield whereas the reduction of the alkali-insoluble carbonyl compounds proceeds satisfactorily in the presence of a solvent such as alcohol or toluene.

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