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REHOVOTH, PALESTINE]

SYNTHESIS OF SIX ISOMERIC $C_{22}H_{20}O_2$ ACIDS

ERNST BERGMANN

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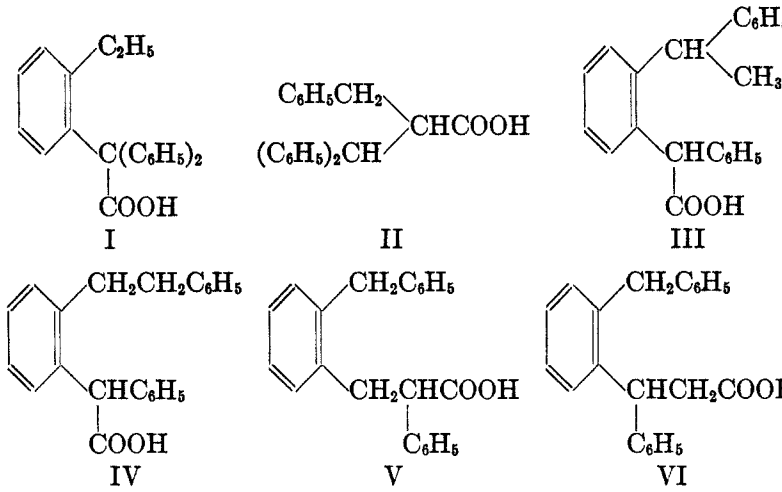
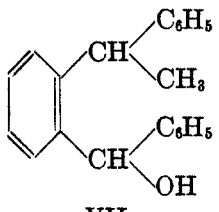
In the course of an investigation, reported elsewhere,[1] on the addition reaction between diphenylketene and styrene, the synthesis of the following acids was undertaken for comparison with an acid of formula $C_{22}H_{20}O_2$ derived from the addition product by hydrolytic fission: (*o*-ethylphenyl)-diphenylacetic acid (I); benzohydrylbenzylacetic acid (II); [*o*-(α-phenylethyl)phenyl]phenylacetic acid (III); [*o*-(β-phenylethyl)phenyl]phenylacetic acid (IV); *o*-benzyl-α-phenylhydrocinnamic acid (V); *o*-benzyl-β-phenylhydrocinnamic acid (VI). As the methods used and the substances newly prepared may be of some interest, the results are recorded in the present paper.



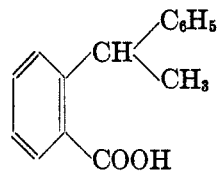
(*o*-Ethylphenyl)diphenylacetic acid (I) was prepared by carbonation of (*o*-ethylphenyl)diphenylmethylsodium, which in turn was obtained from (*o*-ethylphenyl)diphenylcarbinol *via* the chloride. In the preparation of the carbinol from *o*-ethylbenzophenone and phenylmagnesium bromide, part of the ketone was reduced to the corresponding pinacol. Similar observations have been made before by Barnett, Cook, and Nixon,[2]

[1] BERGMANN AND BLUM-BERGMANN, *J. Chem. Soc.*, **1938**, 727.
[2] BARNETT, COOK, and NIXON, *ibid.*, **1927**, 509.

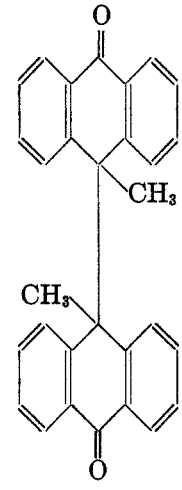
and by Hatt.[3] Benzohydrylbenzylacetic acid (II) was easily available through the condensation of diphenylbromomethane with ethyl sodiobenzylmalonate in the absence of alcohol. In the synthesis of [*o*-(α-phenylethyl)phenyl]phenylacetic acid (III), the last steps were similar to those in the preparation of (I), namely carbonation of the sodium compound, corresponding to (III), which in turn was obtained from *o*-(α-phenylethyl)benzohydrol (VII) *via* its methyl ether. The carbinol (VII) was prepared by reducing *o*-(α-phenylethyl)benzophenone by means of aluminum amalgam and alcohol or by addition of sodium and subsequent hydrolysis of the disodium compound. For the synthesis of *o*-(α-phenylethyl)benzophenone, it was necessary to make *o*-(α-phenylethyl)benzoic acid (VIII) easily available. By interaction of ethyl (*o*-benzoyl)benzoate and methylmagnesium iodide, Ostersetzer[4] had obtained methylphenylphthalide (IX) which could be reduced by zinc and ammonia to yield the desired acid (VIII). We have observed that besides IX, *o*-(α-methylenebenzyl) benzoic acid (X) is formed in the above reaction; catalytic hydrogenation converted it into VIII. The two substances represent tautomeric forms and therefore are interconvertible (ring-chain tautomerism); on drying at 100°, the acid (X) was occasionally converted into methylphenylphthalide (IX).



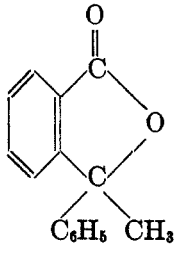
VII



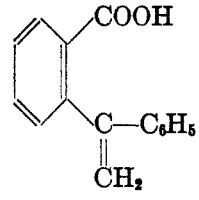
VIII



XI



IX



X

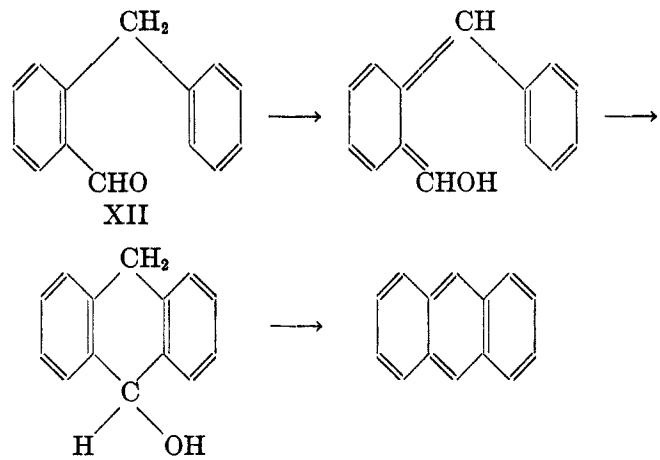
[3] HATT, *ibid.*, **1929**, 1623.

[4] OSTERSETZER, *Monatsh.*, **34**, 796 (1913). For similar observations compare, *inter alia*, FIESER AND NEWMAN, *J. Am. Chem. Soc.*, **58**, 2376 (1936); **59**, 1004 (1937); COOK, ROBINSON, AND GOULDEN, *J. Chem. Soc.*, **1937**, 393.

Treatment of the acid chloride of VIII with benzene in the presence of aluminum chloride did not lead to *o*-(α-phenylethyl)benzophenone, but rather to intramolecular condensation products, *viz.* anthraquinone and a substance which, according to analyses and behavior, most probably is 9,9′-dimethyl-10,10′-diketo-9,9′,10,10′-tetrahydro-9,9′-bianthryl (XI). Hence another method had to be applied to the conversion of VIII into the corresponding substituted benzophenone: the nitrile, which is accessible by heating the acid with lead thiocyanate,[5] was treated with phenylmagnesium bromide.

The synthesis of [*o*-(β-phenylethyl)phenyl]phenylacetic acid (IV), which has recently been prepared by Natelson and Gottfried[6] by a different method, was accomplished in exactly the same way as in the case of the *alpha* compound (III), starting with *o*-(β-phenylethyl)benzoic acid. For the reduction of *o*-(β-phenylethyl)benzophenone, aluminum isopropylate proved most satisfactory, since amalgamated aluminum partly finished its action with the production of the corresponding pinacol.

For the synthesis of *o*-benzyl-α-phenylhydrocinnamic acid (V), the suitable starting material proved to be *o*-benzylbenzaldehyde (XII), which on heating with sodium phenylacetate and acetic anhydride gave *o*-benzyl-α-phenylcinnamic acid. For the preparation of the aldehyde (XII), ethyl orthoformate was treated with the magnesium derivative of *o*-bromodiphenylmethane,[7] and the acetal so obtained was hydrolyzed by boiling hydrochloric acid. In this latter reaction, a certain amount of anthracene was formed, most probably according to the following scheme:



XII

[5] Compare HOUBEN-WEYL, "Die Methoden der organischen Chemie," Leipzig, **1930**, Vol. III, p. 945.

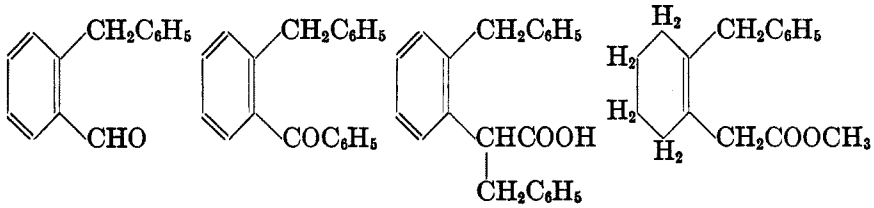
[6] NATELSON AND GOTTFRIED, *J. Am. Chem. Soc.*, **58**, 1432 (1936).

[7] Compare CLARKSON AND GOMBERG, *ibid.*, **52**, 2887 (1930).

This, apparently, is a modification of the Elbs synthesis of anthracene derivatives, especially interesting as it takes place at remarkably low temperatures (120° as compared with the normal 400–450° of the Elbs reaction). As pointed out by Cook,[8] a transanellar migration of hydrogen would most satisfactorily explain the course of the Elbs reaction;[9] in the present instance, too, the above-formulated intermediary enolic form would meet the requirements of a reasonable explanation.

The synthesis of *o*-benzyl-β-phenylhydrocinnamic acid (VI) was accomplished through *o*-benzylbenzonitrile, prepared from the corresponding acid by interaction with lead thiocyanate; reaction of the nitrile with phenylmagnesium bromide led to *o*-benzylbenzophenone (XIII).[10] When this ketone was treated with zinc and ethyl bromoacetate, the two forms of *o*-benzyl-β-phenylcinnamic acid were obtained, which were subsequently hydrogenated.

In the course of these synthetic experiments, we attempted to prepare a seventh isomeric acid, (*o*-benzylphenyl)benzylacetic acid (XIV), but without success. From *o*-benzylcyclohexanone with zinc and methyl bromoacetate we obtained methyl 1-benzylcyclohexene-(1)-acetate-(2) (XV) (or the corresponding α,β-unsaturated ester), but dehydrogenation of this compound to *o*-benzylphenylacetic acid (which was ultimately to be condensed with benzaldehyde) was not achieved, palladium giving anthracene, and bromine giving a crystalline acid, which according to the analysis was *x*-bromo-2-benzylphenylacetic acid.



XII XIII XIV XV

EXPERIMENTAL

(o-*Ethylphenyl*)*diphenylacetic acid* (*I*)

o-*Ethylbenzophenone.*—From *o*-ethylbenzoic acid[11] (26 g.) and thionyl chloride (80 cc.), the chloride (26 g.), b. p. 105–106°/14 mm., was obtained by heating the mixture for three hours. The chloride was heated with anhydrous aluminum chlo-

[8] Cook, *J. Chem. Soc.*, **1931**, 487; compare Fieser, "Chemistry of Natural Products Related to Phenanthrene," New York, **1936**, 1st Ed., pp. 99–108.

[9] Compare, also for references, Bergmann, *Ber.*, **63**, 1037 (1930).

[10] Compare Blicke and Swisher, *J. Am. Chem. Soc.*, **56**, 923 (1934).

[11] Gabriel and Michael, *Ber.*, **10**, 2206 (1877).

ride (20.5 g.) in benzene (130 cc.) for three hours, the mixture decomposed by ice and hydrochloric acid and the *o*-ethylbenzophenone purified by distillation; b. p. 165°/18 mm.; yield, 23 g.

(o-*Ethylphenyl*)*diphenylacetic acid* (*I*).—*o*-Ethylbenzophenone (21 g.) was introduced into a phenylmagnesium bromide solution (from 2.7 g. of magnesium and 11.5 cc. of bromobenzene). The reaction gave a transitory violet color, and was completed by boiling for three hours. The product, isolated by acid decomposition, gave, on trituration with alcohol, beautiful crystals (2.5 g.), which, after recrystallization from propyl and amyl alcohols, melted at 151–152° and were, according to the analysis, the *pinacol of o-ethylbenzophenone*.

Anal. Calc'd for $C_{30}H_{30}O_2$: C, 85.3; H, 7.1.
Found: C, 85.0; H, 7.3.

(o-*Ethylphenyl*)*diphenylcarbinol* itself could not be obtained in a crystalline state; the mother liquor of the above-described crystals, therefore, was evaporated, and the residue (22 g.) was dissolved in benzene and, after addition of acetyl chloride (10 cc.), was saturated with gaseous hydrogen chloride. The solution was evaporated, finally in a desiccator over potassium hydroxide. The oily (o-*ethylphenyl*)-*diphenylchloromethane* (4.5 g.) was shaken with 1% sodium amalgam (150 g.) in a Schlenk tube. The reaction started at once and gave the dark-brown (o-*ethylphenyl*)*diphenylmethylsodium*. It was decomposed with carbon dioxide; the precipitated sodium salt was extracted with water, and the solution was acidified. The acid was dried and recrystallized twice from a mixture of benzene and ligroïn (2:3); m. p. 204–205° (slight decomp.).

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 83.5; H, 6.3.
Found: C, 83.2; H, 6.3.

Benzohydrylbenzylacetic acid (*II*)

Ethyl benzohydrylbenzylmalonate.—To a suspension of sodium powder (3.4 g.) in benzene (100 cc.), ethyl benzylmalonate (35 g.) was added slowly, at a temperature of about 15–20°. Within twelve hours' standing, the mixture was converted into a crystalline magma, to which diphenylbromomethane (34 g.) was added. The spontaneous reaction was completed by three hours' boiling, then water and ether was added, and the ethereal layer was distilled. After a head fraction (b. p. 118–128°/0.1 mm.), the reaction product went over at 185–195°/0.02 mm., and after repeated distillation at 190°/0.02 mm., consisted of a viscous, colorless oil; yield, 33 g.

Anal. Calc'd for $C_{23}H_{20}O_4$: C, 77.9; H, 6.7.
Found: C, 77.8; H, 6.3.

Benzohydrylbenzylacetic acid (*II*).—The foregoing ester (10 g.) was boiled for seven hours with potassium hydroxide (4.1 g.; 3 moles) in amyl alcohol (25 cc.). The solid cake obtained on cooling was filtered, washed with ether, dissolved in water, and after treatment with charcoal, was filtered and acidified. The precipitate was triturated with a mixture of 50% acetic acid in acetone, and was recrystallized, first from 70% acetic acid, and then from light petroleum (b. p. 80–100°); needles, m. p. 175–177°. Analysis showed that the procedure applied had incidentally caused spontaneous decarboxylation.

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 83.6; H, 6.3.
Found: C, 83.1; H, 6.6.

[o-(α-*Phenylethyl*)*phenyl*]*acetic acid* (*III*)

Ethyl (o-*benzoyl*)*benzoate* was prepared from the acid (46 g.) by boiling with alcohol (125 cc.) and concentrated sulfuric acid (10 g.) for four hours. The alcohol was distilled off on a water bath; the residue was poured out into water, extracted with ether, washed with soda solution and then evaporated. The ester crystallized

easily, and was recrystallized from light petroleum, containing some benzene; m. p. 59–61.5°; yield, 40 g.

Reaction with methylmagnesium iodide.—A Grignard solution (from 5.42 g. of magnesium and 14.3 cc. of methyl iodide) was added to a solution of ethyl (*o*-benzoyl)-benzoate (52 g.) in ether (250 cc.); during the vigorous reaction a yellow precipitate separated. After thirty minutes' boiling the mass was decomposed with ice and sulfuric acid. The ethereal layer was washed with sodium thiosulfate solution and then extracted with sodium hydroxide. On acidification, *o*-(α-methylene-benzyl)benzoic acid (X) was obtained (average yield, 11 g., the amount varying from 11 to 15 g.); from 50% acetic acid, needles, m. p. 136–136.5°.

Anal. Calc'd for $C_{15}H_{12}O_2$: C, 80.4; H, 5.4.
Found: C, 80.1, 80.2; H, 5.6, 5.2.

The neutral residue obtained after evaporation of the ethereal layer was purified by distillation in a vacuum; b. p. 162°/1.2 mm. The solidified distillate was triturated with light petroleum and some alcohol, and was finally recrystallized from benzine; leaflets, m. p. 78–81°; yield varying from 7 to 15 g. Occasionally, the methylphenylphthalide (IX) crystallized without previous distillation.

Anal. Calc'd for $C_{15}H_{12}O_2$: C, 80.4; H, 5.4.
Found: C, 80.4; H, 5.4.

Both isomers are reduced easily to form *o*-(α-phenylethyl)benzoic acid.

o-(*α-Phenylethyl*)*benzoic acid* (*VIII*).—(*a*) The foregoing unsaturated acid (14 g.) was hydrogenated for six hours in boiling propyl alcohol (75 cc.) in the presence of palladized barium sulfate (4 g.). The solvent was evaporated in a vacuum and the residue after solidification recrystallized from 50% acetic acid or benzine; m. p. 104–106°, yield, 13 g.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.7; H, 6.2.
Found: C, 79.9; H, 6.1.

(*b*) Phenylmethylphthalide (26.5 g.) was dissolved in alcohol (130 cc.); 15% ammonia solution (700 cc.), zinc dust (93 g.) and copper sulfate solution (37 cc.) were added and the whole mass was heated on a water bath for twenty hours, filtered and acidified; yield, 26 g.

The phthalide may also be reduced by red phosphorus and hydriodic acid, but the yields are rather poor.

In order to obtain the desired *o*-(α-phenylethyl)benzophenone, application of the Friedel and Crafts reaction to the corresponding crude acid chloride was first tried, but this, on reaction with benzene and aluminum chloride, gave only autocondensation products, namely anthraquinone and a substance crystallizing from butyl acetate containing some benzene, in glistening brownish crystals, melting to a greenish liquid at 280–283° in a sealed tube, after discoloration as low as 258°. The substance, exhibiting a beautiful red color with concentrated sulfuric acid, is 9,9′-dimethyl-10,10′-diketo-9,9′, 10,10′-tetrahydro-9,9′bianthryl (XI).

Anal. Calc'd for $C_{30}H_{22}O_2$: C, 87.0; H, 5.3.
Found: C, 87.4, 87.3; H, 4.8, 5.0.

o-(*α-Phenylethyl*)*benzonitrile.*—The foregoing acid (16 g.) and lead thiocyanate (24 g.) were mixed and heated in a stream of hydrogen to 205–210°, until the evolution of carbon dioxide ceased. The mass was extracted with ether and the solution washed with soda; b. p. 166–168°/5.5 mm.; 151°/1.8 mm.; yield 7.8 g. Surprisingly, the substance exploded during the combustion analysis, but its constitution was ascertained by hydrolysis with 50% sulfuric acid, which resulted in the above acid.

Anal. Calc'd for $C_{15}H_{13}N$: C, 87.0; H, 6.3; N, 6.8.
Found: C, 86.3; H, 6.2; N, 6.7.

o-(*α-Phenylethyl*)*benzophenone.*—The above nitrile (18 g.) was added to a phenylmagnesium bromide solution (prepared from 3.2 g. of magnesium and 11.2 cc. of bromobenzene), and the mixture heated for six hours. After about two hours, the reaction product separated suddenly as a yellowish crystalline powder. It was decomposed by ice and ammonium chloride, and the residue from the ethereal layer was heated with acetone (18 cc.), concentrated hydrochloric acid (12 cc.), and water (37.5 cc.) for five hours, poured out into cold water, extracted with ether, and washed with alkali. The ketone is a colorless oil, exhibiting a blue fluorescence; b. p. 184–186°/0.8 mm.; yield, 21.1 g.

Anal. Calc'd for $C_{21}H_{18}O$: C, 88.1; H, 6.3.
Found: C, 87.8; H, 6.5.

o-(*α-Phenylethyl*)*benzohydrol* (*VII*).—Since the compound contains two asymmetric carbon atoms, two isomerides were to be expected and were actually found. One of them is a crystalline substance, the other a viscous oil, which, although having a constant boiling point, may still contain some of the crystalline isomer, and therefore is not definitely sterically homogeneous.

(*a*) An ethereal solution of the ketone was shaken with sodium powder (Schlenk's method) for several days, decanted from the excess of sodium and decomposed with water. The product was isolated by distillation in a vacuum; greenish-yellow oil, exhibiting a blue fluorescence; b. p. 186–189°/1.3 mm. On standing, the oil deposited crystals (half its weight) which were triturated with light petroleum and crystallized from the same solvent; stout crystals, m. p. 91–93°.

Anal. Calc'd for $C_{21}H_{20}O$: C, 87.5; H, 7.0.
Found: C, 87.1; H, 7.0.

The liquid portion of the product was distilled again; b. p. 178–181°/0.9 mm.; $n_D^{29} = 1.6140$.

Anal. Found: C, 87.3; H, 7.2.

(*b*) The ketone (10 g.) was dissolved in a hot mixture of alcohol (62 cc.) and water (8 cc.); then amalgamated aluminum (25 g.) was introduced. After three hours' boiling the liquid was sucked off still hot, the solid was washed with boiling alcohol, and the solvent was evaporated. From the residue the solid isomer crystallized (3.2g.) spontaneously on trituration with light petroleum. The oily residue was twice fractionated in a vacuum; the liquid isomer (4.4 g.) had the b. p. 178–180°/0.5 mm.

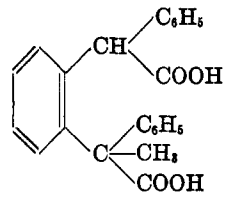
o-(*α-Phenylethyl*)*benzohydryl methyl ether.*—The different isomeric hydrols were methylated separately. It cannot be decided whether and to what extent the configuration of the hydrols is preserved; in any case the interaction of the methylated products and sodium powder gave identical results, which can be accounted for by the alternative assumptions, that configurational change takes place during methylation, or during the formation of the alkali-organic compound. The solid hydrol (2.7 g.) was heated for two hours with methyl alcohol (12 cc.) and concentrated hydrochloric acid (1 cc.); after some minutes the methyl ether started to separate. It was isolated by treatment with ether and water; b. p. 168–172°/0.8 mm.; 164°/0.6 mm.; $n_D^{29} = 1.5910$.

Anal. Calc'd for $C_{22}H_{22}O$: C, 87.4; H, 7.3; OCH_3, 10.3.
Found: C, 87.5; H, 8.0; OCH_3, 11.3, 11.4.

From the liquid hydrol the methyl ether was prepared in the same way; b. p. 171–173°/0.9 mm.; $n_D^{31} = 1.6029$.

[o-(*α-Phenylethyl*)*phenyl*]*phenylacetic acid* (*III*).—Each of the above methyl ether preparations was shaken with sodium powder for six days, and the dark-brown solution was decomposed with dry carbon dioxide. The reaction product was decanted

from the excess of sodium and taken up with water. On acidification, a thick oil separated, which was isolated by extraction with ether. The residue was triturated with a mixture of light petroleum and some acetone. The first crystalline crop (0.25 g. from 5 g. of methyl ether) was recrystallized several times from 50% acetic acid. The analysis of the diamond-shaped crystals, m. p. 261–263° (decomp.), pointed to the formula $C_{23}H_{20}O_4$ of the following acid:



which has been formed by successive splitting of the C-O bond and substitution of the tertiary hydrogen atom.

Anal. Calc'd for $C_{23}H_{20}O_4$: C, 76.7; H, 5.5; mol. wt. 360.
Found: C, 76.5, 76.2; H, 5.5, 5.4; mol. wt. 367 (camphor).

A second crystalline fraction (0.55 g.) still contained the above dicarboxylic acid, which could be separated through its insolubility in boiling benzine. From the benzine solution, leaflets of the desired acid $C_{22}H_{20}O_2$ separated on cooling; they were purified by subsequent recrystallization from dilute acetic acid and benzine; m. p. 140–141°.

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 83.5; H, 6.3.
Found: C, 83.2, 83.5; H, 7.0, 6.8.

[o-(*β-Phenylethyl*)*phenyl*]*phenylacetic acid* (*IV*)

o-(*β-Phenylethyl*)*benzonitrile.*—According to the method already described, lead thiocyanate reacted with *o*-(β-phenylethyl)benzoic acid[12] at 195°. The reaction was accomplished within six hours. The product, isolated by means of ether, was an oil, which on standing at 0° with light petroleum and acetone deposited small quantities of *o*-(β-phenylethyl)benzamide; from propyl alcohol, needles, m. p. 128°.

Anal. Calc'd for $C_{15}H_{15}NO$: C, 80.0; H, 6.7; N, 6.2.
Found: C, 79.8; H, 7.1; N, 6.0.

The *nitrile*, after separation of the above crystals, was purified by distillation; b. p. 168°/4 mm., 150°/1.3 mm.; $n_D^{19} = 1.5762$.

Anal. Calc'd for $C_{15}H_{13}N$: N, 6.7. Found: N, 6.7.

The amide usually amounted to 10% of the nitrile. Its appearance is noteworthy, as according to the literature (*loc. cit.*) this method gives amides along with the nitriles only in the case of aliphatic acids.

o-(*β-Phenylethyl*)*benzophenone.*—The nitrile (18 g.) was heated with phenylmagnesium bromide (3.2 g. of magnesium, 14.2 cc. of bromobenzene) for three hours, and the whole mass was decomposed with ice and ammonium chloride, and boiled with a mixture of acetone (18 cc.), water (37.5 cc.) and concentrated hydrochloric acid (12 cc.) for five hours. The ketone had the b. p. 199–200°/3 mm.; yield, 24 g.

Anal. Calc'd for $C_{21}H_{18}O$: C, 88.1; H, 6.3.
Found: C, 88.0; H, 6.6.

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[12] GABRIEL, *Ber.*, **18**, 2444, 3479 (1885); SCHLENK AND BERGMANN, *Ann.*, **463**, 266 (1928).

o-(*β-Phenylethyl*)*benzohydrol.*—Forty grams of the above-mentioned ketone was heated with 30 g. of aluminum isopropylate and 300 cc. of isopropyl alcohol for five hours. The solvent was then evaporated, the residue was dissolved in isopropyl alcohol, concentrated again and so on, until the distillate gave no positive test for acetone. Then the mass was treated with dilute potassium hydroxide solution and ether; b. p. 195-196°/0.6 mm.; yield, 33 g.; $n_D^{24} = 1.6055$. After some time the colorless oil solidified spontaneously; from light petroleum, prisms, m. p. 57°.

Anal. Calc'd for $C_{21}H_{20}O$: C, 87.5; H, 7.0.
Found: C, 87.1; H, 7.0.

The reduction of the above ketone with amalgamated aluminum turnings in moist ether gave unsatisfactory results; besides the hydrol, 30% of the ketone was found in the form of the corresponding pinacol. This separated on concentration of the solution of the obtained product, and was recrystallized from a mixture of benzene and benzine. Quartz-like crystals, m. p. 141°. The pinacol character of the substance is demonstrated by the fact that the benzene solution develops a deep-blue color on addition of sodium ethoxide solution.

Anal. Calc'd for $C_{42}H_{38}O_2$: C, 87.8; H, 6.6.
Found: C, 87.3; H, 7.1.

o-(*β-Phenylethyl*)*benzohydryl ethyl ether.*—The hydrol (20 g.), alcohol (85 cc.) and concentrated hydrochloric acid (8 cc.), were heated for three hours; ether and water were added, and the ethereal solution was washed with sodium carbonate solution; b. p. 200°/2.5 mm.; $n_D^{24} = 1.3797$; yield 21 g.

Anal. Calc'd for $C_{23}H_{24}O$: C, 87.3; H, 7.6.
Found: C, 87.3; H, 7.8.

The preparation of the methyl ether proceeded less satisfactorily, due to the slight solubility of the hydrol in methyl alcohol. It was a nearly colorless oil, b. p. 177-178°/0.7 mm.

Anal. Calc'd for $C_{22}H_{22}O$: C, 87.4; H, 7.3.
Found: C, 87.5; H, 7.5.

[o-(*β-Phenylethyl*)*phenyl*]*phenylacetic acid* (*IV*).—The above-mentioned ethyl ether was shaken in ethereal solution with sodium powder for three days, and the brown solution was treated with dry, gaseous carbon dioxide. The sodium salt formed was extracted with water and precipitated with acid. From light petroleum (b. p. 80-100°) or cyclohexane, clusters of needles, m. p. 117.5-118.5°.

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 83.5; H, 6.3.
Found: C, 83.4; H, 6.4.

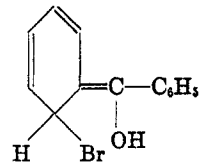
o-*Benzyl-α-phenylhydrocinnamic acid* (*V*)

o-*Bromobenzophenone.*—To a cooled mixture of *o*-bromobenzoyl chloride (50 g.) (b. p. 135°/22 mm.) and benzene (250 cc.), powdered aluminum chloride (33 g.) was added. After some time, reaction set in, the temperature gradually rising to room temperature. After twelve hours' standing, the mass was boiled for three hours, and then decomposed with ice and concentrated hydrochloric acid; b. p. 151-153°/0.05 mm.; yield, 30 g.[13]

o-*Bromodiphenylmethane.*—According to Clarkson and Gomberg[7] the foregoing ketone (30 g.) was reduced with amalgamated zinc wool (30 g.) and concentrated hydrochloric acid. When all the zinc had disappeared, the oily product was separated by extraction with ether. On trituration with methyl alcohol and some acetone, a crystalline by-product (3 g.) separated; the liquid distilled at 175°/22 mm. and was pure *o*-bromodiphenylmethane. The solid was separated by fractional

[13] CATHCART AND MEYER, *Ber.*, **25**, 1498 (1892).

crystallization from methyl ethyl ketone into the diamond-shaped crystals of tetraphenylethylene (m. p. and mixture m. p. with an authentic sample, 222°), and long needles of a second hydrocarbon, m. p. 236°. Its constitution could not be elucidated; in any case, it is not identical with 9,10-diphenyl-9,10-dihydroanthracene,[14] which could easily have been formed in the above reaction.[15] Removal of halogen in similar cases has been observed by Montagne and van Charante;[16] it may be due to the transitory formation of a substance like



containing an allylic bromine atom. With regard to the formation of tetraphenylethylene, attention may be drawn to the experiments of Steinkopf and Wolfram.[17]

o-*Benzylbenzaldehyde diethylacetal.*—When ethyl orthoformate (23 g.) was added to the Grignard solution, prepared from magnesium (2.7 g.) and *o*-bromodiphenylmethane (27.5 g.), no reaction occurred. When the solvent was distilled off, reaction took place with great violence; after addition of some more (7 g.) ethyl orthoformate, the mixture was heated for five hours at 120° (oil bath) and was decomposed with ice-cold ammonium chloride solution. Fractionation of the oily product gave (*a*) diphenylmethane, b. p. 86–117°/0.04 mm., then 84–86°/0.04 mm.; yield 7.7 g.; and (*b*) the desired acetal; b. p. 118°/0.04 mm.; yield, 15.5 g.

Anal. Calc'd for $C_{18}H_{22}O_2$: C, 80.0; H, 8.1.
Found: C, 79.7; H, 8.4.

o-*Benzylbenzaldehyde.*—The acetal (13 g.) was heated at 120° for six hours with dilute hydrochloric acid (52 cc.), anthracene continuously subliming into the reflux condenser. After dilution with water, the reaction product was extracted with ether and isolated by distillation (b. p. 116–118°/0.03 mm.). As anthracene distilled over with the acetal, the distillate had to be diluted with light petroleum (b. p. 40–60°) and alcohol and kept at 0° for twenty-four hours, whereupon the anthracene (0.27 g.) separated quantitatively; m. p. and mixture m. p. 213–214°. The aldehyde was distilled again (b. p. as above); yield, 7.5 g.

Anal. Calc'd for $C_{15}H_{12}O$: C, 85.7; H, 6.1.
Found: C, 85.3; H, 5.9.

o-*Benzyl-α-phenylcinnamic acid.*—The foregoing aldehyde (7.5 g.) was heated at 160° for eight hours with sodium phenylacetate (6.4 g.) and acetic anhydride (14 cc.). The reaction mixture was poured out on ice; after some hours it was taken up with ether, and the ethereal layer was extracted with soda. The sodium salt separated

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[14] Schlenk and Bergmann, *Ann.*, **463**, 153 (1924); Haack, *Ber.*, **62**, 1771 (1929). It may be identical with a substance sometimes formed in reactions with benzohydrylsodium; *cf.* Bergmann, *Ber.*, **63**, 1627 (1930); **65**, 457 (1932).

[15] According to unpublished results from this laboratory, *o*-bromobenzophenone is converted by calcium amalgam into 9,10-diphenylanthracene.

[16] Compare, *inter alia*, Montagne and van Charante, *Rec. trav. chim.*, **31**, 315 (1912); Speer and Hill, J. Org. Chem., **2**, 139 (1937).

[17] Steinkopf and Wolfram, *Ann.*, **430**, 113 (1923).

as a thick oil between the water and the ether layers; on acidification, it gave the crystalline acid, which was recrystallized from 70% acetic acid; brilliant needles, m. p. 161–162°; yield, 6.8 g.

Anal. Calc'd for $C_{22}H_{18}O_2$: C, 84.1; H, 5.4.
Found: C, 84.0; H, 5.8.

o-*Benzyl-α-phenylhydrocinnamic acid* (*V*).—The unsaturated acid (4.5 g.) was catalytically hydrogenated in boiling propyl alcohol (50 cc.) during six hours in the presence of palladized barium sulfate (2 g.). The filtered solution was evaporated, and the residue, after trituration with light petroleum (b. p. 40–60°), recrystallized from light petroleum (80–100°); clusters of white, shiny needles, m. p. 96–98°; yield 3.9 g.

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 83.5; H, 6.3.
Found: C, 83.5, 83.5; H, 6.5, 6.5.

o-*Benzyl-β-phenylhydrocinnamic acid* (*VI*)

o-*Benzylbenzonitrile and* o-*benzylbenzamide.*—An intimate mixture of *o*-benzylbenzoic acid (16 g.) and lead thiocyanate (24 g.) was heated in a current of hydrogen at 200–210° for four hours. The product was extracted with ether, and the ethereal layer was washed with sodium carbonate solution, dried, and evaporated. The residue was triturated with a mixture of benzene and light petroleum, whereupon *o*-benzylbenzamide (0.6–0.8 g.) separated; from glacial acetic acid, glistening prismatic needles, m. p. 164.5°.

Anal. Calc'd for $C_{14}H_{13}NO$: C, 79.6; H, 6.2.
Found: C, 79.4, 79.3; H, 6.6, 6.5.
The nitrile had the b. p. 130–133°/0.02 mm.

Anal. Calc'd for $C_{14}H_{11}N$: C, 86.7; H, 6.0; N, 7.2.
Found: C, 86.5; H, 6.4; N, 7.2.[18]

o-*Benzylbenzophenone* (*XIII*).—*o*-Benzylbenzonitrile (10 g.) was boiled for three hours with phenylmagnesium bromide solution (from 2 g. magnesium and 8.5 cc. bromobenzene); the reaction mass crystallized after thirty minutes' boiling. It was decomposed by means of ice and ammonium chloride, and the product was heated on a water bath for five hours with acetone (10 cc.), concentrated hydrochloric acid (7 cc.) and water (20 cc.). The ketone so obtained was distilled *in vacuo*, b. p. 163°/0.03 mm., and formed a viscous oil, which exhibited an intense green fluorescence and crystallized on standing; m. p. 50°; yield, 12.5 g.[19]

The stereoisomeric o-*benzyl-β-phenylcinnamic acids.*—The foregoing ketone (12 g.) was gently warmed with zinc (10 g.) and methyl bromoacetate (17 cc.) in benzene (75 cc.), until reaction set in, and when it ceased, for three more hours on the boiling water bath. The crude product, isolated as usual, was heated with 85% formic acid[20] at 160° for three hours. Methyl *o*-benzyl-β-phenylcinnamate was so obtained as a thick oil, b. p. 170°/0.005 mm., which according to the analysis was not analytically pure, some disproportionation into *o*-benzylbenzophenone having taken place.

Anal. Calc'd for $C_{23}H_{20}O_2$: C, 86.1; H, 6.1.
Found: C, 86.8; H, 6.0.

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[18] Essentially the same procedure has been used by BLICKE AND SWISHER, *J. Am. Chem. Soc.*, **56**, 923 (1934).

[19] The same synthesis has been briefly mentioned by BLICKE AND SWISHER, *loc. cit.*; compare SEIDEL, *Ber.*, **61**, 2267 (1928).

[20] RUPE, *Ann.*, **395**, 141 (1913); SCHLENK AND BERGMANN, *ibid.*, **463**, 237 (1928).

The same process, apparently, occurred to some extent during the subsequent saponification;[21] when the ester (8 g.) was heated with potassium hydroxide (2.6 g.) in a mixture of methyl alcohol (35 cc.) and butanol (20 cc.) for twelve hours, a neutral and an acid fraction were obtained. The former fraction consisted of *o*-benzylbenzophenone, the latter, of the two isomeric forms of the desired acids. On acidification of its alkaline solution, it was obtained as an oil, which crystallized under the influence of a mixture of benzene and light petroleum.

After recrystallization from cyclohexane, the two forms could be separated mechanically; cubes, m. p. 177° (*A*), and droplets, m. p. 148° (*B*) respectively, after final recrystallization from the same solvent. The lower-melting form begins to decompose at about 160°.

Anal. Calc'd for $C_{22}H_{18}O_2$: C, 84.0; H, 5.7.
Found (*A*): C, 83.7; H, 5.7.
(*B*): C, 84.2; H, 6.0.

When the crude product from the above Reformatsky reaction was hydrolyzed directly by means of boiling alcoholic potash solution (5.4 g. potassium hydroxide), *o-benzyl-β-phenyl-β-hydroxyhydrocinnamic acid* was obtained; it was insoluble in cyclohexane, but crystallized easily from toluene; m. p. 179–180° (decomp.).

Anal. Calc'd for $C_{22}H_{20}O_3$: C, 80.0; H, 6.0.
Found: C, 79.7; H, 6.0.

The hydroxy acid was dehydrated by heating at 180° for one hour in the presence of twice its weight of potassium acid sulfate. The inorganic material was extracted with acid and acetone. On recrystallization from cyclohexane, the product proved to be the lower-melting *o*-benzyl-β-phenylcinnamic acid, by its melting point (148°) and by the form of the crystals.

o-Benzyl-β-phenylhydrocinnamic acid (*VI*).—The mixture of the unsaturated acids (0.5 g.) was hydrogenated in boiling isopropyl alcohol (15 cc.) in the presence of palladized barium sulfate (0.5 g.) for three hours. The filtered solution, on evaporation, left a resin which so far could not be induced to crystallize, but gave the expected analytical figures.

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 83.5; H, 6.3.
Found: C, 83.4; H, 6.3.

o-Benzylcyclohexanone.—*o*-Benzylcyclohexanol (19 g.) which is easily accessible according to the method of Weizmann, Bergmann, and Haskelberg,[22] was dissolved in warm (80°) glacial acetic acid (100 cc.) and a solution of chromic acid anhydride (7.3 g.; excess of 10% over the theoretical amount) in dilute acetic acid added. When the vigorous reaction had ceased, the mass was kept at room temperature for two hours, boiled for the same period and poured out into water. The ketone boiled at 119–121°/0.01 mm.; yield, 16 g.

Anal. Calc'd for $C_{13}H_{16}O$: C, 83.0; H, 8.5.
Found: C, 82.7; H, 8.8.

The semicarbazone formed needles (from 50% methyl alcohol) and had the m. p. 168–169°.[23]

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[21] For similar observation, see BERGMANN, HOFFMANN, AND MEYER, *J. prakt. Chem.*, [2], **135**, 245 (1932).

[22] WEIZMANN, BERGMANN, AND HASKELBERG, *Chem. & Ind.*, **56**, 587 (1937); compare COOK AND CO-WORKERS, *J. Chem. Soc.*, **1936**, 62, 71.

[23] Compare, also for references, COOK, HEWETT, AND LAWRENCE, *J. Chem. Soc.*, **1936**, 69.

Methyl 1-benzyl-1-cyclohexene-2-acetate (*XV*).—*o*-Benzylcyclohexanone (22 g.) reacted with zinc (17 g.) and methyl bromoacetate (28 cc.) in benzene (125 cc.), on gently heating. When the reaction had ceased, the mass was boiled for three hours, and the crude product, isolated as usual, was heated in benzene solution (125 cc.) with phosphoric oxide (20 g.). The product was decomposed with ice water, and the ester was purified by vacuum distillation; colorless oil, b. p. 135–136°/0.02 mm., n_D^{26} 1.5231; yield, 18 g. On standing, the ester crystallized spontaneously; m. p. 63–65°.

Anal. Calc'd for $C_{16}H_{20}O_2$: C, 78.7; H, 8.2.
Found: C, 78.5; H, 8.3.

When the ester (5 g.) was heated for twelve hours at 300° with palladous hydroxide on barium sulfate,[24] and the product, isolated by means of acetone, sublimed at 0.01 mm., crystals were obtained, which, after recrystallization from propyl alcohol, could be identified as anthracene; m. p. and mixture m. p. 215°.

When the above ester (3 g.) was kept at room temperature with bromine (1.3 cc.) in glacial acetic acid (10 cc.) for twelve hours and then heated for three more hours, a copious evolution of hydrobromic acid took place. The product was poured out into water and separated into a neutral fraction (viscous, ill-defined, bromine-containing oil, b. p. 185–190°/0.01 mm.) and an acid, which distilled at 0.7 mm.. and crystallized on standing. After trituration with acetone, it was recrystallized from high-boiling (130°) light petroleum; clusters of needles, m. p. 152°.

Anal. Calc'd for $C_{15}H_{13}O_2Br$: C, 59.0; H, 4.0.
Found: C, 59.5; H, 4.3.

SUMMARY

(*o*-Ethylphenyl)diphenylacetic acid, benzohydrylbenzylacetic acid, [*o*-(α-phenylethyl)phenyl]phenylacetic acid, [*o*-(β-phenylethyl)phenyl]-phenylacetic acid, *o*-benzyl-α-phenylhydrocinnamic acid, and *o*-benzyl-β-phenylhydrocinnamic acid have been synthesized, and the methods involved have been fully discussed. The synthesis of (*o*-benzylphenyl)-benzylacetic acid failed.

[24] KUHN AND STROEBELE, *Ber.*, **70**, 785 (1937).

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

THE PREPARATION OF 2-ALKYLAMINOBENZIMIDAZOLES

ALBERT BLOOM AND ALLAN R. DAY

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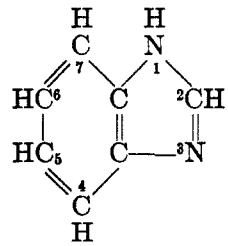
The imidazole ring structure is of considerable interest because of its presence in histidine and histamine. The latter has been isolated from ergot. It exhibits pressor action and, like the ergot alkaloids, has the property of producing marked uterine contraction. In spite of the importance of these properties no extended effort appears to have been made to synthesize and study compounds of similar structure. Similar derivatives of dihydroimidazole have likewise been neglected, although recently F. A. Jones and C. Wilson[1] have reported that trimethoxybenzyldihydroimidazole shows pressor activity. This statement is of interest, as it might indicate that the physiological activity may be inherent in the ring structure itself and thus not be dependent on the presence of an ethylamino side-chain.

A survey of the literature shows that other compounds containing the imidazole ring, such as benzimidazole and 9,10-phenanthrimidazole derivatives, show promise of possessing interesting physiological properties. Various benzimidazole derivatives have been reported as showing anesthetic, antipyretic, or hypnotic action. *N*-Methyl-9,10-phenanthrimidazole has been reported as having morphine-like properties.[2]

The above statements appear to warrant a more comprehensive study of compounds which contain the imidazole grouping. The present paper deals entirely with benzimidazole derivatives. The work is being continued, and is also being extended to the phenanthrimidazoles and the imidazoles. Only a few benzimidazole derivatives showing physiological activity have been reported, and in those few cases, no series of one type of derivative has been investigated. The nomenclature used, for the discussion of benzimidazole derivatives in this paper, is based upon the following formula for benzimidazole.

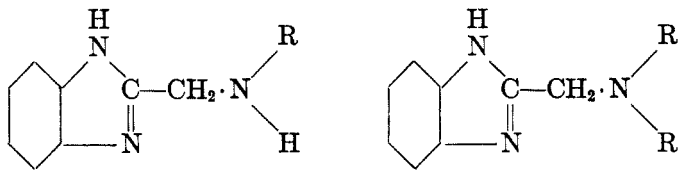


[1] JONES AND WILSON, *Lancet*, **1**, 195, (1938).

[2] VAHLEN, *Arch. exp. Pathol. Pharmak.*, **47**, 368, (1932).

The following compounds, which were prepared by earlier workers, have specific pharmacological properties. 2-Diethylaminopropyl-5-phenoxy-3 benzimidazole was reported to be a local anesthetic.[3] 2-Ethoxymethylbenzimidazole, 5-ethoxy-2-ethoxymethylbenzimidazole, 2-phenoxymethylbenzimidazole, and 5-ethoxy-2-phenoxymethylbenzimidazole have antipyretic action.[4] β-Benzimidazolylethylamine, benzimidazole-2-propionic acid, 5-ethoxybenzimidazole-2-propionic acid and β-5-ethoxybenzimidazolylethylamine have been prepared for possible use as antimalarials.[5] It is interesting to note that even though a close structural resemblance exists between β-benzimidazolylethylamine and histamine, the former is stated to have no pressor action even in large doses. A few other benzimidazole derivatives have been reported as having therapeutic value or simply as pharmaceutical preparations without mention of any specific properties.[6, 7, 8]

K. Miescher,[9] in his studies on local anesthetics, attributed the anesthetic action to basic substituents or those containing oxygen combined with higher aliphatic or hydroaromatic as well as negative groups. He further concluded that heterocyclic groups are effective and that the accumulation of the heterocyclic rings increases local anesthetic activity. It is interesting to compare the structures of the compounds that have just been described and those prepared in this investigation with his conclusions. The compounds prepared in the course of the present work are substituted in the 2 positions and have the following structures.

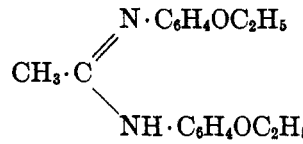


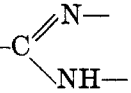
A few of the benzimidazole derivatives previously mentioned have structures similar to those described by Miescher and show local anesthetic action while others have antipyretic activity. If one considers the compounds prepared by the author, it is seen that the carbon atom adjacent to the number two carbon atom has a heterocyclic ring on one side and a substituted amine on the other. The morpholino- and piperidino- derivatives have two heterocyclic rings around this carbon atom. Local anesthetics containing the morpholine ring have already been reported,[9]

[3] I. G. Farbenind. A.-G., *D.R.P.* 550, 317.
[4] F. Bayer and Co., *Brit. Pat.* 243, 766.
[5] Chatterjee, *J. Chem. Soc.*, **1929**, 2965.
[6] Andersag and Jung, *D.R.P.* 578, 488.
[7] I. G. Farbenind. A.-G., *Brit. Pat.* 388, 374.
[8] Maron, *D.R.P.* 282, 375.
[9] Miescher, *Helv. Chim. Acta.*, **15**, 163, (1932).

and certain nitrogen-substituted amines, as well as the imines of high-molecular-weight polymethylenes, have local anesthetic properties.[10, 11] Miescher makes no mention of the imidazole ring, the only heterocyclic rings considered being picoline, pyrrole, thiophene, and furan.

The well known local anesthetic "Holocaine" contains a grouping



found in the imidazole ring. Since it contains no higher aliphatic or hydroaromatic groups attached through oxygen but does contain the structure  , found in the imidazole ring, it would seem that its local anesthetic properties might be due essentially to that structure.[12]

The 2-alkylaminobenzimidazoles were obtained by condensing 2-chloromethylbenzimidazole with a suitable amine. Some difficulties were encountered in the preparation of 2-chloromethylbenzimidazole. In both Sika's[13] and Poole's[14] methods, *o*-phenylenediamine and a fatty acid are heated at the boiling point of the mixture or at 150° in an oil bath. No chloromethylbenzimidazole could be obtained by these methods, and it was later found that the compound decomposed at the temperatures used by Sika and Poole. The chloromethyl derivative was finally prepared in good yields by the method of Phillips.[15]

EXPERIMENTAL

2-Chloromethylbenzimidazole.—*o*-Phenylenediamine (10.8 g.), chloroacetic acid (14.2 g.) and 4*N* hydrochloric acid (100 cc.) were heated under reflux for 45 minutes. The mixture was allowed to stand overnight, filtered, diluted with 200 cc. of water, cooled and carefully neutralized with 6*N* ammonium hydroxide solution. The solution must be kept cold during the neutralization and stirred vigorously to prevent the formation of gums. Solid sodium bicarbonate may also be used. The product was filtered, washed well with cold water, and pressed between porous plates for a few hours. It was then placed in a vacuum desiccator until dry. The yields obtained varied from 80 to 85 per cent. This product was pure enough for the subsequent condensations. Samples for analysis were obtained as colorless prisms by recrystallization from dioxan; m.p. 165°. Care must be taken in handling

[10] GARDNER AND HAMMEL, *J. Am. Chem. Soc.*, **58**, 1360, (1932).
[11] OGATA, *J. Pharm. Soc. Japan*, **456**, 81, (1920).
[12] RUZICKA, SALOMON, AND MEYER, *Helv. Chim. Acta.*, **20**, 127, (1937).
[13] SIKA AND MULLER, *Monatsh.*, **57**, 97, (1931).
[14] POOLE, *J. Am. Chem. Soc.*, **59**, 178, (1937).
[15] PHILLIPS, *J. Chem. Soc.*, **1928**, 2393.

2-chloromethylbenzimidazole since it is a powerful skin and mucous membrane irritant.

Anal. Calc'd for $C_8H_7ClN_2$: N, 16.83. Found: N, 16.76.

G. Hughes and L. Lions[16] recently reported the preparation of this compound. They obtained very low yields by the direct action of chloroacetic acid on *o*-phenylenediamine. Yields of 71 per cent. were obtained by the action of thionyl chloride on 2-hydroxymethylbenzimidazole. The low yield obtained by Hughes and Lions by the first method can be explained by their not allowing the reaction mixture to stand a considerable time after refluxing. It has been noted, during the course of this investigation, that yields as low as 20 per cent. were obtained when that procedure was not followed. When the reaction mixture was allowed to stand overnight at room temperature the yield was always good. Hughes reported a melting point of 161°. When the melting point was taken in a capillary tube the compound became yellow and softened at this temperature but did not melt. Furthermore, the melting point by this method varied with the rate of heating, slow heating raising the melting point and rapid heating lowering it. For these reasons the melting point reported here was taken on a Fisher-Johns melting-point apparatus.

Reaction of 2-chloromethylbenzimidazole with amines.—The reaction in many cases did not proceed smoothly. In preliminaty trials, gums and other side-reaction products were frequently encountered in large quantities. After the time, temperature, and solvent giving the best yields were found, further difficulty was met when the hydrochloride of the condensation product was being precipitated. In most cases oils separated, and variations in solvent were without effect. The gradual addition of a solvent saturated with hydrogen chloride to the chilled solution of the condensation product, or rapid stirring while passing the gas into or over the solution gave no better results. It was finally found that if, after saturation of the solution with hydrogen chloride, the supernatant solvent was removed from the oil, fresh solvent added, and the mixture allowed to stand in the ice box, the oil would solidify and could be recrystallized. This procedure was followed throughout the investigation wherever such conditions occurred.

2-(Methylaminomethyl)benzimidazole.—Five grams of methylamine was dissolved in 100 cc. of ether containing 5 cc. of alcohol, and 13.4 g. of 2-chloromethylbenzimidazole was added in small portions, keeping the temperature below 15°. After the reaction subsided the temperature was slowly raised to 30° and kept there for three hours. The reaction mixture was then allowed to stand overnight at room temperature. Two hundred cubic centimeters of ether was added, the reaction flask placed in an ice bath for a few hours, and the precipitated methylamine hydrochloride was removed. The filtrate was saturated with hydrogen chloride, the precipitate was collected, washed with cold ether, and dried; yield 15.1 g. Recrystallization from alcohol by means of ether gave colorless needless; m.p. 207–209°, dec.

Anal. Calc'd for $C_9H_{11}N_3 \cdot 2HCl$: N, 17.95. Found: N, 17.78.

2-(Ethylaminomethyl)benzimidazole was prepared in the same way as the methyl derivative, using 5.4 g. of ethylamine and 10 g. of 2-chloromethylbenzimidazole; yield 14 g. Recrystallization from alcohol and ether gave colorless prisms; m.p. 223–225°, dec.

Anal. Calc'd for $C_{10}H_{13}N_3 \cdot 2HCl$: N, 16.94. Found: N, 16.79.

2-(Butylaminomethyl)benzimidazole.—*n*-Butylamine (8.8 g.) was dissolved in 75 cc. of alcohol; 10 g. of 2-chloromethylbenzimidazole was added, and the mixture was heated under reflux at 50° for three hours. After standing overnight at room

[16] HUGHES AND LIONS, *J. Proc. Roy. Soc., N. S. Wales*, **71**, 209, (1938).

temperature, most of the alcohol was removed under reduced pressure at 30°, and 300 cc. of ether was added. The mixture was allowed to stand in the ice box for a few hours, and the precipitated *n*-butylamine hydrochloride was removed. The filtrate was washed with a few small portions of water, dried, and saturated with dry hydrogen chloride. The precipitate was collected, washed with ether, and dried; yield 8.8 g. Recrystallization from alcohol and ether gave colorless prisms; m.p. 203–204°, dec.

Anal. Calc'd for $C_{12}H_{17}N_3 \cdot 2HCl$: N, 15.22. Found: N, 15.20.

2-(n-Amylaminomethyl)benzimidazole was prepared in the same way as the *n*-butyl derivative, using 11.6 g. of *n*-amylamine and 11 g. of 2-chloromethylbenzimidazole; yield 8.1 g. Recrystallization from alcohol and ether gave needles; m.p. 190–191°, dec.

Anal. Calc'd for $C_{13}H_{19}N_3 \cdot 2HCl$: N, 14.48. Found: N, 14.29.

2-(Benzylaminomethyl)benzimidazole.—The procedure used was somewhat similar to that used for the methylamino derivative, using 12.3 g. of benzylamine, 10 g. 2-chloromethylbenzimidazole, and 25 cc. alcohol plus 50 cc. ether as the solvent. The reaction mixture was heated at 35° for three hours, allowed to stand overnight at room temperature; then ether was added, and the condensation product was isolated as in the case of the methylamine derivative; yield 16.5 g. Recrystallization, as before, gave colorless plates; m.p. 211–213°, dec.

Anal. Calc'd for $C_{15}H_{15}N_3 \cdot 2HCl$: N, 13.55. Found: N, 13.45.

2-(Cyclohexylaminomethyl)benzimidazole was prepared in the same way as the methylamine derivative, using 12 g. of cyclohexylamine and 10 g. of 2-chloromethylbenzimidazole; yield 14.3 g. The crude derivative was purified by recrystallization from acetone, followed by washing with a few cubic centimeters of cold acetone. The product was then dissolved in a small quantity of hot alcohol, cooled, saturated with hydrogen chloride gas, and then precipitated with ether. It was obtained as colorless needles by recrystallization from boiling dioxan; m.p. 213–214°, dec.

Anal. Calc'd for $C_{14}H_{19}N_3 \cdot 2HCl$: N, 13.9. Found: N, 13.89.

2-(Phenethylaminomethyl)benzimidazole was prepared in the same way as the butylamino derivative, using 8 g. of phenethylamine and 11.7 g. of 2-chloromethylbenzimidazole; yield 6.5 g. On recrystallization, it was obtained as colorless plates; m.p. 238–239°, dec.

Anal. Calc'd for $C_{16}H_{17}N_3 \cdot 2HCl$: N, 12.96. Found: N, 12.98.

Condensation with secondary amines.—With the secondary amines it was not possible to obtain a pure product by the methods described. The precipitate obtained from the hydrogen chloride treatment was usually a gum or an oil which could not be purified. In the methods to be described the pure bases were isolated except in the case of the piperidino and morpholino compounds. Attempts to prepare the hydrochlorides from these bases were unsuccessful. The bases, however, form stable solutions in dilute hydrochloric acid and therefore may be tested physiologically with the same ease as the hydrochlorides prepared.

2-(Diethylaminomethyl)benzimidazole.—Diethylamine (8.8 g.) was dissolved in a mixture of 30 cc. of ether and 5 cc. of alcohol, 10 g. of 2-chloromethylbenzimidazole was then added in small portions, keeping the temperature below 15°. After the reaction had subsided the mixture was heated under reflux for three hours. After standing overnight at room temperature, 100 cc. of ether was added, the mixture was chilled, and the precipitated diethylamine hydrochloride was removed. The filtrate was washed with water and then evaporated to dryness at 35°. The product was collected and pressed on a porous plate. Recrystallization from hot acetone, by the careful addition of water, gave yellow needles; m.p. 170°. The yield after the first recrystallization was 11.7 g.

Anal. Calc'd for $C_{12}H_{17}N_3$: N, 20.68. Found: N, 20.51.

This compound was recently reported by Ahmed, Narang and Ray[17] with a m.p. of 169°.

2-(Di-n-butylaminomethyl)benzimidazole.—Di-*n*-butylamine (15.6 g.) was dissolved in 20 cc. of alcohol, cooled, and 10 g. of 2-chloromethylbenzimidazole was added in small portions. When the reaction had subsided, the temperature was slowly raised to 50° and kept there for three hours. After standing overnight at room temperature, 100 cc. of ether was added, the mixture was cooled, and the precipitate was removed. The filtrate was treated as in the case of the diethylamino derivative. Colorless needles were obtained by recrystallization from acetone and water; m.p. 132°; yield 14.2 g.

Anal. Calc'd for $C_{16}H_{25}N_3$: N, 16.21. Found: N, 16.18.

2-(Dibenzylaminomethyl)benzimidazole.—The procedure was similar to that for the dibutylamino derivative, using 23.7 g. of dibenzylamine dissolved in 50 cc. of alcohol and 10 g. of 2-chloromethylbenzimidazole. The mixture was finally refluxed for 3 hours. Colorless plates were obtained by recrystallization from acetone and water; m.p. 169°; yield 14.6 g.

Anal. Calc'd for $C_{22}H_{21}N_3$: N, 12.84. Found: N, 12.68.

2-(Piperidinomethyl)benzimidazole.—The method of preparation was similar to that for the methylamino derivative, using 10.2 g. of piperidine and 10 g. of 2-chloromethylbenzimidazole in 50 cc. of ether plus 10 cc. of alcohol. Colorless needles were obtained by recrystallization from alcohol and ether; m.p. 204–5°, dec.; yield 15.7 g.

Anal. Calc'd for $C_{13}H_{17}N_3 \cdot 2HCl$: N, 14.58. Found: N, 14.41.

2-(Morpholinomethyl)benzimidazole.—The method of preparation was similar to that for the methylamino derivative, using 10.5 g. of morpholine dissolved in 75 cc. of alcohol and 10 g. of 2-chloromethylbenzimidazole. The reaction mixture was refluxed for three hours. After removal of the morpholine hydrochloride, the filtrate was washed, dried, and saturated with hydrogen chloride. Colorless prisms were obtained by recrystallization from alcohol and ether; m.p. 194–5°, dec.; yield 16.3 g.

Anal. Calc'd for $C_{12}H_{15}N_3 \cdot 2HCl$: N, 14.48. Found: N, 14.36.

The piperidino and morpholino derivatives have been recently reported by Hughes,[16] who gave 193–194° and 211° respectively for the melting points of the free bases.

The semi-micro Kjeldahl method was used for the determination of nitrogen, and the titrations were carried out in boric acid solution as recommended by Meeker and Wagner.[18] All melting points recorded were taken on the Fisher-Johns melting-point apparatus.

SUMMARY

1. Certain 2-alkylaminomethylbenzimidazoles have been prepared to see whether they are physiologically useful.

2. An explanation for a previously-noted low yield in the preparation of 2-chloromethylbenzimidazole is given.

[17] AHMED, NARANG, AND RAY, *J. Indian Chem. Soc.*, **15**, 152, (1938).

[18] MEEKER AND WAGNER, *Ind. Eng. Chem., Anal. Ed.*, **5**, 396 (1933).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE SYNTHESIS OF 12-METHYLPERHYDRORETENE (ABIETANE) AND ITS NON-IDENTITY WITH FICHTELITE

EDWARD CANFIELD STERLING AND MARSTON TAYLOR BOGERT

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In a recent article in *Science*,[1] we announced the synthesis of 12-methylperhydroretene and outlined the steps by which this was accomplished. Unfortunately, mistakes in transcribing two of the structural formulas which appear in that article were overlooked. The present paper describes this synthesis in more detail and corrects the errors mentioned.

Over a century ago, it was called to the attention of chemists and others that in the fossilized remains of coniferous trees in peat and lignite beds in various parts of the world, there often occurred white or yellowish paraffin-like deposits, either crystalline or amorphous in appearance, between the annual rings, in the cracks and crevices of the wood, or disseminated throughout its mass. In general, these deposits appeared to follow the original oleoresin ducts, thus suggesting that they probably owed their genesis to the resins or resin acids of the living tree. They were, therefore, referred to as "earth resins" in some of the older handbooks.[2]

These deposits were given different names by their investigators—such as Fichtelite, Phylloretin, Tekoretin, Scheererite, Branchite, Hartite, Hatschetin, etc., with resulting confusion in the literature. It was soon learned, however, that practically all such naturally-occurring material was a mixture of hydrocarbons, the chief constituents of which were retene (VII) and fichtelite as we now know them, the former taking its name from the Greek *retine*, resin or gum,[3] and the latter from its occurrence in fossilized pine trunks from peat beds of the Fichtelgebirge (German, *Fichte*, pine) region of Bavaria.[4]

One of the earliest investigations of these natural products was that of Trommsdorff,[5] who examined a sample received from Dr. Fikentscher.

[1] BOGERT AND STERLING, *Science*, n.s., **87**, 196 (Feb. 25, 1938).
[2] *Gmelin's Handbook of Chemistry*, XVIII, **1871**, p. 248.
[3] FRITZSCHE, *Ann.*, **109**, 250 (1859).
[4] BROMEIS, *ibid.*, **37**, 304 (1841).
[5] TROMMSDORFF, *ibid.*, **21**, 126 (1837).

The latter obtained it from a peat bed near Redwitz in the Fichtelgebirge, where it occurs in fossilized trunks of conifers, particularly either *Pinus uliginosa N*,[6] or *Pinus sylvestris*.[7] The crystalline product he separated was apparently an impure retene. Later, from some additional material, from the same source, Bromeis[4] succeeded in isolating pure fichtelite, which crystallizes from alcohol in tabular crystals, m.p. 46.5°, and has been studied by a number of other investigators[6, 7, 8, 9] since.

Almost invariably it occurs associated or mixed with retene, or perhaps as a solid solution of the two. This association led early investigators to assume some genetic relationship between them, and in 1889 Bamberger and Strasser[10] concluded that fichtelite was probably perhydroretene, $C_{18}H_{32}$. Liebermann and Spiegel,[11] by treatment of retene with hydriodic acid and phosphorus in sealed tubes at 250°, obtained retenedodecahydride, $C_{18}H_{30}$, from which Spiegel[11b] isolated a crystalline solid, m.p. 48°, which he believed to be retene perhydride, identical with fichtelite, but which he did not secure in sufficient amount for analysis or identification. Twenty years later, Ipatiew,[12] by hydrogenation of retene under high pressure, in the presence of a nickel oxide catalyst, produced a perhydroretene as an oil, b.p. 300–315°, which refused to solidify in an ice-salt mixture, and was not identical with fichtelite. Perhydrophenanthrenes, $C_{14}H_{24}$, prepared by these two methods, showed similar differences.[13, 14]

A definite connection between retene and fichtelite was established by Ruzicka, Balaš, and Schinz,[15] when they obtained retene from fichtelite by heating the latter with sulfur. Later, Ruzicka and Waldman,[16] dehydrogenated fichtelite quantitatively, and obtained, in addition to one mole of retene and approximately six of hydrogen, one mole of methane per mole of fichtelite, a result which indicated that fichtelite was probably a perhydromethylretene with its methyl group in tertiary union, most likely in the same relative position as in abietic acid, *i.e.* on C^{12}. Fichtelite would be structurally identical, then, with abietane, $C_{19}H_{34}$, or

[6] HELL, *Ber.*, **22**, 498 (1889).

[7] CLARK, *Ann.*, **103**, 236 (1857).

[8] MALLET, *Ber.*, **5**, 817 (1872); *Chem. News* (London), **26**, 159 (1872).

[9] BAMBERGER, *Ber.*, **22**, 635 (1889).

[10] BAMBERGER AND STRASSER, *ibid.*, **22** 3361 (1889).

[11] (*a*) LIEBERMANN AND SPIEGEL, *ibid.*, **22**, 780 (1889); (*b*) SPIEGEL, *ibid.*, **22**, 3369 (1889).

[12] IPATIEW, *ibid.*, **42**, 2096 (1909).

[13] LIEBERMANN, SPIEGEL, AND LUCAS, *ibid.*, **22**, 779 (1889).

[14] IPATIEW, JAKOWLEW, AND RAKITIN, *ibid.*, **41**, 1000 (1908). See also Denisenko and Kotel'nikova, *J. Gen. Chem.* (U. S. S. R.), **7**, 2822 (1937).

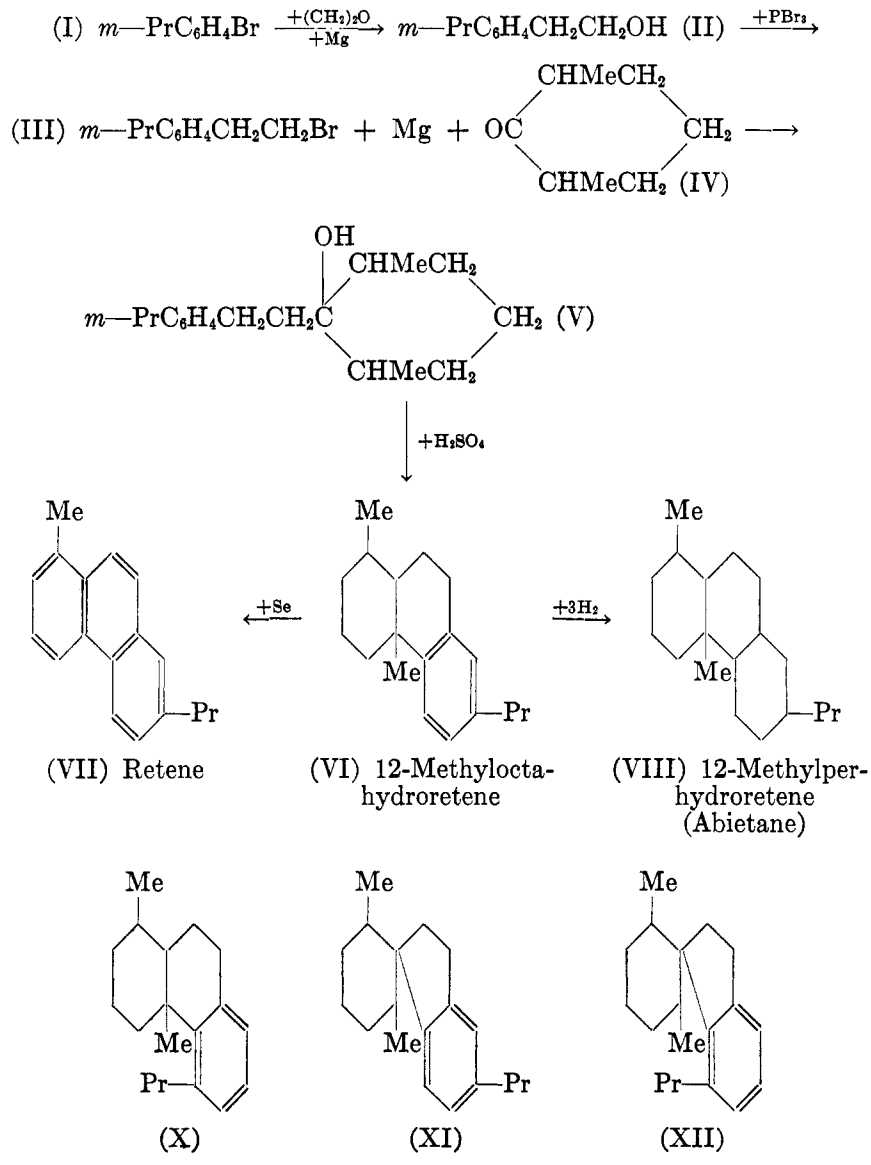
[15] RUZICKA, BALAŠ, AND SCHINZ, *Helv. Chim. Acta*, **6**, 692 (1923).

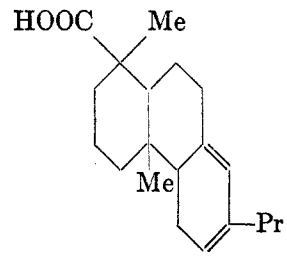
[16] RUZICKA AND WALDMAN, *ibid.*, **18**, 611 (1935).

perhydroabietene, and it was to check this by synthesis that a 12-methylperhydroretene, $C_{19}H_{34}$, was built up by the steps shown in the following flow sheet.

FLOW SHEET

(Pr-isopropyl)





(IX) Abietic acid

Theoretically, the cyclodehydration of the tertiary alcohol (V) might lead to the formation of either (VI), (X), (XI), or (XII), aside from possible stereoisomers.

When the reaction was carried out, practically all the product distilled at 180–181° at 12 mm. pressure, and yielded only retene when fused with selenium. The evidence, therefore, is that (VI) was apparently the only product of the cyclization under the conditions of our experiments.

Catalytically hydrogenated, it absorbed three moles of hydrogen per mole of hydrocarbon, with formation of a saturated $C_{19}H_{34}$ hydrocarbon, as an odorless, colorless, transparent, viscous oil (VIII), which could not be obtained in crystals.

Since fichtelite is a white crystalline solid, m.p. 46.5°, it is obviously different from our synthetic product. Whether the difference between the two is stereochemical,[15] or is due to a difference in the location of the angular methyl group, remains to be determined. A critical comparison of the synthetic with the natural product awaits the receipt from Europe of an additional supply of fichtelite.

The recent X-ray crystallographic and related studies of fichtelite by Crowfoot,[17] give a molecular weight of 264 ± 4($C_{19}H_{34} = 262$) for this hydrocarbon. Her investigation also indicates that the molecules are roughly lath-shaped and that their arrangement, taken together with their low crystal density, is additional evidence for the presence of a methyl group in tertiary linkage.

The synthetic product, however, appears to be identical with the major component of a mixture of saturated hydrocarbons obtained by the catalytic hydrogenation of "abietene" according to the Hasselstrom and Hull patent,[18] and supplied to us through the courtesy of the G. and A. Laboratories of Savannah, Ga. This major component was separated as a colorless mobile oil by repeated fractional distillation over sodium until its boiling point remained practically constant (183–184° at 12 mm.);

[17] CROWFOOT, *J. Chem. Soc.*, **1938**, 1241.

[18] HASSELSTROM AND HULL, *U. S. Pat.* **2,095,548** (Oct. 12, 1937); *Chem. Abstr.*, **31**, 8547 (1937).

its physical constants were those shown in the appended Table, and its percentage composition agreed with that calculated for $C_{19}H_{34}$.

Inasmuch as this abietane may be regarded as the fundamental hydrocarbon of the entire abietic group of resin acids and related compounds, we hope to be able to study it somewhat more fully.

We are now attempting to synthesize abietic acid by a process similar to that described above for the 12-methylperhydroretene.

Acknowledgement.—We are under especial obligations to Professor Homer Adkins, of the University of Wisconsin, for carrying out, in his hydrogenation apparatus, the catalytic reduction of our octahydromethylretene (I).

TABLE

PHYSICAL CONSTANTS OF COMPOUNDS DISCUSSED

COMPOUND	M.P.	B.P., °C.	PRESSURE, (MM.)	SP. GR.	REFR. INDEX	OPT. ROT.
Fichtelite	46.5°	235.6 355.2	43 719	0.938 (d_4^{22})	1.5052 (n_D^{20})[a]	+19.° (α_D^{20}) +18.08° (α_D^{20})
Abietane	Liq.	183–4 345–8	12 760	0.9368 (25°)	1.5022 (n_D^{25})	+10.45° (α_D^{25}) +12.53° (α_D^{25}) ($CHCl_3$)
12-Methylperhydroretene	Liq.	179–80	12	0.9374 (d_4^{25})	1.5025 (n_D^{25})	0°
Vocke $C_{19}H_{34}$	Liq.	128	1			

[a] On supercooled liquid material.[15]

EXPERIMENTAL

The thermometers used in these experiments were calibrated with the aid of U. S. Bureau of Standards certified thermometers. All melting points were determined in an open beaker with vigorous agitation, while raising the temperature at the rate of three degrees per minute, and the readings were corrected for stem exposure. Refractive indices were measured at 25° with an Abbé refractometer. The analytical work was carried out by Dr. Donald Price and Mr. Saul Gottlieb, and was of the micro type.

Fichtelite.—The fichtelite used in our experiments came from "near Wunsiedel, Fichtelgebirge, Bavaria," and was imbedded in and disseminated through some pieces of partially fossilized coniferous wood. This wood was shredded and extracted with petroleum ether in a continuous extractor. The extract was shaken with successive portions of sulfuric acid to remove retene and other contaminants, and was then crystallized from petroleum ether. The product formed white crystals, m.p. 46.5°, in agreement with the literature.[16]

Nitrocumenes.—A mixture of 86 g. of nitric (sp. gr. 1.42) and sulfuric (sp. gr. 1.84) acids was slowly stirred into 100 g. of cumene, prepared from benzene, isopropyl-bromide, and amalgamated aluminum. Maintaining the temperature at 10–20°, the stirring was continued for 2 hrs., after which the product was poured into cold water, washed, and distilled repeatedly at 12 mm. pressure. Three fractions were collected as follows: (1) 18 g., b.p. 117–119°; (2) 67 g., b.p. 128°; and (3) 7 g., b.p. 168–170°.

Of these, (1) gave *o*-nitrobenzoic acid, and (2) *p*-nitrobenzoic acid, when oxidized with chromium trioxide in glacial acetic acid solution. By reduction with tin and hydrochloric acid, both (1) and (2) yielded bases whose oxalates, crystallized from water, melted respectively at 170° (corr.) and 157° (corr.). Constam and Goldschmidt[19] have reported for *o*-cumidine oxalate a m.p. of 173°, and for the *para* isomer 159°. As noted beyond, fraction (3) consisted of dinitrocumene. The approximate composition of our nitrated cumene was 19% *ortho*, 73% *para*, and 8% dinitro.

By varying slightly the proportion of acid (83 g. nitric and 125 g. of sulfuric) to 100 g. of cumene, and operating at a temperature of 40–50°, a yield of 77% of the *p*-nitrocumene was secured, with but very small amounts of the *o*-nitro and dinitro derivatives, and most of the unnitrated cumene was recovered.

2,4-Dinitrocumene.—As already mentioned, the nitration product obtained in fraction (3) above had a b.p. of 168–170° at 12 mm. Purified by freezing, it was obtained in yellow crystals, m.p. 18.5° (corr.), b.p. 136° at 2 mm.

Anal. Calc'd for $C_9H_{10}N_2O_4$: C, 51.40; H, 4.81.
Found: C, 51.79; H, 4.79.

By careful oxidation in glacial acetic acid solution with chromium trioxide and a few drops of hydrochloric acid, a small quantity of *m*-dinitrobenzene was isolated. Considerable difficulty was experienced in achieving an oxidation without complete destruction of the molecule, with separation of oxides of nitrogen.

The nitration of cumene has been carried out before by other investigators[19, 20, 21, 22] but in none of these cases was any description given of the properties of the pure nitro derivatives. The crude product was either reduced direct, or after a partial purification (washing, or steam distillation), to a mixture of amino cumenes.

p-*Cumidine* was prepared by reduction of *p*-nitrocumene with tin and hydrochloric acid, and was purified by distillation with steam, followed by fractionation at atmospheric pressure; b.p. 222.5° (literature; 217–220°[19], 225°[21]); yield, 77%.

Attempts to produce *p*-cumidine by heating a mixture of aniline, isopropyl alcohol, and zinc chloride under pressure,[23] or by the action of high temperature and pressure upon *N*-isopropylaniline hydrochloride,[24] proved much less satisfactory.

Acetyl derivative.—By the action of acetic anhydride upon a solution of *p*-cumidine in dilute acetic acid. White leaflets, from dilute alcohol, m.p. 102.5° (corr.), in agreement with the figure found by other investigators;[19] yield, 92%.

3-Bromo-4-acetamidocumene.—The foregoing acetyl derivative was brominated in glacial acetic acid solution, at 45°, and the crude product was purified by crystallization from water; white leaflets, m.p. 129° (corr.).

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[19] CONSTAM AND GOLDSCHMIDT, *Ber.*, **21**, 1158 (1888).
[20] CAHOURS, *Compt. rend.*, **26**, 315 (1847).
[21] NICHOLSON, *Ann.*, **65**, 59 (1849).
[22] POSPJECHOW, *J. Russ. Phys.-Chem. Soc.*, **18**, 52 (1886).
[23] LOUIS, *Ber.*, **16**, 111 (1883).
[24] HOFMANN, *ibid.*, **7**, 527 (1874).

Anal. Calc'd for $C_{11}H_{14}BrNO$: C, 51.56; H, 5.51; Br, 37.34.
Found: C, 51.93; H, 5.78; Br, 37.21.

3-Bromo-4-aminocumene, obtained by refluxing the preceding crude compound for three hours with a mixture of alcohol and concentrated hydrochloric acid, followed by liberation of the free base with caustic alkali, formed a pale-yellow liquid, b.p. 141–143° at 16 mm. pressure; yield, 46%, calculated upon the basis of initial unbrominated acetocumidide.

Anal. Calc'd for $C_9H_{12}BrN$: C, 50.47; H, 5.61.
Found: C, 51.04; H, 5.79.

Hydrochloride.—Fine white needles, from water or alcohol, melting at 190–195° (corr.) with decomposition and sublimation.

m-*Bromocumene* (*I*).—The amino group was eliminated from the antecedent compound in the customary manner, by digesting the diazonium salt with copper-bronze powder and distilling the resulting mixture with steam. The crude product thus driven over was purified by washing with alkali, to remove phenols, then with concentrated sulfuric acid, followed by water, and finally was distilled at atmospheric pressure. The purified compound formed a colorless clear oil, b.p. 208–210°; yield, 50%.

Anal. Calc'd for $C_9H_{11}Br$: C, 54.23; H, 5.57.
Found: C, 54.50; H, 5.60.

Oxidized by alkaline permanganate, it gave *m*-bromobenzoic acid, m.p. 155° (corr.), in agreement with the literature.[25]

The *o*-nitrocumene, obtained as a by-product in the nitration of cumene, was reduced to *o*-cumidine (b.p. 220–221°) (Constam and Goldschmidt,[19] 213.5–214.5° at 732 mm.), which was acetylated, and the acetyl derivative was then brominated. The product was probably chiefly the 2-acetamido-5-bromocumene mixed with some of the 3-bromo isomer. For our purpose, it was not necessary to separate these isomers, since both gave only *m*-bromocumene when the acetamido group was eliminated. The *m*-bromocumene prepared in this way was identical with that prepared from the *p*-cumidine, and the overall yield was equally good.

beta-m-*Cumylethanol* (*II*), prepared from *m*-bromocumene, ethylene oxide, and magnesium, by the usual Grignard procedure, was fractionated twice with a Widmer column, and a 55% yield of the alcohol was obtained; b.p. 124° at 10 mm. pressure.

Anal. Calc'd for $C_{11}H_{16}O$: C, 80.42; H, 9.83.
Found: C, 80.01, H. 9.92.

3,5-Dinitrobenzoate.—Pale-yellow needles, from dilute alcohol, m.p. 82° (corr.).

Anal. Calc'd for $C_{18}H_{18}N_2O_6$: C, 60.34; H, 5.06.
Found: C, 60.33; H, 5.23.

beta-m-*Cumylethylbromide* (*III*), from the alcohol (II) and phosphorus tribromide; yield, 88%; b.p. 120° at 10 mm. pressure.

Anal. Calc'd for $C_{11}H_{15}Br$: C, 57.89; H, 6.60.
Found: C, 57.72; H, 6.59.

2,6-Dimethyl-1-beta-(m-*cumylethyl*)*cyclohexanol* (*V*).—By condensation of the foregoing bromide (III) with 2,6-dimethylcyclohexanone (IV) (synthesized through *alpha,alpha'*-dimethylpimelic acid,[26,27]) by the Grignard reaction, and fractionation

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[25] FRIEDBURG, *Ann.*, **158**, 19 (1871).

[26] (*a*) KIPPING, *J. Chem. Soc.*, **67**, 350 (1895); (*b*) KIPPING AND EDWARDS, *Proc. Chem. Soc.*, **1896**, 188.

[27] ZELINSKY, *Ber.*, **28**, 781 (1895); **30**, 1541 (1897).

of the crude product under diminished pressure, there resulted a 43% yield of the tertiary alcohol (V) sought. It formed a pale-yellowish oil, b.p. 144–146° at 2 mm. pressure, which could not be crystallized, but congealed to a glassy solid at low temperature.

Anal. Calc'd for $C_{19}H_{30}O$: C, 83.14; H, 11.03.
Found: C, 83.50; H, 10.98.

Attempts to prepare from this alcohol either a phenylurethane or a 3,5-dinitrobenzoate, led only to dehydration with formation of the olefin.

12-Methyl-1,2,3,4,9,10,11,12-octahydroretene (VI).—With efficient cooling, 12 g. of the hexanol (V) was stirred into 30 cc. of 85% sulfuric acid; the mixture then washed into a separatory funnel with 30 cc. of petroleum ether, and shaken with separate portions of 85% sulfuric acid until the acid layer was colorless. The petroleum ether layer, which had acquired a bluish fluorescence, was removed, washed with a 10% sodium carbonate solution, then twice with a 10% sodium sulfate solution, after which it was dried over anhydrous sodium sulfate, and distilled under a pressure of 12 mm. Practically the entire product came over at 177–183°, as a clear, viscous oil, with a faint bluish fluorescence, which boiled at 180° when redistilled over sodium at the same pressure (12 mm.), and possessed a refractive index of n_D^{25} 1.5354; yield, 81%. It could not be obtained in crystalline form.

Anal. Calc'd for $C_{19}H_{28}$: C, 88.99; H, 11.01.
Found: C, 88.97; H, 11.01.

Dehydrogenated by fusion with selenium for 6 hrs. at 300°, this hydrocarbon gave a large yield of retene (VII) (m.p. 100°, corr., mixture m.p. 99.5°, corr.), which was identified also by its picrate (m.p. 126°, corr.; mixture m.p. 125.5°, corr.).

Anal. Calc'd for $C_{18}H_{18}$: C, 92.26; H, 7.74.
Found: C, 92.48; H, 7.80.

Anal. of picrate, $C_{18}H_{18}C_6H_3O_7N_3$: N, 9.07. Found: N, 9.41.

No other hydrocarbon could be isolated from this dehydrogenation reaction.

It will be noted that the m.p. (100°) recorded above for our retene, is slightly higher than that usually found for this compound, and agrees more closely with the m.p. (100.5–101°, corr.) reported by Ruzicka and Waldmann[16] for the retene they obtained by the action of palladium charcoal upon abietic acid. Retene, of course, like other phenanthrene derivatives, may exist in different spatial configurations, and this may account for the different melting-points observed for products obtained by different methods.

12-Methylperhydroretene (VIII).—Through the courtesy of Professor Homer Adkins, of the University of Wisconsin, 3 g. of the above octahydro compound (VII), in methylcyclohexane solution, was hydrogenated at 225° and 150 atmospheres pressure, using Raney nickel as the catalyst. The calculated quantity (3 moles) of hydrogen was absorbed in 4 hrs. Distillation of the product, under 12 mm. pressure, yielded 2.5 g. of liquid, b.p. 180–181°. This was rectified over sodium at the same pressure (12 mm.), and the fraction b.p. 179–180° (1.2 g.) used for analysis and various tests. It was a colorless, water-clear, viscous oil, which slowly congealed to a glassy solid, of indefinite m.p., when chilled by a mixture of "dry ice" and methanol. Futile attempts were made to crystallize it from various solvents, by seeding with pure fichtelite. It was unaffected by cold concentrated sulfuric acid, cold neutral or alkaline permanganate, or by bromine in carbon tetrachloride solution. Its physical constants were: b.p. 179–180° at 12 mm.; d_4^{25} 0.9374; n_D^{25} 1.5025; M_D calc'd 83.25, obs. 82.66. It was optically inactive.

Anal. Calc'd for $C_{19}H_{34}$: C, 86.93; H, 13.07.
Found: C, 87.20; H, 13.22.

Vocke[28] agitated a partially purified tetrahydroabietic acid (m.p. 175–180°, instead of 190°) with concentrated sulfuric acid at 60°, and collected with petroleum ether some oily drops which he observed floating in the liquid. The petroleum ether extract, after washing and evaporation, left a colorless mobile oil (yield not stated), b.p. 128° at 1 mm., whose analysis agreed with that calculated for $C_{19}H_{34}$, but concerning which no further information was given except that the major portion of the reaction product was something else.

The Table (page 24) gives the physical constants of fichtelite, of the abietane from the G. and A. Laboratories' crude product, of the Vocke $C_{19}H_{34}$, and of the 12-methylperhydroretene whose synthesis is described in the foregoing.

SUMMARY

1. 12-Methylperhydroretene has been synthesized from *m*-bromocumene and 2,6-dimethylcyclohexanone as initial materials, and is a colorless clear viscous oil. Hence it is not identical with the fossil resin fichtelite, for which this formula was suggested by Ruzicka and Waldman.

2. It does appear, however, to be identical with a perhydroabietene (abietane) obtained by catalytic hydrogenation of abietene at high temperature and high pressure.

[28] VOCKE, *Ann.*, **497**, 257 (1932).

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

THE CHEMISTRY OF UNSATURATED STEROIDS. V. REARRANGEMENTS AND STRUCTURE OF STEROID PEROXIDES*

WERNER BERGMANN, FRIEDA HIRSCHMANN, AND EVALD L. SKAU

Received January 9, 1939

REARRANGEMENTS OF 2,5-PEROXIDOCHOLESTENE-3

In the last paper of this series[1] it was pointed out that the photoöxidation of 2,4-cholestadiene leads to one of two products depending upon the light source. When a 200-watt Mazda bulb was used, a peroxide of m.p. 113–114° and $[\alpha]_D$ +48° was obtained, which was shown to be 2,5-peroxidocholestene-3 (I). When, on the other hand, sunlight was used, an isomeric substance of m.p. 169° and $[\alpha]_D$ +141°, which did not seem to be a peroxide, was formed. It was shown that this substance could also be obtained by sunlight irradiation of 2,5-peroxidocholestene-3. One can therefore assume that the mechanism of the photoöxidation of 2,4-cholestadiene in sunlight involves the formation of 2,5-peroxidocholestene-3 followed by its rearrangement into the substance of m.p. 169° (172° corr.).

The assumption that this rearrangement product was not a peroxide has now been substantiated. One of its two oxygen atoms is present in the form of a keto group. It reacts with hydroxylamine to give a crystalline monoöxime. This ketone, which will be referred to as ketone A, $C_{27}H_{44}O_2$, does not show the presence of a double bond on titration with perbenzoic acid. Its absorption spectrum shows only general absorption, below 250 mμ. On treatment with acetic anhydride or by distillation at 1 mm. pressure, ketone A is isomerized into ketone B, m.p. 174° and $[\alpha]_D$ +36°. Ketone B resembles ketone A in its absorption spectrum and in its behavior toward perbenzoic acid.

On treatment with a solution of potassium hydroxide in methyl alcohol both ketones give a product of the formula $C_{28}H_{48}O_3$. This substance, which is also a ketone, ketone C, contains one methoxyl group, and is therefore probably formed by some sort of addition of methyl alcohol to the molecule. Ketone C can also be obtained directly from 2,5-peroxido-

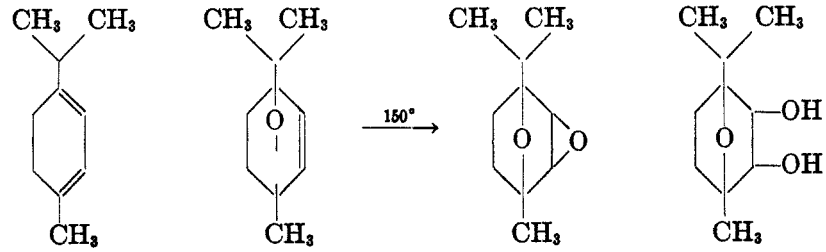
* Aided by grants from The Jane Coffin Childs Memorial Fund for Medical Research and the International Cancer Research Foundation.

[1] SKAU AND BERGMANN, J. ORG. CHEM., **3**, 166 (1938).

cholestene-3 by similar treatment. Ketone C differs from the other two ketones in that it does not absorb ultraviolet light in the region measured. It does not react with perbenzoic acid nor with acetic anhydride. On distillation at 1 mm. pressure ketone C loses one mole of methyl alcohol to form ketone B. On catalytic hydrogenation with platinum oxide catalyst all three ketones take up one mole of hydrogen to form hydroxy compounds which will be discussed in a later communication.

The isomerization of 2,5-peroxidocholestene-3 into ketonic substances resembles the rearrangement undergone by ergosterol peroxide on distillation in vacuum[2]. Here too a ketone is obtained which, apart from the double bond in the side-chain, does not contain a recognizable double bond, and which contains only one hydroxyl group, namely the one at C_3. An oxygen bridge was postulated to account for the nonreactive oxygen of the rearrangement product of ergosterol peroxide.

The rearrangement of the steroid peroxides finds an interesting parallel in the isomerization which ascaridol undergoes on heating to 150°[3]. Ascaridol (VI) is a naturally occurring transannular peroxide of the terpene series. It has been demonstrated that heating causes one of the oxygen atoms to split out of the peroxide bridge and to add to the double bond forming an ethylene oxide (VII), the presence of which has been proved by its conversion into the corresponding glycol (VIII).

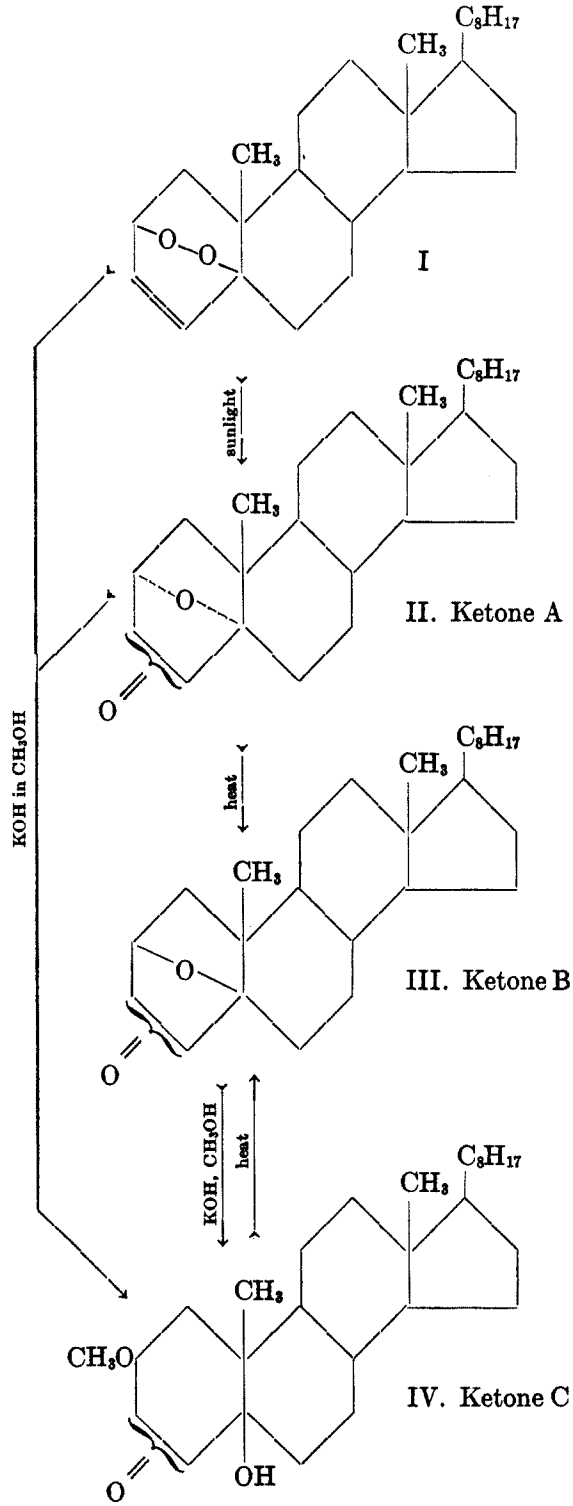


V. α-Terpinene VI. Ascaridol VII VIII

It seems probable that a similar reaction takes place during the rearrangement of the steroid peroxides. In the case of 2,5-peroxidocholestene-3 one of the oxygen atoms of the peroxide bridge probably splits out and adds to the double bond between C_3 and C_4. The ethylene oxide may then rearrange into a C_3- or C_4-ketone (II). Such rearrangements of ethylene oxides are well known in the aliphatic series.

Ketones A and B seem to be stereoisomers of the *cis-trans*-decalin type.

[2] WINDAUS, BERGMANN, AND LÜTTRINGHAUS, *Ann.*, **472**, 195 (1929).
[3] RICHTER AND PRESTING, *Ber.*, **64**, 878 (1931).


C_8H_{17}
CH_3
CH_3
O
O
I
sunlight
II. Ketone A
heat
III. Ketone B
KOH, CH_3OH
heat
CH_3O
OH
IV. Ketone C
KOH in CH_3OH

In the less stable ketone A the transannular oxide ring is probably in the *trans* position with respect to the methyl group at C_{10}. In the rearrangement of ketone A to the more stable ketone B the transannular oxygen bridge is probably shifted into a position *cis* with respect to the methyl group at C_{10} (III).

The nature of the ultraviolet absorption of ketones A and B can perhaps be explained by the fact that the keto group is adjacent to one of the carbon atoms carrying the oxygen bridge. Since ketone C does not show absorption in the ultraviolet it is very likely that it contains no oxygen bridge between C_2 and C_5.

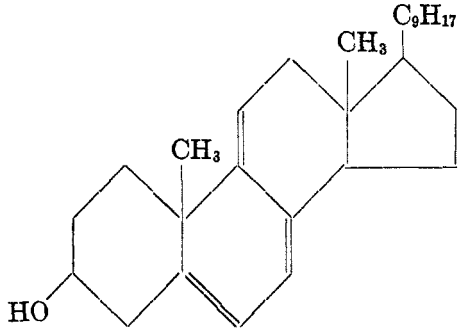
Treatment of ketone B with a solution of potassium hydroxide in methyl alcohol to form ketone C seems therefore to involve the opening of the transannular oxygen bridge and the addition of the elements of methyl alcohol. Thus ketone C would be a monomethoxy monohydroxy ketone. Since it remains unchanged on treatment with acetic anhydride it does not contain a secondary hydroxyl group. The methoxyl group may therefore be placed at C_2 and the hydroxyl group at C_5. Heating of ketone C in vacuum causes the loss of one mole of methyl alcohol and the reestablishment of the transannular oxygen bridge to form ketone B. The transformation of the peroxide (I) and of ketone A into ketone C probably involves the intermediate formation of ketone B.

DISCUSSION OF THE STRUCTURE OF STEROID PEROXIDES

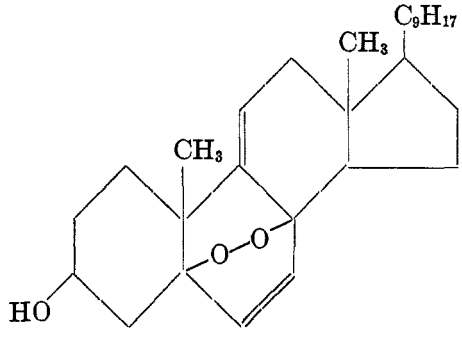
Attention should be called to the fact that all stable steroid peroxides so far known have been derived from compounds which contain conjugation in a cyclohexane ring. The same can be said of a representative of the terpene series, ascaridol (VI), which is a peroxide formed from α-terpinene (V). Attempts have been made in this laboratory to prepare peroxides by the photoöxidation of mono-unsaturated steroids as well as of dienes containing a system of conjugation extending over two rings, but these have always led to negative results. Therefore it seems justifiable to draw the conclusion that in the steroid series the ability to form stable peroxides presupposes the presence of conjugation in a cyclohexane ring. Since 1,4 addition is one of the characteristic properties of such a system of conjugation it seems quite logical to assume that oxygen is always added in such a manner as to give transannular peroxides.

In two of the better known steroid peroxides, *viz.*, those derived from 2,4-cholestadiene[1] (I) and dehydroergosterol[4] (X), the presence of a

[4] MULLER, *Z. physiol. Chem.*, **231**, 75 (1931).



IX. Dehydroergosterol



X. Dehydroergosterol peroxide

transannular peroxide bridge has been definitely established. For ergosterol peroxide[5] however, two fundamentally different structural formulas have been proposed. On the basis of their experimental work, the group of Göttingen investigators[4,6] as well as Heilbron[7], have come to the conclusion that the peroxide bridge in ergosterol peroxide is not transannular but attached to C_5 and C_6 (XI). Fieser[8], on the other hand, has concluded that the available experimental evidence can be better interpreted in favor of a transannular formula for ergosterol peroxide (XVI).

The establishment of formula XI for ergosterol peroxide has been based principally on the study of ergostadiene triol, triol I, which is obtained by the reduction of the peroxide with zinc in alkali[9]. On heating with maleic anhydride, triol I isomerizes into 3,5,6-trihydroxyergostadiene,

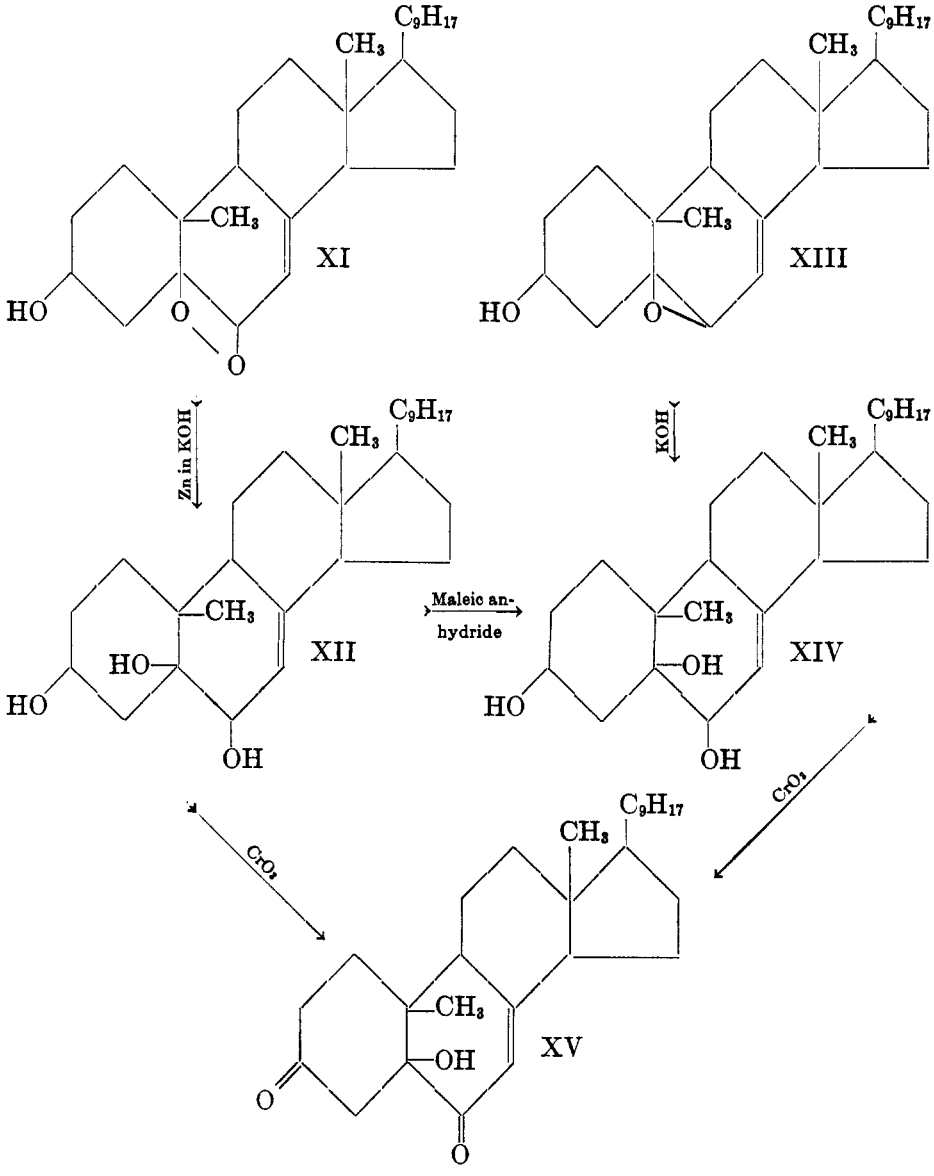
[5] WINDAUS AND BRUNKEN, *Ann.*, **460**, 225 (1928).

[6] ACHTERMANN, *Z. physiol. Chem.*, **217**, 281 (1933).

[7] DUNN, HEILBRON, PHIPERS, SAMANT, AND SPRING, *J. Chem. Soc.*, **1934**, 1576.

[8] FIESER, "The Chemistry of Natural Products Related to Phenanthrene." Reinhold Publishing Corporation, New York, **1936**, p. 174.

[9] WINDAUS AND LINSERT, *Ann.*, **465**, 156 (1928).



triol[6] II (XIV). This triol, whose constitution has been well established, is the product of hydrolysis of ergosterol monoxide[6,10] (XIII). The ease of rearrangement of triol I into triol II seemed to prove that the two com-

[10] WINDAUS AND LÜTTRINGHAUS, *ibid.*, **481**, 119 (1930).

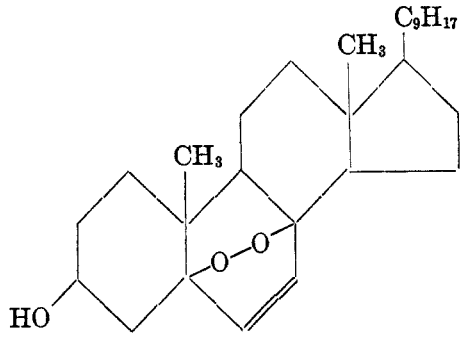
pounds were not mere position isomers but stereoisomers of the *cis*- and *trans*-decalin type. They were assigned the structural formulas XII and XIV respectively. Heilbron[7] gave as additional evidence in favor of such formulations the fact that both triols render the same diketo compound (XV) on oxidation. He reasoned that during the oxidation of triol I (XII) the hydroxyl group at C_5 had undergone inversion from the *trans* into the *cis* position with respect to the methyl group at C_{10}. It seems more logical, however, to interpret the fact that both triols give the same diketo compounds as proof for the identical position of the hydroxyl group at C_5.

Since the reactions mentioned above were thought to prove that triols I and II were stereoisomers, the conclusion was drawn that triol I had the formula XII and that ergosterol peroxide carried a peroxide bridge at C_5 and C_6 (XI). The formulation of triol I as a 3,5,6-trihydroxy compound can not, however, be readily reconciled with several of its properties. On acetylation it gives a monoacetate only[6], and on distillation in vacuum it loses two molecules of water to give dehydroergosterol[9] (IX). In contrast, triol II forms a diacetate, and can be distilled without decomposition[10]. As has already been pointed out by Fieser[8], these observations strongly indicate the presence of two tertiary hydroxyl groups in triol I and favor its formulation as a 3,5,8-triol (XVII), which obviously must have been derived from a trans-annular peroxide (XVI). The transformation of triol I (XVII) into triol II (XVIII) is explained by Fieser as due to an allylic shift.

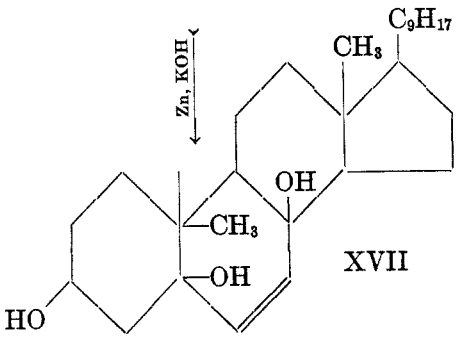
Fieser's formulas for ergosterol peroxide (XVI) and triol I (XVII) seem to be the most logical expressions for all the known properties of these compounds. The fact that triols I and II form the same oxidation product does not contradict Fieser's formula for triol I. It is quite conceivable that as the first step of oxidation of triol I (XVII) a 3-keto tetrahydroxy compound (XIX) is formed; which then loses, first one molecule of water to give a diketo diol (XX), and then a second molecule of water to give Heilbron's diketone (XXI). On the basis of Fieser's formula for ergosterol peroxide one may also postulate that the photoöxidation products of 22-dihydroergosterol[11] and 7-dehydrocholesterol[12] are transannular peroxides with a peroxide bridge between C_5 and C_8.

Ergosterol peroxide differs from 2,5-peroxidocholestene-3 in its reluctance to undergo rearrangements and its stability toward alcoholic solutions of alkali. This stability is probably due to the fact that in ergosterol peroxide the peroxide bridge is attached to two tertiary carbon atoms. If

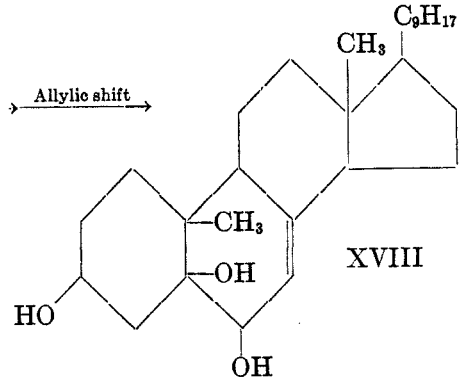
[11] WINDAUS AND LANGER, *ibid.*, **508**, 110 (1934).
[12] SCHENK, BUCHHOLZ, AND WIESE, *Ber.*, **69**, 2699 (1936).



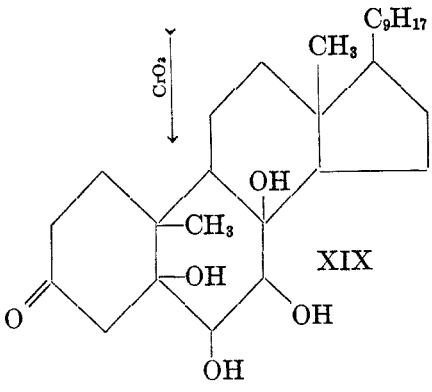
XVI. Ergosterol peroxide



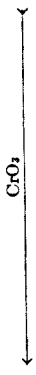
XVII

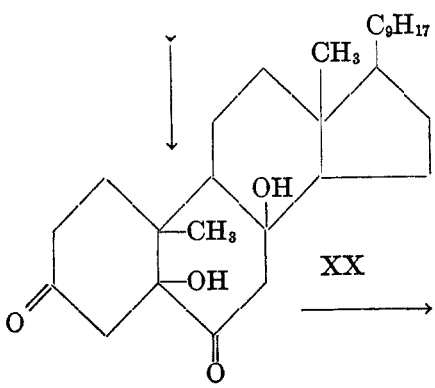


XVIII

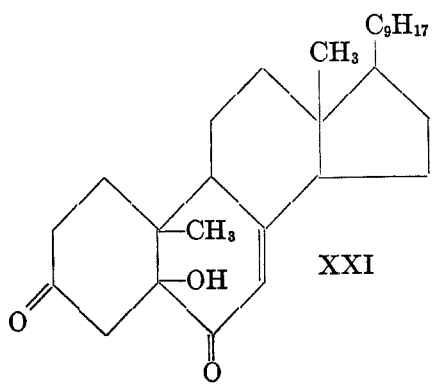


XIX



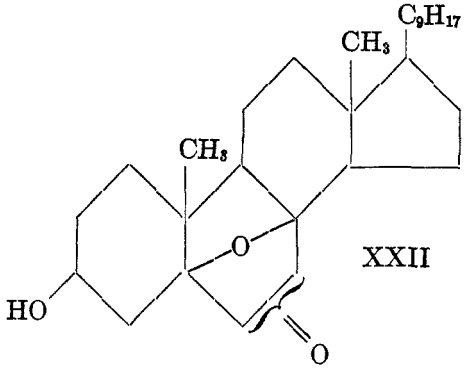


XX



XXI

ergosterol peroxide, however, is heated and then distilled in high vacuum[2] it also rearranges into a ketone which may best be formulated as XXII.



XXII

EXPERIMENTAL†

Ketone A

Preparation.—One part of 2,5-peroxidocholestene-3 was dissolved in 50 parts of absolute alcohol, and the solution was exposed to sunlight in a stoppered Pyrex flask. One week later the dense crystals which had formed were filtered off, washed with small amounts of alcohol, and recrystallized from boiling absolute alcohol (yield 88%). The pure ketone melted at 172°; $[\alpha]_D^{25}$ +141° (30.0 mg. in 3.06 cc. $CHCl_3$).

Anal. Calc'd for $C_{27}H_{44}O_2$: C, 80.93; H, 11.08.
Found: C, 81.13; H, 11.05.

Determination of active oxygen.—A 36.9-mg. sample of substance was introduced into a glass-stoppered bottle, and 20 cc. of a saturated solution of potassium iodide in glacial acetic acid was added. After standing 24 hours at room temperature in the dark, the mixture containing the sample required 3.81 cc., and the blank 3.71 cc. of 0.0990*N* thiosulfate solution. The difference corresponded to 0.07 atoms of active oxygen.

Titration with perbenzoic acid.—Upon titration with perbenzoic acid in the usual manner the ketone was found to take up no oxygen.

Oxime.—An alcoholic solution containing ketone A and an excess of hydroxylamine hydrochloride and potassium acetate was refluxed for three hours. Sufficient water was then added so that the oxime separated on cooling. After several recrystallizations from small amounts of absolute alcohol the oxime melted at 225–229°.

Anal. Calc'd for $C_{27}H_{45}NO_2$: C, 78.01; H, 10.92.
Found: C, 77.89; H, 10.98.

Ketone B

Preparation. (*a*) *By vacuum distillation of ketone C.*—Ketone C was distilled at 220–230° and 1 mm. pressure. The crystalline distillate was then recrystallized several times from small amounts of ether. Ketone B crystallizes in fine long needles; m.p. 173°; $[\alpha]_D^{25}$ +36.0° (39 mg. in 3.06 cc. ether).

† All melting points given below are corrected.

Anal. Calc'd for $C_{27}H_{44}O_2$: C, 80.93; H, 11.08.
Found: C, 81.04; H, 11.32.

(*b*) *By vacuum distillation of ketone A.*—Ketone A was distilled from a small retort at 210–230° and 1 mm. pressure. The solid distillate was then recrystallized several times from alcohol. The yield was 80%. After drying at 100° in an Abderhalden dryer the substance melted at 173.5–174°; $[\alpha]_D^{26}$ +36° (20.4 mg. in 3.06 cc. ether). A mixture of the substance with a sample of ketone B obtained by distillation of ketone C gave no depression of the melting point.

Anal. Calc'd for $C_{27}H_{44}O_2$: C, 80.93; H, 11.08.
Found: C, 80.72; H, 11.28.

(*c*) *By treatment of ketone A with acetic anhydride.*—Ketone A (210 mg.) was refluxed for two and one-half hours with acetic anhydride (0.6 cc.). The crystalline material which separated on cooling was filtered and recrystallized several times from absolute alcohol. The purified ketone melted at 171.5°. A mixture of this ketone with an authentic sample of ketone B of m.p. 173.5° melted at 172.5°. On the other hand, a mixture with a sample of ketone A melted over a range 145–156°. The yield was unsatisfactory due to the formation of resinous impurities.

Titration with perbenzoic acid.—By titration with perbenzoic acid in the usual manner 48 mg. of ketone B took up 0.19 mg. of oxygen in 18 hours, an amount corresponding to 0.10 double bonds.

Semicarbazone.—An alcoholic solution containing ketone B and an excess of semicarbazide hydrochloride and fused potassium acetate was refluxed for one hour. The semicarbazone which separated on cooling was recrystallized from alcohol. It melted at 234° with decomposition.

Anal. Calc'd for $C_{27}H_{47}N_3O_3$: C, 73.46; H, 10.36.
Found: C, 73.39; H, 9.55.

Ketone C

Preparation. (*a*) *From 2,5-peroxidocholestene-3.*—Three grams of the peroxide was refluxed for one and a half hours with 350 cc. of a 5% solution of potassium hydroxide in 95% methyl alcohol. Upon concentration to one-half of the original volume and addition of 4 cc. of water, crystals began to separate. After several recrystallizations from methyl alcohol the ketone melted at 153.5–154°; $[\alpha]_D^{26}$ +35.4° (51.8 mg. in 3.06 cc. $CHCl_3$). The yield was 65%.

Anal. Calc'd for $C_{28}H_{48}O_3$: C, 77.72; H, 11.18; $-OCH_3$, 7.17.
Found: C, 77.87; H, 10.98; $-OCH_3$, 6.88.

(*b*) *From ketone A.*—A 240-mg. portion of ketone A was refluxed for one and a half hours with 25 cc. of a 5% solution of potassium hydroxide in 95% methyl alcohol. The solution was then concentrated to half its volume, and sufficient water added so that the reaction product began to separate on cooling. After several recrystallizations from small amounts of alcohol the substance melted at 152.5–153°; $[\alpha]_D^{26}$ +35.5° (36 mg. in 3.06 cc. ether). A mixture of this substance with a sample of ketone C prepared by method (*a*) gave no depression of the melting point.

Anal. Calc'd for $C_{28}H_{48}O_3$: C, 77.72; H, 11.18.
Found: C, 77.76; H, 11.44.

(*c*) *From ketone B.*—When ketone B was treated with a solution of potassium hydroxide in methyl alcohol in an analogous manner, an 80% yield of a product of m.p. 152.5° was obtained. Mixed with an authentic sample of ketone C it gave no depression of the melting point.

Titration with perbenzoic acid.—Upon titration with perbenzoic acid in the usual

manner 66 mg. of ketone C took up 0.05 mg. of oxygen in 24 hours, an amount corresponding to 0.02 double bonds.

Semicarbazone.—An alcoholic solution containing ketone C and an excess of semicarbazide hydrochloride and fused potassium acetate was refluxed for one hour. The semicarbazone crystallized upon cooling. It was recrystallized several times from absolute alcohol; m.p. 251–254° with decomposition.

Anal. Calc'd for $C_{29}H_{51}N_3O_3$: C, 71.12; H, 10.50.
Found: C, 71.37; H, 10.43.

Treatment with acetic anhydride.—Ketone C (99 mg.) was refluxed for 3 hours with acetic anhydride (0.8 cc.). The crystals which formed on cooling were recrystallized once from methyl alcohol. The product melted at 153° and gave no depression of the melting point when mixed with ketone C.

SUMMARY

(1) 2,5-Peroxidocholestene-3 rearranges quantitatively under the influence of sunlight to give a saturated ketone, ketone A, of m.p. 172° and $[\alpha]_D$ +141°.

(2) On vacuum distillation ketone A rearranges into ketone B, m.p. 174°, and $[\alpha]_D$ +36°, which is probably a stereoisomer of ketone A.

(3) On treatment with a solution of potassium hydroxide in methyl alcohol, 2,5-peroxidocholestene-3, ketone A and B give a monomethoxy monohydroxy ketone, C; m.p. 153.5°; $[\alpha]_D$ +35°.

(4) On distillation in vacuum, ketone C is transformed into ketone B.

(5) The structure of steroid peroxides and their rearrangement products has been discussed.

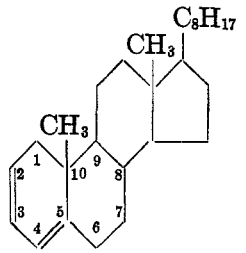
[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

THE CHEMISTRY OF UNSATURATED STEROIDS. VI. THE STRUCTURE OF 3-CHLOROCHOLESTADIENE AND 3-PHENYLCHOLESTADIENE*

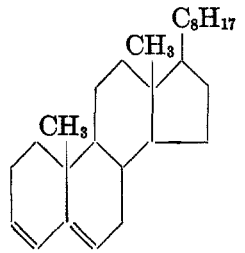
WERNER BERGMANN AND FRIEDA HIRSCHMANN

Received January 10, 1939

A systematic study of the properties of ergosterol, 2,4-cholestadiene[1] (I) and 3,5-cholestadiene[2] (II) has led to the formulation of a series of simple rules, the application of which is of great assistance in determining whether a diene has a system of conjugation restricted to one ring, type I, or



I, 2,4-Cholestadiene, $[\alpha]_D$ +168°



II, 3,5-Cholestadiene, $[\alpha]_D$ −104°†

whether it contains conjugation extending over two rings, type II. These rules may be summarized as follows:

Rule 1. Dienes of type I show selective absorption of ultraviolet light with maxima in the region of 265–280 mμ. Dienes of type II show maximum absorption in the region of 230–245 mμ.

Rule 2. Dienes of type I form normal addition products with maleic anhydride. Dienes of type II may react with maleic anhydride, but only in such a manner as to give complex products of high molecular weight.

Rule 3. Dienes of type I add one mole of hydrogen when treated

* Aided by a grant from The Jane Coffin Childs Memorial Fund for Medical Research and The International Cancer Research Foundation.

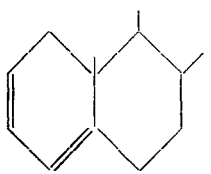
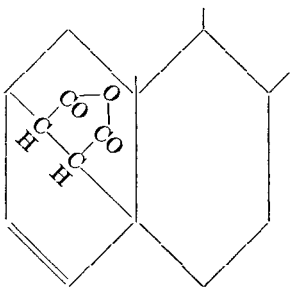
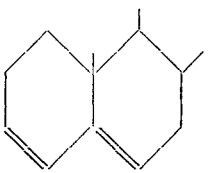
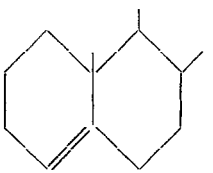
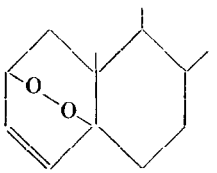
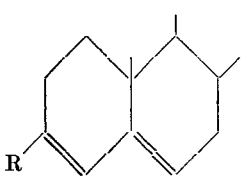
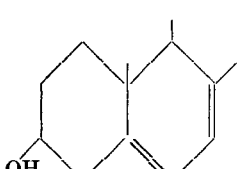
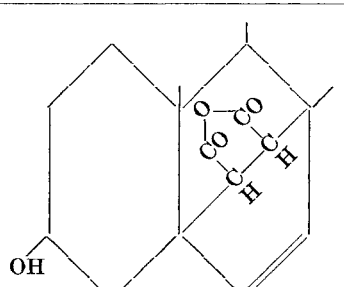
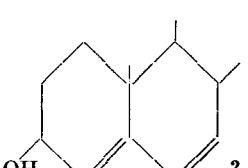
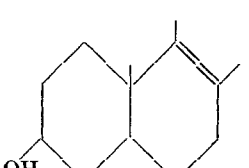
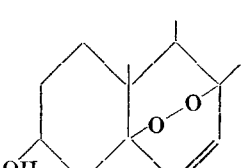
[1] STAVELY AND BERGMANN, J. ORG. CHEM., **1**, 575 (1937).

[2] STAVELY AND BERGMANN, *Ibid.*, **1**, 567 (1937).

† Since this paper was submitted for publication an article by ECK, VAN PEURSEM, AND HOLLINGSWORTH, *J. Am. Chem. Soc.*, **61**, 172 (1939) has appeared in which the authors find the rotation of 3,5-cholestadiene as $[\alpha]_D$ − 123.23°.

TABLE I

Differentiations between Dienes of Type I and Type II

Substance	Absorption maxima $[\alpha]_D$	Reaction with maleic anhydride	Reaction with acid	Reaction with Na in alcohol	Reaction with O_2 and light
Type I  2,4-Cholestadiene	267 mμ 275 mμ + 168°		 3,5-Cholestadiene	 Koprostene	 Peroxide
Type II  (a) R = H (b) R = $CH_3 \cdot CO \cdot O$—	(a) 230–240 mμ (b) 240 mμ (a) −104° (b) −100°	a and b complex compounds	a. no reaction	a. no reaction	a. no reaction
Type I  Ergosterol	280 mμ − 130°		 Isoergosterol	 Dihydroergosterol	 Peroxide

with sodium in alcohol. Dienes of type II are not reduced under these conditions.

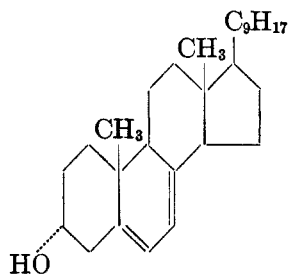
Rule 4. Dienes of type I are unstable toward dilute acid. In acid solution they rearrange to form stable compounds, preferably dienes of type II.

Rule 5. Dienes of type I add oxygen in the presence of light and a sensitizer, such as eosin, to give transannular peroxides[3]. Dienes of type II do not react in such a manner.

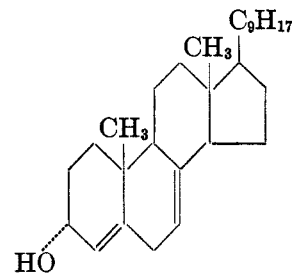
Although these rules are based on a rather limited number of observations (see Table I) we feel, however, that they should be given consideration in the study of the structure of unsaturated steroids as well as other hydroaromatic compounds.

Another helpful rule which, however, enjoys only limited application concerns the influence of a double bond at C_5 on the optical rotation of a steroid[1,4]. This rule states that simple steroids containing a Δ_4 bond always have positive rotations while their isomers containing Δ_5 bonds have negative rotations. In other words a shift of the double bond from the Δ_4 to the Δ_5 position is always accompanied by a change of rotation in the negative direction and vice versa.

No exception to this rule has as yet been found in the steroid series, and thus it should be given consideration when structural formulas for new steroids are proposed. The correctness of this rule may be illustrated by its application to an isomer of ergosterol, which, according to Marker *et al.*,[5] was epiergosterol (III). According to the rule of rotation epiergosterol should, like ergosterol, have a strongly negative rotation. The substance prepared by Marker, however, had a rotation of +50°. This



III



IV, $[\alpha]_D$ +50°

fact alone presented strong evidence that this isomer of ergosterol had a double bond in the Δ_4 position. Recent investigations by Windaus and

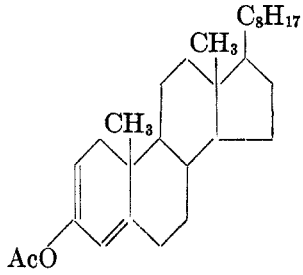
[3] BERGMANN, HIRSCHMANN, AND SKAU, *Ibid.*, **4**, 29 (1939).

[4] CALLOW AND YOUNG, *Proc. Roy. Soc.*, **A157**, 194 (1936).

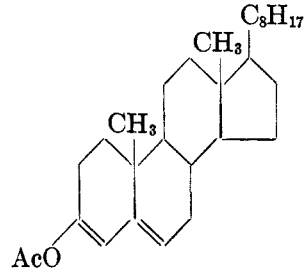
[5] MARKER, KAMM, LAUCIUS, AND OAKWOOD, *J. Am. Chem. Soc.*, **59**, 1840 (1937).

Buchholz[6] have shown that Marker's isomer was not epiergosterol, but a steroid containing double bonds in the Δ_4 and Δ_7 positions (IV). This structure is in full accordance with the rule of rotation.

Application of the rules on conjugation and the rule of rotation has made it possible to decide whether the enol acetates and enol benzoates of α,β-unsaturated ketones were derivatives of 2,4-(V) or 3,5-cholestadiene (VI). Westphal[7] found that these substances have absorption maxima at 240 mμ, that they give abnormal reaction products with maleic anhydride, that they are stable toward dilute acid as shown by the method of their preparation and that they have negative rotations. By comparing these properties with those of 2,4- and 3,5-cholestadiene, Westphal concluded that the enol esters were derivatives of 3,5-cholestadiene (VI).



V

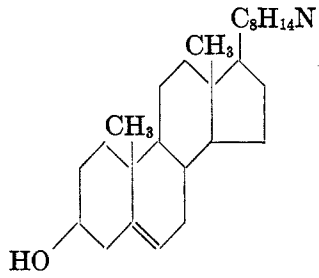


VI

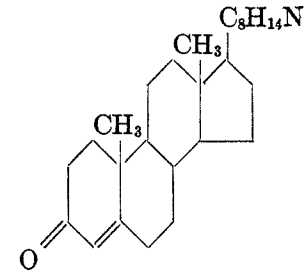
These rules also hold true in the field of steroid alkaloids. Rochelmeyer[8] found that when solatubin (VII) was transformed into its Δ_4 isomer (IX) by way of solatubenone (VIII) a change of rotation from $-27°$ to $+91°$ occurred. Dehydration of Δ_4-solatubin leads to solatubadiene, which has a high negative rotation, an absorption at 228 mμ, is not reduced by sodium in alcohol, and reacts with maleic anhydride to form a complex compound. These facts lead Rochelmeyer to conclude that the dehydration product had a pair of conjugated double bonds extending over two rings and was therefore 3,5-solatubadiene. The dehydration of Δ_4-solatubin therefore proceeds in the same manner as that of allo- and epiallocholesterol[2].

Fieser[9] has successfully applied these rules to the study of the pine resin acids. He concluded that levopimaric acid (XI or XII) contains conjugation restricted to one ring because its properties parallel those of 2,4-cholestadiene. Under the influence of mineral acid levopimaric acid

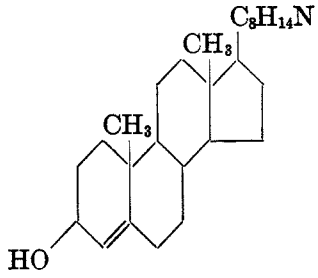
[6] WINDAUS AND BUCHHOLTZ, *Ber.*, **71**, 576 (1938).
[7] WESTPHAL, *Ibid.*, **70**, 2128 (1937).
[8] ROCHELMEYER, *Ibid.*, **71**, 226 (1938).
[9] FIESER AND CAMPBELL, *J. Am. Chem. Soc.*, **60**, 162 (1938).



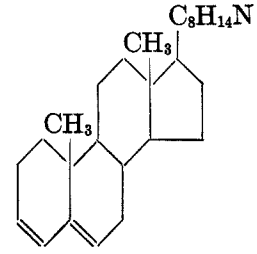
VII. Solatubin,
$[\alpha]_D = -27.3°$



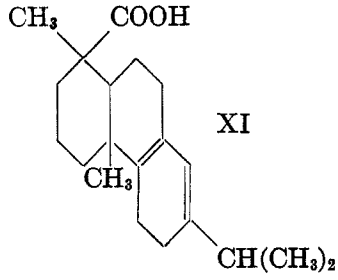
VIII. Solatubenone,
$[\alpha]_D = +152°$



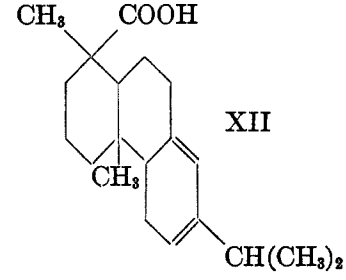
IX. Δ_4-Solatubin,
$[\alpha]_D = +91.5°$



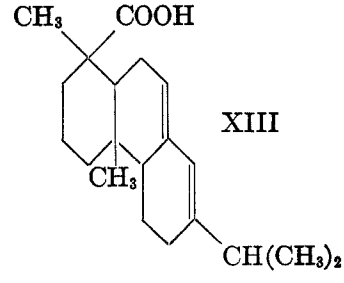
X. 3,5-Solatubadiene,
$[\alpha]_D = -186°$



XI



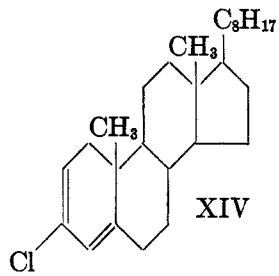
XII



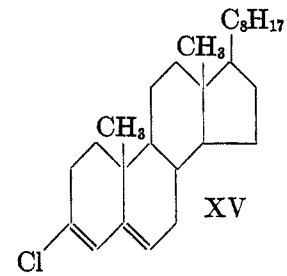
XIII

rearranges into abietic acid (XIII). This fact as well as the observation that abietic acid has properties comparable to those of 3,5-cholestadiene, has led Fieser to assign to abietic acid a structure containing a system of conjugation extending over two rings.

Ruzicka and Fischer[10] have found that the treatment of cholestenone with benzoyl chloride at higher temperatures leads to the formation of a 3-chlorocholestadiene which is either a derivative of 2,4 (XIV) or 3,5-cholestadiene (XV). The evidence which was available at that time did not permit a decision as to which of the two formulas was correct. On the basis of our more recent knowledge we may assume *a priori* that the compound is 3-chloro-3,5-cholestadiene (XV), because it has been prepared under conditions under which the 2,4 isomer is not stable (rule 4). We have found that the chloride shows maximum absorption at 240 mμ (rule 1) and that it has a negative rotation (rule of rotation). All these facts indicate that this compound is 3-chloro-3,5-cholestadiene.



XIV



XV

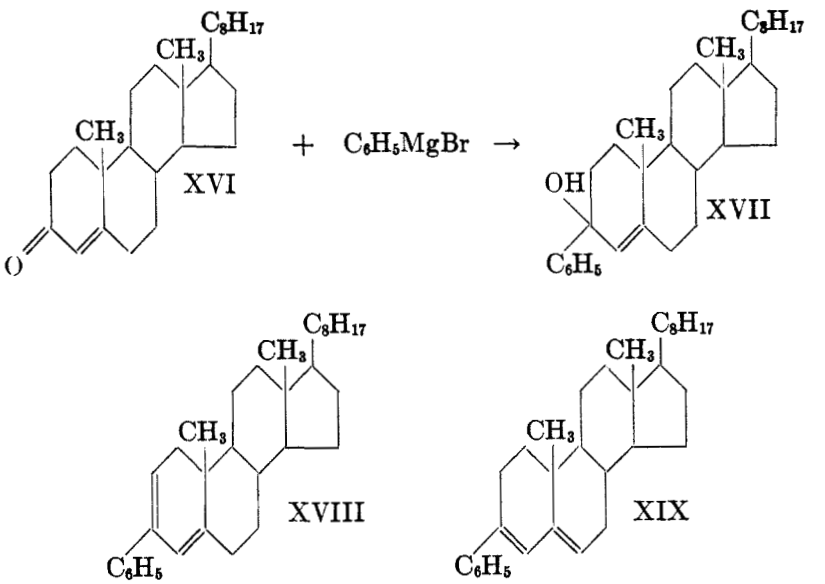
To enlarge upon our study of the properties of unsaturated compounds it was thought desirable to investigate 2,4-dienes carrying substituents at C_3. A 3-phenylcholestadiene has been prepared by a group of Japanese investigators.[11] It was obtained by treatment of cholestenone (XVI) with phenylmagnesium bromide and subsequent decomposition of the Grignard compound with acid. The Japanese investigators felt that the available evidence was insufficient to decide whether the substance was a derivative of 2,4- (XVIII) or 3,5-cholestadiene (XIX). If we apply our rules to this compound, however, we must conclude that it is 3-phenyl-3,5-cholestadiene (XIX), for it was prepared by treatment of the Grignard compound with dilute sulfuric acid (rule 4), it has a maximum absorption at 238 mμ (rule 1) in addition to the specific absorption due to the phenyl group, and it has a strongly negative rotation.

Since the method employed by the Japanese investigators was very

[10] Ruzicka and Fischer, *Helv. Chim. Acta*, **19**, 806 (1936).

[11] Urushibara, Ando, Araki, and Ozawa, *Bull. Chem. Soc. Japan*, **12**, 353 (1937).

unfavorable for the formation of a 2,4-diene, we have attempted to use a synthesis which avoided the use of acids. By treating the Grignard compound obtained from cholestenone and phenylmagnesium bromide with an equivalent of ammonium chloride it was possible to isolate the carbinol (XVII). This compound had a positive rotation, which indicated that the double bond was still in the Δ_4 position. All efforts, however, to obtain the 3-phenyl-2,4-cholestadiene by dehydrating the carbinol under neutral or slightly alkaline conditions failed. In every instance the 3,5-derivative was obtained.



EXPERIMENTAL†

3-Chloro-3,5-cholestadiene.—This chloride was prepared according to the method of Ruzicka and Fischer[10]. Three grams of cholestenone and 15 g. of benzoyl chloride were heated in a sealed tube for 24 hours at 100°. The excess benzoyl chloride was then removed *in vacuo*, and the residue was digested with small amounts of 0.5*N* sodium hydroxide on the water bath until the odor of benzoyl chloride had disappeared. The chloride was recrystallized several times from acetone; m.p. 62–63°; $[\alpha]_D^{22}$ −117.5° (39.2 mg. in 3.06 cc. $CHCl_3$).

3-Phenyl-3-hydroxy-cholestene-4.—Five grams of cholestenone, dissolved in 50 cc. of dry ether, was added drop by drop and with stirring to a freshly prepared solution of phenylmagnesium bromide, which was kept cold by immersion in an ice bath. The phenylmagnesium bromide was prepared in the usual manner from 970 mg. of magnesium ribbon and 6.2 g. of bromobenzene. When all the cholestenone had been

† All the melting points given below are corrected.

added, the solution was refluxed for 150 minutes. After cooling, crushed ice was added to the reaction mixture, and, finally, 2.14 g. of ammonium chloride dissolved in water. The ether layer was removed, washed free of hydroxyl ions, and finally dried over anhydrous sodium sulfate. The solution was concentrated to a small volume and evaporated to complete dryness *in vacuo*. The oily residue was crystallized from acetone. After several recrystallizations the carbinol was obtained in large heavy blocks; yield 80%; m.p. 103–105 5°; $[\alpha]_D^{25}$ +75.5° (29.4 mg. in 3.04 cc. ether).

Anal. Calc'd for $C_{33}H_{50}O$: C, 85.65; H, 10.89.
Found: C, 85.82; H, 11.13.

3-Phenyl-3,5-cholestadiene.—A solution of 99 mg. of the carbinol in 23 cc. 95% ethyl alcohol containing 3 drops of concentrated hydrochloric acid was refluxed for 4 hours. After dilution with water the product was extracted with ether and the ether layer was washed free of acid. The solution was dried over anhydrous sodium sulfate, the solvent was removed, and the residue was recrystallized from acetone. The yield was almost quantitative. The substance changes at 158–159° to an opaque liquid, which, on further heating, undergoes a play of colors and becomes clear at 176–180°; $[\alpha]_D^{25}$ −132° (22.5 mg. in 3.06 cc. $CHCL_3$).

Anal. Calc'd for $C_{33}H_{48}$: C, 89.12; H, 10.88
Found: C, 89.12; H, 10.69

The same 3-phenyl-3,5-cholestadiene was obtained when the carbinol was treated with acetic anhydride, or when it was distilled either alone or in the presence of aluminum oxide (Activated Alumina Grade A) at 1 mm. pressure and 210–240°.

Heating of the carbinol either alone or in the presence of aluminum oxide in an Abderhalden dryer over boiling toluene for 20 hours led to partial dehydration. The products had a negative rotation which indicated that even under such mild conditions the dehydration led to the formation of 3-phenyl-3,5-cholestadiene.

SUMMARY

(1) A series of rules concerning conjugation of double bonds restricted to one ring and conjugation extending over two rings has been formulated, and their application in the field of steroids and other hydroaromatic compounds has been discussed.

(2) It has been shown that the chloride obtained by interaction of cholestenone and benzoyl chloride is 3-chloro-3,5-cholestadiene.

(3) It has been shown that the hydrocarbon obtained by the interaction of cholestenone and phenylmagnesium bromide is 3-phenyl-3,5-cholestadiene.

(4) 3-Phenyl-3-hydroxycholestene-4 has been prepared. Dehydration of this compound has always led to 3-phenyl-3,5-cholestadiene.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON, N. J.]

SOME PROPERTIES OF THE THIOMETHYLENE RADICAL. BEHAVIOR WITH ALUMINUM CHLORIDE IN BENZENE

S. W. LEE AND GREGG DOUGHERTY

Received January 10, 1939

Organic sulfides and mercaptans form addition compounds with anhydrous aluminum chloride in which there is presumably a dative bond between the sulfur and the aluminum atoms, *i.e.*,

$$R:\ddot{S}:R.$$
$$\ddot{A}lCl_3$$

It might be supposed that one effect of the addendum would be to weaken the carbon-sulfur linkage and permit reactions which involve the breaking of this bond to occur. A search of the literature, and our own experiments indicate, however, that, under mild conditions, at room temperature, this is not generally the case. Aryl sulfides, such as diphenyl sulfide, form one-to-one addition complexes with aluminum chloride which remain unchanged in benzene, even in the presence of a substantial excess of aluminum chloride.[1] This is also true of primary alkyl sulfides. Normal primary amyl sulfide was recovered unchanged after heating for two hours at 80° in benzene with more than one equivalent of aluminum chloride. Ethyl mercaptan, and *n*-amyl mercaptan showed little activity at room temperature in similar experiments. At the boiling point of benzene some hydrogen sulfide was evolved, but little or no alkylation of the benzene took place.

It is generally observed that in molecules of the type A—CH_2—B, the bond between CH_2 and A or B is most easily broken when both A and B are negative in nature. It was thought, therefore, that if A, in A—CH_2—$\ddot{S}$—B, $\ddot{A}lCl_3$ were such a negative atom or group, the activity of the complex would be enhanced. This idea was tested using the easily available and suitable compounds: benzyl mercaptan, benzyl sulfide, and *s*-trithiane. It was found that all three were quite active at room temperature when in contact with benzene and aluminum chloride.

[1] BOESEKEN, *Rec. trav. chim.*, **24**, 213 (1905).

Benzyl mercaptan with one molecule of aluminum chloride in a large excess of benzene reacted mainly according to the equation:

(1) $C_6H_5CH_2SH + C_6H_6 + AlCl_3 \rightarrow C_6H_5CH_2C_6H_5 + H_2S + AlCl_3$.

In addition to diphenylmethane, some high-boiling (above 360°) material was obtained. This material contained no sulfur, however, so that it is safe to say that the reaction was mainly one of alkylation.

With benzyl sulfide and one molecule of aluminum chloride, under the mild conditions used, the benzene did not enter into the reaction. The principal product, obtained in good yields, was tribenzylsulfonium chloride. Obviously here the primary reaction was a scission of the carbon-sulfur bond, and the whole process may be expressed as follows:

(2) $C_6H_5CH_2SCH_2C_6H_5 \cdot AlCl_3 \rightarrow C_6H_5CH_2Cl + C_6H_5CH_2S—AlCl_2$
(3) $C_6H_5CH_2SCH_2C_6H_5 \cdot AlCl_3 + C_6H_5CH_2Cl \rightarrow (C_6H_5CH_2)_3SCl \cdot AlCl_3$.

Benzyl chloride and benzyl sulfide do not ordinarily add to form a sulfonium salt. In the above case it is probable that the aluminum chloride not involved in the splitting reaction accelerated the production of the sulfonium salt and formed with it a one-to-one addition compound. This is in agreement with the observation of Hofmann and Ott,[2] who found that ferric chloride catalyzed the addition of benzyl chloride to benzyl sulfide. They, however, apparently did not obtain a pure tribenzylsulfonium chloride by removal of the ferric chloride with water.

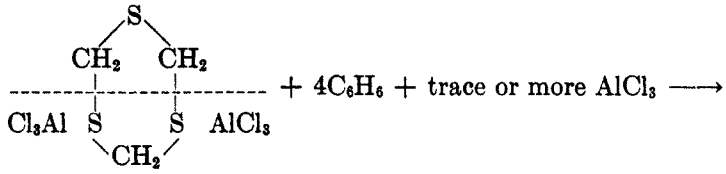
If an excess of aluminum chloride over molecular proportions was used, diphenylmethane became a major product, and the amounts of tribenzylsulfonium chloride and benzyl mercaptan produced were correspondingly less.

(4) $C_6H_5CH_2SCH_2C_6H_5 \cdot AlCl_3 \rightarrow C_6H_5CH_2Cl + C_6H_5CH_2S—AlCl_2$
(5) $C_6H_5CH_2Cl + C_6H_6 + AlCl_3 \rightarrow C_6H_5CH_2C_6H_5 + HCl + AlCl_3$
(6) $C_6H_5CH_2S—AlCl_2 + C_6H_6 + AlCl_3 \rightarrow C_6H_5CH_2C_6H_5 + HS—AlCl_2 + AlCl_3$.

s-Trithiane contains the structural unit A—CH_2—B, in which both A and B are sulfur atoms. This compound varied remarkably in its behavior with aluminum chloride in benzene at room temperature, the products obtained depending on the relative quantity of the aluminum chloride present. The following molecular ratios of *s*-trithiane to aluminum chloride were studied: *a*, 4:3; *b*, 1:1; *c*, 2:3; *d*, 1:2; and *e*, 1:3. In the cases of the ratios *a*, *b*, and *c*, the benzene entered into the reaction

[2] Hofmann and Ott, *Ber.*, **40**, 4933 (1907).

only to a slight extent. The products formed on decomposition of the reaction mixture with water were sulfur and the sulfonium salt, *s*-trithiane methyl chloride, $(CH_2S)_3 \cdot CH_3Cl$. With the ratios *d* and *e*, on the other hand, the main products were diphenylmethane and benzyl sulfide. The results may be explained by assuming that the normal addition compound of *s*-trithiane and aluminum chloride, under the conditions of the reaction, has the composition $(CH_2S)_3 \cdot 2AlCl_3$. It is not until this ratio is exceeded and there is at least a slight excess of aluminum chloride, that the benzene can become active and take part in the reaction.

(7) 

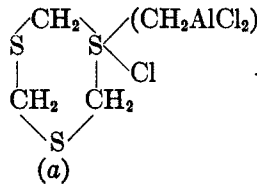
$$C_6H_5CH_2SCH_2C_6H_5 \cdot AlCl_3$$

and

$$C_6H_5CH_2C_6H_5 + 2H_2S + AlCl_3$$

The trithiane molecule breaks, and there is an addition of two moles of benzene. Dimercaptomethane, which is formed, reacts immediately with benzene to give diphenylmethane and hydrogen sulfide. No tribenzylsulfonium chloride was isolated, although it might be expected from a consideration of the results of the benzyl sulfide-aluminum chloride reaction. It is probable that this was due to the fact that hydrogen sulfide forms a complex with aluminum chloride, somewhat diminishing the activity of the latter.

The course of the reaction obtained between one molecule of *s*-trithiane and less than two molecules of aluminum chloride, may be described by the equation:

(8) $(CH_2S)_3 \cdot 2AlCl_3 + (CH_2S)_3 \rightarrow$ 

(a) $+ S + (CH_2S)_2 + AlCl_3$ (b)

Compound (*a*), on hydrolysis, yields trithiane methyl chloride; (*b*) rearranges to $(CH_2S)_3$. The momentary existence of $ClCH_2—AlCl_2$ is assumed in the equation. There is no evidence for such a compound in the literature, but the corresponding ethylene derivative has been postulated in some types of the Friedel-Crafts reaction.

EXPERIMENTAL

Normal primary amyl sulfide.—One-tenth mole of the sulfide and 0.12 mole of aluminum chloride in 60 cc. of benzene were heated at 80° for two hours. The mixture was cooled, and poured into ice water; the benzene layer was separated and fractionated. The sulfide was entirely recovered, except for a small experimental loss. No other substance was found in the benzene layer. The water layer contained no sulfonium compound. A mixture similar to the above was allowed to stand at room temperature for a long period, and the result was the same.

Ethyl and n-*amyl mercaptans.*—One-half mole of the mercaptan and 0.6 mole of aluminum chloride in 300 cc. of benzene were heated at 80° for thirty hours. After decomposition of the mixture with water, the benzene layer was distilled, and found to contain no alkylated benzene derivatives.

Benzyl mercaptan.—Fifty grams of the mercaptan was added slowly with stirring to 0.5 mole of aluminum chloride in 1.0 mole of benzene. There was immediate reaction, the mixture became warm and it was necessary to cool the reaction flask with ice water during most of the addition. There was a copious evolution of hydrogen sulfide. The reaction mass was poured into ice water, and the benzene layer was separated. It gave on fractionation 15 g. of diphenylmethane, and complex hydrocarbons of boiling point higher than 360°.

Benzyl sulfide.—Eleven grams of the sulfide and 6.2 g. of aluminum chloride in 50 cc. of benzene stood at room temperature (protected from moisture in the air) for five days. The mixture was then poured into an open dish, the excess benzene was allowed to evaporate, and the aluminum chloride complex was decomposed by moisture in the air. The white solid mass remaining was washed free of very soluble aluminum compounds with a minimum of cold water. The residue was a white crystalline solid (I) of m. p. 82-84° (corr.). It was soluble in water, alcohol, chloroform, and acetone-water with decomposition. It contained ionizable chlorine. It formed an addition compound with chloroplatinic acid in aqueous solution; m. p. 189°, which is the same as that reported for the complex between tribenzylsulfonium chloride and chloroplatinic acid. It formed a trinitrophenoxide ("picrate") of m. p. 142° and the m. p. was not depressed when it was mixed with a trinitrophenoxide prepared from known tribenzylsulfonium sulfate and picric acid.

Anal. Calc'd for $C_{27}H_{35}N_3O_7S$: S, 6.0. Found: S, 6.3.

Compound I in aqueous solution with silver oxide gave tribenzylsulfonium hydroxide; m. p. 133°.

Anal. Calc'd for $C_{21}H_{22}OS$: S, 9.94. Found: S, 9.84.

When tribenzylsulfonium chloride (I) was heated in acetone-water solution it decomposed, and benzyl sulfide was isolated. The yield of the sulfonium compound was 80% of the theoretical, based on equations (2) and (3). In another experiment the reaction mixture was poured into water after one day, and the benzene layer was separated and concentrated to a b. p. of 130°. Benzyl mercaptan was present in this residue and was identified by formation of its 2,4-dinitrophenyl thioether, m. p. 130°, and oxidation of this derivative to the sulfone.

s-*Trithiane with two or more moles of aluminum chloride.*—In a typical experiment 23 g. of trithiane and 44 g. of aluminum chloride were mixed in the dry state, and to these reactants 100 cc. of benzene was added. Almost immediately the solution became clear and orange-colored; the evolution of much hydrogen sulfide followed. The reaction appeared to be complete within 15–20 minutes, and the mixture was decomposed by pouring on crushed ice. The benzene layer was distilled until it had a b. p. of 135°. The remaining oil was mainly a mixture of

diphenylmethane and benzyl sulfide; it was not easily separated into these constituents. A fractional distillation yielded 10 g. of diphenylmethane, higher hydrocarbons, and decomposition products of benzyl sulfide. If the original concentrated oil was allowed to partition itself between the layers of alcohol-water and petroleum ether, the alcohol-water layer yielded crystalline benzyl sulfide on concentrating and cooling. The benzyl sulfide was identified by its m. p., 49°; oxidation to the sulfone, m. p. 149°; and pyrolysis to stilbene, m. p. 125°. A separation of the benzyl sulfide also resulted from precipitating it as the mercuric chloride complex, formed by mixing hot alcohol solutions of the components. A mixture with the compound made from benzyl sulfide showed no depression in melting point. The complex can be easily recrystallized from alcohol, and may be separated into its parts by warming it in a water solution of ammonium chloride. The purified sulfide solidifies on cooling. This method may be recommended for use in purifying benzyl sulfide prepared in other ways. About 10–11 g. of benzyl sulfide, or about one molecule for each molecule of diphenylmethane, was obtained.

s-Trithiane with less than two moles of aluminum chloride.—In a typical experiment 23 g. of trithiane and 22 g. of aluminum chloride were mixed in the dry state, and 100 cc. of benzene was added. The solution soon became clear, and after it stood for a day or two, crystals of sulfur began to appear in the lower, benzene-insoluble layer. When the sulfur stopped precipitating (after three to four days), the reaction was considered complete, and the mixture was decomposed as usual. The benzene layer contained practically no high-boiling material other than sulfur and small amounts of unchanged trithiane. The amount of sulfur formed corresponded roughly to that required in equation (8), or about one atom for each molecule of the sulfonium compound formed. On addition of potassium iodide solution to the water layer, a 50–60% yield of the sulfonium salt, trithiane methyl iodide was precipitated. This compound was identical with the one prepared as follows.

Preparation of trithiane methyl iodide.—A mixture of trithiane (one mole) and dimethyl sulfate (two moles) was warmed on a boiling water bath until solution was complete, or for about 2–3 hours. The clear, viscous mass was dissolved in about 10 volumes of warm water, and a slight excess of potassium iodide was added to the diluted sulfonium reaction mixture. Long, flat plates of trithiane methyl iodide crystallized from the solution as it cooled. Yields were about 70%. Trithiane methyl iodide may be recrystallized from methanol with difficulty.

Anal. Calc'd for $C_4H_9IS_3$: S, 34.3; I, 45.3; mol. wt. 280.
Found: S, 34.2; I, 44.7; mol. wt. (Rast), 288, 300.

It is stable over long periods of time only if it is pure. It is slightly soluble in cold water, ethyl and methyl alcohols, easily soluble in hot water. It forms molecular compounds with heavy-metal salts. Its trinitrophenoxide melts at 135–137°. Under similar conditions, diethyl sulfate gave a much smaller yield of trithiane ethyl iodide.

SUMMARY

The behavior of six compounds, containing the thiomethylene group, in benzene in the presence of anhydrous aluminum chloride, at ordinary temperature, has been studied. Normal primary amyl sulfide, *n*-primary amyl mercaptan and ethyl mercaptan underwent little or no change under the conditions. Benzyl mercaptan gave diphenylmethane as the principal product. Benzyl sulfide, depending on the quantity of aluminum chloride

present, reacted to form either the sulfonium salt, tribenzylsulfonium chloride, or diphenylmethane. *s*-Trithiane behaved similarly: with less than two moles of aluminum chloride the principal products were the sulfonium salt, *s*-trithiane methyl chloride, and sulfur; with more than two moles of aluminum chloride, diphenylmethane and benzyl sulfide were the major products. An explanation has been offered for the course of the reaction in the cases of *s*-trithiane and benzyl sulfide.

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

ACID CATALYSIS IN AMINES. I. THE CATALYTIC EFFECT OF CYCLOHEXYLAMMONIUM SALTS ON THE REACTION BETWEEN CYCLOHEXYLAMINE AND ESTERS

PAUL K. GLASOE AND L. F. AUDRIETH

Received January 14, 1939

Experimental evidence has already been presented to demonstrate that the ammonolysis of esters in liquid ammonia is susceptible to catalysis by ammonium salts.[1, 2, 3] Since ammonium salts have been shown to behave as acids in liquid ammonia,[4] these findings have been interpreted as possible examples of acid catalysis. In extending these studies to other basic solvents it was regarded as highly probable that related reactions involving the aminolysis of esters, resulting in the formation of *N*-substituted acid amides, could be accelerated by addition of the corresponding amine salts. Equations (1), (2), and (3), representing reactions of hydrolysis, ammonolysis, and aminolysis, respectively, of esters are all strictly analogous and may be regarded broadly as solvolytic reactions.

$$\text{(1)} \qquad \text{RCOOR}' + \text{HOH} \longrightarrow \text{RCOOH} + \text{R}'\text{OH}$$

$$\text{(2)} \qquad \text{RCOOR}' + \text{HNH}_2 \longrightarrow \text{RCONH}_2 + \text{R}'\text{OH}$$

$$\text{(3)} \qquad \text{RCOOR}' + \text{HNHR}'' \longrightarrow \text{RCONHR}'' + \text{R}'\text{OH}$$

Cyclohexylamine was chosen for this preliminary study because of its unusual physical and chemical properties,[5] as well as its ready availability on the market. It is a strongly basic solvent and appears to be a much more powerful proton acceptor than ammonia. It can readily be prepared in a state of high purity. On the basis of the modern concept of acidity it may be predicted that cyclohexylammonium salts will behave as acids in cyclohexylamine:

$$\underset{\text{(base)}}{C_6H_{11}NH_2} + \underset{\text{(acid)}}{HX} \longrightarrow \underset{\text{(acid)}}{C_6H_{11}NH_2 \cdot H^+} + \underset{\text{(base)}}{X^-}$$

[1] SLOBUTSKY AND AUDRIETH, *Proc. Nat. Acad. Sci.*, **23**, 611 (1937).

[2] FELLENGER AND AUDRIETH, *J. Am. Chem. Soc.*, **60**, 579 (1938).

[3] AUDRIETH AND KLEINBERG, J. ORG. CHEM., **3**, 312 (1938).

[4] FRANKLIN, "The Nitrogen System of Compounds," A.C.S. Monograph. Reinhold Publishing Corporation, New York City, **1935**, p. 26.

[5] CARSWELL AND MORRELL, *Ind. Eng. Chem.*, **29**, 1247 (1937).

EXPERIMENTAL

Preparation of materials.—The cyclohexylamine used in this study was purified by dehydration over solid caustic potash and repeated fractional distillation. All esters were dried carefully, and purified by distillation under reduced pressure.

Preparation of cyclohexylammonium salts.—During the course of a preliminary study of solubility relationships in cyclohexylamine as solvent it was observed that ammonium salts react with the solvent with evolution of ammonia. Further study of this reaction led to the development of a simple method for the preparation of cyclohexylammonium salts. These reactions, which may be regarded as simple cases of solvolysis, specifically aminolysis, may best be represented by the following type equation:

$$C_6H_{11}NH_2 + NH_4X \rightarrow C_6H_{11}NH_2 \cdot HX + NH_3$$

It is interesting to note, in this connection, that the rate of solvolysis, as evidenced by the effervescence of the solutions due to the evolution of ammonia, varies in the decreasing order:

$$NH_4NO_3 > NH_4I > NH_4Br > NH_4Cl.$$

TABLE I

CYCLOHEXYLAMMONIUM SALTS

(Prepared by interaction of cyclohexylamine and the ammonium salt.)

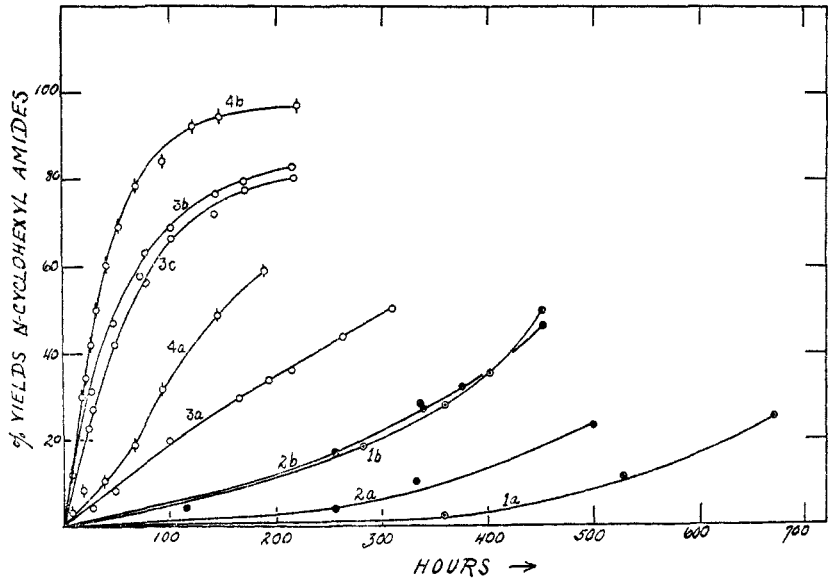
FORMULA	MELTING POINT (UNCORR.)	N ANAL.	
		Calc'd	Found
$C_6H_{11}NH_2 \cdot HBr$	196–197°	7.77	7.68
$C_6H_{11}NH_2 \cdot HNO_3$	156	17.29	17.06
$C_6H_{11}NH_2 \cdot HI$	193–194	6.15	6.12
$(C_6H_{11}NH_2)_2 \cdot HI$	185–187	8.59	8.40

The solubility of the resulting cyclohexylammonium salts in cyclohexylamine at 25° also decreases in the same order, the chloride and the bromide being but slightly soluble. A qualitative knowledge of these solubilities was of interest in the present investigation, since it precluded the use of the bromide and chloride as catalysts at 25°.

In preparing cyclohexylammonium salts the solid ammonium salt was added to an excess of cyclohexylamine, and the solution was heated on the steam cone under slightly reduced pressure until evolution of ammonia had ceased. The solutions were then cooled, cooling resulting, in the case of the chloride and bromide, in the formation of the solid salts, which were removed by filtration. The addition of ether to the solution, or filtrate, resulted in further precipitation of the desired cyclohexylammonium salt.

In the case of the nitrate, chloride, and bromide, the normal salts, $C_6H_{11}NH_2 \cdot HX$, were obtained. However, the product obtained by the addition of ether to a solution of the iodide in cyclohexylamine was found by analysis to be the solvated salt containing an extra molecule of cyclohexylamine. Recrystallization of this product from ethanol was found to give the normal iodide. Salts prepared by this method, with melting points and analyses, are listed in Table I.

Procedure.—Two methods were used to determine the rate of reaction between cyclohexylamine and the dissolved ester. In both cases stock solutions containing definite quantities of amine and ester were made up, either with or without cyclohexylammonium salt. In some runs the whole solution was kept in a thermostat at 25°, and samples were withdrawn at definite time intervals. In other experiments, especially in the case of the reaction between ethyl malonate and cyclohexylamine,



AMINOLYSIS OF ESTERS IN CYCLOHEXYLAMINE (Concn. of ester = 0.5*M*)

CURVE	ESTER	CATALYST	CONCN. OF CATALYST IN MOLES PER LITER
1A	Ethyl acetate	None	0.00
1B	Ethyl acetate	$C_6H_{11}NH_2 \cdot HI$	0.20
2A	Ethyl phenylacetate	None	0.00
2B	Ethyl phenylacetate	$C_6H_{11}NH_2 \cdot HI$	0.20
3A	Ethyl lactate	None	0.00
3B	Ethyl lactate	$C_6H_{11}NH_2 \cdot HI$	0.20
3C	Ethyl lactate	$C_6H_{11}NH_2 \cdot HNO_3$	0.20
4A	Ethyl malonate	None	0.00
4B	Ethyl malonate	$C_6H_{11}NH_2 \cdot HI$	0.10

where the solid reaction product precipitates from solution, aliquot portions of the stock solution were at the very beginning pipetted into separate containers, which were then placed in the thermostat for definite time periods.

After a certain time had elapsed samples were removed from the thermostat and treated immediately with an excess of standard hydrochloric acid; the excess was back-titrated with standard alkali. From a knowledge of the acid requirement of

equal volumes of the solution at the beginning of the reaction and again at various time intervals, it was possible to calculate the extent to which the reaction had proceeded. The amount of cyclohexylamine disappearing is equivalent to the quantity of ester used up and also equivalent to the molar quantity of *N*-cyclohexyl amide formed. No difficulty was encountered in carrying out titrations, as cyclohexylamine is a strong base in aqueous solution.

Quantitative studies of this sort were carried out using the ethyl esters of acetic, phenylacetic, lactic and malonic acids. The formation of the corresponding *N*-cyclohexyl amides was verified by actual isolation of these derivatives from the reaction mixture. In view of the limited solubilities of the cyclohexylammonium bromide and chloride in cyclohexylamine at 25°, the catalytic effects of the nitrate and iodide only were investigated.

The composite experimental material is depicted graphically in the accompanying figure. The percentage conversion of the esters into the corresponding *N*-cyclohexyl amides is plotted against the time in hours. In every case 0.05 mole of the ester was diluted with cyclohexylamine to give 100 cc. of solution. The explanatory

TABLE II

AMINOLYSIS OF ESTERS AT 25°

(0.05 mole ester diluted to 100 cc. with $C_6H_{11}NH_2$)
Catalyst, 0.02 mole $C_6H_{11}NH_2 \cdot HI$

ESTER	CONVERSION			
	100 Hours		200 Hours	
	No Catalyst	With Catalyst	No Catalyst	With Catalyst
Ethyl acetate	0.5	5.0	1.0	11.0
Ethyl phenylacetate	1.2	5.7	3.0	12.0
Ethyl lactate	20.	69.0	52.0	81.0
Ethyl malonate	34.0	88.5*	61.0	97.0*

* Only 0.01 mole of catalyst was employed in the experiments with ethyl malonate.

legend with the figure also indicates the moles of "onium" salt added where experiments were carried out to determine the effect of adding cyclohexylammonium salts.

Discussion.—The relative reactivities of the various ethyl esters towards cyclohexylamine may be compared from the summary presented in Table II. These data were obtained by interpolation from the curves given in the figure, and refer to the percentage conversions of the esters into the corresponding *N*-cyclohexyl amides after 100 and 200 hours at 25°. The effect of the α-substituent on the reactivity of the ethyl esters is given by the series:

$$\left.\begin{array}{l} \text{H—CH}_2\text{COOEt} \\ \text{C}_6\text{H}_5\text{—CH}_2\text{COOEt} \\ \text{HO—CH(CH}_3\text{)COOEt} \\ \text{H}_5\text{C}_2\text{OOC—CH}_2\text{COOEt.} \end{array}\right.$$

This order also holds qualitatively for these same esters in so far as their susceptibility to hydrolysis[6] and to ammonolysis[3] is concerned. These findings lend additional weight to our contention that reactions of hydrolysis, ammonolysis, and aminolysis are all similar in character and may be considered broadly as "solvolytic" reactions.

Furthermore, just as reactions of ammonolysis and hydrolysis are catalyzed by the ammonium and hydronium ions, respectively, so solvolytic reactions in cyclohexylamine are catalyzed by the corresponding "onium" ion, the $C_6H_{11}NH_2 \cdot H^+$ ion, furnished by the cyclohexylammonium salt. It is evident that the mechanism which accounts for the catalytic effect of acids upon the rate of hydrolysis of esters may be applied also to ammonolytic and aminolytic reactions. That the catalytic effect is one which may be ascribed to the solvated proton, the $C_6H_{11}NH_2 \cdot H^+$ ion, is apparent from the fact that both the nitrate and iodide exert approximately the same catalytic effect in equimolar concentrations (see curves 3B and 3C in figure).

TABLE III

PREPARATION OF SOME *N*-CYCLOHEXYL AMIDES

FORMULA	MELTING POINT (UNCORR.), °C.	N ANAL.		SOLUBILITIES*
		Calc'd	Found	
1. $CH_2(CONHC_6H_{11})_2$.....	175	10.52	10.45	Insol. H_2O; sol. C_2H_5OH
2. $C_6H_5CH_2CONHC_6H_{11}$.....	134	6.44	6.51	Insol. H_2O; sol. C_2H_5OH
3. $CH_3CHOHCONHC_6H_{11}$.....	59	8.17	8.33	Sol. H_2O; sol. C_2H_5OH

* 1 and 2 were recrystallized from alcohol-water, and 3 from acetone by cooling to −30°.

In the case of ethyl malonate the plotted data (see curves 4A and 4B in figure) are based upon the assumption that the amount of amine used up corresponds to the formation of the *N,N'*-dicyclohexylmalonamide. The reaction obviously goes through an intermediate stage, involving only partial aminolysis:

$$H_2C(COOC_2H_5)_2 \xrightarrow[\text{(slow)}]{C_6H_{11}NH_2} H_2C(COONHC_6H_{11})(COOC_2H_5) \xrightarrow[\text{(very rapid)}]{C_6H_{11}NH_2} H_2C(CONHC_6H_{11})_2$$

Presumably, the circumstances here are similar to those observed in the reaction between liquid ammonia and ethyl malonate.[3] The intermediate compound is very rapidly converted into the completely solvolyzed product, and its concentration in solution is never very great. It may, therefore, be assumed that the first step is relatively slow and that this initial solvolytic action determines the speed of the reaction. The designation of the C_2H_5OOC— grouping in the α position as having the greatest effect upon the rate of aminolysis is based upon the overall reaction.

It should be emphasized that the preliminary observations reported in this paper indicate that the concept of "onium" ion catalysis is one which should be of real value in synthetic organic chemistry. In the present case, it has been shown that

[6] OLSON, *Z. physik. Chem.*, **133**, 233 (1928).

the yields of *N*-cyclohexyl amides over comparable time periods are increased markedly by adding a relatively small quantity of cyclohexylammonium salt to the reaction mixture. The *N*-cyclohexyl amides of lactic, phenylacetic, and malonic acids were prepared in quantity using this method. Analytical data, solubilities, and melting points are recorded in Table III.

SUMMARY

The reactions between the ethyl esters of acetic, phenylacetic, lactic, and malonic acids, respectively, and cyclohexylamine, leading to the formation of the corresponding *N*-cyclohexyl amides, are catalyzed by the addition of cyclohexylammonium salts. These findings have been interpreted as examples of acid catalysis in an amine.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE COUPLING OF DERIVATIVES OF POLYCYCLIC HYDROCARBONS WITH GLYCINE

W. E. BACHMANN AND WAYNE COLE*

Received January 23, 1939

In recent years it has been shown that cancer may be produced in animals by means of chemical compounds, most of which are polycyclic hydrocarbons. From investigations of cell-free filtrates obtained from certain types of tumors in birds many investigators consider that the active agent in these cases is a submicroscopic organism or virus. From the results of these studies some investigators have considered that there is little connection between the modes of action of the virus and the hydrocarbons. Attention has been directed particularly to the different periods of time which elapse between the inoculation and the appearance of tumors. Thus, in contrast to an induction period of a week or two when an active tumor filtrate is used for inoculation, a matter of months may be required for the production of tumors by a chemical compound. It has been pointed out recently, however, that this phase of the subject requires further attention in view of the rapid production of tumors which has been observed with certain synthetic compounds, particularly with 9,10-dimethyl-1,2-benzanthracene, which has yielded tumors in five weeks when applied externally to the skin of mice.[1]

Recently, Wyckoff[2] has demonstrated that the active agent of the Shope papilloma is a protein of high molecular weight. It is apparent, then, that the two different lines of investigation have approached each other.[3] It is of interest, therefore, to study compounds prepared by combining a protein with an active carcinogenic compound or with a derivative of an active compound. The latter has already been accomplished by Creech and Franks,[4] who reported their results at the time our investigation was initiated. These investigators coupled 1,2,5,6-dibenzanthranylisocyanate, a derivative of the carcinogenic hydrocarbon 1,2,5,6-dibenzanthracene, with various proteins and with glycine and

* Du Pont Post-doctorate Fellow.

[1] BACHMANN, KENNAWAY, AND KENNAWAY, *Yale J. Biol. and Med.* **11**, 97 (1938).

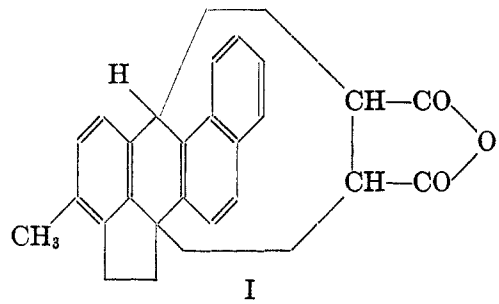
[2] WYCKOFF, *Compt. rend. soc. & biol.*, **125**, 5 (1937); *Science*, **86**, 92 (1937).

[3] See, for example, the excellent lecture by COOK, *Yale J. Biol. and Med.* **11**, 1 (1938).

[4] CREECH AND FRANKS, *Amer. J. Cancer*, **30**, 555 (1937).

studied the chemical and serological properties of the resulting compounds. Although the isocyanate and the protein compounds proved to be inactive, the compound obtained with glycine was capable of inducing tumors in mice in a relatively short time.

The successful preparation of compounds of the type of 3-methylcholanthrene-endo-succinic anhydride† (I) provided us with compounds which could be employed for coupling with the proteins in virtue of the active acid anhydride group in the molecule. These compounds are readily obtained by means of a Diels-Alder reaction involving the addition of maleic anhydride to the polycyclic hydrocarbon under the proper conditions of temperature and concentration.[5]



I

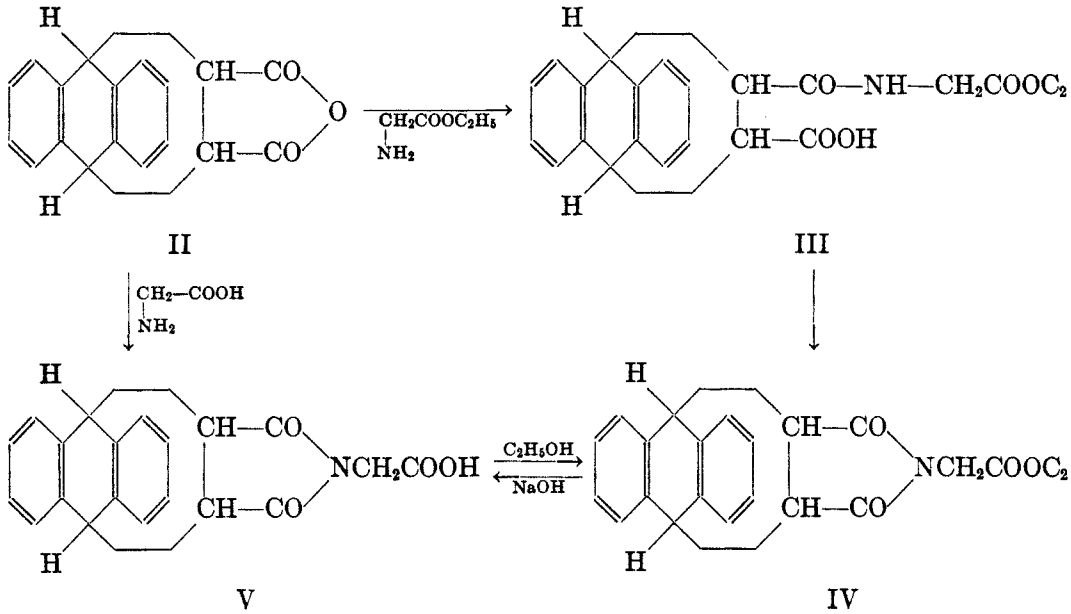
For purposes of orientation we studied the reaction between the endo succinic anhydrides and glycine, as the free amino acid and in the form of its ethyl ester, and the results are presented in this paper. In these compounds is illustrated the type of linkage which would be present in the protein derivatives, although probably not in the same relative position with respect to the carboxyl group. Anthracene- and 1,2-benzanthracene-endo-succinic anhydride were employed first in order to determine the most favorable conditions for reaction.

Anthracene-endo-succinic anhydride (II) reacts with glycine ethyl ester in benzene solution and forms the acid succinylglycine derivative (III). This compound is not very stable but exhibits a strong tendency to pass into the imido ester (IV). Thus, in organic solvents it slowly loses water; when heated it cyclizes readily; and hot dilute solutions of its sodium salt slowly precipitate the ester (IV). The latter ester may also

† The numbering system for the cholanthrene molecule is that employed in the index of *Chemical Abstracts*.

[5] (*a*) BACHMANN AND KLOETZEL, *J. Am. Chem. Soc.*, **60**, 481 (1938). (*b*) BACHMANN AND CHEMERDA, *ibid.*, **60**, 1023 (1938). (*c*) BACHMANN, J. ORG. CHEM., **3**, 434 (1938).

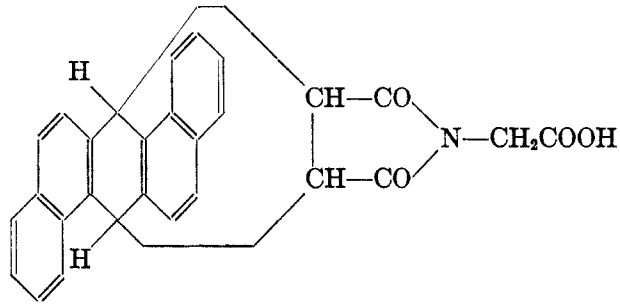
be prepared by interaction of II and glycine ethyl ester hydrochloride in pyridine.



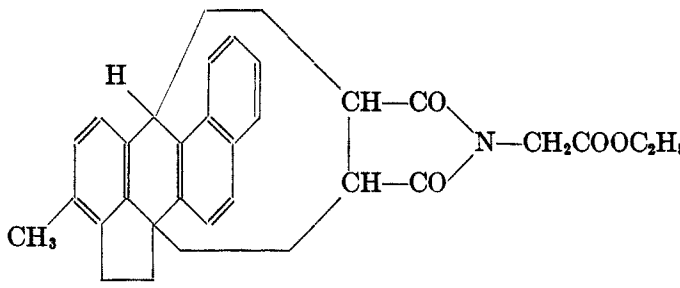
Moderate hydrolysis of IV gives the corresponding acid (V); more vigorous hydrolysis results in cleavage of the acid amide linkage as well and the formation of the dicarboxylic acid corresponding to the anhydride (II). The substituted glycine (V) has also been obtained from the reaction of II with glycine in aqueous alkaline solution. This acid (V) may be esterified to the ethyl ester, which is identical with the ester obtained by the methods described above.

The reactions of 1,2-benzanthracene-endo-succinic anhydride and 1,2,5,6-dibenzanthracene-endo-succinic anhydride with glycine ethyl ester were quite analogous to that of the anthracene derivative. No attempt was made to isolate the intermediates analogous to III; instead, the crude products were warmed to increase the yields of the stable esters. The corresponding acids were best prepared by alkaline hydrolysis of the esters in dioxane solution. The product (VI) from 1,2,5,6-dibenzanthracene-endo-succinic anhydride is of particular interest in view of the carcinogenic activity of the disodium salt of 1,2,5,6-dibenzanthracene-endo-succinic acid.[6]

[6] Barry, Cook, Haslewood, Hewett, Hieger, and Kennaway, *Proc. Roy. Soc.* (*London*), **B117**, 331 (1935).



VI



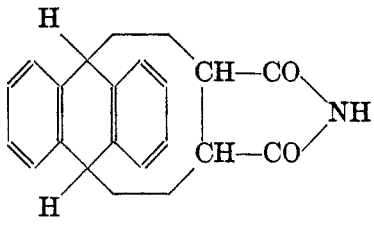
VII

3-Methylcholanthrene-endo-succinic anhydride (I) appeared to react more slowly with glycine ethyl ester than did the anhydrides mentioned above, unchanged anhydride usually being found along with its reaction products when these were formed under the mild conditions employed for preparing the anthracene derivatives. At higher reaction temperatures, dissociation of the anhydride into methylcholanthrene and maleic anhydride caused low yields of the ester (VII) and impure product. The use of excess glycine ester led to side reactions: the formation of a salt whose water solution slowly deposited the ester (VII); the glycine ester itself polymerizes quite rapidly[7] and the polymers also react with the anhydride to form very high-melting by-products.

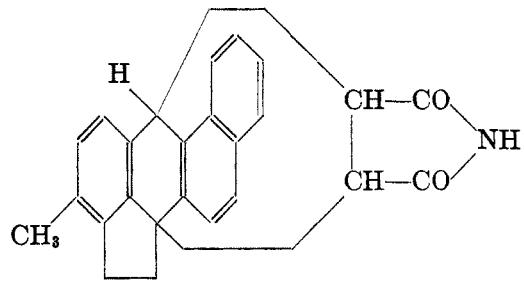
The imides of anthracene-endo-succinic acid and 3-methylcholanthrene-endo-succinic acid were also prepared. Anthracene-endo-succinimide (VIII) formed spontaneously in a warm aqueous solution of the ammonium salt of anthracene-endo-succinic acid. The 3-methylcholanthrene-endo-succinimide (IX) was prepared by reaction of the anhydride in dioxan solution with aqueous ammonia. The ease of imide formation

[7] CURTIUS AND GOEBEL, *J. prakt. Chem.*, [2], **37**, 159 (1888).

is characteristic of the endo succinic acid derivatives and is analogous to the ease of formation of their anhydrides.[5a]



VIII



IX

The derivatives of 3-methylcholanthrene and 1,2,5,6-dibenzanthracene are being tested for their carcinogenic activity in mice, the acids in the form of their water-soluble sodium salts, and the esters in organic solvents by external application and by subcutaneous injection.

Similar derivatives of other simple amino acids, as well as protein compounds formed from the hydrocarbon-endo-succinic anhydrides and crystalline egg albumin are being studied.

EXPERIMENTAL

Reaction of anthracene-9,10-endo-α,β-succinic anhydride with glycine ethyl ester.— To a suspension of 12 g. of powdered anthracene-endo-succinic anhydride in 90 cc. of warm benzene was added 8 g. of glycine ethyl ester. Warming and swirling the solution for ten minutes caused all of the anhydride to dissolve. The clear warm solution was allowed to stand fifteen hours without further heating. Washing with water caused the benzene solution to solidify to a jelly-like mass. It was diluted with much ethyl acetate and extracted with 5% sodium carbonate solution—thus separating the acidic product described below. The benzene-ethyl acetate solution yielded 6.5 g. of product melting at 183–185°. Three recrystallizations from ethyl acetate gave small white prisms of *anthracene-9,10-endo-α,β-succinoglycine ethyl ester* (IV) melting at 187–188°.

Anal. Calc'd for $C_{22}H_{19}NO_4$: N, 3.90. Found: 4.04.

Acidification of the sodium carbonate extract precipitated 4.8 g. of a white powdery acid which melted at 118–121° to a cloudy liquid. After slight effervescence the melt resolidified, and melted again to a clear liquid at 174–176°. Two recrystallizations from ethyl acetate (without much heating) gave the material as small colorless prisms which melted at 154–156°, resolidified partly by 162°, and remelted at 175–177°.

Anal. Calc'd for $C_{22}H_{21}NO_6$: N, 3.69. Found: N, 3.51.

Neutral. equivalent, Calc'd: 379. Found: 369.

A sample (0.1 g.) of the acid was heated in a bath until it melted and resolidified. The resulting solid was dissolved in ethyl acetate and crystallized, giving fine prisms melting at 186–187° which gave no depression in melting point when mixed with the imido ester (IV). The acid therefore appears to be *anthracene-9,10-endo-α,β-(acid succinyl)-glycine ethyl ester* (III).

Treatment of the acid in ether with diazomethane did not give a stable methyl ester; instead, this treatment converted the acid into the imido ester (IV), melting at 187–188°.

When a benzene solution of 4.14 g. of anthracene-endo-succinic anhydride and 2.3 g. of glycine ethyl ester was refluxed for thirty minutes, then concentrated, 4.0 g. (75 per cent. of the theoretical yield) of the imido ester was obtained; but none of the acid (III) could be found.

The same ester (IV) was obtained in 74 per cent. yield when a mixture of 4.14 g. of anthracene-endo-succinic anhydride, 2.1 g. of glycine ethyl ester hydrochloride, and 20 cc. of dry pyridine were heated on a steam bath for two hours.

Anthracene-9,10-endo-α,β-succinoglycine (V).—A suspension of 2 g. of the powdered ethyl ester in 35 cc. of 2% sodium hydroxide and 5 cc. of ethanol was refluxed for fifteen minutes. Acidification of the resulting clear solution precipitated 1.7 g. of an acid melting at 220–250°. Recrystallizations from acetic acid and from ethyl acetate gave 1 g. of small colorless prisms melting at 270–271°.

Anal. Calc'd for $C_{20}H_{15}NO_4$: N, 4.20. Found: N, 4.18.

The acid is more readily obtained by the reaction of anthracene-endo-succinic anhydride with glycine. A solution of 2.4 g. of the anhydride in 14 cc. of hot pyridine was added to a solution of 1.1 g. of glycine and 1.1 g. of sodium carbonate in 5 cc. of water. The mixture was held at 90° for one hour, diluted and acidified. Crystallization of the precipitate from acetone gave 2.2 g. of anthracene-endo-succinoglycine melting at 269–270°. Quite similar results were obtained when the reaction was repeated using 30 cc. of dioxan in place of the 14 cc. of pyridine.

Shaking warm solutions of anthracene-endo-succinic anhydride in benzene or ethyl acetate with alkaline solutions of glycine gave no satisfactory yield of the substituted glycine; most of the anhydride was recovered unchanged.

A suspension of 0.5 g. of anthracene-endo-succinoglycine in 10 cc. of absolute ethanol containing 12 drops of sulfuric acid was warmed over a steam bath for two hours. Cooling the resulting clear solution deposited 0.3 g. of the ethyl ester (IV) melting at 185–186°.

Anthracene-9,10-endo-α,β-succinimide (*VIII*).—One-half gram of anthracene-endo-succinic anhydride was dissolved in 20 cc. of hot 1*N* sodium hydroxide, diluted to 100 cc., and acidified to precipitate the acid. The washed precipitate was dissolved in 20 cc. of ammonium hydroxide (the anhydride itself would not dissolve in ammonium hydroxide) and heated over a steam bath. The clear solution slowly turned cloudy then precipitated 0.45 g. of the granular imide. It was difficultly soluble in hot toluene, from which it separated as colorless prisms melting at 303–304.5° with decomposition.

Anal. Calc'd for $C_{18}H_{13}NO_2$: N, 5.09. Found: N, 4.90.

1,2-Benzanthracene-9,10-endo-α,β-succinoglycine ethyl ester.—A suspension of 0.85 g. of powdered 1,2-benzanthracene-endo-succinic anhydride (m.p. 241–242°, dec.) in 50 cc. of warm benzene was treated with 0.5 g. of glycine ethyl ester dissolved in 5 cc. of benzene. After warming for one hour on a steam bath, the solution was washed with dilute hydrochloric acid and concentrated to 15 cc. The white powder which separated was recrystallized from ethyl acetate, giving 0.55 g. of platelets of the imido ester melting at 226–227°. The ester is soluble in warm benzene, ethyl acetate, or dioxan; very slightly soluble in ethanol. It gives no color with cold concentrated sulfuric acid.

Anal. Calc'd for $C_{26}H_{21}NO_4$: N, 3.40. Found: N, 3.30.

1,2-Benzanthracene-9,10-α,β-succinoglycine.—A solution of 0.3 g. of the ethyl ester

in 16 cc. of dioxan was warmed to 75°, 3 cc. of 2*N* sodium hydroxide was added, the mixture shaken for five minutes, then allowed to stand at 40° for four hours. Dilution with water gave no precipitate. Acidification gave 0.2 g. of crude acid melting at 217–224°, which, after recrystallization from acetic acid then from acetone, gave 0.12 g. of colorless microscopic prisms melting at 242–244°, dec.

Anal. Calc'd for $C_{24}H_{17}NO_4$: N, 3.65. Found: 3.40.

*3-Methylcholanthrene-6,12*b-*endo-α,β-succinoglycine ethyl ester* (*VII*).—To a suspension of 1 g. of powdered 3-methylcholanthrene-endo-succinic anhydride in 80 cc. of hot benzene was added 0.68 g. of glycine ethyl ester in three portions, with ten minutes' warming on the steam bath between additions. After standing for forty-five minutes at 65–70°, the resulting clear solution was washed with dilute hydrochloric acid and water, and concentrated to 10 cc. The crude white product (0.9 g., m.p. 145–190°) partly dissolved in 25 cc. of warm ethyl acetate, leaving 0.2 g. of residue which did not melt below 270°, at which point it began to decompose. Fractional crystallization of the ethyl acetate solution gave 0.2 g. of recovered anhydride and 0.4 g. of methylcholanthrene-endo-succinoglycine ethyl ester melting at 180–181°. The ester is soluble in hot benzene, ethyl acetate, acetone, and dioxan; very slightly soluble in ethanol. It crystallized from ethyl acetate in colorless microscopic plates, melting at 181–182° (bath preheated to 170°) to a clear liquid which decomposes after a few seconds.

Anal. Calc'd for $C_{29}H_{25}NO_4$: N, 3.10. Found: N, 3.18.

Powdered methylcholanthrene-endo-succinic anhydride (0.3 g.) was found to dissolve slowly at 25° in 10 cc. of benzene containing 0.3 g. of glycine ethyl ester, but the solution could not be crystallized. Washing with water extracted some unchanged ester and a salt which, during two days' standing, changed into 0.1 g. of the ester melting at 180–181°. The benzene solution yielded high-melting substances and a very small amount of the ester melting at 180–181°.

A solution of 0.6 g. of methylcholanthrene-endo-succinic anhydride in 5 cc. of dry pyridine at 65° (decomposition occurs above 75°) was treated with portions of powdered glycine ethyl ester hydrochloride until 0.3 g. had been added. The yellow solution was kept at 70° for four hours, cooled, diluted with water, and extracted with benzene. The washed benzene solution yielded 0.42 g. of recovered anhydride and 0.1 g. of methylcholanthrene-endo-succinoglycine ethyl ester melting at 179–180°.

*3-Methylcholanthrene-6,12*b-*endo-α,β-succinoglycine.*—A mixture of 0.21 g. of the ethyl ester in 8 cc. of dioxan and 1.5 cc. of 2*N* sodium hydroxide was held at 50–55° for nine hours, with occasional shaking. Dilution with water gave a faint precipitate of unchanged ester; acidification deposited a crystalline powder, which crystallized from ethyl acetate in short, microscopic prisms (0.15 g.) melting at 233–234.5° with decomposition.

Anal. Calc'd for $C_{27}H_{21}NO_4$: N, 3.31. Found: N, 3.12.

*3-Methylcholanthrene-6,12*b-*endo-α,β-succinimide* (*IX*).—A solution of 0.1 g. of 3-methylcholanthrene-endo-succinic anhydride in 8 cc. of dioxan was treated with 3 cc. of concentrated ammonium hydroxide during three hours, the solution being kept hot by a steam bath. Evaporation to 4 cc. and cooling deposited 0.07 g. of white imide melting at 250–252°, dec. It was difficultly soluble in hot benzene, from which it separated as white microscopic plates melting at 252–253°, dec.

Anal. Calc'd for $C_{25}H_{19}NO_2$: N, 3.85. Found: N, 4.09.

The above three methylcholanthrene derivatives, the ester, the acid, and the imide give similar characteristic clear-red solutions with cold concentrated sulfuric acid. The corresponding anhydride (I) does not dissolve in cold sulfuric acid, but warming gives a red color, then decomposition.

1,2,5,6-Dibenzanthracene-9,10-endo-α,β-succinoglycine ethyl ester.—A suspension of 2.2 g. of powdered 1,2,5,6-dibenzanthracene-endo-succinic anhydride (m.p. 232-233°, prepared by the method of Bachmann and Kloetzel[5a] and by heating the acid described by Cook[8] with acetic anhydride) in 100 cc. of hot benzene was treated with 1.7 g. of glycine ethyl ester in 5 portions at intervals of a few minutes. The resulting clear solution was heated over a steam bath for two hours, then washed with water and concentrated. Recrystallization of the crude product (2.3 g., m.p. 215-217°) from ethyl acetate gave 2.2 g. of platelets of the ester melting at 220-221°.

Anal. Calc'd for $C_{30}H_{23}NO_4$: N, 3.03. Found: N, 2.90.

1,2,5,6-Dibenzanthracene-9,10-endo-α,β-succinoglycine (VI).—A solution of 0.35 g. of the ester in 30 cc. of dioxan was mixed with 2.2 cc. of 1*N* sodium hydroxide. After heating at 90° for eight hours, dilution with 50 cc. of water caused the solution to deposit 0.25 g. of pure unchanged ester. Acidification of the filtrate from this ester gave 0.09 g. of the acid melting at 251-253°. Much more complete hydrolysis was effected by adding 1 cc. portions of 2*N* sodium hydroxide at intervals of several hours to the refluxing dioxan solution of the ester, but the purity of the acid obtained was less. The acid crystallized from acetic acid in small colorless plates melting at 252-253°, dec.

Anal. Calc'd for $C_{28}H_{19}NO_4$: N, 3.23. Found: N, 3.24.

SUMMARY

The maleic anhydride addition products of four polycyclic hydrocarbons have been converted into derivatives of *N*-succinoglycine. Such derivatives of 3-methylcholanthrene and 1,2,5,6-dibenzanthracene were desired for testing their carcinogenic activity.

[8] Cook, *J. Chem. Soc.*, **1931**, 3273.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY, CHICAGO, ILLINOIS]

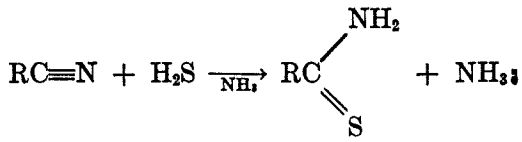
THE PREPARATION AND PROPERTIES OF HIGH-MOLECULAR-WEIGHT ALIPHATIC THIOAMIDES

A. W. RALSTON, R. J. VANDER WAL AND M. R. McCORKLE

Received January 23, 1939

Investigations of the preparation and properties of thioamides have been confined to aromatic and low-molecular-weight aliphatic thioamides. Two general methods for the preparation of thioamides have been described: the thiohydrolysis of nitriles and the action of phosphorus pentasulfide upon amides. Bernthsen[1] described the preparation of thiobenzamide and thioacetamide by the action of an alcoholic ammonium solution of hydrogen sulfide upon benzonitrile and acetonitrile, respectively. Hofmann[2] prepared thiobenzamide and thioacetamide by the action of phosphorus pentasulfide upon the corresponding amides. More recently Kindler[3] has shown that the presence of an ammonium or alkali hydrosulfide catalyzes the thiohydrolysis of nitriles.

High-molecular-weight aliphatic thioamides, such as thiostearamide, have not been previously prepared. The authors have prepared such thioamides by heating the nitriles with alcoholic solutions of ammonium hydrosulfide under pressure in a steel bomb at 150° to 160° for several hours. The reaction is represented by the following equation:



The amount of ammonium hydrosulfide used was greatly in excess of that employed by Kindler.[3] By this method we obtained substantial yields of several long-chain aliphatic thioamides. A few of their characteristic reactions have been investigated.

In general, the high-molecular-weight thioamides are characterized by reactions similar to those reported for the other members of the series. An exception is the formation of amines by reduction with sodium and alcohol. Bernthsen[1] reported that thiobenzaldehyde resulted from the

[1] BERNTHSEN, *Ber.*, **10**, 36 (1877).
[2] HOFMANN, *ibid.*, **11**, 340 (1878).
[3] KINDLER, *Ann.*, **431**, 187 (1923).

action of sodium amalgam upon an alcoholic solution of thiobenzamide. The behavior of the high-molecular-weight thioamides is somewhat similar to that of the corresponding amides. Pyrolysis produced the corresponding nitriles with the loss of hydrogen sulfide. Pyrolysis into the nitrile and hydrogen sulfide takes place at a somewhat lower temperature than is necessary for the analogous reaction with the amides. The hydrogen sulfide formed does not react with the remaining thioamide. Ralston, Harwood, and Pool[4] report the pyrolysis of stearamide to yield both stearonitrile and stearic acid. Hydrolysis with concentrated acids, aqueous or alcoholic alkali solutions gave carboxylic acids and not thio acids.

EXPERIMENTAL

Thiostearamide.—One hundred cubic centimeters of absolute ethyl alcohol was saturated with dry ammonia and dry hydrogen sulfide at 0°. This solution was then added to 10 g. of stearonitrile previously placed in a steel bomb. The steel bomb had a capacity of 80 cc. and was equipped with a valve for the release of gas. This valve was kept tightly closed during the reaction period. After the addition of the reactants the bomb was closed quickly and placed in an oil bath. The temperature of the bomb was then raised over a period of two hours to 160°, and kept at this temperature for two hours. Heating was then discontinued, and the bomb was allowed to cool for ten hours. The reaction product was filtered and washed with cold alcohol. The product melted at 94–95°, and, after three recrystallizations from ethyl alcohol, 7.5 g. of thioamide melting at 96–97° was obtained.

Anal. Calc'd for $C_{18}H_{37}NS$: S, 10.7; N, 4.7.
Found: S, 10.6; N, 4.8.

The following thioamides were also prepared by the above-described procedure:

COMPOUND	M.P., °C.	ANALYSIS, %			
		S		N	
		Calc'd	Found	Calc'd	Found
Thiolauramide	82–3	14.8	14.9	6.5	6.7
Thiomyristamide	87–8	13.1	12.9	5.7	5.7
Thiopalmitamide	93–4	11.7	12.1	5.2	5.0

Reduction of thiostearamide.—One gram of thiostearamide was reduced with metallic sodium in *n*-butyl alcohol. The butyl alcohol solution was then washed with water, and the butyl alcohol was removed by distillation. The residue was dissolved in ether, washed with water, and the ether was then removed by distillation. The product was dissolved in alcohol, from which it was precipitated as the hydrochloride by the addition of concentrated hydrochloric acid. It was immediately acylated with acetic anhydride and crystallized from water and alcohol and from alcohol. The product melted at 78–80°. A mixture with *N*-acetyloctadecylamine prepared by another method* showed no depression in melting point.

[4] RALSTON, HARWOOD, AND POOL, *J. Am. Chem. Soc.*, **59**, 986 (1937).

* Reduction of stearonitrile by sodium in *n*-butyl alcohol, followed by acetylation. This product melted at 78–80°.

Hydrolysis of thiostearamide by 15% alcoholic potassium hydroxide.—Thiostearamide (0.5 g.) was refluxed for thirteen hours with 20 cc. of a 15% solution of potassium hydroxide in ethyl alcohol. The stearic acid obtained weighed 0.28 g. and melted at 66–8°. The melting point of a mixture with known stearic acid showed no depression. A benzimidazole[5] prepared from this product melted at 93–94.5° and showed no melting point depression when mixed with known 2-heptadecylbenzimidazole.

Hydrolysis of thiostearamide by 80% sulfuric acid.—Thiostearamide (0.5 g.) was refluxed for one hour with an 80% solution of sulfuric acid. Hydrogen sulfide was evolved, and 0.25 g. of stearic acid was obtained. This melted at 68–69° and showed no depression in melting point when mixed with known stearic acid. The benzimidazole melted at 93–94°.

Pyrolysis of thiostearamide.—Thiostearamide (0.5008 g.) was heated in a test-tube immersed in an oil bath, and the gaseous products were swept out with dry nitrogen into a slightly acidic 20% cadmium sulfate solution. Initial decomposition was observed at 150° and was rapid at 175–180°. The sample was heated at 175–200° for twenty-four hours.

The residue melted at 38.5–43°. The melting point of a mixture with known stearonitrile was 38.5–39.5°. Hydrolysis of 0.086 g. of this product with concentrated sulfuric acid at room temperature for one and one-half hours gave stearamide melting at 104–106°. A mixture with known stearamide melted at 106–107.5°. A portion was distilled under high vacuum and gave a distillate melting at 106–107.5°.

The same procedure applied to thiopalmitamide gave approximately a theoretical yield of hydrogen sulfide and a product identified as palmitonitrile.

SUMMARY

The thioamides of lauric, myristic, palmitic, and stearic acids have been prepared from the nitriles by thiohydrolysis of the corresponding nitriles. Several characteristic reactions have been investigated.

[5] POOL, HARWOOD, AND RALSTON, *J. Am. Chem. Soc.*, **59**, 178 (1937).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

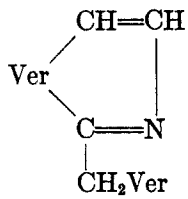
RESEARCHES ON QUINAZOLINES. XLIV. THE SYNTHESIS OF SOME NEW QUINAZOLINE DERIVATIVES OF VERATROLE AKIN TO ALKALOIDS

CHARLES ARTHUR FETSCHER* AND MARSTON TAYLOR BOGERT

Received January 27, 1939

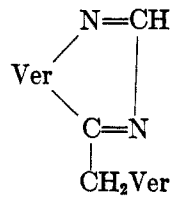
Continuing the investigations in this field which have already appeared from these laboratories,[1,2] experiments have been conducted with veratrole derivatives, whose purpose was the synthesis of the true papaverine analog in the quinazoline series. Although this goal has not yet been reached, some interesting reactions and products have been discovered and are here recorded.

For convenience in what follows, the abbreviation *Ver* will be used for $(MeO)_2C_6H_3$—, or $(MeO)_2C_6H_2<$, as the case may be. The simplified formulas for papaverine (I), the true papaverine analog (II), and the isomer (III), synthesized by Marr and Bogert,[1b] may be depicted thus:

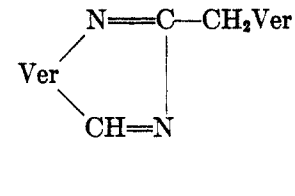


(I)

(Papaverine)



(II)



(III)

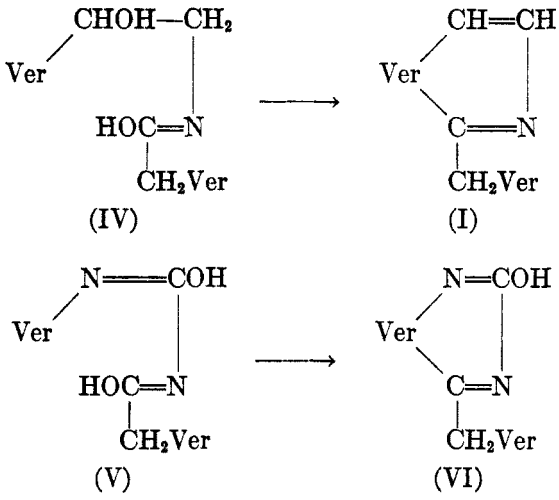
The methods applied in the course of this study are outlined briefly in what follows.

The first line of attack was the attempted paralleling, in the quinazoline series, of the familiar Pictet papaverine synthesis:

* Squibb Fellow, Columbia University, 1936–1938.

[1] (*a*) MARR AND BOGERT, *J. Am. Chem. Soc.*, **57**, 729 (1935); (*b*) *ibid.*, **57**, 1329 (1935).

[2] PAPA AND BOGERT, *ibid.*, **58**, 1701 (1936).



In applying this reaction in the quinazoline series, it seemed simpler to attempt the preparation of the 2-hydroxy derivative (VI), rather than of the unhydroxylated compound (II), because of the readier accessibility of the initial material (V). Further, there was the possibility that this hydroxy quinazoline, or some of its derivatives (*e.g.* its methyl ether), might prove more active physiologically, and the probability that the hydroxyl group could be replaced by hydrogen either directly or indirectly.

N. Palit[3] was unsuccessful in his efforts to cyclize *sym*-acetylphenylurea to 4-methyl-2-quinazolone. He reported that, "The task proved to be very difficult . . . the results of which will be communicated later." So far as the writers are aware, there has been no publication on the subject since.

In view of the fact that veratrole derivatives often react in quite a different manner from the unmethoxylated benzenes, it was decided to give this reaction a further trial, and for that purpose there were prepared the acetyl, phenylacetyl, and homoveratroyl derivatives of 3,4-dimethoxyphenylurea. All attempts to condense these ureides to quinazolones proved fruitless. It is perhaps worth noting in this connection that 3,4-dimethoxyphenylurea, although structurally somewhat akin to the sweet compound dulcin (*p*-phenetylurea), is wholly tasteless. In the preparation of this urea by refluxing an aqueous solution of urea and 4-aminoveratrole hydrochloride for 30 minutes, there were formed approximately 50 per cent. of the mono-, 5 per cent. of the *sym*-di-, and 10 per cent. of the *asym*-disubstituted ureas.

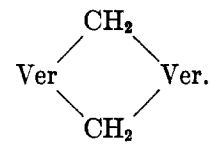
[3] PALIT, *J. Indian Chem. Soc.*, **11**, 479 (1934).

The Riedel[4] quinazoline synthesis was extended to 6-nitroveratraldehyde, and excellent yields of 6,7-dimethoxyquinazoline were obtained. Unfortunately, this reaction is apparently inapplicable to ketones, at least under the conditions which are so successful with the aldehydes. Formamide could not be condensed with acetophenone, benzophenone, or their *o*-nitro derivatives. The synthesis of 4-R-quinazolines by this process, therefore, seems unlikely.

The *o*-aminoketone, $Ver\begin{cases}NH_2\\COCH_2Ver,\end{cases}$ if obtainable in sufficient quantity and purity, should be easily convertible into quinazolines of the type sought. The preparation of this aminoketone, therefore, has been the subject of some study.

Structurally, the ketone is an *o*-aminodesoxyveratroin, but cannot be made by the direct nitration of desoxyveratroin, followed by reduction of the NO_2 group to NH_2, for the reason that desoxyveratroin nitrates *ortho* to its CH_2 and not to its CO group, and reduction of such a nitro derivative to the corresponding amine would result in an immediate condensation to the corresponding phenylated indole.[5]

It was hoped to obtain the aminoketone by the interaction of 6-nitroveratronitrile and veratrylmagnesium chloride, but veratryl chloride would not form a Grignard complex,[6] and the nitroveratronitrile proved to be entirely inert to Grignard reagents. Angeli[7] and Gilman and Kirby[8] report a similar difficulty in the case of *p*-cyananisole. In the preparation of the veratryl chloride, by the Blanc process, the major product was the tetramethoxydihydroanthracene,



Another possible road to the required *o*-aminoketone was offered by 6-nitroveratroylacetic ester, (6) $O_2NVerCOCH_2COOR$, prepared by a Claisen condensation between ethyl 6-nitroveratrate and ethyl acetate. The plan was to effect a double decomposition between the sodio derivative of the nitroveratroylacetate and the 4-halogen veratrole, eliminate the

[4] (*a*) Riedel, *Ger. Pat.* 174,941 (1905); (*b*) Bogert and McColm, *J. Am. Chem. Soc.*, **49**, 2651 (1927).

[5] Pictet, *Ber.*, **19**, 1063 (1886).

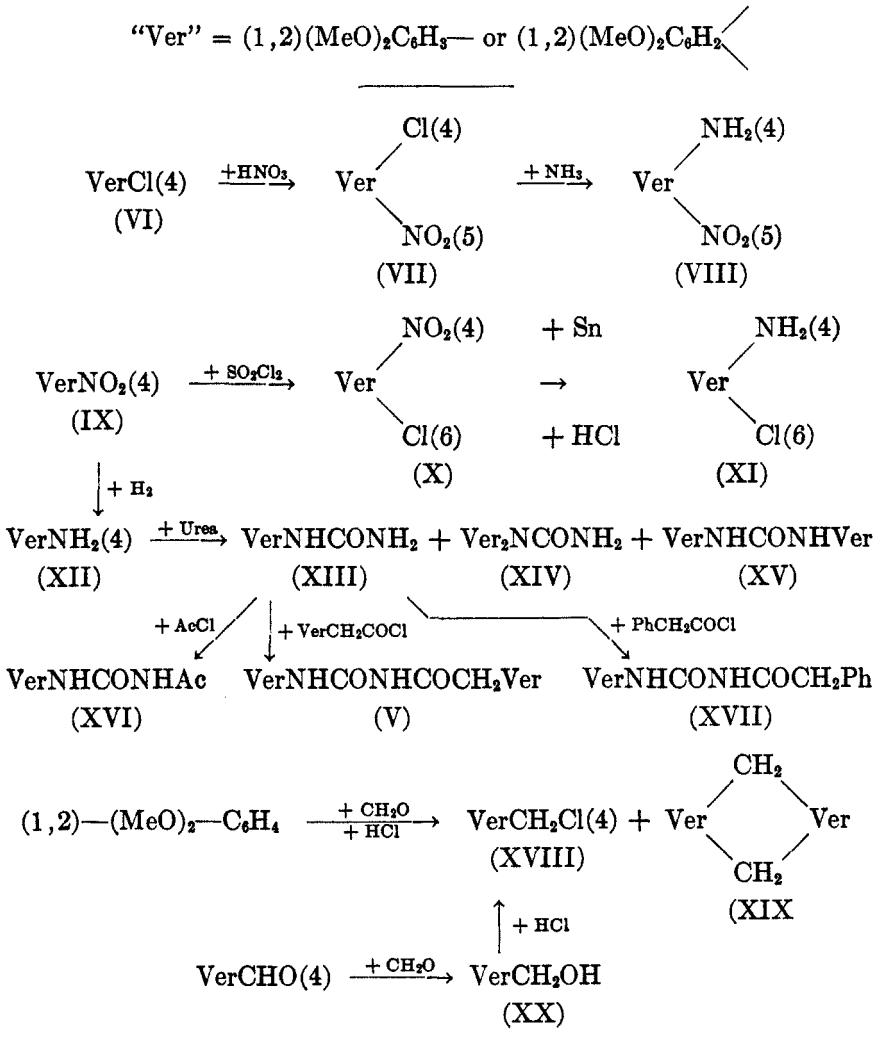
[6] Pschorr and Decker, *Ber.*, **37**, 3404 (1904).

[7] Angeli, *Atti accad. Lincei*, [6], **3**, 450 (1926).

[8] Gilman and Kirby, *J. Am. Chem. Soc.*, **55**, 1265 (1933).

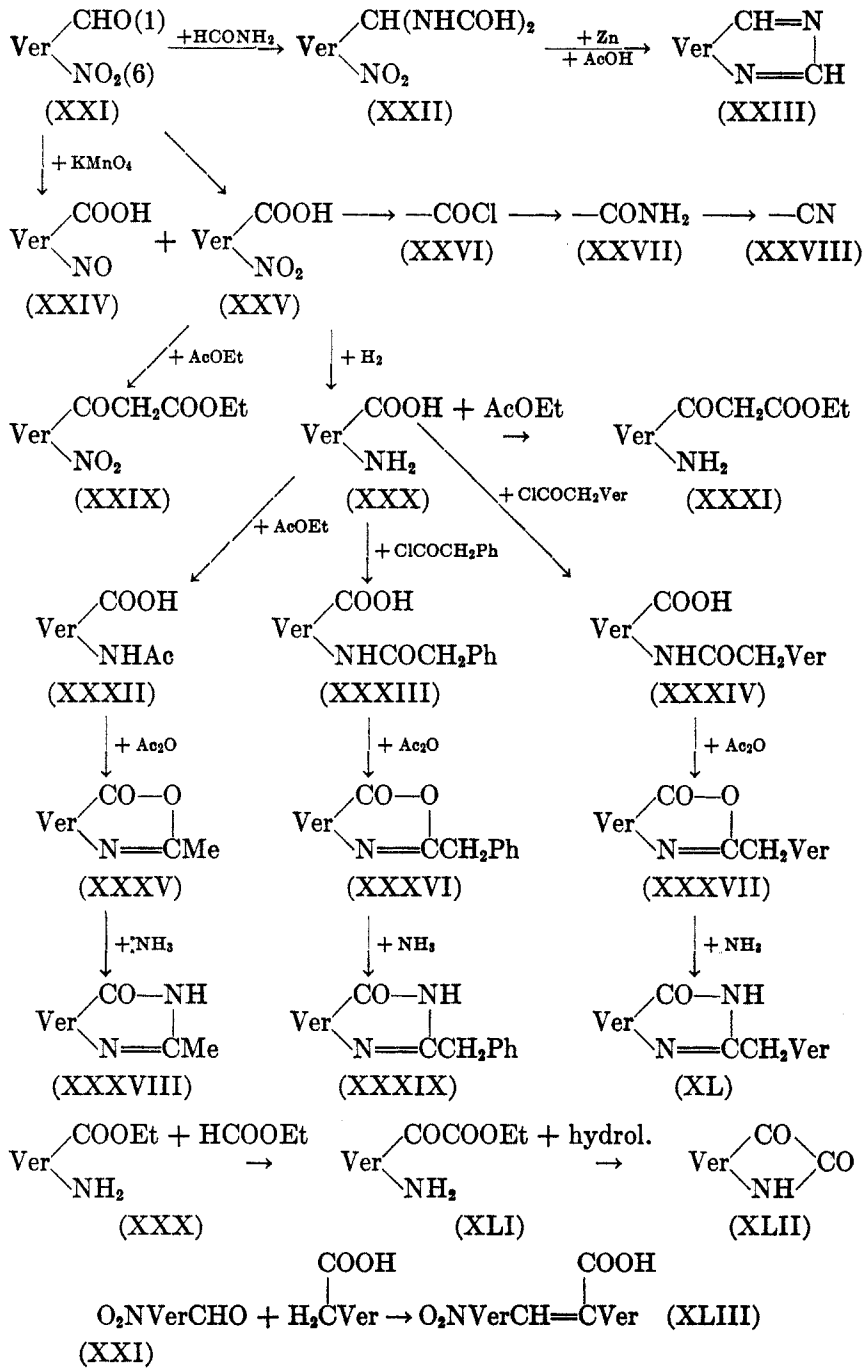
COOR from the product, and then reduce the NO_2 group to NH_2. This route was blocked by the refusal of the sodio derivative to react with either 4-chloro-, 4-bromo-, or 4-iodoveratrole.

FLOW SHEET A



The resistance of 4-aminoveratrole to formylation was quite surprising. All the usual methods were tried without success, although acetyl, benzoyl, and oxalyl derivatives were prepared readily. Similarly, all attempts to obtain the formyl derivative of ethyl 6-aminoveratrate proved fruitless.

FLOW SHEET B


Ver CHO(1) NO2(6) (XXI)
+HCONH2
Ver CH(NHCOH)2 NO2 (XXII)
+ Zn + AcOH
Ver CH=N N=CH (XXIII)
+ KMnO4
Ver COOH NO (XXIV)
+
Ver COOH NO2 (XXV)
—COCl (XXVI)
—CONH2 (XXVII)
—CN (XXVIII)
+ AcOEt
+ H2
Ver COCH2COOEt NO2 (XXIX)
Ver COOH NH2 (XXX)
+ AcOEt →
Ver COCH2COOEt NH2 (XXXI)
+ ClCOCH2Ver
+ AcOEt
+ ClCOCH2Ph
Ver COOH NHAc (XXXII)
Ver COOH NHCOCH2Ph (XXXIII)
Ver COOH NHCOCH2Ver (XXXIV)
+ Ac2O
Ver CO—O N=CMe (XXXV)
Ver CO—O N=CCH2Ph (XXXVI)
Ver CO—O N=CCH2Ver (XXXVII)
+ NH3
Ver CO—NH N=CMe (XXXVIII)
Ver CO—NH N=CCH2Ph (XXXIX)
Ver CO—NH N=CCH2Ver (XL)
Ver COOEt + HCOOEt NH2 (XXX) →
Ver COCOOEt + hydrol. NH2 (XLI) →
Ver CO NH CO (XLII)
O2NVerCHO + H2CVer(COOH) → O2NVerCH=CVer(COOH) (XLIII)
(XXI)

When the latter was heated in a sealed tube with ethyl formate, ethyl 6-aminoveratroylformate was the product, as was proved by its hydrolysis to 6-aminoveratric acid and 6-aminoveratraldehyde, and its conversion into the corresponding dimethoxyisatin. The reaction of ethyl acetate with the aminoveratrate was quite different, for there was obtained a 70 per cent. yield of the acetaminoveratrate, AcNHVerCOOR, and no aminoveratroyl acetate, $H_2NVerCOCH_2COOR$, could be detected among the other products. Upon this ester, ethyl acetate was without action. Its identity was established by conversion into the corresponding dimethoxyacetanthranil and 2-methyl-6,7-dimethoxy-4-quinazolone. Similarly anthranils and quinazolones were prepared from the analogous 6-phenylacetamino- and 6-homoveratroylaminoveratric acids.

Some experiments were conducted also in the cinnamic acid field. By the condensation of 6-nitroveratraldehyde with homoveratric acid, *alpha*-(3′,4′-dimethoxyphenyl)-3,4-dimethoxy-6-nitrocinnamic acid, $O_2NVerCH{:}C(COOH)Ver$, was prepared. Einhorn[9] has reported that hydrogen bromide can be added to 6-nitrocinnamic acid to give *beta*-bromo-6-nitrohydrocinnamic acid, $O_2NC_6H_4CHBrCH_2COOH$; but the same reaction applied to the above tetramethoxynitrocinnamic acid yielded only gums. This result is not altogether surprising, in view of the demethylating action of hydrobromic acid, and the fact that hydrochloric acid attacks the ring in veratrole derivatives.[10,11]

See also the experiments recorded beyond under chloronitroacetovanillone.

In this connection, we found the process of Kindler and Pesche,[12] for the preparation of homoveratric acid far superior to the older azlactone process.[1b]

A few reduction experiments also were tried in the quinazoline series. Benzoyleneurea, which is easily prepared in any desired quantity from anthranilic acid,[13] could not be reduced directly by any of the methods employed. Indirect reduction, by conversion first into the 2,4-dichloroquinazoline, followed by reduction of the latter by red phosphorus and iodine, gave minute yields of the dihydroquinazoline.

Quinazoline itself was easily reduced catalytically to 3,4-dihydroquinazoline[1a] which, as Gabriel[14] has shown, readily yields the tetrahydro

[9] EINHORN, *Ber.*, **16**, 2208 (1893).
[10] SEER AND KARL, *Monatsh.*, **34**, 644 (1913).
[11] SIMONSEN AND RAU, *J. Chem. Soc.*, **113**, 27 (1918).
[12] KINDLER AND PESCHE, *Arch. Pharm.*, **271**, 431 (1933).
[13] BOGERT AND SCATCHARD, *J. Am. Chem. Soc.*, **38**, 1606 (1916).
[14] GABRIEL, *Ber.*, **36**, 811 (1903).

derivative when its aqueous solution is subjected to the action of 2.5 per cent. sodium amalgam. We have now found that, by the use of a stronger amalgam (4 per cent.), quinazoline passes easily and smoothly to its tetrahydro derivative, in yields of approximately 80 per cent.

Acknowledgments.—This investigation was made possible by the generous financial assistance of E. R. Squibb & Sons, New York, N. Y., to whom we are most grateful. We are also indebted to the American Medical Association, for aid in the purchase of chemicals and equipment, and to Mr. Saul Gottlieb, who ran the analyses for us.

EXPERIMENTAL

6-Nitro-3,4-dimethoxychlorobenzene (4-Chloro-5-nitroveratrole) (VII).—4-Chloroveratrole (VI) was added slowly to concentrated nitric acid (sp. gr., 1.4), at room temperature. The reaction was complete within a few minutes and the mixture was poured into cold water. The yellow precipitate was removed and crystallized thrice from 95% ethanol, giving pale yellow needles, m.p. 118° (corr.).

Anal. Calc'd for $C_8H_8ClNO_4$: C, 44.13; H, 3.71.
Found: C, 43.95; H, 3.69.

6-Nitro-3,4-dimethoxyaniline (4-Amino-5-nitroveratrole) (VIII).—The above compound was converted into the 4-amino-5-nitroveratrole (orange-brown needles, m.p. 171°, corr.) by dissolving it in absolute ethanol, saturating the solution with ammonia, and then heating it in sealed tubes for 10 hours at 130°. The substance has been prepared before, by various investigators, by other methods.

5-Chloro-3,4-dimethoxynitrobenzene (4-Nitro-6-chloroveratrole) (X).—A solution of 1 g. of 4-nitroveratrole (IX) in 5 cc. of sulfuryl chloride was refluxed gently for 30 minutes, and the sulfuryl chloride was then decomposed by the careful addition of 50% alcohol as long as it caused ebullition. Cold water (50 cc.) was added, and a yellow oil separated, which congealed to a pasty mass as the mixture cooled. Crystallized thrice from alcohol, the crude material was secured in beautifully lustrous pale-yellow needles, m.p. 95° (corr.), which m.p. was greatly lowered when mixed with some of the original 4-nitroveratrole (m.p. 96°).

Anal. Calc'd for $C_8H_8ClNO_4$: C, 44.13; H, 3.71.
Found: C, 44.14; H, 3.80.

When Cousin[15] brominated 4-nitroveratrole, he found that the reaction proceeded with difficulty, and heating to 100° was necessary. The product was the 4-nitro-6-bromo derivative (m.p. 111°), and Jones and Robinson[16] cited this as one of the very few instances in which the negative substituent overcomes the directive influence of the methoxyl group.

Thus, 4-nitroveratrole is brominated with much more difficulty than veratrole, and the product formed is not the 4,5 (m.p. 123°), but the lower-melting 4,6 derivative. Similarly, chlorination of 4-nitroveratrole proceeds with difficulty, and the chloronitro derivative formed has a lower melting point than the one we believe to be the 4,5 derivative. Hence, we assume the above product to be the 4-nitro-6-chloroveratrole. Further, it does not react with ammonia or alkylamines, as it should if the halogen were adjacent to a nitro group.

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[15] COUSIN, *Ann. chim. phys.*, [7], **13**, 504 (1898).
[16] JONES AND ROBINSON, *J. Chem. Soc.*, **111**, 903 (1917).

5-Chloro-3,4-dimethoxyaniline (*4-Amino-6-chloroveratrole*) (*XI*).—A mixture of 0.5 g. of the nitro compound (X) with 1 g. of mossy tin and a trace of graphite was covered with 10 cc. of 50% hydrochloric acid, heated for 1.5 hrs. with vigorous stirring, and filtered hot. The cooled filtrate was made strongly alkaline by the addition of solid sodium hydroxide, and the amine was extracted from the precipitate with ether. Recrystallized thrice from petroleum ether, it formed colorless needles, m.p. 89° (corr.), while the 4-amino-5-chloroveratrole melts at 72–73°.

Anal. Calc'd for $C_8H_{10}ClNO_2$: C, 51.19; H, 5.38.
Found: C, 51.20; H, 5.51.

3,4-Dimethoxyaniline (*4-Aminoveratrole*) (*XII*).—Heretofore this has been prepared by other methods of reducing the nitro compound, the yields being recorded as 60% or less. We have now found that much larger yields are obtainable by catalytic reduction, using a platinum catalyst. The dark-red product was purified by distillation at about 20 mm. pressure, when its boiling point was approximately 172°. At lower pressures, and consequently lower temperatures, the distillate is likely to congeal in the delivery tube of the flask; yield of pure amine, m.p. 86° (corr.), 92%.

The snow-white free amine is very unstable, turning pink almost immediately, then red, and finally deep purple.

Its *hydrochloride*, crystallized from absolute ethanol by refrigeration or the addition of petroleum ether, formed white needles, m.p. 240° (corr.), which rapidly darkened on standing exposed to light and air, and after a few days were almost black.

Anal. Calc'd for $C_8H_{12}ClNO_2$: N, 7.39. Found: N, 7.25.

Heinisch[17] prepared this hydrochloride and reported its m.p. as 238°, but did not mention its instability.

Repeated attempts to *formylate* this amine, varying the method and the conditions, proved fruitless. Only gummy products were obtained, aside from unaltered initial material, in spite of the fact that other acyl derivatives were prepared without difficulty by the usual processes.

The *acetyl derivative* from the amine and acetic anhydride, white plates, m.p. 133° (corr.), has been described also by Jacobson, Jaenicke and Meyer.[18]

The *benzoyl derivative*, from the amine and benzoyl chloride, crystallized thrice from ethanol, formed clusters of small white needles, m.p. 178° (corr.), with a faint bluish tinge and a peculiar mousy odor.

Anal. Calc'd for $C_{15}H_{15}NO_3$: N, 5.45. Found: N, 5.43.

Oxalyl derivative, $(MeO)_2C_6H_3NHCOCOOH$.—A mixture of 2 g. of the amine with 1 g. of potassium acid oxalate was heated for an hour at 120°, cooled, extracted with 300 cc. of boiling water, and the hot extract was quickly acidified with sulfuric acid. As the solution cooled, a curdy, white precipitate separated, and was crystallized thrice from toluene. White needles were thus secured; m.p. 168° (corr.); yield, about 40%.

Anal. Calc'd for $C_{10}H_{11}NO_5$: C, 53.31; H, 4.93.
Found: C, 53.49; H, 5.01.

3,4-Dimethoxyphenylurea (*4-Carbamidoveratrole*) (*XIII*).—A mixture of 2 g. of 4-aminoveratrole hydrochloride, 2 g. of urea, and 20 cc. of water, was refluxed for

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[17] HEINISCH, *Monatsh.*, **15**, 232 (1894).

[18] JACOBSON, JAENICKE, AND MEYER, *Ber.*, **29**, 2690 (1896).

30 minutes, at the end of which time there was considerable bumping. After 45 minutes, the solution was filtered hot; the filtrate was cooled and again filtered. The product, which was soluble in boiling water, and separated from the filtrate on cooling, was an amorphous red powder. By repeated crystallization from water, in the presence of a decolorizing carbon, it yielded about 50% of a white microcrystalline product, m.p. 210° (corr.), whose composition corresponded to that of 3,4-dimethoxyphenylurea.

Anal. Calc'd for $C_9H_{12}N_2O_3$: C, 55.06; H, 6.17.
Found: C, 54.82; H, 5.96.

Although structurally related to dulcin (*p*-phenetylurea), it was entirely tasteless.

sym-*Di-(3,4-dimethoxyphenyl)urea* (*XV*).—The solid filtered out of the hot aqueous solution, in the initial reaction for the production of the mono(dimethoxyphenyl)urea (XIII) above, consisted of pinkish needles. This mixture of crystals, when boiled with ethanol, was separated into a soluble and an insoluble portion. The insoluble portion crystallized from toluene in small white needles, m.p. 313° (corr.); yield, about 5%.

Anal. Calc'd for $C_{17}H_{20}N_2O_5$: C, 61.41; H, 6.07.
Found: C, 61.54; H, 5.87.

asym-*Di-(3,4-dimethoxyphenyl)urea* (*XIV*).—In the purification of the foregoing compound (XV), the alcohol extracts obtained therefrom contained another substance, which was crystallized from alcohol and decolorized. It consisted of beautifully lustrous white needles, m.p. 219° (corr.); yield, about 10%. Mixed with the monosubstituted urea (XIII), of m.p. 210°, the m.p. was 165–175°.

Anal. Calc'd for $C_{17}H_{20}N_2O_5$: C, 61.41; H, 6.07.
Found: C, 61.30; H, 6.17.

The structure assigned to the two isomeric disubstituted ureas (XIV and XV) is based upon analogy, since *sym*-diphenylurea (m.p. 235°) melts much higher than the *asym* isomer (m.p. 181°). The amounts of these isomers obtained in purity were inadequate for a chemical proof by hydrolysis.

sym-*Acetyl-3,4-dimethoxyphenylurea* (*XVI*).—A suspension of 1 g. of 3,4-dimethoxyphenylurea (XIII) in 30 cc. of dry pyridine, in a flask equipped with thermometer, dropping funnel, and calcium chloride guard tube, was cooled to 0° and treated slowly with 0.9 g. of acetyl chloride with continued refrigeration. After all the acetyl chloride had been added, the mixture was left for 5 hours at room temperature with occasional shaking. The copious white precipitate gradually turned yellow. The mixture was poured into 400 cc. of water and left for a half-hour at room temperature; the precipitate was collected, washed with 500 cc. of cold water, and repeatedly crystallized from toluene in the presence of Norite. The product so obtained formed white needles, m.p. 227° (corr.).

Anal. Calc'd for $C_{11}H_{14}N_2O_4$: N, 11.55. Found: N, 11.36.

Acylation of such ureas with acetic anhydride or glacial acetic acid, and sodium acetate, is not satisfactory. As both Alberti[19] and Abrahart[20] have found, the use of acetyl chloride and pyridine gives much better results.

Heated above its melting point, the compound changed to a brown gum. Boiled for 2 hours, in toluene or xylene solution, with 5 times its weight of phosphorus pentoxide, it remained unaltered.

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[19] ALBERTI, *Gazz. chim. ital.*, **65**, 922 (1935).
[20] ABRAHART, *J. Chem. Soc.*, **1936**, 1273.

Palit[3] seems to have experienced similar difficulties in trying to cyclize phenylated ureas to quinazolines.

sym-*Phenylacetyl-3,4-dimethoxyphenylurea* (*XVII*), prepared in the same way as the acetyl derivative (XVI) just described, with the use of 1 g. of the 3,4-dimethoxyphenylurea, 30 cc. of dry pyridine, and 1 g. of phenylacetyl chloride, was purified by repeated crystallization from 50% alcohol, in the presence of Norite, and then formed white needles, m.p. 249° (corr.).

Anal. Calc'd for $C_{17}H_{18}N_2O_4$: N, 8.92. Found: N, 8.79.

Heated above its melting point, or boiled for 2 hours in toluene or xylene solution with 5 times its weight of phosphorus pentoxide, its behavior was similar to that of the acetyl analog (XVI).

sym-*Homoveratroyl-3,4-dimethoxyphenylurea* (*V*) was obtained; like the two preceding ureides (XVI and XVII), from the 3,4-dimethoxyphenylurea and the appropriate acid halide, except that it was found more convenient to use a chloroform solution of the syrupy homoveratroyl chloride to add to the pyridine suspension of the urea. The crude product was purified by crystallization from toluene, in the presence of Norite, until the melting point remained constant at 256° (corr.), and the compound appeared in pale-yellowish needles.

Anal. Calc'd for $C_{19}H_{22}N_2O_6$: C, 61.13; H, 5.71.
Found: C, 61.39; H, 5.39.

Heated above its melting point, or boiled for 2 hours in toluene or xylene solution, with 5 times its weight of phosphorus pentoxide, its behavior was similar to that of its acetyl analog (XVI).

Veratryl chloride (*XVIII*).—Veratryl alcohol (XX) was prepared by the crossed Cannizzaro reaction, as described by Davidson and Bogert,[21] in a yield of 87%, and with a b.p. of 188-192° at 20 mm. This alcohol was dissolved in dry benzene and converted into the chloride by the action of hydrogen chloride, as recorded by Pschorr and Decker;[6] colorless needles, m.p. 51°; yield, 65%.

Pschorr and Decker reported that this chloride did not react with magnesium. Presumably they meant that it did not form a simple Grignard compound, and that we can corroborate. It did, however, react vigorously with carefully dried magnesium in the presence of ether, but the resulting mixture was indifferent to acetone or even to water.

2,3,6,7-Tetramethoxy-9,10-dihydroanthracene (*XIX*).—In an attempt to prepare veratryl chloride (XVIII) by a modification of the Blanc synthesis, a rapid stream of dry hydrogen chloride was bubbled through a cooled mixture of 20 g. of veratrole, 5 g. of paraformaldehyde, and 10 g. of powdered fused zinc chloride. Temperatures below 35° tended to freeze the mixture and clog the system. After an hour, the mixture set to a vitreous solid, which was promptly washed with ice water, and fractionally crystallized from absolute ethanol. The first, and largest, fraction (10 g.) consisted of small white needles, m.p. 235° (corr.), and we believe was the above anthracene derivative, a veratryl dimer.

Anal. Calc'd for $C_{18}H_{20}O_4$: C, 71.01; H, 7.92.
Found: C, 71.14; H, 7.71.

This compound has been prepared, in other ways, by Robinson,[22] who found a somewhat lower m.p. (227°).

From the mother-liquors of this anthracene derivative, there was recovered about

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[21] DAVIDSON AND BOGERT, *J. Am. Chem. Soc.*, **57**, 905 (1935).

[22] ROBINSON, *J. Chem. Soc.*, **107**, 270 (1915).

2 g. of veratryl chloride, in colorless needles, m.p. 51°, identical with that described above.

6-Nitroveratraldehyde (*XXI*).—A further study of this preparation has shown that a nitrating temperature of 15–25° is best, and that it is only necessary to keep the reaction flask in a bath of cold water. Because of the sensitivity of the product to light, the entire procedure must be conducted in semi-darkness.

To 100 cc. of nitric acid (sp. gr., 1.4), there was added slowly (30 minutes) with vigorous stirring 15 g. of veratraldehyde. After 10 minutes' further stirring, the mixture was poured into a liter of cold water, the precipitate removed, washed with an additional liter of cold water, dried at room temperature, and crystallized from alcohol, m.p. 133° (corr.); yield, 78%.

This aldehyde reacted quietly, and apparently normally, with phenylmagnesium bromide. While the product was not isolated, there was no evidence of side reactions or other complications.

6-Nitroveratrylidenediformamide (*XXII*).—Dry hydrogen chloride was bubbled for an hour through a suspension of 5 g. of the above-described aldehyde (XXI) in 10 g. of formamide. At the beginning of the introduction of the hydrogen chloride the mixture was warmed to 45°, after which it was kept at 50° by suitable cooling, and throughout the entire process the flask was protected from the light. After an hour's treatment with hydrogen chloride, the mixture was almost solid. It was crushed in 5 cc. of absolute ethanol, left in the refrigerator for an hour; the solid material then collected by filtration and crystallized thrice from water. The product consisted of yellow needles, m.p. 195.5° (corr.); yield, 4.5 g., or 65% calculated on the basis of the aldehyde used.

Anal. Calc'd for $C_{11}H_{13}N_3O_6$: C, 46.62; H, 4.63.
Found: C, 46.40; H, 4.49.

6,7-Dimethoxyquinazoline (*XXIII*).—To a mixture of 5 g. of the diformamide (XXII), 10 g. of zinc dust, and 40 g. of finely crushed ice, there was added slowly, with vigorous agitation, 12 g. of glacial acetic acid. After the shaking had been continued for an hour, the excess of zinc was filtered out, the filtrate was cooled to below 10°, and was made strongly alkaline by the addition of 60 cc. of 50% potassium hydroxide solution. A copious white crystalline precipitate, which was apparently a mixture of the base with some double salts, separated. This precipitate was removed and dissolved in 5 cc. of water, and the solution extracted repeatedly with ether. Evaporation of the ether extracts left a yellow residue which, crystallized thrice from petroleum ether, gave yellow needles of the quinazoline, m.p. 143° (corr.); yield, 50%.

Anal. Calc'd for $C_{10}H_{10}N_2O_2$: C, 63.13; H, 5.24.
Found: C, 63.16; H, 5.20.

Hydrochloride.—White microcrystalline powder, with a faint pinkish tint, m.p. 227° (corr.).

Anal. Calc'd for $C_{10}H_{10}N_2O_2 \cdot HCl$: C, 53.41; H, 4.90.
Found: C, 53.56; H, 5.11.

6-Nitroveratric acid (*XXV*) was prepared, according to the method of Pschorr and Sumuleanu,[23] by the oxidation of the corresponding aldehyde with potassium permanganate; yellow needles, m.p. 189–190° (corr.). Pschorr and Sumuleanu found a m.p. of 188–190°.

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[23] PSCHORR AND SUMULEANU, *Ber.*, **32**, 3412 (1899).

Ethyl ester.—Pale yellow needles (from alcohol), m.p. 99.5° (corr.). Tiemann and Matsmoto[24] recorded the m.p. as 99–100°.

Chloride (XXVI).—When 20 g. of the acid was added to a solution of 15 cc. of thionyl chloride in 70 cc. of chloroform, there was a brief and vigorous reaction. The mixture was left for 24 hours at room temperature, protected by a calcium chloride guard tube, and was then evaporated to dryness under diminished pressure. The yellow viscous residue, after several crystallizations from petroleum ether, yielded feathery yellow needles, m.p. 88–89° (corr.).

Anal. Calc'd for $C_9H_8ClNO_5$: C, 43.99; H, 3.28.
Found: C, 44.28; H, 3.46.

Amide (XXVII).—Prepared from the chloride and ammonium hydroxide solution, and purified by crystallization from petroleum ether, this amide formed yellow needles, m.p. 193° (corr.).

Anal. Calc'd for $C_9H_{10}N_2O_5$: N, 12.30. Found: N, 12.57.

Nitrile (XXVIII).—The amide was dissolved in toluene, phosphorus pentoxide was added, and the mixture was refluxed for 2 hours, and filtered hot; the filtrate was concentrated and allowed to cool. The nitrile separated in pinkish-yellow plates, which, after several crystallizations from toluene, melted at 168° (corr.); yield over 90%. Keffler,[25] who obtained this compound by the nitration of veratronitrile, recorded its m.p. as 165°.

Anal. Calc'd for $C_9H_8N_2O_4$: C, 51.94; H, 3.86.
Found: C, 52.29; H, 3.67.

This nitrile could not be made to react with either butyl- or phenylmagnesium bromide. Angeli,[7] and Gilman and Kirby,[8] have reported that *p*-cyananisole likewise refuses to react with Grignard reagents.

6-Nitrosoveratric acid (XXIV).—In the preparation of 6-nitroveratric acid, as described above, if an insufficient quantity of potassium permanganate was used, an orange-brown product of much lower melting point was formed. This was separated by fractional crystallization from water into the 6-nitro acid (80%) and a tan microcrystalline powder (20%), m.p. 175–190°. A mixture of the latter with an equal amount of the pure 6-nitro acid, melted, roughly, from 150° to 180°. The second product agrees in its properties with the 6-nitrosoveratric acid (m.p. 180–190°) obtained by Sumuleanu[26] by boiling an aqueous suspension of 6-nitroveratraldehyde in the sunlight.

Ethyl ester (?)—In an attempt to prepare ethyl 6-aminoveratrate by catalytic reduction of the nitro ester in ethyl acetate solution with the aid of palladous chloride as catalyst, the absorption of hydrogen ceased abruptly when only about one-third of the calculated amount had been taken up. Evaporation of the bright-red solution left a pasty red mass, which, after several recrystallizations from petroleum ether, yielded orange needles, m.p. 70° (corr.), whose analysis and mol. wt. determination gave figures agreeing with those calculated for the nitroso or oximino ester.

Anal. Calc'd for $C_{11}H_{13}NO_5$: N, 5.86; mol. wt., 239.11.
Found: N, 5.80; mol. wt. (Rast), 231.

Ethyl 6-nitroveratroyl acetate (XXIX).—A solution of 5 g. of ethyl 6-nitroveratrate in 10 cc. of ethyl acetate, was treated with 0.7 g. of sodium wire, in a flask equipped

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[24] TIEMANN AND MATSMOTO, *ibid.*, **9**, 941 (1876).
[25] KEFFLER, *J. Chem. Soc.*, **119**, 1497 (1924).
[26] SUMULEANU, *Ann. sci. Univ. Jassy*, **2**, 139 (1903); *Chem. Zentr.*, **1903**, II, 32.

with a mercury-sealed mechanical stirrer and a reflux condenser carrying a calcium chloride guard tube. When necessary, a few drops of absolute alcohol were added to initiate the reaction. After refluxing gently for 3 hours, the mixture was cooled, 10 cc. of ice water was added and, with careful cooling, the solution was made acid to litmus by the addition of 33% hydrochloric acid. The acid mixture was extracted several times with ether; the extracts were united, and washed with dilute sodium bicarbonate solution, and the solvent removed. The gummy residue was purified by repeated crystallization from petroleum ether, when it formed yellow needles, m.p. 73° (corr.).

Anal. Calc'd for $C_{18}H_{15}O_7N$: C, 52.52; H, 5.09.
Found: C, 52.58; H, 5.29.

The sodio derivative of this ester could not be made to condense with chloro- or bromobenzene; or with 4-chloro-, 4-bromo-, or 4-iodoveratrole.

6-Nitroveratroylacetic acid was obtained by the gentle hydrolysis of its ethyl ester, and was crystallized from benzene in yellow needles; m.p. 219° (corr.).

Anal. Calc'd for $C_{11}H_{11}NO_7$: C, 49.09; H, 4.12.
Found: C, 49.35; H, 4.14.

Chloronitroacetovanillone (or -isovanillone), $(Cl)(O_2N)C_6H(Ac)(OMe)(OH)$.—Refluxing of this acid for 12 hours with a saturated aqueous solution of barium hydroxide, left it apparently unaltered. Further refluxing for 30 hours, however, hydrolyzed it, but the resultant product proved difficult to isolate and purify. It was easily soluble in aqueous alkali. In an attempt to isolate it by steam distillation of its solution acidified with hydrochloric acid, no volatile product was obtained, but the original substance was changed and a new compound was isolated, and was purified by repeated crystallization from water, and then formed microcrystalline yellow needles, m.p. 165° (corr.), which contained both chlorine and nitrogen, were easily soluble in aqueous alkali, formed an addition compound with sodium bisulfite, and gave the following figures on analysis:

Anal. Calc'd for $C_9H_8ClNO_5$: C, 43.99; H, 3.28.
Found: C, 44.14; H, 3.28.

These figures and chemical properties seem adequate to identify the compound as a chloronitroacetovanillone (or -acetoisovanillone).

It is not improbable that the hydrochloric acid was responsible for both the hydrolysis of one of the methoxyl groups and the chlorination of the benzene nucleus, since the work of Seer and Karl,[10] Simonsen and Rau[11], and others, has shown the possibility of chlorinating the ring in veratrole derivatives by the action of hydrochloric acid, and this reagent has been used successfully also for the hydrolysis of methoxyl groups. Further, Caldwell and Robinson[27] have used aqueous hydrogen bromide for the quantitative conversion of nitroveratrole into nitroguaiacol.

6-Aminoveratic acid (XXX).—After experimentation with various ways of reducing the nitro acid, the ammonia-ferrous sulfate method proved the most satisfactory, although the yield was only about 30%. The purification of the crude acid was very troublesome. The pure acid crystallized from ethyl acetate in white needles, which melted at 186° (corr.) when heated rapidly, but began to decompose at 100° when heated slowly. Heidelberger and Jacobs,[28] who obtained the acid by hydrolysis of the ethyl ester, gave the m.p. as 186° also. The nitro acid was reduced catalytically also, in ethanol solution, in the presence of the Adams platinum

[27] CALDWELL AND ROBINSON, *J. Chem. Soc.*, **107**, 257 (1915).
[28] HEIDELBERGER AND JACOBS, *J. Am. Chem. Soc.*, **41**, 2142 (1919).

catalyst, and in one run a yield of 90% of the pure amino acid was secured. In other experiments, however, the yields varied from 10 to 70%.

The *ethyl ester* was obtained by direct esterification (absolute ethanol and hydrogen chloride) of the acid, in a yield of 48%, but this method was unsatisfactory because of the difficulty of preparing the pure amino acid.

A far preferable way of making this ester was the catalytic reduction of an ethanol solution of the nitro ester in the presence of the Adams platinum catalyst, which occupied only 3–5 minutes, and gave yields of 85–98% of pure product, in white needles, m.p. 88° (corr.), in agreement with the literature.

Anal. Calc'd for $C_{11}H_{15}NO_4$: N, 6.27. Found: N, 6.37.

Ethyl 6-aminoveratroyl formate (*XLI*).—Attempts to formylate ethyl 6-aminoveratrate by usual methods all failed. Either there was no interaction, or the products were tars.

Finally, a mixture of equal weights of ethyl 6-aminoveratrate and ethyl formate was heated in a sealed tube for 4 hours at 130°, and, on concentration of the tube contents, a mass of pale-brown needles was obtained. This crude product was purified by 14 crystallizations from "Skelly D" solvent (a petroleum fraction, b.p. 75–111°), and 3 from low-boiling petroleum ether; white needles; m.p. 70° (corr.).

Anal. Calc'd for $C_{12}H_{15}NO_5$: C, 56.89; H, 5.97; mol. wt., 253.
Found: C, 56.74; H, 6.08; mol. wt., 246.

The compound dissolved in caustic alkali. Upon boiling with ammonium hydroxide solution, no quinazolone was produced, as would have been the case with the isomeric formamidoveratrate, but the substance decomposed with a vigorous evolution of carbon dioxide and carbon monoxide, and formation of 6-aminoveratraldehyde and 6-aminoveratric acid, the products one would expect from the decomposition of the aminoveratroylformic acid. As an additional proof of the identity of the ethyl aminoveratroylformate, it was converted into the corresponding isatin.

5,6-Dimethoxyisatin (*XLII*).—A suspension of 1 g. of ethyl 6-aminoveratroylformate (ethyl dimethoxyisatate) in 50 cc. of 10% potassium hydroxide solution, after standing for 3 hours at 40°, was filtered from unsaponified ester, the filtrate was neutralized with hydrochloric acid, extracted with ether, and the ether extract was evaporated, leaving clusters of brown needles. Recrystallization from benzene yielded orange-brown needles, which changed to a brown powder on drying, melting raggedly around 180–195°. Repeated crystallization failed to change this product further. Shaken with concentrated sulfuric acid and with benzene containing thiophene, it gave a deep blue-green color, as would be expected of an isatin.

Anal. Calc'd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76; CH_3O, 29.94.
Found: C, 57.78; H, 4.55; N, 6.99; CH_3O, 29.68.

6-Acetamidoveratric acid (*XXXII*) was obtained by careful hydrolysis of the ester. Repeated crystallization from petroleum ether yielded white needles; m.p. 233° (corr.).

Anal. Calc'd for $C_{11}H_{13}NO_5$: C, 55.20; H, 5.48.
Found: C, 55.21; H, 5.60.

Ethyl ester.—This compound was formed when ethyl 6-aminoveratrate was treated with ethyl acetate, in an attempt to effect a simple Claisen condensation to ethyl 6-aminoveratroyl acetate (XXXI).

The ethyl 6-acetamidoveratrate was obtained in 70% yield, and crystallized from petroleum ether containing a little ethyl acetate in white needles, m.p. 130° (corr.). This melting point was considerably higher than was expected for the aminoveratroyl

acetate, since the corresponding nitroveratroyl acetate melts at 73°. Further, the fact that it was extracted by ether from an acid solution proved its non-basic character. It was not surprising, therefore, that on careful hydrolysis it gave 6-acetaminoveratric acid, together with some 6-aminoveratric acid.

Anal. Calc'd for $C_{13}H_{17}NO_5$: C, 58.40; H, 6.41; N, 5.24.
Found: C, 58.80; H, 6.42; N, 5.25.

Refluxing with sodium and ethyl acetate (even in large excess) for periods up to 30 hours, was without effect upon this ethyl acetamidoveratrate.

In the initial reaction of the aminoveratrate and ethyl acetate, the acid solution from which the acetamidoveratrate had been extracted with ether was made alkaline and again extracted with ether to recover any aminoveratroyl acetate present, but none was found.

2-Methyl-6,7-dimethoxy-4-quinazolone (*XXXVIII*).—6-Acetaminoveratric acid was dissolved in acetic anhydride, and the solution was concentrated to crystallization. The 6,7-dimethoxyacetanthranil (XXXV) separated in clusters of very fine white needles, which were added to a boiling solution of 10*N* ammonium hydroxide solution containing a drop or two of potassium hydroxide solution, and the whole was boiled for 20 minutes, with the addition of more ammonium hydroxide solution if necessary. Upon concentration and cooling, a white curdy precipitate separated from the solution which, after 3 crystallizations from water, formed long white needles; m.p. 312° (corr.).

Anal. Calc'd for $C_{11}H_{12}N_2O_3$: N, 12.73. Found: N, 12.98.

6-Phenylacetamidoveratric acid (*XXXIII*) was prepared by mixing a solution of 1.4 g. of 6-aminoveratric acid in 6.5 cc. of glacial acetic acid with 12 cc. of a saturated solution of sodium acetate, cooling to 0°, and adding gradually (30 minutes) 1.5 g. of phenylacetyl chloride. After standing at 0° for five hours with occasional shaking, the orange precipitate was collected, washed with 50 cc. of 25% acetic acid, followed by 50 cc. of cold water. Decolorized and crystallized repeatedly from absolute ethanol, it was obtained in very small white needles, m.p. 226° (corr.).

Anal. Calc'd for $C_{17}H_{17}NO_5$: C, 64.82; H, 5.44.
Found: C, 64.73; H, 5.63.

2-Benzyl-6,7-dimethoxy-4-quinazolone (*XXXIX*).—By solution of 6-phenylacetamidoveratric acid (XXXIII) in acetic anhydride and concentration of the solution to crystallization, the crude benzyldimethoxyanthranil (XXXVI) was obtained in yellow needles, which were converted into the quinazolone by the action of ammonia in essentially the same way as described above for the methyl analog (XXXVIII). This quinazolone, when decolorized and crystallized repeatedly from toluene, formed large white needles; m.p. 253° (corr.).

Anal. Calc'd for $C_{17}H_{16}N_2O_3$: C, 68.88; H, 5.30.
Found: C, 68.74; H, 5.22.

6-Homoveratroylamidoveratric acid (*XXXIV*), prepared from 6-aminoveratric acid and homoveratroyl chloride, by the process described above for the phenylacetyl analog, and purified by decolorization and crystallization from a 1:1 mixture of ethanol and ethyl acetate, formed a faintly yellowish microcrystalline powder; m.p. 241° (corr.).

Anal. Calc'd for $C_{19}H_{21}NO_7$: C, 60.78; H, 5.64.
Found: C, 61.06; H, 5.63.

2-Veratryl-6,7-dimethoxy-4-quinazolone (*XL*).—The 6-homoveratroylamidoveratric acid (XXXIV) was converted in the corresponding crude veratryldimethoxyanthranil (XXXVII) (yellow crystals), and this in turn into the quinazolone, as in

the case of the phenylacetyl analog. By repeated crystallization from toluene, the quinazolone was secured in white needles; m.p. 269° (corr.).

Anal. Calc'd for $C_{19}H_{20}N_2O_5$: C, 64.07; H, 5.66; N, 7.87.
Found: C, 64.24; H, 5.54; N, 7.66.

The closely related 2-veratryl-6,7-dimethoxyquinazoline has been described by Marr and Bogert.[1b]

alpha-(*3',4'-Dimethoxyphenyl*)-*3,4-dimethoxy-6-nitrocinnamic acid* (*XLIII*).—A suspension of 1 g. of sodium homoveratrate and 0.75 g. of 6-nitroveratraldehyde in 10 cc. of acetic anhydride was heated at 105° for 2.5 hours. After the interruption of the heating and addition of a few cc. of hot water, to destroy the excess of acetic anhydride, the mixture was poured into 200 cc. of 2*N* hydrochloric acid, and left overnight. The brownish precipitate was removed, dissolved in cold glacial acetic acid, reprecipitated by dilution with 10 volumes of water, and the oily precipitate was collected by repeated extraction with ether. The combined ether extracts were extracted thrice with an equal volume of normal sodium hydroxide. The alkaline extracts were precipitated by acidification, the precipitate was taken up in ether, the ether was removed, the residue was dissolved in alcohol, and the solute was reprecipitated by dilution. Since two repetitions of this alcohol-water treatment seemed to accomplish but little further purification, the pasty product was dissolved in benzene and reprecipitated by the addition of petroleum ether. After the third repetition of this treatment with benzene and petroleum ether, final purification was possible with benzene alone. By slow cooling of a dilute benzene solution, the product was obtained in pale-yellowish transparent diamond-shaped plates, up to 5 mm. on a side, m.p. 187° (corr.); yield, 60%.

Anal. Calc'd for $C_{19}H_{19}NO_8$: C, 58.59; H, 4.92.
Found: C, 58.77; H, 5.13.

Working with larger amounts, the yields were 70–75%.

When this acid was heated in sealed tubes at 90–100° with five times its weight of glacial acetic acid saturated with hydrogen bromide, oily products, from which chemically pure compounds could not be isolated, were obtained.

Veratril was formed when attempts were made to nitrate veratroin. Nor was a satisfactory nitration of veratril achieved. Ordinary concentrated nitric acid (sp. gr., 1.42) was without action at 65°; while with fuming acid (sp. gr., 1.50) reaction was vigorous at 35°, with production of intractable gummy masses.

3,4-Dihydroquinazoline was obtained in yields of 70–86% by the catalytic reduction of quinazoline, essentially as described by Marr and Bogert.[1b] It was prepared also from benzoyleneurea, by conversion of the latter into 2,4-dichloroquinazoline and reduction of this dichloro derivative by iodine and red phosphorus, but the process was unsatisfactory because of the very poor yield in the final step. Direct reduction of benzoyleneurea to either the dihydro or tetrahydro quinazoline could not be achieved.

1,2,3,4-Tetrahydroquinazoline.—This has usually been prepared by sodium amalgam (2.5%) reduction of the 3,4-dihydroquinazoline. We have now found that it can be obtained more conveniently from quinazoline itself by reduction with a somewhat stronger amalgam (4%).

To a solution of 3 g. of quinazoline in 150 cc. of water at 30°, there was added, in small pieces, 100 g. of 4% sodium amalgam, and the mixture was shaken for an hour. After the addition of 120 cc. of 33% potassium hydroxide solution, the mixture was extracted thrice with ether, the extracts were dried over sodium sulfate, the hydrochloride of the base was precipitated and crystallized from alcohol. Small white needles resulted; m.p. 191–192° (corr.), in agreement with the literature; yield, 79%.

SUMMARY

1. A number of 6,7-dimethoxyquinazolines have been prepared from veratrole derivatives by standard reactions.

2. The Riedel quinazoline synthesis, from formamide and aldehydes, is not applicable to ketones.

3. Tetrahydroquinazoline is conveniently prepared by direct reduction of quinazoline with a 4 per cent. sodium amalgam.

4. Veratryl chloride does not form a Grignard complex under the conditions employed, nor does 6-nitroveratronitrile react with Grignard compounds.

In the preparation of veratryl chloride from veratrole by the Blanc reaction, the main product is the tetramethoxydihydroanthracene. Veratrole derivatives are apt to be chlorinated by the action of aqueous hydrochloric acid.

5. 4-Aminoveratrole cannot be formylated by any of the usual methods, although its acetyl, oxalyl, and benzoyl derivatives are easily obtained.

6. The sodio derivative of ethyl 6-nitroveratroylacetate does not react with 4-halogen veratroles.

7. Ethyl 6-aminoveratrate is very resistant to formylation. Heating with ethyl formate yields the aminoveratroyl formate; but with ethyl acetate, the product is the acetamidoveratrate.

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

THE CLEAVAGE OF CERTAIN SUBSTITUTED DIBENZOYLMETHANES ON BROMINATION

PAUL D. BARTLETT AND SAUL G. COHEN

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Bromotribenzoylmethane was reported[1] as a substance of melting point 89°, prepared by the action of bromine on tribenzoylmethane in chloroform solution. When a sample of this compound was wanted in this laboratory recently, it was prepared by the procedure of Werner and found to be identical with bromo*di*benzoylmethane. The results of a further study of this cleavage reaction are reported in this paper.

When the reaction was carried out with a double quantity of bromine, dibromodibenzoylmethane was the product. No other solid could be obtained from the mother liquors. The other cleavage product was identified as benzoyl bromide by the conversion of aniline, added to the mother liquor, into benzanilide in poor yield (27%). No reaction occurred between tribenzoylmethane and hydrogen bromide alone in chloroform under these conditions.

The bromination of tribenzoylmethane takes a normal course when a reagent is present to neutralize the hydrogen bromide formed. Thus, bromotribenzoylmethane, m.p. 119°–120°, is produced if acetic acid containing pyridinium acetate is substituted for the chloroform. This shows that both bromine and hydrogen bromide are involved in the cleavage reaction.

$$\underbrace{Br_2 + (C_6H_5CO)_3CH \rightleftharpoons HBr}_{\downarrow} + (C_6H_5CO)_3CBr \qquad (1)$$

$$C_6H_5COBr + (C_6H_5CO)_2CHBr + HBr$$

It does not show whether the reaction is between these two reagents and the tribenzoylmethane, or between bromotribenzoylmethane and hydrogen bromide, since the equilibrium (1) is a very mobile one. Reaction (1) from right to left is faster than the cleavage, for if we treat bromotribenzoylmethane in acetic acid with hydrogen bromide in the presence of cyclohexene, tribenzoylmethane is precipitated.

The group that might be expected to be the most readily cleaved from a dibenzoylmethane is triphenylmethyl. We brominated triphenylmethyl-

[1] WERNER, *Ber.*, **39**, 1289 (1906).

dibenzoylmethane, benzohydryldibenzoylmethane, and benzyl- and phenyldibenzoylmethane in chloroform, with the following results. Phenyl- and benzyldibenzoylmethane were brominated normally under all conditions, and could not be cleaved in a fuming solution of hydrogen bromide in glacial acetic acid. Benzohydryldibenzoylmethane was cleaved in chloroform but not when brominated with pyridinium acetate, behaving like tribenzoylmethane. Triphenylmethyldibenzoylmethane was cleaved under all conditions of bromination that were tried. The structure of triphenylmethyldibenzoylmethane was shown by its cleavage by sodium ethoxide to triphenylmethylacetophenone.

No experiments were devised which would give proof of the mechanism of the brominative cleavage. We present a mechanism here merely to show that the reaction can be formulated as one involving the normal intermediates in ketone bromination, and favored by structural features in a way consistent with modern views of the mechanism of bromination. If we extend to the bromination of the enol form of a dibenzoylmethane the conclusion previously reached in this laboratory in the cases of stilbene[2] and the dimethylmaleate ion,[3] the reversible bromination of the di- or triketone is pictured as occurring in the steps:

(1) $C_6H_5\underset{\underset{O}{\|}}{C}CHR\underset{\underset{O}{\|}}{C}C_6H_5 \rightleftharpoons C_6H_5\underset{\underset{OH}{|}}{C}{=}CR\underset{\underset{O}{\|}}{C}C_6H_5$

(2) $C_6H_5\underset{\underset{OH}{|}}{C}{=}CR\underset{\underset{O}{\|}}{C}C_6H_5 + Br_2 \rightleftharpoons C_6H_5\underset{\underset{OH^+}{\|}}{C}CRBr\underset{\underset{O}{\|}}{C}C_6H_5 + Br^-$

(3) $C_6H_5\underset{\underset{OH^+}{\|}}{C}CRBr\underset{\underset{O}{\|}}{C}C_6H_5 + Br^- \rightleftharpoons C_6H_5\underset{\underset{O}{\|}}{C}CRBr\underset{\underset{O}{\|}}{C}C_6H_5 + HBr$

Since the present reaction is occurring in a non-polar medium, it may well be that steps (2) and (3) should be replaced by the equivalent steps involving atoms instead of charged intermediates. Our only evidence on this point is that the cleavage of tribenzoylmethane proceeds just as well in the presence of tetrabromohydroquinone as in its absence. From this we conclude that the cleavage reaction does not depend for its occurrence upon an atomic chain reaction, since Price[4] has found that tetrabromohydroquinone is an effective inhibitor for the chain bromination of phenanthrene. This does not rule out the incidental existence of such a mechanism, nor does it eliminate atomic intermediates which do not

[2] BARTLETT AND TARBELL, *J. Am. Chem. Soc.*, **58**, 466 (1936).
[3] TARBELL AND BARTLETT, *ibid.*, **59**, 407 (1937).
[4] PRICE, *J. Am. Chem. Soc.*, **58**, 1834 (1936).

propagate a chain. In the proposed cleavage step below, such uncharged intermediates might be substituted for the ions shown without altering the essential nature of the explanations involved.

By a fundamental principle of kinetics the mechanism must be the same whether we start with the ketone and bromine or with the bromoketone and hydrogen bromide. The mechanism shown here differs from that usually cited in that bromine is not represented as being added completely to the double bond of the enol. In view of the established two-step nature of the bromination process in other cases, this completed addition would seem to be an unnecessary step, even though such an addition product has been isolated in the case of dihydroresorcinol.[5]

The brominative cleavage can be represented as an alternative mode of reaction of the left-hand members of equation (3):

$$C_6H_5\underset{\underset{OH^+}{\|}}{C}CRBr\underset{\underset{O}{\|}}{C}C_6H_5 + Br^- \rightleftharpoons C_6H_5\underset{\underset{OH}{|}}{C}{=}CBr\underset{\underset{O}{\|}}{C}C_6H_5 + RBr$$

This reaction can occur whenever the group R is capable of being transferred to combination with the bromide ion in competition with the hydrogen and bromine which are transferred in equation (3) and in the reverse of equation (2), respectively. Although the hydrogen alone is represented as carrying a positive charge, the transfer of R or Br from the molecule to the bromide ion depends upon the ability of these parts of the molecule to develop "electrophilic" centers at the moment of reaction, and thus to be transferred with a positive charge (sextet of valence electrons). The carbonyl group readily develops such an electrophilic center at its carbon atom. Indeed this center is the seat of the reactivity of the carbonyl group toward most reagents, the cyanide ion representing a particularly clear case.[6] It is not clear why a bromine atom and three benzoyl groups must be present on the central carbon atom in order for one of the latter to be split off, unless the full amount of stabilization of the double bond in the resulting enol,

$$C_6H_5\underset{\underset{OH}{|}}{C}{=}CBrCOC_6H_5,$$

by resonance involving the phenyl and benzoyl groups and the unshared electrons of the bromine, is necessary to lower the activation energy of the cleavage to correspond to an observable reaction. The development of an electrophilic center on the benzohydryl and triphenylmethyl groups is to be correlated with the ease with which these groups, the latter much more

[5] MERLING, *ibid.*, **278**, 42, (1894).

[6] LAPWORTH, *J. Chem. Soc.*, **83**, 995 (1903).

than the former, appear as cations when their halides are dissolved in special solvents. In contrast to the benzoyl group, these radicals can tolerate either a positive or a negative charge through the stabilization of the ion, and transition states containing it, by relatively large resonance energies. Whether these groups separate as free ions, or are transferred continuously from one combination to another, is a problem related to that of the mechanism of alcoholysis of the related secondary and tertiary chlorides, in which at present no generally satisfactory conclusions have been reached.

Since the observations of Meisenheimer[7] and of Goldschmidt[8] indicate ketonic and enolic modifications of phenyldibenzoylmethane, but do not show the position of the equilibrium between them in solution, we have applied the usual tests for enolic structure to the two isomers and have determined the enol content of a solution in ethyl alcohol as about 8 per cent., both after two and after four days' refluxing. The yellow enolic isomer is prepared by acidification of the sodium derivative of the white ketonic form suspended in ether. The yellow form is converted at 133°, with sintering, into the white form, which melts at 146°. A mixture of the two isomers sinters at 126°.

Solutions of bromine in chloroform and of permanganate in acetone reacted instantly with the yellow form, much more slowly with the white. The yellow form gave a purplish-black coloration with ferric chloride in acetone, while the white form began to develop a slight color only after several hours. A solution of the white isomer in ethyl alcohol reacted positively to the enol tests and showed a yellow color after being refluxed for 1.5 hours.

EXPERIMENTAL

Bromotribenzoylmethane.—Four and one-tenth grams of tribenzoylmethane was suspended in 60 cc. of hot glacial acetic acid containing 5 cc. of pyridine, and 2 g. of bromine in acetic acid was gradually added. It was rapidly decolorized, and the suspended material went into solution. The product was isolated as a white solid by pouring the reaction product into ice-water, and was recrystallized from acetic acid and from methyl alcohol. The product amounted to 3.7 g. (73%) of material melting at 119–120°.

Anal. Calc'd for $C_{22}H_{15}BrO_3$: C, 64.86; H, 3.72.
Found: C, 64.95; H, 3.95.

This analysis was performed by Mrs. G. M. Wellwood.

The cleavage of tribenzoylmethane.—Tribenzoylmethane (2.95 g.) was suspended in 18 cc. of warm chloroform, and 2.9 g. of bromine in chloroform was added. The suspended material went into solution. The solution was refluxed 1.5 hours, and then dry air was sent through it for several hours. When much of the chloroform was replaced by ligroïn, 2.5 g. of a solid, melting at 70°–90° was obtained, and from

[7] MEISENHEIMER, *Ber.*, **54**, 3195 (1921).
[8] GOLDSCHMIDT, *ibid.*, **63B**, 1212 (1930).

this 1.8 g. of pure dibromodibenzoylmethane was obtained (53% yield). On addition of 1.9 cc. of aniline to the mother liquor, benzanilide was obtained, with a 27% yield of purified product.

The cleavage of tribenzoylmethane in the presence of tetrabromohydroquinone.—Tetrabromohydroquinone (0.25 g.) was dissolved in 50 cc. of chloroform and the solution was boiled fifteen minutes. Tribenzoylmethane (0.5 g.) was dissolved in this and the solution was boiled twenty minutes. Then 0.1 cc. of bromine, dissolved in chloroform, was added, and the solution was boiled. Within one and one-half hours the color of bromine was nearly discharged. Bromodibenzoylmethane was obtained in 61% yield.

Tetrabromohydroquinone.—Bromine (30 g.) was added to a solution of 5 g. of hydroquinone in 50 cc. of glacial acetic acid. This was allowed to stand sixteen hours at 30°, and then 6.35 g. of tetrabromohydroquinone was filtered off. The filtrate was warmed on the steam bath for forty-five minutes and 5.25 g. more of tetrabromohydroquinone was obtained. This compound was previously obtained by the reduction of bromanil.

Triphenylmethyldibenzoylmethane.—This was made in 35% yield by warming equivalent quantities of triphenylmethyl chloride and the sodium derivative of dibenzoylmethane in dry benzene for one hour. The mixture was washed with water and dried with sodium sulfate. The solvent was removed *in vacuo*, and the residue was crystallized from alcohol. After several crystallizations various samples were obtained melting between 148.5°–153° with decomposition, the purest melting sharply at the latter temperature.

Anal. Calc'd for $C_{34}H_{26}O_2$: C, 87.52; H, 5.62.
Found: C, 87.50, 87.10; H, 5.74, 5.69.

Triphenylmethylacetophenone.—One gram of triphenylmethyldibenzoylmethane was refluxed for 12 hours with sodium ethoxide (0.5 g. of sodium dissolved in 75 cc. of alcohol). Hydrogen chloride was passed into the solution, and the residue on evaporation was suspended in ether, washed with water, and crystallized from alcohol. White crystals were obtained; m.p. 164–165°.

Anal. Calc'd for $C_{27}H_{22}O_2$: C, 89.46; H, 6.12.
Found: C, 89.90, 89.28; H, 6.12, 6.16.

The reaction of 0.005 mole of triphenylmethyldibenzoylmethane and bromine in 15 cc. of chloroform resulted in the recovery of bromodibenzoylmethane, after recrystallizations, in 59% yield and, on hydrolysis, triphenylcarbinol in 17% yield of purified product. Similar results were obtained when the same quantity of ketone was brominated in glacial acetic acid in the presence of 0.83 cc. of pyridine. The reaction mixture was warmed on the steam bath for 1.5 hours.

In carrying out this bromination in carbon tetrachloride with two equivalents of bromine, similar cleavage results were obtained, but, in this case, dibromodibenzoylmethane was one of the products.

Triphenylmethyldibenzoylmethane was warmed for two days in dry ether with sodium wire. To the yellow sodium compound thus formed, suspended in chloroform, an equivalent quantity of bromine was added, with rapid decolorization; however, no crystalline product could be obtained.

Benzohydryldibenzoylmethane.—From the reaction of 0.0067 mole of benzohydryldibenzoylmethane and 0.015 mole of bromine in 35 cc. of chloroform there were recovered 4% of starting material, 48% of the theoretical quantity of dibromodibenzoylmethane, and about 42% of mixed mono- and dibromodibenzoylmethane totaling about 90% recovery of the one cleavage product. Since the residual oil,

benzohydryl bromide, could not be crystallized, it was converted into benzhydrol, in 41.5% yield, by refluxing for several hours in acetone in the presence of a few cubic centimeters of water and a small quantity of pyridine.

Bromobenzohydryldibenzoylmethane was prepared by the reaction of 0.5 g. of benzohydryldibenzoylmethane, and 0.29 g. of bromine, (1.33 equivalents) in 10 cc. of glacial acetic acid, in the presence of 1 cc. of pyridine. There were recovered 0.25 g. of starting material, and then the desired bromination product; m.p. 114.5–115.5° after crystallization from methyl alcohol.

Anal. Calc'd for $C_{28}H_{21}BrO_2$: C, 71.60; H, 4.51.
Found: C, 72.02; H, 4.60.

This analysis was performed by Mrs. G. M. Wellwood.

Benzyldibenzoylmethane was made by the method of Abell.[9]

A solution of 0.255 cc. of bromine and 1.57 g. of benzyldibenzoylmethane in chloroform was refluxed until the color of bromine was discharged. The solvent was removed in a stream of air and the residue was crystallized from ligroïn, giving slightly colored crystals, m.p. 103.5–104°.

In another bromination, using only 85% of the theoretical quantity of bromine, a 62% yield of bromination product was obtained, and a 25% yield of product mixed with starting material. No evidence of cleavage was found.

A bromination was carried out in a solution of hydrogen bromide in glacial acetic acid, again with no evidence of cleavage. One gram of benzyldibenzoylmethane and 0.16 cc. of bromine were warmed for five hours in a solution of hydrogen bromide in glacial acetic acid; the solution was poured into water and the solid thus precipitated was crystallized from ligroïn. There were recovered 25% of the starting material, and a mixture of starting material and bromination product accounting for another 50% of the starting material. No evidence of any cleavage products was found.

Anal. Calc'd for $C_{22}H_{17}BrO_2$: C, 67.17; H, 4.36.
Found: C, 67.13, 66.85; H, 4.54, 4.42.

Phenyldibenzoylmethane was made[10] by the action of benzylmagnesium bromide and two equivalents of benzaldehyde. After several crystallizations from alcohol and ether-petroleum ether, a 20% yield of product melting 144.5–145.6° was obtained. The melting point of Marshall's product was 149°.

Bromophenyldibenzoylmethane was made by the treatment of phenyldibenzoylmethane with an equivalent quantity of bromine in boiling chloroform. After the solvent was removed in a stream of air, the residue was crystallized from absolute alcohol. In another experiment the chloroform solution was concentrated, and ligroïn was added, and the product was seeded out. In one experiment a 63% yield of bromination product, melting 86–87°, was obtained, together with 21% of less pure product, which melting point determinations showed to be contaminated with starting material. No evidence of cleavage was found.

Anal. Calc'd for $C_{21}H_{15}BrO_2$: C, 66.50; H, 3.98.
Found: C, 66.73, 66.77, 66.94; H, 4.04, 4.31, 4.03.

Goldschmidt[11] reported this bromodiketone, melting at 80° and likewise made by refluxing with bromine in chloroform. Marshall[10] reported bromophenyldibenzoylmethane, m.p. 147°, produced by mixing equivalent amounts of ketone and bromine in carbon tetrachloride, but gave no analyses.

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[9] Abell, *J. Chem. Soc.*, **101**, 997 (1912).
[10] Marshall, *ibid.*, **107**, 520 (1912).
[11] Goldschmidt, *Ber.*, **63B**, 1212 (1930).

The position of the ketone-enol equilibrium of phenyldibenzoylmethane in alcohol was determined as follows:

Phenyldibenzoylmethane (0.2701 g.) was refluxed for 2 days in 35 cc. of absolute alcohol. The solution was then cooled for 3 minutes in a freezing mixture, 0.06 cc. of bromine in 5 cc. of alcohol was added, followed in 15 seconds by 0.2 g. of β-naphthol in 5 cc. of alcohol. Then 0.6 g. of potassium iodide in 5 cc. of water was added, and the solution was warmed and shaken four minutes. The iodine color was discharged by 6.68 cc. of 0.0219 *N* thiosulfate; % enol: 8.1.

Phenyldibenzoylmethane (0.2807 g.), refluxed for 4 days in 35 cc. of absolute alcohol, consumed 6.80 cc. of 0.0219 *N* thiosulfate; % enol: 7.9.

Attempts to benzoylate the enolic form in benzene solution in the presence of pyridine resulted in ketonization, and the recovery of the original white ketonic modification.

SUMMARY

The bromination of tribenzoylmethane in hot chloroform solution results in cleavage to benzoyl bromide and bromodibenzoylmethane. The latter has apparently been mistaken for bromotribenzoylmethane in the past. Tribenzoylmethane can be brominated normally in acetic acid containing pyridinium acetate. The cleavage requires both bromine and hydrogen bromide.

The bromination of phenyl- and benzyldibenzoylmethane takes a normal course. Benzohydryldibenzoylmethane is cleaved to benzohydryl bromide and bromodibenzoylmethane when brominated in hot chloroform solution, but yields benzohydrylbromodibenzoylmethane when brominated in the presence of pyridinium acetate in acetic acid. Triphenylmethyldibenzoylmethane is cleaved to triphenylmethyl bromide and bromodibenzoylmethane in both media, and has not been brominated normally. A mechanism for the cleavage is discussed but not proved.

An alcoholic solution of phenyldibenzoylmethane at the boiling point contains at equilibrium 8 per cent. of the enolic form.

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

CIS-β-(*p*-BROMOBENZOYL)-α-METHYLACRYLIC ACID AND ITS ESTERS

ROBERT E. LUTZ, DANIEL T. MERRITT, JR.,* AND MONROE COUPER

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Cis- and *trans*-β-(*p*-bromobenzoyl)-β-methylacrylic acids,† $BrC_6H_4COC(CH_3) = CHCOOH$, and their esters, have been investigated in some detail.[1] Of the two possible stereoisomeric α-methyl acids, $BrC_6H_4COCH = C(CH_3)COOH$, only the *trans* form has previously been prepared; it was made from mesaconyl chloride by the Friedel-Crafts reaction on bromobenzene, the reaction stopping at this stage in contrast with the analogous reaction on benzene which goes further to give the expected unsaturated 1,4-diketone. The Friedel-Crafts reaction between citraconic anhydride and bromobenzene gave largely the *cis* β-methyl derivative and only a small amount of α-methyl acid which, however, proved to be the *trans* compound, stereochemical inversion having occurred.

In continuation of investigations on unsaturated 1,4-ketonic acid systems and on the ring-chain tautomerism involved,[1] it seemed worthwhile to prepare and study the hitherto unknown *cis* α-methyl acid, II. The synthesis, which is being reported at this time, was accomplished in a simple way through rearrangement of the *trans* acid, I, by exposure in a suitable solvent to the action of sunlight. The various intertransformations of the *cis* and *trans* acids and the methyl esters are summarized in the accompanying diagram (1).

Reduction of the new *cis* acid gives β-bromobenzoyl-α-methylpropionic acid, V, which has already been made by a similar reduction of the *trans* acid, I. The position of the methyl group, previously established by hydrolysis of the *trans* acid to *p*-bromoacetophenone,[1] has been confirmed by synthesis of this acid from methylacetoacetic ester, VII, through the monoethyl ester of mesaconic acid, VIII, followed by a Friedel-Crafts reaction on the acid chloride, IX, and hydrolysis of the resulting *trans* ethyl ester, X, as outlined in diagram (2).

* The larger part of the work described in this paper was presented by the second author in a thesis for the M.A. degree (1936).

† These acids have previously been called the β-bromobenzoylcrotonic acids.

[1] (*a*) LUTZ AND TAYLOR, *J. Am. Chem. Soc.*, **55**, 1168 (1933); (*b*) LUTZ AND WINNE, *ibid.*, **56**, 445 (1934); (*c*) LUTZ, *ibid.*, **56**, 1378 (1934).

The *cis* α-methyl acid undergoes rearrangement to the more stable *trans* isomer when exposed to the action of sunlight in a chloroform solution with iodine as catalyst or through contact with alcoholic alkali, conditions under which the *cis* β-methyl acid is stable. It dissolves readily without sig-

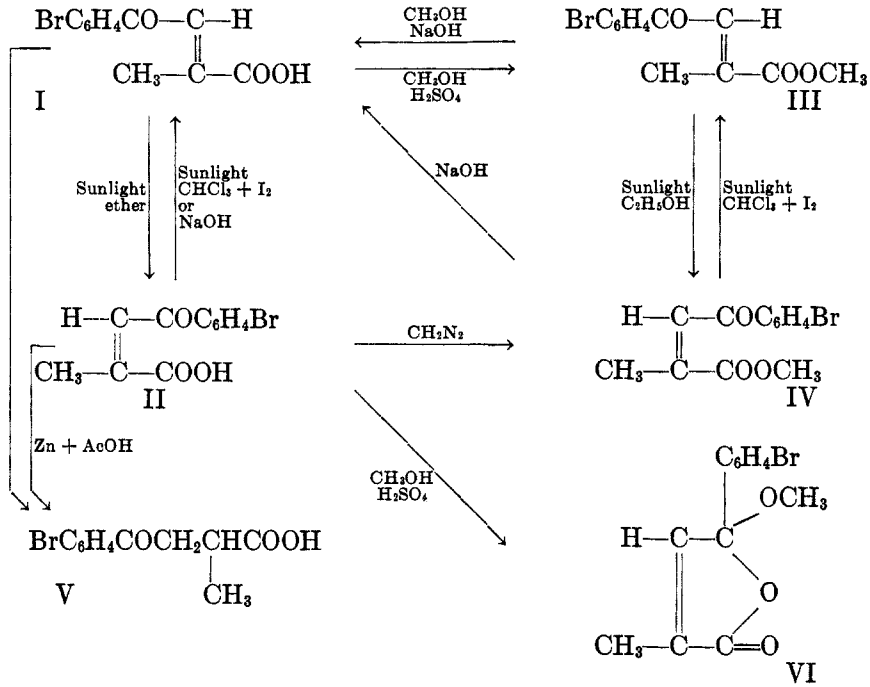


Diagram (1)

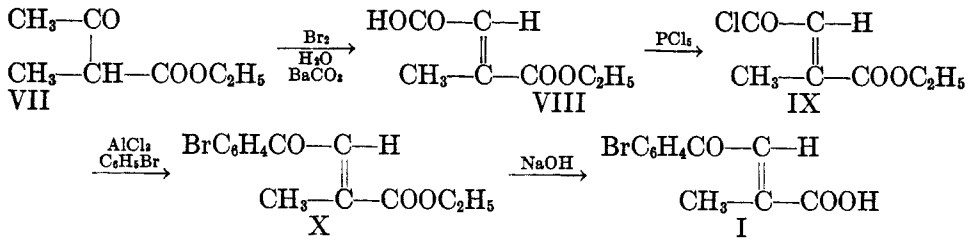


Diagram (2)

nificant lag in sodium bicarbonate solution in contrast with the *cis* β-methyl acid which dissolves slowly.

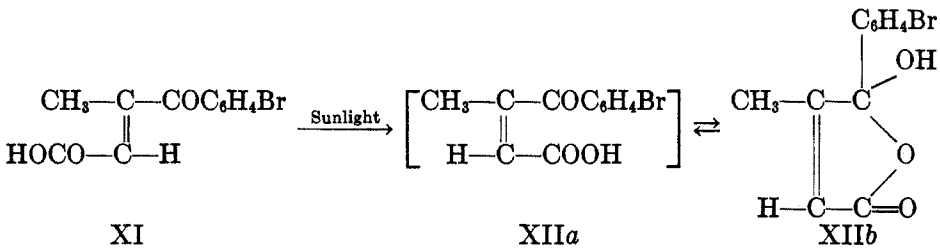
The open-chain *cis* ester, IV, was prepared in the customary way by the action of diazomethane on the *cis* acid, and also by the action of sunlight on a solution of the *trans* ester III. It undergoes inversion to the *trans*

ester when exposed to sunlight in chloroform solution with iodine as catalyst. Hydrolysis by means of alcoholic alkali usually gives the *trans* acid exclusively, although in one isolated experiment hydrolysis was accomplished without stereochemical inversion.

The isomeric cyclic ester, VI, is obtained by esterification of the *cis* acid by Fischer's method. The cyclic structure is shown by the refractive index which differs from that of the open-chain ester in the expected degree and direction,[2] and by the fact that, unlike the open-chain ester, this isomer is not rearranged to the *trans* ester by the action of sunlight on a chloroform-iodine solution. Hydrolysis under alkaline conditions gives the *trans* acid.

It is evident from the various reactions cited above, that the *cis* configuration is inherently less stable in the α- than in the β-methyl series. This point is best illustrated by the relative stabilities of the sodium salts of the acids in alkaline solution where presumably only the open-chain structures are involved.

The *cis* β-methyl acid, XII, as already pointed out,[1b] probably exists chiefly or exclusively in the cyclic lactonol form, XII*b*, since it dissolves slowly in sodium bicarbonate solution in contrast with the *trans* acid, XI, which dissolves rapidly.



XI XII*a* XII*b*

Pertinent to this is the fact that the *cis* acid is not rearranged into the *trans* isomer by the action of sunlight on a chloroform-iodine solution in contrast with the rapid inversion of the open-chain *cis* ester under these conditions (and also the ready inversions in the reverse direction from *trans* to *cis* by the action of sunlight alone). The unique stability of the *cis* β-methyl acid toward stereochemical inversion might conceivably be accounted for if this acid were assumed to exist exclusively in the lactonol form, XII*b*; however, this explanation is questionable since the more acidic open-chain form must be present in equilibrium in solution as shown by methylation with diazomethane to the open-chain ester.

In this connection, we have made ultraviolet absorption measurements

[2] *Cf.* AUWERS AND HEINZE, *Ber.*, **52**, 584 (1919); MEERWEIN, *J. prakt. Chem.*, **116**, 253 (1927).

on the *cis* β-methyl acid, XII, and on its open-chain and cyclic methyl esters and have observed a definite absorption band for the open-chain ester at about 2550–2700 Å, but no marked absorption in this region for the cyclic ester or for the free acid. A more careful investigation with better equipment is needed before these results can be regarded as conclusive. Nevertheless, there appears to be little doubt from these results that the *cis* acid is structurally like the cyclic ester and unlike the open-chain ester and that it exists chiefly in the cyclic form, XII*b*.

EXPERIMENTAL

The problem of preparation of the *cis* β-bromobenzoyl-α-methylacrylic acid (II) became one of getting the *trans* acid (I) consistently in good yield. The *trans* acid is formed in small amounts in the Friedel-Crafts reaction on citraconic anhydride and it is separated with difficulty from the major product, *cis* β-bromobenzoyl-β-methylacrylic acid (II). This separation was facilitated by taking advantage of the slow rate of solution of the latter in aqueous sodium carbonate solution. If the mixture of solids is extracted by digesting with successive portions of sodium carbonate solution and filtered, the *trans* acid (I) together with some *cis* acid (XII) is leached out, leaving nearly pure *cis* β-bromobenzoyl-β-methylacrylic acid as the residue. This source of the *trans* α-methyl acid is inadequate, of course, as a means of preparation of large quantities.

The best yields of the *trans* acid were obtained in the Friedel-Crafts reaction on mesaconyl chloride, but we have been unable to find conditions which would give consistently the favorable yields obtained in several individual experiments, such as that reported previously.[1a] A great variety of conditions, using mesaconyl chloride, carbon disulfide, and bromobenzene, with varying amounts of aluminum chloride, time of heating, temperature, and order of adding reagents, gave yields varying from 19–25%, although in two instances (not duplicable) the yields reached 50%. When nitrobenzene was used as the solvent, the mixture being allowed to stand for five to seven days at room temperature, consistent yields of 40% were obtained. While these yields have been bettered and do not represent the maximum, this method seems the best so far worked out since it gives the most consistent results. Under these conditions standing for a still longer time gave poorer yields and a product of poorer quality.

In a typical experiment a mixture of 25 g. of mesaconyl chloride, 75 g. of bromobenzene, 70 g. of anhydrous aluminum chloride, and 100 cc. of nitrobenzene was allowed to stand for one week at room temperature, and was then decomposed in ice and hydrochloric acid, the nitrobenzene solution then being washed with water. The product was isolated either by steam distillation and extraction of the residue with ether, or by diluting the nitrobenzene solution with benzene, cooling and allowing the mixture to stand, the *trans* acid (I) crystallizing slowly. The yield was 40%.

The *methyl ester* (*III*) was prepared by refluxing a solution of 20 g. of the acid and 20 cc. of concd. sulfuric acid in 200 cc. of methanol for one hour. On diluting with a little water, 20 g. of nearly pure methyl ester separated.

Cis-*β-bromobenzoyl-α-methylacrylic acid* (*II*).—One gram of the *trans* acid (I) in 40 cc. of ether was exposed to direct sunlight for twelve hours. The ether was partly evaporated, benzene was added, and the rest of the ether was boiled off. The colorless *cis* acid then separated and was recrystallized from benzene; m.p. 97°; yield 0.8 g.

Anal. Calc'd for $C_{11}H_9BrO_3$: C, 49.1; H, 3.4.
Found: C, 49.5; H, 4.0.

When ethanol was used in the above experiment no inversion took place.

Reduction of a sample of the *cis* acid (II) with zinc and concentrated acetic acid, in the usual way, gave β-bromobenzoyl-α-methyl propionic acid (V), which was identified by mixture melting point with a sample prepared by the similar reduction of the *trans* acid (I).

Isomerization back to the *trans* acid (I) was effected by exposing a solution of the *cis* acid in chloroform solution containing iodine to the action of sunlight for twelve hours. A sample of 0.5 g. of the *cis* acid was converted quantitatively into the *trans* isomer upon standing overnight in dilute ethanol containing 0.01 g. of sodium hydroxide.

The synthesis of the trans *acid (I). Mesaconyl-α-ethyl acid ester (VIII)*, prepared according to the method of Anschütz[3] from methyl acetoacetic ester (VII), was converted into the acid chloride (IX) by means of phosphorus pentachloride. Without removing the phosphorus oxychloride, the acid chloride was treated with carbon disulfide, bromobenzene, and aluminum chloride, and the reaction mixture was decomposed in ice and acid. The oily ester which was produced (X) was hydrolyzed with dilute alcohol and sodium hydroxide, and a good yield of the *trans* acid (I) was isolated and identified.

Cis-*β-bromobenzoyl-α-methylacrylic methyl ester (IV)* was obtained as an oil by exposure of one gram of the *trans* ester (III) in alcohol solution to direct sunlight for ten hours. This oil was hydrolyzed with 0.15 g. of sodium hydroxide in 70 cc. of 40% ethanol (the mixture being allowed to stand overnight). The mixture was diluted with water, extracted with ether, and acidified, and the *cis* acid was extracted with ether, 0.7 g. of nearly pure material being obtained on evaporation of the solvent.

Several other attempts to hydrolyze the ester (III), using alcohol, water, and sodium hydroxide, gave only *trans*-β-bromobenzoyl-α-methylacrylic acid (I). We did not, however, make an exhaustive study to determine the necessary conditions for effecting hydrolysis without inversion of the configuration.

Esterification of the *cis* acid with diazomethane in ether solution took place rapidly with the evolution of nitrogen. The ester was obtained as an oil, and again attempts to induce it to crystallize failed. It was converted back to the *trans* ester by exposing it to sunlight in chloroform solution containing iodine. It distilled at 146° under 2 mm. pressure, but at higher pressures or under prolonged heating it was partly rearranged into the *trans* ester. To minimize this inversion during distillation a sample was evaporated in the high-vacuum oven at 85–90° and collected dropwise on a cold finger condenser, the refractive index being followed on the consecutive drops. The first few drops showed a slightly low index of refraction, and the bulk of the material showed a practically constant value of n_D^{25} 1.5763 to 1.5765 and a dispersion of $(n_F - n_C)$ 0.0237.

Anal. Calc'd for $C_{12}H_{11}BrO_3$: C, 50.9; H, 3.9; Br, 28.2.
Found: C, 50.8; H, 3.7; Br, 28.0.

4-Bromophenyl-4-methoxy-2-methylcrotolactone (the cyclic methyl ester of *cis* β-bromobenzoyl-α-methylacrylic acid) (VI) was prepared by refluxing a solution of 10 g. of the *cis* acid (II) and 10 cc. of concentrated sulfuric acid in 100 cc. of methanol for half an hour, and diluting with water. The product was an oil boiling at 162° at 2 mm. pressure. It did not crystallize. It contained a small amount of the *trans*

[3] ANSCHÜTZ, *Ann.*, **353**, 149 (1907).

ester, formed undoubtedly through rearrangement by the acid catalyst used in the esterification, even when the amount of acid and time of heating were minimized.

In a typical experiment a solution of 2 g. of *cis* acid and 1 cc. of concentrated sulfuric acid in 20 cc. of methanol was refluxed for 30 minutes, cooled, diluted with water, and made slightly alkaline. The oily ester was extracted with ether, and distilled dropwise in the vacuum oven onto a cold finger condenser, the refractive index becoming quickly constant on successive drops at n_D^{25} 1.5675; dispersion (n_F-n_C) 0.0202. Even this product, however, contained traces of the *trans* ester and could not be regarded as really pure in spite of the constant refractive index.

Anal. Calc'd for $C_{12}H_{11}BrO_3$: C, 50.9; H, 3.9; Br, 28.2.
Found: C, 51.0; H, 3.9; Br, 28.0.

The cyclic ester was slowly hydrolyzed by dilute alcohol and sodium hydroxide, and gave the *trans* acid (I) in good yield. Exposure to sunlight in chloroform containing iodine was without effect.

Preliminary experiments show that it is not as easily reduced as the analogous cyclic ester of β-bromobenzoyl-β-methylacrylic acid.

β-(p-Bromobenzoyl)-α-methylpropionic methyl ester, $BrC_6H_4COCH_2CH(CH_3)COOCH_3$.—A sample of the acid (V) was treated with an ether solution of an excess of diazomethane, reaction taking place immediately. After standing, the solution was shaken, first with 10% hydrochloric acid, then with 10% sodium hydroxide, and finally with water. From the ether solution the oily ester was obtained. It could not be induced to crystallize. Distillation dropwise onto a cold finger condenser or ordinary distillation under 2 mm. pressure gave a colorless oil boiling at 147–148° of n_D^{25} 1.5460 and dispersion (n_F-n_C) 0.0312.

Anal. Calc'd for $C_{12}H_{13}BrO_3$: C, 50.5; H, 4.6.
Found: C, 50.6; H, 4.7.

Hydrolysis was easily accomplished by refluxing for one minute a solution of the ester in dilute methanol containing an excess of sodium hydroxide, the corresponding acid (V) being produced in good yield.

Inversion of trans-*β-(p-bromobenzoyl)-β-methylacrylic acid*‡ was brought about by exposure of its solution in methanol for 4 hours to the direct action of sunlight. The *cis* acid was isolated by concentration of the solution to the point of crystallization and identified by mixture melting point.

Cis-*β-(p-bromobenzoyl)-β-methylacrylic acid*‡ was recovered unchanged when subjected to the action of sunlight for 6 hours in chloroform solution containing enough iodine to maintain a definite iodine coloration throughout the experiment.

Cis-*β-(p-bromobenzoyl)-β-methylacrylic methyl ester* was prepared in nearly quantitative yield by the action of an excess of diazomethane in ether solution on the *cis* acid; this product was identical with a sample prepared by the silver salt method.[15b]

SUMMARY

The preparation of *cis*-β-bromobenzoyl-α-methylacrylic acid and its open-chain and cyclic methyl esters is reported. Inversions to and from the *trans* isomers are described.

The difference in properties of the α- and β-methyl types and the greater stability of the *cis* configuration in the β-methyl series, are considered.

Evidence is presented indicating that the β-methyl acid has the lactonol structure.

‡ These two experiments were carried out by Mr. F. B. Hill, Jr.

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

N-MENTHYL-SUBSTITUTED AMIDES

ALLAN R. DAY AND CHARLES F. KELLY

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Menthylurea has been shown to exert a marked narcotic action when injected intraperitoneally into white rats.[1] It acted rapidly and left no apparent after effects. Its rapid absorption action was somewhat unexpected since it is practically insoluble in water. The rather interesting physiological properties of menthylurea made it desirable to prepare and study other *N*-menthyl-substituted amides.

Read and Storey[2] prepared a series of *N*-menthyl-substituted amides for the purpose of correlating physical properties and structure in their series of papers "Researches in the Menthone Series." Physiological studies were not made.

The present series of amides consists of amides of monobasic acids. Structural variations were introduced by using normal and iso fatty acids, bromosubstituted acids, and aromatic acids. One additional compound (menthylidenehydantoin) was prepared. While it is not a simple substituted amide, the menthyl ring system is directly attached to one of the nitrogen atoms and in that sense is related to the other compounds prepared.

Seven of these compounds have been tested through the courtesy of the Merck Therapeutic Institute. Comparisons between the narcotic and toxic doses indicated that none of the compounds appear promising. The hydantoin has not yet been tested, but it appears that the mere attachment of the menthyl group to amide nitrogen is not sufficient in itself to enhance narcotic action.

EXPERIMENTAL

Preparation of the N-*menthyl-substituted amides.*—They were prepared by warming equivalent quantities of the free base and acyl chloride in dry benzene until no more hydrogen chloride was evolved. The benzene solution was washed with dilute sodium hydroxide solution, dilute hydrochloric acid, and finally with water. After drying over anhydrous sodium sulfate, the substituted amides were obtained by slow evaporation of the benzene solution. Compounds 1, 2, 3, 4, 6, 7, 9, 11, 12, 14, 15, and 16 were purified by recrystallization from aqueous alcohol. Compounds 8, 10 and 13 were recrystallized from ethylene glycol containing a little alcohol. The yields were good in all cases (80–90%) based on the menthylamine actually used. All of the compounds were obtained as colorless prisms or needles.

[1] BATEMAN AND DAY, *J. Am. Chem. Soc.*, **57**, 2496, 1935.

[2] READ AND STOREY, *J. Chem. Soc.*, **1930**, 2761.

Reduction of N-*menthyl*-p-*nitrobenzamide.*—Two grams of the nitro compound was dissolved in ethyl alcohol, and 4 cc. of concentrated hydrochloric acid was added. Three grams of iron powder was added in small portions with stirring, and the mixture was maintained at 15–20°. More hydrochloric acid was added as needed until a total of 10 cc. was used. When the solution became pale yellow, it was filtered, and the precipitate was extracted with hot alcohol. The amino compound was obtained from the alcohol extract by careful dilution with water.

Preparation of 5-(2-isopropyl-5-menthylpentamethylene)hydantoin.—This derivative was prepared by the method of Bucherer.[3] One-tenth of a mole of *l*-menthone, 0.13

TABLE

N-MENTHYL SUBSTITUTED DERIVATIVES

DERIVATIVE	M.P., °C. (CORR.)	α^{25} IN 95% ALCOHOL	NITROGEN	
			Calc'd	Found
1. *N*-Menthylacetamide*	145°	−83.6	7.09	6.98
2. *N*-Menthylbromoacetamide*	106.5°	−57.2	5.07	5.09
3. *N*-Menthylpropionamide*	87.5°	−68.9	6.62	6.52
4. *N*-Menthyl-α-bromopropionamide	138.5°	−45.0	4.82	4.74
5. *N*-Menthyl-β-bromopropionamide	86°	−47.1	4.82	4.75
6. *N*-Menthyl-*n*-butyramide*	79°	−69.3	6.21	6.05
7. *N*-Menthylisobutyramide*	130.6°	−66.7	6.21	6.17
8. *N*-Menthyl-α-bromo-*n*-butyramide	150°	−52.9	4.60	4.41
9. *N*-Menthyl-α-bromoisobutyramide	94.5°	−49.9	4.60	4.45
10. *N*-Menthyl isovaleramide*	96°	−62.9	5.85	5.71
11. *N*-Menthyl-α-bromo-*n*-valeramide	166°	−47.3	4.40	4.55
12. *N*-Menthyl-α-bromoisovaleramide	184–184.5°	−41.03	4.40	4.38
13. *N*-Menthylphenylacetamide*	106°	−62.4	5.12	5.03
14. *N*-Menthyl-*p*-nitrobenzamide	172.5–173°	−67.5	4.60	4.40
15. *N*-Menthyl-*p*-aminobenzamide	190.5–191°	−81.6	5.10	4.97
16. 5-(α-Isopropyl-5-methylpentamethylene)hydantoin	223–5°	0.0	12.48	12.40

* Previously prepared by Read and Storey.

mole of potassium cyanide, and 0.3 mole of ammonium carbonate in 50 per cent. alcohol solution were heated at 60° for 6–8 hours. The crude derivative was removed by filtration, washed thoroughly with water and recrystallized from alcohol. The resulting compound was optically inactive, racemization apparently having occurred during the reaction.

SUMMARY

1. Fifteen *N*-menthyl-substituted amides have been prepared, eight of which represent new compounds.

2. Seven of these compounds have been tested for narcotic action but appeared to be of little value as hypnotics.

3. 5-(2-Isopropyl-5-methylpentamethylene)hydantoin was prepared by the Bucherer method from laevo menthone.

[3] BUCHERER, *J. prakt. Chem.*, [2], **140**, 291 (1934).

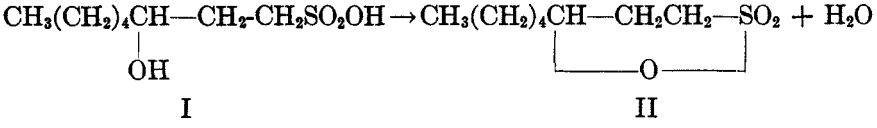
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

SYNTHESIS OF POTASSIUM AND SODIUM 3-HYDROXY-1-OCTANESULFONATE

R. L. SHRINER, H. A. RENDLEMAN, AND ARTHUR BERGER

Received December 7, 1938

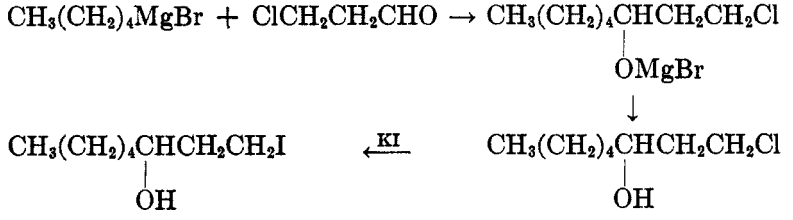
Although the lactones of many *gamma*-hydroxy carboxylic acids are well known, the analogous sultones derived from hydroxy sulfonic acids have been reported in only a few cases.[1] No purely aliphatic sultone has been synthesized, but Baldeschwieler and Cassar[2] isolated a crystalline compound from the residues obtained in the treatment of petroleum fractions with sulfuric acid. Its analyses and properties indicated that it was the octane sultone (II).



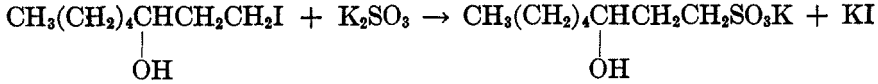
I II

The purpose of the present work was to synthesize the 3-hydroxy-1-octanesulfonic acid (I) from which the sultone (II) is derived.

The sodium and potassium salts of this acid were obtained by treating β-chloropropionaldehyde with *n*-amylmagnesium bromide. Hydrolysis of the addition product yielded 1-chloro-3-octanol.



The halogen in the chloroalcohol was not sufficiently reactive to combine with the alkali sulfites, hence it was converted to the iodide and the 1-iodo-3-octanol treated with potassium and sodium sulfites.



[1] SCHULTZ, *Ber.*, **20**, 3158 (1887); ERDMANN, *Ann.*, **247**, 306 (1888); LIST AND STEIN, *Ber.*, **31**, 1648 (1898); MARCHWALD AND FAHNE, *ibid.*, **31**, 1854 (1898); SHEARING AND SMILES, *J. Chem. Soc.*, **1937**, 1348.

[2] BALDESCHWIELER AND CASSAR, *J. Am. Chem. Soc.*, **51**, 2969 (1929).

Both the sodium and potassium salts of 3-hydroxy-1-octanesulfonic acid were isolated, and there compositions were checked by analysis.

The following methods of converting the alkali hydroxy sulfonates to the free acid and then to the sultone all proved unsuccessful:

(1) passage of dry hydrogen chloride into the alkali hydroxy sulfonates in absolute ethyl, isopropyl, and butyl alcohols;

(2) refluxing with 50 per cent sulfuric acid for forty-eight hours;

(3) treatment of the potassium salt with chloroplatinic acid, which gave a precipitate of potassium chloroplatinate. Evaporation of the filtrate yielded the hydroxy sulfonic acid in an impure state. This acid could not be dehydrated by heating in a vacuum or distillation with toluene. Attempts to prepare the acid through the calcium or barium salts were also unsuccessful.

EXPERIMENTAL

β-Chloropropionaldehyde.[3]—Dry hydrogen chloride was passed into 100 g. of acrolein cooled to −10° until approximately the theoretical gain in weight was obtained. It was distilled as quickly as possible under reduced pressure in a nitrogen atmosphere and used immediately in the next reaction. A 65% yield of the product was obtained as a colorless liquid which distilled at 40–44° under 19 mm. pressure.

1-Chloro-3-octanol.—To a well-stirred solution of an excess of *n*-amylmagnesium bromide there was slowly added 105 g. of β-chloropropionaldehyde. The Grignard mixture was decomposed with ice and ammonium chloride. The ether layer was separated and dried over magnesium sulfate. The ether was removed by distillation and the residue vacuum-distilled. A 43% yield of 1-chloro-3-octanol was obtained, which distilled at 110–115° under 14 mm.

Anal. Calc'd for $C_8H_{17}ClO$: Cl, 21.53; mol. ref., 45.5.
Found: Cl, 21.64; mol. ref., 45.1; d_{24}^{24} 0.982; n_D^{18} 1.4519.

1-Iodo-3-octanol.—Sixty grams of 1-chloro-3-octanol, 500 cc. of acetone, and 57 g. of sodium iodide were refluxed with stirring overnight. The acetone solution was separated from the salt by filtration. The acetone was evaporated on a steam cone, and the remaining liquid was extracted from the solid salt with ether. The ether was evaporated, and the 1-iodo-3-octanol was obtained as a brown oil. It could not be satisfactorily purified and was used directly in the next reaction.

Sodium 3-hydroxy-1-octanesulfonate.—Thirty grams of 1-iodo-3-octanol was dissolved in 300 cc. of 95% alcohol. It was heated to boiling, and water was added until the 1-iodo-3-octanol began to come out of solution (about 72% alcohol). Now 18 g. of anhydrous sodium sulfite was added, and the mixture was refluxed for forty-eight hours with stirring. The alcohol solution was filtered and evaporated to dryness. The sodium 3-hydroxy-1-octanesulfonate was crystallized from 95% and then from absolute alcohol. The yield was 11%.

Anal. Calc'd for $C_8H_{17}NaO_4S$: Na, 9.91; S, 13.79.
Found: Na, 10.01; S, 13.93.

Potassium 3-hydroxy-1-octanesulfonate.—To a well-stirred saturated solution of potassium sulfite heated under reflux 60 g. of 1-iodo-3-octanol was slowly added. The mixture was stirred and refluxed overnight or until the two layers had com-

[3] *Organic Syntheses*, Coll. Vol. I, John Wiley and Sons, New York, 1932, p. 160.

pletely disappeared. On cooling, a solid mass formed which was dissolved in 10% hydrochloric acid and evaporated almost to dryness to remove all of the sulfite ion. Dilute hydrochloric acid was added to dissolve the salt and the iodide ion completely removed with hydrogen peroxide and carbon tetrachloride. The remaining solution was evaporated to dryness to remove the acid and peroxide. The potassium 3-hydroxy-1-octanesulfonate was extracted from this mixture in three ways: (1) by the addition of silver oxide to remove the chloride ion, followed by neutralization with sulfuric acid and extraction with 80% alcohol; (2) by extraction of the mixture with absolute alcohol, using a Sohxlet extractor; and (3) by Sohxlet extraction with acetone. The best yield was obtained by method 1 but this method gave only 15% of the desired product. The potassium 3-hydroxy-1-octanesulfonate was recrystallized from absolute alcohol.

Anal. Calc'd for $C_8H_{17}KO_4S$: K, 15.73; S, 12.93.
Found: K, 15.88; S, 13.07.

SUMMARY

Treatment of β-chloropropionaldehyde with *n*-amylmagnesium bromide gave 43 per cent yield of 1-chloro-3-octanol. This chloroalcohol was converted to the iodoalcohol and the latter, when treated with sodium or potassium sulfites, yielded the sodium and potassium salts of 3-hydroxy-1-octanesulfonic acid in 11 and 15 per cent yields respectively. Attempts to convert these salts into octane sultone were unsuccessful.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

THE REACTIONS OF ALD-CHLORIMINES WITH GRIGNARD REAGENTS

J. W. LEMAISTRE, A. E. RAINSFORD, AND CHARLES R. HAUSER

Received December 14, 1938

In connection with a study of the reactions of compounds of the type RCH=NX (where X is halogen, acetate, etc.) with bases[1], it seemed of interest to investigate the reactions of these compounds with Grignard reagents. The results obtained with ald-chlorimines and certain Grignard reagents are reported in this paper.

The characteristic group of ald-chlorimines, (—CH=NCl), should be capable of undergoing at least three different types of reaction, involving, (1) the elimination of hydrogen chloride, (2) a reaction in which the nitrogen-chlorine group is attacked (as in hydrolysis), or (3) addition to the carbon-nitrogen double bond. A previous study[1a] has shown that in the presence of certain bases, such as alcoholic alkali, only the first reaction occurs to an appreciable extent, giving in certain cases practically quantitative yields of nitrile. The present investigation shows that in the presence of Grignard reagents, the first two types of reaction occur, the second predominating; apparently, addition to the carbon-nitrogen double bond (third type) does not take place to an appreciable extent with these reagents.

The reactions of ald-chlorimines with Grignard reagents has been carried out by slowly adding the latter to the chlorimine in ether solution. In this way secondary reactions of the Grignards with the products (*e. g.*, nitriles) was minimized. The products obtained from the reactions of ald-chlorimines with ethyl-, phenyl-, or *p*-chlorophenylmagnesium bromide may be accounted for by equations (I) and (II). In I, the Grignard reagent removes hydrogen chloride from the ald-chlorimine to form a nitrile and R'H, while in II, the Grignard reagent is chlorinated, giving R'Cl and a nitrogen-magnesium compound.

$$\text{(I)} \qquad \text{RCH=NCl} + \text{R'MgX} \rightarrow \text{RCN} + \text{R'H} + \text{MgXCl}$$

$$\text{(II)} \qquad \text{RCH=NCl} + \text{R'MgX} \rightarrow \text{RCH=N—MgX} + \text{R'Cl}$$

The yields of nitrile and of nitrogen-magnesium compound isolated are given in the accompanying table. The ald-chlorimine used up is not fully accounted for by the products isolated, but the yields given are

[1] See especially: (*a*) HAUSER, LEMAISTRE, AND RAINSFORD, *J. Am. Chem. Soc.*, **57**, 1056 (1935); (*b*) HAUSER AND JORDAN, *ibid.*, **57**, 2450 (1935).

based on rather pure compounds. The identities of the nitriles were established by the mixture melting point method, those of the nitrogen-magnesium compounds by hydrolysis to the aldehydes, which were identified by mixture melting points or by derivatives. In one case the products R'H of equation I and R'Cl of equation II were isolated.

It is seen from the table that the principal reaction is II, although I occurs to a considerable extent. The quantitative relationships are probably of little significance because of the losses attendant on isolation of pure products. It is interesting however to note that in the reactions of 4-chlorobenzalchlorimine, the yield of nitrile was greater with ethylmagnesium bromide than with phenylmagnesium bromide.

Like the Grignard reagents, phenyllithium reacts with 4-chlorobenzalchlorimine to give the nitrile and a nitrogen lithium compound, which on hydrolysis yields the aldehyde.

TABLE

YIELDS OF PRODUCTS FROM CERTAIN BENZALCHLORIMINES AND GRIGNARD REAGENTS

BENZALCHLORIMINE	GRIGNARD REAGENT	TEMP. OF REACTION, °C.	PERCENTAGE YIELDS	
			RCN	RCH=NMgX
2-Chloro-	C_2H_5MgBr	−45	13	43
4-Methoxy-	C_2H_5MgBr	0	17	50
4-Chloro-	C_2H_5MgBr	0	20	45
4-Chloro-	C_2H_5MgBr	23–28	34	45
4-Chloro-	C_6H_5MgBr	0	10	61
4-Chloro-	p-ClC_6H_4MgBr	0	5[a]	18[a]

[a] In addition to nitrile and aldehyde, chlorobenzene (20 per cent.) and p-dichlorobenzene (25 per cent.) were isolated.

Reaction II of the ald-chlorimines with Grignard reagents apparently involves the removal of chlorine from nitrogen with a sextet of electrons (positive chlorine). This is the characteristic manner in which chlorine is removed from nitrogen in hydrolysis and in most other reactions. Coleman[2] has shown that chloroamines of the type R_2NCl react with Grignard reagents predominately in this manner.[3] Reaction II may involve the initial formation of a coördination compound of the type

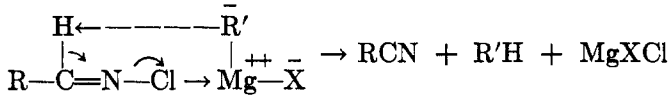
$$RCH{=}N(Cl)(R')\rightarrow MgX.$$

[2] COLEMAN, *ibid.*, **55**, 3001 (1933).

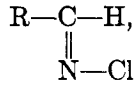
[3] An interesting reaction that appears to be an exception to this type of substitution is the formation of primary amines from Grignard reagents and monochloramine. In this reaction the chlorine is apparently removed from nitrogen with a complete octet of electrons. See COLEMAN AND CO-WORKERS, *ibid.*, **50**, 1193 (1928); **51**, 567 (1929).

The coördination should facilitate the release of positive chlorine and of the negative R group; an α, γ shift would give the products of reaction, R'Cl and RCH=N—MgX.

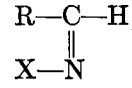
Reaction I of the ald-chlorimines with Grignard reagents presumably involves the removal of the hydrogen as a proton, and of the chlorine as chloride ion, the Grignard reagent functioning as a base. While there may be an initial coördination of the chlorine of the chlorimine with the magnesium of the Grignard reagent, it is believed that this in itself would not effect the elimination of hydrogen chloride. There is evidence[1a] that the removal of hydrogen chloride from ald-chlorimines by alkali involves a primary attack by the base on the aldehydic hydrogen atom. It is believed therefore, that the removal of hydrogen chloride from these compounds by Grignard reagents is brought about primarily by an attack of the negative R group, which is present at least potentially in these reagents, on the aldehydic hydrogen atom of the chlorimine. An initial coördination of the chlorimine and Grignard, RCH=NCl → MgXR, might however, facilitate the release of the proton from the former, and of the negative R group from the latter. The elimination may be represented as follows:



It is of interest to note that if the "*syn*" configuration* is assigned to ald-chlorimines,



it might appear that a cyclic mechanism[4] would be applicable to the elimination reaction. A preliminary experiment† has shown, however, that an *anti* compound,



also eliminates HX in the presence of a Grignard reagent. This shows that ald-chlorimines do not need to react by a cyclic mechanism.

* No ald-chlorimine has been isolated in two geometrically isomeric forms. It seems likely that the configuration of the ald-chlorimines isolated is the more stable "syn" structure.

[4] In this connection see JOHNSON, Gilman's "Organic Chemistry," John Wiley and Sons, **1938**, Vol. I, pp. 1636–1651.

† A preliminary experiment with acetyl-β-3,4-methylenedioxybenzaldoxime and ethylmagnesium bromide gave a 25 per cent. yield of the corresponding nitrile.

EXPERIMENTAL

Reactions of ald-chlorimines with Grignard reagents.—In general, these reactions were carried out according to the following procedure. The ald-chlorimine (.025–.07 mole) prepared and purified as previously described,[5] was dissolved in 100–200 cc. of dry ether and the solution brought to the desired temperature, which in most cases was 0°. To this solution was added, drop by drop, with stirring, a molar equivalent of Grignard reagent which was prepared and analyzed in the usual manner,[6] and cooled to the temperature of the chlorimine solution. A precipitate of RCH=NMgX formed, but in certain cases, in which a rather large amount of ether was used, a portion of this nitrogen-magnesium compound remained in solution. After standing a few hours the reaction mixture was filtered, and the nitrogen-magnesium compound in the funnel was hydrolyzed to aldehyde. The filtrate usually gave a faint test for active chlorine. Analysis of the filtrate for active chlorine indicated that about 10 per cent. of the chlorimine remained. This was converted to aldehyde by shaking the solution with hydrochloric acid, which also hydrolyzed the nitrogen-magnesium compound that was present in the ether solution. The ether layer was separated and allowed to stand with saturated sodium bisulfite solution for 24–36 hours. In certain cases, the ether was first evaporated, and the residue was allowed to stand with the bisulfite solution. The aldehyde-bisulfite addition compound was collected by filtration and decomposed with sodium carbonate to obtain the aldehyde. Nitrile was obtained by evaporation of the ether solution. The solid nitriles and aldehydes were identified by the mixture melting point method. The liquid aldehydes were converted into their corresponding semicarbazones or phenylhydrazones. The percentage yields of nitrile and nitrogen-magnesium compound (including that isolated as aldehyde) are given in the table.

In the reaction of 4-chlorobenzalchlorimine (12 g.) with 4-chlorophenylmagnesium bromide, the ether filtrate, obtained by filtering off the nitrogen-magnesium compound from the reaction mixture, was fractionally distilled. The ether was distilled off on a water bath. The oily residue was transferred to a Claisen flask with a ten-inch side-neck fractionating column, and was distilled under reduced pressure. A small fraction of chlorobenzene (boiling at 130–132° at atmospheric pressure), and a higher-boiling fraction, which solidified in the condenser, were collected. The latter melted at 52°, and was identified as dichlorobenzene. A dark-colored residue was left in the flask. When this residue was fractionally crystallized from acetone, alcohol, and water, 4-chlorobenzonitrile was isolated. 4-Chlorobenzaldehyde was obtained by hydrolysis of the nitrogen-magnesium compound which was removed by filtration from the original reaction mixture. The yields of these products are given in the table. No other pure product could be isolated.

Reaction of 4-chlorobenzalchlorimine with phenyllithium.—Phenyllithium solution was prepared and analyzed according to the method of Gilman, Zoellner, and Selby.[7] Fifty cc. of this solution (.025 mole) was added slowly to an equivalent of the chlorimine in 100 cc. of ether at 0°. After an hour the solution, together with the small precipitate present, was shaken with acid, and the ether layer was allowed to stand with bisulfite solution for 36 hours. The aldehyde-bisulfite addition compound which formed was collected by filtration and decomposed with sodium carbonate. A yield of 34 per cent. of 4-chlorobenzaldehyde was obtained in this way. A 20 per cent. yield of the corresponding nitrile was obtained by evaporation of the ether solution.

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[5] HAUSER, GILLASPIE, AND LEMAISTRE, *ibid.*, **57**, 567 (1935).

[6] See GILMAN, ZOELLNER, AND DICKEY, *ibid.*, **51**, 1577 (1929).

[7] GILMAN, ZOELLNER, AND SELBY, *ibid.*, **54**, 1957 (1932).

SUMMARY

1. A study has been made of the reactions of ald-chlorimines with certain Grignard reagents.

2. It has been shown that in the presence of these reagents ald-chlorimines undergo two types of reaction. In one, the Grignard reagent functions as a base, removing hydrogen chloride from ald-chlorimines to form nitriles, while in the other, the chlorine of the chlorimine is substituted by —MgX.

3. These types of reaction are discussed.

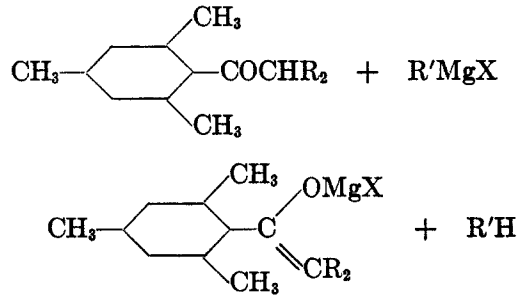
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

REACTIONS OF BROMOMAGNESIUM ENOLATES OF MESITYL KETONES. I

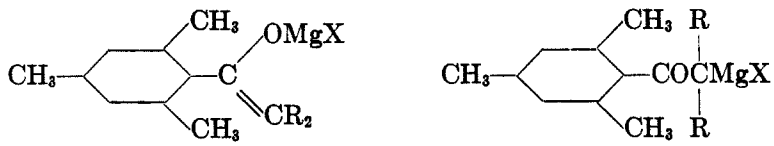
REYNOLD C. FUSON, C. HAROLD FISHER, G. E. ULLYOT, AND W. O. FUGATE

Received December 15, 1938

Mesityl ketones which have one or more *alpha* hydrogen atoms react with the Grignard reagent in an abnormal fashion. Since addition to the carbonyl group is inhibited by the steric hindrance offered by the two *ortho* methyl groups, enolization occurs with the resulting formation of the corresponding halomagnesium enolates:[1]



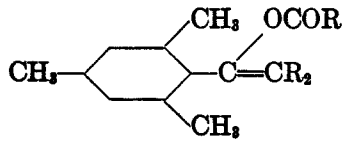
These enolates are of great interest because they give products which would suggest either of the following structures:



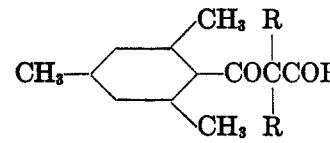
The evidence for this is that they react with acid chlorides to give enol esters (I) or 1,3-diketones (II), *i.e.*, they undergo *O*-acylation or *C*-acylation, respectively.[2a]

[1] (*a*) KLAGES, *Ber.*, **35**, 2635 (1903); (*b*) KOHLER AND BALTZLY, *J. Am. Chem. Soc.*, **54**, 4015 (1932).

[2] (*a*) KOHLER, TISCHLER, AND POTTER, *ibid.*, **57**, 2517 (1935); (*b*) KOHLER AND POTTER, *ibid.*, **58**, 2166 (1936).



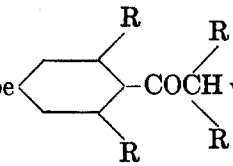
I

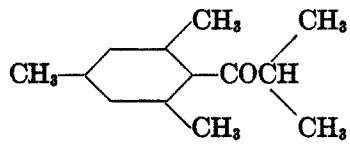


II

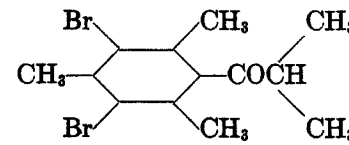
Similar results have been obtained with alkylating agents. In polar solvents tosylacetomesitylene[2b] and cyanoacetomesitylene[3] yield *O*-alkylation products exclusively.

The tendency of carbonyl compounds to undergo *O*-acylation and *O*-alkylation is usually associated with the readiness with which they enolize. Thus phenols and permanent enols generally give *O*-alkyl and *O*-acyl derivatives. In harmony with this point of view is the observation that mesityl ketones show a pronounced tendency to enolize.

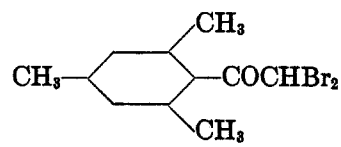
There is evidence also that this tendency is not limited to mesityl ketones but may be general for ketones whose addition reactions are highly restricted by the radicals surrounding the functional group, *i.e.*, it is in part, at least, a manifestation of steric hindrance.[4] In view of this the effect should be extreme in a ketone of the type  whose hindrance to addition reactions of the carbonyl group is prohibitive. The present paper deals principally with compounds of this general type. Isobutyromesitylene (III), 3,5-dibromoisobutyromesitylene (IV) and α,α-dibromoacetomesitylene (V) were examined in some detail with regard to their tendency to undergo acylation.



III



IV



V

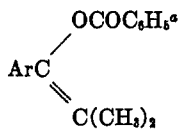
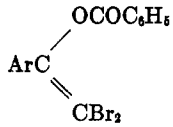
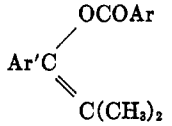
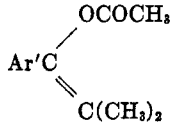
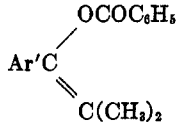
[3] FUSON, ULLYOT, AND GEHRT, *ibid.*, **60**, 1199 (1938).

[4] SMITH AND GUSS, *ibid.*, **59**, 804 (1937); ROSS AND FUSON, *ibid.*, **59**, 1508 (1937).

The desired bromomagnesium derivatives were obtained from the mesityl ketones by use of ethylmagnesium bromide. They were then treated with reagents designed to explore their capacities for behaving as enolates, on the one hand, as Grignard reagents on the other.

TABLE

ENOL ESTERS OBTAINED BY TREATMENT OF THE BROMOMAGNESIUM ENOLATES WITH ACID CHLORIDES

FORMULA OF ENOL ESTER	M.P., °C.	ANALYSES %					
		Calculated			Found		
		C	H	Br	C	H	Br
	87–88	81.63[b]	7.48		81.2 82.04 81.18	7.6 7.55 7.31	
	73–74.5	50.94	3.77	37.7	51.20	3.64	37.5
	113–114	55.87	5.24	32.4	55.88	5.13	32.6 32.2
	77–78	46.15	4.61	41.0	46.08	4.71	41.
	109–109.5	53.09	4.42	35.4	53.08	4.82	35.6

[a] Ar = mesityl; Ar′ = 3,5-dibromomesityl.

[b] All of the analytical data reported in this paper were obtained by microanalysis. The analyses were performed by Mr. Charles W. Beazley.

O-ACYLATION

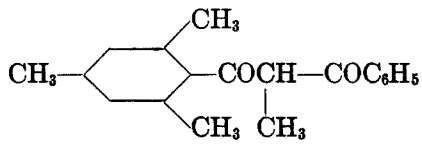
The former objective was fully realized by the use of acid chlorides. In every instance enol esters were formed and in no case could any trace of diketone be isolated. Evidently acid chlorides gave only *O*-derivatives. These are shown in the table of the experimental part.

The structures of the enol esters were deduced from the fact that these compounds were readily cleaved by bromine or alkalies. Confirmation of the structures was obtained by comparing the enol benzoate of isobutyromesitylene with the corresponding diketone (VII). The ester was found to be different from the diketone.

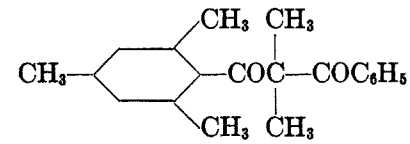
CONDENSATION REACTIONS

The synthesis of the diketones, α-benzoylpropiomesitylene (VI) and α-benzoylisobutyromesitylene (VII), serves to illustrate the capacity of the bromomagnesium enolates to act as true Grignard reagents.[2a] The reaction proceeds as though the bromomagnesium compound had the structure $RCOC(R)_2MgBr$.

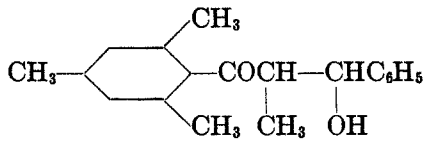
Thus the bromomagnesium derivative of propiomesitylene reacts with benzaldehyde to give the carbinol, VIII, in excellent yields. Similarly the bromomagnesium derivative of isobutyromesitylene with benzaldehyde yields the carbinol, IX. Oxidation of carbinols VIII and IX gave the corresponding mono- and dimethyl diketones. The monomethyl diketone (VI) prepared in this way was identical with that obtained from α-methyl-



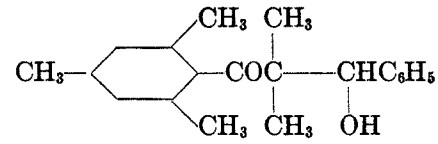
VI



VII

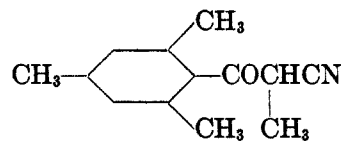


VIII



IX

β-methoxy-β-mesitylacrylonitrile (X) by the action of phenylmagnesium bromide.[5] Long treatment with alkali converted the diketone (VI) into

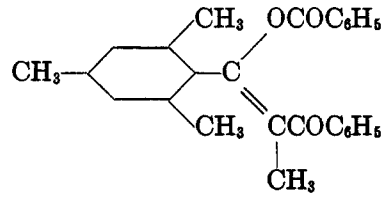


X

benzoic acid and propiomesitylene. The latter was identified by condensation with benzaldehyde. Benzalpropiomesitylene was formed; it gave a dibromide when treated with bromine.

[5] FUSON, ULLYOT, STEDMAN, AND TAWNEY, *ibid.*, **60**, 1447 (1938).

Propiomesitylene, in contrast to the more highly substituted acetomesitylenes, appears to undergo C-acylation. The action of benzoyl chloride on its bromomagnesium derivative failed to give a monobenzoyl derivative, however; instead the product was the enol benzoate of α-benzoylpropiomesitylene (XI).



XI

The compound was identified by hydrolysis with dilute alkali to give benzoic acid and α-benzoylpropiomesitylene (VI). This latter product was identified by comparison with the compound obtained by oxidation of the keto alcohol (VIII). Presumably *C*-benzoylation first occurs yielding the diketone (VI) which then undergoes *O*-benzoylation to give the benzoate (XI). Kohler and Baltzly[1b] found that acetomesitylene also gave a dibenzoyl derivative; their compound, however, was a triketone. This must mean that the methyl group in the intermediate diketone (VI) favors *O*-benzoylation. This result accords well with the foregoing, since the diketone (VI), like the dimethyl (III, IV) and dibromo (V) compounds, has only one *alpha* hydrogen atom.

Summarizing, it would appear that only *O*-acylation occurs with mesityl ketones which are of the type $(CH_3)_3C_6H_2COCHA_2$ where A may be a methyl group, a bromine atom or a ketone group. It seems probable that this will prove to be general for mesityl ketones which have only one *alpha* hydrogen atom.

EXPERIMENTAL

The preparation of the enol esters.—These compounds were made by the interaction of a bromomagnesium enolate with an acid chloride. The following description of the preparation of the enol benzoate of 3,5-dibromoisobutyrylmesitylene is typical.

A solution of 18.8 g. of dibromoisobutyrylmesitylene in 125 cc. of ether was added from a separatory funnel during thirty minutes to 42 cc. (0.082 mole) of ethylmagnesium bromide. The white precipitate was treated with 23 g. of benzoyl chloride and the mixture was stirred for two hours. Decomposition with water gave a 72% yield of the enol benzoate. The enol ester was purified by recrystallization from 95% alcohol. Similar results were obtained when α,3,5-tribromoisobutyromesitylene was used in place of 3,5-dibromoisobutyromesitylene.

The enol benzoate of α-benzoylpropiomesitylene (XI).—A solution of 17.6 g. (0.1 mole) of propiomesitylene in 40 cc. of ether was added slowly to 100 cc. of a solution containing 0.107 mole of ethylmagnesium bromide. The mixture was refluxed for thirty minutes, cooled in an ice bath and treated with 21 g. (0.15 mole) of benzoyl

chloride. The mixture was refluxed for four hours, decomposed with iced hydrochloric acid and extracted with ether. Extraction with sodium carbonate solution removed 9 g. of benzoic acid. The ether was evaporated, and the residue was treated with ligroïn and cooled. Ten grams of colorless crystals was obtained. After recrystallization from methanol they melted at 95.5–96°.

Anal. Calc'd for $C_{26}H_{24}O_3$: C, 81.21; H, 6.3.
Found: C, 81.47, 81.22, 81.10; H, 6.56, 6.51, 6.23.

Three grams of propiomesitylene was recovered from the ligroïn filtrate.

Hydrolysis of the enol benzoate of α-benzoylpropiomesitylene (XI).—A mixture of 3.85 g. of the enol benzoate, 0.6 g. of sodium hydroxide and 150 cc. of ethyl alcohol was refluxed for one and one-half hours. After distillation of the solvent the residue was shaken with a mixture of dilute sodium hydroxide solution and ether. Acidification of the alkaline layer gave 0.78 g. of benzoic acid. Treatment of the ether layer with a solution of copper acetate gave 0.8 g. of the copper derivative of α-benzoylpropiomesitylene. It was transformed into the diketone; n_D^{20} 1.5888. The diketone gave an intense color with ferric chloride.

2-Methyl-2-(2,4,6-trimethylbenzoyl)-1-phenyl-1-propanol (IX).—Twenty grams of isobutyromesitylene was converted into a bromomagnesium derivative with one equivalent of ethylmagnesium bromide. Eleven and nineteen-hundredths grams of freshly distilled benzaldehyde was added to the new Grignard reagent over a period of one and one-half hours and the mixture was refluxed one-half hour. It was then decomposed with ice and hydrochloric acid and the product when isolated from the ether layer crystallized from high-boiling ligroïn to give a colorless solid; yield, 13 g.; m.p. 85–85.5°.

Anal. Calc'd for $C_{20}H_{24}O_2$: C, 81.02; H, 8.16.
Found: C, 81.28; H, 8.07.

α-Benzoylisobutyromesitylene (VII).—One cubic centimeter of a solution of 1.12 g. of chromic oxide in 10 cc. of glacial acetic acid and 3 cc. of water was added to a solution of 5 g. of the carbinol (IX) in 40 cc. of glacial acetic acid. The mixture was heated nearly to boiling. After reaction set in, as indicated by the development of a green color, the rest of the chromic oxide solution was added in three portions. The mixture was boiled ten minutes and poured into a beaker of ice. The precipitated solid was collected and crystallized from alcohol. The yield was 4 g.; m.p. 100–100.2°.

Anal. Calc'd for $C_{20}H_{22}O_2$: C, 81.58; H, 7.53; OCH_3, 0.0.
Found: C, 81.26, 81.29; H, 7.62; OCH_3, 0.69.

The *semicarbazone* was crystallized by dissolving it in hot carbon tetrachloride and adding low-boiling ligroïn; m.p. 151–152.5°.

Anal. Calc'd for $C_{21}H_{25}O_2N_2$: C, 71.75; H, 7.17; N, 11.96.
Found: C, 71.6; H, 7.05; N, 11.94.

Synthesis of 2-(2,4,6-trimethylbenzoyl)-1-phenyl-1-propanol (VIII).—One hundred nineteen grams of propiomesitylene was converted into a Grignard reagent with ethylmagnesium bromide. The new Grignard reagent was caused to react with 72 g. of benzaldehyde as in the preparation of VIII. Seventy-eight grams of product was obtained by crystallization first from high-boiling ligroïn and then from slightly diluted alcohol; m.p. 94.5–96°.

Anal. Calc'd for $C_{19}H_{21}O_2$: C, 80.89; H, 7.52.
Found: C, 80.79, 80.69; H, 8.06, 7.78.

The first filtrate was evaporated and the residue was distilled *in vacuo*. Thirty-eight grams of propiomesitylene was recovered. A second fraction consisting of 23.3 g. of a pale-yellow liquid boiling at 178–180°/3 mm. was obtained. Redistillation

gave a product boiling at 172–174°/2 mm.; n_D^{20} 1.5991. This was identified as benzalpropiomesitylene by conversion into the corresponding dibromide.

A sulfuric acid solution of the hydroxy ketone (VIII) was heated on a steam bath and the resulting deep-red solution was poured into water; 2,4,6-trimethylbenzoic acid was formed.

α-Benzoylpropiomesitylene (VI) and its copper derivative.—A hot solution of 10 g. of the keto alcohol (VIII) in 50 cc. of glacial acetic acid was mixed slowly, with shaking, with a hot solution of 2.3 g. of chromic oxide, in 20 cc. of glacial acetic acid and 10 cc. of water. The mixture was heated on a steam cone for twenty minutes and then boiled for three minutes. The resulting dark green solution was poured into a beaker of ice, diluted with water and extracted several times with ether. The ether solution was treated with solid sodium carbonate, washed with a solution of sodium carbonate and then with water. The resulting ether solution was shaken intermittently over a period of one-half hour with a saturated aqueous solution of cupric acetate. The deep green ether solution was separated and evaporated; alcohol was added to the residue and the green copper derivative was collected on a filter. The yield was 1.8 g. The copper derivative was crystallized by dissolving it in a minimum of hot benzene and adding ligroïn.

Anal. Calc'd for $(C_{19}H_{19}O_2)_2Cu$: C, 73.34; H, 6.16; Cu, 10.2.
Found: C, 73.66, 73.64; H, 6.43, 6.19; Cu, 9.68, 9.83.

The copper was determined by weighing the copper oxide remaining after the combustion determination.

The copper derivative was decomposed by shaking it with ether and dilute hydrochloric acid in a separatory funnel. It was washed with water, dried with calcium chloride and evaporated. The residual diketone (VI) was distilled *in vacuo*. A heavy, viscous oil, slightly yellow in color was obtained. It did not crystallize; b.p. 183–184.5°/3 mm.; n_D^{20} 1.5880. It gives an intense purple color with ferric chloride.

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19.
Found: C, 81.14, 81.12, 81.27; H, 7.48, 7.53, 7.32.

Alkaline hydrolysis of α-benzoylpropiomesitylene (VI).—One gram of α-benzoylpropiomesitylene was refluxed overnight with a mixture of 80 cc. of 15% aqueous potassium hydroxide and 5 cc. of methyl alcohol. The reaction mixture was cooled and extracted with ether. The ether extract was dried over calcium chloride and evaporated. Three-tenths of a gram of oil was obtained; it was cooled in an ice bath, and a mixture of 5 cc. of concentrated nitric acid and 5 cc. of concentrated sulfuric acid, cooled to 0°, was added. The mixture was kept in an ice bath fifteen minutes, or until a precipitate formed, and was then poured into a beaker of ice. The precipitate was collected, dried and crystallized from benzene and a little ligroïn. Fine, colorless needles, melting at 230–233°, were obtained. The substance was alkali-soluble, and was shown by a mixture melting point determination to be 3,5-dinitro-2,4,6-trimethylbenzoic acid. The same product was obtained from 0.3 g. of propiomesitylene under exactly the same conditions. From the aqueous filtrate 0.3 g. of pure benzoic acid was obtained.

Benzalpropiomesitylene.—Twenty grams of propiomesitylene and 12 g. of benzaldehyde were added to a solution of 4.5 g. of sodium hydroxide in 30 cc. of alcohol and 60 cc. of water. The mixture was stirred at room temperature for eight hours and then for two hours at 70–80°. It was allowed to stand for two days; an oily layer settled to the bottom of the flask. The mixture was diluted with water and extracted with ether. The ether solution was washed with water, with a bisulfite

solution, then water again. The solution was dried over calcium chloride and the solvent evaporated. The remaining oil was distilled *in vacuo*. Twenty grams of product was obtained; b.p. 178–180°/3 mm.; n_D^{20} 1.5996.

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.46; H, 7.64.
Found: C, 86.01; H, 7.4.

Dibromobenzalpropiomesitylene.—A small amount of benzalpropiomesitylene was dissolved in carbon tetrachloride, and the solution was placed in an ice bath. Bromine, dissolved in chloroform, was added in portions to the cooled solution, the color being allowed to disappear from the reaction mixture after each addition of bromine. After sufficient bromine had been added so that the reaction mixture remained colored, ligroïn was added to hasten crystallization which had already commenced. The colorless solid was collected and crystallized by dissolving it in hot carbon tetrachloride, adding ligroïn and cooling. The melting point varied between 134 and 139°. Decomposition accompanied melting, and red bromine vapors were evolved.

Anal. Calc'd for $C_{19}H_{20}Br_2$: C, 53.77; H, 4.75.
Found: C, 53.69; H, 5.10.

It was necessary to add the bromine in the cold in order to inhibit substitution reactions.

SUMMARY

The bromomagnesium enolates of isobutyromesitylene (III), 3,5-dibromoisobutyromesitylene (IV) and α,α-dibromoacetomesitylene (V) have been shown to react with acid chlorides to give only enol esters.

The bromomagnesium enolates of propiomesitylene and isobutyromesitylene have been condensed with benzaldehyde to give keto alcohols. These yielded diketones when oxidized.

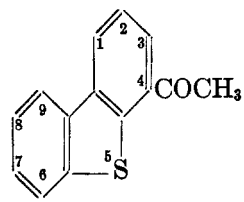
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

ACYL DERIVATIVES OF DIBENZOTHIOPHENE. II

ALFRED BURGER AND HAROLD W. BRYANT

Received January 2, 1939

The acylation of dibenzothiophene has been the subject of two recent investigations. Gilman and Jacoby[1] found that the acetyl group enters position-2, and Burger, Wartman, and Lutz[2] isolated an additional acetyldibenzothiophene in small amounts from the mixture of methyl ketones formed in low temperature acetylation. The structure of this isomer has now been established as 4-acetyldibenzothiophene (I)* since oxidation yields dibenzothiophene-4-carboxylic acid, and the oxime of the ketone may be rearranged to 4-acetaminodibenzothiophene.



I

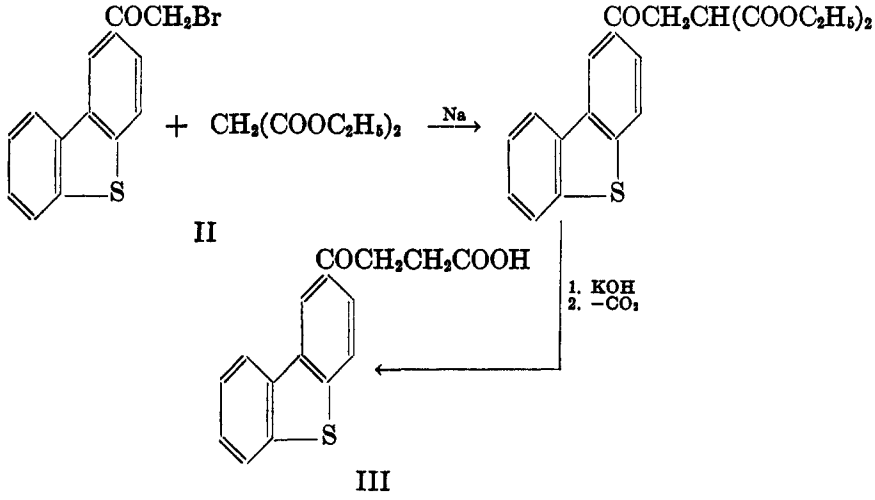
4-Acetyldibenzothiophene was isolated from the mother liquors of the main product of the Friedel-Crafts reaction, 2-acetyldibenzothiophene. Repeated attempts to duplicate the yield of this compound obtained by Gilman and Jacoby did not have the desired results; the yield of the mixture of ketones was 70 per cent, but the yield of pure 2-acetyldibenzothiophene averaged only 25 per cent. On the other hand, we did not experience any difficulty in duplicating the results of these authors in introducing the succinyl group into dibenzothiophene by the Friedel-Crafts reaction. The structure of 2-succinyldibenzothiophene (III) which had been postulated correctly by Gilman and Jacoby on the basis of its formation by the Friedel-Crafts reaction, was confirmed by synthesizing the compound by

[1] GILMAN AND JACOBY, J. ORG. CHEM. **3**, 108 (1938).

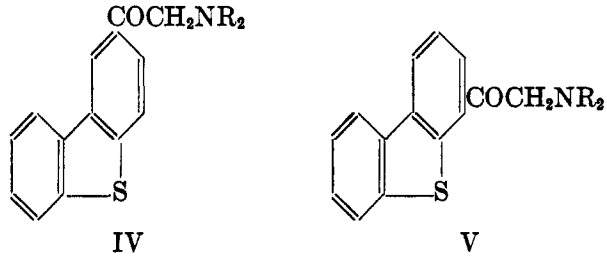
[2] BURGER, WARTMAN, AND LUTZ, *J. Am. Chem. Soc.*, **60**, 2628 (1938).

* In order to avoid confusion in the nomenclature of derivatives of dibenzothiophene and similar ring systems, the numbering system proposed by Gilman, and recommended by *Chemical Abstracts*, will be used in this and future publications. The 3 and 3,6 derivatives of dibenzothiophene reported in our first paper[2] should be renumbered as 2 and 2,8 derivatives, respectively.

reaction of 2-ω-bromoacetyldibenzothiophene (II) and sodium ethyl malonate, and subsequent hydrolysis and decarboxylation.



Both 2- and 4-acetyldibenzothiophene may be halogenated in the α-position to the carbonyl group. In the bromination, as well as in other reactions involving the carbonyl group, the 4-isomer reacts markedly more slowly than the sterically unhindered 2-derivative. Both ω-bromo ketones exchange their halogen atoms with tertiary amino groups equally easily and yield the corresponding amino ketones (IV and V). The reduction of these amino ketones and the pharmacological action of the resulting amino alcohols will be reported in the next communication of this series.



EXPERIMENTAL

Structure of 4-acetyldibenzothiophene.—Three-tenths gram of 4-acetyldibenzothiophene (m.p. 129°) was oxidized by the method of Fuson and Tullock[3]; the carboxylic acid was reprecipitated from dilute sodium carbonate solution and recrystallized from methanol. The yield was 0.2 g. Sublimation at 0.1 mm. pressure and 170° yielded colorless prisms, m.p. 261–262° (dec., evacuated tube).

[3] FUSON AND TULLOCK, *ibid.*, **56**, 1638 (1934).

The methyl ester was prepared by the action of diazomethane in ether solution. It was purified by distillation at 0.1 mm. pressure and recrystallized from dilute methanol. It appeared as fine colorless needles, m.p. 94–95°. These data agree with those furnished by Gilman and Jacoby[1].

4-Acetyldibenzothiophene oxime, prepared in pyridine solution[4], appeared as colorless prisms, m.p. 155–156°. The yield was 93%.

Anal. Calc'd for $C_{14}H_{11}NOS$: N, 5.81. Found: N, 6.04.

The *oxime acetate* separated when a solution of the oxime in 8 parts of acetic anhydride and 16 parts of glacial acetic acid was saturated with hydrogen chloride at room temperature. It was filtered, washed with water, and recrystallized from methanol; small colorless plates, m.p. 142–143°; yield, 80%.

Anal. Calc'd for $C_{16}H_{13}NO_2S$: N, 4.99. Found: N, 4.91.

Neither the oxime, nor its acetate, formed chelated metal compounds.

Beckmann rearrangement of 4-acetyldibenzothiophene oxime.—A mixture of 0.5 g. of the oxime, 0.5 g. of phosphorus pentachloride, and 10 ml. of dry benzene was heated at 40° for six hours. The mixture was treated with water, a yellowish precipitate was brought into solution with benzene, the benzene solution was concentrated and allowed to crystallize. The product was washed with ether and recrystallized from benzene; 4-acetaminodibenzothiophene separated as colorless crystals, m.p. 195–197°. The melting point reported for this compound[1] is 198°.

4-ω-Bromoacetyldibenzothiophene.—A solution of 0.2 ml. of bromine in 10 ml. of dry ether was added to a suspension of 1.0 g. of finely powdered 4-acetyldibenzothiophene in 20 ml. of ether. Addition of a few drops of an ethereal hydrogen chloride solution and exposure to sunlight brought about decolorization after 25 minutes. The bromo ketone crystallized; the yield was 0.6 g. Recrystallization from 12 ml. of boiling ethanol rendered fine colorless needles, m.p. 149–151°.

Anal. Calc'd for $C_{14}H_9BrOS$: C, 55.07; H, 2.97.
Found: C, 55.44; H, 3.25.

4-(2-Piperidino-1-oxoethyl)dibenzothiophene.—Addition of 3 ml. of piperidine to a solution of 0.6 g. of 4-ω-bromoacetyldibenzothiophene in 6 ml. of dry benzene caused immediate precipitation of piperidine hydrobromide. The reaction mixture was diluted with ether, washed with water, the solution was dried and evaporated under reduced pressure. The residue was converted to the *hydrochloride* in acetone solution, and the salt was recrystallized from ethanol-ether; it appeared as yellow needles which sintered at 250° and melted at 258–260° (dec., evacuated tube).

Anal. Calc'd for $C_{19}H_{20}ClNOS$: N, 4.05. Found: N, 4.17.

2-ω-Bromoacetyldibenzothiophene.—The bromination of 2-acetyldibenzothiophene was carried out as in the case of the 4-isomer. Decolorization of the ethereal suspension took place after three minutes. The bromo ketone crystallized from ethanol as long colorless needles, m.p. 115–116°. The yield was 62%.

Anal. Calc'd for $C_{14}H_9BrOS$: C, 55.07; H, 2.97.
Found: C, 54.84; H, 3.02.

2-(2-Piperidino-1-oxoethyl)dibenzothiophene.—Piperidine reacted with 2-ω-bromoacetyldibenzothiophene in benzene solution almost immediately. The mixture was washed with water, the benzene solution was evaporated, and the piperidino ketone was converted into its *hydrochloride* in acetone solution. Recrystallization of the salt from alcohol-ether rendered colorless fine needles, which sintered at 242°; m.p. 245–246° (dec.). The yield was 55%.

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[4] BACHMANN AND BOATNER, *ibid.*, **58**, 2099 (1936).

Anal. Calc'd for $C_{19}H_{20}ClNOS$: N, 4.05. Found: N, 4.44.

2-(2-Diethylamino-1-oxoethyl)dibenzothiophene.—Diethylamine also reacted with 2-ω-bromoacetyldibenzothiophene almost immediately. The reaction mixture was worked up in the customary way. The diethylamino ketone *hydrochloride* crystallized from ethanol-ether as a yellowish powder, m.p. 200–202° (dec.).

Anal. Calc'd for $C_{18}H_{20}ClNOS$: N, 4.20. Found: N, 4.10.

Synthesis of 2-succinyldibenzothiophene.—A solution of 5 g. of 2-ω-bromoacetyldibenzothiophene and 2.7 g. of diethyl malonate in 25 ml. of dry benzene was added slowly to a suspension of 0.4 g. of powdered sodium in 25 ml. of benzene. The mixture became hot, and was boiled under reflux for nine hours. A small amount of unchanged sodium was decomposed with ethanol, and the solution was extracted with dilute hydrochloric acid. The solvent was evaporated, the residue was boiled with 25 ml. of a 5% alcoholic potassium hydroxide solution for two hours, and the alcohol was evaporated under reduced pressure. The potassium salts were dissolved in water, impurities were removed by extraction with ether, the aqueous solution was acidified, and the dicarboxylic acid was extracted into ether. The dry, solid residue from the ether solution was decarboxylated by heating at 150–160° for two hours, the black material was reprecipitated from sodium carbonate solution, and purified by recrystallization from ethyl acetate from which it was obtained as colorless crystals, m.p. 158–159°. A mixture melting point with a sample prepared by direct succinylation of dibenzothiophene[1] showed no depression.

2-Cyanodibenzothiophene.—One and four-tenths gram of crude 2-bromodibenzothiophene and 0.53 g. of cuprous cyanide was heated at 240–270° for six hours. The cyano compound was distilled from the reaction mixture in vacuum and recrystallized from ethanol. The yield was 0.4 g. The pure, colorless cyano compound melted at 159–160°.

Anal. Calc'd for $C_{13}H_7NS$: N, 6.70. Found: N, 6.98.

SUMMARY

The mixture of methyl ketones formed in the direct acetylation of dibenzothiophene contains 2-acetyldibenzothiophene as the main reaction product, and small amounts of 4-acetyldibenzothiophene. Bromo and tertiary amino ketones were prepared from the two isomers. The structure of 2-succinyldibenzothiophene was confirmed by synthesis from 2-acetyldibenzothiophene.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NATIONAL UNIVERSITY OF CHEKIANG CHINA]

CONDENSATION OF AMINO ETHERS WITH NAPHTHOLS, CRESOLS, AND NAPHTHYLAMINES*

HEOU-FEO TSEOU AND CHANG-TSING YANG

Received January 4, 1939

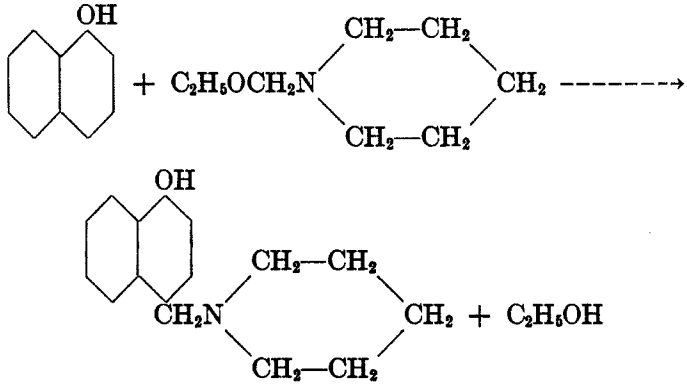
It is remarkable that, while the α-amino ethers have been known since 1921, little study has been made, up to the present, of their chemical behavior. Only Macleod and Robinson[1] made a brief study of the reactions of this class of compound with acetophenone and 2,4-dinitrotoluene. Although the reactions were not thoroughly investigated, the results indicated undoubtedly a condensation with the elimination of alcohol.

$$C_5H_{10}NCH_2OC_2H_5 + CH_3COC_6H_5 \rightarrow C_5H_{10}NCH_2CH_2COC_6H_5 + C_2H_5OH$$

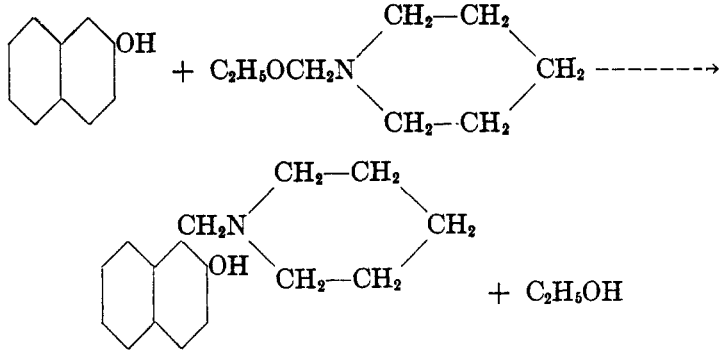
$$C_5H_{10}NCH_2OC_2H_5 + (NO_2)_2C_6H_3CH_3 \rightarrow C_5H_{10}NCH_2CH_2C_6H_3(NO_2)_2 + C_2H_5OH$$

The present authors think that this class of ethers awaits further investigation and that they may be susceptible of entering into reaction with various compounds containing active hydrogen atoms as revealed in other condensation reactions.

The research is begun with naphthols, cresols, and naphthylamines. With α- and β-naphthols the reactions with piperidinomethyl ethyl ether take place with such facility that no heating is necessary, and the reactions take uniquely the following course:

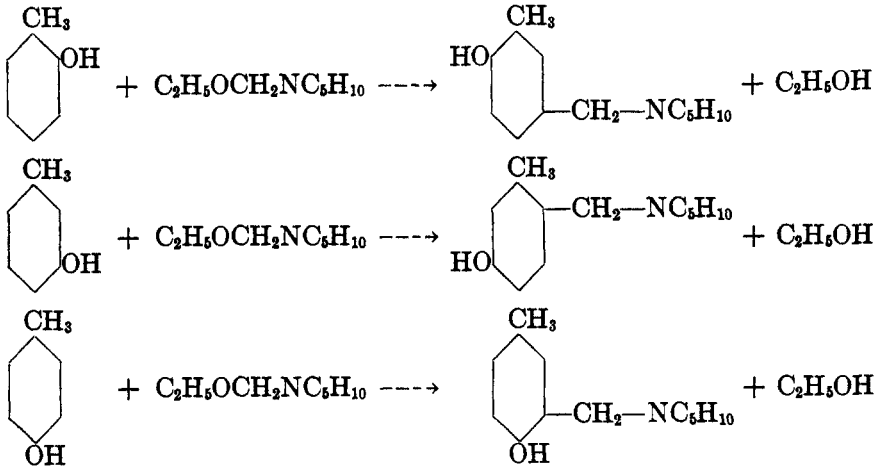


* *Editor's Note.*—This communication calls attention to an interesting synthesis of aminomethyl derivatives of compounds containing an active hydrogen atom. Although the authors offer no proof that the condensation takes the indicated course,



In both cases the yield is high when care is taken to carry out the condensation under moderate conditions. If heat is applied, a viscous mass is obtained, and the yield is considerably lowered.

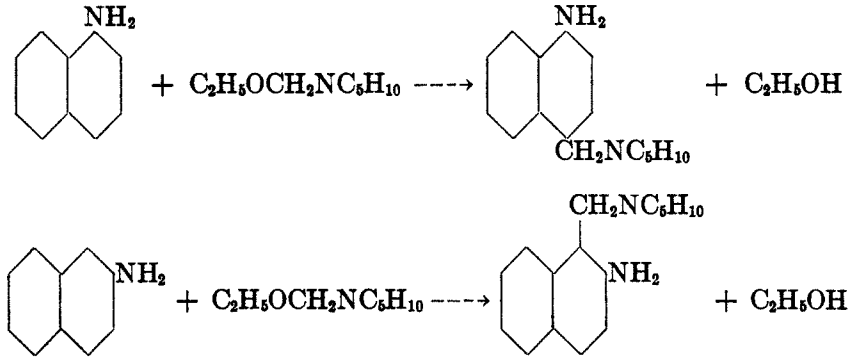
With cresols it is found that the working conditions are somewhat different from those with the naphthols, as heating is necessary to effect the reactions. With *ortho-*, *meta-*, and *para*-cresols the results of the condensation can be represented by the following equations:



or that the products obtained have the structure shown, we find that their conception of the reaction is correct. Five of the compounds described, namely the condensation products with α- and β-naphthol, and with *o*-, *m*-, and *p*-cresol, are already recorded in the literature [AUWERS AND DOMBROWSKI, *Ann.*, **244**, 289 (1906); HILDEBRANDT, *Arch. expt. Path. Pharmakol.*, **44**, 278 (1900); Farbenfabr. vorm. F. Bayer and Co., German Patent 89,979, March 1, 1895], and have the properties of the condensation products here reported. The paper is brought to publication because of its possible value to those interested in the preparation of such compounds. LYNDON F. SMALL.

[1] MACLEOD AND ROBINSON, *J. Chem. Soc.*, **119**, 1470 (1921).

When the reaction is extended to naphthylamines, the question which naturally arises is whether the hydrogen in the amino group or that in the nucleus is attacked. Experiments have shown that only the hydrogen attached to carbon atoms enters into reaction, because the end-products are shown by the benzenesulfonyl chloride test to contain the primary amino group. The reaction therefore takes the following course.



With aniline, benzamide, and phthalimide the amino ether reacts with the hydrogen atom attached to nitrogen. These are therefore not condensation reactions and cannot be discussed under the same topic.

EXPERIMENTAL

1-Hydroxy-4-piperidinomethylnaphthalene.—Twenty grams of α-naphthol was gradually added with stirring to twenty grams of piperidinomethyl ethyl ether in a beaker. The liquid became more and more viscous during the addition, until finally the whole was turned into a solid mass. The beaker was then put into a desiccator under vacuum to evaporate the alcohol formed in the condensation. After standing overnight, the solid was powdered and extracted repeatedly with a 10% sodium hydroxide solution to remove any unreacted naphthol, filtered under suction and washed with water until free from alkali. It was then recrystallized from acetone from which it separated as find needles. The yield of the crude product was thirty-two grams, and that of the pure compound twenty-four grams. The latter amounts to fifty-five per cent. of the theoretical quantity. It melts at 133°. It is soluble in most organic solvents, insoluble in water, and soluble in acid.

Anal. Calc'd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81.
Found: C, 79.7; H, 7.87; N, 5.90.

Picrate.—Yellow crystals from alcohol; m.p., 98°.

Anal. Calc'd for $C_{22}H_{22}N_4O_7$: N, 11.91. Found: N, 12.05.

1-Piperidinomethyl-2-hydroxynaphthalene.—Twenty grams of β-naphthol was slowly added, with stirring, to twenty grams of piperidinomethyl ethyl ether. Much heat was developed. When all the naphthol was added a solid mass resulted. The alcohol was sucked off, and the residue was allowed to stand overnight under vacuum in a desiccator. The same treatment as in the preceding operation then followed and the product was finally recrystallized from alcohol. The pure compound consists of colorless needles melting at 96°. The yield is about sixty-five per cent. of the

theoretical quantity. It is soluble in common organic solvents and acids but insoluble in water.

Anal. Calc'd for $C_{16}H_{19}NO$: C, 79.7; H, 7.87; N, 5.81.
Found: C, 79.9; H, 7.97; N, 5.89.

Picrate.—Yellow crystals melting at 101°.

Anal. Calc'd for $C_{22}H_{22}N_4O_7$: N, 11.91. Found: N, 12.07.

1-Hydroxy-2-methyl-4-piperidinomethylbenzene.—To fifteen grams of *o*-cresol in a 200-cc. round-bottomed flask was slowly added twenty-two grams of piperidinomethyl ethyl ether. The mixture was then heated on the water bath under a reflux condenser protected from moisture by a calcium chloride tube. At the end of two hours the content, which became yellow in color, was transferred to a Wurtz flask and subject to vacuum distillation. The alcohol was first removed, together with some unreacted amino ether and methylene-bis-piperidine. The main portion distilled at 156–7° under 6 mm. pressure as a colorless liquid. The yield is 29 g.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.02; H, 9.36; N, 6.81.
Found: C, 75.93; H, 9.51; N, 6.56.

Picrate.—Yellow crystals from alcohol; m.p. 177°.

Anal. Calc'd for $C_{19}H_{22}N_4O_8$: N, 12.90. Found: N, 12.65.

Platinichloride.—Yellow crystals, soluble in hot hydrochloric acid, insoluble in water and organic solvents; m.p. 194°.

Anal. Calc'd for $C_{26}H_{40}Cl_6N_2O_2Pt$: Pt, 23.78. Found: Pt, 23.52.

1-Hydroxy-3-methyl-4-piperidinomethylbenzene.—Ten grams of *m*-cresol was mixed with fifteen grams of piperidinomethyl ethyl ether in a 200-cc. round-bottomed flask and heated under reflux on the water bath for three hours. The content was then subjected to vacuum distillation. The main portion was collected at 158–61°. The colorless distillate crystallized in the form of needles on cooling. The yield was about 18 g. The recrystallized product (from ether) melts at 56°. It is colorless and soluble in most organic solvents, slightly soluble in water, and soluble in acids.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.02; H, 9.36; N, 6.81.
Found: C, 76.31; H, 9.42; N, 7.03.

Picrate.—Yellow crystals from alcohol; m.p. 127°.

Anal. Calc'd for $C_{19}H_{22}N_4O_8$: N, 12.90. Found: N, 12.81.

1-Hydroxy-4-methyl-6-piperidinomethylbenzene.—Twenty-two grams of piperidinomethyl ethyl ether was mixed with fifteen grams of *p*-cresol in a 200-cc. round-bottomed flask and the content was heated on the water bath for four hours. After evaporating the low-boiling fraction the content of the flask solidified to a compact mass. It was then recrystallized from alcohol, yield 28 g. It consists of snow white crystals melting at 45°C. It is soluble in most organic solvents, slightly soluble in water, and soluble in acids.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.02; H, 9.36; N, 6.81.
Found: C, 76.14; H, 9.52; N, 6.91.

Picrate.—Yellow crystals from alcohol; m.p., 149°.

Anal. Calc'd for $C_{19}H_{22}N_4O_8$: N, 12.90. Found: N, 12.78.

Platinichloride.—Yellow crystals; m.p. 199°. It is soluble in hot hydrochloric acid, insoluble in water and organic solvents.

Anal. Calc'd for $C_{26}H_{40}CL_6N_2O_2Pt$: Pt, 23.78. Found: Pt, 23.70.

1-Amino-4-piperidinomethylnaphthalene.—Ten grams of piperidinomethyl ethyl ether was added to ten grams of α-naphthylamine in a 200-cc. round-bottomed flask. The mixture was then heated on the water bath for two hours. The content turned into a dark-red, viscous, fluorescent liquid which solidified on standing. To facili-

tate the formation of crystals 10 cc. of petroleum ether was added and strongly stirred while the flask was kept in a freezing mixture. The crystals which formed were recrystallized twice from benzene. The melting point is 124°. The yield is almost quantitative.

Anal. Calc'd for $C_{16}H_{20}N_2$: C, 79.93; H, 8.41; N, 11.66.
Found: C, 80.09; H, 8.45; N, 11.31.

Benzenesulfonyl chloride test.—To 4 cc. of 5% sodium hydroxide solution 0.2 g. of *p*-piperidinomethyl-α-naphthylamine was added, followed by 0.2 g. of benzenesulfonyl chloride, and the mixture was heated gently. The liquid was then filtered and acidified. The precipitate which formed assumed leaf-like crystalline form on standing. On recrystallization from ether it gave the pure compound melting at 163°.

1-Piperidinomethyl-2-aminonaphthalene.—Twenty grams of piperidinomethyl ethyl ether was added to twenty grams of β-naphthylamine in a 200-cc. round-bottomed flask. The mixture was heated on the water bath for four hours. A red fluorescent viscous liquid was obtained. On cooling in freezing mixture and vigorous stirring, the content solidified. After recrystallization from benzene, white crystals melting at 114° were obtained. The yield is almost quantitative.

Anal. Calc'd for $C_{16}H_{20}N_2$: C, 79.93; H, 8.41; N, 11.66.
Found: C, 79.80; H, 8.58; N, 11.41.

Benzenesulfonyl chloride test.—To 4 cc. of a 5% sodium hydroxide solution was added 0.2 g. of 1-piperidinomethyl-2-amino-naphthalene, followed by 0.2 g. of benzenesulfonyl chloride. The mixture, after being gently heated, was filtered and acidified. The precipitate was filtered by suction and recrystallized from ether; m.p. 83°.

SUMMARY

(1) Piperidinomethyl ethyl ether reacts with α- and β-naphthol to form 1-hydroxy-4-piperidinomethylnaphthalene and 1-piperidinomethyl-2-hydroxynaphthalene respectively.

(2) With *o*-, *m*-, and *p*-cresol a similar condensation, with the elimination of alcohol, was observed. The products were 1-hydroxy-2-methyl-4-piperidinomethylbenzene, 1-hydroxy-3-methyl-4-piperidinomethylbenzene and 1-hydroxy-4-methyl-6-piperidinomethylbenzene.

(3) When piperidinomethyl ethyl ether acts on α- and β-naphthylamine the amino group is not attacked. The products obtained were 1-amino-4-piperidinomethylnaphthalene and 1-piperidinomethyl-2-aminonaphthalene respectively.

(4) With aniline, benzamide and phthalimide the amino ether reacts only with the hydrogen attached to nitrogen.

ON THE INFLUENCE OF SOLVENTS ON THE STEREOCHEMICAL COURSE OF ADDITION OF HYDROGEN BROMIDE TO MONOBASIC ACETYLENIC ACIDS AND THE RELATION OF SOLVENT EFFECT TO CHEMICAL STRUCTURE

ARTHUR MICHAEL (EXPERIMENTAL PART WITH G. H. SHADINGER)

Received January 5, 1939

About fifty years ago, Michael and co-workers[1] showed that the two bromocinnamic acids, obtained by the action of alkali upon cinnamic acid dibromide[2], were not the isomeric, α- and β-bromocinnamic acids, as was then accepted, but stereomeric α-bromocinnamic acids and that phenylpropiolic and hydrobromic acids gave two stereomeric β-bromocinnamic acids. Corresponding results were obtained from crotonic acid dibromide and tetrolic acid[3]. The formation of β-bromoderivatives in the additions agreed with, and were explained by, the positive-negative addition rule[4], but observations, which did not concord, were later made by Sudborough and Thompson[5], in a study of the addition of hydrogen bromide to phenylpropiolic acid in non-aqueous solvents. Light, temperature and concentration of aqueous hydrogen bromide were practically without effect upon the course of addition. However, in acetic acid solution the relative proportion of β-bromocinnamic acid (m.p. 134°) increased decidedly and, with benzene, chloroform, and carbon disulfide as solvents, the main product was the *trans* α-bromo acid (m.p. 120°).

The formation of the α-bromo acid was directly opposed to the positive-negative addition rule[4], which hitherto had been applicable to the addition reactions of all classes of unsaturated, organic compounds and addenda, except hypochlorous and hypobromous acids[6]. This rule was based upon

[1] MICHAEL *et al.*, *Ber.*, **18**, 1378 (1886); **19**, 887 (1887); **20**, 550 (1888); *Am. Chem. J.*, **9**, 221, 281 (1887).

[2] GLASER, *Ann.*, **143**, 330 (1867).

[3] MICHAEL AND CO-WORKERS, *Am. Chem. J.*, **2**, 12 (1879); *J. prakt. Chem.*, **35**, 257 (1887); **38**, 1 (1888); **40**, 62, 96 (1889); **46**, 266 (1892).

[4] MICHAEL, *J. prakt. Chem.*, **37**, 525 (1888); **40**, 171 (1889); **60**, 332 (1899); *J. Am. Chem. Soc.*, **32**, 1005 (1910).

[5] SUDBOROUGH AND THOMPSON, *J. Chem. Soc.*, **83**, 1152 (1903).

[6] MICHAEL, *J. prakt. Chem.*, **60**, 454 (1899); **64**, 1026 (1901); *J. Am. Chem. Soc.*, **32**, 990 (1910); MICHAEL AND LEIGHTON, *Ber.*, **39**, 2157 (1906). These acids add in dilute aqueous solution and, being strong oxidants, exert a peroxide effect upon the course

the affinity-energy relations of the respective, unsaturated atoms for the components of the addenda; the heats of formation of the possible isomers are regarded as the major factors contributing to the energy degradation in the reactions and, therefore, largely determining the course of the additions[7]. When the thermal difference is large, the addition should yield the isomer or stereomer with the larger heat of formation almost exclusively. But, when the thermal values are nearer together, both derivatives should be formed and in relative amounts proportionate to the approximation deduced from the principle of partition[7]. Under these conditions, physical energy factors, associated in determining the maximum energy degradation, should play a more important rôle in directing the mode of addition. Thus, the solvent may alter, more or less, the course of addition when the heats of solution of the formed isomers or stereomers differ materially and when their solubility relations differ decidedly. When a mixture results in an addition, the physical factors, by favoring the formation of one or the other of the possible intermolecular structures of the preliminarily-formed polymolecules[8], will function the more decisively the nearer together are the values of the involved chemical energy factors.

No theoretical explanation of the mechanism of the addition process is probable unless it can coördinate the course of addition with the chemical structures of the unsaturated compounds and successfully predict the outcome of unexamined reactions[9].

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of addition. For an explanation of partially abnormal additions to several unsaturated hydrocarbons, that proceed with intramolecular migration of tertiary hydrogen, see *Ann.*, **385**, 244-247 (1911).

[7] MICHAEL, *J. prakt. Chem.*, **60**, 348 (1899); **68**, 199 (1903); *Ber.*, **39**, 2138 (1906).

[8] MICHAEL, *Ber.*, **34**, 4029 (1901); *Am. Chem. J.*, **39**, 2 (1908).

[9] The frequently quoted Markownikoff addition rule is wholly empirical and is not even entirely valid for the two groups to which it was applied, *i.e.*, alkenes-1 and alkines-1. For other classes of unsaturated, organic compounds it usually leads to wrong conclusions, *e.g.*, with the α,β-unsaturated acids and, as a general rule for addition to double and triple linkages, it is only of historic interest. Lauer and Stodola [*J. Am. Chem. Soc.*, **56**, 1215 (1934)] found that pentene-2 adds hydrogen bromide to form a mixture of 2- and 3-bromopentane in nearly equal amounts and therefore concluded that the Wagner-Sayzeff rule [*Ann.*, **179**, 313 (1873)] is not valid. These chemists, and also Lucas and Morse [*J. Am. Chem. Soc.*, **47**, 1450 (1925)], overlooked that this subject had been theoretically and experimentally developed previously [Michael, *J. prakt. Chem.*, **60**, 348 (1899); *Ber.*, **39**, 2141, 2143, 2149 (1906)] and that the same conclusions had been reached. It is of interest that Lauer and Stodola concluded that the results conflict with the current views on electronic displacement and Kharasch's partial polarity speculations. Their criticism is supported by the experimental results obtained by the writer, which are consistently explained by the principle of partition.

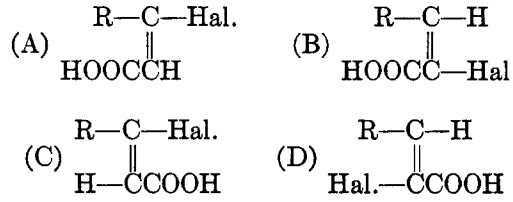
With a view to explain the abnormal results obtained in the addition of hydrogen bromide to phenylpropiolic acid in non-aqueous solutions, the reaction was re-examined. We confirmed the above observations in benzene solution and found that the *trans* α-acid was also largely formed in toluene and bromobenzene. On the other hand, with nitromethane and nitrobenzene as solvents, the *trans* β-bromo acid was formed exclusively, and the same derivative was obtained in ethyl bromide, ether, and acetone. Since the mineral acid can transform the *cis* β-derivative (159°) catalytically into the *trans* form (134°), the latter product may have resulted from a secondary change, coincident with or subsequent to, the addition. We proved that a stereomerization of the *cis* β-bromo acid (159°) did occur. In the latter solvents, hydrogen bromide readily converted the *cis* β-bromo acid into the *trans* β-modification, but, after only a short reaction period in nitromethane, the reaction yielded the *cis* β-bromo acid (type A, see formulae below) as the sole product of the addition.

The proof of the direct formation of the *trans* α-acid was more difficult, because the *cis* α-bromo acid (type B), in all the solvents leading to the formation of the α-derivative, was isomerized rapidly into the *trans* stereomer, although the ease of the conversion varied somewhat with the solvent. When hydrogen bromide was passed into a saturated solution of phenylpropiolic acid in benzene, the *trans* α-bromo acid (type D) was precipitated almost immediately; but under the same conditions, only 30 per cent. of the *cis* α-bromo acid (type B) was stereoisomerized during one-half hour. These facts make it probable that the *trans* α-bromo acid is a direct product of addition in benzene; accordingly this addition would be a *trans* process. Sudborough and Thompson[5] concluded that associating and ionizing solvents favored formation of the α- and the β-bromocinnamic acids, respectively. In our experiments with phenylpropiolic acid, however, more solvents were used, and the results show that no connection exists between the course of addition and the ionizing or associating properties of the solvents (see Table V). The above results place the abnormal formation of the α-bromo acid from hydrogen bromide and phenylpropiolic acid in certain solvents in a different theoretical aspect.

Unfortunately for the development of organic theory, a systematic study of thermal data for organic compounds and reactions has been not only largely neglected but undervalued for years. Fortunately, however, for the subject of this paper, the K values of the stereomeric α- and β-chlorocinnamic acids are known. According to Stohmann's rule, the heats of combustion of position-isomeric[10] and stereomeric acids rise and falls

[10] Stohmann, in his first two papers on this subject [*J. prakt. Chem.*, **40**, 357 (1890); **45**, 341 (1892)], showed the validity of this rule for isomeric acids, formed by replacing hydrogen, in different positions with respect to the carboxyl, by the same group of

with their K values. *Cis*-addition of halogen hydride to phenylpropiolic acid may yield β-haloisocinnamic (type A) and α-haloisocinnamic acid (type B); the *trans* process, β-halo- (type C) and α-halocinnamic acid



(type D). The K values of the β-chloro acids (A and C) differ but slightly, 28×10^{-5} and 27.2×10^{-5},[11] and those of the α-chloro acids are 107×10^{-5} and 97×10^{-5}. The K values for the corresponding bromo acids have not been determined, but there can be no doubt that the numerical relationship is approximately the same as that for the corresponding chloro acids, which is about as 1:3.5. The K values for the α- and β-chloro- and bromohydrocinnamic acids are undetermined, but they may be deduced approximately from those for the corresponding α- and β-halogen-sub-

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atoms. Such acids were called "Stellungsisomere" (position-isomers). In the following paper, Stohmann [*ibid.*, **46**, 530 (1892)] gave a resumé of his conclusions with an extension of the experimental work. In rule (1), "Isomere" instead of "Stellungsisomere" was used, although this alteration was not supported by new experimental work. It was apparently an erratum, as in the following, final paper on this subject [*ibid.*, **49**, 118 (1894)] "Stellungsisomere" was again used to designate the groups of acids in question. Unfortunately rule (1) has been discredited through misrepresentation of Stohmann's viewpoint. Verkade [*Rec. trav. chim.*, **44**, 1006 (1925)] found that the respective experimental data associated with the "stereomeric" meso- and *d*-tartaric acids do not conform with the rule. However, by no stretch of imagination can these compounds be considered as "Stellungsisomere", or as stereomeric acids. Roth and Ostling [*Ber.*, **46**, 309 (1913)] showed that the relation between the isomeric, stereomeric, and cyclic acids of the formula C_3H_5COOH and C_4H_7COOH conform to Stohmann's rule connecting the heats of combustion and K values of the respective acids, but believed that the values for the isomeric tanacetone carboxylic and pinonic acids probably do not conform. However, with these acids the comparison is between cyclopropane and cyclobutane derivatives, which contain highly energetic groups in positions exerting a slight influence upon the K values, and that the relationship between the thermal and electrolytic constants should prevail for such isomers is evidently improbable. The same misconstruction of rule (1) generally occurs in the literature, *e.g.*, Hückel, "Theoretische Grundlagen der orgianischen Chemie, II, p. 298 (1931), but no experimental results are known discrediting Stohmann's rule in its original form. Between the α- and β-carboxylic derivatives of acids considerable differences in the heats of combustion and, also, in the K values occur and the first relation has been accepted in this paper for the corresponding chloro and bromo derivatives.

[11] MULLIKEN, Dissertation, **1890**. Beilstein, IX, 595 (1926).

stituted, aliphatic acids, *i.e.*, about as 1:16–17. Accordingly, solvents may affect the mode of addition of hydrogen bromide to phenylpropiolic acid, but should not with cinnamic acid. Actually, with the first acid, in aqueous and nitromethane solution, β-bromoisocinnamic and in benzene solution the corresponding α-acid was formed, while with cinnamic acid no solvent was found that changed the mode of addition, *i.e.*, β-bromohydrocinnamic acid was formed under all tested conditions.

The stereomeric course of addition of hydrogen bromide to tetrolic acid differs from that to phenylpropiolic acid. In aqueous solution, the latter acid yielded β-bromoisocinnamic acid (type A), while tetrolic acid gave β-bromocrotonic acid (type C), and the same acid appeared in nitromethane. On the other hand, in benzene and propyl bromide solutions, the α-bromocrotonic acid (m.p. 104°; type D) was formed. The K values for β-chloroisocrotonic (type A), and for the *trans* α-acid (type D), 14.4×10^{-5} and 72×10^{-5} respectively, are in the ratio of 1:4.9, and, on the basis that these relations, hold approximately for the corresponding bromo derivatives, it is evident that the course of addition of hydrogen bromide to tetrolic acid may be subject to solvent effect. In accordance, it was found that the course of addition of hydrogen bromide to tetrolic acid varied with the solvent used, but the addition to crotonic acid, concordant with the comparatively large difference in the K values (ratio of 1:16–17) for the respective, possible addition isomers, showed no solvent susceptibility; *i.e.*, the reaction gave only β-bromobutyric acid[12]. Experiments on the behavior of *cis* α- and *trans* β-bromocrotonic acids towards hydrogen bromide in nitromethane solution confirmed the conclusion, which had been drawn previously from other results, *viz.*, that the *cis* bromocrotonic derivative (type A) is much more stable towards the mineral acid than the corresponding *cis* bromocinnamic derivative. Accordingly, no change was noticed with the *cis* β-, and only a partial conversion with the α-bromocrotonic acid. The above results make the conclusion probable that in additions of halogen hydride to structurally, closely related groups of unsaturated compounds, the smaller the difference in the heats of combustion of the addition products, and with acids the smaller the divergence in the K values, the greater may be the solvent effect[13].

[12] MICHAEL, *J. prakt. Chem.*, **52**, 289 (1895). See Table III.

[13] The mechanism of "oxygen and peroxide effect" upon hydrogen bromide addition is analogous to that of solvent and that it has the corresponding relation to the structures of the unsaturated, organic compounds is evident from the existing experimental data. Contrary to the conclusion of Kharasch [J. ORG. CHEM., **2**, 289 (1937)] "peroxide effect" in alkenes does not depend upon the existence of terminal unsaturation. With N. Weiner, the previous observation [Michael and Zeidler,

EXPERIMENTAL

By Arthur Michael and G. H. Shadinger

General procedure.—Hydrogen bromide, prepared from C.P. bromine, red phosphorus and water, was passed through a long U-tube filled with red phosphorus, and dried by passing successively through tubes filled with calcium bromide and phosphoric anhydride. The dried gas was absorbed in solutions, or suspensions, of the unsaturated organic acids listed in the tables. Solid products were collected by filtration and purified by recrystallization, or the bromo acids were isolated as barium salts. These salts are not completely insoluble, and the aqueous filtrates, after acidification, yielded acidic products which were purified as indicated in the footnotes to the tables summarizing the results. In the early experiments, the bromo acids were dissolved in 40 parts of water and neutralized with a 10% barium hydroxide solution, but the salts separated incompletely at this dilution[14] and, in

TABLE I

Rates of Hydrogen Bromide Elimination

	CINNAMIC ACIDS				TIME, HRS.
	α-Bromoallo- m.p. 120°	α-Bromo- m.p. 130°	β-Bromoallo- m.p. 159°	β-Bromo- m.p. 134°	
% Available Br Eliminated	0		12	100	2
	0	11.0	60		20
	0	37.0	93		46
	0	79.0	100		118

the later work, the bromo acids were dissolved in only 20 parts of water. For identification, the bromo acids, obtained from the precipitated barium salts and from the aqueous filtrates, were treated in the cold with alkali of known concentration, and the

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Ann., **385**, 271 (1911)] of a solvent effect with isoamylene-2 has been confirmed and it has been shown that the hydrocarbon is sensitive to "peroxide effect." The extent of the latter influence depends upon the solvent and with methanol *increases with fall of temperature.* It seems probable, therefore, that "oxygen and peroxide effects" function through the formation of a double molecule ("polymolecule") in which contact between oxygen and unsaturated carbon linkage occurs more largely at the more positive of the atoms. When the difference between the positivities of the unsaturated carbons is comparatively slight, the previously relatively positive of the unsaturated carbons may become the relatively negative and thus lead to abnormal additivity. Solvent effect may be attributed to an analogous mechanism.

Corresponding influences undoubtedly occur in other chemical processes. An interesting illustration was noticed by Roth and Stoermer [*Ber.*, **46**, 276 (1913)] who examined the velocity of stereomerisation of cinnamic and cumarinic acids and derivatives in ultraviolet light. They found that the smaller the difference in the *K* values of the stereomeric pair of acids, the larger was the amount of acid stereoisomerised. In other words, the percentage change decreased with the increase in work required to effect the isomerisation.

[14] Michael and Browne, *Ber.*, **20**, 554 (1887).

TABLE II

ADDITION OF HYDROGEN BROMIDE TO PHENYLPROPIOLIC ACID

EXPT. NO.	PHENYLPROPIOLIC ACID, G.	SOLVENT, G.	ABSORPTION		TIME OF REACTION, HRS.	PRODUCT				
			Time, mins.	Temp., °C.		Crude		Acid	g.	M.p., °C.
						g.	m.p., °C.			
I[a]	5.0	Benzene, 30	50	R.T.	15	2.5	128–129	α-Bromo-	2.5	128–129
II[b]	0.1	Toluene, 1		R.T.				α-Bromo-		128–129
III[c]	1.0	Bromobenzene, 30	20	0				α-Bromo-	0.73	128.5–129.5
IV[d]	0.15	Acetone,		−20				β-Bromo-		134–135
V[e]	0.15	Ethylbromide,		R.T.				β-Bromo-		132–133
VI[f]	1.0	Ether, 5	45	−20	2	1.44	113–116	β-Bromo-		134–136
VII[g]	0.5	Nitromethane, 15		R.T.	12	0.37	126–140	β-Bromo-		133
VIII[h]	1.0	Nitrobenzene, 30		0	24			β-Bromo-	0.9	133–135

[a] Solvent was evaporated from the benzene filtrate, and the residue, purified through the barium salt; yield, 1.9 g. of α-bromo acid, m.p. 127–128°. The aqueous filtrate, from which the barium salt had separated, was concentrated, and yielded 0.4 g. of acid, which, after recrystallization from benzene, melted at 123–133°. Elimination of hydrogen bromide from the bromo acid was complete after treatment with alkali for 2 hours; the bromo acid, therefore, was β-bromocinnamic acid (m.p. 134°) and it constituted 10% of the addition product.

[b] Hydrogen bromide was absorbed until all the organic acid dissolved.

[c] No solid separated from the bromobenzene solutions during 24 hours at 0°. Solvent was distilled off with steam, and the residue was converted to the barium salt; acidification of this salt liberated α-bromocinnamic acid. A solution of the bromo acid in 2% alkali was acidified after 1.5 hours; the precipitate, after conversion to the barium salt, and recrystallization of the free acid, melted at 129.5–130.5°.

In a similar experiment, the solvent was distilled off with steam, and the dried residue (0.8 g.; m.p. 119–124°) was converted into the barium salt, which, on acidification, yielded 0.6 g. of α-bromo acid, m.p. 131–132°. The filtrate from the barium salt was acidified, and yielded 0.2 g. of α-bromo acid, m.p. 119–124°. The aqueous filtrate from the original crude addition product yielded 0.52 g. of acid, which, after purification through the barium salt, gave 0.1 g. of α-bromo acid, m.p. 131–132°.

[d] The hydrogen bromide was absorbed at the temperature of an ice-salt mixture. Solvent was distilled off *in vacuo*, and the residue was purified through the barium salt. The filtrate from the salt was acidified, and gave a small amount of acid, m.p. 117–122°.

[e] Solvent was distilled off *in vacuo*; the residue, m.p. 126–128°, was purified through the barium salt, and yielded the β-bromo acid.

[f] Absorption was made at the temperature of a salt-ice mixture. The crude product was purified through the barium salt; the aqueous filtrate was acidified, and yielded 0.7 g. of acid, m.p. 123–130°.

[g] Absorption of hydrogen bromide was stopped when solid began to separate from the reaction mixture; the crude product was purified through the barium salt. In a second experiment, 1 g. of phenylpropiolic acid was used; the crude addition product, after purification through the barium salt, yielded 0.8 g. of acid, m.p. 117–131°, which,

TABLE II—*Continued*

repurified through the barium salt, gave pure β-bromocinnamic acid, m.p. 134–135°. The aqueous filtrate was acidified, and yielded 0.1 g. of acid, m.p. 118–150°, which, after recrystallization from alcohol, gave pure β-bromoallocinnamic acid, m.p. 158.5–159.5°. In a third experiment, absorption of hydrogen bromide was stopped after 10 minutes; the solid which had separated from the solution during 1 hour was filtered off, washed with water and ligroïn, and then gave 0.15 g. of pure β-bromoallocinnamic acid, m.p. 156–157°.

[h] No solid separated from the nitrobenzene solution during 24 hours at 0°. Solvent was distilled off with steam, the organic residue, since it gave no insoluble barium salt, was recrystallized from alcohol and then yielded β-bromocinnamic acid, which readily gave an insoluble barium salt, and from which 0.9 g. of the β-bromo acid was recovered. Halogen was completely removed from the bromo acid by alkali during 2 hours.

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amount of liberated hydrogen bromide was determined by titration. This method is applicable because the rate of elimination of hydrogen bromide from the fumaroid is much greater than from the maleinoid product[15]. The relative rates of elimination were determined by dissolving 1 g. each of the bromo acids in 31.75 cc. of 1.25% NaOH (3 moles) solution, prepared from metallic sodium; at intervals aliquot portions (6 cc.) of the solutions were titrated by the Volhard method. Typical results are given in Table I.

Addition of hydrogen bromide to phenylpropiolic acid.—The acid was dissolved in carbon tetrachloride, and the hot solution filtered to remove insoluble cinnamic acid. Solvents were dried over phosphoric anhydride. The results of the additions are summarized in Table II.

Addition of hydrogen chloride to phenylpropiolic acid.—A solution of phenylpropiolic acid in chloroform, saturated with hydrogen chloride, yielded, after 6 weeks, only a very small amount of addition product (calc'd for $C_9H_7O_2Cl$: Cl, 19.45; found: Cl, 1.89) and, during 3 days at 60°, only a trace of the halogen acid was formed. Similar results were obtained in toluene and ether: at room temperature only very little of the addition product was formed and, in toluene, after heating for 3 days at 60°, the product contained only 2.5% Cl.

Addition of hydrogen bromide to cinnamic, tetrolic, and crotonic acids.—The solutions, or suspensions, of the unsaturated acids were saturated with hydrogen bromide at 0°, and the reaction mixtures were heated in sealed tubes; when addition was very slow at room temperature. Solid addition products were separated by filtration, solvents were distilled off *in vacuo* from the filtrates, and the residual products were purified as indicated in the tables and footnotes. The results are summarized in Table III.

No relation exists between the course of addition of hydrogen bromide to phenylpropiolic acid and the dielectric and dissociation constants of the solvents (Table V).

SUMMARY

1. Aqueous hydrogen bromide unites with phenylpropiolic acid by *cis*-addition to yield β-bromoisocinnamic acid.

2. The course of addition of hydrogen bromide to phenylpropiolic acid

[15] MICHAEL AND WHITEHORNE, *Ber.*, **34**, 3647 (1901).

TABLE III

ADDITION OF HYDROGEN BROMIDE TO CINNAMIC, TETROLIC, AND CROTONIC ACIDS

EXPT. NO.	UNSATURATED ACID, G.	SOLVENT	TEMP.	TIME	BROMO ACID		
					Crude	Fractions, g.	M.p., °C.
I	Cinnamic, 3	Benzene	60°	2 days	β-Bromohydrocinnamic	1	137
II[a]	Cinnamic, 3	Toluene	60°	7 hrs.	β-Bromohydrocinnamic	1, 1.5	135–136
III[b]	Cinnamic, 10	Water	R.T.	2 days	β-Bromohydrocinnamic	1, 8.18	138
IV[c]	Cinnamic, 0.2	Bromobenzene	R.T.	5 days	β-Bromohydrocinnamic	1, 0.14	133–134
V	Tetrolic, 0.5	Benzene	R.T.	5 mins.	α-Bromocrotonic	1, 2, 3, } 0.94	105.5 104–105 102–105
VI[d]	Tetrolic, 0.2	Propyl bromide	R.T.	12–15 hrs.	α-Bromocrotonic	1 2 3	105–106 102–103 87–93
VII	Tetrolic, 0.3	Water	R.T.	2 days	β-Bromocrotonic		93–94
VIII[e]	Tetrolic, 0.5	Nitromethane	R.T.		β-Bromocrotonic	1 2 3 4	86–89 92–92.5 85–86 67–75
IX[f]	Crotonic, 5.0	Benzene	R.T.	1 week	β-Bromobutyric	9.5	B.p., 117° at 12 mm.
X	Crotonic, 5.0	Water	R.T.	4 days	β-Bromobutyric		B.p., 117° at 12 mm.

[a] The crude addition product contained 99.3% of the amount of bromine corresponding to complete conversion of the cinnamic to the bromohydrocinnamic acid (calc'd for $C_9H_9O_2Br$: Br, 34.93; found: Br, 34.6). The bromo acid was recrystallized from benzene and carbon disulfide.

[b] The crude product (10.1 g.; m.p. 135–136°) was crystallized from carbon disulfide.

[c] The bromobenzene solution was saturated with hydrogen bromide at −15°.

[d] During 12–15 hours, a small amount of bromo acid, m.p. 103–105°, separated from the solution. Solvent was distilled *in vacuo* from the filtrate, and the residue, fractionally crystallized, gave fractions 1–3; fraction 3 contained only a very small amount of the bromo acid.

[e] Relatively pure β-bromocrotonic acid, m.p. 86–89°, separated from the reaction mixture. The filtrate yielded a crude product, m.p. 80–83°, which, on fractional recrystallization, gave fractions 2–4.

[f] With dilute alkali, the β-bromobutyric acid liberated HBr much more readily than the α-halogen acid and the isomers were thus distinguished. Typical determinations of the relative rates of elimination of HBr are given in Table IV.

in non-aqueous solvents may vary with the solvent. In benzene, bromobenzene, and toluene, α-bromocinnamic acid was formed, whilst in nitromethane, nitrobenzene, ether, and acetone, the *trans* β-derivative appears exclusively. However, in nitromethane, the *cis* β-acid is the primary

TABLE IV

ELIMINATION OF HYDROGEN BROMIDE FROM α- AND β-BROMOBUTYRIC ACIDS

	BUTYRIC ACID		TIME, HRS.
	α-Bromo-	β-Bromo-	
% Available Br Eliminated	5.84	81.83	4
	11.70	98.16	27
	16.80	100.00	72

TABLE V

SOME PHYSICAL CONSTANTS OF PRODUCTS OF ADDITION OF HYDROGEN BROMIDE TO PHENYLPROPIOLIC ACID

PHENYLPROPIOLIC ACID GAVE		DIELECTRIC CONSTANT AT[a], °C.		DISSOCIATION FACTOR[b]	ASSOCIATION FACTOR[c]
Bromo acid	Solvent				
α-Bromocinnamic	Benzene	2.26	19	Weak (*1*)	1.18
α-Bromocinnamic	Toluene	2.31	19	Weak (*2*)	1.08
α-Bromocinnamic	Bromobenzene	5.2	18	Weak (*3*)	
β-Bromocinnamic	Acetone	20.2	17	74 (*4*)	1.53
β-Bromocinnamic	Ethylbromide	9.5	20	Strong (*5*)	1.28
β-Bromocinnamic	Ether	4.37	18	Weak (*6*)	1.00
β-Bromocinnamic	Nitromethane	38.2	20	92 (*7*)	
β-Bromocinnamic	Nitroethane	29.5	18		
β-Bromocinnamic	Nitrobenzene	36.45	18	88 (*8*)	1.82

[a] The dielectric constants are taken from the *International Critical Tables.*

[b] The dissociation factors were reported by:

(*1*) BECKMANN AND LOCKEMANN, *Z. physikal. Chem.*, **60**, 398 (1907).

(*2*) KAHLENBERG AND LINCOLN, *J. Phys. Chem.*, **3**, 19 (1899).

(*3*) WALDEN, *Z. physikal. Chem.*, **54**, 129 (1905). These values were obtained with triethylammonium iodide as electrolyte at a concentration of 1/1000.

(*4*) TIMMERMANN, *Bull. soc. chim. Belg.*, **20**, 305 (1906); *Chem. Zentr.*, **78**, I, 1006.

(*5*) KABLUKOFF, *Z. physikal. Chem.*, **4**, 430 (1889).

[c] The values for the association factor are those reported by TRAUBE, *Ber.*, **30**, 273 (1897).

product, but it is quickly converted by the bromide into the *trans* β-derivative. This stereomeric rearrangement occurs in all solvents of the latter group.

3. Similar solvent relations have been found in the addition of hydrogen bromide to tetrolic acid in water and in non-aqueous solvents. However,

the catalytic transformation of the bromoisocrotonic acids proceeds much less readily than that of the corresponding bromocinnamic acids and the products isolated under the experimental conditions are mainly the primarily-formed bromo acids.

4. The difference between the degradation of energy in the formation of α- and β-halogen derivatives of saturated acids is very considerable. Accordingly, the addition of hydrogen bromide to cinnamic and crotonic acids yielded, respectively, β-bromohydrocinnamic and β-bromobutyric acids, irrespective of the nature of the solvent.

5. From these results, it is concluded that solvents exert an influence upon the course of addition of hydrogen bromide to α,β-unsaturated acids only when the involved physical energy factors are strong enough to depress the degradation of chemical energy sufficiently to favor formation of abnormal addition products, *i.e.*, those opposed to the course indicated by the positive-negative addition rule. The partial or complete reversal in the mode of addition, caused by solvent effect, occurs only when the difference between the degradation of energy in the two possible directions of addition is relatively small. The above relation of solvent effect to structure is believed to prevail in all energetically analogous reactions.

5. No direct relationship existed between the examined solvent effect and the associating, dissociating, or dielectric constants of the solvents.

6. Markownikoff's wholly empirical addition rule is valid solely in the alkene-1 and alkine-1 series and then only when the addition does not proceed with migration of hydrogen or methyl. Applied to other classes of organic compounds with unsaturated carbon linkages, it generally leads to conclusions opposed to those obtained by experiment. As a general rule, it is now a hindrance to the development and recognition of a rational addition theory.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

THE REDUCTION OF α-KETOL ESTERS

L. S. BIRNBAUM AND G. POWELL

January 16, 1939

In the course of work on adrenaline, the authors had occasion to note the claim by Voswinckel[1] that α, 3, 4-triacetoxyacetophenone could be reduced to α, 3, 4-triacetoxyethylbenzene by means of zinc dust and acetic acid. The general course of the reduction of ketones of the type —$COCH_2X$, where X is a negative group, by reagents of the type quoted appears to be, from examination of the literature, to the group —$COCH_3$ or —CH_2CH_3 and not to the group —CH_2CH_2X[2-12]. If the work of Voswinckel could be established we would be in possession not only of a compound required in our research, but also of a method of conversion of the halogenated compounds —$COCH_2X$ to the alcohols —CH_2CH_2OH and thus a synthesis of such substances as the valuable β-phenethyl alcohols and amines from the easily accessible phenacyl halides.

No account was found in the literature of any repetition of the reduction of α,3,4-triacetoxyacetophenone and accordingly it was attempted in these laboratories. We were unable to isolate the compound claimed by Voswinckel. The major product of the reaction appears to be not α,3,4-triacetoxyethylbenzene but 3,4-diacetoxyacetophenone. Analogously the reduction of α-acetoxyacetophenone under approximately the same conditions led to acetophenone and not phenethyl alcohol.

Voswinckel reported a decomposition of the so-called α,3,4-triacetoxyethylbenzene at 130° into acetaldehyde and 3,4-diacetoxyphenylacetaldehyde. The latter was described as melting one degree lower than the isomeric 3,4-diacetoxyacetophenone isolated by us.

[1] VOSWINCKEL, *Ber.*, **42**, 4651 (1909).
[2] LINNEMAN, *Ann.*, **134**, 171, (1865).
[3] KLING, *Bull. soc. chim.*, [3], **35**, 211, 215 (1906).
[4] FAVORSKII, *J. prakt. Chem.*, [2], **51**, 536 (1895).
[5] KLING, *Ann. Chim.* [8], **5**, 506 (1905).
[6] FITTIG AND ERLENBACH, *Ann.*, **269**, 27 (1892).
[7] GARDEUR, *Chem. Zentr.*, **1897**, II, 661.
[8] IRVINE AND WEIR, *J. Chem. Soc.*, **91**, 1388 (1907).
[9] DZIERGOWSKI, *Ber.*, **26**, Ref. 589 (1893).
[10] V. AUWERS AND POHL, *Ann.*, **405**, 264 (1914).
[11] JOHNSON AND HODGE, *J. Am. Chem. Soc.*, **35**, 1023 (1913).
[12] HORII, *J. Pharm. Soc. Japan*, **53**, 1239 (1933).

EXPERIMENTAL

Chloracetyl catechol was prepared by the method of Dziergowski[9].

α,3,4-Triacetoxyacetophenone.—This compound was prepared according to Voswinckel's directions; m.p. 95°.

Anal. Calc'd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.76.
Found: C, 57.22; H, 4.79.

Reduction of α,3,4-triacetoxyacetophenone.—The procedure of Voswinckel was followed and the temperature kept at 90°. After the first solidification of the product it was recrystallized three times from water; m.p., 84–85°; yield, 8 g. Voswinckel reported m.p., 85°.

Anal. Calc'd for $C_{14}H_{16}O_6$, α,3,4-triacetoxyethylbenzene: C, 59.98; H, 5.67.
Calc'd for $C_{12}H_{12}O_5$, 3,4-diacetoxyacetophenone: C, 61.01; H, 5.12.
Found: C, 61.20; H, 5.47.

This analysis suggested 3,4-diacetoxyacetophenone. The preparation was repeated at 40°, and anhydrous solvents were used for purification. Two recrystallizations from absolute alcohol gave white crystals, m.p. 87°.

Anal. Calc'd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12.
Found: C, 60.90; H, 5.22.

Semicarbazone of the reduction product.—A semicarbazone was formed in the usual manner from the reduction product of α,3,4-triacetoxyacetophenone. The white, crystalline semicarbazone was insoluble in cold water or alcohol. It was recrystallized from alcohol, m.p. 212–213°.

Anal. Calc'd for $C_{14}H_{17}N_3O_5$: C, 53.22; H, 5.16; N, 14.32.
Found: C, 53.00; H, 5.25; N, 14.23.

Hydrolysis of the reduction product.—The reduction product was treated with a concentrated solution of sodium carbonate. The reaction was completed by warming for several minutes until the solution became yellow. After acidification it was extracted with ether, and the ether was evaporated. The amorphous residue was vacuum-sublimed and recrystallized from xylene; m.p. 114–115°. The same compound was obtained by refluxing with five per cent. sulfuric acid for fifteen minutes.

Anal. Calc'd for $C_8H_8O_3$: C, 63.16; H, 5.30.
Found: C, 63.46; H, 5.52.

Acetocatechol was prepared by the method of Stephen and Weizman[13], by reduction of chloracetocatechol. The product was purified by vacuum sublimation as by Mosettig and Burger[14]. This was melted with the hydrolysis product of the preceding experiment; mixture m.p., 117°.

3,4-diacetoxyacetophenone.—Acetocatechol was acetylated by adding acetic anhydride to an iced solution of its potassium salt. The diacetate was recrystallized from alcohol; m.p. 86°. This was melted with the second reduction product of α,3,4-triacetoxyacetophenone; mixture m.p., 86°.

3,4,-Diacetoxyacetophenone semicarbazone.—This semicarbazone was prepared in the usual manner from the product of the preceding experiment. It was recrystallized from alcohol; m.p., 212°.

Anal. Calc'd for $C_{14}H_{17}N_3O_5$: C, 53.22; H, 5.16.
Found: C, 52.23; H, 5.15.*

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[13] STEPHEN AND WEIZMAN, *J. Chem. Soc.*, **105**, 1051 (1914).

[14] MOSETTIG AND BURGER, *J. Am. Chem. Soc.*, **52**, 2988 (1930).

* We wish to thank Mr. Saul Gottlieb for the microanalyses.

This was melted with the semicarbazone of the reduction product of α,3,4-triacetoxyacetophenone: mixture m.p., 213°.

Reduction of α-acetoxyacetophenone.—Six grams of α-acetoxyacetophenone was dissolved in 100 cc. of glacial acetic acid; 10 g. of zinc dust was added in the course of four hours to the mechanically stirred mixture at 40°. The mixture was then filtered, and the diluted filtrate was extracted with ether; yield 80% of the theoretical.

Acetophenone semicarbazone.—One gram of the product from the preceding experiment was converted in 95% yield to acetophenone semicarbazone; m.p. 201°.

SUMMARY

The reported preparation by Voswinckel of α,3,4-triacetoxyethylbenzene from α,3,4-triacetoxyacetophenone could not be duplicated. The so-called 3,4-diacetoxyphenylacetaldehyde was not obtained, but only the isomeric 3,4-diacetoxyacetophenone. The reduction of α-acetoxyacetophenone similarly yields acetophenone, and not β-phenethyl alcohol or an ester thereof.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TORONTO]

THE ACTION OF BROMOCYANOGEN ON FURAN

ALLEN H. KLOPP AND GEORGE F. WRIGHT

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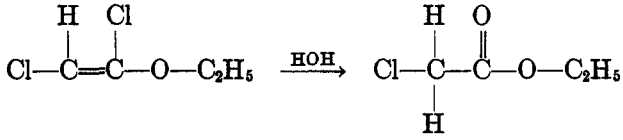
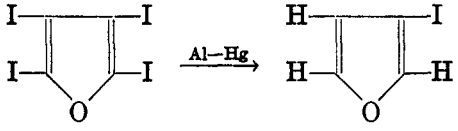
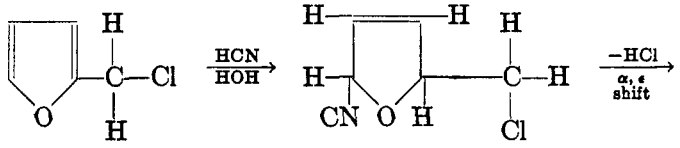
It is evident from inspection of the commonly accepted furan formula that the reactions of this substance should resemble analogous transformations of divinyl ether and of butadiene. The similarities are more than purely formal; thus, the halogen substituent in β-halovinyl ethers is much less reactive than that in α-halovinyl ethers.



The exact replica of this reaction has not been demonstrated with furans, but a multitude of reactions indicate that the β-substituted furan is always less reactive than the corresponding α-isomer. As one of a number of examples,[1] may be cited the preparation of β-iodofuran by reduction of tetraiodofuran.

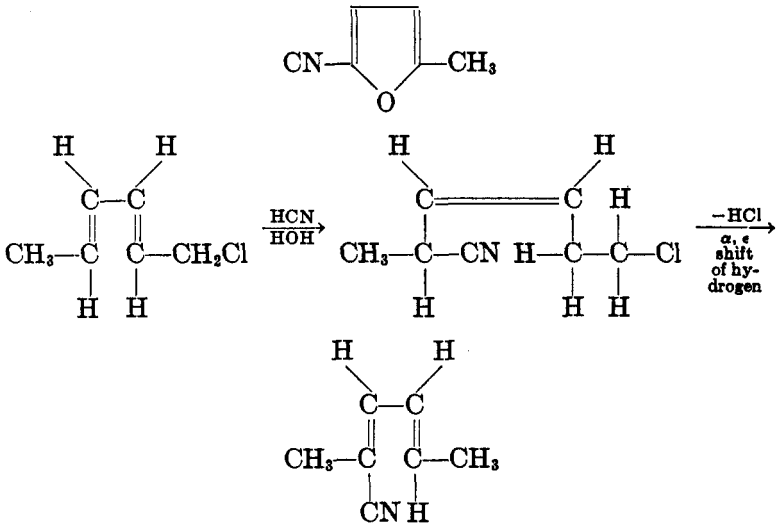


The resemblance between furan and butadiene is no less marked. Reichstein[2] has demonstrated that the conversion of furfuryl chloride into 5-methyl-2-furonitrile has its replica in the formation of 2-cyanohexadiene-2,4 (or 2-cyanohexadiene-3,5) from sorbyl chloride. The 1,4 addition characteristic of the conjugated unsaturation satisfactorily explains both systems. This may be formulated as shown here.



[1](a) HILL AND SANGER, *Proc. Amer. Acad.*, **21**, 135 (1885). (b) GILMAN AND WRIGHT, *Rec. trav. chim.*, **53**, 13 (1934). (c) GILMAN AND BURTNER, *J. Am. Chem. Soc.*, **55**, 2903 (1933). (d) SHEPARD, WINSLOW, AND JOHNSON, *ibid.*, **52**, 2083 (1930).

[2](a) REICHSTEIN, *Ber.*, **63**, 749 (1930); *Helv. Chim. Acta*, **15**, 254 (1932). (b) SCOTT AND JOHNSON, *J. Am. Chem. Soc.*, **54**, 2549 (1932).



These analogies must, however, be modified in respect to furan because of its cyclic structure. According to a certain interpretation, the rigidity conferred upon cyclic unsaturated structures causes the substitution reaction to predominate over addition. In the extreme case of structural rigidity (benzene) such a system is unable to dissipate the energy of the activated complex by any means other than reversion to the original reactants or decomposition into the products expected for the substitution reaction.

$$AB + CD \rightleftarrows \begin{bmatrix} AB \\ CD \end{bmatrix} \rightleftarrows AC + BD$$

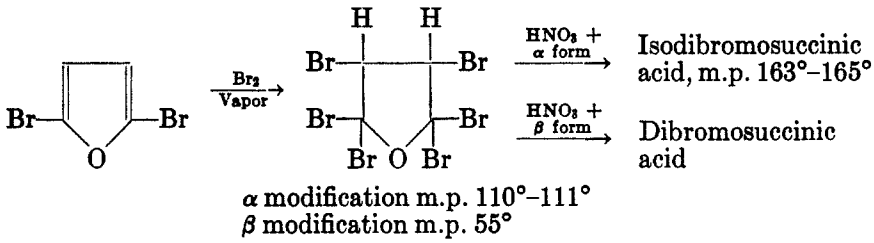
It has long been known that furan compounds are less prone to absolute substitution reactions than are the corresponding benzene analogues, since frequently the intermediate furan addition compound may be isolated, and this has led Johnson[3] to suggest that furans occupy a classification intermediate between benzene and unsaturated aliphatic compounds. Actually it is doubtful[4] that any other ring system is so aromatic as the benzene nucleus, since only in benzene is the ultimate in structural rigidity realized. All other cyclic unsaturated systems show tendencies toward addition-complex formation prior to, or concomitant with, substitution. It so

[3](*a*) HUGHES AND JOHNSON, *J. Am. Chem. Soc.*, **53**, 737 (1931). (*b*) STEVENSON AND JOHNSON, *ibid.*, **59**, 2525 (1937).

[4](*a*) GILMAN AND WRIGHT, *ibid.*, **52**, 3349, (1930). (*b*) GILMAN, "Organic Chemistry," John Wiley & Sons, New York, N. Y., 1938, p. 52.

happens that the divinyl ether- and butadiene-like characteristics of furan are modified to such a degree by the cyclic structure that the substitution or addition reaction can be effected at will, depending on the conditions of the reaction and the substituent groups already attached to the furan nucleus.

It has been shown[5] with at least one furan-bromine addition product that the addendum actually saturates the double bonds of the furan ring since diastereomeric forms of the addend were isolated. It is reasonable, therefore, to assume that all addition compounds of furans are substances



α modification m.p. 110°–111°
β modification m.p. 55°

with normal chemical bonds, and interest naturally turns to the question whether this addition is characteristic of the divinyl ether or the butadiene nature of furan; that is, whether addition is predominantly 1,2 or 1,4. Although 1,4 addition of halogen to a furan was postulated many years before Thiele's exposition of this phenomenon[6], proof of such addition has never been substantiated in a reaction which subsequently leads to the substitution product of a furan.

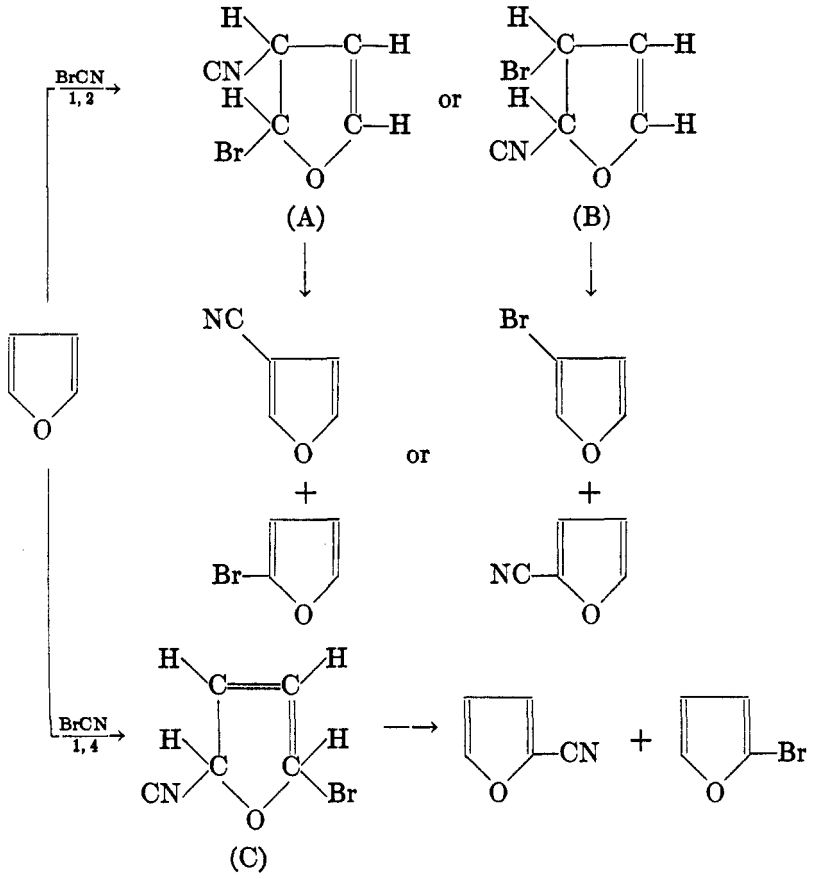
There seems to be no experimental evidence to support an alternative mechanism of substitution involving dissociation of the addition product into its constituents followed by so-called direct substitution. The position of the substituent, therefore, marks the point of attachment of one part of the addendum. This being true, the addition of an unsymmetrical addend like cyanogen bromide should indicate by examination of the pair of substitution products, whether addition occurred in the 1,2 or 1,4 position.

We treated furan with bromocyanogen, following Steinkopf's[7] directions for the similar reaction with thiophene, and obtained 2-furonitrile and 2-bromofuran. The former was identified as 2-furoic acid and the latter as 2-bromofurylmercuric chloride. These results indicate that bromocyanogen adds exclusively 1,4 to furan. We found, however, that furan, unlike

[5](*a*) HILL AND HARTSHORN, *Ber.*, **18**, 448 (1885); see also (*b*) TÖNNIES, *ibid.*, **11**, 1085 (1878).

[6]HILL AND CORNELISON, *Am. Chem. J.*, **16**, 20 (1894).

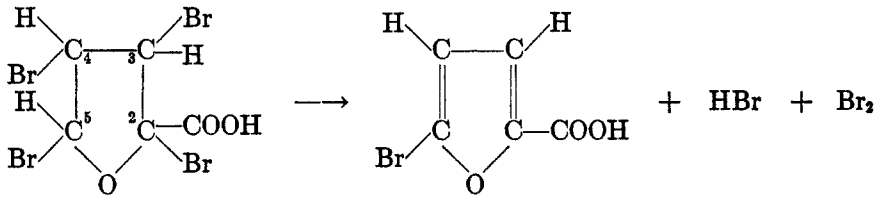
[7]STEINKOPF, *Ann.*, **430**, 78 (1922).



thiophene, gives distressingly low yields (4–5%), the greater part of the furan being destroyed as a green, dense, tarry solid. This is not surprising in view of the unusual sensitivity of furan towards mineral acids. In order to increase the yield we varied solvent and temperature, and used neutralizing agents such as calcium carbonate, but were unsuccessful until dioxane at room temperature was employed as the solvent. Using this medium it was found that yields of 2-bromofuran and 2,5-dibromofuran of 49 per cent. and 5 per cent., respectively, were obtained, but *no trace* of furoic acid could be detected.

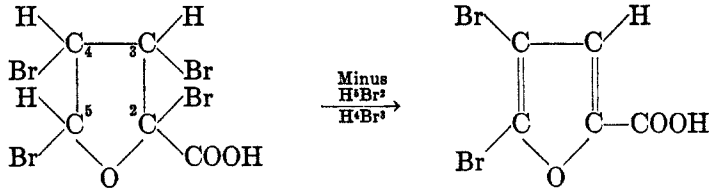
This behavior is subject to several interpretations. Firstly, the addition compound C may decompose in dioxane to give hydrogen cyanide exclusively. Secondly, the dioxane environment may encourage 1,2 rather than 1,4 addition, the addition compound A subsequently losing hydrogen cyanide preferentially. In support of the latter mechanism may be

mentioned the formation of 2,5-dibromofuran in measurable amount in dioxane medium but not in absence of this solvent. Furthermore, the specific HX elimination required for the second mechanism (namely, H from the α carbon and X from the β carbon) is not an unprecedented phenomenon. When 2,3,4,5-tetrabromotetrahydrofuroic acid is decomposed thermally only 5-bromofuroic acid and neither of the β-bromofuroic acids can be isolated as a recognizable product[8].



Further evidence relating to the two mechanisms would depend on isolation of the furan-bromocyanogen addition product. The addend with furan was too unstable to be isolated and a more stable compound like furoic acid, to which bromine can be added with ease, will not add bromocyanogen.

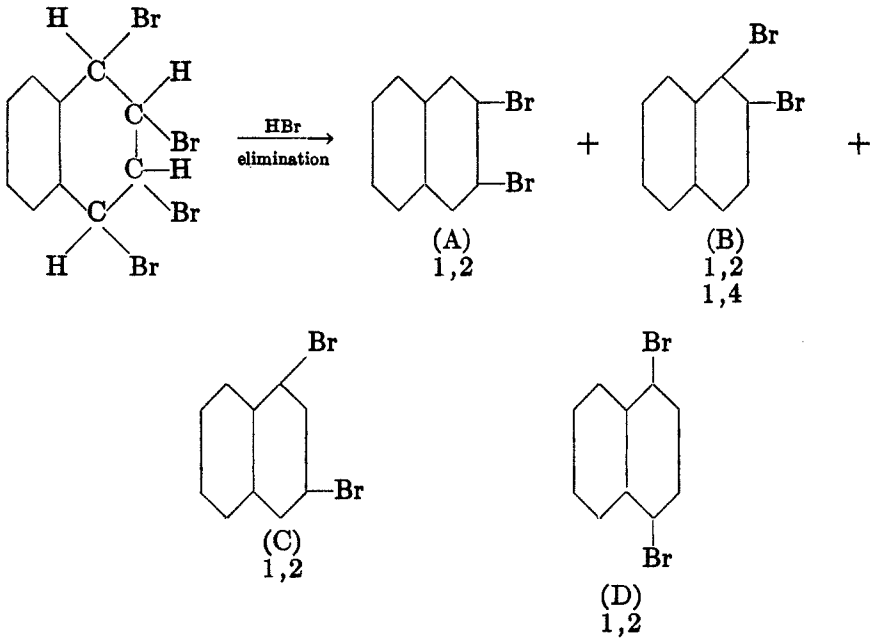
It is unfortunate that the furan-bromocyanogen addend C cannot be isolated, because the existence of the addition compound as an intermediate in the substitution reaction would confirm the possibility of 1,4-elimination of HX. The existence of this latter mode of elimination is a corollary of the work of Gilman and co-workers[9] which demonstrated that the so-called β,δ-dibromofuroic acid of Hill and Sanger[10] was actually 4,5-dibromofuroic acid. The latter could be formed only by 1,4 elimination of hydrogen bromide from 2,3,4,5-tetrabromotetrahydrofuroic acid.



This 1,4 elimination of HX is required by all postulates of 1,4 addition of X_2 to furan or other diene nuclei as a prerequisite of the substitution reaction. Gilman's example is unique since we are aware of no case where such elimination has been demonstrated elsewhere in organic chemistry.

[8]TÖNNIES, *Ber.*, **11**, 1085 (1878).
[9]GILMAN, VANDER WAL, FRANZ, AND BROWN, *J. Am. Chem. Soc.*, **57**, 1146 (1935).
[10]HILL AND SANGER, *Proc. Amer. Acad.*, **21**, 135 (1885); *Ann.*, **232**, 42 (1885).

Indeed this mode of HX elimination is conspicuous by its absence. Thus of the possible dibromo substitution products resulting by elimination of hydrogen bromide from naphthalene tetrabromide, only B (which cannot be formed except by 1,4 elimination of hydrogen bromide) is absent among the reaction products.*



EXPERIMENTAL

Reaction without solvent.—A mixture of 26 g. (0.25 mole) of freshly prepared bromocyanogen and 29 g. (0.43 mole) of furan was refluxed twelve hours on the water bath. To this was added 100 cc. of 10% aqueous sodium hydroxide solution. The resulting mixture was refluxed two to three hours longer and was then steam distilled to yield 0.80 g. of 2-bromofuran (4% of the theoretical) which was identified as 5-bromo-2-furylmercuric chloride, m.p. 172–174°, twice recrystallized from 8:1 ethanol-water to melt at 175°. The melting point of a mixture with the same mercurial prepared from 5-bromofuroic acid showed no depression[11], and oxidation of 1 g. in 3 cc. of acetic acid with 1 cc. of nitric acid (sp. gr. 1.43) gave fumaric acid as the only isolable product. No bromofumaric acid could be detected, although the fumaric acid purified for mixture melting point determination (m.p. 277–278°) still gave a

*In private communications, Professors Henry Gilman and C. F. H. Allen have noted that this apparent 1,4 elimination can be explained as a successive process, involving 1,2 elimination of hydrogen bromide followed by a 1,3 shift of hydrogen and a subsequent 1,2 elimination of a second molecule of hydrogen bromide. We consider the two processes to be identical on the probability basis.

[11]GILMAN AND WRIGHT, *J. Am. Chem. Soc.*, **55**, 3302, (1933).

positive Beilstein test for halogen. The same halogen impurity was noted on oxidation of authentic 5-bromofurylmercuric halide.

The steam-distillation residues were evaporated almost to dryness on the steam bath, acidified with hydrochloric acid, and then allowed to evaporate spontaneously to dryness. The residue was sublimed at 100° to yield 0.54 g. (4% of the theoretical) of crude 2-furoic acid m.p. 121–128°. This was dissolved in water to remove 10 mg. of non-acidic constituent melting at 181–182° after crystallization from carbon tetrachloride. This unidentified compound contained halogen and was only slightly soluble in benzene and in ethanol. The aqueous solution of furoic acid was evaporated to dryness and fractionally sublimed at 130° (10 mm.) to yield a first fraction, m.p. 127–128°, and a second fraction, m.p. 120–122°. The first fraction was crystallized from carbon tetrachloride to melt at 129–130°, mixture m.p. with pure 2-furoic acid not lowered. Nine parts of the lower-melting fraction was mixed with one part of pure 2-furoic acid; the mixture melted at 123°. A mixture containing these relative proportions of 3-furoic acid and 2-furoic acid melts at 117–118°. The two sublimates were then recombined and boiled with aqueous mercuric chloride solution for four hours in order to decarboxylate the 2-furoic acid but to leave any 3-furoic acid unchanged. No furoic acid remained in the residue.

Alteration of the above procedure by adding sodium bisulfite to the reaction mixture prior to treatment with alkali did not alter the yield. It was found that a mixture of one equivalent of furan and one equivalent of bromocyanogen with an excess of precipitated calcium carbonate gave results identical with those outlined above. No yields were obtained using carbon tetrachloride, carbon disulfide, or anhydrous ethanol as solvents under otherwise comparable conditions. The pyridine-bromocyanogen complex would not react with furan.

Dioxane as solvent.—A mixture of 6.8 g. (0.10 mole) of furan, 10.6 g. (0.10 mole) of bromocyanogen and 50 cc. of anhydrous peroxide-free dioxane was allowed to stand under efficient reflux at 25° for eight days. To this mixture was added 80 cc. (0.2 mole) of 10% aqueous sodium hydroxide solution containing 12.6 g. (0.1 mole) of sodium sulfite. This mixture was heated to 100° for one hour, then steam-distilled until no more oil came over in the receiver. The bromofuran-dioxane mixture was washed with three 200-cc. portions of water; the volume of oil did not decrease after the second washing. The resultant oil was dried with calcium chloride. It weighed 9.81 g. On distillation two fractions were collected; the first, boiling at 62–65° (210 mm.) weighed 7.18 g. (49% of the theoretical) and was identified as pure 2-bromofuran as follows: b.p. 102–103° (744 mm.); n_D^{20} 1.4980, and by conversion to 5-bromofurylmercuric chloride as before. The second fraction (wt. 1.16 g., 5% of the theoretical) boiled at 51–52° (12 mm.). On redistillation it boiled at 52° (13 mm.); n_D^{25} 1.5419; n_D^{30} 1.5455; d_{20}^{20} 2.27. It would not mercurate, and after oxidation of 0.91 g. in 3 cc. of acetic acid and 1 cc. of nitric acid (sp. gr. 1.42) for four hours at room temperature, evaporation of the solvent under reduced pressure left only fumaric acid, and no bromofumaric acid as an identifiable product. This designates the substance as 2,5-dibromofuran.

The residual steam-distillation liquors were acidified to Congo paper and then continuously extracted with ether. After drying of the ether solution with magnesium sulfate the ether was distilled at 20 mm. pressure. Less than 0.1 mg. of the material remaining did not give a red coloration with ferric chloride and did not have the characteristic odor of furoic acid.†

†The authors wish to thank the Quaker Oats Company for generous supplies of furoic acid used in this work.

SUMMARY

1. The reaction of bromocyanogen with furan gives small yields of 2-furonitrile and 2-bromofuran, indicating that 1,4 addition and subsequent 1,4 elimination of hydrogen bromide and hydrogen cyanide has occurred.

2. Upon dilution of the reaction mixture with dioxane a good yield of bromofuran, but no furonitrile, is obtained. This solvent causes exclusive elimination of hydrogen cyanide.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

2-METHYL-*l*-RHAMNOSE AND 2-METHYL-*d*-FUCOSE AND THEIR BEARING ON THE CONFIGURATION OF DIGITALOSE

HAROLD B. MACPHILLAMY AND ROBERT C. ELDERFIELD

Received January 26, 1939

INTRODUCTION

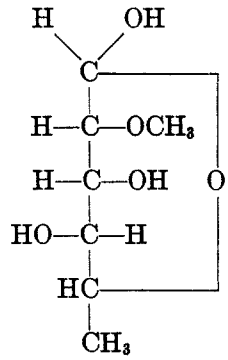
The chemistry of cardiac glycosides has interested investigators for a number of years. However, it has been only within the last few years that substantial progress has been made in the elucidation of their chemical structure[1]. Investigations in this field can be divided into two groups. The first, in which structural studies have been by far the more productive, is concerned with the non-carbohydrate or aglycone portion of the glycosides. The second, in which our knowledge is still comparatively meager, deals with the sugar components of the glycosides. It is to this latter group that the present investigation relates.

In addition to the relatively common sugars, such as glucose and rhamnose, a number of much rarer sugars, many of which are characterized by unusual structural features, are found as components of the cardiac glycosides[1]. The chemical structure and configuration of two of these sugars, digitoxose[2] and cymarose[3] have been established. Of the remaining sugars isolated from the hydrolytic products of the glycosides the configuration of digitalose and the structures and configurations of oleandrose and sarmentose, are still to be determined. The purpose of this research was to aid in establishing the configuration of digitalose.

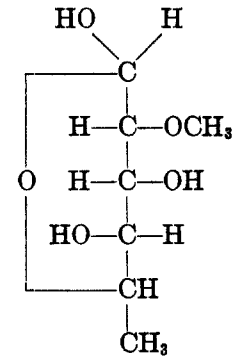
Digitalose was first obtained as a syrup by Kiliani[4] in 1892 from the products of hydrolysis of *Digitalinum verum*. On oxidation of the sugar with bromine water, he obtained a crystalline digitalonic lactone having the formula $C_7H_{12}O_6$. Hence the sugar itself must have the formula $C_7H_{14}O_6$. The seventh carbon atom was diagnosed as comprising a methyl ether group. On further oxidation with silver oxide Kiliani obtained acetic acid, thus indicating the presence of a terminal methyl group. Digitalonic lactone gave, on nitric acid oxidation, an α,β-dihydroxy-α'-

[1] ELDERFIELD, *Chem. Rev.*, **17**, 187 (1935).
[2] MICHEEL, *Ber.*, **63**, 347 (1930).
[3] ELDERFIELD, *J. Biol. Chem.*, **111**, 527 (1935).
[4] KILIANI, *Ber.*, **25**, 2116 (1892).

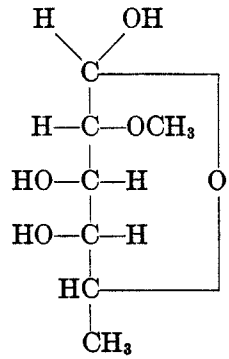
methoxyglutaric acid[5]. Kiliani also observed that digitalose formed a phenylhydrazone but not an osazone. This indicated that the methoxyl group was located on the second carbon atom of the hexose chain, thus blocking osazone formation. Later Schmidt and Zeiser[6] showed that the dihydroxymethoxyglutaric acid obtained by Kiliani, on complete methylation, gave *l*-arabotrimethoxyglutaric acid, thus establishing its steric configuration. From this evidence it follows that digitalose must therefore have one of the following formulas:



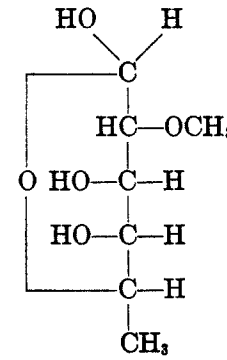
2-Methyl-
d-gulomethylose



2-Methyl-
l-rhamnose



2-Methyl-
d-fucose



2-Methyl-
l-altromethylose

More recently Lamb and Smith[7] have succeeded in obtaining the sugar in crystalline form by hydrolysis of a glycoside from *Strophanthus eminii* seeds.

[5] KILIANI, *ibid.*, **38**, 3621 (1905); **55**, 92 (1922); **64**, 2027 (1931).
[6] SCHMIDT AND ZEISER, *ibid.*, **67**, 2127 (1934).
[7] LAMB AND SMITH, *J. Chem. Soc.*, **1936**, 442.

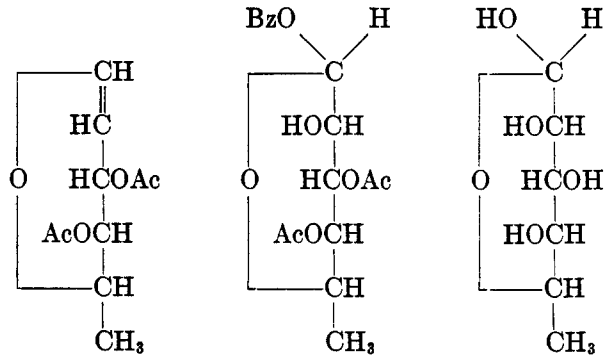
The simplest and most direct method of determining which of these configurations represents that of digitalose is to compare a completely methylated derivative of each sugar with the corresponding one of digitalose. However, since digitalose is so exceedingly difficult to obtain, this method of procedure was rejected in favor of direct synthesis.

The synthesis of two of the above four possibilities, namely *2-methyl*-l-*rhamnose* and *2-methyl*-d-*fucose*, has been accomplished. A comparison of the constants of these two sugars with those of digitalose, showed that neither was identical with digitalose. 2-Methyl-*l*-rhamnose as here obtained is a syrup, showing a final value of $[\alpha]_D$ of 31°; 2-methyl-*d*-fucose shows a variable melting point between 155° and 161° and a final value for $[\alpha]_D$ of 87°; digitalose[7] melts at 106° or 119° and shows a final value for $[\alpha]_D$ of 106°. Therefore, digitalose must be either 2-methyl-*d*-gulomethylose or 2-methyl-*l*-altromethylose. On the basis of biogenetic considerations, the latter alternative is much to be preferred.

A review of available methods for the preparation of 2-methyl sugars showed that one of the most promising was that of oxidizing the corresponding acetoglycal with perbenzoic acid according to the method of Bergmann and Schotte[8]. This procedure results in a sugar having an unsubstituted hydroxyl group only on the second carbon atom which could then be readily methylated by the Purdie and Irvine method. Final hydrolysis of the blocking groups would result in the desired 2-methyl sugar.

In discussing the structures of the sugars which are produced predominately by the perbenzoic acid oxidation of glycals, Levene and Tipson[9] made the following generalizations: when the hydroxyl group on carbon atom three is unsubstituted, the resulting hydroxyl group produced on carbon atom two, will be in the *cis* position to the one on carbon atom three. On the other hand, when the hydroxyl group on carbon atom three is substituted, the new hydroxyl group will be *trans* to it. If this is a general rule, it would be expected that if diacetylrhamnal (I) be similarly oxidized, the resulting substance would be a derivative of *epi*rhamnose instead of rhamnose. Bergmann and Schotte[8] report that, whereas rhamnal is oxidized by perbenzoic acid to give rhamnose, diacetylrhamnal is not oxidized in aqueous solution by this reagent. It has now been found that when the oxidation is carried out in chloroform, diacetylrhamnal yields a compound furnishing analytical figures for the expected 1-benzoyl-3, 4-diacetylhexomethylose (II). On subsequent hydrolysis of this substance without methylation, the sugar produced was not rhamnose. Definite identification of the latter as *epi*rhamnose (III) was not made, although it is presumably this sugar, thus confirming Levene and Tipson's rule.

[8] BERGMANN AND SCHOTTE, *Ber.*, **54**, 440, 1569 (1921).
[9] LEVENE AND TIPSON, *J. Biol. Chem.*, **93**, 631 (1931).



However, in the case of the oxidation of acetogalactal, a galactose derivative should be and is formed, as was shown by Levene and Tipson. This method then could be used for the preparation of 2-methylgalactose. But the long series of reactions necessary to convert this to 2-methyl-*d*-fucose, make it less attractive than two other methods.

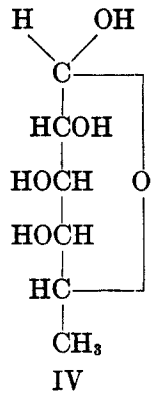
The first of these methods proceeds directly from *d*-fucose (IV), which was prepared from galactose according to the method of Freudenberg and Raschig[10]. Appropriate blocking of the hydroxyl groups was then accomplished by forming methyl-*d*-fucopyranoside. This on condensation with acetone resulted in 3,4-acetonemethyl-*d*-fucopyranoside (V) which after methylation with Purdie's reagents and hydrolysis gave the desired 2-methyl-*d*-fucose (VI).

In this series of reactions, the mixture of α- and β-methyl-*d*-fucopyranosides was used directly for the subsequent steps. However, in one experiment, the crystalline α-methyl-*d*-fucopyranoside was isolated. Votoček and Valentin[11] prepared α-methyl-*d*-fucopyranoside and gave $[\alpha]_D$ as 189.9° but did not report a melting point. Our material showed $[\alpha]_D^{25°}$ 190°, and melted at 155–156°.

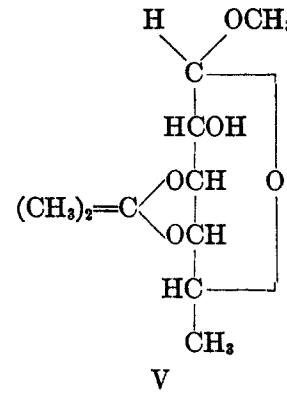
While this work was in progress a paper by Oldham and Bell[12], in which the preparation of 2-methyl- and 2,6-dimethyl-*d*-galactose was described, appeared. Their synthesis was similar to the above, except that the blocking group in position 6 was the nitrate group instead of the *p*-toluenesulfonyl group here used.

The second route to 2-methyl-*d*-fucose started with α-methyl-*d*-galactopyranoside. Upon unimolecular tosylation[13] the primary hydroxyl group was selectively tosylated, although in rather poor yield, to give 6-tosyl-

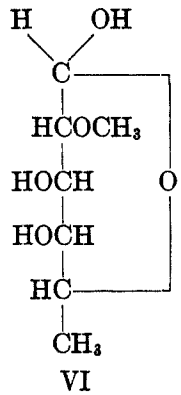
[10] FREUDENBERG AND RASCHIG, *Ber.*, **60**, 1633 (1927).
[11] VOTOČEK AND VALENTIN, *Coll. Czech. Chem. Com.*, **2**, 36 (1930).
[12] OLDHAM AND BELL, *J. Am. Chem. Soc.*, **60**, 323 (1938).
[13] LEVENE AND RAYMOND, *J. Biol. Chem.*, **102**, 317 (1933).



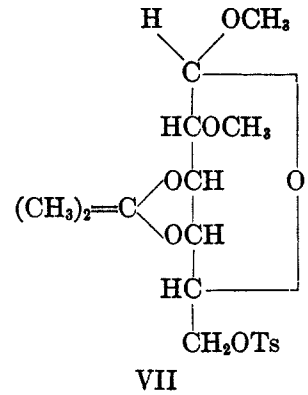
IV



V



VI



VII

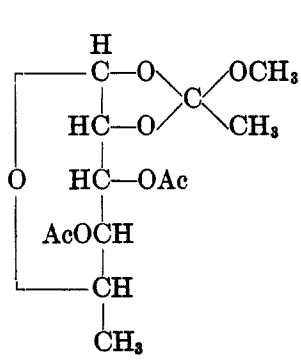
α-methyl-*d*-galactopyranoside, a compound prepared in a more indirect way by Ohle and Thiel[14]. Condensation with acetone produced 3,4-acetone-6-tosyl-α-methyl-*d*-galactopyranoside, in which all the hydroxyl groups but the one on the second carbon atom are blocked. Methylation with Purdie's reagents led to 2-methyl-3,4-acetone-6-tosyl-α-methyl-*d*-galactopyranoside (VII) which on heating with sodium iodide in acetone gave 2-methyl-3,4-acetone-6-iodo-α-methyl-*d*-galactopyranoside. Catalytic reduction of the latter with Raney nickel gave 2-methyl-3,4-acetone-α-methyl-*d*-fucopyranoside, from which the blocking groups were easily removed, yielding 2-methyl-*d*-fucose (VI).

The preparation of 2-methyl-*l*-rhamnose was not as simple. Due to the configuration of the hydroxyl groups it is not possible to block them selectively with acetone or other bridging reagents. The reactions finally used were based on a peculiar behavior of sugar 1,2-orthoacetates. These compounds are formed on treatment of acetobromo sugars with quinoline

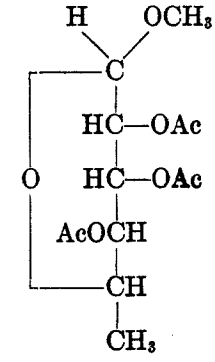
[14] OHLE AND THIEL, *Ber.*, **66**, 525 (1933).

or similar bases in methyl alcoholic solution and their structures have been definitely proved.[15]

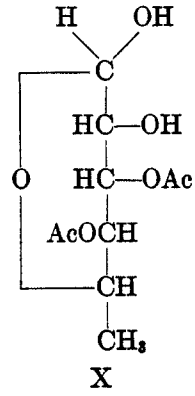
Isbell[16], in a study of the action of methyl alcoholic hydrogen chloride on heptaacetyl-4-glucosidomannose-1,2-orthoacetate, obtained hexaacetyl-4-glucosidomannose, presumably by selective hydrolysis of the orthoester group. However, beyond the facts that this substance contained no methoxyl and that it gave on acetylation the known octaacetyl-4-glucosidomannose, the position of the free hydroxyl groups was not further demonstrated. If the removal of the orthoester group was carried out in chloroform 1-chloroheptaacetyl glucosidomannose was obtained. In a later paper, Pigman and Isbell[17] advanced a general theory governing the configuration necessary for the formation of such orthoacetates. When the above reactions were applied to the corresponding rhamnose derivatives the analogous compounds were formed, and the correctness of Isbell's interpretation was shown.



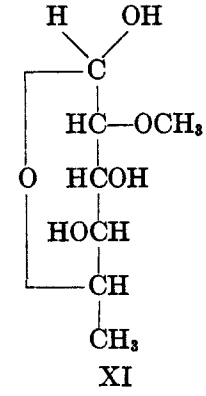
VIII



IX



X



XI

[15] HAWORTH, HIRST, AND SAMUELS, *J. Chem. Soc.*, **1931**, 2861.
[16] ISBELL, *Bur. Standards J. Research*, **7**, 1115 (1931).
[17] PIGMAN AND ISBELL, *ibid.*, **19**, 198 (1937).

3,4-Diacetyl-*l*-rhamnopyranose-1,2-orthoacetate (VIII) was prepared according to Haworth, Hirst, and Samuels.[15] This, on treatment with methyl alcoholic hydrogen chloride, gave the expected mixture of the previously known 2,3,4-triacetyl-β-methyl-*l*-rhamnopyranoside[18] (IX) and, presumably, 3,4-diacetyl-*l*-rhamnose (X). The former compound was easily isolated by crystallization from water. The latter, excessively soluble in water, could not be crystallized, and decomposed on attempted distillation. Therefore it was methylated directly, and the subsequent products were purified. In this way 2-methyl-3,4-diacetyl-methyl-*l*-rhamnopyranoside was obtained, which on deacetylation and hydrolysis of the glycosidic methyl group gave 2-methyl-*l*-rhamnose (XI). The location of the methyl group was shown by formation of *l*-rhamnose *p*-nitrophenyl osazone with loss of the methoxyl group. Such loss of a methyl group in the 2-position of a hexose is not without parallel. Brigl and Schinle[19] and Levene, Meyer, and Raymond[20] have noted a similar behavior of 2-methyl glucose, and Oldham and Bell[12] report that 2-methyl-, 2,3-dimethyl- and 2,6-dimethylgalactose give osazones with loss of the methyl group in position 2.

2-Methyl-*l*-rhamnose is not readily attacked by bromine water. This again parallels roughly the low reducing values obtained when 2-methyl-glucose derivatives are estimated by various copper methods[21]. No further study was made of this resistance to oxidation, it being felt that the whole question of the behavior of methylated sugars on oxidation warranted fuller investigation as a separate project, particularly in view of the fact that bromine water is not a general reagent. It is significant that digitalose on similar treatment yields digitalonic lactone[4,7].

EXPERIMENTS WITH *d*-GALACTOSE

*6-Tosyl-α-methyl-*d*-galactoside.*—α-Methyl-*d*-galactoside[22] was treated according to the directions of Levene and Raymond[13] for the monomolecular tosylation of monoacetone xylose. Thirty-seven grams of anhydrous α-methyl-*d*-galactoside was dissolved in 190 cc. of dry pyridine, and 40 g. of *p*-toluenesulfonyl chloride, dissolved in 75 cc. of chloroform, was added. The reaction mixture was kept at 0° for an hour and then allowed to stand at room temperature for 24 hours. It was then poured into a mixture of ice and dilute sulfuric acid with rapid stirring, when a white crystalline solid separated. This was filtered, washed with cold methanol, and finally recrystallized from methyl alcohol. It melted at 172° as stated by Ohle and Thiel[14]. The yield was 25 g., or about 40% of the theoretical. A small additional quantity was obtained by concentration of the chloroform solution.

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[18] HAWORTH, HIRST, AND MILLER, *J. Chem. Soc.*, **1929**, 2469.

[19] BRIGL AND SCHINLE, *Ber.*, **63**, 2884 (1930).

[20] LEVENE, MEYER, AND RAYMOND, *J. Biol. Chem.*, **91**, 497 (1931).

[21] SOBOTKA, *J. Biol. Chem.*, **69**, 267 (1926).

[22] MICHEEL AND LITTMANN, *Ann.*, **466**, 115 (1928).

6-Tosyl-3,4-acetone-α-methyl-d-*galactoside.*—6-Tosyl-α-methyl-*d*-galactoside was subjected to acetone condensation by a modification of the method of Ohle and Thiel[14]. Twenty-four grams of 6-tosyl-α-methyl-*d*-galactoside was added to a mixture of 120 g. of anhydrous copper sulphate, 3.6 g. of concentrated sulfuric acid, and a few drops of acetaldehyde with 1050 cc. of acetone. This mixture was shaken at room temperature for 48 hours. The copper sulfate was filtered off, 100 cc. of water was added, and the acid was neutralized by shaking with an excess of wet calcium hydroxide. After filtration, the acetone solution was concentrated *in vacuo* until crystalline material separated. Water was then added until all of the material had precipitated. The product was washed with water, dried, and recrystallized from benzene-petroleum ether. The melting point was 129°, in agreement with that reported by Ohle and Thiel[14]. The yield was 22 g. of recrystallized material, or about 82% of the theoretical.

2-Methyl-3,4-acetone-6-tosyl-α-methyl-d-*galactoside.*—Seventeen grams of 6-tosyl-3,4-acetone-α-methyl-*d*-galactoside was methylated with Purdie's reagents. The yield was 12 g. of material which crystallized on rubbing. It was recrystallized from ether-petroleum ether. The melting point was 86–87°; yield 70%.

Anal. Calc'd for $C_{18}H_{26}O_8S$: C, 53.7; H, 6.5; OCH_3, 15.4.
Found: C, 53.8; H, 6.8; OCH_3, 15.0.

2-Methyl-3,4-acetone-6-iodo-α-methyl-d-*galactoside.*—Nine grams of the preceding substance was dissolved in 30 cc. of acetone and heated with 9 g. of sodium iodide in bomb tubes at 140° for five hours. The acetone was removed under reduced pressure, and the residue taken up in chloroform. This was washed with dilute sodium thiosulfate and finally with water. The chloroform was removed, and 5 g. of yellow oil was obtained. Inasmuch as a suitable means of purification could not be found the material was reduced directly. The yield was about 50%.

2-Methyl-3,4-acetonemethyl-d-*fucoside.*—Four grams of crude 2-methyl-3,4-acetone-6-iodo-α-methyl-*d*-galactoside was reduced with Raney nickel catalyst in alkaline methyl alcohol solution according to Levene and Compton[23]. On distillation, 3 g. of material was obtained which boiled at 77–78° at 2 mm. pressure; yield about 60%.

Anal. Calc'd for $C_{11}H_{20}O_5$: C, 56.9; H, 8.7.
Found: C, 57.1; H, 8.8.

EXPERIMENTS WITH *d*-FUCOSE

d-*Fucose.*—This was prepared according to Freudenberg and Raschig[10] from *d*-galactose with the exception that 6-iododiacetone-*d*-galactose was reduced to diacetone-*d*-fucose catalytically with Raney nickel in alkaline methyl alcohol solution according to Levene and Compton[23]. The *d*-fucose obtained showed a final rotation of $[\alpha]_D^{20}$ 75.3°. Freudenberg and Raschig[10] report $[\alpha]_D^{19°}$ 76.3°.

α-Methyl-d-*fucopyranoside.*—Twenty grams of *d*-fucose was refluxed with 300 cc. of absolute methyl alcohol containing 4% of hydrogen chloride for 8 hours, when the solution no longer reduced Fehling's solution. After removal of the chloride ion with silver carbonate, the solution was boiled with Norite, filtered and concentrated to about 50 cc., when copious crystallization occurred. After 2 crystallizations from methyl alcohol the α-methyl-*d*-fucopyranoside melted constantly at 155–156°; $[\alpha]_D^{25°}$ 190.0° (*C* = 4.166 in water). Votoček and Valentin[11] report $[\alpha]_D$ 189.9°.

Anal. Calc'd for $C_7H_{14}O_5$: C, 47.2; H, 7.9.
Found: C, 47.4; H, 8.4.

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[23] LEVENE AND COMPTON, *J. Biol. Chem.*, **111**, 325 (1935).

*3,4-Acetonemethyl-*d*-fucopyranoside.*—Twenty grams of mixed α- and β-methyl fucopyranosides obtained as above was dissolved in 250 cc. of acetone containing 1.5% of hydrogen chloride and 5 drops of paraldehyde. After standing 20 minutes at room temperature, the solution was poured into 1300 cc. of dilute ammonia. The ammoniacal solution was extracted 10 times with chloroform. After drying and removal of the chloroform, 11 g. of a syrup remained, and was distilled at 0.2 mm. pressure. After a slight forerun the main fraction boiled at 88–92°. On standing over the summer this crystallized for the most part. After recrystallization from acetone-petroleum ether, the crystalline 3,4-acetone-methyl-*d*-fucopyranoside melted at 98–100° when air dried. On drying in an evacuated desiccator the material lost solvent and became syrupy. The syrup was analyzed:

Anal. Calc'd for $C_{10}H_{18}O_5$: C, 55.0; H, 8.3.
Found: C, 54.5; H, 8.4.

The aqueous ammoniacal solution after extraction with chloroform was concentrated to dryness, and the residual salts were thoroughly extracted with hot acetone. From the acetone extracts, 6 g. of α-methyl-*d*-fucopyranoside was recovered.

*2-Methyl-3,4-acetonemethyl-*d*-fucopyranoside.*—The material obtained in the preceding experiment was methylated with Purdie's reagents. After removal of the solvent, the residual syrup crystallized spontaneously. After recrystallization from petroleum ether, the crystalline 2-methyl-3,4-acetonemethyl-*d*-fucopyranoside melted at 100° after preliminary softening.

Anal. Calc'd for $C_{11}H_{20}O_5$: C, 56.9; H, 8.7; OCH_3, 26.7.
Found: C, 56.9; H, 8.8; OCH_3, 25.7.

*2-Methyl-*d*-fucose.*—2-Methyl-3,4-acetonemethyl-*d*-fucopyranoside was hydrolyzed by boiling with 4% sulfuric acid for 6 hours. After neutralization with barium carbonate, the solution was treated with Norite, and concentrated to dryness, leaving a crystalline mass. This was recrystallized from alcohol. 2-Methyl-*d*-fucose shows a somewhat variable melting point, different samples of the same purity melting from 155 to 161° depending on the rate of heating. The 2-methyl-*d*-fucose prepared by either route crystallized as leaflets indistinguishable in form, and a mixture of the substances prepared in both ways showed no depression in the melting point. The sugar from both sources showed the same optical behavior; $[\alpha]_D^{27°}$ 73° (10 minutes after preparing the solution), and becoming constant at 87° in twenty hours (C = 1.309 in water).

Anal. Calc'd for $C_7H_{14}O_5$: C, 47.2; H, 8.1; OCH_3, 17.4.
For the substance from fucose Found: C, 47.0; H, 7.9; OCH_3, 16.8.
For the substance from galactose Found: C, 47.4; H, 8.0; OCH_3, 17.0.

EXPERIMENTS WITH *l*-RHAMNOSE

*Reaction of 3,4-diacetyl-*l*-rhamopyranoside-1,2-orthoacetate with methyl alcoholic hydrogen chloride.*—Fifty-eight grams of 3,4-diacetylrhamnopyranoside-1,2-orthoacetate, prepared according to Haworth, Hirst and Samuels[15] was dissolved in 580 cc. of absolute methyl alcohol, and sufficient 6% methyl alcoholic hydrogen chloride solution was added to furnish 4 g. of hydrogen chloride. After standing for 10 minutes at room temperature the mixture was poured onto a paste of 116 g. of silver carbonate and 23 cc. of water and stirred mechanically until all of the chloride ion was removed. The filtrate from the silver salts was concentrated under reduced pressure to a syrup which was dissolved in hot water and treated with Norite. On

cooling, 9.2 g. of crystals separated. These were recrystallized from water to a constant melting point of 150–151°; $[\alpha]_D^{25}$ 46° (*C* = 1.674 in acetylene tetrachloride). Haworth, Hirst, and Miller[13] report 2,3,4-triacetyl-β-methyl-*l*-rhamnopyranoside melting at 151–152° and showing $[\alpha]_D^{15}$ 45.7°.

Anal. Calc'd for $C_{13}H_{20}O_8$: C, 51.3; H, 6.6.
Found: C, 51.5; H, 6.6.

The mother liquor from the above crystalline material was concentrated to a syrup, which was dried by repeated concentration with absolute alcohol and benzene. This material was strongly reducing toward Fehling's solution. By analogy with the substance prepared by Isbell[16] from heptaacetyl-4-glucosidomamnose-1,2-orthoacetate, this is predominately 3,4-diacetyl-*l*-rhamnose-1,2-orthoacetate. It could not be crystallized, and, on attempted distillation under high vacuum, it decomposed. Therefore it was methalated as such.

*2-Methyl-3,4-diacetylmethyl-*l*-rhamnopyranoside.*—The syrup (47 g.) obtained in the preceding experiment was methylated twice with Purdie's reagents. The material thus obtained was fractionally distilled at 0.2 mm. pressure, the fraction boiling at 110–130° being collected. This was dissolved in hot water, and, on cooling, the solution deposited crystalline material which was identified as more of the triacetylmethylrhamnopyranoside described above. The mother liquor was concentrated to dryness, and the residue was again distilled at 0.2 mm. The fraction boiling at 110–115° was a light oil, and consisted of higher methylation products apparently formed as the result of partial saponification of the acetyl groups during the methylation. The main fraction weighed 22 gms. and boiled at 115–120°. This was redistilled at 0.2 mm. and boiled constantly at 116–118°. It furnished analytical figures corresponding to 2-methyl-3,4-diacetylmethyl-*l*-rhamnopyranoside.

Anal. Calc'd for $C_{12}H_{20}O_7$: C, 52.2; H, 7.3; OCH_3, 22.5.
Found: C, 52.4; H, 7.4; OCH_3, 22.8.

*2-Methylmethyl-*l*-rhamnopyranoside.*—Ten grams of 2-methyl-3,4-diacetylmethyl-*l*-rhamnopyranoside was dissolved in 250 cc. of ice-cold absolute methyl alcohol; 17 cc. of 0.208 molar barium methylate solution was added, and the solution was placed in the refrigerator for 48 hours. After addition of 400 cc. of water and saturation with carbon dioxide, the solution was heated 1 hour on the steam bath and then chilled. The filtrate from the barium salts was concentrated under reduced pressure to a syrup which crystallized from a large volume of "Skelly-solve D". After six crystallizations the melting point was 139–140° and still rising. Inasmuch as the substance was probably still a mixture of α- and β-glycosides, further crystallization was not carried out.

Anal. Calc'd for $C_8H_{16}O_5$: C, 50.0; H, 8.4; OCH_3, 32.3.
Found: C, 50.3; H, 8.7; OCH_3, 29.9.

The material from the mother liquors of the above crystalline substance was a syrup and probably consisted of a mixture of stereoisomers.

*2-Methyl-*l*-rhamnose.*—2-Methylmethyl-*l*-rhamnopyranoside as previously obtained was hydrolyzed by heating on the steam bath with 3.7% hydrochloric acid for 6–7 hours. After removal of the inorganic ions in the usual manner, the solution was concentrated to a syrup under reduced pressure. This was dried by repeated concentration with absolute alcohol and benzene. All attempts at crystallization, both with and without seeding with digitalose*, failed. For analysis the syrup was

* We wish to express our appreciation to Dr. Sidney Smith of the Wellcome Chemical Works, Dartford, England, for a sample of crystalline digitalose.

further dried at 80° over calcium chloride and analyzed as such, although it was still impure. The material was strongly reducing toward Fehling's solution.

Anal. Calc'd for $C_7H_{14}O_5$: C, 47.2; H, 8.1; OCH_3, 17.4.
Found: C, 48.2; H, 7.9; OCH_3, 18.8.

$[\alpha]_D^{27}$ 31° (20 minutes after preparing the solution; no change after 24 hours) (C = 1.136 in water).

Attempted oxidation of 2-methylrhamnose with bromine water.—One-half gram of 2-methylrhamnose was allowed to stand for four days with 100 cc. of bromine water. After removal of the inorganic constituents in the usual manner, concentration left a syrup which was strongly reducing towards Fehling's solution.

*Oxidation of 2-methyl-*l*-rhamnose with nitric acid.*—Three-tenths gram of 2-methylrhamnose was dissolved in 10 cc. of 50% nitric acid, and the solution was allowed to stand for 3 days at room temperature. The nitric acid was removed by repeated concentration at reduced pressure with addition of water. A syrupy residue, which offered some difficulty in crystallization, remained. The acid was accordingly isolated as the di-*N*-methyl amide. The syrup was heated with 5 cc. of 3% absolute methyl alcoholic hydrogen chloride in a sealed tube at 100° for 6 hours. After removal of chloride ion by silver carbonate the solution was concentrated to a syrup. This was dissolved in 10 cc. of absolute methyl alcohol and saturated with dry methylamine. After standing for twenty-four hours at room temperature, the solvent was removed, and the residue was crystallized twice from ethyl acetate; m. p. 204–205°; $[\alpha]_D^{28}$ 71° (C = 0.453 in water). The analysis corresponded to that of the di-*N*-methyl amide of *l*-arabomonomethoxyglutaric acid. A free acid isomeric with the above was obtained as an oxidation product of digitalose by Kiliani[5].

Anal. Calc'd for $C_6H_{16}N_2O_5$: C, 43.6; H, 7.3; OCH_3, 14.1; N, 12.7.
Found: C, 43.1; H, 7.3; OCH_3, 13.0; N, 13.0.

*Action of methyl alcoholic hydrogen chloride on 2-methyl-*l*-rhamnose.*—Three-tenths gram of 2-methyl-*l*-rhamnose was boiled with 10 cc. of 4% absolute methyl alcoholic hydrogen chloride solution for 6 hours. After removal of the chloride ion as usual and concentration, a syrup remained which could not be crystallized. It no longer reduced Fehling's solution, thereby showing that glycoside formation had occurred.

*Rhamnose-*p*-nitrophenylosazone from 2-methyl-*l*-rhamnose.*—Three-tenths gram of 2-methyl-*l*-rhamnose was heated on the steam bath with 3 equivalents of *p*-nitrophenylhydrazine hydrochloride in 10 cc. of water containing 2 drops of concentrated hydrochloric acid for one hour. A copious red precipitate formed after five minutes. The precipitate was collected and washed well with dilute hydrochloric acid and water. After recrystallization from a large volume of alcohol, the substance melted with decomposition at 209–211°. Feist[24] reports *l*-rhamnose *p*-nitrophenylosazone as melting at 208° with decomposition.

Anal. Calc'd for $C_{18}H_{20}O_7N_6$: C, 50.0; H, 4.7.
Found: C, 50.0; H, 4.6.

The substance did not contain methoxyl.

Oxidation of diacetylrhamnal with perbenzoic acid.—Six and nine-tenths grams of diacetylrhamnal was dissolved in 220 cc. of an ice-cold chloroform solution of perbenzoic acid containing 0.0222 g. of perbenzoic acid per cc. After standing 4 days in the refrigerator the calculated amount of perbenzoic acid had been consumed. The solution was concentrated to dryness and the residual solid was repeatedly extracted with ligroïn for the removal of benzoic acid. The portion which was in-

[24] FEIST, *Ber.*, **33**, 2099 (1900).

soluble in ligroïn crystallized readily from absolute alcohol. It melted at 193°; $[\alpha]_D^{24}$ −15.2° (*C* = 1.220 in chloroform). The substance furnished analytical figures for 1-benzoyl-3,4-diacetylrhamnose or *epi*rhamnose.

Anal. Calc'd for $C_{17}H_{20}O_8$: C, 57.9; H, 5.7.
Found: C, 58.2; H, 5.7.

On catalytic removal of the benzoyl and acetyl groups, a reducing syrup was obtained which could not be seeded with rhamnose. Therefore the *epi*rhamnose configuration seems preferable.

The analyses here reported were made by Mr. Saul Gottlieb.

SUMMARY

2-Methyl-*l*-rhamnose and 2-methyl-*d*-fucose have been prepared and shown not to be identical with digitalose.

Digitalose is either 2-methyl-*d*-gulomethylose or 2-methyl-*l*-altromethylose.

A general method has been developed for the preparation of 2-methyl derivatives of sugars having the configuration demanded by the theory of Pigman and Isbell[17].

Diacetylrhamnal has been shown to be oxidized by perbenzoic acid, presumably with the formation of an *epi*rhamnose derivative.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

REACTIONS BETWEEN ORGANOLEAD COMPOUNDS AND SOME METALLIC HALIDES

HENRY GILMAN AND L. D. APPERSON

Received January 30, 1939

INTRODUCTION

Incidental to studies on the low-temperature formation of free radicals from organometallic compounds, it was desirable to determine the effect of some metallic halides (particularly, aluminum chloride) on different types of organolead compounds.

Phenyllead compounds and aluminum chloride.—The essential reactions in petroleum ether (b.p., 90–115°) or hexane appear to be the following:

$$(C_6H_5)_4Pb + AlCl_3 \rightarrow (C_6H_5)_3PbCl + C_6H_5AlCl_2 \quad [I]$$

$$(C_6H_5)_4Pb + C_6H_5AlCl_2 \rightarrow (C_6H_5)_3PbCl + (C_6H_5)_2AlCl \quad [II]$$

$$(C_6H_5)_3PbCl + AlCl_3 \rightarrow (C_6H_5)_2PbCl_2 + C_6H_5AlCl_2 \quad [III]$$

No biphenyl, chlorobenzene, or lead dichloride were isolated. The reaction is halted at the diphenyllead dichloride stage, and this compound was shown to be unaffected when treated separately with aluminum chloride. The phenylaluminum chlorides [$(C_6H_5)_2AlCl$ and $C_6H_5AlCl_2$] are undoubtedly in an equilibrium mixture, and this equilibrium may include triphenylaluminum at elevated temperatures. The organoaluminum compounds were qualitatively analyzed by the color test[1a], and semi-quantitatively determined both by measuring the benzophenone resulting after treatment with benzoyl chloride,[1b] and by the formation of RH compounds by hydrolysis. Under the experimental conditions followed, there is no reaction of benzoyl chloride with tetraphenyllead, triphenyllead chloride and diphenyllead dichloride.

The triphenyllead chloride and diphenyllead dichloride may owe their formation to reactions other than those indicated in I, II, and III. Austin[2] has shown that triphenyllead chloride is converted, by heating in butyl alcohol for six hours, to diphenyllead dichloride and tetraphenyllead in about 10 per cent. yields. Under our more moderate conditions, the

[1] (*a*) GILMAN AND SCHULZE, *J. Am. Chem. Soc.*, **47**, 2002 (1925). (*b*) Other studies have shown that acid halides are suitable reagents for characterizing organoaluminum compounds.

triphenyllead chloride was shown to be essentially unaffected. Accordingly, the diphenyllead dichloride isolated from our cleavage experiments is not due to pyrolysis. There is a possibility that some of our triphenyllead chloride may have resulted from interaction of tetraphenyllead and diphenyllead dichloride. However, here, too, our conditions were more moderate than those used by Austin[2] for this particular reaction. Furthermore, it is highly probable on theoretical grounds that the reaction proceeds stepwise, and that triphenyllead chloride is a precursor of diphenyllead dichloride in the cleavage reactions. Finally, we have shown that a 75 per cent. yield of diphenyllead dichloride is obtained from triphenyllead chloride and aluminum chloride.

Ethyllead compounds and aluminum chloride.—The first reactions of tetraethyllead are like reactions I and II shown by tetraphenyllead. Also it is quite likely that a reaction like III occurs, even though diethyllead dichloride is not isolated. What very probably happens is that diethyllead dichloride is formed, and then breaks down in accordance with the following transformations, reaction IV predominating.[3]

$$2(C_2H_5)_2PbCl_2 \rightarrow (C_2H_5)_3PbCl + PbCl_2 + C_2H_5Cl \quad \text{[IV]}$$

$$(C_2H_5)_2PbCl_2 \rightarrow PbCl_2 + 2C_2H_5 \quad \text{[V]}$$

We have found that the yields of lead chloride and ethyl chloride increase when the ratio of aluminum chloride to tetraethyllead is increased. Under such conditions, one would not expect to find any significant quantity of triethyllead chloride because this compound with aluminum chloride gives the relatively unstable diethyllead dichloride, in accordance with reaction III. This agrees with our observation on the reaction between diethyllead dichloride and aluminum chloride. Incidental to the formation of ethyl chloride, it is significant that small quantities of hexaethylbenzene were isolated when benzene was used as the reaction medium. Of course, this Friedel-Crafts reaction product may have come from the disproportionation of ethyl radicals (reaction V) to ethylene.

Reaction IV has been shown recently to be the predominant reaction when solid di-*n*-butyllead dichloride was heated at 130° for one-half hour[3a]. Evidence was obtained earlier[3b] for both reactions IV and V when solid diethyllead *dibromide* was allowed to decompose spontaneously at room temperatures or heated at 100°.

[2] AUSTIN, *ibid.*, **54**, 3287 (1932).

[3] (*a*) EVANS, *J. Chem. Soc.*, **1938**, 1466. (*b*) Unpublished communication by Dr. George Calingaert, Regional A.C.S. Meeting, Columbus, Ohio, Nov. 1937.

There is a possibility that the R_2PbX_2 compounds may be converted to $RPbX_3$ types, by aluminum chloride or otherwise, and that the $RPbX_3$ compounds then decompose to $RX + PbX_2$. For a general account of $RPbX_3$ types see LESBRE, *Compt. rend.*, **200**, 559 (1935); **204**, 1822 (1937).

The organoaluminum compounds formed were chiefly diethylaluminum chloride and ethylaluminum dichloride, together with occasional small quantities of triethylaluminum. These ethylaluminum compounds appeared to form complexes with the various ethyllead compounds, and the complexes were broken up by hydrolysis, by distillation, or by reaction with acyl halides. The mixture of diethylaluminum chloride and ethylaluminum dichloride (prepared both by the reaction of aluminum with ethyl chloride, and the reaction of aluminum chloride with triethylaluminum) cleaved tetraethyllead [II] and triethyllead chloride. The cleavage of triethyllead chloride was effected by heating the solid reactants to 150°, but no cleavage took place under the milder conditions when ether or petroleum ether was used as a medium.

Tetraethyllead and other inorganic halides.—Anhydrous ferric chloride is reduced promptly to ferrous chloride, which was obtained in a high state of purity and in excellent yield. Chloroplatinic acid was reduced immediately to platinum, and bismuth chloride gave ethylbismuth compounds. The other reaction products were ethyllead chlorides and lead chloride.

The literature contains accounts of earlier reactions of organolead compounds with metallic halides. Browne and Reid[4a] reported a vigorous reaction between tetraethyllead and aluminum chloride to give triethyllead chloride and an unidentified gas. With silicon tetrachloride they obtained triethyllead chloride; and titanium tetrachloride was reduced by tetraethyllead. Goddard and co-workers treated tetraphenyllead with the halides of arsenic, antimony, bismuth, tellurium, and tin, to obtain in each case diphenyllead dihalide as well as the halides of the other RM compounds such as diphenylbismuth bromide.[4b] Thallic chloride and tetraphenyllead gave diphenyllead dichloride and diphenylthallium chloride; and thallic chloride with triethyllead chloride gave diethyllead dichloride and thallous chloride.[4c] From reaction between thallic chloride and tri-*m*-xylyllead there resulted di-*m*-xylyllead dichloride and thallous chloride.[4d] Krause and Schmitz[4e] obtained phenylmercuric chloride from triphenylethyllead and mercuric chloride; Kocheskov and Nesmeyanov[4f] treated phenyllead compounds with mercuric chloride to obtain phenylmercuric chloride as a product wherever reaction occurred. These authors noted no reaction between diphenyllead dichloride and mercuric chloride in alcohol; but the same reactants with sodium hydroxide gave phenylmercuric chloride and lead dioxide.

[4] (*a*) Browne and Reid, *J. Am. Chem. Soc.*, **49**, 830 (1937); (*b*) Goddard, Ashley, and Evans, *J. Chem. Soc.*, **121**, 978 (1922); (*c*) Goddard and Goddard, *ibid.*, **121**, 260 (1922); (*d*) Goddard, *ibid.*, **123**, 1172 (1923); (*e*) Krause and Schmitz, *Ber.*, **52**, 2159 (1919); (*f*) Kocheskov and Nesmeyanov, *ibid.*, **67**, 317 (1934).

We have also shown that ethylmercuric chloride is formed from tetraethyllead and mercuric chloride.

The experimental part describes some reactions of triaryllead compounds with aluminum chloride.

EXPERIMENTAL

Tetraphenyllead and aluminum chloride.—A petroleum ether (100 cc.) suspension of 0.025 mole of tetraphenyllead and 0.1 mole of aluminum chloride was heated, with stirring, for 6 hours in a flask contained in a bath of boiling water. Nitrogen was used as the inert atmosphere. The practically colorless upper layer was separated from the yellowish lower, solid layer. The upper layer gave a weak positive color test[1a], and steam distillation yielded no chlorobenzene nor biphenyl. The lower solid layer yielded 26% of triphenyllead chloride, 46.5% of diphenyllead dichloride, and a small amount (2.5 g.) of tetraphenyllead. The diphenyllead dichloride was characterized by conversion to tetraphenyllead by means of phenylmagnesium bromide.

In another experiment under corresponding conditions, 0.03 mole of tetraphenyllead was cleaved by 0.025 mole of aluminum chloride. The products were triphenyllead chloride (60%), diphenyllead dichloride (39%) and a trace of tetraphenyllead. The phenylaluminum compounds were decomposed by the ammonium acetate solution used in working up the products.

In order to characterize the phenylaluminum compounds, the reaction mixture from 0.027 mole of tetraphenyllead and 0.025 mole of aluminum chloride was cooled and treated with 0.025 mole of benzoyl chloride. After standing overnight, the mixture was hydrolyzed. In addition to the usual phenyllead compounds, there was isolated (as the oxime) a 40% yield of benzophenone.

Triphenyllead chloride and aluminum chloride.—A mixture of 0.0175 mole of triphenyllead chloride and 0.020 mole of aluminum chloride in petroleum ether was heated for 6 hours in a bath containing boiling water. The yield of diphenyllead dichloride was 75%.

Tetraethyllead and aluminum chloride.—To a hexane solution of 0.05 mole of tetraethyllead was added slowly, by means of a hopper, 0.05 mole of aluminum chloride. The reaction was slightly exothermic, and the mixture soon separated into two layers. After refluxing for one hour (during which time no gas was evolved), the mixture was hydrolyzed. The products isolated were 76% of triethyllead chloride and a trace of lead chloride. In a check run, the yield of triethyllead chloride was 83%.

In other experiments, the upper layer was shown to contain some tetraethyllead, but to be free of aluminum. The lower layer was distilled directly under reduced pressure. The initial distillation proceeds quite slowly, and is accompanied by gas evolution incidental to some decomposition of ethyllead compounds even with the use of an efficient pump used to get low pressures in all the distillations made. Subsequent fractionations proceeded more smoothly. The several fractions were shown by analysis to contain ethylaluminum dichloride and lesser amounts of diethylaluminum chloride and triethylaluminum. It is known that at room temperature ethylaluminum dichloride and triethylaluminum give diethylaluminum chloride. The organoaluminum compounds will be reported separately later.

In another series of experiments in which the excess of aluminum chloride was progressively increased so that one mole equivalent of tetraethyllead was treated with two and three mole equivalents, respectively, of aluminum chloride, the products were triethyllead chloride, a greater amount of lead chloride, ethyl chloride, and ethylaluminum dichloride as the preponderant ethylaluminum product. From

one reaction between 0.24 mole of tetraethyllead and 0.5 mole of aluminum chloride, the yields were 21% of triethyllead chloride, 9% of lead chloride, 56% of ethylaluminum dichloride and a trace of ethyl chloride. The ethylaluminum dichloride was characterized, in part, by the formation of propiophenone subsequent to reaction with benzoyl chloride, and by evolution of ethane on hydrolysis. When these reactions using an excess of aluminum chloride were carried out in benzene, there was always isolated small quantities of hexaethylbenzene (mixture melting point).

From an experiment using three mole equivalents of aluminum chloride, the yields of lead compounds were: 15% of triethyllead chloride and 72% of lead chloride. The ethylaluminum compounds were characterized by both the color test and the preparation of propiophenone; and the ethyl chloride, isolated to the extent of about 10%, was characterized by first forming ethylmagnesium chloride and then using this Grignard reagent to prepare ethylmercury chloride (mixture melting point).

Triethyllead chloride and aluminum chloride.—A mixture of 0.02 mole of triethyllead chloride and 0.02 mole of aluminum chloride in petroleum ether was warmed for one-half hour. Again, two layers formed: the upper layer gave a weak color test; the lower layer, on hydrolysis, yielded 63% of lead chloride and 38% of recovered triethyllead chloride. No diethyllead dichloride was isolated.

Diethyllead dichloride and aluminum chloride.—A 72% yield of lead chloride and a 20% yield of triethyllead chloride were obtained from reaction, in petroleum ether, between 0.11 mole of diethyllead dichloride and 0.1 mole of aluminum chloride. From the evolved gases there was isolated about 15% of ethyl chloride, and a hydrocarbon mixture consisting of 7.2% of unsaturates and 30% of saturates. The saturated hydrocarbon mixture appears to consist largely of ethane.

Triethyllead chloride with triethylaluminum, and with diethylaluminum chloride and ethylaluminum dichloride.—Triethyllead chloride dissolved exothermally in a hexane solution of triethylaluminum; and when most of the lead compound was added, there was a separation into two layers. Subsequent to hydrolysis, 75% of the triethyllead chloride was recovered. There was no evidence of lead chloride or diethyllead dichloride.

There was no cleavage of triethyllead chloride by a mixture of diethylaluminum chloride and ethylaluminum dichloride when ether or petroleum ether were used as media. However, after heating the mixture of solids gradually to 150° there was isolated 10% of lead chloride, 30% of lead and about a 50% recovery of triethyllead chloride. No check experiment was made to determine how much of this reaction was due to simple pyrolysis. The mixture of ethylaluminum chlorides was prepared by direct action of ethyl chloride on aluminum turnings, using a crystal of iodine (or a few drops of ethyl iodide) as a catalyst. The aluminum, contained in a flask, was heated while ethyl chloride gas was admitted slowly and under a slight positive pressure[5]. The mixture was heated by means of a hot plate until fuming began; thereafter, a water bath was used. When no more ethyl chloride was absorbed, as shown by the U-tube with mercury[5], the light-brown solution was filtered and then distilled to give a colorless distillate (b.p., 63°/3 mm.). The mixture of ethylaluminum chlorides was also prepared by adding aluminum chloride to triethylaluminum. The mixture fumes, and often inflames, in the air. It was derivatized by treatment with benzoyl chloride to give propiophenone.

[5] For a related technique on the preparation of methyl- and ethylmagnesium chlorides, see GILMAN, ZOELLNER, SELBY, AND BOATNER, *Rec. trav. chim.*, **54**, 584 (1935).

The mixture of ethylaluminum chlorides was prepared earlier by Hall and Nash[6a] from aluminum, aluminum chloride, and ethylene; and by Hnizda and Kraus[6b] from aluminum and ethyl chloride.

Incidental to the preparation of etherates of organoaluminum compounds, the mono-etherate of aluminum chloride[7] was prepared. The compound distils at 108°/2–3 mm. and melts at 34°.

Anal. Calc'd for $AlCl_3 \cdot (C_2H_5)_2O$: Cl, 51.4. Found: Cl, 51.0, 51.2.

Tetraethyllead with diethylaluminum chloride and ethylaluminum dichloride.—A mixture of tetraethyllead and the ethylaluminum chlorides in petroleum ether was heated just below reflux for one hour. Although there was no separation into layers in this case, there was the characteristic yellow color. From two experiments, the yields of triethyllead chloride were 60% and 56%, respectively. The effective cleavage agent in these experiments is probably ethylaluminum dichloride, for when relatively pure diethylaluminum chloride was used the yields of triethyllead chloride were only 5% and 3%, respectively. The triethylaluminum mentioned earlier may owe its formation to the following reaction:

$$(C_2H_5)_4Pb + (C_2H_5)_2AlCl \rightarrow (C_2H_5)_3PbCl + (C_2H_5)_3Al$$

Tetraethyllead and Group VIII halides. [By M. Lichtenwalter].—To a solution of 11.5 g. of anhydrous ferric chloride in 200 cc. of ether was added 20.6 g. of freshly distilled tetraethyllead. A slight warming occurred with the formation of a voluminous precipitate. The precipitate was extracted with boiling ether until free of organolead compounds (triethyllead chloride and diethyllead dichloride). The residue consisted of 9 g., or a 90% yield, of anhydrous ferrous chloride.

Anal. Calc'd for $FeCl_2$: Fe, 44.1; Cl, 55.9.
Found: Fe, 44.02; Cl, 56.0.

Under corresponding conditions, tetraethyllead was found to be without action on ferrous iodide, ferrous chloride, cobaltous bromide, and nickelous bromide.

Chloroplatinic acid was reduced immediately by tetraethyllead to metallic platinum.

Tetraethyllead and bismuth chloride. [By H. L. Yablunky].—To a stirred solution of 0.032 mole of anhydrous bismuth chloride in 20 cc. of ether was added dropwise 0.0294 mole of tetraethyllead. A yellow solid precipitated immediately and the ether refluxed. When refluxing was continued for 4.5 hours, by the external application of heat, the solid turned white. When the solid was dried and exposed to the air it ignited spontaneously; this is characteristic of triethylbismuth and diethylbismuth chloride.

In a second experiment, no solvent was used, and the mixture of 0.03 mole of tetraethyllead and 0.4 mole of bismuth chloride was heated between 100°–130° for two hours. Dense white fumes were evident and the reaction was vigorous. There was isolated 1.15 g. of triethyllead chloride and 5 g. of lead chloride. Heating at this temperature under atmospheric pressure, with or without an inert atmosphere, would destroy any triethylbismuth.

The fuming was probably due to decomposition of the ethylbismuth compounds and not to tetraethyllead, for no fuming was noted when finely ground bismuth metal and tetraethyllead were heated between 100°–130° for 5 hours. The tetraethyllead was recovered quantitatively.

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[6] (*a*) Hall and Nash, *J. Inst. Petroleum Tech.*, **23**, 679 (1933); (*b*) Hnizda and Kraus, *J. Am. Chem. Soc.*, **60**, 2276 (1938). Also Grosse, Abstracts, American Chemical Society, Dallas meeting, 1938, and Baltimore meeting, 1939.

[7] Frankforter and Daniels, *J. Am. Chem. Soc.*, **37**, 2560 (1915).

Triphenyllead with aluminum chloride.—A mixture of 7 g. (0.016 mole) and 3 g. (0.0225 mole) of aluminum chloride in 100 cc. of petroleum ether (b.p., 90–115°) was heated, with stirring in an atmosphere of nitrogen, by means of a steam bath for six hours. Hydrolysis was effected by addition of water. The solid material was separated by filtration, and the filtrate was distilled under reduced pressure. The combined solids were extracted with ammonium acetate solution and filtered. The filtrate, after treatment with dichromate solution, gave a quantity of lead chromate equivalent to 2 g. (45%) of lead chloride. The residue from the ammonium acetate extraction was treated with boiling chloroform, and the resulting residue was 0.4 g. (5.8%) of diphenyllead dichloride. The chloroform solution was evaporated under reduced pressure, and the residue was dissolved in an excess of hot alcohol. Upon cooling 2.5 g. (30%) of tetraphenyllead was isolated. The mother liquor, upon evaporation, yielded 0.5 g. (6.6%) of triphenyllead chloride.

In a corresponding experiment, but with an excess of triphenyllead, the products were 3.6 g. (44%) of tetraphenyllead and 2.1 g. (47%) of lead chloride. A color test was obtained from the petroleum ether solution indicating the presence of organoaluminum compounds. Hydrolysis of the entire reaction mixture gave benzene upon fractionation.

Triphenyllead chloride and triphenylaluminum.—A mixture of 4 g. (0.00845 mole) of triphenyllead chloride and an excess of triphenylaluminum (prepared from 0.034 mole of diphenylmercury and aluminum in xylene solution) was heated on a steam bath for six hours. A quantitative conversion to tetraphenyllead took place under these conditions.

Tri-o-tolyllead and aluminum chloride.—A mixture of equivalent amounts (0.02 mole) of tri-*o*-tolyllead and aluminum chloride was heated on a steam bath for four hours, during which time there was a separation into two layers. The upper layer gave no color test and did not react with benzoyl chloride. Hydrolysis of the lower layer yielded 2.2 g. (40%) of lead chloride, 4 g. (35%) of tetra-*o*-tolyllead and 2 g. (21%) of unchanged tri-*o*-tolyllead.

In another experiment, the mixture was heated for six hours. The products isolated were 1.4 g. (13.5%) of tri-*o*-tolyllead chloride, 3.5 g. (30.5%) of tetra-*o*-tolyllead, and 2.5 g. (45%) of lead chloride.

SUMMARY

The following cleavage reactions have been shown to take place with phenyl- and ethyllead compounds: $R_4Pb + AlCl_3 \rightarrow R_3PbCl + RAlCl_2$; $R_4Pb + RAlCl_2 \rightarrow R_3PbCl + R_2AlCl$; $R_3PbCl + AlCl_3 \rightarrow R_2PbCl_2 + RAlCl_2$.

With ethyllead compounds, the R_2PbCl_2 compound is not isolated, and the aluminum compounds accelerate its decomposition to lead chloride, ethyl chloride and disproportionation products of the ethyl radicals.

Tetraethyllead reacts promptly with anhydrous ferric chloride to give excellent yields of ferrous chloride of high purity; with chloroplatinic acid to give platinum; and with bismuth chloride to give ethylbismuth compounds.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ON 1,2 AND 1,4 ADDITION[1]. III. NITROGEN TRIOXIDE AND TRIMETHYLETHYLENE

ARTHUR MICHAEL AND G. H. CARLSON

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In 1878, Lunge[2] showed that arsenous oxide and nitric acid of density 1.35 gave a gas containing nitrogen monoxide and dioxide in approximately equimolecular amounts, and that a more concentrated acid, in proportion to the density, gave nitrogen dioxide in excess. The significance of these results, however, has not been generally recognized in organic research[3]. In some of the researches on the "addition of nitrogen trioxide", the "nitrous fumes" were generated from the concentrated acid; in these investigations, the reaction mixtures contained a relatively large proportion of products derived from nitrogen tetroxide and were, therefore, only partially representative of the reactions of the trioxide. Extensive studies have been made on the addition of the higher oxides of nitrogen to alkenes, but the conflicting conclusions set forth in the literature, especially concerning the addition of the trioxide, attest to an imperfect understanding of the complex reactions.

Wallach[4] showed that trimethylethylene in acetic acid solution reacted with "nitrous fumes" from "concentrated" nitric acid to give the maximum yield (50%) of the so-called trimethylethylene nitrosate, subsequently shown to be the dimeric nitric ester of 2-methyl-3-nitrosobutanol-2[5], $[(CH_3)_2C(ONO_2)CH(NO)CH_3]_2$(I), and that with diluted acid lower yields

[1] For previous papers, see: (*a*) MICHAEL AND WEINER, *J. Am. Chem. Soc.*, **59**, 744 (1937); (*b*) MICHAEL AND CARLSON, *ibid.*, **59**, 843 (1937).

[2] (*a*) LUNGE, *Ber.*, **11**, 1641 (1878). (*b*) For a complete resumé of the literature on this subject see, Gmelin, Handbuch, 8th ed. (1936), Syst. no. 4, 739.

[3] WIELAND AND BLÜMICH [*Ann.*, **424**, 75 (1921)] showed that stilbene and "nitrous fumes" from concentrated nitric acid yielded a mixture of the nitroso-nitro, and the dinitro addition product, while the first compound was obtained almost exclusively with fumes from a diluted acid.

[4] WALLACH, *Ann.*, **241**, 292 (1887).

[5] SCHMIDT, *Ber.*, **35**, 2336 (1902). Instead of the trivial names nitrosite and nitrosate, chemically correct terms are used. Even more irrelevant is the designation "pseudonitrosite", advanced by WIELAND [*Ann.*, **328**, 156 (1903)] for nitroso-nitroxyl addition products to ethylene derivatives.

were produced. On the other hand, according to Schmidt[6], the moist gas generated from concentrated nitric acid (density 1.43) reacted with trimethylethylene in cold ether solution to form, primarily, a blue, oily product, which was assumed to be mainly the nitrous ester of 2-methyl-3-nitrosobutanol-2, $(CH_3)_2C(ONO)CH(NO)CH_3$(II); chiefly, because of its color and the gradual deposition of a crystalline compound, which was assumed to be the dimeric form of II, with a structure analogous to that of the nitric ester (I). The crude product decomposed on distillation, and the composition of the oil could not be ascertained definitely, yet Schmidt concluded that the primary reaction product consisted mainly of II and a small amount of I, which was assumed to be formed by oxidation of II. Although this conclusion is generally accepted in the literature, our results with trimethylethylene and nitrogen tetroxide[1b] show that, with addenda of such protean chemical properties as the higher oxides of nitrogen, the addition reactions are complex. We have, therefore, re-examined the reaction between trimethylethylene and "nitrous fumes", in order to determine the structure and the relative yields of the reaction products and to correlate the proportions of these products with the composition of the gases generated from arsenous oxide and nitric acid of varied concentration.

In our attempts to duplicate Schmidt's experiments, as far as is possible from the indefinite descriptions, we passed the moist gas generated from technical arsenous oxide and nitric acid (density 1.43 at 20°) into cooled ether solutions of trimethylethylene (experiments 1 and 2, Table I), but we obtained, instead of the polymerized nitrous ester (II), the corresponding, dimeric nitric ester, in amounts representing 1 per cent. and 0.8 per cent., respectively, of the reaction products; the main product, a greenish-blue oil, deposited no solid during two weeks. In Schmidt's and in these experiments the air in the apparatus was not removed; the oxygen, available for conversion of nitrogen trioxide to tetroxide, with consequent formation of organic products derived from the latter oxide, corresponded, in our experiments, to a maximum yield of tetroxide derivatives amounting to only 10–15 per cent. of the isolated reaction product, whereas the actual yield of tetroxide derivatives was much higher, as subsequent experiments showed. In an atmosphere of nitrogen, the moist gas, generated from nitric acid of density 1.43, acted upon trimethylethylene without solvent, to yield (experiment 4) 40.5 per cent. of the nitric ester (I); with acid of density 1.30, the yield decreased to 6.6 per cent. (experiment 5); yet 1 per cent. of the bisnitrate was formed with acid so dilute (density 1.23) that the "nitrous fumes" contained an excess of the monoxide, manifested by a continuous evolution from the reaction mixture (experi-

[6] SCHMIDT, *Ber.*, **35**, 2323 (1902).

ment 6). These results lead to the conclusion that "nitrous fumes", even in the absence of atmospheric oxygen, yield derivatives of nitrogen tetroxide.

In previous experiments[1b], it was found that the dimeric nitrate (I), produced by the action of nitrogen tetroxide upon trimethylethylene without solvent, represented about 45 per cent. of the reaction product, and that an average yield of 33 per cent. was formed in petrol solution. As-

TABLE I

REACTION OF "NITROUS FUMES" WITH TRIMETHYLETHYLENE

EXPT. NO.	1	2	3	4	5	6
Trimethylethylene, g.	20	20	20	10	10	15
HNO_3, $d^{20°}$	1.433	1.431	1.41	1.431	1.302	1.225
Atmosphere	Air	Air	Air	Nitrogen	Nitrogen	Nitrogen
Temp., °C.	3–5	5–8	−10	0–10	0–5	0–5
Time, mins.	300	60	150	45	75	90
Products: Solid (A), g.	0.3	0.3	0.8	5.5	0.6	0.05
Products: Liquid: Total, g.	29.5	35.8	32.5	9.3	8.6	7.6
Products: Liquid gave (A), g.	0	0	0.7	0.5	0	0
Products: Liquid gave (B), g.	0	0	0	0	0.7	0.6
Products: Liquid gave (a) Blue Filtrate, g.	29.5	35.8	28.2	3.3	7.8	6.7
% (A)	1.0	0.8	4.5	40.5	6.6	0.6
% (B)					7.6	7.8

Technical arsenous oxide (120 g.), 80 cc. of nitric acid and 60 cc. of ether were used in experiments 1–3; in 4–6, no solvent was used, and the gaseous reactant was generated from 60 g. of arsenous oxide and 40 cc. of the acid. Filtrate (*a*) gradually turned green, but deposited no solid (experiments 1, 2, and 4); the oil in experiment 3 distilled at low pressure to give 13.3 g. of blue distillate and 14.6 g. of green, residual oil; neither product was identified. The blue filtrate (*a*) (experiment 5) gave: (*1*) 2.7 g. of blue distillate, and (*2*) 5.2 g. of green, residual oil (molecular weight in freezing benzene, 235). On refractionation at 2 mm., fraction (*1*) gave a blue distillate (yield about 2 g.; n_D^{20} 1.4430; *Anal.* Found: C, 49.39; H, 7.41) and about 0.5 g. of greenish-blue, residual oil, n_D^{20} 1.4535. The blue distillate appeared to be identical with the corresponding oils isolated from the products prepared in ether solution (see Table III). Letter A designates $[(CH_3)_2C(ONO_2)CH(NO)CH_3]_2$ and B represents $[(CH_3)_2C(NO_2)CH(NO)CH_3]_2$.

suming that the bis-nitrate isolated in experiments 5 and 6 represents, similarly, 45 per cent. of the total product derived from nitrogen tetroxide, derivatives of the latter oxide constitute 14.5 per cent. and 1.4 per cent. of the respective reaction products. Whereas these values appear to be in accord with the chemical behavior of nitrogen trioxide, the estimated concentration of tetroxide derivatives, 90 per cent. and 57.5 per cent., respectively, in experiments 4 and 27 (Table IV), the former without and

the latter with petrol as solvent, cannot be reconciled with Lunge's analytical data[2a]. An entirely satisfactory explanation for these anomalies does not present itself. However, the course of reaction with nitrogen tetroxide varied greatly with the solvent[1b], and a similar "solvent effect" is not unlikely in reactions with nitrogen trioxide. Furthermore, the "trioxide" is largely dissociated, except at low temperature[2b] and, since the $-NO_2$ residue has a strong, but the $-NO$ residue a weaker, affinity for the unsaturated carbons of an alkene, loss of nitric oxide from the reaction mixture, with a preferential formation of a nitrogen tetroxide product, is not improbable. A gas mixture of anhydrous nitrogen tetroxide and the monoxide, with the latter in large excess, acted upon trimethylethylene, in ether solution at $-25°$, to yield an oil from which no solid product separated; at $-80°$ in ether solution, a low (4.3 per cent.), and in petroleum ether a higher (the actual value cannot be stated because the filtered, liquid product decomposed vigorously), yield of nitrate (I) was obtained by treating trimethylethylene with the blue liquid formed by saturating nitrogen tetroxide with the monoxide at $-80°$. Whereas the solid product in these experiments was derived from nitrogen tetroxide, in experiments 5 and 6, with gases of approximately the composition of nitrogen trioxide[2a], a crystalline solid, undoubtedly identical with Schmidt's "bis-trimethylethylene-nitrosite", was obtained in low yields, 7.6 per cent. and 7.8 per cent., respectively. However, the product, contrary to Schmidt, is not the dimeric form of the nitroso-nitrite (II), but it is the dimeric nitroso-nitro derivative of trimethylethane, $[(CH_3)_2C(NO_2)CH(NO)CH_3]_2$(III), yielding the corresponding, monomeric diamine when reduced catalytically. Because neither "nitrous fumes", though containing an excess of the monoxide, nor the relatively pure, liquid "nitrogen trioxide" acted upon trimethylethylene to yield compound III, and the latter appeared in only low yields in experiments 5 and 6, notwithstanding that the experimental conditions were seemingly favorable for the formation of the derivative of nitrogen trioxide, the formation of III as the main product, under the conditions of Schmidt's experiments and with acid of density 1.43, is inexplicable.

From the results of thirty-five experiments, made under controlled conditions, a correlation between the yields of the reaction products and the experimental conditions is not discernible. The total product in experiment 11 (Table II) was 1.7 times that of experiment 10, and more than twice that of experiment 12, in which the reaction time was longer and the density of the acid only slightly less than in experiments 10 and 11. The results of the grouped experiments 2–4, 9–11, and 15–16 (Tables I and II) do not accord with the experimental conditions, and in the paired experiments 1–2, 7–8, 17–18, and 20–21 (Tables I, II, and IV),

the yields of product are actually in an inverse order with respect to the time of reaction. The results obtained with moist "nitrous fumes" are no more consistent in the absence of than in the presence of air and, although almost identical yields of total product appeared in three experiments (24–26, Table IV), made with dried gas in an atmosphere of nitrogen, comparison with the result of experiment 23, made in the presence of air, shows that even under anhydrous conditions results differed widely. Equally discordant were the yields of the solid reaction products. At −10° (experiment 3, Table I), the product yielded 4.5 per cent. of the dimeric nitrate (I), but, in experiments 7 and 8 (Table II), the dimeric nitroso-nitro compound (III) separated in yields of 9.4 per cent. and 3.4 per cent., respectively, from the blue oils formed at 4° and 7°. These wide divergencies in the results of experiments 7–8 may depend, not only upon slight changes in experimental conditions, but, also, upon uncontrollable variations in the composition of the gaseous reactant. With nitric acid yielding nitrogen monoxide and dioxide in nearly the same quantity, a slight change in the concentration of the acid may alter the composition of the evolved gas materially, whereas a corresponding change, with an acid yielding a large excess of one of the oxides, may be comparatively slight. However, even with acids (density 1.242–1.312) yielding an excess of nitric oxide[2a], the results were not consistent, and the anomalous behavior of the arsenous oxide and nitric acid mixtures extends to acids of density varying from 1.242–1.433[7].

The moist gas, generated with nitric acid of density 1.30–1.312 (experiments 9–16, Table II), acted upon trimethylethylene in ether solution to form products yielding 8.6–17.4 per cent. of the dimeric nitroso-nitro compound (III). The best yield (17.4 per cent.) appeared in experiment 10, in which the product, immediately after preparation, was separated by distillation at low pressure into a slightly volatile green, and an easily volatile blue, oil from which the dimeric compound separated.

[7] Although Schmidt, and other early investigators, reported no difficulty in reproducing results with "nitrous fumes", Klemenc and co-workers [*Z. anorg. Chem.*, **115**, 131 (1921); **141**, 239 (1925)] found that the rate of oxidation of arsenous oxide by nitric acid varied, even under rigidly controlled conditions. Smith and Miller [*J. Ind. and Eng. Chem.*, **16**, 1168 (1924)] found that mercury, depending upon the concentration, promoted or inhibited the oxidation, yet, with respect to other varied and controlled factors, the experimental results could not be correlated and, although Ashenasy and Elöd [*Z. anorg. Chem.*, **162**, 161 (1927)] have shown that the rate of oxidation is dependent to a great extent upon the rate of solution of the arsenous acid, important factors which strongly influence the oxidation process remain unknown. In our experiments, the nitric acid and arsenous oxide mixtures were heated under identical conditions, yet the rate of formation of the "nitrous fumes" differed greatly, as was manifested by the formation, under seemingly comparable conditions, of variable yields of the organic products.

TABLE II

REACTION OF "NITROUS FUMES" WITH TRIMETHYLETHYLENE

EXPT. No.	7[a]	8[b]	9[c]	10[d]	11[e]	12[f]	13[f]	14[g]	15[h]	16[i]
HNO_3 d^{20}	1.4138	1.4138	1.3054	1.3054	1.3054	1.3011	1.3011	1.30	1.312	1.312
Reaction: Time, mins.	90	60	120	120	120	150	300	60	120	120
Reaction: Temp., °C.	4	7	4	4	5	5	5	−12	3	3
Crude Product: Total, g.	26.0	36.0	27.0	19.0	33.0	16.0	20.7	26.0	10.0	17.4
Crude Product gave: (B) g. deposited	2.4		2.8		0.7	1.1		4.0	0.8	1.5
Crude Product gave: during, hrs.	72		84		12	24		36	70	42
Crude Product gave: (*a*) Blue Filtrate, g.	23.1		23.6		32.3	14.9		22.0	8.7	14.7
Distillation of Crude Product or Filtrate (*a*): Oil used, g.	21.7	36.0	22.4	19.0	32.3	35.6		22.0	8.7	14.7
gave: (*b*) Blue dist. deposited Total g.	7.8	18.3	9.4	10.5	15.3	17.2		8.7	3.8	9.1
gave: (*b*) Blue dist. deposited (B) g.		1.2		3.3		3.6			0.1	
gave: (*b*) Blue dist. deposited during hrs.		40		60		36				
gave: (*c*) Residual Green Oil, g.	13.9	16.9	12.6	8.8	17.2	17.6		9.5	4.6	5.4
Sulphone from Oil (*c*): Oil used, g.		2.0	3.0	2.0					3.8	4.3
gave: $NaNO_2$, g.			0.5	0.4					0.45	0.6
gave: Crude thioether, g.		2.8	2.1	2.0					2.8	3.2
gave: Sulphone (N), g.		1.1	0.35	0.7					1.4	1.0
Fractionation of Blue Oil (*b*): Oil (*b*) used, g.		16.1	9.1	6.7	15.3	12.8			3.0	8.7
gave: (*d*) Blue dist. deposited Total g.		9.7	7.0	2.8	12.4	9.2			2.0	6.4
gave: (*d*) Blue dist. deposited (B) g.					2.7					
gave: (*d*) Blue dist. deposited during hrs.					36					
gave: (*e*) Residual Green Oil, g.		5.2	1.7	3.4	2.7	3.3			1.0	2.0
% (B)	9.4	3.4	13.2	17.4	11.2	13.0		11.0	9.0	8.6

See notes on following page.

Notes to Table II

Experiment 15 was made with 15 g. of trimethylethylene and 45 cc. of ether; otherwise 20 g. of the alkene and 60 cc. of ether were used. Generally 120 g. of technical arsenous oxide and 80 cc. of nitric acid were used; in 12 and 13, 200 g. of the oxide reacted with 100 cc. of the acid and, in 16, 120 g. of the analytical grade of the oxide with 80 cc. of the acid. Letter B designates $[(CH_3)_2C(NO_2)CH(NO)CH_3]_2$; C the dinitro compound, $(CH_3)_2C(NO_2)CH(NO_2)CH_3$; M an alcoholic solution of sodium thiophenylate (prepared by dissolving two equivalents of sodium, assuming that the analysed oil consisted entirely of C, in 20–25 cc. of methyl alcohol and adding the corresponding amount of thiophenol); and N the sulfone, $(CH_3)_2C(SO_2C_2H_5)CH(NO_2)CH_3$.

[a] Filtrate *a*, at 2 ± 2°, deposited 0.05 g. of B during 43 days. In duplicate experiments, 5 g. of oil *c*, with M, gave: 0.9 g.; 1.0 g. of $NaNO_2$ and (*1*) 4.3 g.; (*2*) 4.6 g. of oily product. The combined oils distilled to give: (*1*) 1.1 g. (b.p. 43–45° at 2 mm.), and (*2*) 6.0 g. of oil, b.p. 132–135° at 2 mm.; oxidation of 1 g. of *2* gave 0.7 g. of N.

[b] Distillate *d*, b.p., 38–50° at 2 mm., decomposed when distilled at ordinary pressure.

[c] Filtrate *a*, at 2 ± 2°, deposited 0.75 g. of B during 50 hours. Oil *c*, mol. wt., 213. Oil *e*, with M, gave 0.5 g. of $NaNO_2$ and 1.6 g. of oil which was oxidized, yielding 1 g. of N.

[d] Distillate *b* deposited B: the filtrate gave distillate *d*, b.p. 30–34° (nearly all at 31–32°) at 2 mm., and the residual, bluish-green oil *e*. Oil *e* gave: 2 g. of blue distillate, b.p., 50–55° at 2 mm., and 0.6 g. of residual, green oil, which, with M, gave 1.5 g. of oil, yielding, after oxidation, 0.5 g. of N.

[e] Oil *c* steam-distilled: the residual oil (2.5 g.) was not investigated; the volatilized oil (10 g.) distilled, at 2 mm., to give 4 g. of blue distillate (not investigated) and 6 g. of residual, green oil which solidified at −80°. Adhering oil was separated from the bluish wax (4.5 g.; m.p. 40–50°) with an inverted filter; recrystallization at −80° gave 2.1 g. of pale blue wax, which was sublimed at low pressure and gave pure *C*. The oily material (3.3 g.) isolated during purification of *C* gave, with M, 1.2 g. of impure $NaNO_2$ and 3.5 g. of oily product which was oxidized, and yielded 1.9 g. of N.

[f] Filtrate *a* of 12 and the total product of 13 were combined. Oil *c*, mol. wt., 235; 15 g. of the oil, distilled with steam, gave: (*1*) 8 g. of blue distillate, and (*2*) 4.4 g. of residual green oil of mol. wt., 273. From oil (*2*), at 100° at low pressure, a small amount of material volatilized, leaving a residual oil of mol. wt. 360. Using a fractionating column, a portion (7.8 g.) of blue oil (*1*) was separated into (*3*) 2.8 g. of blue distillate and (*4*) 5 g. of green, residual oil. Oil (*4*), distilled in a small Claisen flask at 2 mm., gave 3–4 drops of easily volatile blue liquid and a colorless wax. With M, 4.6 g. of the wax gave 5 g. of an organic product (*f*); oxidation of 2 g. of *f* yielded 1.6 g. of N.

A portion (2.5 g.) of (*3*) was fractionated and gave (*5*) 1.2 g. of blue distillate (n_D^{20} 1.4433; *Anal.* Found: C, 48.75; H, 8.04) and (*6*) 1 g. of residual blue oil, n_D^{20} 1.4482, from which 0.05 g. of B separated during 24 hours.

Distillate *d*, with the bath-temperature at 32°, gave (*7*) 4.1 g. of bluish distillate (*Anal.* Found: C, 49.96; H, 7.37) and (*8*) 5.1 g. of bluish-green, residual oil, which, after extraction with 5% alkali, gave: C, 48.13; H, 7.18. A solution of 3.8 g. of (*7*) in 10 cc. of ether was saturated with dry HCl at 0°: after 15 hours, solvent and excess HCl were removed *in vacuo*, the residual oil was diluted with ether, and the solution was washed with water. Solvent was removed *in vacuo* from the dried solu-

tion; the residual oil, with a solution prepared from 1.5 g. of Na, 30 cc. of methyl alcohol and 7.3 g. of thiophenol, gave 3.4 g. of oily product, and oxidation of 1.5 g. of the latter oil yielded 0.5 g. of N.

Oil *e*, treated with M, gave 0.9 g. of $NaNO_2$ and 2.6 g. of oil, yielding, after oxidation, 1 g. of N.

[g] Distillate *b* was fractionated and gave: (*1*) pale green oil, b.p., 32° at 4 mm.; n_D^{20} 1.4375; (*2*) blue oil, b.p., 44–46° at 2 mm.; n_D^{20} 1.4470 (*Anal.* Found: C, 46.49; H, 7.59; N, 14.87); and (*3*) blue residue, n_D^{20} 1.4480.

[h] Distillate *b* deposited 0.1 g. of B: a portion (3 g.) of the filtrate gave blue distillate *d*; n_D^{20} 1.4411 (*Anal.* Found: C, 48.00; H, 7.47), and oil *e* which, with M, gave 0.8 g. of oily product, yielding, after oxidation, 0.2 g. of N. A solution of 1.2 g. of *d* in 10 cc. of ether, saturated with HCl at 0°, was treated as described above, and the washed and dried product was analysed: 0.2315 g. gave 0.0410 g. AgCl. Oil *c*, mol. wt. 226.

[i] A portion (8.7 g.) of distillate *b* was fractionated, and gave distillate *d*; n_D^{20} 1.4416 (*Anal.* Found: C, 48.78; H, 7.55), and oil *e* which, with M, gave 1.8 g. of oily product, yielding, after oxidation, 0.7 g. of N. A solution of 1.9 g. of *d* in ether, saturated with HCl, was treated as above: the residual oil was analysed, 0.2789 g. gave 0.695 g. AgCl. Oil *c*, mol. wt., 253.

Accordingly, the lower yields of compound III, obtained when it was isolated from the crude and from the distilled, blue oils separately, are not attributable to decomposition during distillation. In an atmosphere of nitrogen, although the technical and the analytical grades of arsenous oxide were used, respectively, in experiments 15 and 16, the reaction products yielded nearly the same proportion (9.0 per cent. and 8.6 per cent.) of compound III; an indication that the composition of the gaseous reactant was the same in the two experiments. But the agreement in the relative yields of the dimeric compound may have been accidental, for the yields of total product in these two experiments differed greatly and, in subsequent experiments, neither with moist "nitrous fumes" (experiments 20–22, Table IV), nor under anhydrous conditions (experiments 23–26, Table IV) were concordant results obtained. The yield (20 per cent.) of compound III obtained with dried gas generated from nitric acid of density 1.35 (experiment 23, Table IV) is higher than the best yield (17.4 per cent.) obtained with moist gas (experiment 10, Table II), but the difference, in view of the wide variation (20 per cent.) in the results obtained under anhydrous conditions, is not significant. With dry "nitrous fumes" at −80°, a product was formed which decomposed briskly below 0°, with evolution of gas, leaving an oil from which compound III separated in a yield of 20 per cent. (experiment 28, Table IV). In view of this result, the inconsistent yields of compound III, with respect to reaction temperature, may be attributable to a primary formation of a reaction product, which undergoes spontaneous decomposition to yield products isolable under ordinary conditions. Although our experimental conditions, much more than those of Schmidt, favored the formation of derivatives of nitrogen

trioxide, the results were not reproducible, nor reconcilable with the experimental conditions, and under no conditions could the high yields (55–66 per cent.) of Schmidt's "bis-nitrosite" be approached.

The liquid products formed by the action of "nitrous fumes" upon trimethylethylene in ether solution were separated by low pressure distillation into an easily volatile, blue distillate (oil *b*, Table II), representing approximately 50 per cent. of the reaction product, and a much less volatile, green oil (oil *c*; Table II) from which, as the only pure product, a 6 per cent. yield of a waxy product was isolated in experiment 11 (Table II). This wax is identical with that formed from nitrogen tetroxide and trimethylethylene, and hitherto has been considered as the nitro-nitrite derivative of trimethylethane[1b], $(CH_3)_2C(ONO)CH(NO_2)CH_3$; mainly because of the facile and quantitative conversion, with sodium thiophenylate, to the corresponding thio-ether, $(CH_3)_2C(SC_6H_5)CH(NO_2)CH_3$. However, the wax is reduced catalytically to isoamylenediamine, and, consequently, must be the dinitro addition product of 2-methylbutene-2, $(CH_3)_2C(NO_2)CH(NO_2)CH_3$(IV). Although a part of the dinitro compound (IV) was volatilized during low-pressure distillation and could be recovered as a greenish oil (oil *e*, Table II) by fractionation of the distilled blue oil (oil *b*, Table II), a semi-quantitative separation of the dinitro compound was not possible; the best separation was effected by steam-distillation, but the method is unsatisfactory because some of the product is decomposed, and the volatilized oil contained, besides 70–80 per cent. of the dinitro compound, unidentified blue, or greenish-blue, products. Indirect determinations, made by treating portions of the crude green oil (oil *c*, Table II) with alcoholic sodium thiophenylate and oxidizing the thio-ether thus formed to the corresponding sulfone[1b], showed that the dinitro compound (IV) constituted 14, 16, 8.5, 12 and 7 per cent., respectively, of the products in experiments 7, 8, 12, 13, 15, and 16. Although the pure sulfone is fairly resistent to the action of chromic anydride, as oxidant for the crude thio-ether, the anydride proved unsatisfactory because in several experiments the oxidation was destructive. With hydrogen peroxide, beside the sulfone, oily products were sometimes produced, which resisted the action of the peroxide, but were destructively oxidized by chromic anhydride. Neither with the anhydride, nor with the peroxide, was the yield of sulfone equivalent to the yield of sodium nitrite formed in the reaction with sodium thiophenylate and, although the salt may have been formed, in part, from other products than the dinitro compound (IV), the yields of the sulfone are considered only as minimum values. Experiments showed that the nitroso-nitro compound (III), by treatment with "nitrous fumes" in benzene, or with ozone in chloroform, is oxidized to the dinitro compound (IV). However, while the appearance of the dinitro compound in the addition products, formed from "nitrous fumes",

may be attributed, in part, to oxidation of compound III, or the corresponding, primarily-formed, monomeric nitroso-nitro derivative, yet, because nitrogen dioxide adds very facilely to the alkene, the dinitro compound probably is mainly formed by direct addition of the dioxide. Accordingly, the yield of the dinitro compound (IV) should depend upon the composition of the "nitrous fumes", but a definite correlation is not established by the results of our experiments.

Molecular-weight determinations indicated that the green oil (oil *c*, Table II), which did not distill at the pressure of a mercury pump, contained products of high molecular weight; the values 213, 235, 226 and 253 were obtained, respectively, in experiments 9, 12, 13, 15, and 16. These values varied with the extent of separation of the volatile products attained by low-pressure distillation. After removing, by steam-distillation, the major part of the dinitro compound (IV) from the crude oil, in experiments 12 and 13, the residual green oil gave the value 273 in a molecular-weight determination, but, after heating to 100° at the pressure of a mercury pump, a small amount of oil, apparently impure dinitro compound (IV), volatilized, leaving a very viscous oil of molecular weight 360. The chemical nature of the viscous liquids, constituting 10–20 per cent. of the reaction product, could not be determined: probably the products are formed by the action of "nitrous fumes" upon polymers of trimethylethylene, which are rapidly formed by the action of strong acids upon the alkene.

The distilled blue reaction product (oil *b*, Table II) in experiments 8, 10, 12, 13, and 15, deposited the recorded amounts of the dimeric nitroso-nitro compound (III). The filtrates in these experiments, and the distilled blue oils (oil *b*, Table II), from which no dimeric product separated in experiments 9, 11, and 16, were fractionated (at 2 mm.) with an efficient column, and gave blue distillates (oil *d*, Table II) and greenish residual oils (oil *e*, Table II) of which the dinitro compound (IV) constituted 20–50 per cent., as determined indirectly by converting the dinitro compound to the corresponding phenylsulfone. The intensely blue distillate (oil *d*, Table II) was a mixture of products and, in experiment 11, deposited a 22 per cent. yield of the dimeric compound III; usually no solid appeared after the second distillation. By redistilling the blue oil very slowly, a markedly less colored fraction (fraction I, Table III) was obtained, which gave values on analysis closely approaching those calculated for 2-methyl-3-nitrobutene-2 ("nitroamylene")[8].

[8] Haitinger [*Monatsh.*, **2**, 290 (1881)], by the action of concentrated nitric acid upon tertiary amyl alcohol, obtained mainly oxidation products and a low yield of impure "nitroamylene." The synthesis undoubtedly proceeded through the preliminary formation of nitrous fumes and isopentylene-2.

These results led us to the conclusion that the fractionated blue oils consisted mainly of the depolymerized nitroso-nitro compound (III) and nitroamylene. No direct relationship is discernable between the refractive

TABLE III

FRACTIONATION OF PRODUCTS

EXPT. NO.	FRACTIONS	GRAMS	n_D^{20}	% C	% H	NITROALKENE, %
7[a]	I	1.3	1.4364			
	II	2.6	1.4405			
	III	2.7	1.4485			
9[b]	I	2.9	1.4426	51.94	7.88	99
	II	1.3	1.4447	50.10	7.56	80
	III	2.6				
	IV	1.9	1.4480	47.22	8.74	50
10[c]	I	0.95	1.4365	51.17	7.61	96
	II	0.95	1.4382	50.82	7.93	90
	III	0.90	1.4416			
11[d]	I	1.7	1.4381	51.53	7.88	95
	II	2.8	1.4408			
	III	3.8	1.4449			
	IV	3.5	1.4440	48.70	7.22	69

Distillate *d* (Table II) in experiments 9, 10, and 11 and distillate *b* (Table II) of experiment 7 were redistilled very slowly and gave fractions I–III of Table III: the bath temperature was 30–35°; 40° in experiment 7. An all-glass condensing apparatus, cooled to −25°, was used; distillation temperatures could not be determined. The nitroalkene content was estimated from the analytical data, assuming that the distillates contained only the nitroalkene and compound III.

[a] Distillate *b* (Table II) gave fractions I–III.

[b] Distillate *d* (Table II) gave fractions I–III; residual oil III was distilled in a small Claisen flask and gave 1.9 g. of blue distillate (IV), b.p., 95–102° at 60 mm., leaving 0.5 g. of green residual oil.

[c] Distillate *d* (Table II) gave fractions I–III. The distillates, at 2 ± 2°, deposited no solid during 14 days, and were then analysed: the refractive index of fraction I had changed to 1.4373 at 20°; the value for fraction II remained at 1.4383 at 20°.

[d] Distillate *d* (Table II) (b.p., 35–42° at 2 mm.; bath temperature 70°) deposited 2.7 g. of the dimeric compound III; the filtrate (9.1 g.) yielded 0.3 g. of the same solid. The filtrate (8.3 g.) gave fractions I–III; residue III was distilled and gave distillate IV.

indices and the analytical data, but the irregularities may be attributable to variations in the refractivity of dissolved nitroso-nitro compound (III), whose refractivity varies with the degree of polymerization, concentration, and solvent[6]. An attempt to estimate the concentration of the nitroamyl-

ene, by comparing the refractive indices of the blue distillates with those of the supposed components, failed; the difference between the values of the respective compounds is apparently small, and the monomeric nitroso-nitro compound (III), prepared by depolymerization of the bis-derivative at 70–80°, completely repolymerized to the crystalline solid within 2–3 minutes, with a rapid shift in the refractive index. Estimation of the composition of the liquid, assuming the oil to contain only the above-mentioned two components, was made on the basis of analytical data. The results indicated that the fractionated blue oils contained 70–80 per cent. of the nitroalkene; accordingly, the latter constitutes 10–20 per cent. of the reaction product. A summary of typical fractionations, with related analytical data, is given in Table III. An indirect determination of the concentration of the nitroalkene was made by saturating the fractionated blue oil with gaseous hydrogen chloride and determining the amount of organic chloride formed. The results indicated the presence of 10–18 per cent of the nitroalkene in experiments 15 and 16. In experiments 12 and 13, the fractionated blue oil was saturated with gaseous hydrogen chloride, and the product, treated with alcoholic sodium thiophenylate, gave a crude thio-ether from which 2-methyl-3-nitro-2-phenylsulfonebutane was obtained in a yield of 15 per cent. Although this small yield does not agree with the analytical data, which indicates the presence of 70–80 per cent. of the nitroalkene in the blue oil, the low yield of the sulfone (experiments 12 and 13), and of the corresponding chloride (experiments 15 and 16), may be attributed to elimination of hydrogen chloride from the primarily-formed, tertiary chloride, which loses hydrogen chloride very easily. The formation of the sulfone, however, even in the above amount, showed definitely that 2-methyl-3-nitrobutene-2 constituted a not inconsiderable proportion of the reaction product, formed by the action of "nitrous fumes" upon trimethylethylene.

While catalytic reduction of the crude and of the fractionated, blue oils in alcohol solution, in the presence or absence of hydrogen chloride, soon stopped, in acetic acid the reduction, at first, proceeded rapidly, but the rate then decreased, and reduction was complete only after several days. Ammonia, in varying amounts, was formed in all reductions of the blue liquid products. Reduction of the fractionated oils (experiments 39–41; Table VI) yielded, together with other basic products, 2-methyl-3-aminobutane, which confirms the presence of nitroisoamylene-2 in the crude addition products. The yield of the easily volatile amine, identified through the *p*-nitrobenzoate, indicated that the crude blue oils (oil A) in experiments 39–41 contained, respectively, 7.8, 2.5 and 1.3 per cent. of the nitroalkene. These results, since the amine was difficult to isolate, are not so inconsistent as it would seem, and support the estimated con-

centrations of the nitroalkene based on the analytical data (Table III). The widely divergent estimates, though the values are considered as only very approximate, undoubtedly indicate that the concentration of the nitroalkene in the crude addition products varies with the conditions under which the latter product is formed. However, the accuracy of the method of estimation is not known, and a direct correlation of the yield with the experimental condition is, therefore, not possible.

Diamines have been obtained, generally in low yields, by reduction of the crude, and of the purified, solid products formed by the action of "nitrous fumes" upon ethylene[9a], propylene[9b], butene-1[9c] and isobutylene[9d], but Schmidt[6,10], although a number of reduction methods were used, obtained basic compounds, other than ammonia, neither from the products prepared from trimethylethylene and "nitrous fumes", nor from those obtained with nitrogen tetroxide. Whereas the structure of the dimeric nitroso-nitrate (I) was definitely established by its chemical reactions[11], no direct evidence for the structure of the dimeric nitrogen trioxide addition product could be obtained, yet, because only ammonia was obtained upon reduction and treatment with organic bases apparently eliminated nitrogen dioxide, Schmidt[6] assumed that both nitrogen atoms could not be attached to carbon in the trioxide addition product and that it must have the nitroso-nitrite structure (II). However, since the trioxide derivative is catalytically reduced to isoamylenediamine, the nitroso-nitrite structure must be replaced by the nitroso-nitro formula (III)[12]. In the first reduction (experiment 31, Table V), the solvent was distilled *in vacuo*, and the residual syrup was alkalinized. Under these conditions, together with the diamine, some ammonia was liberated. Yet, hydrogen chloride, when bubbled into the acetic acid solution of the reduction product of experiment 32, precipitated only pure isoamylenediamine dihydrochloride (yield 87.8 per cent.) and, accordingly, catalytic reduction

[9] (*a*) DEMJANOW, *Chem. Zentr.* **1899**, I, 1064; (*b*) *ibid.*, **1901**, II, 333; (*c*) *Ber.*, **40**, 245 (1907); (*d*) SSIDORENKO, *Chem. Zentr.*, **1907**, I, 399.

[10] SCHMIDT, *Ber.*, **35**, 2336 (1902).

[11] The nitrate, with organic bases, yielded nitrolamines [WALLACH, *Ann.*, **241**, 296 (1887)]; with KNC, "cyanoisopropylmethylketoxime," $CH_3C(NOH)C(CH_3)_2CN$ [WALLACH, *Ann.*, **248**, 169 (1888)]; and, with sodium methylate, methylmethoxylisopropylketoxime [SCHMIDT AND AUSTIN, *Ber.*, **35**, 3722 (1902)]. It is not known whether these reactions proceed by direct or by pseudo-substitution, *i.e.*, by elimination and addition.

[12] The formation of nitroso-nitro addition products from mono- and diarylethenes has been demonstrated experimentally [*Ann.*, **328**, 154 (1903)] and, in view of these and Demjanow's results, Wieland [*Ann.*, **424**, 74 (1921)] suggested that nitrogen trioxide forms nitroso-nitro derivatives, so-called pseudonitrosites, with all alkenes and that Schmidt's "bis-trimethylethylene nitrosite" very probably belongs to this same group. No experimental evidence was given in support of this view.

does not eliminate much nitrogen, as ammonia, from the addition product. The diamine, as well as its dihydrochloride, yielded a crystalline dibenzoate, which proved to be identical with the dibenzoate prepared from the diamine formed by reducing the mono-, or the dihydrochloride of 2-methyl-2-aminobutanone-3 oxime[13] (experiments 35–37, Table V).

Formation of the nitro-nitrite of isopentane, $(CH_3)_2C(ONO)CH(NO_2)$-CH_3, by addition of nitrogen tetroxide to the alkene, the addendum functioning as $-ONO + -NO_2$, is theoretically possible and, indeed, the waxy addition compound, because its behavior towards sodium thiophenylate appeared to be analogous to that of the nitroso-nitrate (I), was assumed to be the nitrous ester. However, on reduction the products corresponding to the nitro-nitrite structure, ammonia and 2-methyl-3-aminobutanol-2, were not obtained, instead the waxy compound, whether prepared by the action of "nitrous fumes" or nitrogen tetroxide upon trimethylethylene, yielded isoamylenediamine (experiments 33 and 34, Table V) and, consequently, the waxy addition product must be the 2,3-dinitro derivative of isopentane. The diamine was identified through the toluenedisulfonamide and the dibenzoate. These products were identical with the corresponding derivatives of the reduction product of the bis-nitroso-nitro compound (III) and, also, of 2-methyl-2-aminobutanone-3 oxime.

Addition of nitrogen trioxide, with $-ONO$ and $-NO$ as the functional groups, may yield the nitroso-nitrite (II) which, in view of the facile conversion of the nitroso-nitro derivative (III) to the dinitro compound, may be oxidized, more or less completely, to the nitro-nitrite. But the latter product may also be formed by direct addition of nitrogen tetroxide to the alkene, and, like the nitroso-nitrite, would yield ammonia and 2-methyl-3-aminobutanol-2 on catalytic reduction. Consequently, through the reduction products, since a quantitative isolation was not realized, the presence of a mixture of the nitroso- and the nitro-nitrite in the blue oils could not be ascertained, nor did the volume of absorbed hydrogen give an insight into the composition of the product reduced. The nitrogen trioxide and tetroxide derivatives require, respectively, 5 and 6 moles of hydrogen for complete reduction, yet, since neither the original nor the reduced products could be separated semi-quantitatively, the relation between the volume of absorbed hydrogen and the composition of the liquid product, formed by the action of "nitrous fumes" upon trimethylethylene, is not apparent.

On reduction, the crude and the distilled blue products yielded ammonia,

[13] In the preparation of this oxime, and in its reduction, we followed methods employed by DREW AND HEAD [*J. Chem. Soc.*, **1934**, 49] for the preparation of isobutylenediamine.

but, although 2-methyl-3-aminobutanol-2, was probably formed in equivalent amount, but the amino alcohol could not be isolated, nor could crystalline derivatives be separated from the viscous oils obtained on acylation of the crude, or the distilled, reduction products (experiments 38–41; Table VI). While the yield of ammonia (experiment 41) indicated that the fractionated blue oil (oil A; Table VI) contained 21.5 per cent. of the nitro-nitrite derivative (II), the corresponding amino alcohol could not be isolated from the reduction products. The easily volatile 2-methyl-3-aminobutane was readily identified through the *p*-nitrobenzoate, but benzoylation of the higher-boiling amines yielded a viscous oil from which a very small amount of the dibenzoate of isoamylenediamine was isolated as the only crystalline and identifiable product. Acylation with *p*-nitrobenzoyl chloride gave, similarly, viscous, oily products, and camphorsulfonic acid, although it forms a crystalline salt with the isoamylenediamine (experiment 38), yielded an inappreciable amount of solid product with the high-boiling amines of experiment 39, and was not satisfactory as a means of separation of the basic reduction products. The diamine, undoubtedly derived mainly from the dinitro compound (IV), but possibly formed in part from the nitroso-nitro derivative (III), was isolated from the mixed amines as the dihydrochloride, but, as subsequent experiment showed, the salt, although only very slightly soluble in hot, secondary butyl alcohol, did not separate quantitatively from solutions containing an appreciable amount of the hydrochloride of 2-methyl-3-aminobutanol-2. Accordingly, the total yield of the diamine could not be determined, but, based on the yield of the isolated dihydrochloride (experiment 41), the diamine constituted at least 25 per cent. of the high-boiling reduction product. Almost the same yield (24 per cent.) of the diamine was isolated as the dibenzoate in experiment 38, but the concordance in the yields is probably accidental, and the values do not represent the total yield of the diamine.

The benzoylated reduction product (experiment 41, Table VI) yielded, on low pressure distillation, a viscous distillate and a residual oil, from which a small amount of the dibenzoate of isoamylenediamine was isolated. The distilled, viscous oil could not be crystallized, yet the crude product gave values on analysis in approximate agreement with those calculated for the benzoate of 2-methyl-3-aminobutane. While the separation of this easily volatile amine from the higher-boiling, basic products may have been incomplete in experiment 41, the separation was undoubtedly complete in experiment 38. Yet oily benzoylation products were obtained with the mixed amines, and in yields increasing with the boiling-point of the base acylated. Accordingly, since the reduction product (experiment 38, Table VI) boiled at a slightly higher temperature

than isoamylenediamine and, since benzoylation of the pure diamine yielded a product which crystallized readily (experiments 31–37, Table V), the oily benzoates of experiments 38–41 (Table VI), largely because of the appearance of ammonia in the crude reduction products, appeared to be derived in part from 2-methyl-3-aminobutanol-2 which, as subsequent experiments showed, yields oily acylation products that are difficult to crystallize and purify. The bis-nitroso-nitrate (I) was reduced catalytically (experiments 29 and 30, Table V) and, in accord with the previously determined structure[11], yielded, together with ammonia, 2-methyl-3-aminobutanol-2, but the easily soluble benzoate, and the toluene sulfonamide of the amino alcohol, crystalline products identical with the corresponding derivatives of the amino alcohol prepared from amylene bromohydrine, were obtained in varying and generally low yields, notwithstanding the fact that the amino alcohol used in the acylation was essentially pure. Accordingly, failure to isolate derivatives of the amino alcohol from the viscous oils obtained on acylation of the reduction products of the crude and the distilled blue oils (experiments 38–41, Table VI) may be attributed to the difficulty of isolating and crystallizing the relatively soluble acylation derivatives of the amino alcohol. Although the isolation was not realized, the amino alcohol was probably formed, yet our results do not definitely establish that nitrogen trioxide yield an addition product in which nitrogen is attached to carbon through oxygen.

EXPERIMENTAL

General procedure.—The trimethylethylene was prepared by heating tertiary amyl alcohol with 10% hydrochloric acid[14] and after fractionation, had the following properties: b.p., 37.5–38.5°; n_D^{20} 1.3872.

The three-necked reaction flask, provided with a mechanical stirrer and a thermometer, was connected by a glass tube, the lower end of which dipped below the ethene solution, to the top of a reflux condenser, which was attached to a 1-l. flask, charged with nitric acid and arsenous oxide, mixed with glass wool to prevent caking. The technical grade of arsenous oxide was used, except in experiments 16 and 22 in which the analytical grade was employed. In experiments 4–6, 15–16, 17–22, and 24–28, a 500-cc. flask, provided with a ground-glass joint and sealed-in tubes required to flush the apparatus with nitrogen, was sealed to the lower end of a reflux condenser. The latter was attached at the upper end, by a bent tube, to a 100-cc. bulb, which terminated in a tube extending below the ethene solution, contained in a three-necked flask provided with a stirrer, thermometer, and an exit tube of the bubble-counter type. The gas evolution was slow at ordinary temperature, and the generator was therefore heated in a boiling water bath, except in experiment 16 when the temperature was 45–50°. The reaction mixture was diluted with ether, except in experiment 27 (see notes, Table IV); suspended solid, if present, was removed by filtration, and the ether solution was washed with cold water, except in experiment 25 (see notes, Table IV). Solvent was removed from the dried ether solution *in*

[14] MICHAEL AND ZEIDLER, *Ann.*, **385**, 259 (1911).

vacuo, and the blue residual oil was distilled immediately, or after the dimeric compound III had separated. An all-glass apparatus, attached by a heavy rubber tube to a mercury vapor pump was used in the low-pressure distillations. The blue distillate (oil *b*, Table II) was refractionated at 2 mm., using a small modified Podbielniak column, and gave distillate *d* and residual oil *e*. In experiments 7, 14, and 23, the distillates were treated as described in the notes to Tables II, III and IV. In the distillations, the bath-temperature was gradually raised (during 2–3 hours) to 80°; the distillation temperatures were not recorded, except when the bath-temperature was kept constant (experiments 10 and 11). This distillation effected a separation of the more volatile products from the dinitro derivative (IV). Fraction *d* (Table II) was redistilled and gave fractions I–III (Table III).

A portion of the non-volatile green residual oil (*c*, Table II) was added to an alcoholic solution of sodium thiophenylate, most of the solvent was distilled and the inorganic salt was filtered off, if present in appreciable quantity. Solvent was distilled *in vacuo* from the filtrate, or from the partially concentrated reaction mixture, when no inorganic salt was isolated. The residual mixture was shaken with water and ether, the ether solution was washed with dilute alkali and dried, and the solvent was removed. The residual oil, or a portion, was oxidized with chromic anhydride, or with 30% hydrogen peroxide. The chromic anhydride, in weight equal to the crude thio-ether, was added in small portions to the hot, acetic acid solution of the thio-ether, the mixture was heated 5–10 minutes on a steam-bath and poured into ice-water (experiments 8, 10, and 11); the pure sulfone generally separated; if not, the oily products were re-oxidized. In the oxidations with hydrogen peroxide, the oils, dissolved in 5–10 cc. of glacial acetic acid, were treated with 4–5 times the required amount of 30% hydrogen peroxide, and sufficient acetic anhydride was added to give a clear solution. The temperature was not allowed to exceed 40°; after the vigorous reaction was completed, the solutions were kept at room-temperature for 12–15 hours and were then added to ice-water. The precipitated sulfone was generally pure; if not, it was purified by sublimation at low pressure.

Preparation of products used for reduction.—The experimental procedure previously described was followed and all the preparations were made in an atmosphere of nitrogen. The liquid product of experiment 23, which was made in air, and the oily products of experiments 27 and 28 were not reduced. Technical arsenous oxide (120 g.), 80 cc. of nitric acid, 20 g. of trimethylethylene, and 60 cc. of ether were used, except when the analytical grade of the oxide (experiment 22) and 60 cc. of petrol (experiment 27) were used. In experiments 17–22 and 27 moist, in experiments 23–26 and 28, dry "nitrous fumes" were used; in experiments 23 and 24 the gas passed, successively, through calcium chloride and phosphoric anhydride, but through two tubes of the anhydride in the other experiments. The results are summarized in Table IV. Letter A designates $[(CH_3)_2C(ONO_2)CH(NO)CH_3]_2$, and B the nitroso-nitro compound, $[(CH_3)_2C(NO_2)CH(NO)CH_3]_2$.

Catalytic reduction.—Acetic anhydride (50 cc.) was used as solvent in experiment 29, and glacial acetic acid (50 cc., except that 25 cc. was used in experiment 33) in the other experiments. At first, reduction of the solid addition products, the crude and the fractionated blue oils, proceeded rapidly in glacial acetic acid with platinum oxide catalyst, but the rate of reaction then dropped off suddenly and addition of fresh catalyst increased it for a short period only. Catalyst was removed by filtration, hydrogen chloride was bubbled into the filtrate, and the solid product (ammonium chloride, or, in experiment 32, the dihydrochloride of isoamylenediamine) was removed by filtration. Solvent was distilled at reduced pressure

TABLE IV

PREPARATION OF PRODUCTS FOR REDUCTION

EXPT. NO.	17	18	19	20	21[a]	22	23[b]	24[c]	25[c]	26[d]	27[e]	28[f]
HNO_3, $d^{20°}$	1.311	1.311	1.311	1.242	1.242	1.247	1.35	1.3075	1.3075	1.3075	1.242	1.3075
Reaction Time, mins.	150	210	120	180	420	300	120	120	120	120	180	120
Reaction Temp., °C.	3–5	0–3	0–7	−20	0–3	−10	−20	−20	−20	−15	−20	−80
Product Total g.	24.5	17.3	20.6	13.7	20.3	22.8	10.5	23.9	23.7	26.1	12.1	11.5
Product (B), g.	0			1.75	1.0		2.1	3.9	1.2	2.6	0.2	2.3
Product (A), g.	0										2.3	
% (B)	0		0	12.8	4.9	0	20	16.3	5.06	10	1.6	20

[a] After 3 hours, a test indicated that 14.2 g. of product had formed; 80 cc. of nitric acid (density 1.242) was added to the partially spent acid-oxide mixture, and gas absorption was continued for 3 hours.

[b] On steam-distillation the blue oil (7.5 g.) gave 4.5 g. of blue, and 0.7 g. of green, distillate, leaving 0.7 g. of green residual oil; the distillates deposited no solid.

[c] The filtrates deposited no solid during 11 days at 2 ± 2°; the reaction product in experiment 25 was not washed with water.

[d] The reaction product deposited 1.7 g. of B, and the filtrate yielded 0.9 g. of B.

[e] Solid (A, 1.6 g.) was removed by filtration; the heavy blue oil (*1*) was separated from the petrol solution (*2*). An ether solution of *1* was washed with water, dried and the solvent distilled *in vacuo*: the residual oil (4.6 g.) deposited 0.6 g. of A; the filtrate deposited 0.2 g. of B. Petrol solution *2* was washed with water and dried, and the solvent was distilled *in vacuo*; the residual oil (6 g.) deposited 0.2 g. of A.

[f] The "nitrous fumes" deposited solid nitrogen tetroxide in the cold gas-entrance tube. The reaction product evolved gas below 0° and about ⅓ of the solution was suddenly blown out of the flask: the residual solution (60 cc.) was washed with water and dried, and the solvent was distilled *in vacuo*. The residual oil (11.5 g.) deposited 1.5 g. of B during 10 hours; the filtrate deposited 0.8 g. of B during 9 days at 2 ± 2°.

from the filtrate, the residue was diluted with secondary butyl, or tertiary amyl, alcohol and the solid product (ammonium chloride, or, in experiments 32 and 33, the dihydrochloride of isoamylenediamine) was removed by filtration. Solvent was distilled *in vacuo* from the filtrate, and left syrupy products which, in some experiments, could not be identified; in other experiments, the regenerated, basic products were distilled and converted to crystalline derivatives, which were identified. Conversion to the benzoyl and the *p*-toluenesulfone derivative was made in the usual way; the reaction mixture was heated on a steam bath for about one-half hour. Solid products were filtered off, washed with water, dried and recrystallized from a benzene-ether solution. When an oily product was formed, the mixture was extracted with chloroform, the solution was washed, dried; the solvent was distilled *in vacuo*, and the residue was crystallized from a benzene-ether solution. Identity of the crystalline derivatives of 2-methyl-3-aminobutanol-2, and of isoamylenediamine, was established by comparison with the respective derivatives of the amino alcohol and of the diamine, prepared as described below. In the reduction experiments (29–34), the solid addition products yielded the results given in Table V.

Preparation of 2-methyl-3-aminobutanol-2 and derivatives.—Isoamylene bromohydrine (43.2 g.) was added to aqueous ammonia (200 cc., saturated with the gas at 25°), and the mixture was shaken for 36 hours (petrol extracted 4.8 g. of colorless oil). The basic aqueous solution was distilled at ordinary pressure until the temperature of the vapor reached 102°. The cooled residual liquid was saturated with potassium hydroxide, extracted with ether, and the dried extract, on fractionation, yielded: (*1*) 1.4 g., b.p. up to 161.5° (mainly ether); (*2*) 11.9 g. of the aminoalcohol, b.p., 161.5–165°; and (*3*) 0.5 g. of residual oil.

(*a*) *Toluenesulfonamide.*—One gram of (*2*), treated with 3.7 g. of *p*-toluenesulfonyl chloride in the usual manner, yielded 2.2 g. of oily product which gave 1 g. of the sulfonamide (m.p. 127–129°: *Anal.* calc'd for $C_{12}H_{19}NO_3S$; C, 56.1; H, 7.4; N, 5.41; S, 12.45. Found C, 56.22; H, 7.48; N, 5.64; S, 12.44).

(*b*) *Benzoate.*—Benzoylation of 1 g. of *2* gave 2 g. of oily product, from which 1 g. of crystalline benzoate, m.p. 95–96°, was isolated. (*Anal.* calc'd for $C_{12}H_{17}NO_2$; C, 69.5; H, 8.2; N, 6.86. Found C, 69.66; H, 8.47; N, 6.85). The remainder of the product could not be separated from adhering oil.

Reduction of crude and fractionated blue oils.—The reductions were made in the usual manner with platinum oxide catalyst. When reduction stopped (experiments 38–40), catalyst was removed by filtration, solvent was distilled *in vacuo*, the residual syrup was alkalinized, and the mixture was extracted with ether. The dried ether solution gave the indicated fractions. In experiment 41, gaseous hydrogen chloride was bubbled into the filtered acetic acid solution of the reduction products, the precipitated ammonium chloride was removed by filtration, solvent was distilled *in vacuo*, and the residual syrup, treated as before, gave fractions *a–3*. The residual green oil (oil G; experiment 39) could not be reduced catalytically. The amines were acylated in the usual manner: acylation with *p*-nitrobenzoyl chloride was made in the cold, but, with benzoyl, or toluenesulfonyl, chloride, the reaction mixtures were heated on the steam bath for about one-half hour. Letter O designates the dibenzoate of isoamylenediamine, P the hydrochloride, and Q the *p*-nitrobenzoate of 2-methyl-3-aminobutane. The results are tabulated in Table VI.

Oxidation of nitroso-nitro compound (III): (*a*) *With "nitrous fumes".*—The moist gas generated from 60 g. of technical arsenous oxide and 40 cc. of nitric acid (density 1.416 at 20°) was passed, during ½ hour, into a mechanically stirred solution of 3 g. of the bis-nitroso-nitro compound in 25 cc. of benzene. The brown solution was

TABLE V

REDUCTION OF SOLID ADDITION PRODUCTS

EXPT. NO.	29[a]	30[b]	31[c]	32[d]	33[e]	34[f]	35[g]	36[h]	37[i]
Product Reduced, g. — Isopentane deriv. — Bis-Nitroso-nitrate	8.7	10							
Product Reduced, g. — Isopentane deriv. — Bis-Nitroso-nitro-			10	9.5					
Product Reduced, g. — Isopentane deriv. — Dinitro-					5.5	4.9			
Product Reduced, g. — 2-Methyl-2-amino-butanone-3 oxime — HCl salt							7		
Product Reduced, g. — 2-Methyl-2-amino-butanone-3 oxime — 2HCl salt								7	5.7
Hydrogen absorbed — Liters	5.11	5.33	7.55	7.39	4.01	3.94			
Hydrogen absorbed — Time, hrs	27.6	22		12.6	32	20			
Product (P) — Hydroxy-amine, g	1.8	2.0							
Product (P) — B.p., °C	140–160	160–200							
Product (P) — Diamine, g			1.1						
Product (P) — B.p., °C			139–143						
Product (P) — Diamine 2HCl, g				10	3.1	3.7	0.7	0.8	1.4
Acylation — Gave benzoate of — Sample P, g	0.8	0.8		0.5	1.0	1.0	0.7	0.8	1.4
Acylation — Gave benzoate of — Hydroxy-amine, g	0.7	0.2							
Acylation — Gave benzoate of — M.p., °C	95–96	95–96							
Acylation — Gave benzoate of — Diamine, g				1.0	1.4	1.8	0.9	0.8	0.75
Acylation — Gave benzoate of — M.p., °C				147–148	147–148	147–148	147–148	147–148	147–148
Acylation — Gave tosyl deriv. of — Sample P, g	1.0	1.0	0.9	0.5					
Acylation — Gave tosyl deriv. of — Hydroxy-amine, g	1.9	1.0							
Acylation — Gave tosyl deriv. of — M.p., °C	128–129	128–129							
Acylation — Gave tosyl deriv. of — Diamine, g			1.0	0.8					
Acylation — Gave tosyl deriv. of — M.p., °C			162–163	162–163					

See notes on following page.

Notes to Table V

[a] The bis-nitrate was reduced in acetic anhydride, catalyst was filtered off, solvent was distilled *in vacuo*, the residual syrup was heated with dilute hydrochloric acid for 4 hours and the solution evaporated to dryness *in vacuo*. The residue, when warmed with secondary butyl alcohol, yielded 1.3 g. of ammonium chloride. Solvent was distilled *in vacuo* from the filtrate and the syrupy residue, when alkalinized at 0°, yielded an oil which gave fractions: (*a*) 0.3 g., b.p. up to 140°; (*b*) 1.8 g., b.p. 140–160° (mostly at 150–155°); and (*c*) 0.2 g. of residual oil.

[b] The filtered solution of the reduction product yielded, with gaseous HCl, 1.3 g. of ammonium chloride. The syrupy hydrochloride was alkalinized at 0°, and the liberated oil was fractionated, yielding: (*a*) 0.4 g., b.p. up to 160°, and P, 2 g., b.p. 160–200°. A mixture of the toluenesulfonamide with that of experiment 29 melted at 127–129°.

[c] The filtered solution of the reduction product was concentrated *in vacuo*, and the resulting syrup was made alkaline at 0°. The dried ether solution was fractionated, yielding, besides the ether distillate: (*a*) 0.05 g., b.p. 56°; P, 1.1 g., b.p. 139–143°, and (*b*) 0.3 g. of residual oil. The basic, aqueous solution was distilled, and the distillate (20 cc.; $\frac{1}{3}$ of the original solution), was acidified with gaseous HCl and evaporated to dryness, yielded 5.2 g. of ammonium chloride.

[d] Hydrogen chloride precipitated 5.3 g. of solid (*1*) from the acetic acid solution of the reduction product. The filtrate, evaporated *in vacuo*, yielded a paste from which secondary butyl alcohol precipitated 4.7 g. of solid (*2*), m.p. 290° with decomposition; the alcohol solution yielded 2.2 g. of syrup, which could not be identified. The combined solids (*1* and *2*; 9.6 g.) were alkalinized, and the mixture was heated to 100°, but evolved no ammonia. The cooled mixture was extracted with ether, and the dried extract was fractionated, yielding: (*a*) an ether distillate, which, with gaseous HCl, yielded 4.6 g. of the dihydrochloride of isoamylenediamine (*S*: *Anal.* calc'd for $C_5H_{16}Cl_2N_2$; Cl, 40.6. Found: Cl, 40.6); (*b*) 0.3 g., b.p. up to 135° (mostly ether); and (*c*) 2 g. of basic liquid, b.p., 135–138°, from which a benzoate and a toluenesulphonamide was prepared. (*Anal.* of benzoate: calc'd for $C_{19}H_{22}N_2O_2$: C, 73.50; H, 7.15; N, 9.03. Found; C, 73.52; H, 7.03; N, 8.96. *Anal.* of sulfonamide; calc'd for $C_{19}H_{26}N_2O_4S_2$; C, 55.56; H, 6.39; N, 6.83; S, 15.57. Found: C, 55.57; H, 6.11; N, 6.82; S, 15.34.)

One gram of solid yielded 1.2 g. of the dibenzoate of isoamylenediamine, m.p. 147–148°, identical with the dibenzoate prepared from *c*.

[e] Nitrogen tetroxide (22.6 g.) was added, during 2 hours, to a mechanically-stirred solution of 25 g. of trimethylethylene in 75 cc. of ether, cooled to −6°. The blue, oily product (43.6 g.) was steam-distilled, and the volatilized oil was fractionated, yielding: (*1*) 17.5 g. of blue distillate, and (*2*) 6.8 g. of pale-green wax, which, crystallized from ether at −80°, gave the dinitro compound (5.5 g.; m.p. 30–40°) used in the reduction experiment. When boiled with secondary butyl alcohol, the syrupy hydrochloride of the reduction product yielded 3.1 g. of the dihydrochloride of isoamylenediamine (*Anal.* calc'd for $C_5H_{16}Cl_2N_2$; Cl, 40.6. Found: Cl, 40.5) and 2.7 g. of syrup; the syrup was made alkaline, the mixture was extracted with ether and the dried extract gave, with gaseous HCl, a gummy hydrochloride, which could not be identified.

[f] In two experiments, moist "nitrous fumes", generated from 80 cc. of nitric acid (density 1.315 at 20°) and 120 g. of technical arsenous oxide, were bubbled, during 2–4 hours, into ether solutions of trimethylethylene (20 g.), cooled to −7°. The preparations were made in an atmosphere of nitrogen. The crude products (33.2

Notes to Table V—Continued

g. and 32 g., respectively) were combined and distilled at the pressure of a mercury pump, yielding: (*1*) 28.1 g. of blue distillate, and (*2*) 33.1 g. of green residual oil, which was steam-distilled. The volatilized oil, distilled at 2 mm., gave: (*a*) 7.8 g. of blue distillate, and (*b*) 12.7 g. of green residual oil, which was distilled from a small Claisen flask and yielded: (*c*) 2.5 g. of bluish distillate and (*d*) 10.1 g. of pale-greenish distillate (b.p. 65–85° at 2 mm.; m.p. 30–35°). The wax (*d*) was centrifuged at 0° and the almost colorless product was sublimed at the pressure of a mercury pump; the sublimate was pressed between filter paper, and the product was then reduced. The crude hydrochloride of the reduction product was extracted with tertiary amyl alcohol and gave 3.7 g. of the dihydrochloride of isoamylenediamine and 1.7 g. of syrupy product which was not identified. The benzoate prepared from the dihydrochloride did not depress the melting point of the benzoate prepared from the dihydrochloride of experiment 33.

[g] Isoamylene nitrosyl chloride (15.5 g.) was dissolved in 100 cc. of methyl alcohol, saturated with ammonia at 0°, and, after 1 hour, the solution was heated on a steam bath, while a stream of ammonia was bubbled into the solution. Solvent was distilled *in vacuo*, the residue was extracted with hot benzene, the insoluble product (*1*) was removed by filtration, solvent was distilled *in vacuo* from the filtrate, and left 3.8 g. of oil from which 2 g. of 2-methyl-2-aminobutanone-3 oxime (m.p. 103–104°; *Anal.* calc'd for $C_5H_{12}N_2O$: C, 51.68; H, 10.43; N, 24.12. Found: C, (*1*) 51.88; (*2*) 51.78; H, (*1*) 10.26; (*2*) 10.30; N, (*1*) 23.93; (*2*) 24.23) separated, yielding a dibenzoate, m.p. 146–147°, identical with that prepared from the oxime hydrochloride isolated from *1*.

Solid *1* was extracted with hot secondary butyl alcohol, the insoluble ammonium chloride (1.3 g.) was removed by filtration, and the filtrate yielded 11.8 g. of the oxime hydrochloride (*2*) (m.p., 192–193°: *Anal.* calc'd for $C_5H_{12}N_2O \cdot HCl$: Cl, 23.24. Found: Cl, 22.88). One gram of *2* gave 1.1 g. of crude dibenzoate, m.p. 136–138°, which melted at 146–147° after recrystallization from an alcohol-ether solution. (*Anal.* calc'd for $C_{19}H_{20}N_2O_3$: C, 70.45; H, 6.18; N, 8.64. Found: C, 70.33; H, 6.21; N, 8.96.) Small amounts of impurities, or possibly stereomeric products, were isolated in the purification of the oxime and its benzoate: the oily product isolated in the purification of the oxime yielded a benzoate, m.p. 145–146°, identical with that prepared from the crystalline oxime and that obtained from the hydrochloride (*2*).

Seven grams of *2*, dissolved in 150 cc. of ethyl alcohol, was reduced by gradually adding 2.5% amalgam (prepared from 620 g. of mercury and 15.5 g. of sodium) and 50 cc. of glacial acetic acid. Water was added to dissolve precipitated salts, the mercury was separated, the aqueous solution was acidified with gaseous HCl, the precipitated salt (*3*) was removed by filtration, and solvent was distilled *in vacuo* from the filtrate, leaving a solid residue (*4*). The combined solids (*3* and *4*) were extracted with hot ethyl alcohol; the insoluble sodium chloride (38.8 g.) was removed by filtration, solvent was distilled *in vacuo* from the filtrate, the syrupy residue was made alkaline, the mixture was distilled, the distillate was acidified with gaseous HCl and evaporated to dryness *in vacuo*. The residue was extracted with hot secondary butyl alcohol, the insoluble ammonium chloride (2.5 g.) was removed by filtration, solvent was distilled *in vacuo* from the filtrate, and left 4.6 g. of syrupy residue. The syrup was dissolved in hot, secondary butyl alcohol, the cooled solution was added to ether, and the precipitated gummy product, after a second treatment with hot secondary butyl alcohol, yielded 0.7 g. of the dihydrochloride of isoamylenediamine (P), which yielded the dibenzoate of isoamylenediamine (*Anal.* calc'd for $C_{19}H_{22}N_2O_2$; C, 73.55; H, 7.1; N, 9.04. Found: C, 73.63; H, 7.0; N, 9.21).

[h] Isoamylene nitrosyl chloride (21 g.), treated with alcoholic ammonia, as described above, yielded 1.4 g. of ammonium chloride, 4.5 g. of 2-methyl-2-aminobutanone-3 oxime, and 15 g. of the corresponding oxime hydrochloride (*1*).

Seven grams of *1*, dissolved in 25 cc. of methyl alcohol, was treated with excess gaseous HCl, solvent was distilled *in vacuo*, the residual dihydrochloride (7 g.) was dissolved in a mixture of 50 cc. of glacial acetic acid and 75 cc. of ethyl alcohol and reduced by gradually adding 2.5% amalgam (prepared from 620 g. of mercury and 15.5 g. of sodium). The product, isolated as described above, was converted to the dibenzoate; the dibenzoate did not depress the melting point of the dibenzoate prepared from the reduction product of experiment 31.

[i] Isoamylene nitrosyl chloride (6 g.), treated as above, yielded 0.4 g. of 2-methyl-2-aminobutanone-3 oxime and 5.9 g. of the corresponding oxime hydrochloride (*1*), m.p. 192°. A suspension of *1* in 50 cc. of glacial acetic acid, containing 0.9 g. of dissolved sodium, absorbed, with platinum oxide catalyst, only 290 cc. of hydrogen during 32 hours. Gaseous HCl was bubbled into the solution, catalyst and sodium chloride were removed by filtration, solvent was distilled *in vacuo*, and, from the residue, the dihydrochloride of *1* was extracted with hot secondary butyl alcohol. A solution of 2.5 g. of the recovered product in 25 cc. of ethyl alcohol, containing platinum oxide catalyst, absorbed only 20 cc. of hydrogen during 4 hours: the dihydrochloride of *1* was recovered.

A solution of 5.7 g. of the dihydrochloride of *1* was reduced, as before, with 2.5% amalgam (prepared from 500 g. of mercury and 12.5 g. of sodium) and the product was isolated as in experiment 35.

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stirred one-half hour, solvent was distilled *in vacuo*, an ether solution of the residual oil was washed with water, and dried, and the solvent was removed. The blue residual oil (3 g.) deposited no solid; with a solution prepared from 0.9 g. of sodium, 25 cc. of methyl alcohol, and 4.1 g. of thiophenol, the blue oil gave 1.1 g. of sodium nitrite (Calc'd: Na, 33.3. Found: Na, 33.1), and 3.1 g. of oily product, which, after oxidation with hydrogen peroxide, gave: (*a*) 1.3 g. of impure solid, and (*b*) 1.4 g. of oily product. Oxidation of *b*, with chromic anhydride, gave 0.65 g. of 2-methyl-3-nitro-2-phenylsulfone butane; sublimation of *a* gave 1.1 g. of the pure sulfone.

(*b*) *With ozone.*—Ozone was bubbled, at 0°, into a suspension of 2 g. of the nitrosonitro compound in 25 cc. of chloroform for one hour after the blue coloration was discharged (total time, 4 hours). Solvent was distilled *in vacuo*; the residue was dissolved in ether, and the solution was washed with water. The dried solution gave 2.3 g. of a waxy solid which, with a solution prepared from 0.6 g. of sodium, 25 cc. of methyl alcohol and 3.1 g. of thiophenol, gave 0.9 g. of sodium nitrite (calc'd: Na, 33.3; found: Na, 33.3) and 2.2 g. of crude, thio-ether, yielding, after oxidation with hydrogen peroxide, (*a*) 0.8 g. of impure solid, and (*b*) 1. g. of oily product. Oxidation of *b*, with chromic anhydride, gave 0.6 g. of 2-methyl-3-nitro-2-phenylsulfone butane: *a*, with 0.3 g. of chromic anhydride, gave 0.7 g. of the pure sulfone, m.p. 100–102°.

Experimental evidence for the formation of the nitrous ester of nitroisopentane.—Isolation of the nitro-nitrite has not been realized, but its appearance in the distilled blue product, formed by the action of nitrogen tetroxide upon trimethylethylene in ether solution, is manifested in the formation of ammonia and 2-methyl-3-aminobutanol-2 on reduction of the volatile blue oil. The yield of the amino alcohol, isolated as the benzoate, indicated that the nitro-nitrite constituted 9% of the crude addition product. However, quantitative isolation of the amino alcohol

TABLE VI

REDUCTION PRODUCTS OF BLUE OILS

EXPT. NO.	LOW-PRESSURE DISTILLATION				BLUE OIL REDUCED				ETHER EXTRACT GAVE FRACTIONS:		
	Liquid, g.	Product from Expt. No.	Blue dist. (A), g.	Residual Oil (A), g.	g.	Solvent, cc.	Hydrogen absorbed		No.	g.	B.p., °C.
							lts.	hrs.			
38[a]	20.6	19			20.6	75	11.7	25	*1*	1.2	Up to 145 (mainly 140–145)
									2	3.3	145–155 (mainly 145)
									3	1.7	Residual oil; b.p. 140–180 six months after prep'n
39[b]	11.6	20	27.2	21.7	27.2	50	17.01	57	*a*	Ether	34.5–35.3
	16.1	21							*1*	5.5	Up to 100
	22.8	22							*2*	0.6	100–145
									3	3.6	Residual oil
40[c]	19.1	24	29.5	31.0	20.8	50	12.7	66	*a*	Ether	34.7–35.4
	22.1	25							*1*	6.3	37–59 (mainly ether)
	22.4	26							*2*	1.1	59–92 (mainly 86–92)
									3	0.7	60–70 at 2 m.m.
									4	1.5	Tarry residue
41[d]	28.4	(a)	24.9	25.5	20.1	50	10.01	89	*a*	Ether	34–35.2
	24.6	(b)							*1*	1.1	50–100
									2	4.0	100–160
									3	0.5	Residual oil

[a] Crude product 19 was reduced. During the distillation at low pressure, about one-half of the reduction product was lost by volatilizing through a condenser cooled to −25°. The residual oil (6.4 g.) gave fractions *1*–*3*. A portion (0.1 g.) of *3* with camphorsulfonic acid (0.5 g.) in hot acetic ester solution, gave 0.3 g. of the camphorsulfonate of isoamylenediamine, m.p. 263°; 0.1 g. of *2* gave 0.45 g. of the same salt (*Anal.* calc'd. for $C_{25}H_{44}N_2O_8S_2$: C, 53.25; H, 7.85; N, 4.95; S, 11.35. Found: C, 53.12; H, 8.30; N, 4.86). An identical salt was obtained from the reduction product of the dimeric nitroso-nitro derivative of isopentane: 1 g. of the bis derivative, in 25 cc. of glacial acetic acid containing platinum oxide catalyst, absorbed 790 cc. of hydrogen during 79 minutes. The product, isolated in the usual manner, was distilled *in vacuo* and, with a solution of camphorsulfonic acid in hot acetic ester solution, gave the camphorsulfonate of isoamylenediamine (m.p. 264°: *Anal.* Found: C, 53.14; H, 8.19; N, 4.91; S, 11.44).

A portion (0.3 g.) of *1* gave 0.4 g. of O, m.p. 147–148°: 1 g. of *2* gave 0.7 g. of O, m.p. 147–148°: 1 g. of *3* gave 0.4 g. of O, m.p. 147–148°, and a pasty, unidentified product.

[b] Distillate *a*, with gaseous HCl, gave 1.8 g. of P (crude product, m.p. 190–200; after crystallization from acetone, m.p. 209°). [Barrows and Ferguson (*J. Chem. Soc.*, **1937**, 114) have previously described the *p*-nitrobenzoate and the hydrochloride of 2-methyl-3-aminobutane.]

Refractionation of *1* gave: (*4*) 2.2 g., b.p. 34.5–36° (mainly ether), and (*5*) a residual oil which, combined with *2*, gave 1.8 g. of 2-methyl-3-aminobutane, b.p. 85–89°: 0.2 g. of the amine gave 0.5 g. of Q (m.p. 114–115°: *Anal.* calc'd for $C_{12}H_{16}N_2O_3$: C, 61.0; H, 6.8; N, 11.85. Found C, 61.14; H, 6.95; N, 11.63).

Residual oil *3*, at 2 mm., gave a colorless distillate *6*, 2.4 g., which, at ordinary pressure, yielded: (*7*) 1.7 g. of basic liquid (b.p., 152–162°; n_D^{20} 1.4454), leaving a residual oil (0.5 g.; n_D^{20} 1.4471). Distillate *7* gave only a trace of crystalline product with camphorsulfonic acid, and oily products with *p*-nitrobenzoyl chloride.

[c] The blue distillate A, refractionated at 2 mm., with the bath temperature gradually increased from 60° to 75° during 2 hours, gave: (*b*) 22.3 g. of blue distillate, and (*c*) 6.2 g. of green residual oil. During 15 hours *b* deposited 1.5 g. of the bis-nitroso-nitro derivative of isopentane. The blue filtrate (20.8 g.) was reduced.

Distillate *a* and *1*, with gaseous HCl, gave 0.8 g. of P, m.p. 208°: 0.5 g. of P gave 1.1 g. of crude Q which, after crystallization from ether, yielded 0.9 g. of pure Q, m.p. 114–115°.

A portion (0.5 g.) of *2* gave 0.8 g. of crude Q, m.p. 110°, which, after crystallization from an ether-petrol solution, melted at 113–114°.

[d] The crude addition products (*a* and *b*), prepared in the usual manner in an atmosphere of nitrogen, using 120 g. of technical arsenous oxide, 80 cc. of nitric acid (density 1.314), 20 g. of trimethylethylene and 60 cc. of ether, were distilled at low pressure. During 12 hours, the blue distillate (A) deposited 4.1 g. of the bis-nitroso-nitro derivative of isopentane: the blue filtrate (20.1 g.) was reduced. With gaseous HCl, the reduction products gave 1.4 g. of ammonium chloride and a syrupy product which, after extraction with ether, was made alkaline; the mixture was extracted with ether and the dried extract gave fractions *a–3*.

Gaseous HCl gave an inappreciable precipitate with *a*. A portion (0.3 g.) of *1* gave 0.4 g. of crude Q, which, after two recrystallizations from ether, yielded 0.1 g. of pure Q; m.p. 115°. With gaseous HCl, 0.65 g. of *1* gave 0.15 g. of P; 0.15 g. of P gave 0.3 g. of crude Q, from which 0.1 g. of pure Q, m.p. 114–115°, was isolated.

One gram of *2*, with benzoyl chloride, gave 1.2 g. of oily product which yielded 0.25 g. of O, m.p. 146–148°. A solution of 3 g. of *2* in 25 cc. of ether gave, with gaseous HCl, a syrup, which, boiled with secondary butyl alcohol, yielded 1.2 g. of the dihydrochloride of isoamylenediamine (*4*) (0.5 g. of the salt gave 0.8 g. of crude O, from which 0.6 g. of pure O, m.p. 146–147°, was isolated) and (*5*) a syrup (3.5 g.) which could not be crystallized.

The syrupy product (*5*) was made alkaline, using 8 g. of KOH and 25 cc. of water, and the mixture was warmed with 7 g. of benzoyl chloride. The oily product (3.9 g.), at the pressure of a mercury pump, gave: (*6*) 2.2 g. of pale-yellow, viscous distillate, and (*7*) 1 g. of residual oil which yielded 0.2 g. of O, m.p. 147–148°, and products that could not be purified. Distillate *6*, dissolved in 20 cc. of ether, gave, with gaseous HCl, a clear solution from which petrol precipitated an oil. This oil was only partly soluble in water; the mixture was made alkaline, and the liberated impure benzoate of 2-methyl-3-aminobutane was redistilled at the pressure of a mercury pump. The crude distillate was analyzed. (*Anal.* calc'd for $C_{12}H_{17}NO$: C, 75.7; H, 8.42; N, 7.36; found C, 74.39; H, 8.98; N, 8.13.)

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was not realized and the estimated concentration of the nitro-nitrite represents, therefore, the minimum value.

Nitrogen tetroxide (21.1 g.), distilled, during 70 minutes, into a mechanically stirred solution of 20 g. of trimethylethylene in 60 cc. of ether, cooled to −8°, yielded 2.7 g. of the dimeric nitroso-nitrate derivative of isopentane, m.p. 104°, and a liquid

product (35.3 g.) which, on distillation at low pressure, yielded: (*a*) 14.9 g. of blue distillate, and (*b*) 19.2 g. of green, residual oil. Oil *a* was fractionated at 2 mm., and gave: (*c*) 7.6 g. of blue distillate, and (*d*) 5.7 g. of bluish-green residual oil, which was distilled in an all-glass apparatus and gave a distillate of 5.2 g. (*e*).

A solution of 6.6 g. of *c* in 25 cc. of glacial acetic acid, containing platinum oxide catalyst, absorbed 4.3 l. of hydrogen during 89 hours. Catalyst was removed by filtration, gaseous hydrogen chloride was bubbled into the filtrate, the precipitated ammonium chloride (0.5 g.) was removed by filtration, solvent was distilled from the filtrate, *in vacuo*, and the residual syrup was made alkaline. The mixture was extracted with ether, and the dried ether solution, on fractionation, yielded: (*1*) an ether distillate, b.p. 34.5–35°, and (*2*) 1.7 g. of basic oil, b.p. 120–180° (nearly all at 160–165°). Distillate *1* gave, with gaseous hydrogen chloride, 0.5 g. of crystalline hydrochloride which, with 0.8 g. of *p*-nitrobenzoyl chloride, gave 1.2 g. of crude product, m.p. 110–112°, from which, after extraction with hot sodium carbonate solution and recrystallization of the product from ether solution, the pure *p*-nitrobenzoate of 2-methyl-3-aminobutane, m.p. 114°, was isolated.

Benzoylation of 1 g. of *2* gave 1.8 g. of oily product which, distilled at the pressure of a mercury pump and with the bath temperature at 180°, yielded (*3*) 1.4 g. of a viscous distillate, and (*4*) 0.4 g. of residual oil, from which 0.05 g. of isoamylenediamine dibenzoate, m.p. 145–146°, was isolated. An ether solution of *3* deposited 0.8 g. of impure benzoate of 2-methyl-3-aminobutanol-2, m.p. 85–90°, which, after recrystallization from ether, melted at 90–92° and did not depress the melting point of a specimen of the pure benzoate.

A solution of *e* in 25 cc. of glacial acetic acid, containing platinum oxide catalyst, absorbed 3.9 l. of hydrogen during 103 hours. Catalyst was filtered off, gaseous hydrogen chloride was bubbled into the filtrate and, since no precipitate was formed, the solvent was distilled *in vacuo*. The residual syrup, dissolved in hot secondary butyl alcohol, deposited 1 g. of the dihydrochloride of isoamylenediamine (*f*). One-half gram of *f* gave 0.5 g. of pure, recrystallized dibenzoate of isoamylenediamine, m.p. 147–148°: 0.5 g. of *f* gave 1 g. of crude *p*-nitrodibenzoate of isoamylenediamine, from which, after extraction with hot sodium carbonate solution and recrystallization of the product from acetone, 0.7 g. of pure *p*-nitrodibenzoate (m.p. 229°. *Anal.* calc'd for $C_{19}H_{20}N_4O_6$; C, 57.0; H, 5.0; N, 14.0; found C, 57.0; H, 5.09; N, 14.07) was obtained. The filtrate yielded a syrup, which was made alkaline and the mixture extracted with ether. The dried, ether solution was fractionated, and gave: (*5*) an ether distillate (b.p., 35–36°; with gaseous hydrogen chloride, and inappreciable yield of salt was formed), and (*6*) 3.5 g. of basic oil, b.p., 120–160° (mostly at 155–160°).

With *p*-nitrobenzoyl chloride, 0.3 g. of *6* gave 0.8 g. of oily product; with camphorsulfonic acid, 0.3 g. of *6* gave 0.1 g. of crystalline product, which could not be purified, and with benzoyl chloride (0.5 g.), 0.7 g. of oily product was obtained from which 0.1 g. of the benzoate of 2-methyl-3-aminobutanol-2, m.p. 92°, was isolated. Benzoylation of 2 g. of *6* yielded 3.3 g. of viscous oil, which was distilled, at the pressure of a mercury pump, with the bath-temperature at 180° gave: (*7*) 2.5 g. of a viscous distillate, and (*8*) 0.4 g. of residual oil, which, dissolved in ether, yielded 0.25 g. of the dibenzoate of isoamylenediamine, m.p. 146–147°. Distillate 7 solidified completely; on fractional crystallization, it yielded the benzoate of 2-methyl-3-aminobutanol-2 [the three fractions of crystals: (*a*) 0.7 g., m.p. 93°; (*b*) 0.6 g., m.p. 92–93°, and (*c*) 0.2 g., m.p. 90° were slightly impure, but it did not depress the melting point of a pure specimen of the benzoate of the amino alcohol], and an oily product

(*9*, 1 g.) which contained approximately equal amounts of the benzoate of 2-methyl-3-aminobutanol-2 and the dibenzoate of isoamylenediamine, and could not be crystallized. Redistillation of *9* yielded: (*10*) 0.4 g. of distillate, and (*11*) 0.4 g. of residual oil. An ether solution of *10* yielded 0.2 g. of the benzoate of 2-methyl-3-aminobutanol-2, m.p. 91–92°, and *11* yielded 0.15 g. of the dibenzoate of isoamylenediamine, m.p. 146–147°.

SUMMARY

1. The action of "nitrous fumes" upon trimethylethylene has been re-investigated. Schmidt, with "nitrous fumes", generated from nitric acid of density 1.43, obtained 55–66 per cent. yields of a solid product, assumed to be the dimeric nitrous ester of 2-methyl-3-nitrosobutanol-2. We obtained, under comparable conditions, the corresponding dimeric nitric ester, and the main product, a greenish-blue oil, deposited no solid during two weeks. It is shown that the solid nitrogen trioxide addition product is not the dimeric, nitroso-nitrite compound, but is the corresponding nitroso-nitro derivative, which, with "nitrous fumes", or with ozone, is oxidized to 2,3-dinitro-2-methylbutane, and is catalytically reduced to isoamylenediamine.

2. Precautions were taken to treat the arsenous oxide and nitric acid mixtures uniformly; yet, because of variable behavior, the results could not be reproduced quantitatively. The variations in the results obtained with nitric acid of density 1.41 were most marked. At −10°, the product yielded 4.5 per cent. of the dimeric nitric ester of 2-methyl-3-nitrosobutanol-2, but the corresponding bis-nitroso-nitro derivative separated in yields of 9.4 and 3.4 per cent., respectively, from the products formed at 4° and 7°. The results obtained with moist "nitrous fumes" were no more consistent in nitrogen than in air, and equally discordant results were obtained in experiments made under anhydrous conditions.

3. The yield of dimeric 3-nitroso-2-nitro-2-methylbutane, produced with nitric acid (density 1.30–1.312) yielding an excess of nitric oxide, varied from 8.6 to 17.4 per cent. Under anhydrous conditions and in an atmosphere of nitrogen, conditions seemingly more favorable for the formation of derivatives of nitrogen trioxide than those described by Schmidt, the bis-nitroso-nitro derivative was obtained in a maximum yield of 20 per cent., and under no conditions could Schmidt's high yields (55–66 per cent.) be duplicated.

4. At −80°, products were formed which decomposed, below 0°, with evolution of gas, and it is suggested that the inconsistent yields of the addition products may be attributed to a primary formation of a reaction product that undergoes spontaneous decomposition to yield the isolated products.

5. The liquid reaction products were separated by low-pressure distil-

lation into an easily volatile blue and a much less volatile, green oil, from which a small amount of 2,3-dinitro-2-methylbutane was isolated. Indirect determinations showed that the dinitro compound constituted 10–20 per cent. of the crude reaction product, but, since the method gives low results, the actual concentration is probably higher. Undoubtedly the dinitro compound is formed mainly by direct addition of nitrogen tetroxide to the alkene, although the compound may also be formed by oxidation of the corresponding nitroso-nitro derivative of isopentane. Accordingly, the yield of the dinitro derivative probably varied with the experimental conditions and with the composition of the "nitrous fumes", but a correlation is not apparent from our results. Beside the dinitro compound, oils of high molecular weight (213–360) appeared in the non-volatile green oils. The chemical nature of these viscous liquids, constituting 10–20 per cent. of the reaction product, could not be established, but the formation may be attributed to the action of "nitrous fumes" upon polymers of trimethylethylene, which are formed rapidly by the action of acidic reagents upon the alkene.

6. From the volatile blue oils, dimeric 3-nitroso-2-nitro-2-methylbutane separated in varying yields. The residual oils, after fractionation, gave values on analysis closely approaching those calculated for 2-methyl-3-nitrobutene-2 and, from the analytical data, it is estimated that the nitroalkene constituted 10–20 per cent. of the reaction product. The presence of the nitroalkene was established by (1) conversion to 2-methyl-3-nitro-2-phenylsulfone butane, and (2) by reduction to the corresponding amine. The nitroalkene appears, not only in the products formed from "nitrous fumes", but, also, in those obtained with nitrogen tetroxide. The suggestion is made that a primarily formed addition product undergoes spontaneous decomposition to yield the nitroalkene.

7. Previous work has shown that reduction with metal and acid removes most of the nitrogen from the addition products formed with nitrogen trioxide and tetroxide. Catalytic reduction, however, reduces the addition compounds without severing the nitrogen from carbon; the dimeric nitric ester of 2-methyl-3-nitrosobutanol-2 yielded ammonia and 2-methyl-3-aminobutanol-2, the dimeric nitroso-nitro, and the dinitro, derivative of isopentane yielded isoamylenediamine. These results confirm the structure of the nitroso-nitrate and establish the structures of the nitroso-nitro and the dinitro derivative, which was previously formulated as the nitro-nitrite because of the facile and quantitative conversion, with sodium thiophenylate, to the corresponding sulfone, 2-methyl-3-nitro-2-phenylsulfone butane.

8. Reduction of the crude and the fractionated blue oils gave mixtures of amines which were difficult to separate. The easily volatile amine,

2-methyl-3-aminobutane, formed from 2-methyl-3-nitrobutene-2, was readily isolated and identified through the *p*-nitrobenzoate, but the higher-boiling amines yielded oily acylation products from which only the derivatives of isoamylenediamine could be isolated. It is suggested that the oily acylation products were mainly derived from 2-methyl-3-aminobutanol-2.

9. Reduction of the volatile blue oil, formed by the action of nitrogen tetroxide upon trimethylethylene in ether solution, gave ammonia, 2-methyl-3-aminobutanol-2 and isoamylenediamine. The appearance of ammonia and the amino alcohol in these products leads to the conclusion that the nitro-nitrite derivative of isopentane is formed in the addition of nitrogen tetroxide to trimethylethylene. A corresponding nitroso-nitrite derivative may appear in the products formed by the action of "nitrous fumes" upon the alkene, but our results do not definitely prove that a derivative of the trioxide, in which a nitrogen atom is attached to carbon through oxygen, is formed.

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

THE ACTION OF GRIGNARD REAGENTS ON OXIMES. I. THE ACTION OF PHENYLMAGNESIUM BROMIDE ON MIXED KETOXIMES

KENNETH N. CAMPBELL AND JAMES F. McKENNA

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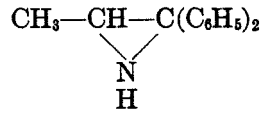
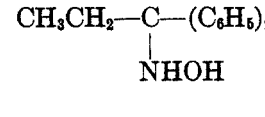
Very few studies have been made on the reaction between Grignard reagents and oximes. Busch and Hobein[1] report the formation of diphenylanilinomethane instead of the expected hydroxylamine, when benzaldoxime was treated with phenylmagnesium bromide. Diels and ter Meer[2] found that no reaction occurred when diacetyl monoxime was treated with methylmagnesium iodide, but that the *O*-methyl ether reacted normally, through the carbonyl group, to give the corresponding carbinol. In a study of the action of Grignard reagents on isonitrosoketones, Orekoff and Tiffeneau[3] found that the carbonyl group alone reacted. Angeli and his co-workers[4] obtained the expected disubstituted hydroxylamine from the action of phenylmagnesium bromide on the *N*-phenylether of benzaldoxime. Hoch[5] in recent years has studied the action of Grignard reagents on various ketoximes. He reported[5a] that propiophenone oxime reacted with phenylmagnesium bromide to give a compound (I) of the formula $C_{15}H_{15}N$, and a second substance (II) of the formula $C_{15}H_{17}NO$. He assigned to compound I the ethyleneimine structure, and to compound II the structure of a hydroxylamine.



I



II

According to Hoch, propiophenone oxime and ethylmagnesium bromide yielded solely an ethylene imine and no hydroxylamine. Later papers of Hoch's have dealt with the action of Grignard reagents on benzophenone oxime[5b] and *alpha*-trisubstituted acetophenone oximes.[5c]

[1] BUSCH AND HOBEIN, *Ber.*, **40**, 2096 (1907).

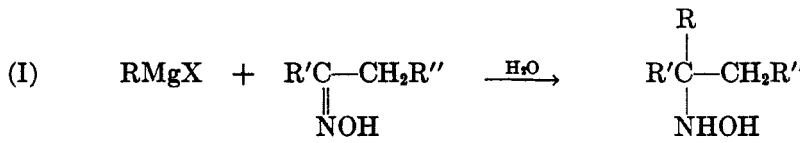
[2] DIELS AND TER MEER, *ibid.*, **42**, 1940 (1909).

[3] OREKOFF AND TIFFENEAU, *Bull. soc. chim.*, **41**, 839 (1927).

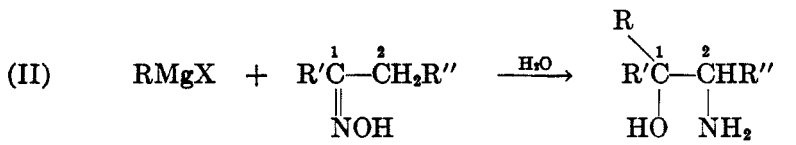
[4] ANGELI, ALLESSANDRI, AND AIAZZI-MANCINI, *Chem. Zentr.*, **1911**, II, 606.

[5] (*a*), HOCH, *Compt. rend.*, **198**, 1865 (1934); (*b*), *ibid.*, **203**, 799 (1936); (*c*), *ibid.*, **204**, 358 (1937).

Some years ago, when the late Professor Stieglitz was studying the rearrangements of substituted hydroxylamines, he and his students investigated the possibility of preparing them by the action of Grignard reagents on mixed ketoximes. This work resulted in the discovery of what was, apparently, a new type of rearrangement, the migration of a nitrogen atom from one carbon atom to another, for instead of the expected hydroxylamines, which would be formed in accordance with equation I, the products were *beta*-amino alcohols, formed in accordance with equation II. The nitrogen atom which was originally attached to carbon atom 1 has migrated to carbon atom 2.



(I) $RMgX + R'C(=NOH)-CH_2R'' \xrightarrow{H_2O} R'C(R)(NHOH)-CH_2R''$



(II) $RMgX + R'\overset{1}{C}(=NOH)-\overset{2}{C}H_2R'' \xrightarrow{H_2O} R'\overset{1}{C}(R)(HO)-\overset{2}{C}H(NH_2)R''$

Stieglitz and his students confined their studies to the reaction between phenylmagnesium bromide and the oximes of acetophenone,[6] propiophenone,[7] desoxybenzoin,[8] and benzophenone.[9] We are continuing the work on this problem, and have under investigation the action of aliphatic and aromatic Grignard reagents on alkyl, aryl, and mixed ketoximes. In this paper we are reporting the results of a study of the reaction between phenylmagnesium bromide and mixed ketoximes.

[6] J. E. COLE, Doctoral Dissertation, University of Chicago, 1929. Acetophenone oxime reacted with a concentrated solution of phenylmagnesium bromide to yield 1,1-diphenyl-1-hydroxy-2-aminoethane.

[7] (*a*) W. E. STURGEON, Doctoral Dissertation, Chicago, 1929. (*b*) G. H. LOVINS, Master's Dissertation, Chicago, 1934. Propiophenone oxime reacted with a concentrated solution of phenylmagnesium bromide to give 1,1-diphenyl-1-hydroxy-2-aminopropane. Since the structure of this compound was not unequivocally established, and since Hoch reported that the reaction yielded a hydroxylamine, we have reinvestigated the reaction.

[8] K. N. CAMPBELL, Doctoral Dissertation, Chicago, 1932. Desoxybenzoin oxime reacted with phenylmagnesium bromide to give the expected 1,1,2-triphenyl-1-hydroxy-2-aminoethane, but the yields were very poor, and a variety of by-products were isolated.

[9] CAMPBELL, *loc. cit.* In this case, since there is no alpha hydrogen atom, an amino alcohol was not obtained. The product was identified as *o*-phenylbenzhydrylaniline by means of analyses, hydrolysis to aniline and 9-phenylfluorene, and by comparison with an authentic sample which was kindly supplied by Professor Henry Gilman. This work confirms that of Hoch,[5c] which appeared later.

As stated earlier, Hoch[5a] reported that propiophenone oxime and phenylmagnesium bromide gave a hydroxylamine and an ethylene imine. The physical constants given by Hoch for the hydroxylamine and its derivatives are identical with those reported by Sturgeon[7a] and by Lovins[7b] for the compound they assumed to be 1,1-diphenyl-1-hydroxy-2-aminopropane and its derivatives. We have prepared the compound by the procedure of Sturgeon (Hoch gave very meagre experimental data) and have also synthesized it from alanine ester hydrochloride and phenylmagnesium bromide.[10] The product from both methods was identical, and hence the substance must be 1,1-diphenyl-1-hydroxy-2-aminopropane, and not a hydroxylamine, as erroneously assumed by Hoch. We have not obtained any product corresponding to the ethyleneimine of Hoch under the conditions we used.

We have also studied the action of phenylmagnesium bromide on the oximes of *p*-methylacetophenone, *p*-chloroacetophenone, and methyl α-naphthyl ketone. The expected amino alcohol was obtained in each case, and its identity was established by direct comparison with a sample synthesized in another way. The ketoximes do not react readily with phenylmagnesium bromide*, and it is necessary to use a large excess of Grignard reagent, to concentrate the Grignard reagent, and to add the oxime at an elevated temperature†. When the Grignard reagent is sufficiently concentrated, a definite color change takes place. Calculations made from the amount of ether originally used and that recovered on concentration indicate that the color change occurs when about one mole of ether remains per mole of Grignard reagent. Instead of concentrating the Grignard reagent, about half of the diethyl ether may be replaced by diisoamyl ether, and the reaction may be run at the same temperature as with the concentrated reagent. The amino alcohol is obtained in about the same yields, and the method presents no advantages. When, however, part of the diethyl ether is replaced by toluene, the reaction seems to take a different course, but the products have not yet been identified.

EXPERIMENTAL

1,1-Diphenyl-1-hydroxy-2-aminopropane

Propiophenone oxime.—This was prepared by a method similar to that of Lovins.[7b] Forty grams of ketone, 24 g. of hydroxylamine hydrochloride, 25 g. of sodium hydroxide and 150 cc. of 95% alcohol were refluxed for one hour and allowed to stand over-

[10] THOMAS AND BETTZIECHE, *Z. physiol. Chem.*, **140**, 251 (1924).

* Unpublished results of Campbell and Hess show that the ketoximes react much more readily with aliphatic Grignard reagents, but that in this case the reaction does not seem to take the same course.

† The optimum temperature of an oil-bath surrounding the reaction flask is about 160–165°, although this varies somewhat with the different oximes.

night. The product, which weighed 37 g., was purified by conversion to the sodium salt and subsequent liberation by dilute sulfuric acid. The purified oxime melted at 53–55°.

Effect of temperature on reaction of propiophenone oxime with phenylmagnesium bromide.—Since the temperature at which the reaction is carried out greatly affects the course of the reaction, a preliminary study was made to determine a suitable temperature. Ether was distilled from an ethereal solution of phenylmagnesium bromide until the color changed from brown to grey-green. This color change occurred when the temperature within the reaction flask reached about 135° (the oil-bath temperature was 160°). Dry propiophenone oxime was then added at different temperatures. At 115° there was little reaction, at 125° the reaction was mild, while at 135° (inside temperature) the reaction was vigorous and exothermic, and a dense white smoke was evolved. At this point the temperature of the oil-bath was 160–165°.‡

Reaction of propiophenone oxime with phenylmagnesium bromide.[7]—Phenylmagnesium bromide was prepared in the usual way from 20.4 g. (0.84 mole) of magnesium turnings, 350 cc. of ether and 131.5 g. of phenylbromide, in a 1-liter, 3-necked flask. The water in the reflux condenser was turned off, and the flask was heated in an oil bath until the latter reached 160°, and the Grignard color change took place. This occurred when about 270 cc. of ether had been recovered, and about 78 cc. (0.74 mole) remained in the flask. Water was again allowed to circulate in the reflux condenser, and 25 g. (0.167 mole) of dry, finely powdered propiophenone oxime was added in portions to the concentrated Grignard reagent while the oil bath temperature was maintained at 155–165°. Heating and stirring were continued for thirty minutes after the addition of the last portion of oxime, and the mixture was then allowed to cool somewhat. It was hydrolyzed by slow addition to a mixture of 200 cc. of concentrated hydrochloric acid and 800 g. of ice. The acid solution was extracted with several portions of ether to remove unreacted oxime and other non-basic impurities. These extracts were discarded. The acid solution was filtered to remove material not extracted by the ether. The solid so obtained weighed 21 g., and on recrystallization from absolute alcohol-ether yielded 3.8 g. of 1,1-diphenyl-1-hydroxy-2-aminopropane hydrochloride. The rest was tar.

The aqueous acid filtrate was treated with a few grams of ammonium chloride and made basic with ammonium hydroxide. The alkaline solution was extracted several times with ether; the ether extracts were dried over potassium carbonate and refluxed to remove dissolved ammonia. Hydrogen chloride gas was then passed in until no more precipitate appeared. There was obtained 8.3 g. of alkamine hydrochloride, m.p. 246–247°. The total yield of the amino alcohol hydrochloride was 12.1 g., or 27% of the theoretical amount.

The free base was prepared by shaking 1.0 g. of the hydrochloride with 20 cc. of 10% sodium hydroxide solution and taking the product up in ether. The material remaining after evaporation of the ether was recrystallized from benzene and ligroïn and then melted at 103–104°.

The benzamide was prepared by treatment of the hydrochloride with 10% sodium hydroxide and benzoyl chloride. It melted at 189.5–190.5°.

Preparation of 1,1-diphenyl-1-hydroxy-2-aminopropane from alanine ester hydrochloride.—The procedure of Thomas and Bettzieche,[10] was used. A Grignard reagent

‡ CAMPBELL, *loc. cit.*, observed that desoxybenzoin oxime reacted with phenylmagnesium bromide when the oil bath temperature was 160–165°, and Bloch (Doctoral Dissertation, Chicago, 1936) found the same temperature most satisfactory for the reaction of acetophenone oxime with the Grignard reagent.

prepared from 8 g. of magnesium, 325 cc. of ether and 80 g. of bromobenzene was treated with 10.2 g. of alanine ethyl ester hydrochloride, to yield 15.1 g. of 1,1-diphenyl-1-hydroxy-2-aminopropane (99% of the theoretical). Portions of the alkamine were converted to the hydrochloride and benzamide. For a comparison of these products with those obtained above, see Table I.

*1-Phenyl-1-*p*-tolyl-1-hydroxy-2-aminoethane*

p-*Methylacetophenone.*—The procedure of Adams and Noller[11] was used. From 540 g. of toluene, 375 g. of aluminum chloride, and 102 g. of acetic anhydride there was obtained 114 g. of *p*-methylacetophenone, b.p. 101°/15 mm.

p-*Methylacetophenone oxime.*—A mixture of 30 g. of ketone, 100 cc. of 95% alcohol, a saturated aqueous solution of 19 g. of hydroxylamine hydrochloride and a saturated aqueous solution of 43 g. of sodium hydroxide was boiled under a reflux condenser for three hours. The cooled mixture was poured into an equal volume of water and neutralized with dilute sulfuric acid. The mixture was allowed to stand for fifteen minutes, the oxime was then collected and washed with about 700 cc. of water. The dried crude material weighed 32 g., a 95% yield. After recrystallization from low-boiling petroleum ether it melted at 85–87°.

TABLE I

MELTING POINTS OF 1,1-DIPHENYL-1-HYDROXY-2-AMINOPROPANE AND DERIVATIVES

COMPOUND	FROM ALANINE ESTER	FROM OXIME	MIXTURE	HOCH'S HYDROXYLAMINE	STURGEON'S COMPOUND
Free base	103–104	103–104	103–104	103	103–104
Hydrochloride	246–247	246–247	246–247	258	246–247
Benzamide	190.5–191.5	189.5–190.5	189.5–191	189	191

Reaction of p-*methylacetophenone oxime with phenylmagnesium bromide.*—A Grignard reagent was prepared from 30.4 g. (1.25 mole) of magnesium, 450 cc. of ether and 210 g. of bromobenzene. Ether was distilled off until the color change occurred. At this point 333 cc. of ether had been recovered, leaving 117 cc. (1.13 mole) in the flask. *p*-Methylacetophenone oxime (36.7 g., 0.25 mole) was added in small portions to the concentrated Grignard reagent, while the oil bath was kept at 155–160°. Stirring and heating were continued for ten minutes after the last portion of oxime was added. The somewhat cool reaction product was poured onto 800 g. of ice, and the mixture made slightly acid with concentrated hydrochloric acid and extracted three times with ether. Distillation of this ether extract yielded 2.0 g. of biphenyl and a considerable amount of tar. The aqueous acid solution was then made basic with ammonium hydroxide and was again extracted with ether. This extract, after drying over potassium carbonate, was evaporated to dryness to yield 17.0 g. of amino alcohol, a 30.4% yield. After recrystallization from absolute alcohol the substance melted at 107–108°.

The hydrochloride was prepared and repeatedly recrystallized from absolute alcohol-ether mixture. The benzamide was prepared by the Schotten-Baumann reaction and purified by recrystallization from benzene and petroleum ether. The alkamine nitrate was made by dissolving a portion of the alkamine in 8% hydro-

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

chloric acid, and adding ammonium nitrate. After several hours the nitrate precipitated, and was recrystallized from absolute alcohol-ether mixture.

*Preparation of 1-phenyl-1-*p*-tolyl-1-hydroxy-2-aminoethane from α-aminoacetophenone hydrochloride and* p*-tolylmagnesium bromide.*—The procedure of McKenzie, Mills and Myles[12] was used, with double quantities. A 43% yield of amino alcohol was obtained. This substance, after recrystallization from benzene and petroleum ether, melted at 107–108°. Portions of it were converted to the hydrochloride, nitrate, and benzamide. For a comparison of these substances with those obtained from the oxime reaction, see Table II.

1-Phenyl-1-α-naphthyl-1-hydroxy-2-aminoethane

Methyl α-naphthyl ketoxime.—Methyl α-naphthyl ketone was prepared from naphthalene by the procedure of St. Pfau and Ofner[13] and separated from the β-isomer by means of the picrate. Thirty grams of methyl α-naphthyl ketone (b.p. 166–167°/12 mm.), 125 cc. of 95% alcohol, a saturated aqueous solution of 24 g. of hydroxylamine hydrochloride, and a saturated aqueous solution of 28 g. of sodium hydroxide were boiled under reflux for five hours. The solution was allowed to stand for several hours, and was then diluted with an equal volume of water and acidified with

TABLE II

MELTING POINTS OF 1-PHENYL-1-*p*-TOLYL-1-HYDROXY-2-AMINOETHANE AND DERIVATIVES

COMPOUND	FROM AMINO KETONE	FROM OXIME	MIXTURE
Free base	107–108	107–108	107–108
Hydrochloride	183–184	182–183	182–182.5
Nitrate	175–176	174–175	176
Benzamide	145–146	143–145	143–145

dilute sulfuric acid. The oxime obtained weighed 32 g., a 98% yield. After recrystallization from 50% alcohol it melted at 136.5–137.5°.

Reaction of methyl α-naphthyl ketoxime with phenylmagnesium bromide.—The Grignard reagent was prepared from 20.4 g. (0.84 mole) of magnesium, 142 g. of bromobenzene and 300 cc. of ether. The color change occurred when 190 cc. of ether had been recovered, leaving 1.0 mole in the flask. The oil bath was maintained at about 170° while 21.1 g. (0.114 mole) of methyl α-naphthyl ketoxime was added. Heating and stirring were continued for an additional ten minutes. The product was poured onto 700 g. of ice and made faintly acid with hydrochloric acid. Most of the amino alcohol hydrochloride, mixed with tar, separated at this point. The acid aqueous solution was extracted with ether, and was then adjusted to a pH of about 5. Ammonium nitrate was added, and the solution was allowed to stand for several hours, when a precipitate of alkamine nitrate (2.2 g.) separated. The total yield of alkamine salts was 35.5%. The free base and the benzamide were prepared by the usual methods.

Preparation of 1-phenyl-1-α-naphthyl-1-hydroxy-2-aminoethane from α-amino-

[12] MCKENZIE, MILLS, AND MYLES, *Ber.*, **63**, 904 (1930).

[13] ST. PFAU AND OFNER, *Helv. Chim. Acta.*, **9**, 669 (1926).

acetophenone hydrochloride and α-naphthylmagnesium bromide.—The method of Luce[14] was used. Ten grams of the amino ketone hydrochloride was added to a Grignard reagent prepared from 8.5 g. of magnesium, 91 g. of α-bromonaphthalene and 350 cc. of ether. A 99% yield of amino alcohol hydrochloride (19.0 g.) was obtained. The free base, nitrate, and benzamide were made. For a comparison of these derivatives with those obtained above, see Table III.

1-Phenyl-1-p-chlorophenyl-1-hydroxy-2-aminoethane

p-*Chloroacetophenone oxime.*—This was made from *p*-chloroacetophenone[15] in a manner similar to that described for methyl α-naphthyl ketoxime. Thirty grams of ketone, 43 g. of sodium hydroxide and 19 g. of hydroxylamine hydrochloride

TABLE III

MELTING POINTS OF 1-PHENYL-1-α-NAPHTHYL-1-HYDROXY-2-AMINOETHANE AND DERIVATIVES

COMPOUND	FROM AMINO KETONE	FROM OXIME	MIXTURE
Free base	162–163	161	161–162
Hydrochloride	237	236.5	237
Nitrate	202	204	203.5
Benzamide	194–195	192–193	193–194

TABLE IV

MELTING POINTS OF 1-PHENYL-1-*p*-CHLOROPHENYL-1-HYDROXY-2-AMINOETHANE AND DERIVATIVES

COMPOUND	FROM AMINO KETONE	FROM OXIME	MIXTURE
Free base	121.5–122	121.5–122	121.5–122
Hydrochloride	203	203	203
Nitrate	183	182–182.5	182.5
Benzamide	147–148	147–148	147–148

yielded 31 g. of oxime, a 93.5% yield. After recrystallization from 50% alcohol the product melted at 97.5–98°.

Reaction of p-*chloroacetophenone oxime with phenylmagnesium bromide.*—A Grignard reagent made from 20.4 g. (0.84 mole) of magnesium, 142 g. of bromobenzene and 300 cc. of ether was concentrated until the color change occurred. There was recovered 206 cc. of ether, leaving 94 cc. (0.91 mole) in the flask. The Grignard reagent was treated with 25 g. (0.15 mole) of *p*-chloroacetophenone oxime, while the oil bath was maintained at 160°. Heating and stirring were continued for an additional thirty minutes. The product was poured onto 700 g. of ice, acidified with hydrochloric acid and extracted with ether. The pH of the aqueous layer was then adjusted to about 5 by the addition of ammonium hydroxide. About 50 g. of am-

[14] LUCE, *Compt. rend.*, **180**, 145 (1925).

[15] *Organic Syntheses*, **V**, 17 (1925).

monium nitrate was added, and the solution was kept cold for thirty minutes. The precipitated alkamine nitrate was collected and dried. It weighed 9.5 g., a 21% yield. The benzamide, hydrochloride, and free base were made and purified as in earlier cases.

p-*Chloro-α-aminoacetophenone hydrochloride.*—*p*-Chlorophenacyl bromide was made in 90% yield from *p*-chloroacetophenone by the method of Collet.[16] An addition product was formed from 96.8 g. of *p*-chlorophenacyl bromide and 61.3 g. of hexamethylenetramine in chloroform solution, by the general procedure of Slotta.[17] It was hydrolyzed by means of alcoholic hydrochloric acid to yield 35 g. of amino ketone hydrochloride, a 41% yield.

*1-Phenyl-1-*p*-chlorophenyl-1-hydroxy-2-aminoethane from* p*-chloro-α-aminoacetophenone hydrochloride and phenylmagnesium bromide.*—This amino alcohol, which has not been described before, was made as follows. Phenylmagnesium bromide was made from 6 g. of magnesium, 42 g. of bromobenzene and 105 cc. of ether. To this was added 10 g. of amino ketone hydrochloride over a period of twenty minutes. The mixture was warmed on a hot plate for one hour, and was then cooled and poured onto a mixture of 500 g. of ice and 55 cc. of 8% hydrochloric acid. The acid solution was extracted with ether, and was then made basic with ammonium hydroxide and again extracted with ether. The latter extracts were dried, and the ether was removed, leaving 3.5 g. of amino alcohol, a 29% yield. The alkamine, which is soluble in alcohol and benzene, slightly soluble in ether, and insoluble in ligroïn, was obtained as very fine white plates on recrystallization from a mixture of benzene and ligroïn.

Anal. Calc'd for $C_{14}H_{14}ClNO$: C, 67.91; H, 5.70; N, 5.66; Cl, 14.32.
Found: C, 67.99; H, 6.09; N, 5.89; Cl, 14.57.

The hydrochloride was obtained as fine needles, soluble in water and alcohol, insoluble in ether and benzene.

Anal. Calc'd for $C_{14}H_{15}Cl_2NO$, Cl, 24.98. Found: Cl, 25.03.

The benzamide formed fine needles which were soluble in benzene and insoluble in ligroïn.

Anal. Calc'd for $C_{21}H_{18}ClNO_2$: N, 3.98. Found: N, 3.66.

The nitrate was obtained as a very fine crystalline powder, slightly soluble in water, soluble in alcohol, insoluble in benzene and ether.

For a comparison of these substances with those obtained from the oxime reaction, see Table IV.

SUMMARY

1. It has been shown that mixed ketoximes react with phenylmagnesium bromide in a concentrated solution at elevated temperatures.

2. The product of the reaction is not a hydroxylamine, as might be expected, but a beta amino alcohol, which results from the migration of a nitrogen atom from one carbon atom to another.

3. The reaction has been carried out with the oximes of *p*-methylacetophenone, *p*-chloroacetophenone, propiophenone, and methyl α-naphthyl ketone, and the amino alcohol obtained in each case has been compared with a sample synthesized in another way.

[16] COLLET, *Bull. soc. chim.*, [3], **21**, 69 (1899).
[17] SLOTTA AND HELLER, *Ber.*, **63**, 1027 (1930).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

PREPARATION AND BEHAVIOR OF MIXED DIACYL DERIVATIVES OF *o*-AMINOPHENOL CONTAINING A CARBOARYLOXY RADICAL AND THE *p*-TOLYLSULFONYL GROUP

L. CHAS. RAIFORD AND J. REID SHELTON

February 2, 1939

When two acyl radicals, R—C(=O)— and R′—C(=O)—, are introduced into an ortho aminophenol only one mixed diacyl derivative can generally be obtained, regardless of the order of introduction of the radicals; and in this product the heavier and more acidic of these acyl radicals is usually attached to nitrogen. To meet this requirement the migration of acyl from nitrogen to oxygen[1] must occur in one of these reactions. If the acyls are R—C(=O)— and R—O—C(=O)— the latter is most frequently found attached to nitrogen.[2] In the cases thus far tested when one of the acyls is Ar—S(=O)(=O)— isomeric mixed diacyl derivatives are obtained when the groups are introduced in different orders and no rearrangement takes place.[3]

After the above observations were made it was desired to prepare a diacyl derivative containing the radical Ar—O—C(=O)—, where Ar is an aromatic residue. Although it was found possible to obtain *N*-carboaryloxy derivatives of ortho aminophenols, attempts to introduce a second acyl derived from a carboxylic acid were unsuccessful.[4] When these *N*-carboaryloxy compounds were mixed with caustic alkali solution or pyridine, for the purpose of further acylation, they were converted into

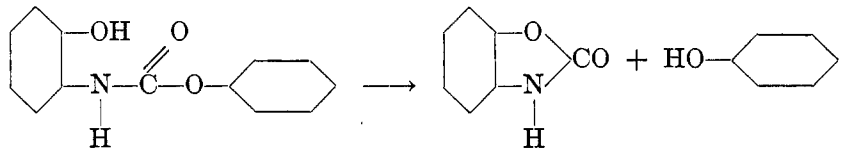
[1] RAIFORD AND CO-WORKERS, *J. Am. Chem. Soc.*, **48**, 483 (1926).

[2] RANSOM AND NELSON, *ibid.*, **36**, 393 (1914).

[3] RAIFORD AND LANKELMA, *ibid.*, **47**, 1123 (1925); RAIFORD AND GROSZ, *ibid.*, **53**, 3420 (1931).

[4] RAIFORD AND INMAN, *ibid.*, **56**, 1586 (1934).

the corresponding benzoxazolones with elimination of the required phenol, as shown.



Before trying to prepare a diacyl derivative containing both a carboaryloxy and an arylsulfonyl radical the possibility that the latter might migrate in compounds closely related to the previous ones was tested further. To do this 2-aminophenol and 2-amino-4-methyl-6-bromophenol were, in turn, converted into mixed diacyl derivatives in which one of the acyl groups was always the 4-tolylsulfonyl radical. When the *N*-sulfonyl and *O*-sulfonyl derivatives of the specified aminophenols were converted into diacylated compounds by the introduction of the acetyl, benzoyl, and carboethoxy radicals, respectively, isomers were obtained in each case. When these products were hydrolyzed the *p*-tolylsulfonyl radical was found on nitrogen in every instance in which it had been attached there in the starting material, while in those cases where it had been bound to oxygen in the starting material it was lost by hydrolysis and the other acyl group was found on nitrogen. It is evident that no rearrangement took place either during acylation or hydrolysis[5]. These relations are shown in Figure 1 for the behavior of one pair of acyl groups with *o*-aminophenol.

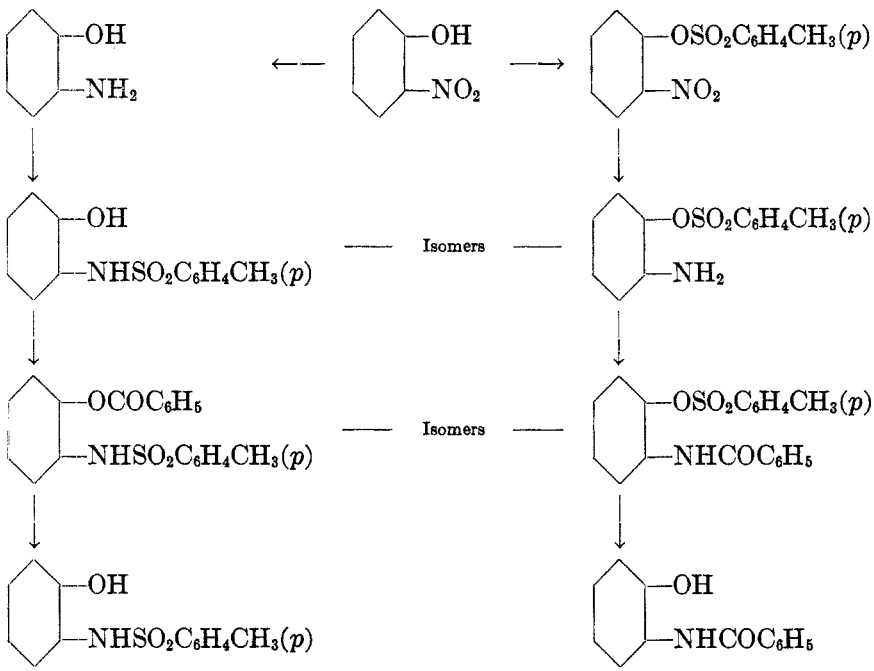
After confirmation of the previous work several experiments were carried out in attempts to obtain a mixed diacyl derivative of *o*-aminophenol in which the carbophenoxy group is attached to oxygen. In one of them an ether solution of 2-*p*-tolylsulfonylaminophenol was refluxed with phenyl chlorocarbonate while dimethylaniline was slowly added. Nothing but starting material could be isolated from the mixture. When the aminophenol and the acid chloride were brought together in pyridine solution, and likewise when subjected to the Schotten-Baumann method, none of the required diacyl derivative was obtained, but about 70 per cent. of the starting materials was recovered, while there was isolated a small portion of a product that melted at 141–142°. When the reaction was carried through in a dioxane solution starting material was again recovered and also a somewhat larger portion of the derivative that melted at 141–

[5] This is a matter of importance because RAIFORD AND COLLABORATORS [*J. Am. Chem. Soc.*, **46**, 2318 (1924); *ibid.*, **47**, 1123 (1925); J. ORG. CHEM., **2**, 217 (1937)] have shown that in some instances migration does occur during hydrolysis of certain of these diacyl derivatives obtained from carboxylic acids.

142° was secured. This was identified as 2-*p*-tolylsulfonylbenzoxazolone by comparison with an authentic sample obtained by the action of *p*-tolylsulfonyl chloride on benzoxazolone. Though none of this required diacyl derivative was isolated it was probably formed but was too unstable to exist under the conditions. The changes are indicated in Figure 2.

When 2-*p*-tolylsulfonylamino-4-methyl-6-bromophenol was used and the reaction was carried out in pyridine solution, 27 per cent. of the required diacyl derivative, m.p. 154–156°, was obtained. Much starting

FIGURE 1



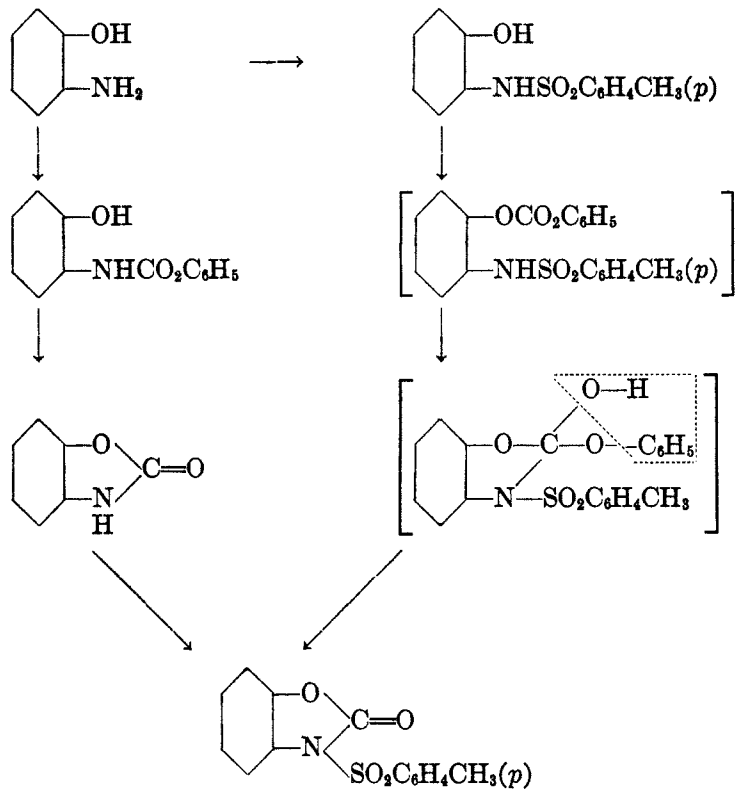
material was recovered. In a repetition of the experiment, modified to the extent that dioxane was used as a solvent and dimethylaniline was added to interact with the hydrogen chloride evolved, only starting material and the corresponding *p*-tolylsulfonylbenzoxazolone were isolated.

Experiments were made to introduce the acyls in the opposite order. When a pyridine solution of 2-aminophenyl *p*-toluenesulfonate was treated with phenyl chlorocarbonate there was obtained a product that melted at 114° and which gave a satisfactory analysis for the expected 2-carbophenoxyaminophenyl *p*-toluenesulfonate. Treatment of 2-amino-4-

methyl-6-bromophenyl *p*-toluenesulfonate with phenyl chlorocarbonate gave a compound that melted at 129–131°, and analysis of this for halogen and sulfur agreed with the requirements of the desired diacyl derivative.

It is of interest here to record that hot alcohol in the presence of decolorizing carbon* caused the replacement of the carbophenoxy by the carboethoxy group in the diacyl derivative melting at 129–131°[6]. The resulting product, 2-carboethoxyamino-4-methyl-6-bromophenyl *p*-

FIGURE 2



toluenesulfonate, was identified by analysis and also by its behavior toward alcoholic potash. In the latter case hydrolysis caused the loss of the *p*-tolylsulfonyl radical and the formation of 3-methyl-5-bromo-6-hydroxy-

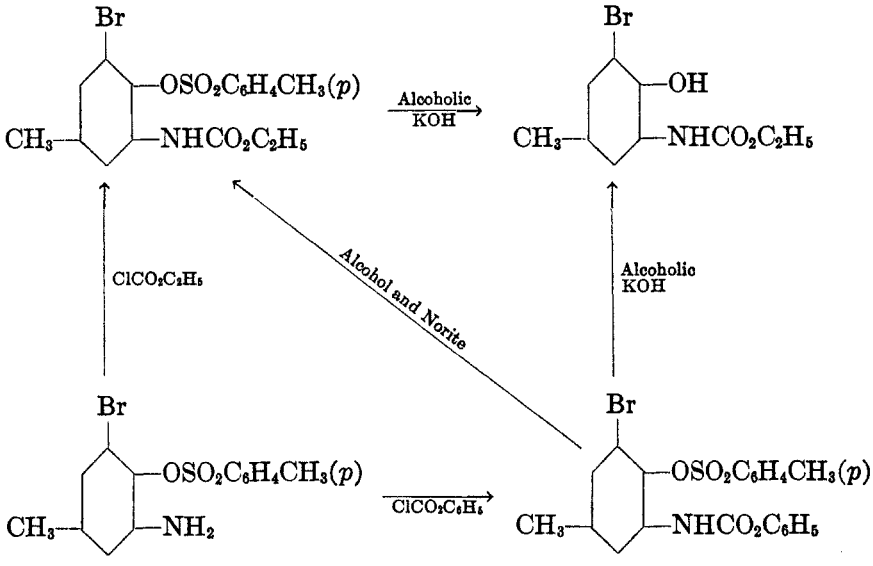
* Norite was used here.

[6] The interaction of esters with alcohols to replace one alkyl group by another has long been known. Following the observations of DUFFY [*J. Chem. Soc.*, **5**, 303 (1853)], this change has frequently been observed in the aliphatic series but seldom

phenylurethane, previously obtained by Upson[7] by rearrangement of 2-amino-4-methyl-6-bromophenyl ethyl carbonate. The relations involved in the present work are shown in Figure 3.

In addition to the compound melting at 129–131° there was isolated from the reaction mixture a small portion of a product that melted above 200°. By varying the experimental procedure (see below) the high-melting product was secured in 53 per cent. yield, while the diacyl derivative amounted to 27 per cent. When a portion of the diacyl derivative was dissolved by heating it for a few minutes with pyridine, the liquid was

FIGURE 3



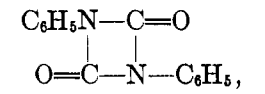
allowed to stand overnight, and the solution was diluted with water, there was deposited the high-melting product mentioned above. The aqueous filtrate contained phenol, which suggested that a benzoxazolone ring

in the aromatic group. In nearly every case reported some alkali was present, and this was regarded as a catalyst. More recently BELLET [*Compt. rend.*, **198**, 1785 (1934)] has extended the study. He used an alcoholic solution of caustic alkali and in some instances conducted the experiments in sealed tubes at elevated temperatures. In general, an ester containing an alkyl group of high molecular weight was found to react to give an ester of low molecular weight and liberate the heavier alcohol. Such a change in the case of urethanes is certainly less common. Thus, the phenyl ester of phenylaminoformic acid first obtained by HOFMANN [*Ber.*, **4**, 249 (1871)] was later obtained by several others, who crystallized it from alcohol, but did not record any interaction with the solvent.

[7] UPSON, *Am. Chem. J.*, **32**, 36 (1904).

closure may have occurred and that the product, m.p., 208–209°, might be an impure sample of a substituted benzoxazolone. Mixture melting-point determinations of the product in question with 4-methyl-6-bromobenzoxazolone, m.p., 220–222°[8], and its *N*-*p*-tolylsulfonyl derivative, m.p., 175–176° (see below), respectively, gave pronounced depressions.

Further study of the product melting at 208–209° indicated that its formation involved two molecular proportions of the diacyl derivative, m.p., 129–131°. Molecular-weight measurements by two different methods gave values ranging from 666 to 681, while the values for the diacyl derivative and the *N*-*p*-tolylsulfonylbenzoxazolone are 476 and 382, respectively. Analytical data for bromine, nitrogen, and sulfur correspond closely to the formula $C_{30}H_{24}Br_2N_2O_8S_2$, and this, in turn, agrees with that required by a product formed by elimination of phenol from the diacyl derivative and combination of two of the remaining residues. Such a residue would represent 3-methyl-5-bromo-6-(*p*-tolylsulfonyloxy)phenyl isocyanate, two molecular proportions of which could interact to give a product of the composition and molecular weight found (see below). This interpretation agrees in general with the behavior of phenyl isocyanate which, in contact with triethylphosphine[9], and also when boiled with pyridine, gives a crystalline product that has been recorded as diphenyl diisocyanate[10]. Still more striking is the observation that this product has recently been obtained by a reaction which closely parallels that involved in the present work, for Warren and Wilson[11] found that phenylurethane reacts with thionyl chloride to eliminate alcohol and give diphenyl diisocyanate. Staudinger[12] regards this product as a four atomic ring derivative,



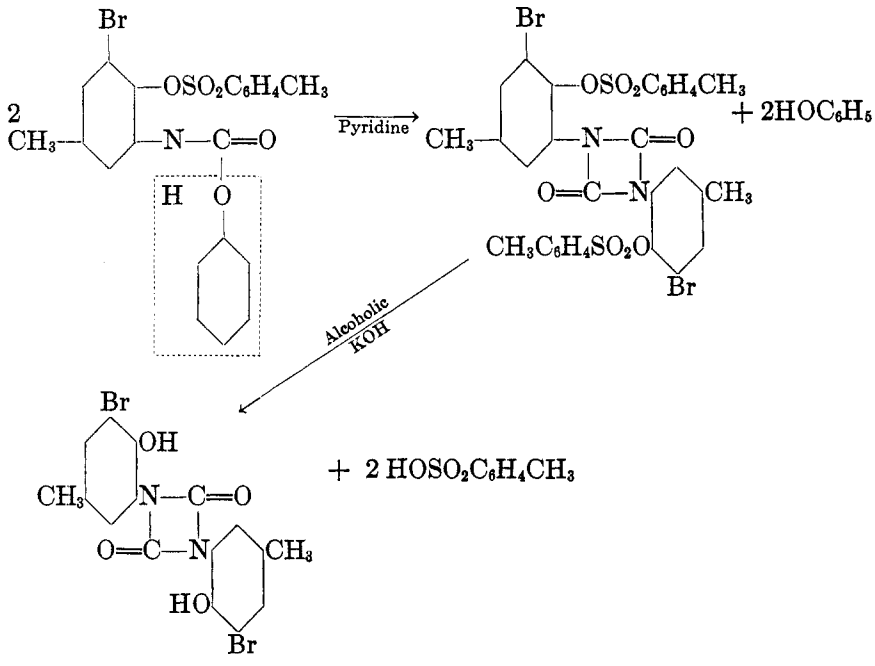
which has more recently been listed as diphenyluretidone[13]. The compound melting at 208–209° should therefore be 1,3-di-(3-methyl-5-bromo-6-*p*-tolylsulfonyloxyphenyl)uretidone.

In the formation of this product from the diacyl derivative the urethane grouping only was involved. The sulfonyl radical remained attached to oxygen because hydrolysis of the new compound readily caused the loss of *p*-toluenesulfonic acid, which was isolated from the reaction mixture,

[8] RAIFORD AND INMAN, *J. Am. Chem. Soc.*, **56**, 1589 (1934).
[9] HOFMANN, *Ann. Suppl.*, **1**, 57 (1861).
[10] SNAPE, *J. Chem. Soc.*, **49**, 254 (1886).
[11] WARREN AND WILSON, *Ber.*, **68**, 957 (1935).
[12] STAUDINGER, "Die Ketene," Enke, Stuttgart, **1912**, p. 126.
[13] *Chem. Abstr.*, **30**, 9899 (1936).

and left a product that contained no sulfur but showed the correct percentages of bromine and nitrogen for the structure indicated below. It is proposed to call this substance 1,3-di-(3-methyl-5-bromo-6-hydroxyphenyl)uretidone. The relations are summarized in Figure 4.

FIGURE 4



EXPERIMENTAL

The 2-aminophenol used was obtained by sublimation of the best commercial grade. 2-Amino-4-methyl-6-bromophenol was prepared as directed by Raiford and Grosz,[14] and was stored in the form of the hydrochloride.

Many acylations here involved were carried out by Einhorn and Hollandt's method.[15] In some cases the Groenvik[16] scheme was employed, but this involves the conversion of one-half the aminophenol into the hydrochloride, and may cause the formation of some diacyl derivative.[17] In cases where the above methods did not work well, satisfactory results were obtained by treatment of a 1,4-dioxane solution of the aminophenol and dimethylaniline with the required acid chloride. The third compound listed in Table I was obtained by the last method indicated above, and the

[14] RAIFORD AND GROSZ, *J. Am. Chem. Soc.*, **53**, 3422 (1931).
[15] EINHORN AND HOLLANDT, *Ann.*, **301**, 95 (1898).
[16] GROENVIK, *Bull. soc. chim.*, [2], **25**, 177 (1876).
[17] RAIFORD AND WOOLFOLK, *J. Am. Chem. Soc.*, **46**, 2251 (1924).

TABLE I

DERIVATIVES OF 2-AMINOPHENOL

DERIVATIVE	YIELD, %	SOLVENT	CRYSTAL FORM	M. P., °C	FORMULA	ANALYSES					
						Carbon		Hydrogen		Sulfur	
						Calc'd	Found	Calc'd	Found	Calc'd	Found
N-Benzoyl-*O*-*p*-tolylsulfonyl-[a]	83	Carbon tetrachloride	Colorless granules	109–110	$C_{20}H_{17}NO_4S$	65.39	65.10	4.63	4.71	8.72	8.88
N-*p*-Tolylsulfonyl-*O*-benzoyl-[b]	Nearly quant.	Alcohol	Colorless needles	141	$C_{20}H_{17}NO_4S$					8.72	8.40
N-Carboethoxyl-*O*-*p*-tolylsulfonyl-[c]	65	Benzene	Colorless prisms	72–74	$C_{16}H_{17}NO_5S$					9.55	9.73
N-*p*-Tolylsulfonyl-*O*-carboethoxyl-[b]	Nearly quant.	Alcohol	Colorless flakes	128–130	$C_{16}H_{17}NO_5S$					9.55	9.62

[a] Hydrolysis gave 2-benzoylaminophenol, m.p. 167°, previously obtained by HÜBNER [*Ann.*, **210**, 388 (1881)].

[b] Hydrolysis gave 2-*p*-tolylsulfonylaminophenol, m.p., 137–138°. TROEGER AND UHLMANN [*J. prakt. Chem.*, [2], **51**, 441 (1895)] found 138–139°.

[c] Hydrolysis gave 2-hydroxyphenylurethane, m.p., 83–85°. GROENVIK [*Bull. soc. chem.*, [2], **25**, 178 (1876)] found 85°.

other three by following Einhorn and Hollandt's directions. In Table II the methods are indicated by footnotes. By these methods 2-aminophenol and 2-amino-4-methyl-6-bromophenol were converted into a number of mixed diacyl derivatives in good yields. Analytical and other data for these compunds are given in the accompanying tables.

2-Carbophenoxyaminophenyl p-*toluenesulfonate.*—To a pyridine solution of 2-aminophenyl *p*-toluenesulfonate 10% more than the required phenyl chlorocarbonate was added with shaking, this mixture was allowed to stand for several hours and was then poured into dilute acid to precipitate the product. The yield was nearly quantitative. Crystallization from carbon tetrachloride gave material that was contaminated with a sticky brown oil which was removed in large part by extracting the crystals with small portions of fresh solvent. The remaining solid was recrystallized from alcohol and was obtained in small colorless needles that melted at 114°. Though the experiment was repeated several times the yield of purified product was never higher than 50%.

Anal. Calc'd for $C_{20}H_{17}NO_5S$: C, 62.66; H, 4.43; N, 3.65.
Found: C, 62.60; H, 4.84; N, 3.60.

Attempts to hydrolyze this product with alcoholic potash gave only a dark oil from which no definite product could be isolated.

*Action of phenyl chlorocarbonate on 2-*p-*tolylsulfonylaminophenol.*—When the reactants were brought together in pyridine solution and also when the Schotten-Baumann method was tried, some starting material was recovered, and a small portion of a product that melted at 141–142° was obtained. Refluxing a mixture of the reactants in ether solution caused no change. To a warm dioxane solution of these substances the theoretical quantity of dimethylaniline was added dropwise, the liquid was heated for ten minutes on the steam bath, during which time the mixture became purple. After three hours it was diluted with water, which precipitated an oil that solidified upon standing. Crystallization from alcohol gave a 31% yield of colorless slender rods that melted at 141–142°, and which were identified as 2-*p*-tolylsulfonylbenzoxazolone by determination of the melting point of a mixture with an authentic sample obtained by the action of *p*-toluenesulfonyl chloride on benzoxazolone.

Anal. Calc'd for $C_{14}H_{11}NO_4S$: S, 11.07. Found: S, 11.01.

*2-*p-*Tolylsulfonylamino-4-methyl-6-bromophenyl phenyl carbonate.*—A pyridine solution of the required acylaminophenol was treated with phenyl chlorocarbonate as described above, and after standing overnight this mixture was poured into water. The sticky oil, which would not solidify, was extracted with ether, the extract was shaken with dilute ammonia water which removed some starting material, the ether was distilled, and the residue was crystallized from alcohol. Evaporation of the mother liquor gave more starting material. The new product was isolated as small nearly colorless needles that melted at 154–156°. Analysis indicated that the substance was the required diacyl derivative probably contaminated with the corresponding 2-*p*-tolylsulfonylbenzoxazolone. Hydrolysis of the compound gave 2-*p*-tolylsulfonylamino-4-methyl-6-bromophenol, which was used as starting material for the product just described.

Anal. Calc'd for $C_{21}H_{18}BrNO_5S$: Br, 16.80. Found: Br, 17.16.

In a second experiment a warm 1,4-dioxane solution of 5 g. of the sulfonylaminophenol was mixed with phenyl chlorocarbonate, dimethylaniline was slowly added, the mixture was warmed on a steam bath for a few minutes, allowed to stand overnight, and then diluted with water. The oil that separated solidified in a short time. It was removed, washed with dilute hydrochloric acid, extracted with a small volume

TABLE II

DERIVATIVES OF 2-AMINO-4-METHYL-6-BROMOPHENOL

DERIVATIVE*	YIELD,[a] %	SOLVENT	CRYSTAL FORM	M. P., °C.	FORMULA	ANALYSIS, HALOGEN	
						Calc'd	Found
1. *N*-*p*-Tolylsulfonyl-	68	Acetic acid	Colorless prisms	171–172	$C_{14}H_{14}BrNO_3S$	22.47	22.53
2. *N*-Acetyl-*O*-*p*-tolylsulfonyl-[b]	66	Alcohol	Small colorless needles	131–132	$C_{16}H_{16}BrNO_4S$	20.10	20.00
3. *N*-*p*-Tolylsulfonyl-*O*-acetyl-[c]	50	Alcohol[d]	Colorless prisms	150–151.5	$C_{16}H_{16}BrNO_4S$	20.10	20.15
4. *N*-Benzoyl-*O*-*p*-tolylsulfonyl-[e]	62	Alcohol	Small colorless needles	149–151[f]	$C_{21}H_{18}BrNO_4S$	17.39	17.49
5. *N*-*p*-Tolylsulfonyl-*O*-benzoyl-[c]	82	Alcohol	Colorless flakes	163–164	$C_{21}H_{18}BrNO_4S$	17.39	17.11
6. *N*-Carboethoxyl-*O*-*p*-tolylsulfonyl-[g]	67	Alcohol	Colorless fibers	124.5–125	$C_{17}H_{18}BrNO_5S$	18.69	18.84
7. *N*-*p*-Tolylsulfonyl-*O*-carboethoxyl-[c]	50	Alcohol	Colorless flakes	140–142[f]	$C_{17}H_{18}BrNO_5S$	18.69	18.73

[a] These represent purified material.

[b] Hydrolysis of this gave 2-acetylamino-4-methyl-6-bromophenol, previously obtained by RAIFORD [*J. Am. Chem. Soc.*, **41**, 2073 (1919)].

[c] Hydrolysis gave 2-*p*-tolylsulfonylamino-4-methyl-6-bromophenol described above.

[d] Previously crystallized repeatedly from acetic acid.

[e] Hydrolysis gave 2-benzoylamino-4-methyl-6-bromophenol previously identified by RAIFORD [*J. Am. Chem. Soc.*, **41**, 2074 (1919)].

[f] Although this was not obtained as a sharp-melting compound, it gave a satisfactory analysis, and hydrolysis gave the expected product.

[g] Hydrolysis gave 3-methyl-5-bromo-6-hydroxyphenylurethane, m.p., 83°, previously obtained in a different way by UPSON [*Am. Chem. J.*, **32**, 36 (1902)].

* Compounds 1, 4, 5 and 6 were obtained by Einhorn and Hollandt's method; 2 and 3 by warming the required amino compound with acetic anhydride, and 7 by treatment of a dioxane solution of the required phenol and dimethylaniline with ethyl chlorocarbonate.

of hot alcohol which removed the blue color and most of the starting material. Crystallization of the residue from a larger volume of alcohol gave nearly colorless needles that melted at 175–176°, and which were identified as 2-*p*-tolylsulfonyl-4-methyl-6-bromobenzoxazolone by determination of the melting point of a mixture with an authentic sample of the latter prepared from 4-methyl-6-bromobenzoxazolone[8] and the required acid chloride.

Anal. Calc'd for $C_{15}H_{12}BrNO_4S$: Br, 20.94. Found: Br, 20.90.

Action of phenyl chlorocarbonate on 2-amino-4-methyl-6-bromophenyl p-*toluene sulfonate.*—Five grams of the required toluenesulfonate was dissolved in 15–20 cc. of pyridine, one molecular proportion of phenyl chlorocarbonate was added, the mixture was allowed to stand overnight and then diluted with five volumes of water. The viscous solid that separated was washed with dilute acid, then with water, and was crystallized from carbon tetrachloride. The resulting nearly colorless solid, which weighed 3.7 g., was boiled with 175 cc. of alcohol, and the mixture was filtered. On cooling, the filtrate deposited about 1 g. of long, thin, nearly colorless fibers that resembled asbestos and which melted at 208–209°. They were identical with the small portion of solid that had not dissolved. Evaporation of the alcoholic mother liquor to a small volume gave about 2 g. of the desired diacyl derivative that melted at 129–131°.

In a second experiment one molecular proportion of phenyl chlorocarbonate was added with stirring and cooling to 50 cc. of a pyridine solution containing 15 g. of the required amino compound. A gummy solid soon separated. The mixture was then warmed on a hot plate until the solid dissolved, the liquid was allowed to cool slowly and after three hours was diluted with three volumes of water. The tan solid that separated was dried and boiled with 125 cc. of carbon tetrachloride, the mixture was filtered, and the residue was washed with pure solvent. Crystallization of the residue from benzene gave 7.5 g. of the product that melted at 208–209°. Evaporation of the carbon tetrachloride filtrate and washings gave first 0.5 g. of the high-melting compound and finally 5.5 g. of the diacyl derivative melting at 129–131°. The yield of the latter was 27%, thus accounting for 84% of the starting material.

In a third experiment the Groenvik method was used. Ten per cent. more than the calculated half-molecular proportion of phenyl chlorocarbonate was added slowly to an ether solution of 25 g. of the required amino compound. The mixture soon became turbid, and after a few hours colorless crystals began to separate. The mixture was allowed to stand overnight, the solid was removed and washed with water. Recrystallization from alcohol gave 11.5 g. of colorless rods that melted at 129–131°. Evaporation of the ether filtrate gave 4 g. of the same substance in slightly less pure condition. On the basis of a 50% conversion of the starting material the yield was 94%.

The above experiment was repeated with the modification that 5 g. of the amino compound was dissolved in 50 cc. of ether, 10% more than one molecular proportion of phenyl chlorocarbonate was added, an equivalent amount of dimethylaniline was run in slowly with shaking, and the mixture was allowed to stand. A colorless solid began to separate within four hours. After twenty-four hours the liquid was decanted and the residue washed with water. Crystallization from alcohol gave 2-carbophenoxyamino-4-methyl-6-bromophenyl *p*-toluenesulfonate. A small amount of the same substance was recovered from the ether solution. The total yield of purified material was 81%.

Anal. Calc'd for $C_{21}H_{18}BrNO_5S$: Br, 16.80; S, 6.72.
Found: Br, 16.75; S, 6.76.

The residues obtained by evaporation of the ether solutions left from the last two preparations indicated above were mixed and crystallized from alcohol. The product that separated was considerably colored and melted at 128–130°. It was dissolved in alcohol, the solution was boiled with decolorizing charcoal and filtered. The product then separated in colorless fibrous masses that melted at 123–124°. The same product was obtained when an alcoholic solution of a portion of purified 2-carbophenoxyamino-4-methyl-6-bromophenyl *p*-toluenesulfonate was boiled for about three minutes with Norite. The new substance did not depress the melting point of the compound obtained by the action of ethyl chlorocarbonate on 2-amino-4-methyl-6-bromophenyl *p*-toluenesulfonate. Analyses for bromine and for sulfur showed that treatment with alcohol had replaced the C_6H_5O— radical by C_2H_5O—.

Anal. Calc'd $C_{17}H_{18}BrNO_5S$: Br, 18.69; S, 7.48.

Found: Br, 18.73; S, 7.34.

A 2-g. portion of the product melting at 123–124° was mixed with 20 cc. of 1*N* alcoholic potash, warmed on a steam bath until solution took place, and the liquid acidified. The precipitated material was removed, dissolved in alkali solution and was re-precipitated unchanged by addition of acid. Crystallization from alcohol gave pale-brown irregular prisms that melted at 82–83°. The same compound was obtained when 2-carbophenoxyamino-4-methyl-6-bromophenyl *p*-toluenesulfonate was subjected to the action of alcoholic potash. The final compound was identified as 3-methyl-5-bromo-6-hydroxyphenylurethane by comparison with a sample of the latter which was prepared for this purpose.

*1,3-Di-(3-methyl-5-bromo-6-*p*-tolylsulfonyloxyphenyl)uretidone.*—Two grams of the purified diacyl derivative melting at 129–131° was dissolved in 10 cc. of pyridine by warming, the solution was allowed to stand overnight and was then diluted with five volumes of water. The product separated as an oil that solidified on standing. This material was collected, washed with dilute acid and then with water. The filtrate (*F*) was reserved for further examination. The solid was boiled with 50 cc. of alcohol which dissolved but a portion of it, and the mixture was filtered. On cooling the filtrate deposited about 1 g. of colorless solid. Recrystallization of this from benzene gave colorless, fluffy, fibrous material that melted at 208–209°. The melting point of a mixture of this material with the high-melting compound that separated during the preparation of the diacyl derivative showed no depression. The remaining solid that did not dissolve in alcohol was crystallized from benzene and was found to be identical with the portion that was dissolved by alcohol.

Anal. Calc'd for $C_{30}H_{24}Br_2N_2O_8S_2$: Br, 20.94; N, 3.66; S, 8.37; mol. wt., 764.

Found: Br, 20.83; N, 3.74; S, 8.39; mol. wt., (Rast camphor method) 681, (freezing-point method with benzene) 666.

Filtrate (*F*) was acidified and extracted with ether, the extract evaporated to dryness, the residue dissolved in water and the resulting solution treated with bromine water. 2,4,6-Tribromophenol was precipitated.

1,3-Di-(3-methyl-5-bromo-6-hydroxyphenyl)uretidone.—Three grams of the above sulfonyl derivative was dissolved in 25 cc. of alcoholic potash, containing 2 g. of alkali, by warming on a steam bath. After cooling, the mixture was acidified with 10 cc. of 6*N* hydrochloric acid and then 150 cc. of water was added. This precipitated 1.6 g. of nearly colorless solid which decomposed at about 168°. The filtrate (F_1) was reserved. Repeated crystallization of the solid from dilute alcohol, from which it tended to separate as an oil, gave gray, fluffy fibers that melted with decomposition at 169–170°. Analysis of the product obtained as described gave a value for halogen 1.5% higher than that demanded by theory. Hydrolysis of a

second portion of the sulfonyl derivative was carried through, and the reaction mixture was acidified with dilute nitric acid. After one recrystallization of this material from dilute alcohol it melted with decomposition at 170°.

Anal. Calc'd for $C_{14}H_{12}Br_2N_2O_4$: Br, 35.08; N, 6.14.
Found: Br, 35.83; N, 6.15.

Filtrate (F_1) was evaporated to dryness under reduced pressure on a steam bath. The residue was repeatedly extracted with small portions of anhydrous ether and finally with absolute alcohol. The extracts were separately evaporated to dryness, the new residues were dissolved in small portions of water, the liquids were filtered to remove insoluble matter, and the filtrates were evaporated to dryness over sulfuric acid in a desiccator. In each case the final residue melted at 100–102°, and mixtures of each with known samples of *p*-toluenesulfonic acid, m.p., 103–105°, melted at 100–103°.

SUMMARY

1. 2-Aminophenol and 2-amino-4-methyl-6-bromophenol, respectively, have been converted into a number of mixed diacyl derivatives in which one of the radicals was always the *p*-tolylsulfonyl group. When the other one was R—C(=O)—, R—O—C(=O)—, or Ar—C(=O)—, isomers were obtained when the acyls were introduced in different orders, and no migration was observed.

2. When the second radical was Ar—O—C(=O)— isomeric mixed compounds were again formed, but under the conditions these products may suffer further change. Thus, the *N*-*p*-tolylsulfonylaminophenol obtained from each base reacts with phenyl chlorocarbonate to give the expected *O*-carbophenoxy derivative. That formed from the first base was not isolated; it lost phenol immediately to give the corresponding *N*-*p*-tolylsulfonylbenzoxazolone. With the second base both diacyl derivatives and the substituted benzoxazolone were isolated.

3. Treatment of 2-carbophenoxyamino-4-methyl-6-bromophenyl *p*-toluenesulfonate with hot pyridine caused the loss of phenol and the formation of a "condensation" product which it is proposed to call 1,3-di-(3-methyl-5-bromo-6-*p*-tolylsulfonyloxyphenyl)uretidone.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, AND THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

REDUCTION STUDIES IN THE MORPHINE SERIES. IX. HYDROXYCODEINONE*

ROBERT E. LUTZ AND LYNDON SMALL

Received February 9, 1939

When thebaine (I), in glacial acetic acid solution, is treated with hydrogen peroxide[1] the ketone, hydroxycodeinone, of the generally accepted[2,3] structure II is formed. The process apparently involves a 1,4-addition reaction, with the equivalent of hydrolysis at the enol ether group of thebaine, whereby a tertiary alcoholic hydroxyl appears at C-14, and a carbonyl group at C-6 in the end product. The position of the carbonyl group and the existence of the intact morphine skeleton in hydroxycodeinone seem well established by the facts that bromocodeinone (III) can be transformed to hydroxycodeinone oxime through the action of hydroxylamine, and can also, by reductive elimination of bromine, be converted to the well known morphine derivatives codeinone (IV)[2,4] and dihydrocodeinone.[5] The only structural features of hydroxycodeinone involving any uncertainty beyond that inherent in the morphine formula, are the locations of the alicyclic unsaturation and of the alcoholic hydroxyl group. (See p. 221.)

The hydroxycodeinone formula originally advanced by Freund and Speyer represented the hydroxyl as occupying C-7, and since the group has not the properties of an enolic hydroxyl, this necessitated locating the unsaturation between C-8 and C-14. As Robinson has pointed out, hydroxycodeinone does not behave like an α-hydroxy ketone, nor do the results of cyanogen bromide degradation[1,5] point to location of the double

* The work reported in this paper is part of a unification of effort by a numbr of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the Nationa 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.

Number VIII of this series, see Small and Browning, J. ORG. CHEM., **3**, 618 (1939). This communication was erroneously numbered VII.

[1] FREUND AND SPEYER, *J. prakt. Chem.*, **94**, 135 (1916).

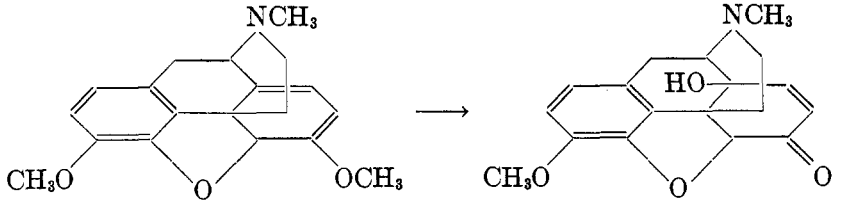
[2] GULLAND AND ROBINSON, *Mem. Proc. Manchester Lit. Phil. Soc.*, **69**, 79 (1925).

[3] SCHÖPF AND BORKOWSKY, *Ann.*, **452**, 211 (1927).

[4] FREUND, *Ber.*, **39**, 844 (1906).

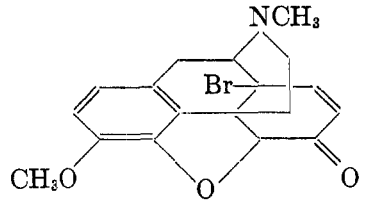
[5] SPEYER AND SARRE, *ibid.*, **57**, 1404 (1924).

bond in the β, γ position to nitrogen. The hydroxyl group can scarcely be at carbon 8, for such a β-hydroxy ketone should undergo dehydration easily, in contrast to hydroxycodeinone and its derivatives; this structure would, moreover, make it impossible to locate an unsaturated linkage in ring III. The remaining probability, C-14, permits a reasonable mechanism for the formation of hydroxycodeinone from thebaine, and explains the retention of the vinyl group on C-13 in the degradation reactions that lead to dihydrohydroxycodeinone.[1, 3]

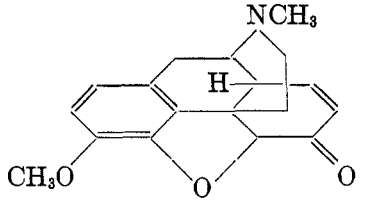


I. Thebaine

II. Hydroxycodeinone



III. Bromocodeinone



IV. Codeinone

The present studies on hydroxycodeinone were undertaken to increase our knowledge of the physiological action of derivatives of this series, as well as with the hope of obtaining more direct evidence concerning the nuclear position of the hydroxyl group. Although the last objective has not been attained, the results of the investigation must be brought to publication at this time because of the unavoidable termination of our collaborative work.

According to formula II, the reduction product, dihydrohydroxycodeinone, is a saturated, tertiary alcohol, and should undergo dehydration with relative ease to yield the ketone corresponding to the secondary alcohol neopine or, by rearrangement, codeinone. All of our attempts to dehydrate dihydrohydroxycodeinone have failed. Dehydration with phosphorus pentoxide[6] resulted in extensive decomposition, and with phos-

[6] HILL AND FISCHER, *J. Am. Chem. Soc.*, **44**, 2582 (1922).

phorus oxychloride gave unchanged material. Dehydration in the presence of iodine[7] was not more successful. Dehydration with anhydrous oxalic acid[6, 8] at elevated temperatures, which has been carried out with other tertiary alcohols, yielded unchanged material, as did also Willstätter's method,[9] phthalic anhydride in benzene or in dekalin. Attempts to split acetic acid out of 14-acetyldihydrohydroxycodeinone likewise failed, although the higher esters[10] were not investigated. The only evidence of a dehydration of this tertiary alcohol appears in the work of Schöpf,[11] who believed he had split out water between C-14 and C-8 in dihydrohydroxythebainonemethine. Since, however, the hydrogenation product (not analyzed) obtained from this supposed dehydration compound was not identical with dihydrothebainonedihydromethine, nor with the C-14 diastereoisomeric β-dihydrothebainonedihydromethine which Small and Browning[12] claim to have isolated from degradation of β-dihydrothebainone, the Schöpf experiments cannot be advanced as valid evidence for a dehydration of a dihydrohydroxycodeinone derivative. It is nevertheless remarkable that a tertiary alcohol of this type should offer such resistance to dehydration.

Speyer[5] investigated the zinc-acetic acid reduction of hydroxycodeinone, from which isomeric phenolic and non-phenolic compounds were obtained. The non-phenolic isomer, which exhibited no ketonic properties, was designated hydroxycodeine and, according to the Robinson idea, would be represented by V. Speyer's conception of the secondary alcoholic group is probably correct, for we find that hydroxycodeine forms two acetyl derivatives (one of which may be a diacetyl compound) that readily undergo hydrolysis with alkali to regenerate hydroxycodeine. It is remarkable that Speyer mentions no difficulty in the analysis of the hydroxycodeine base. Analysis in this laboratory indicate that it holds a molecule of water with unusual tenacity, and only after boiling out with chlorobenzene, and crystallization from this solvent could it be obtained in anhydrous form for analysis.

Catalytic hydrogenation of hydroxycodeine proceeds slowly with absorption of one mole of hydrogen. The product, for which formula VI is logical, we have named dihydrohydroxycodeine-A, to distinguish it from the isomers to be described. It shows a striking similarity to hydroxycodeine in physical properties, but gives analytical values corresponding to the

[7] HIBBERT, *ibid.*, **37**, 1748 (1915).

[8] WALLACH, *Ann.*, **275**, 107 (1893). SAYTZEFF, JUN., *J. prakt. Chem.*, **57**, 38 (1898). ZELINSKY AND ZELIKOW, *Ber.*, **34**, 3249 (1901).

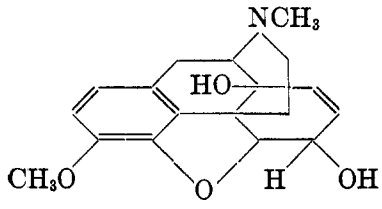
[9] WILLSTÄTTER, *Ann.*, **378**, 109 (1911).

[10] Method of KRAFFT, *Ber.*, **16**, 3020 (1883).

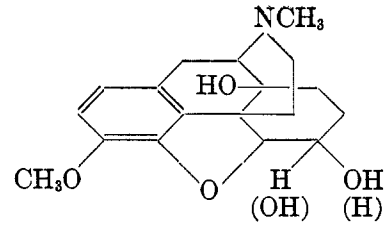
[11] SCHÖPF AND BORKOWSKY, *Ann.*, **452**, 255 (1927).

[12] SMALL AND BROWNING, J. ORG. CHEM., **4**, 00 (1939).

expected formula, $C_{18}H_{23}NO_4$, and shows a decisive depression in mixture melting point with hydroxycodeine.



V. Hydroxycodeine



VI. Dihydrohydroxycodeines-A (?), -B and -C

Hydroxycodeinone is reduced readily in the presence of palladium-barium sulfate to give the well-known dihydrohydroxycodeinone. This compound still contains the carbonyl and hydroxyl groups; it forms an oxime, or a monoacetyl derivative, and we find that under more vigorous acetylation conditions it yields acetyldihydrohydroxycodeinone enol acetate, the analog of the drug Acedicon (dihydrocodeinone enol acetate). Gentle acid hydrolysis converts the enol acetate back to acetyldihydrohydroxycodeinone, and by vigorous hydrolysis both acetyl groups are removed.

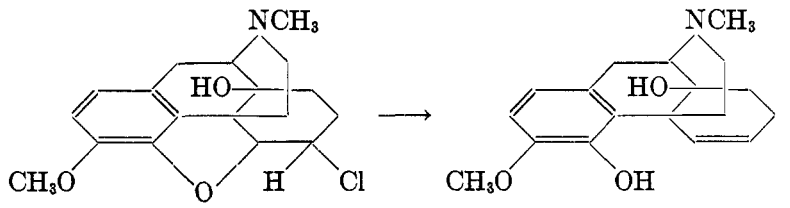
Dihydrohydroxycodeinone can be hydrogenated further (platinum catalyst), and takes up one mole of hydrogen to give unequal amounts of two compounds that can be separated through salts of their diacetyl derivatives. The major product is dihydrohydroxycodeine-B, the minor product is an isomer, dihydrohydroxycodeine-C. Both compounds have the same empirical formula as the above described dihydrohydroxycodeine-A, are non-phenolic, and contain two alcoholic hydroxyl groups, as is shown by the results of acetylation. The method of preparation predicts that the A isomer should be identical with one of the last described isomers. These were prepared under such mild conditions, catalytic reduction in two stages, that a rearrangement (at C-14?) hardly comes into consideration. It seems more probable that a structural change took place in the zinc and acid reduction to the supposed hydroxycodeine, the first stage in the formation of dihydrohydroxycodeine-A. This idea is supported by the pharmacological studies,[13] for the isomers B and C differ in their physiological action in about the same degree as the members of other diastereoisomeric pairs that have been compared, such as dihydrocodeine and dihydroisocodeine, whereas dihydrohydroxycodeine-A deviates widely in effect from the other two isomers.

[13] SMALL, EDDY, MOSETTIG, AND HIMMELSBACH, "Studies on Drug Addiction", p. 33 (Suppl. No. 138 to the Public Health Reports, Washington, 1938).

Dihydrohydroxycodeine-B methiodide undergoes ring scission in the normal way, and the product, dihydrohydroxycodeine-B-methine, takes up one mole of hydrogen to form the dihydromethine.

The action of thionyl chloride on dihydrohydroxycodeine-B resulted in substitution of a chlorine atom into the aromatic nucleus, presumably at the 1 position.[14] This was evident not only from the analytical values, but also from the course of the sodium and alcohol reduction of the chloro compound, which regenerated dihydrohydroxycodeine-B. The nuclear chlorination is not surprising, for we have observed a similar reaction of all four isomeric dihydrocodeines. It is apparent that the success of the thionyl chloride reaction in replacement of the alcoholic hydroxyl of morphine and codeine by chlorine[15] is due to the activation of the hydroxyl group by the 7,8 double bond, although it is remarkable that with these alkaloids the reaction does not proceed further, with involvement of the aromatic nucleus.

Phosphorus pentachloride replaces a hydroxyl group of dihydrohydroxycodeine-B with chlorine, yielding a dihydrohydroxychlorocodide (VII). Proof that the hydroxyl replaced is that at the 6 position rests on sodium and alcohol reduction, in which the chlorine is eliminated with simultaneous reductive rupture of the ether bridge, to give a new phenolic compound, dihydrodesoxyhydroxycodeine (VIII). The reaction is analogous to the sodium-alcohol reduction of dihydrochlorocodide to dihydrodesoxycodeine-C, and indicates that the halogen and the ether-linked oxygen in dihydrohydroxychlorocodide are reacting as though in a conjugated system,[16] *i. e.*, in such a way that reductive elimination of chlorine involves the ether bridge. Were the chlorine at C-14, its replacement by hydrogen should yield dihydrocodeine or dihydroisocodeine. Dihydrodesoxyhydroxycodeine takes up one mole of hydrogen, giving tetrahydrodesoxyhydroxycodeine. Repeated attempts to reduce dihydrohydroxychlorocodide to a non-phenolic product, or to eliminate hydrogen chloride to obtain a substance of the desoxycodeine-C type (of pharmacological interest) have failed.



VII. Dihydrohydroxychlorocodide VIII. Dihydrodesoxyhydroxycodeine

[14] Small and Turnbull, *J. Am. Chem. Soc.*, **59**, 1541 (1937).
[15] Wieland and Kappelmeier, *Ann.*, **382**, 306 (1911).
[16] *Cf.* Small and Lutz, *J. Am. Chem. Soc.*, **56**, 1378 (1934).

The different chlorinating reactions of thionyl chloride and phosphorus pentachloride can be carried out successively, regardless of the order, to produce chlorodihydrohydroxychlorocodide, in which a hydroxyl group and a hydrogen atom have been replaced by chlorine.

If formula VI is correct for dihydrohydroxycodeine-B, it is surprising that only one of the two hydroxyls should be replaced in the reaction with phosphorus pentachloride, and that this one should be the 6-hydroxyl rather than the tertiary hydroxyl at C-14. The unexpected resistance of this group toward replacement (or dehydration) reactions might be ascribed to its position at the junction of two fused rings, yet the bromine atom in bromocodeinone shows no reluctance to reaction with hydroxylamine (elimination as hydrogen bromide to the contrary, however), nor do similarly located (angular) hydroxyl groups in the cyclopentenophenanthrene series (heart poisons, toad poisons) display a like inertia.

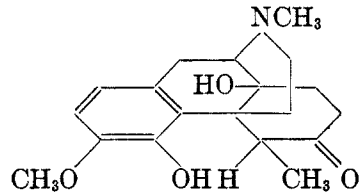
Dihydrohydroxycodeine-C reacts with phosphorus pentachloride to give products containing phosphorus. This difference in the behavior of the B and C isomers is reminiscent of that already observed in the epimeric pair, dihydrocodeine and dihydroisocodeine. This fact can scarcely be considered as valid evidence for the assignment of the comparative configurations, but is suggestive of a similar relationship in the two pairs of isomers. Lacking more direct evidence, we may mention that there is nothing in the pharmacological picture that is inconsistent with the conception that dihydrohydroxycodeine-B has the dihydrocodeine configuration at C-6, and that dihydrohydroxycodeine-C has the dihydroisocodeine configuration.

With compounds of the hydroxycodeinone series, phosphorus pentachloride and phosphorus tribromide gave for the most part intractable products. The reaction of hydroxycodeinone with phosphorus pentachloride has been most extensively studied. Under various conditions, yields of crystalline material amounting to about 20 per cent. of the starting material have been obtained. The crude product is a complex mixture, from which six compounds have so far been isolated. Four of these are so weakly basic that they do not dissolve in dilute acetic acid, but do dissolve in hydrochloric acid, a property that was utilized for partial separation. Of the six compounds, one is monochlorinated, two are dichlorinated, and three are trichlorinated derivatives. The dichloro compounds are believed to contain a ketochloride group, and are analogous to the ketochlorides obtained from the α,β-unsaturated ketones. The trichloro compounds are probably also ketochlorides, but have, in addition, the 14-hydroxyl replaced by chlorine. This replacement reaction contrasts with the indifference of the hydroxyl in the saturated derivatives, and may be ascribed to the activating influence of the 7,8-double bond. The work which is now under way to elucidate the nature and relationships of

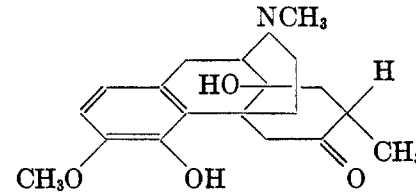
these compounds and to apply the reaction to other ketones of the morphine series will be reported in later papers. The catalytic reduction of one of the trichloro compounds, 14-chlorocodeinone ketochloride-A may be mentioned at this time. The products isolated were dihydrodesoxycodeine-D and tetrahydrodesoxycodeine. Thereby is demonstrated conclusively, that in the trichloro compound as well as in hydroxycodeinone, the original morphine skeleton has been maintained intact.

Reduction of hydroxycodeinone with stannous chloride results in rupture of the oxide ring and formation of hydroxythebainone, which is further reduced catalytically (or by metal combinations) to dihydrohydroxythebainone.[1] The last named compound is obtained also from dihydrohydroxycodeinone through the action of metal combinations. We have carried out many such reductions in this series, and in the sodium-alcohol and Clemmensen reductions of hydroxythebainone have found only dihydrohydroxythebainone, with no evidence of a non-phenolic compound such as the so-called "dihydrohydroxythebacodine" of Ochiai.[17]

It has been shown in previous papers from this laboratory that organomagnesium halides react with pseudocodeine types,[18] and that the products resulting from the reaction of the enol ethers and enol esters of the morphine dihydroketones are of special interest because they can be reconverted through 4,5-ether ring closure to nuclear substituted dihydromorphine derivatives.[19] The promising therapeutic action of methyldihydromorphinone has led us to undertake the preparation of a similar compound derived from the 14-hydroxy series, an attempt that has met with only partial success.



IX.



X.

Methyldihydrohydroxythebainones

As in several of the examples already reported, the reaction of methylmagnesium iodide with acetyldihydrohydroxycodeinone enol acetate produced two phenolic compounds in unequal amounts. Neither the bases

[17] OCHIAI, *J. Pharm. Soc. Japan*, No. **568**, 91 (1929). KONDO AND OCHIAI, *Ann.*, **460**, 224 (1929).

[18] SMALL AND YUEN, *J. Am. Chem. Soc.*, **58**, 192 (1936).

[19] SMALL, FITCH, AND SMITH, *ibid.*, **58**, 1547 (1936). SMALL, TURNBULL, AND FITCH, J. ORG. CHEM., **3**, 204 (1938).

nor their salts have been isolated in crystalline condition, but the two compounds were separated and characterized as the crystalline oxime hydrochlorides. In analogy with the still unsettled speculative constitutions already referred to, the phenolic compounds may be tentatively represented as in formulas IX and X.

The oxime of the major product, on hydrolysis, gives a *new, non-phenolic* crystalline base, which, in turn, gives a new oxime. The oximation or hydrolysis seems to have involved simultaneous ring closure, but the exact nature of the reaction must await further investigation. Bromination of the phenolic bases from the Grignard reaction, followed by ring closure in the usual way resulted in non-phenolic products that have not yet been obtained in well defined condition. These results, which constitute only a preliminary report on the reaction, demonstrate again the applicability of the Grignard reagent to those of the morphine derivatives having a double bond "conjugated" with the cyclic ether group.

We are indebted to Merck and Co., Inc., Rahway, N. J. for the gift of thebaine used in this research.

EXPERIMENTAL*

Hydroxycodeinone.—[1] The preparation of starting material was carried out by the general method of Freund and Speyer, adapted to a larger scale. In a series of runs, 50 g. of thebaine was added to 200 cc. of glacial acetic acid, the solution was heated quickly to boiling, and the flame removed. Twenty-five cubic centimeters of 30% hydrogen peroxide solution was added, and the ensuing vigorous ebullition was maintained by heating until ten minutes had elapsed from the start of the reaction. The solution was poured immediately onto a large quantity of ice, and succeeding oxidations were added to the same mixture. After neutralization of the acetic acid with concentrated ammonia (ice addition), the crude dark-brown solid was separated by filtration, and purified by trituration with successive portions of cold ethanol, which removed resinous impurities. The yield of brown crystalline powder was 36–40% of the thebaine employed. Further purification was effected by dissolving the product in boiling chloroform, cooling, and diluting with ethanol. The product retains color obstinately, and a colorless sample can be obtained through purification as the hydrochloride. The pure base melts at 275–276° (evac. tube) and has $(\alpha)_D^{25}$ −111° (10% acetic acid, c = 0.90).

The hydrochloride dihydrate crystallizes from water and melts at 272–274° (evac. tube); $(\alpha)_D^{24}$ −89° (water, c = 0.86). Freund[1] described the salt as the monohydrate and observed $(\alpha)_D^{20}$ −149.7°.

Anal. Calc'd from $C_{18}H_{20}ClNO_4 + 2H_2O$: H_2O, 9.3. Found: H_2O, 9.4.
Calc'd for $C_{18}H_{20}ClNO_4$: Cl, 10.1. Found: Cl, 10.1.

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* Previously known compounds, for which supplementary data are given are designated with literature references.

All melting points are corrected.

The hydriodide crystallizes from water as flat needles, or thin, broad, striated scales, and melts at 255–260° (evac. tube) with decomp.; $(\alpha)_D^{22}$ −74° (water, c = 0.42).

Anal. Calc'd for $C_{18}H_{20}IO_4N + H_2O$: H_2O, 3.9. Found: H_2O, 3.6.
Calc'd for $C_{18}H_{20}IO_4N$: I, 28.8. Found: I, 28.4.

The perchlorate crystallizes from water as long, thin, rectangular plates of m. p. 241–242° (decomp.), having $(\alpha)_D^{25}$ −80° (water, c = 0.58).

Anal. Calc'd for $C_{18}H_{20}ClNO_8 + 2H_2O$: H_2O, 8.0; Cl, 7.9.
Found: H_2O, 7.8; Cl, 8.2.

Acetylhydroxycodeinone[1] was obtained in good yield by heating the base under reflux for 5 minutes in acetic anhydride. It crystallizes from 80% ethanol in thin rectangular or six-sided scales and melts at 185°; $(\alpha)_D^{25}$ +21° (10% acetic acid, c = 0.77). The compound gives hydroxycodeinone in good yield when boiled with alcoholic alkali.

Acetylhydroxycodeinone hydrochloride[1] crystallizes from water in thin scales of m. p. 260–261° (evac. tube); $(\alpha)_D^{25}$ +15.7° (water, c = 0.87).

Anal. Calc'd for $C_{20}H_{22}ClNO_5$: Cl, 9.1. Found: Cl, 9.0.

Dihydrohydroxycodeinone[1,20] was obtained readily by catalytic reduction of partly purified hydroxycodeinone in 10% acetic acid with palladium barium sulfate. The reduction product was purified easily from ethanol, m. p. 218°, $(\alpha)_D^{25}$ −97° (10% acetic acid, c = 0.76).

Anal. Calc'd for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.7.
Found: C, 68.6; H, 6.7.

It was not affected by the action of zinc and acetic acid at 80–90°. Clemmensen reduction of 3 g. of the base with amalgamated zinc and a total of 50 cc. of concentrated technical hydrochloric acid during 8 hours produced an oil from which treatment with ethyl acetate gave 1.2 g. of dihydrohydroxythebainone (m. p. 143°, no depression in mixture melting point). Continued Clemmensen reduction had no further effect on the product (*cf.* Ochiai, Kondo and Ochiai[17]). Attempts to demethylate dihydrohydroxycodeinone with 48% hydrobromic acid or hydriodic acid resulted in non-crystalline products.

Dihydrohydroxythebainone hydrochloride[1] was prepared in absolute ethanol and purified from 95% ethanol. It melts at 270–272° (decomp.); $(\alpha)_D^{25}$ −123° (water, c = 0.67). Freund described the salt as anhydrous, and found $(\alpha)_D^{20}$ −52.47°.

Anal. Calc'd for $C_{18}H_{24}ClNO_4 + 2.5H_2O$: H_2O, 11.3. Found: H_2O, 10.9.
Calc'd for $C_{18}H_{24}ClNO_4$: Cl, 10.0. Found: Cl, 9.9.

Acetyldihydrohydroxythebainone, prepared according to Freund and Speyer, was found to agree in physical properties with the description in the literature.

Acetyldihydrohydroxycodeinone enol acetate.—A mixture of 500 cc. of acetic anhydride, 60 g. of fused sodium acetate, and 67 g. of dihydrohydroxycodeinone was boiled under reflux for 6 hours, and decomposed with ice and water. The solution was kept cold during neutralization with ammonia, and the filtered precipitate was washed with water. The yield (crude) was 71 g., m. p. after crystallization from ethanol 207.5°; $(\alpha)_D^{29}$ −167° (ethanol, c = 0.6).

Anal. Calc'd for $C_{22}H_{25}NO_6$: C, 66.1; H, 6.3; $COCH_3$, 21.6.
Found: C, 65.8; H, 6.5; $COCH_3$, 21.8.

The enol acetate yielded acetyldihydrohydroxycodeinone when heated for 4 minutes with 6*N* hydrochloric acid, and with more concentrated acid was converted to dihydrohydroxycodeinone.

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[20] FREUND AND SPEYER, German Patent 296,916 (1916); U. S. Patent 1,468,805 (1923); FREUND, U. S. Patent 1,485,673 (1924).

Hydroxycodeine[1].—The following is typical of several parallel reductions. To a solution of 60 g. of hydroxycodeinone in 300 cc. of glacial acetic acid, 50 g. of zinc dust was added slowly with mechanical stirring. The temperature rose to 50–55°, and was so maintained for 30 minutes. The mixture was then stirred for 1.5 hours without heating, and the product was isolated by filtering, washing the zinc residue with hot concentrated acetic acid, and neutralizing the filtrate with concentrated ammonia. The product was extracted into chloroform, and the bases were extracted fractionally from this solution with successive portions of 0.1*N* sulfuric acid, 100 cc., 100 cc., 200 cc., 300 cc., and 150 cc., the several extracts being separately neutralized with ammonia and extracted into chloroform, and the products crystallized from ethanol.

The three compounds present were separated by fractional crystallization from alcohol, and were easily recognizable by their different crystal form, hydroxycodeine, wedge-shaped (13–17%); hydroxycodeinone, prismatic rods; hydroxythebainol, long thin scales. Microscopic examination of the crystal fractions greatly facilitated the separation.

Hydroxycodeine was purified from alcohol-chloroform mixture and melted at 304–305° (evac. tube); $(\alpha)_D^{25}$ −143° (10% acetic acid, c = 0.48). (Freund observed the m. p. 293°, $(\alpha)_D^{20}$ −119°.)

Anal. Calc'd for $C_{18}H_{21}NO_4 + H_2O$: C, 64.9; H, 7.0.
Found: C, 65.7, 65.5; H, 6.7, 6.5.

Prolonged drying at 120° in a vacuum did not remove water. The sample was boiled in chlorobenzene until half the solvent had distilled, and was allowed to crystallize.

Anal. Calc'd for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.7.
Found: C, 68.4; H, 7.0.

The hydrochloride crystallized from dilute hydrochloric acid, but not from water; m. p. 269–275° (decomp.). It was difficult to purify the salt for analysis.

Anal. Calc'd for $C_{18}H_{22}ClNO_4$: C, 61.6; H, 6.3.
Found: C, 62.2; H, 6.5

Dihydrohydroxycodeine-A.—Five grams of hydroxycodeine in 55 cc. of 10% acetic acid with 0.1 g. of platinum oxide catalyst absorbed one mole of hydrogen in 12 hours. The product was isolated with ammonia and chloroform, and the oily product was crystallized from ethanol; yield, 4.4 g. The base did not form crystalline salts, and was purified from chloroform-ethanol mixture; rectangular scales of m. p. 301–302° (evac. tube); $(\alpha)_D^{20}$ −64° (10% acetic acid, c = 0.42). The mixture melting point with hydroxycodeine was 280–285°. The base showed no phenolic properties. Crystalline monoacetyl or diacetyl derivatives could not be obtained.

Anal. Calc'd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3.
Found: C, 68.1; H, 7.3.

Reduction of dihydrohydroxycodeinone.—Hydrogenation of 30 g. of dihydrohydroxycodeinone in 150 cc. of 10% acetic acid with platinum oxide catalyst proceeded very slowly, and necessitated addition of successive portions of catalyst to a total of one gram. In 24 hours, approximately one mole of hydrogen was absorbed. The product crystallized from ethyl acetate, yield 23.5 g. It was a mixture of dihydrohydroxycodeine-B with a small amount of dihydrohydroxycodeine-C, from which the former could be obtained by repeated crystallization from ethyl acetate. To obtain both isomers, 50 g. of crude product was dissolved in 175 cc. of acetic anhydride and 25 cc. of purified pyridine, the solution was heated in the water bath for one hour, and decomposed with ice. The base was precipitated with ammonia

(addition of ice) and the precipitate was rubbed with water and filtered several times. The pasty mass was treated with a solution of 30 g. of tartaric acid, and a coarse crystalline precipitate of the tartrate of the diacetylated C-isomer formed. From the cooled solution, on long standing with seed, the tartrate of the diacetylated B-isomer separated in fine needles. The diacetyl derivatives were regenerated from the salts with ammonia, purified, and hydrolyzed by heating under reflux with an excess of ethanolic sodium hydroxide for 8 minutes.

Dihydrohydroxycodeine-B.—The base is very soluble in alcohol, dilute alcohol, benzene, and butanone. It separated from ethyl acetate in thin rectangular plates of m. p. 145–145.5°, having $(\alpha)_D^{26}$ −136° (10% acetic acid, c = 0.81). It did not form an oxime.

Anal. Calc'd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3.
Found: C, 68.3; H, 7.3.

The methiodide was prepared by heating the base with excess methyl iodide in a sealed tube at 100° for 4 hours. It crystallized from absolute ethanol in nearly quantitative yield; m. p. 223–224° (decomp.), $(\alpha)_D^{21}$ −87° (water, c = 0.66).

Anal. Calc'd for $C_{19}H_{26}INO_4$: I, 27.6. Found: I, 27.8.

Diacetyldihydrohydroxycodeine-B.—Separated from the C-isomer as described above, or prepared from the purified B-isomer, the diacetyl compound was purified from dilute alcohol and had the m. p. 181–182°; $(\alpha)_D^{22}$ −127° (10% acetic acid, c = 1.31). The action of boiling acetic anhydride-pyridine caused no change in the compound.

Anal. Calc'd for $C_{22}H_{27}NO_6$: C, 65.8; H, 6.8; $(COCH_3)_2$, 21.4.
Found: C, 65.9; H, 6.8; $COCH_3$, 21.8.

The acid tartrate hydrate crystallized slowly from water in very fine needles, m. p. 181–182° (decomp.); $(\alpha)_D^{29}$ −78°, −82° (water, c = 0.72, 0.57).

Anal. Calc'd for $C_{26}H_{33}NO_{12} + H_2O$: C, 54.8; H, 6.2.
Found: C, 54.8; H, 6.0.

Dihydrohydroxycodeine-B-methine.—The methiodide prepared from 15 g. of crude dihydrohydroxycodeine-B was boiled for 15 minutes with 100 cc. of water containing 17 g. of sodium hydroxide. From ether, 14 g. of acicular crystals was obtained. The compound melted at 103° after purification from ether. $(\alpha)_D^{21}$ −70° (10% acetic acid, c = 0.14).

Anal. Calc'd for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.6.
Found: C, 68.5; H, 7.8.

The acid tartrate crystallized from water, m. p. 190–191° (gas evol.) $(\alpha)_D^{21}$ −25° (water, c = 0.38).

Anal. Calc'd for $C_{23}H_{31}NO_{10} + 4H_2O$: C, 50.0; H, 7.1; H_2O, 13.0.
Found: C, 50.0; H, 6.5; H_2O, 12.7.
Calc'd for $C_{23}H_{31}NO_{10}$: C, 57.4; H, 6.5.
Found: C, 57.4; H, 6.6.

Dihydrohydroxycodeine-B-dihydromethine.—Catalytic hydrogenation of 12 g. of the methine in 37 cc. of 75% acetic acid with platinum (oxide) proceeded with absorption of one mole of hydrogen. The product was precipitated crystalline by ammonia in nearly quantitative yield. After purification from ethyl acetate it melted at 168°; it was sublimed in a high vacuum for analysis. $(\alpha)_D^{22}$ −44° (10% acetic acid, c = 0.88).

Anal. Calc'd for $C_{19}H_{27}NO_4$: C, 68.5; H, 8.2.
Found: C, 68.7; H, 8.4.

The acetate of the dihydromethine occasionally separated crystalline from the

reduction, or could be prepared from the constituents. It could not be dehydrated without loss of acetic acid.

Anal. Calc'd for $C_{21}H_{31}NO_6 + 1.5\ H_2O$: C, 60.0; H, 8.1.
Found: C, 60.3; H, 8.0.

Dihydrohydroxychlorocodide.—To 5 g. of dihydrohydroxycodeine-B in 50 cc. of dry chloroform was added slowly 7 g. of phosphorus pentachloride, the mixture being kept at about room temperature. After one hour, the clear yellow solution was poured into water, and the aqueous layer was treated with an excess of sodium carbonate. When the milky emulsion was boiled, the product precipitated quickly in crystalline form, yield 4.1 g. It was sparingly soluble in ethanol, and was purified from ethyl acetate, m. p. 213.5–214°, $(\alpha)_D^{22}$ −151° (10% acetic acid, c = 1.26).

Anal. Calc'd for $C_{18}H_{22}ClNO_3$: C, 64.3; H, 6.6; Cl, 10.6.
Found: C, 64.2; H, 6.4; Cl, 10.6.

The chloro compound was not reduced by platinum and hydrogen in 5% acetic acid, nor by 5 hours Clemmensen reduction. After 32 hours at 140° in sodium ethoxide solution it gave a liquid phenolic product, halogen-free; gentler treatment yielded the starting material.

Chlorodihydrohydroxycodeine-B.—One part of dihydrohydroxycodeine-B was dissolved cautiously in eight parts of thionyl chloride, with cooling, and after a few minutes the solution was poured into water. The granular amorphous product was washed well with water, and distilled in a high vacuum, yielding an oil that was redistilled for analysis. It gave a negative test for sulfur, and could not be obtained crystalline.

Anal. Calc'd for $C_{18}H_{22}ClNO_4$: C, 61.4; H, 6.3.
Found: C, 61.2; H, 6.1.

The hydrochloride crystallized from acetone with alcoholic hydrogen chloride in hair-like needles, and was recrystallized from absolute ethanol (slow cooling, balls of radiating crystals). It melted at 238–239°, $(\alpha)_D^{21}$ −106° (water, c = 0.81).

Anal. Calc'd for $C_{18}H_{23}Cl_2NO_4$: Cl, 18.3. Found: Cl, 17.9.

Attempted hydrolysis (17 hours boiling in 10% acetic acid), or Clemmensen reduction, did not affect the base. Reduction with sodium and absolute ethanol under nitrogen gave a good yield of dihydrohydroxycodeine-B.

Chlorodihydrohydroxychlorocodide.—One-half gram of dihydrohydroxychlorocodide was added to 2 cc. of thionyl chloride, and after the vigorous reaction ceased, the mixture was decomposed with ice. The precipitate formed with sodium carbonate was crystallized from alcohol, yield 0.3 g.; from ethanol or ethyl acetate, rectangular prisms, m. p. 163.5°, $(\alpha)_D^{22}$ −141° (10% acetic acid, c = 0.47). The same compound was obtained when chlorodihydrohydroxycodeine-B was treated with phosphorus pentachloride.

Anal. Calc'd for $C_{18}H_{21}Cl_2NO_3$: C, 58.4; H, 5.7.
Found: C, 58.3, 58.1; H, 5.8, 5.6.

Dihydrodesoxyhydroxycodeine.—Dihydrohydroxychlorocodide was reduced under nitrogen with a large excess of sodium in boiling absolute ethanol with vigorous stirring, to the point where the sodium became molten, and could be churned through the solution in finely divided form. The base, recovered in the usual way, was an oil, which distilled in a high vacuum to form crystals on a cold finger, m. p. 134–137°, from ether or petroleum ether m. p. 137–138°, showing typical phenolic properties. $(\alpha)_D^{22}$ −19° (10% acetic acid, c = 0.62).

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.7.
Found: C, 71.6; H, 7.7.

Tetrahydrodesoxyhydroxycodeine.—A solution of dihydrodesoxyhydroxycodeine in 3% acetic acid, with platinum oxide catalyst, absorbed one mole of hydrogen, yielding a product that could be characterized only as the perchlorate, which crystallized from water or alcohol, m. p. 242–244°; $(\alpha)_D^{21}$ −28° (water, c = 0.43).

Anal. Calc'd for $C_{18}H_{26}ClNO_7$: C, 53.5; H, 6.5.
Found: C, 53.9; H, 6.6.

Dihydrohydroxycodeine-C.—A solution of 3.4 g. of the diacetyl derivative obtained from the above described separation of the B and C isomers was heated under reflux for 8 minutes with 3.5 g. of sodium hydroxide in 35 cc. of ethanol. The solution was diluted with water (no precipitate) and extracted several times with ether, from which was obtained 3 g. of oil that rapidly crystallized. From 40% ethanol it separated as long thin rectangular scales of m. p. 166–167°, $(\alpha)_D^{23}$ −152° (10% acetic acid, c = 0.56). It showed no phenolic properties.

Anal. Calc'd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3.
Found: C, 67.9; H, 7.3.

By treatment of the base with phosphorus pentachloride in chloroform, a phosphorus-containing product of m. p. 136–139° was obtained; it could not be sublimed. Thionyl chloride gave a liquid product that could be distilled in a high vacuum, but that yielded no crystalline derivatives.

Diacetyldihydrohydroxycodeine-C.—This product, separated from the acylation of the crude reduction product from dihydrohydroxycodeinone, crystallized from 80% ethanol as sheaves of needles melting at 203°; $(\alpha)_D^{22}$ −107° (10% acetic acid, c = 0.62).

Anal. Calc'd for $C_{22}H_{27}NO_6$: C, 65.8; H, 6.8; $(COCH_3)_2$, 21.4.
Found: C, 66.2; H, 7.35; $COCH_3$, 20.1.

No evidence of rearrangement to the B-isomer could be observed after prolonged treatment with boiling acetic anhydride-pyridine mixture.

The acid tartrate crystallized from water as long thin six-sided scales melting at 209–210°; $(\alpha)_D^{20}$ −67°, −72° (water, c = 0.80, 0.66).

Anal. Calc'd for $C_{26}H_{33}NO_{12} + H_2O$: C, 54.8; H, 6.2.
Found: C, 54.2; H, 6.1.

SUMMARY

1. Dihydrohydroxycodeine-A is formed when the unsaturated linkage in hydroxycodeine is hydrogenated.

2. Catalytic reduction of the ketonic group in dihydrohydroxycodeinone yields the isomeric pair, dihydrohydroxycodeines-B and -C. These probably differ in the configuration of the new asymmetric group at carbon 6, but the nature of their isomerism with dihydrohydroxycodeine-A is still uncertain.

3. Thionyl chloride acts on dihydrohydroxycodeine-B to chlorinate the aromatic nucleus, whereas phosphorus pentachloride replaces the 6-hydroxyl with chlorine to give dihydrohydroxychlorocodide. The latter compound undergoes stepwise reduction through dihydrodesoxyhydroxycodeine to tetrahydrodesoxyhydroxycodeine.

4. Hydroxycodeinone reacts with phosphorus pentachloride with formation of six halogenated derivatives, five of which appear to be ketochloride types. By reduction of 14-chlorohydroxycodeinone ketochloride-A,

dihydrodesoxycodeine-D and tetrahydrodesoxycodeine are obtained, which proves that the 14-hydroxyl group of hydroxycodeinone was replaced by halogen in this ketochloride.

5. Acetyldihydrohydroxycodeinone enol acetate reacts with methylmagnesium iodide to give two phenolic products that are probably analogous to the methyldihydrothebainones.

6. In none of the reactions of hydroxycodeinone and its derivatives can any direct evidence be found in support of, or against the 14-position for the hydroxyl group.

[CONTRIBUTION NO. 156 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

KETO ETHERS. V. β-CHLOROISOPROPOXYMETHYL KETONES DERIVED FROM PROPYLENE CHLOROHYDRIN[1]

JAMES J. SPURLOCK[2] WITH HENRY R. HENZE

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Although propylene chlorohydrin has been shown to react with a formalin solution and dry hydrogen chloride to form chloromethyl β-chloroisopropyl ether,[3] the latter appears not to have been used in further synthesis. It was to be anticipated that from this chloro ether there might be produced β-chloroisopropoxyacetonitrile, which should be useful in the preparation of a series of β-chloroisopropoxymethyl ketones (I) whose structures are intermediate between those of the 1,3-dichloroisopropoxy ketones (II)[4] and the non-chlorinated isopropoxy ketones (III),[5] as well as being higher homologs of the β-chloroethoxy ketones[6] previously prepared in this laboratory.

$ClCH_2CH(CH_3)OCH_2COR$ (I) $\qquad$ $(ClCH_2)_2CHOCH(CH_3)COR$ (II)

$(CH_3)_2CHOCH_2COR$ (III) $\qquad$ $ClCH_2CH_2OCH_2COR$ (IV)

The chloro keto ethers are of interest because of the fact that the halogen atom is relatively unreactive, whereas the carbonyl group enters readily into reaction so that various types of chlorine-substituted heterocyclic derivatives may be formed. These compounds offer some promise of possible value in medicinal use.

In this investigation the α-chloro ether was obtained readily[7] and more adequately characterized than had been done by Stappers.[3] Usually α-chloro ethers are converted easily into α-cyano ethers by digestion with

[1] Preceding paper in series, ROGERS WITH HENZE, *J. Am. Chem. Soc.*, **61**, in press (1939).

[2] From the M.A. Thesis, August, 1937.

[3] STAPPERS, *Rec. trav. chim.*, **24**, 256 (1904).

[4] ALLEN WITH HENZE, *J. Am. Chem. Soc.*, **59**, 540 (1937).

[5] MATTHEWS, M. A. Thesis, August, 1933.

[6] LINGO, *J. Am. Chem. Soc.*, **61**, in press (1939).

[7] HENRY, *Bull. soc. chim.*, [2], **44**, 458 (1885).

cuprous cyanide.[8] Unexpected difficulty was encountered in our attempts to prepare β-chloroisopropoxyacetonitrile by this method and to purify it adequately by distillation. Hence, the synthesis

$$2\ ClCH_2CH(CH_3)—O—CH_2Cl + Cu_2(CN)_2 \rightarrow Cu_2Cl_2 + ClCH_2CH(CH_3)—O—CH_2CN$$

of this cyano ether was reattempted utilizing a sample of this chloro ether obtained by another method, namely, through interaction of di(β-chloroisopropyl)formal and benzoyl chloride.[9] The purity and physical proper-

$$(CH_2O)_3 + 6\ CH_3CH—CH_2 + 6\ HCl \longrightarrow$$

$$3\ [ClCH_2CH(CH_3)—O—]_2CH_2 + 3\ H_2O$$

$$[ClCH_2CH(CH_3)—O—]_2CH_2 + C_6H_5COCl \longrightarrow$$

$$ClCH_2(CH_3)—O—CH_2Cl + C_6H_5COOCH(CH_3)CH_2Cl$$

ties of the chloro ether thus obtained were essentially identical with those of the material prepared by the simpler method of Henry.[7] Additional attempts at preparation of the nitrile were made using mercuric cyanide and potassium cyanide, respectively; the yield of the nitrile from use of the mercuric cyanide was less than that from the cuprous cyanide, while from the potassium cyanide the chloro ether was regained unchanged. Still another effort to purify the nitrile involved converting it into ethyl β-chloroisopropoxyacetate, and the latter into the corresponding amide, which was then dehydrated over phosphorus pentoxide. This product was no purer than the initial material. Most efficient purification of the cyano ether was obtained through distillation utilizing a fractionating column of the type reported by Lesesne and Lochte,[10] equipped, however, for vacuum distillation.

From β-chloroisopropoxyacetonitrile there have been obtained, by means of the Grignard reaction, seven new keto ethers; included are the five simplest members of the *n*-alkyl series and the benzyl and phenyl analogs. In this series, as in those of the closely related keto ethers reported from this laboratory, the molecular refractions were found to be a better index of the purity of the compounds than were the parachors.

[8] GAUTHIER, *Compt. rend.*, **143**, 831 (1906).

[9] BLAISE, *ibid.*, **139**, 1211 (1904); *ibid.*, **140**, 161 (1905); POST, J. ORG. CHEM., **1**, 231 (1936).

[10] LESESNE AND LOCHTE, *Ind. Eng. Chem., Anal. Ed.*, **10**, 450 (1938).

EXPERIMENTAL

Preparation of chloromethyl β-chloroisopropyl ether.—This chloro ether has been synthesized previously by Stappers,[3] who reported only the following data for its physical properties: b.p. 162–164°; d^{20} 1.197.

A. Utilizing the method of Henry,[7] we prepared the compound by mixing 282.5 g. of 1-chloropropanol-2 (3.0 moles) and 294.0 g. of 36% formalin solution (3.5 moles of formaldehyde), cooling the stirred mixture in an ice-bath while dry hydrogen chloride was passed in for six hours. The upper ether layer was separated, dried over anhydrous calcium chloride for six hours and aerated for one hour before being distilled. The distillate boiling at 106–110° (146 mm.) weighed 243 g. (56.8% yield). After fractionation chloromethyl β-chloroisopropyl ether boils at 106–107° (146 mm.); and at 160–161° (747 mm.); d_4^{20} 1.2011; n_D^{20} 1.4521; γ^{20} 32.72 dynes/cm.;[11] [*M*] calc'd 32.05; [*M*] found 32.13; *P* calc'd 284.6;[12] *P* found 284.8; molal free surface energy $[\gamma(M/d)^{2/3}]$ 791.9 ergs.

Anal. Calc'd for $C_4H_8Cl_2O$: Cl, 49.58. Found: Cl, 49.42.

B. The chloro ether was prepared also according to a reaction studied by Blaise;[9] namely, 49.9 g. of benzoyl chloride (0.36 mole) were placed in a flask provided with a reflux condenser, mercury-sealed stirrer and a dropping funnel, and treated dropwise with 71.4 g. of the formal of propylene chlorohydrin (0.36 mole). No sign of reaction was noted, so the flask was immersed for four hours in an oil bath maintained at 100–110°. Then the temperature of the bath was raised to 145–155° for five hours, the reaction mixture becoming deep red in color. This product was fractionated under diminished pressure, yielding 33.3 g. of chloro ether (65.6% of the theoretical); b.p. 58–59° (16 mm.); d_4^{20} 1.1995; n_D^{20} 1.4528; [*M*] found 32.21; Cl, found 49.49%.

There was formed also in this reaction 45.6 g. of β-chloroisopropyl benzoate (64.7% yield), b.p. 106–107° (2–3 mm.); d_4^{20} 1.1550; n_D^{20} 1.5182; [*M*] calc'd 51.91; [*M*] found 52.13.

Anal. Calc'd for $C_{10}H_{11}ClO_2$: Cl, 17.85. Found: Cl, 17.91.

Preparation of β-chloroisopropoxyacetonitrile.—A. From chloro ether prepared by Henry's method.—Thirty-one and seven-tenths grams of previously dried cuprous cyanide (0.18 mole) and 40 cc. of anhydrous toluene were placed in a flask provided with mercury-sealed stirrer, reflux condenser, and dropping funnel, and the flask was immersed in an oil bath heated to 120°. Forty-six grams of chloromethyl β-chloroisopropyl ether (0.32 mole) was then dropped in over a period of ten minutes. The toluene refluxed vigorously and paraformaldehyde deposited in the condenser. The temperature was raised slowly through a three-hour period until 140° was reached. The flask and its contents were cooled, the cuprous salts were separated by filtration, and the light-brown colored filtrate distilled under diminished pressure; 35 g. of product (81.5% yield) was collected of b.p. 98–99° (14 mm.). After repeated fractionation, the nitrile had d_4^{20} 1.1216; n_D^{20} 1.4436; [*M*] calc'd 31.62; [*M*] found 31.60.

Anal. Calc'd for C_5H_8ClNO: Cl, 26.55; N, 10.49.
Found: Cl, 26.94; N, 9.36.

Final purification of the β-chloroisopropoxyacetonitrile was effected by two distillations of 125 cc. of material through a fractionating column of the type reported by Lesesne and Lochte,[10] equipped however for vacuum distillation. The following

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[11] CASSEL, *Chem.-Ztg.*, **53**, 479 (1929).
[12] SUGDEN, *J. Chem. Soc.*, **125**, 1177 (1924).

data for these physical properties were then found to be: b.p. 98–99° (corr.) (15 mm.); d_4^{20} 1.1211; n_D^{20} 1.4422; γ^{20} 36.14 dynes/cm.; [*M*] calc'd 31.62; [*M*] found 31.54; *P* calc'd 294.2; *P* found 292.1; molal free surface energy 875.1 ergs.

Anal. Calc'd for C_5H_8ClNO: C, 44.95; H, 6.03; Cl, 26.55; N, 10.49.
Found: C, 44.88; H, 6.17; Cl, 26.64; N, 10.51.

B. From chloro ether obtained from di(β-chloroisopropyl)formal.—One hundred twenty-eight grams of propylene oxide (2 moles plus a 10% excess) was placed in a flask cooled by an ice-salt bath, and saturated with dry hydrogen chloride; slightly more than the theoretical quantity (79.2 g.) was absorbed, the time required being two hours. Thirty grams of trioxymethylene (0.33 mole) was then added, and the mixture was again saturated with hydrogen chloride until solution of the solid had taken place (four hours); the total hydrogen chloride absorbed was 157.7 g. The reaction mixture was dried with calcium chloride overnight, aerated, and distilled under diminished pressure. After four distillations, the last two being through a fractionating column with a high reflux ratio, 74.4 g. of liquid boiling at 112.5–113.5° (16 mm.) (37% yield, based on trioxymethylene used); d_4^{20} 1.1418; n_D^{20} 1.4503; [*M*] calc'd 47.55; [*M*] found 47.37.

Anal. Calc'd for $C_7H_{14}ClO_2$: Cl, 35.26. Found: Cl, 35.13.

Forty-nine and nine-tenths grams of benzoyl chloride (0.36 mole) was placed in a flask and 71.4 g. of the formal was added with mechanical stirring; no sign of reaction was noted. The flask was then immersed in an oil bath at 100–110° for four hours, during which time the contents of the flask darkened slightly. The temperature of the bath was raised to 145–155° and the stirring was continued for five hours, at the end of which time the solution had a deep-red color. The mixture was fractionated, yielding fractions boiling at 57–62° (15 mm.) and 145–149° (15 mm.), respectively.

A second distillation of the lower-boiling fraction gave 33.3 g. of chloro ether boiling at 58–59° (16 mm.); d_4^{20} 1.1995; n_D^{20} 1.4528; [*M*] calc'd 32.05; [*M*] found 32.21. The chloro ether obtained represented a yield of 65.6% based on the quantity of formal used and only 24.2% based on the propylene oxide (less the 10% excess) used.

Anal. Calc'd for $C_4H_8Cl_2O$: Cl, 49.58. Found: Cl, 49.49.

Redistillation of the higher-boiling fraction, composed of impure β-chloroisopropyl benzoate, gave 45.6 g. of liquid (64.7% based on formal used) boiling at 146–149° (16 mm.). The ester, purified by further distillation; b.p. 106–107° (2–3 mm.); *d* 1.1550; n_D^{20} 1.5182; [*M*] calc'd 51.91; [*M*] found 52.13.

Anal. Calc'd for $C_{10}H_{11}ClO_2$: Cl, 17.85. Found: Cl, 17.91.

Thirty-two and one-tenth grams of the chloro ether (0.22 mole), as produced from the formal, was added dropwise to 21.5 g. of dried cuprous cyanide (0.12 mole, a 10% excess over the calculated) moistened with 40 cc. of anhydrous benzene and warmed for five and one-half hours. The benzene was removed by distillation and 24.5 g. of material boiling at 100–102° (16 mm.) was collected (81.7% yield). After a second distillation d_4^{20} 1.1204; n_D^{20} 1.4432; [*M*] calc'd 31.62; [*M*] found 31.61.

Anal. Calc'd for C_5H_8ClNO: Cl, 26.55; N, 10.49.
Found: Cl, 26.56; N, 9.59.

C. Preparation using mercuric cyanide.—A mixture of 41.8 g. of dried mercuric cyanide (0.17 mole), enough dry benzene to form a thin paste, and 43 g. of chloromethyl β-chloroisopropyl ether was refluxed for three hours. A decided heat effect was noted, the color changed through red to reddish-brown, and a dark, tarry mass formed. After fractionation 19.3 g. of product was obtained (48.1% yield), b.p. 100–104° (19 mm.). Repeated distillation of the non-homogeneous liquid yielded a

small amount of nitrile, b.p. 97–98° (17 mm.); d_D^{27} 1.1194; n_4^{20} 1.4410; [*M*] calc'd 31.62; [*M*] found 31.18.

Anal. Calc'd for C_5H_8ClNO: Cl, 26.55; N, 10.49.
Found: Cl, 25.31; N, 10.41.

D. Attempted preparation using potassium cyanide.—An attempt to prepare the nitrile using 0.10 molar quantities of potassium cyanide and the chloro ether, diluted with benzene, resulted in recovery of essentially all of the chloro ether, unreacted.

E. Preparation from β-chloroisopropoxyacetamide.—Initially, ethyl β-chloroisopropoxyacetate was prepared by mixing 42.5 g. of β-chloroisopropoxyacetonitrile (0.32 mole), 85 g. of 95% ethyl alcohol (1.75 mole ethanol), and 40 cc. of concentrated hydrochloric acid, some heat being evolved on addition of the acid. The solution was then cooled in an ice bath and saturated with dry hydrogen chloride, heat again being evolved during the process; at the point of saturation ammonium chloride precipitated. The mixture was then warmed gently on the steam-bath and saturation with hydrogen chloride maintained for a period of four hours. Air was blown through the mixture for one hour, the ammonium chloride was removed by filtration, and water was added to cause separation of the ester. After removal of the upper ester layer, the aqueous layer was extracted twice with ether, the ether extracts were combined with the main bulk of the product, and the whole was dried with anhydrous sodium sulfate over night. On the first distillation 35.0 g. of product boiling at 110–115° (19 mm.) was obtained (61% yield). The ester was purified by redistillation; b.p. 110–111° (19 mm.); d_4^{20} 1.1088; n_D^{20} 1.4370; [*M*] calc'd 42.69; [*M*] found 42.68.

Anal. Calc'd for $C_7H_{13}ClO_3$: Cl, 19.63. Found: Cl, 19.63.

Thirteen grams (0.072 mole) of β-chloroisopropoxyacetate was mixed with 65 g. of concentrated ammonia water and shaken until the ester had dissolved. The water and ammonia were removed under reduced pressure at room temperature, and the amide was distilled, yielding 8.5 g. (77.8% yield) of product boiling at 140–141° (4–5 mm.). The amide melts at 31.2° (corr.); d_4^{40} 1.1966; n_D^{40} 1.4710; [*M*] calc'd 35.67; [*M*] found 35.40.

Anal. Calc'd for $C_5H_{10}ClNO$: Cl, 23.39; N, 9.24.
Found: Cl, 23.34; N, 9.26.

Seven and one-half grams (0.05 mole) of β-chloroisopropoxyacetamide was mixed with 7.7 g. (0.055 mole) of phosphorus pentoxide in a 50-cc. distilling flask fitted with a capillary inlet for dry air. The flask was placed in an oil bath heated to 130° and the reaction mixture became light-brown in color but the nitrile distilled without coloration; b.p. 104–105° (20 mm.); 3.7 g. (56% yield); d_4^{20} 1.1226; n_D^{20} 1.4428; [*M*] calc'd 31.62; [*M*] found 31.52.

Anal. Calc'd for C_5H_8ClNO: Cl, 26.55; N, 10.49.
Found: Cl, 26.06; N, 9.49.

Preparation of β-chloroisopropoxymethyl ketones.—The β-chloroisopropoxymethyl ketones were synthesized by adaptation of Sommelet's[13] method by reaction of β-chloroisopropoxyacetonitrile with the appropriate Grignard reagents and subsequent acid-hydrolysis of the addition products formed. In general, the quantity of reactants used was: of nitrile about 0.3 mole, of magnesium turnings 10% in excess of the stoichiometrical, and of halide 10% more than that equivalent to the metal. Anhydrous ether used was in the ratio of 5 moles to 1 mole of nitrile. Approximately one-third of the ether was used to cover the magnesium, the remainder was mixed

[13] SOMMELET, *Ann. chim. phys.*, [8], **9**, 484 (1906).

with the halide, and this mixture was added dropwise to the magnesium at a rate sufficient to cause gentle refluxing of the ether. In a few cases it was necessary to heat the reaction mixture for from thirty to sixty minutes, in order to complete reaction of the magnesium with the halide. The ether solutions of the Grignard reagents were a cloudy grey in all cases except that derived from benzyl chloride which was almost black in color.

The appropriate quantity of β-chloroisopropoxyacetonitrile, diluted with an equal volume of anhydrous ether, was then added just rapidly enough to cause slight refluxing of the ether. After about two-thirds to three-fourths of the nitrile solution had been added the addition product began to separate, in some cases as a white precipitate and in others as a grey-green oil which solidified on standing over night. With the exception of the methyl and ethyl derivatives, the addition products were heated for one hour, and in all cases were allowed to stand overnight before further treatment.

Since, following acid-hydrolysis, it was found very difficult to purify merely by distillation the methyl, ethyl, and propyl ketones of this series, it was found desirable to purify the Grignard reagent addition products in order to obtain purer ketones. Since these were somewhat soluble in ethyl ether, most of this solvent was removed by evaporation from a steam-bath, allowing enough ether to remain to render the mass semi-solid. Two hundred cc. of anhydrous petroleum ether, in which the addition products were sparingly soluble, was added, the mixture was stirred, and most of the solution was removed through a glass tube containing an asbestos mat supported on a Witte plate, by forcing dry air into the reaction flask. This treatment was followed by two successive washings with 100-cc. portions of petroleum ether, the washings being discarded. One hundred cc. of ethyl ether was then added to the addition product, the flask and its contents were cooled in an ice-salt mixture, and small pieces of ice were added cautiously to the flask. The calculated amount of concentrated hydrochloric acid was added drop by drop, pieces of ice being added simultaneously and the mixture being stirred. As hydrolysis proceeded the solution became deeply yellow-colored, and in the cases of the *n*-propyl, *n*-amyl, and phenyl ketones, there appeared between the ether and the acid layers an additional deep-red, relatively viscous layer. The latter was sparingly soluble in ether as long as the mixture was strongly acidic, but soluble on neutralization of the acid. It was found convenient therefore to neutralize the acid by addition of solid sodium bicarbonate prior to removal of the ether layer from the hydrolysis mixture. In those cases where the ether layer was removed while still acidic, the aqueous layer was extracted three times with ether, the ether extracts combined and washed free of acid with 5% sodium bicarbonate solution. The ether solution of the ketone was dried overnight by contact with anhydrous sodium sulfate, the ether was removed under reduced pressure, and the ketone was fractionated under 2-7 mm. pressure.

The keto ethers when carefully purified are colorless liquids sparingly soluble in water but miscible with solvents such as alcohols, ether, acetone, chloroform, and benzene. The phenyl ketone possesses a limited solubility in petroleum ether. The freshly distilled ketones have a very slight sweet odor, but on standing develop a decidedly rancid odor, due probably to oxidation to acids, and become more or less colored. Boiling points were taken with short, calibrated Anschütz thermometers, and the temperatures reported are properly corrected values. Surface tensions of the liquids were measured by means of Cassel's[11] precision capillarimeter at 20°. Densities were taken using a small U-type pycnometer having a volume of 1.4186 cc. and weighing 2.9465 g. The data resulting from the determination of physical

TABLE I

β-CHLOROISOPROPOXYMETHYL KETONES

$ClCH_2CH(CH_3)—O—CH_2COR$

R	B. P.		d_4^{20}	n_D^{20}	γ^{20} (DYNES PER CM.)	FREE SURFACE ENERGY	YIELD, %
	°C. (corr.)	mm.					
$—CH_3$	73–74	4	1.0911	1.4421	34.37	919.0	45.8
$—C_2H_5$	77–78	4	1.0651	1.4443	33.46	963.7	63.0
$—C_3H_7$	95–96	6	1.0400	1.4438	31.98	988.2	67.8
$—C_4H_9$	101–102	3	1.0206	1.4463	31.49	1036.8	57.2
$—C_5H_{11}$	109–110	3	1.0050	1.4470	31.18	1086.4	65.0
$—C_6H_5$	135–136	3	1.1614	1.5341	40.84	1315.0	45.5
$—CH_2C_6H_5$	151–152	4	1.1319	1.5199	40.36	1381.4	31.3

TABLE II

β-CHLOROISOPROPOXYMETHYL KETONES

$ClCH_2CH(CH_3)—O—CH_2COR$

R	CHLORINE, %		MOLECULAR REFRACTION			PARACHOR		
	Calc'd	Found	Calc'd	Obs.	ΔM_D	Calc'd	Obs.	ΔP
$—CH_3$	23.54	23.43	36.43	36.52	+.09	334.4	334.1	−0.3
$—C_2H_5$	21.54	21.71	41.05	41.08	+.03	373.4	371.7	−1.7
$—C_3H_7$	19.85	19.52	45.67	45.62	−.05	412.4	408.6	−3.8
$—C_4H_9$	18.40	18.37	50.28	50.41	+.13	451.4	450.1	−1.3
$—C_5H_{11}$	17.15	17.14	54.90	54.96	+.06	490.4	486.0	−4.4
$—C_6H_5$	16.67	16.57	56.70	56.81	+.11	468.3	461.9	−6.4
$—CH_2C_6H_5$	15.64	15.40	60.54	60.88	+.34	507.3	504.8	−2.5

TABLE III

2,4-DINITROPHENYLHYDRAZONES OF β-CHLOROISOPROPOXYMETHYL KETONES

$Cl—CH_2—CH(CH_3)—O—CH_2C(R)=NNHC_6H_3(NO_2)_2$

R	M.P., °C. (CORR.)	PER CENT. NITROGEN	
		Calc'd	Found
$—CH_3$	120.5–121.5	16.94	16.70
$—C_2H_5$	85.5–86.5	16.25	16.06
$—C_3H_7$	80.5–81.0	15.62	15.73
$—C_4H_9$	69–69.5	15.03	14.85
$—C_5H_{11}$	91.5–92.5	14.49	14.41
$—C_6H_5$	181–182	14.26	14.23
$—CH_2C_6H_5$	77–78*	13.77	13.72

* After fusion and resolidification the melting point is 89–90° and is unchanged by subsequent resolidification and fusion.

properties, the values derived from the latter by calculation, and such information as was obtained through analysis of the chloro keto ethers have been arranged in Tables I and II. For calculation of the parachors the atomic parachor values of Sugden[12] were used.

All the β-chloroisopropoxymethyl ketones synthesized in this study formed solid derivatives with 2,4-dinitrophenylhydrazine. These derivatives were prepared by mixing equimolar proportions of the reactants (approximately 0.05 mole of each) and adding 90–100 cc. of 95% ethyl alcohol and boiling gently for ten minutes. As the heating progressed the solid dissolved and the solution became a deep orange-red in color. Three or four drops of concentrated hydrochloric acid were then added, and the boiling was continued for five minutes, during which time the solution lightened in color. Water was added until the solution began to cloud, and the solution was allowed to cool. In most cases the dinitrophenylhydrazones separated from solution as oils which solidified on standing, and which were recrystallized from ethyl alcohol. For the benzyl ketone recrystallization it was necessary to use petroleum ether. These derivatives were obtained in 75% yield. Data for these compounds are tabulated in Table III.

SUMMARY

1. Chloromethyl β-chloroisopropyl ether has been resynthesized, utilizing four different methods, and more adequately characterized. For the preparation of this ether the method of Henry required least time and was productive of best yield.

2. This dichloro ether was converted into β-chloroisopropoxyacetonitrile.

3. From the chloroalkoxy nitrile have been obtained by means of the Grignard reaction seven examples of a new type of keto ether. For these compounds the molecular refraction was found to be a better index of purity than was the parachor.

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

ACTIVITY OF THE METHYLENE GROUP IN THE ISOMERIC MONONITROBENZYL *p*-TOLYL SULFONES AND IN 2,4-DINITROBENZYL *p*-TOLYL SULFONE

R. L. SHRINER AND S. O. GREENLEE

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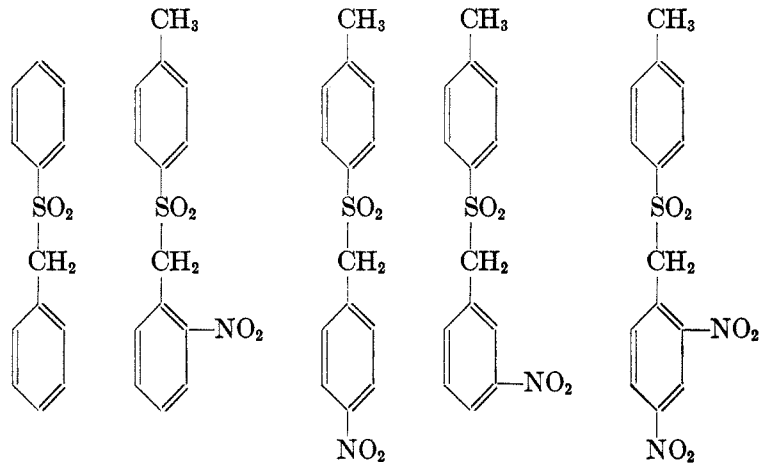
A previous study of the activating effect exerted by the sulfone group on an adjacent methylene group showed that the methylene group in benzyl phenyl sulfone (I) was not especially reactive. It reacted with sodium very slowly and did not undergo bromination or alkylation.[1] Since nitro groups in the *ortho* and *para* positions activate many groups, it was of interest to synthesize the four nitrobenzyl *p*-tolyl sulfones, shown in formulas II, III, IV, and V, and to study the properties of the methylene



I II III IV V

groups in these compounds. The specific reactions studied were: (*a*) salt formation, (*b*) bromination, (*c*) alkylation, and (*d*) condensation with ethyl oxalate and benzaldehyde. It may be stated at once that the *ortho* and *para* nitro groups did activate the methylene group, the most reactive compound being V. These compounds differed in their reactions in several respects and the purpose of this paper is to point out these reactions and contrast them with the activating effect exerted by the nitro group in other compounds.

[1] SHRINER, STRUCK, AND JORISON, *J. Am. Chem. Soc.*, **52**, 2060 (1930).

These nitrobenzyl *p*-tolyl sulfones were prepared by treating sodium *p*-toluene sulfinate with the proper nitrobenzyl halide according to the general method described by Otto.[2]

Nitration of benzyl chloride under drastic conditions produced 2,4-dinitrobenzyl chloride[3] which was used for the synthesis of compound V. In order to synthesize the *meta* isomer (IV) *m*-nitrobenzaldehyde was first reduced to *m*-nitrobenzyl alcohol by means of aluminum ethoxide. Hydrobromic acid converted this alcohol to *m*-nitrobenzyl bromide, which was then treated with an absolute alcohol solution of sodium *p*-toluenesulfinate to produce *m*-nitrobenzyl *p*-tolyl sulfone (IV).

Properties of the mononitrobenzyl p-tolyl sulfones.—None of the mononitro derivatives, II, III, or IV was appreciably soluble in aqueous 10% sodium hydroxide solution. In alcoholic sodium hydroxide at room temperature, however, the *ortho* compound II produced a deep purple color while the *meta* (IV) and *para* (III) gave red solutions. Acidification of these solutions regenerated the original sulfone. When dry benzene solutions of these compounds were treated with metallic sodium, the metal became coated with a layer of product with the same colors mentioned above. Attempts to isolate the pure potassium salts were unsuccessful. None of these sulfones could be alkylated with sodium ethoxide and methyl iodide in absolute alcohol solution. They were not brominated at room temperature by treatment with bromine in acetic acid. However, the salts of the *o*- and *p*-nitrobenzol *p*-tolyl sulfones, which are present in alcoholic sodium ethoxide solutions, did react with bromine to produce the monobromo derivatives, VI.

$$\begin{array}{l} C_7H_7SO_2CHNa \\ \quad\quad | \\ \quad C_6H_4NO_2(o)(p) \end{array} + Br_2 \longrightarrow \begin{array}{l} C_7H_7SO_2CHBr + NaBr \\ \quad\quad\quad | \\ \quad\quad C_6H_4NO_2(o)(p) \\ \quad\quad\quad\quad \text{VI} \end{array}$$

These monobromo derivatives gave only a slight precipitate with hot alcoholic silver nitrate solution—a behavior similar to that exhibited by phenacyl halides.[4] Treatment of these bromo compounds with cold ammonium sulfide regenerated the parent sulfones in each case. The ease with which the halogen was removed shows that it was attached to the side-chain carbon atom and not in one of the aromatic rings. In contrast to the *o*- and *p*-nitrobenzyl *p*-tolyl sulfones the *m*-isomer produced no bromo derivative.

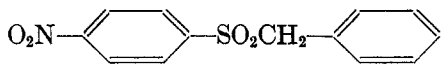
[2] Otto, *Ber.*, **21**, 1696 (1888).

[3] Alway, *J. Am. Chem. Soc.*, **24**, 1062 (1902); Friedländer and Cohn, *Monatsh.*, **23**, 546 (1902).

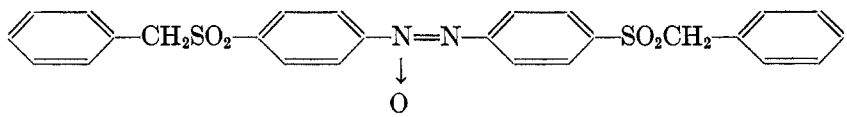
[4] Shriner and Fuson, "Systematic Identification of Organic Compounds", p. 23, John Wiley and Sons, Inc., New York, **1935**.

The alcohol solution of the potassium derivative of *o*-nitrobenzyl *p*-tolyl sulfone was treated with iodine in order to determine whether two molecules would couple at the methylene carbon atoms—a reaction which takes place readily in active methylene compounds of the malonic ester[5] type. In the present instance, coupling did not take place, but, instead, a monoiodo derivative of II was obtained analogous to the above monobromo derivative VI.

It may be mentioned that Tröger and Nolte[6] studied a miscellaneous group of phenyl benzyl sulfones substituted by nitro-, chloro-, and hydroxyl groups in both the phenyl and benzyl radicals, and found that the methylene group was not reactive. However, Fromm and Wittman[7] reported that 4-nitrophenyl benzyl sulfone (VII) did undergo alkylation with methyl iodide in the presence of alcoholic sodium hydroxide to produce a dimethyl derivative. An examination of this work by Tröger and Nolte[6] however, showed that the melting point of 169° reported for the dimethyl derivative was exactly the same as that of the original sulfone (VII). An attempt to duplicate this alkylation, in the course of the present work, using exactly the procedure described[7], gave a very insoluble compound with a melting point of 340–342°. It did not give a test for a nitro group and analyses indicated that it was the azoxy compound (VIII).



VII



VIII

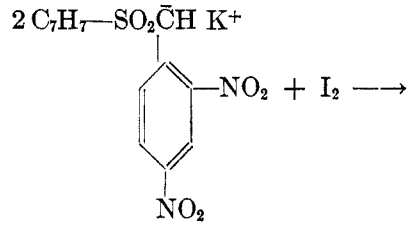
The same compound was obtained by the action of alcoholic sodium hydroxide alone on benzyl *p*-nitrophenyl sulfone.

It is evident that the presence of the nitro group in the *ortho* or *para* position does activate the methylene group to some extent. The sodium derivatives can be halogenated but cannot be alkylated. They also do not undergo the Claisen condensation when treated with ethyl oxalate and sodium ethoxide or the Knoevenagel reaction with benzaldehyde with piperidine as the catalyst.

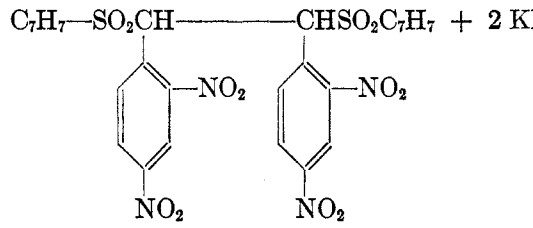
Properties of 2,4-dinitrobenzyl p-*tolyl sulfone* (*V*).—The methylene group in compound V was much more reactive. A purple crystalline potassium

[5] Bischoff and Rach, *Ber.*, **17**, 2781 (1884).
[6] Tröger and Nolte, *J. prakt. chem.*, **101**, 136 (1920).
[7] Fromm and Wittman, *Ber.*, **41**, 2270 (1908).

derivative was formed which could be isolated and analyzed. Acidification regenerated the parent compound V. Treatment with bromine produced a monobromo derivative and the halogen was removed by treatment with cold ammonium sulfide. Treatment of an alcoholic solution of the potassium derivative (IX) with iodine caused coupling to take place leading to the formation of the very insoluble compound, X, which decomposed at 375°. Treatment of the potassium derivative with

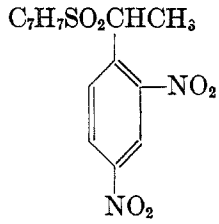


IX

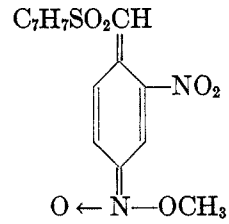


X

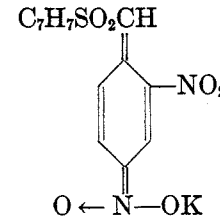
methyl iodide produced a monomethyl derivative which was shown to be the carbon-alkylated compound XI, and not an oxygen-alkylated product such as the nitronic ester XII. The latter structure should result if the potassium derivative had tautomerized to a structure such as XIII. Similar structures had been suggested by Hantzsch and Picton[8] for salts and alkylation products derived from ethyl 2,4-dinitrophenylmalonate.



XI



XII



XIII

In the present work the structure of the alkylated product was shown to be the carbon-alkylated compound, XI, by the following observations.

[8] HANTZSCH AND PICTON, *Ber.*, **42**, 2119 (1909).

(1) The alkyl derivative forms nearly colorless crystals. (2) The product is stable and can be recrystallized several times without decomposition. Nitronic esters[9] are very unstable, decomposing into an oxime and an aldehyde.

$$R_2C{=}\overset{\overset{O}{\nearrow}}{N}{-}OCH_3 \longrightarrow R_2C{=}N{-}OH + HCHO$$

(3) When the alkylated compound was treated with hydriodic acid no methyl iodide was liberated. Nitronic esters such as XII do liberate methyl iodide when treated with hydriodic acid since they contain the oxygen-methyl grouping[9]. These results indicate that carbon alkylation has taken place, and show that the two nitro groups in the *ortho* and *para* positions have activated the methylene group to such an extent that alkylation now takes place.

No dialkylated product could be obtained even though the monomethyl derivative was again treated with methyl iodide and sodium ethoxide. Kohler and Potter[10] noted a similar behavior in the case of tosylacetomesitylene.

The *o*-nitro-, *p*-nitro- and 2,4-dinitrobenzyl *p*-tolyl sulfone are vinylogs[11] of *p*-toluenesulfonylnitromethane XIV. This compound had been prepared by Arndt and Rose[12] but not much information concerning the

$$\underset{\text{XIV}}{C_7H_7SO_2CH_2NO_2} \underset{HCl}{\overset{KOC_2H_5}{\rightleftharpoons}} \underset{\text{XV}}{C_7H_7SO_2\overset{-}{C}H\ K^+}\ (NO_2)$$

reactions now under consideration was given. A sample of this compound was prepared by refluxing an alcoholic solution of bromonitromethane and sodium *p*-toluenesulfinate. It readily formed an isolable salt (XV) with potassium ethoxide, which salt regenerated the parent compound upon acidification. The salt brominated readily to give a dibromo derivative. The salt was practically colorless, in sharp contrast to the colored salts of II, III and V. Alkylation experiments were unsatisfactory; no pure com-

[9] RATZ, *Monatsh.*, **26**, 1487 (1905); KOHLER AND STONE, *J. Am. Chem. Soc.*, **52**, 761 (1930); NENITZESCU AND ISACESCU, *Ber.*, **63**, 2484 (1930); *Bull. soc. chim. Rom.*, **14**, 53 (1932); *ibid.*, **18**, 63 (1936); ARNDT AND ROSE, *J. Chem. Soc.*, **1935**, 1; THURSTON AND SHRINER, *J. Am. Chem. Soc.*, **57**, 2163 (1935); J. ORG. CHEM., **2**, 183 (1937); ARNDT, LOEWE, AND ISIK, *Rev. fac. sci. Univ. Istanbol*, **2**, 1 (1937); SHRINER AND BROWN, J. ORG. CHEM., **2**, 560 (1938).

[10] KOHLER AND POTTER, *J. Am. Chem. Soc.*, **58**, 2166 (1936).

[11] FUSON, *Chem. Rev.*, **16**, 1 (1935).

[12] ARNDT AND ROSE, *J. Chem. Soc.*, **1935**, 1.

pounds could be isolated. Most of the original compound was recovered from experiments in which condensations with ethyl oxalate and benzaldehyde were attempted.

It is of interest to point out the differences in reactions exhibited by 2,4-dinitrobenzyl *p*-tolyl sulfone and 2,4-dinitrotoluene in which the nitro groups activate the methyl group. 2,4-Dinitrotoluene will condense with benzaldehyde in the presence of piperidine, but all reactions involving treatment with metal alkoxides do not proceed normally.[13] It forms a potassium derivative which is an amorphous brown powder. This potassium derivative does not analyze for any simple salt, and acidification does *not* regenerate 2,4-dinitrotoluene but produces a reddish-brown powder, decomposing about 275° whose structure is not yet known.[8, 14]

It is evident, therefore, that the sulfone group contributes to the properties of the methylene group in V. The isolation of the pure potassium salt of V and the carbon-alkylation of V stand out in sharp contrast to the oxygen alkylation of ethyl 2,4-dinitrophenylmalonate reported by Hantzsch and Picton.[8] All the reactions of the potassium salt of V, bromination, coupling, and carbon alkylation indicate that the anion involved in these reactions is the carbanion of formula IX.

The purple color of this crystalline potassium salt (IX) parallels the observations of Schlenk and Holtz[15] who found that sodium benzyl is a deep-red crystalline compound. The colors of the anions in these salts may be characteristic of such carbanions which can resonate between several structures. The production of colored metal alkyls is peculiar to the benzyl type of compounds (benzyl, benzhydryl, triphenylmethyl) since sodium methyl and sodium phenyl are practically colorless. The salt (XV) from *p*-toluenesulfonyl nitromethane is also nearly colorless.

EXPERIMENTAL

p-*Tolyl mononitrobenzyl sulfones and* p-*tolyl 2,4-dinitrobenzyl sulfone.*—A mixture of 0.5 mole of each of the nitrobenzyl halides and 1.0 mole of sodium *p*-toluenesulfinate in 600 cc. of absolute alcohol was refluxed for seven to eight hours. The sulfinate did not dissolve completely, but this did not interfere with the reaction. The hot reaction mixture was poured into 300 cc. of ice water. The crude product was separated by filtration and recrystallized from acetone. The yields were 80–85%. The melting points, and analyses were as follows.

p-*Tolyl* o-*nitrobenzyl sulfone* (*II*).—M.p., 131–132°;

Anal. Calc'd for $C_{14}H_{13}NO_4S$: S, 11.02. Found: S, 11.05.

p-*Tolyl* p-*nitrobenzyl sulfone* (*III*).—M.p., 188–189°;

Anal. Calc'd for $C_{14}H_{13}NO_4S$: S, 11.02. Found: S, 11.17.

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[13] THIELE AND ESCALES, *Ber.*, **34**, 2842 (1901).

[14] GINA, *Gazz. chim. ital.*, **45**, II 361 (1915).

[15] SCHLENK AND HOLTZ, *Ber.*, **50**, 262 (1917).

p-*Tolyl* m-*nitrobenzyl sulfone* (*IV*).—M.p., 160–161°;

Anal. Calc'd for $C_{14}H_{13}NO_4S$: S, 11.02. Found: S, 10.84.

p-*Tolyl 2,4-dinitrobenzyl sulfone* (*V*).—M.p., 159–160°;

Anal. Calc'd for $C_{14}H_{12}N_2O_6S$: S, 9.53; N, 8.34.
Found: S, 9.55; N, 8.65.

Bromination of p-*tolylnitrobenzyl sulfones.*—To 5 g. of the *p*-tolylnitrobenzyl sulfone dissolved in 50 cc. of warm nitrobenzene was added exactly one equivalent of sodium ethoxide in 18 cc. of absolute alcohol. The reaction mixture was cooled in an ice bath, and slightly more than the theoretical amount of bromine (about 1.5 cc.) was added slowly with shaking. The addition of bromine was stopped when the color of the solution changed to a light yellow. This change of color occurs when the sodium salt is converted into the bromide. The solution was concentrated on a steam cone and the sodium bromide which separated was removed by filtration. The filtrate was reduced to a volume of about 10 cc. by distillation under diminished pressure. Twenty-five cubic centimeters of ether was added to the residue. The mixture was cooled in an ice bath, the solid product was separated by filtration, and recrystallized twice from acetone. The melting points, yields, and analyses were as follows.

p-*Toluenesulfonyl-2,4-dinitrophenylbromomethane.*—M.p., 178–180°; yield, 5.6 g. (91%).

Anal. Calc'd for $C_{14}H_{11}BrN_2O_6S$: S, 7.70, N, 6.73.
Found: S, 7.67; N, 7.19.

p-*Toluenesulfonyl*-o-*nitrophenylbromomethane.*—M.p., 116–117°; yield 5.5 g. (86.5%).

Anal. Calc'd for $C_{14}H_{12}BrNO_4S$: S, 8.65. Found: S, 8.75.

p-*Toluenesulfonyl*-p-*nitrophenylbromomethane.*—M.p., 166–167°; yield 3.3 g. (53%).

Anal. Calc'd for $C_{14}H_{12}BrNO_4S$: S, 8.65. Found: S, 8.74.

These three bromides and the iodide described below gave only a slight precipitate when boiled with alcoholic silver nitrate.[4] The halogen was readily removed when the compounds were refluxed with sodium acetate in 80% alcohol. The halogen in all of these compounds was also readily removed by reduction with ammonium sulfide. The procedure was as follows. To 50 cc. of acetone or alcohol, containing 5 g. of the halide, was added 15 cc. of concentrated ammonium hydroxide. This solution was saturated with hydrogen sulfide for two hours. The solvent was distilled, and the residue was cooled. The solid was removed by filtration and washed with water. The crude products were recrystallized from acetone. The melting points and mixture melting points showed the products to be the original non-halogenated *p*-tolyl nitrobenzyl sulfones. In the case of *p*-toluenesulfonyl-2,4-dinitrophenylbromomethane the ammonium sulfide not only removed the halogen but caused further reduction.

p-*Toluenesulfonyl*-o-*nitrophenyliodomethane.*—To 1 g. (0.0034 mole) of *p*-tolyl-*o*-nitrobenzyl sulfone, dissolved in 10 cc. of nitrobenzene, at room temperature, was added 0.14 g. (0.0034 mole) of potassium in 5 cc. of absolute alcohol. After standing for thirty minutes with occasional shaking 1 g. (0.0036 mole) of iodine was added. The reaction mixture was stoppered tightly and placed on a mechanical shaker for two hours. Most of the solvent was removed by distillation under diminished pressure. To the remaining reaction mixture was added 25 cc. of ether and by shaking and cooling in an ice bath the crude product precipitated. It was separated by filtration and washed with water. The compound was twice recrystallized from acetone, giving white crystals; m.p. 145–146°.

Anal. Calc'd for $C_{14}H_{12}INO_4S$: S, 7.69; N, 3.36.
Found: S, 7.77; N, 3.53.

Potassium salt of p-*tolyl 2,4-dinitrobenzyl sulfone.*—To 2 g. (0.006 mole) of *p*-tolyl 2,4-dinitrobenzyl sulfone, dissolved in 20 cc. of nitrobenzene, at room temperature, was added a solution of 0.24 g. (0.006 mole) of potassium dissolved in 10 cc. of absolute alcohol. The mixture was stirred for about five minutes, and the potassium salt which separated from the solution was removed by filtration and washed with ether. A beautifully crystalline purple salt was obtained.

Anal. Calc'd for $C_{14}H_{11}N_2O_6KS$: S, 8.55; N, 7.45; K, 10.44.
Found: S, 8.32; N, 7.51; K, 10.40.

Alkylation of p-*tolyl 2,4-dinitrobenzyl sulfone.*—To 2 g. of *p*-tolyl 2,4-dinitrobenzyl sulfone, dissolved in 20 cc. of nitrobenzene, at room temperature, was added 0.24 g. (0.006 mole) of potassium in 10 cc. of absolute alcohol. After standing for about thirty minutes with occasional shaking 1.5 cc. of methyl iodide was added. The reaction mixture was stoppered tightly and placed on the mechanical shaker for two hours. The excess solvent was decreased to a volume of about 5–10 cc. by distillation under diminished pressure. To the remaining mixture, 25 cc. of ether was added, and the crude monomethylated product was separated by filtration and washed with water to remove the potassium iodide formed in the reaction. Two crystallizations from acetone gave colorless crystals of 1-(*p*-toluenesulfonyl)-1-(2,4-dinitrophenyl)ethane (XI); yield, 1.3 g. (63%); m.p., 167–168°; melting point of mixture with the original sulfone (m.p., 159–160°), 140–150°.

Anal. Calc'd for $C_{15}H_{14}N_2O_6S$: S, 9.15; N, 8.01.
Found: S, 9.12; N, 8.14.

1,2-Bis(2,4-dinitrophenyl-4-methylbenzenesulfonyl)ethane (*X*).—To 3 g. (0.009 mole) of *p*-tolyl 2,4-dinitrobenzyl sulfone, dissolved in 30 cc. of nitrobenzene, at room temperature, was added 0.36 g. (0.009 mole) of potassium which had been dissolved in 15 cc. of absolute alcohol. After standing for thirty minutes with occasional shaking, 1.23 g. (0.0045 mole) of iodine was added. The reaction mixture was stoppered tightly and placed on a mechanical shaker for two hours. The reaction product separated from the solvent, was removed by filtration and washed with water. The crude product was then separated from any unchanged starting material by washing with hot alcohol and with hot acetone leaving a white product. The coupled product (X) could not be recrystallized due to its insolubility in all solvents tried. The yield was 1.15 g. (38%); decomposition point, 375° (Maquenne block).

Anal. Calc'd for $C_{28}H_{22}N_4O_{12}S_2$: S, 9.57; N, 8.34.
Found: S, 9.75; N, 8.55.

4,4'-Bis(Benzylsulfonyl)azoxybenzene (*VIII*).—To 2.77 g. (0.01 mole) of *p*-nitrophenyl benzyl sulfone dissolved in 100 cc. of absolute alcohol, was added 1.2 g. of sodium hydroxide. This mixture was boiled under reflux for thirteen hours. The reaction mixture was then cooled in an ice bath and filtered. The precipitate was washed with water to remove the sodium iodide. The product was then purified from unchanged sulfone by washing in boiling alcohol. A small amount of the product could be dissolved in boiling acetone, in which it gave none of the color reactions with alkali, as did the original compound, indicating that the nitro group had been altered The yield was 1.2 g. (47.5%); m.p., 340–342°.

Anal. Calc'd for $C_{26}H_{22}N_2O_5S_2$: S, 12.67; N, 5.53.
Found: S, 12.48; N, 5.51.

The above procedure was repeated except that 3 g. of methyl iodide was added in an attempt to effect methylation as described by Fromm and Wittman.[7] Exactly the same azoxy compound (VIII) resulted and no alkylation product could be isolated.

Potassium salt of p-*toluenesulfonylnitromethane* (*XV*).—To 50 cc. of absolute alcohol solution containing 0.9 g. (0.023 mole) of potassium was added 5 g. (0.023

mole) of *p*-toluenesulfonylnitromethane. After stirring for about five minutes, 25 cc. of ether was added and the resulting precipitate separated by filtration and washed several times with ether. A crystalline almost colorless salt was obtained.

Anal. Calc'd for $C_7H_8KNO_4S$: K, 15.69; S, 12.56.
Found: K, 15.50; S, 12.38.

p-*Toluenesulfonyldibromonitromethane.*—To 50 cc. of % sodium hydroxide containing 1 g. of *p*-toluene sulfonylnitromethane was added 2 cc. of bromine. This reaction mixture was refluxed for one hour, cooled, and filtered The precipitate was recrystallized three times from alcohol. The yield was practically quantitative; m.p., 127°.

Anal. Calc'd for $C_7H_7Br_2NO_4S$: Br, 42.9; S, 8.58.
Found: Br, 42.8; S, 8.51.

Attempts to condense ethyl oxalate with o-, m-, *and* p-*nitrobenzyl* p-*tolyl sulfones, 2,4-dinitrobenzyl* p-*tolyl sulfone, and* p-*toluenesulfonylnitromethane.*—Two methods were used in attempts to bring about condensation between ethyl oxalate and these compounds. 1. The method used by Reissert[16] for the condensation of ethyl oxalate with *o*- and *p*-nitrotoluene.

In a round-bottomed flask was placed two moles of sodium dissolved in twenty times its weight of absolute alcohol which had been dried by refluxing with magnesium methoxide. To the sodium ethoxide solution was added two moles of ethyl oxalate and one mole of the sulfone. The flask was closed with a cork containing a capillary outlet tube and placed in a thermostat for three days at 35–40°. The calculated quantity of 20% hydrochloric acid (187.5 g.) necessary to neutralize the sodium used was added. The alcohol was removed by distillation, and cold water was added. The precipitate formed was recrystallized from acetone, and in every case shown to be the original sulfone.

2. The method used by Wislicenus and Thoma[17] for the condensation of ethyl oxalate with *o*- and *p*-nitrotoluene.

To 200 cc. of absolute alcohol, dried by refluxing with magnesium methoxide, containing one-third mole of potassium was added 800 cc. of well-dried absolute ether. This solution was cooled externally with ice, and one-third mole of ethyl oxalate was added. After the potassium ethoxide had dissolved, one-third mole of the sulfone was added. The reaction mixture was allowed to stand overnight. The ether was removed by distillation, the remaining solution was acidified with dilute hydrochloric acid and poured into cold water. The precipitate formed was recrystallized from acetone, and in every case shown to be the original sulfone.

Attempts to condense benzaldehyde with o-, m-, *and* p-*nitrobenzyl* p-*tolyl sulfones, 2,4-dinitrobenzyl* p-*tolyl sulfone, and* p-*toluensulfonylnitromethane.*—The method used in attempts to bring about condensation between benzaldehyde and these sulfones was that described by Thiele and Escales.[18]

To one mole of the sulfone and one mole of benzaldehyde was added 30 drops of piperidine. This reaction mixture was heated to 160° for two hours and was then extracted with alcohol. Water was added to the alcohol solution giving a precipitate, which was separated by filtration and recrystallized from acetone. The original sulfone was recovered in every case.

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[16] Reissert, *Ber.*, **30**, 1030 (1897).
[17] Wislicenus and Thoma, *Ann.*, **436**, 42 (1924).
[18] Thiele and Escales, *Ber.*, **34**, 2842 (1901).

SUMMARY

2,4-Dinitrobenzyl *p*-tolyl sulfone and *o*-, *m*-, and *p*-nitrobenzyl *p*-tolyl sulfones have been prepared by treating sodium *p*-toluenesulfinate with the proper nitrobenzyl halide.

Treatment of *o*- and *p*-nitrobenzyl *p*-tolyl sulfones with sodium ethoxide yielded colored salts which underwent bromination but which did not alkylate with methyl iodide or couple with iodine. *m*-Nitrobenzyl *p*-tolyl sulfone did not undergo bromination in the presence of sodium ethoxide.

A purple crystalline potassium salt was obtained by treatment of 2,4-dinitrobenzyl *p*-tolyl sulfone with potassium ethoxide. This salt regenerated the original upon acidification, brominated when treated with bromine, and underwent carbon-alkylation with methyl iodide. Iodine caused coupling of two moles to yield 1,2-bis(2,4-dinitrophenyl-4-methylbenzenesulfonyl)ethane. All these reactions indicate that the anion of the salt involved in these reactions is a carbanion and not one of the possible tautomeric aci-nitro structures.

The properties of these nitro-substituted benzyl *p*-tolyl sulfones are contrasted with the properties of the nitro- and dinitrotoluenes and with *p*-toluenesulfonylnitromethane.

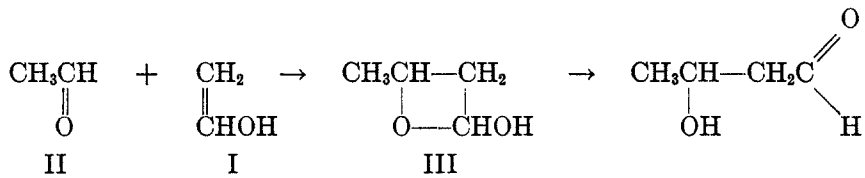
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE CONDENSATION OF ACETALDEHYDE AND VINYL ACETATE

C. S. MARVEL, J. HARMON AND E. H. RIDDLE

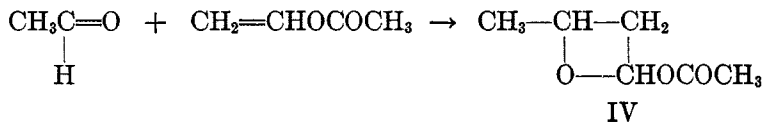
Received March 3, 1939

The condensation of acetaldehyde to aldol[1] has been formulated as an addition of the enol form (I) to the keto form (II) followed by opening of the cyclic acetal (III).



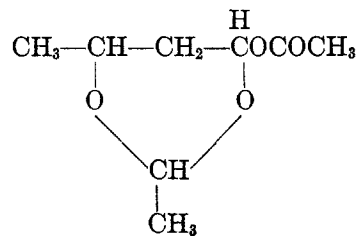
II I III

This hypothesis suggested that it might be possible to condense acetaldehyde with vinyl acetate to produce a stable cyclic intermediate (IV).



IV

Various attempts to bring about the reaction between acetaldehyde and vinyl acetate showed that metallic sodium would cause a condensation to take place. The product of this reaction was not the expected cyclic hemiacetal acetate shown by formula IV but rather the cyclic acetal (V) resulting from the combination of two molecules of acetaldehyde with one of vinyl acetate.

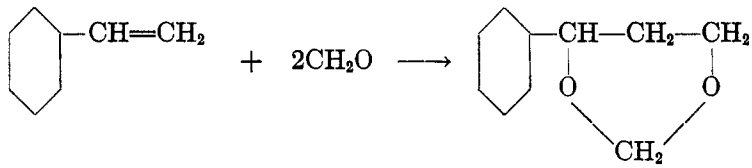


(V)

[1] BODENDORF, *Ber.*, **67B**, 1338 (1934); **68B**, 831 (1935).

The assignment of structure V to the addition product is based on the composition and molecular weight together with the fact that the compound could be hydrolyzed to give acetaldehyde, acetic acid and aldol.

This condensation between acetaldehyde and vinyl acetate resembles the reaction between formaldehyde and styrene which was first reported by Prins[2] and later investigated by Fourneau, Benoit, and Firmenich.[3] How-



ever, a mixture of sulfuric acid and acetic acid was the condensing agent used in the earlier work. Acid catalysts did not give a similar condensation when tried with acetaldehyde and vinyl acetate. It has thus far been impossible to substitute any other aldehyde for acetaldehyde in our condensation reactions.

EXPERIMENTAL

Condensation of acetaldehyde with vinyl acetate.—A flask containing 11 g. (0.25 mole) of acetaldehyde, freshly distilled through a column from paraldehyde and sulfuric acid, was cooled in an ice-salt bath. A 4-mm. cube of freshly-cut sodium was added, and the flask was mounted under an ice condenser. The ice bath was removed, and the sodium was allowed to react with the acetaldehyde for about fifteen minutes. During part of this time the acetaldehyde refluxed quite vigorously as the flask warmed up to about 35–40°, but at the end of fifteen minutes, very little acetaldehyde was refluxing, and the solution, previously cloudy, became clear and syrupy. After the flask had been cooled, the sodium which had not reacted was removed with a spatula, and 22 g. (0.25 mole) of freshly-distilled vinyl acetate was added. The flask was stoppered and shaken for several minutes, during which time a flocculent precipitate formed. After re-cooling of the flask, 25 cc. of cold absolute ethanol was added, a clear solution resulting. The flask was then stoppered tightly and allowed to stand for two days at room temperature. After this time, distillation under reduced pressure from a modified Claisen flask heated to 90° in a water bath removed the low-boiling unchanged reactants and ethanol. Distillation of the residue with an oil pump gave 12 g. of colorless liquid distilling at 70–77° at 6 mm. Redistillation gave 10 g. of pure cyclic acetal (46% of the theoretical amount) boiling at 74–75° at 6 mm.; n_D^{20} 1.4310; d_4^{20} 1.0655. M_D calc'd, 41.88; found, 42.28.

Anal. Found: C, 55.21; H, 8.16; mol. wt. (titration) 178, 181, 173. Calc'd for $C_8H_{14}O_4$: C, 55.2; H, 8.05; mol. wt., 174.

Hydrolysis of cyclic acetal.—To 10 cc. of the purified product from the condensation of acetaldehyde and vinyl acetate was added 40 cc. of water. The mixture was

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[2] PRINS, *Chem. Weekblad*, **16**, 1072, 1510 (1919); *Proc. Acad. Sci. Amsterdam*, **22**, 51 (1919); *C. A.* **14**, 1662 (1920).

[3] FOURNEAU, BENOIT, AND FIRMENICH, *Bull. soc. chim.*, [4], **47**, 860 (1930).

stirred mechanically and gradually warmed to 60° on a water bath. All the oil had dissolved in forty-five minutes. After standing for one-half hour the water was distilled below 60° under reduced pressure. The water distillate was acidic to litmus. From the residue 2 cc. of a clear viscous liquid was distilled at 40–48° at 3 mm. This distillate had a typical aldol odor and gave Tollen's test for an aldehyde. With 2,4-dinitrophenylhydrazine it gave a derivative which after recrystallization from alcohol melted at 189–190° (corr.). The product was identical with one formed from a known specimen of aldol. Apparently aldol gives the derivative of crotonaldehyde by this treatment.[4]

The water distillate was neutralized with sodium hydroxide, evaporated to dryness, dissolved in water, filtered to remove the aldehyde resin formed during the first evaporation, again evaporated to dryness, dissolved in water, acidified with dilute sulfuric acid, and distilled. The distillate was acidic to litmus, and a Duclaux[5] constant was determined.

TABLE

DETERMINATION OF DUCLAUX CONSTANTS

ACID TITRATED	MILLILITERS NaOH REQUIRED	DUCLAUX VALUE FOUND	ACCEPTED DUCLAUX VALUES[5] FOR ACETIC ACID
Original 10 cc.	11.85		
1st 10 cc.	7.27	6.14	6.8
2nd 10 cc.	7.63	6.45	7.1
3rd 10 cc.	8.6	7.25	7.4

In a 50-cc. distilling flask was placed 10 cc. of the cyclic acetal, 30 cc. of water, and 10 cc. of dilute hydrochloric acid. The side-arm of the distilling flask was connected to a tube leading to the bottom of a test-tube containing 15 cc. of 2,4-dinitrophenylhydrazine reagent and immersed in an ice-salt mixture. A stream of nitrogen gas was washed with Fieser's solution[6] and then passed through the distilling flask to carry over any aldehyde which might form. The flask containing the reaction mixture was heated in a water bath to 60° for about one hour, when the acetal was all in solution. After removal of the water bath, nitrogen was run through at a moderate rate for half an hour, a yellow precipitate forming in the 2,4-dinitrophenylhydrazine reagent. This precipitate was collected on a filter, washed with a little cold alcohol, and recrystallized from hot alcohol. It melted at 166–167° (corr.), and no depression of the melting point was observed when it was mixed with an authentic sample of acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 168°.

Other attempted condensations.—Propionaldehyde, *n*-butyraldehyde, isobutyraldehyde, and benzaldehyde did not add to vinyl acetate under similar conditions. No reaction between acetaldehyde and vinyl acetate was obtained when alcoholic potassium hydroxide, zinc chloride, barium hydroxide, magnesium methoxide,

[4] BRADY, *J. Chem. Soc.*, 756 (1931), gives the m.p. of crotonaldehyde 2,4-dinitrophenylhydrazone as 190°.

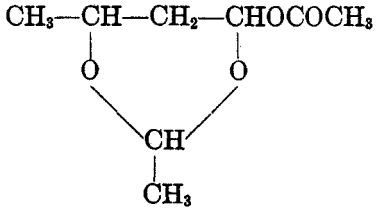
[5] SHRINER AND FUSON, "Identification of Organic Compounds," John Wiley and Sons Inc., New York, **1935**, p. 65.

[6] FIESER, *J. Am. Chem. Soc.*, **46**, 2639 (1924).

sodium ethoxide, sodium phenoxide, anhydrous sodium carbonate, stannic chloride, acetic acid, and *p*-toluenesulfonic acid, dry hydrogen chloride, or dry *p*-toluenesulfonic acid in benzene were used as catalysts.

SUMMARY

Acetaldehyde and vinyl acetate combine in the presence of sodium to give the cyclic acetal.



This addition reaction has not been observed with other aldehydes.

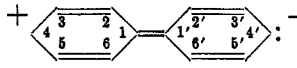
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

RESONANCE AND SOME PHYSICAL AND CHEMICAL PROPERTIES OF BIPHENYL TYPES

MELVIN CALVIN

Received March 14, 1939

If pure states of the type*



I

are to contribute to the ground state of biphenyl it is necessary that the two rings be capable of assuming a coplanar configuration. When such is the case the C_1—$C_{1'}$ bond will acquire some double-bond character, and the distance C_1—$C_{1'}$ will be decreased.[1] This has an important consequence for the rate of racemization of certain optically active biphenyls. The activation energy for the racemization of a biphenyl is almost entirely the energy required to overcome the repulsion between the valence saturated *o*-substituents in order to bring the rings into the coplanar position.[2] Whether the racemization is effected by the actual interpenetration of the electronic charge distribution, or a change in bond angles is immaterial. The repulsive forces acting between already paired and shared electrons must be overcome. Since this repulsive force is a very sharp function of the distance (usually represented by c/r^{12} or $ae^{-r/b}$, where r is the interatomic or intergroup distance, and a, b, and c are constant parameters) it may readily be understood how very small changes in r could effect huge changes in the repulsive potential of a pair of groups.

The kinetics of the racemization of a number of optically active diphenyls have been studied both in solution and in the gas phase.[3] The significant

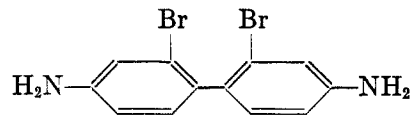
* Pauling and Sherman [*J. Chem. Phys.*, **1**, 679 (1933)] used similar conjugated first excited canonical states but in a form which would be equivalent to the diradical since non-adjacent exchange integrals were neglected. Hückel [*Z. Physik.*, **83**, 651 (1933)] includes the ionic states as here written. In either case the bond C_1—$C_{1'}$ is double, but for the present purposes the ionic states are the more important.

[1] (*a*) PENNEY, *Proc. Roy. Soc.*, **A158**, 306 (1937); (*b*) COULSON, *Proc. Roy. Soc.*, **A169**, 413 (1939).

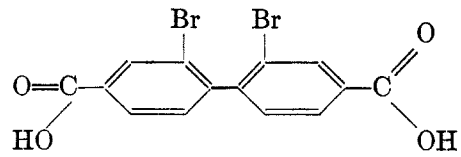
[2] SHRINER, ADAMS, AND MARVEL, "Optical Isomerism," p. 259 in Vol. 1 of Gilman's "Organic Chemistry."

[3] (*a*) KISTIAKOWSKY AND SMITH, *J. Am. Chem. Soc.*, **58**, 1043 (1936); (*b*) KUHN AND ALBRECHT, *Ann.*, **455**, 272, 458, 221 (1927).

differences in the first-order rate constants are due primarily to changes in the activation energy. Thus at 0°C. a change of 3000 calories in the activation energy could change the half-life of a racemization from 1 sec. to 5 min.; *i.e.* make the difference between a resolvable compound and a non-resolvable compound under ordinary experimental conditions. Using a Lennard-Jones potential function of the type[4] $V(r) = 4\epsilon\,(1/R^{12} - 1/R^{6})$ where $R = r/\sigma$, r = distance between group centers, σ = distance between group centers for $V(\sigma) = 0$, and ϵ = the depth of the van der Waals minimum, and R^{-12} represents the repulsion with R^{-6}, the van der Waals attraction, it can be seen that decreases of the order of a few hundredths of an Ångstrom would be sufficient to produce the required changes in potential. Just such a case has been observed.[5] The 2,2′-dibromo-4,4′-diaminobiphenyl (II) is not resolvable, while the 2,2′-dibromo-4,4′-dicarboxybiphenyl (III) is resolvable and has a half-life for racemization of 5–10 minutes at 0°C.

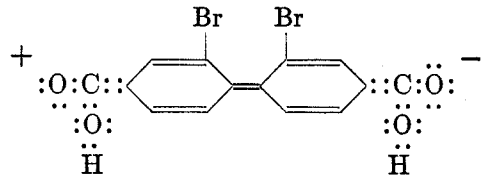


II



III

In II the amino groups are incapable of accepting electrons and are of no assistance in lowering the energy of the ionic resonance state I and thus increasing its contribution to the ground state of the molecule. In III however, although the carboxyl group functions more generally as an electron accepting group, it is not impossible that it function as a source of electrons (IV) as well and be of some assistance in promoting the contribution of the ionic state to the ground state of the molecule.

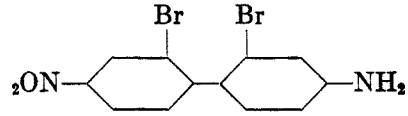


IV

[4] DeBoer and Michels, *Physica*, **6**, 97 (1939).

[5] Adams, *et al.*, *J. Am. Chem. Soc.*, **56**, 2112 (1934); *ibid.*, **55**, 1649 (1933).

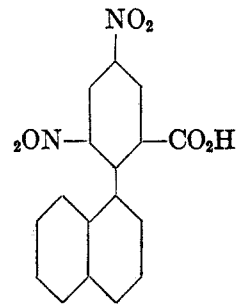
The activation energy for the racemization of III (half-life 5 minutes at 0°C.) using the temperature-independent factor of 10^{11} is 17,500 cals. If this is reduced in II to 14,000 cals. the half-life at 0° would be 1 sec. and presumably the compound II would be unresolvable. This would require a change in each Br-H interaction of only 1,750 cals. and it is quite evident that only a small additional contribution of IV could easily account for the few hundredths of an Å change in the C_1—$C_{1'}$ distance necessary. It is thus to be expected that 2,2′-dibromo-4-nitro-4′-aminobiphenyl (V) would be easily resolvable, and that the half-life of the racemization would be considerably longer than 10 minutes.



V

The effects of other meta and para substituents on the racemization rate of biphenyls may be accounted for at least in part by such a mechanism.

Recently an attempt has been made to demonstrate the participation of I in the structure of diphenyls by a study of the catalysis of the racemization by catalysts which affect the rate of *cis-trans* isomerizations.[6] But it is apparent from what has just been said that such an experiment should fail. In the first place the biphenyl which was used, VI,



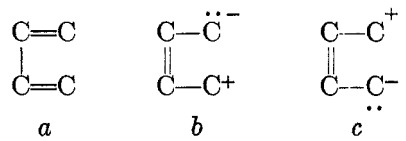
VI

was tri-*o*-substituted by large groups and hence the interaction of the pair of *o*-substituted groups would be sufficient to produce a slow racemization even if the C_1—$C_{1'}$ bond were as large as possible (1.53 Å). In the second place the acid catalysts which produce *cis-trans* isomerization would probably themselves be incapable of reaching the π bond between the rings if

[6] GILBERT, TURKEVITCH, AND WALLIS, J. ORG. CHEM., **3**, 611 (1939).

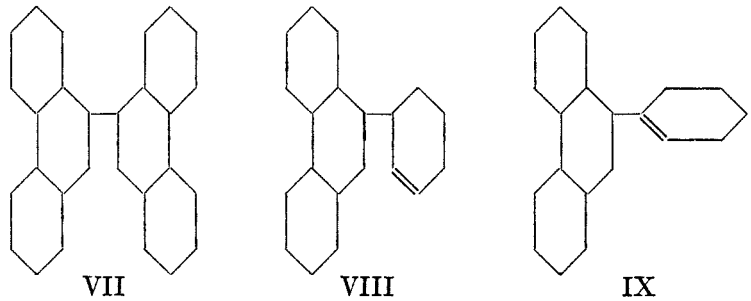
it existed. Such a phenomenon has already been observed in some substituted stilbenes.[7]

Another correlation which follows from these considerations appears in the absorption spectra of substituted biphenyl types in which the coplanar arrangement is prohibited. When this is the case the contribution of states of the type I to both the ground state and the excited states is reduced or eliminated, and the spectrum of such a molecule should be very close to that of the two independent groups.[8] If, however, the coplanar configuration is possible, the individual fine structure is completely lost, and a great increase in intensity results.[8] The precise mechanism by which this takes place will be taken up in a later discussion of absorption spectra of organic molecules in general. It is sufficient for this discussion to note that such a correlation exists and that in molecules exhibiting this washed-out absorption spectrum conjugated structures of the type I do contribute to the actual state of the molecule. This leads to the expectation that molecules exhibiting this characteristic washed-out spectrum will have chemical properties associated with the conjugated resonating states which contribute to their structure. Such a property is the ability to undergo a Diels-Alder condensation which would be expected of a conjugated series *a* in which the structures *b* and *c* contribute appreciably.



a *b* *c*

Such cases have recently been reported[9] in which the correlation between absorption spectrum and the ability to undergo the diene condensation has been observed. The compounds 9,9′-biphenanthryl (VII) and 9-cyclohexenylphenanthrene (VIII)



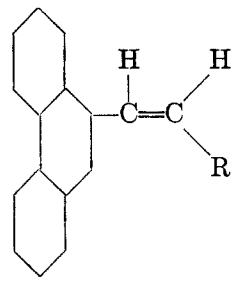
VII VIII IX

[7] TAYLOR AND MURRAY, *J. Chem. Soc.*, **1938**, 2078.

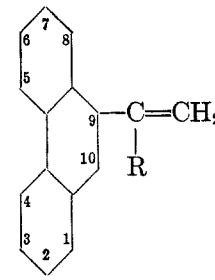
[8] PICKETT, WALTER, AND FRANCE, *J. Am. Chem. Soc.*, **56**, 2296 (1936).

[9] (*a*) HENRI AND BERGMANN, *Nature*, **143**, 278 (1939); (*b*) BERGMANN AND BERGMANN, *J. Am. Chem. Soc.*, **59**, 1443 (1937).

fail to react with maleic anhydride, and their absorption spectra are close to those of their components, whereas 9-cyclopentenylphenanthrene (IX), which does condense, has the washed-out spectrum. Thus the small contraction in the size of the cylcopentenyl group as compared with that of the cylcohexenyl is sufficient to permit the coplanar arrangement of the rings and hence all of its concomitant properties. Another case in point, for which the absorption spectra are not yet available, is that of the substituted 9-phenanthrylethylenes, X(*a*) and X(*b*).[9b]



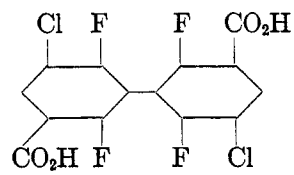
X(*a*)



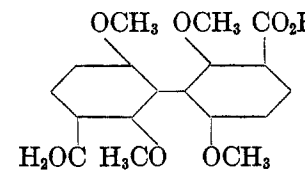
X(*b*)

When R = CH_3 both X(*a*) and X(*b*) undergo the diene synthesis; when R = C_6H_5, X(*b*) is incapable of this condensation. This may be due to one of two causes. The ortho C—H of the phenyl may interfere with C_8—H of the phenanthryl and be fixed in the *trans*-planar position opposite C_{10}—H so as to prevent the condensation by sheer spatial arrangement (pure steric effect), or the interference of the ortho C—H of the phenyl with C_{10}—H may be large enough to prevent the coplanar configuration in that direction as well and thus prevent the conjugation resonance. In the first case the absorption spectrum would show the conjugation broadening and intensity increase whereas in the second case it would not.

We are thus led to the prediction that optically active compounds of the type VII and VIII should be preparable and perhaps resolvable, and conversely unresolvable biphenyls of the type XI and XII[10]



XI



XII

should exhibit the conjugation absorption spectrum.

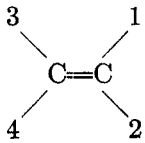
It should be borne in mind that such conclusions as these based upon the

[10] ADAMS, *et al.*, *J. Am. Chem. Soc.*, **55**, 4219 (1933); **55**, 4225 (1933); **54**, 2973 (1932).

failure to observe a given reaction are contingent upon reversals due to improvement in technic or the discovery of new experimental conditions. It should also be noted that the correlation between the conjugation absorption spectrum and the non-resolvability of a biphenyl or the ability to undergo a diene condensation need not be complete. There is as yet no theoretical criterion by which we can determine how much of a contribution of the conjugated states is required to produce the washed-out spectrum or how much of a contribution is required to prevent rotation through the coplanar position. So it may be possible to find cases in which the contribution is sufficient to produce one effect and not the other. For example, in III (IV) the conjugation may be sufficient to prevent the rapid racemization but the molecule in its equilibrium position may be insufficiently far removed from the coplanar configuration so that a sufficient contribution of the conjugated states exists to produce the washed-out spectrum. Also in XI and XII the equilibrium position may be sufficiently far removed from the coplanar one to prevent the conjugation spectrum and still permit rapid racemization. The only one of these borderline cases which seems at all likely to occur, however, is the one in which the racemization is slow but there is still sufficient contribution to produce the optical effects. It is clear that these are all matters of degree.

SUMMARY

1. The requirement that the four bonds extending from a double bond



must be coplanar is applied to the contributing resonating states of biphenyls.

2. The effect of non-*o*-substituents on the rate of racemization of certain biphenyls is discussed and it is predicted that 2,2′-dibromo-4-nitro-4′-aminobiphenyl should be resolvable and have a racemization half-life greater than 10 minutes.

3. The effect of the possibility or impossibility of conjugated resonating states on the absorption spectrum of substituted biphenyls is considered and it is predicted that certain non-resolvable tetra-*o*-substituted biphenyls should show the conjugation absorption spectrum, whereas other tetra-*o*-substituted biphenyls in which the coplanar arrangement of the rings is impossible will have an absorption spectrum very similar to the uncoupled parts.

4. It is predicted that optically active derivatives of 9,9′-biphenanthryl and of 9-cyclohexenylphenanthrene should be preparable.

5. The relationship between the contributing resonating states and the reactivity toward a diene condensation is discussed.

[CONTRIBUTION FROM THE DABNEY CHEMICAL LABORATORY, UNIVERSITY OF TENNESSEE]

THE IDENTIFICATION OF AROMATIC SULFONES

C. A. BUEHLER AND JOHN E. MASTERS

Received March 16, 1939

The literature reveals little in the way of derivatives suitable for the identification of sulfones. The most recent method as applied to alkyl phenyl sulfones is that of Ipatieff and Friedman.[1]

In this investigation ten aromatic sulfones were studied. Since nearly all the sulfones contained alkyl groups, oxidation was resorted to first. In Table I the carboxylic acid thus obtained are listed. The value of these acids as derivatives is limited, for they are frequently not sufficiently characteristic, and their melting points are high. To overcome the latter difficulty conversion into the esters, as shown in Table II, was undertaken.

More satisfactory derivatives for the aromatic sulfones were obtained by nitration, a method already applied by Ipatieff and Friedman to some alkyl phenyl sulfones. The dinitro sulfones obtained are assembled in Table III. These compounds are easily prepared in a pure form in good yield, they melt sharply throughout a convenient range, and they permit a differentiation to be made among the sulfones investigated.

EXPERIMENTAL

All sulfones were prepared by the Friedel-Crafts reaction, using anhydrous aluminum chloride, benzenesulfonyl, *p*-toluenesulfonyl or *p*-bromobenzenesulfonyl chloride, and the proper hydrocarbon or phenyl halide. The yields of the final products from 75 to 150 grams of the sulfonyl chloride varied from 47 to 79%. One of the sulfones, *p*-tolyl *p*-ethylphenyl, has not been described previously. It melted at 112.0–113.0° and gave S, 12.43% (theoretical, 12.35%). Since it gave a dicarboxylic acid (Table I) and a diethyl ester (Table II) agreeing in melting points with those obtained from *p*, *p'*-ditolylsulfone, its structure may be accepted as indicated.

The alkyl or dialkyl sulfones were oxidized by means of chromium trioxide in glacial acetic acid, a method similar to that employed by Newell[2]. The oxidation products with yields and melting points are given in Table I.

For esterification the mono- or dicarboxy sulfones were treated with absolute alcohol and concentrated sulfuric acid. The esters obtained with yields, melting points, and analyses are given in Table II.

In preparing the dinitro derivatives, 1.5 g. of sulfone was placed in a small beaker containing 6 cc. of concentrated sulfuric acid. After the beaker and its contents were immersed in cold water, 6 cc. of concentrated nitric acid was added, drop by

[1] IPATIEFF AND FRIEDMAN, *J. Am. Chem. Soc.*, **61**, 684 (1939).

[2] NEWELL, *Am. Chem. J.*, **20**, 305 (1898).

drop, with constant stirring. Considerable heat was developed during this process, but at no time was the temperature allowed to rise above 60°. The mixture was then

TABLE I

OXIDATION PRODUCTS OF AROMATIC SULFONES

SULFONE	ACID FORMED	M.P., °C.		% S		% YIELD[a]
		Found (uncorr.)	Lit.	Found	Calc'd	
Phenyl *p*-tolyl[b]	Phenyl *p*-carboxyphenyl sulfone	266–68	273[c]			38
p,p'-Ditolyl[d]	Bis-*p*-carboxyphenyl sulfone	358–63	370[e]			64
p-Chlorophenyl *p*-tolyl	*p*-Chlorophenyl *p*-carboxyphenyl sulfone	274.1–275.3		10.49	10.79	51
p-Bromophenyl *p*-tolyl	*p*-Bromophenyl *p*-carboxyphenyl sulfone	283.8–285.5		9.26	9.39	68

[a] Based on 10 to 25 grams original sulfone.
[b] Result identical with phenyl *p*-ethylphenyl sulfone.
[c] NEWELL, *Am. Chem. J.*, **20**, 305 (1898).
[d] Result identical with *p*-tolyl *p*-ethylphenyl sulfone.
[e] MEYER, *Ann.*, **433**, 338 (1923).

TABLE II

ESTERS OF SULFONE ACIDS

ACID	ESTER	M.P., °C.		% S		% YIELD[a]
		Found (uncorr.)	Lit.	Found	Calc'd	
Phenyl *p*-carboxyphenyl sulfone	Phenyl *p*-carbethoxyphenyl sulfone[b]	70.0–70.5		10.99	11.08	24
Bis-*p*-carboxyphenyl sulfone	Bis-*p*-carbethoxyphenyl sulfone	156.0–156.5	158[c]	8.77	8.85	27
p-Chlorophenyl *p*-carboxyphenyl sulfone	*p*-Chlorophenyl *p*-carbethoxyphenyl sulfone	132.0–133.0		9.95	9.88	56
p-Bromophenyl *p*-carboxyphenyl sulfone	*p*-Bromophenyl *p*-carbethoxyphenyl sulfone[d]	133.0–134.0		8.53	8.69	38

[a] Based on 3 to 8 grams acid.
[b] Has an odor similar to cooked cabbage.
[c] MEYER, *Ann.*, **433**, 338 (1923).
[d] Has an odor similar to onions.

heated on a water bath maintained at 60° for fifteen minutes. At the end of this period, it was poured on 50 g. of cracked ice, and the solid that separated, was collected on filter paper. Purification was accomplished by one crystallization from

TABLE III

DINITRO DERIVATIVES OF AROMATIC SULFONES

SULFONE	M.P., °C.[a] (UNCORR.)	DINITRO SULFONE	M.P., °C.			% S		% YIELD[b]
			Found		Lit.	Found	Calc'd	
			uncorr.	corr.				
Diphenyl	122.5–123.5	Bis-*m*-nitrophenyl	197.0–198.0	202.1–203.1	197[c]	10.23	10.40	52
Phenyl *p*-tolyl	125.0–125.5	Dinitro phenyl *p*-tolyl[d]	149.0–150.0	151.7–152.7		9.77	9.95	70
Phenyl *p*-ethylphenyl	93.0– 93.5	Dinitro phenyl *p*-ethylphenyl[d]	135.5–136.6	137.7–138.8		9.63	9.54	72
Phenyl *p*-chlorophenyl	91.0– 91.5	*m*-Nitrophenyl *m*-nitro-*p*-chlorophenyl	144.0–145.0	146.6–147.6	146[e]	9.24	9.36	65
Phenyl *p*-bromophenyl	104.0–105.0	Dinitro phenyl *p*-bromophenyl[d]	159.0–160.0	162.1–163.1		8.17	8.28	62
p,p'-Ditolyl	156.0–158.0	Bis-*m*-nitro-*p*-tolyl	161.0–162.0	164.2–165.2	160[f]	9.62	9.54	81
p-Tolyl *p*-ethylphenyl	112.0–113.0	Dinitro *p*-tolyl *p*-ethylphenyl[d]	115.0–116.0	116.4–117.4		9.09	9.16	89
p-Tolyl *p*-chlorophenyl	123.0–123.5	*m*-Nitro-*p*-tolyl *m*-nitro-*p*-chlorophenyl	149.5–150.0	151.2–151.7	152[e]	9.00	8.99	64
p-Tolyl *p*-bromophenyl	135.0–136.0	Dinitro *p*-tolyl *p*-bromophenyl[d]	158.0–159.0	160.1–161.1		7.87	7.99	74
Bis-*p*-bromophenyl	170.0–171.0	Dinitro bis-*p*-bromophenyl[d]	234.4–236.4	235.3–237.3		6.93	6.88	36

[a] Our own values.

[b] Based on 10 grams sulfone.

[c] GNEHM, *Ber.*, **9**, 79 (1876).

[d] Although the constitution of these compounds has not been determined, it is to be expected that the nitro groups are meta to the sulfone group.

[e] LOUDEN, *J. Chem. Soc.*, **1936**, 221.

[f] MEYER, *Ann.*, **433**, 340 (1923).

ethyl acetate and two from glacial acetic acid. This procedure gave light-yellow, well-defined crystals. In Table III a list of the dinitro derivatives with yields, melting points, and analyses will be found.

SUMMARY

In a study of the reactions of ten aromatic sulfones it was found that the dinitro derivatives are satisfactory for identification purposes.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, REHOVOTH, PALESTINE]

PHENANTHRENE SYNTHESES WITH 2,3-DIMETHYL-2-CYCLOHEXEN-1-ONE

ERNST BERGMANN AND (MISS) A. WEIZMANN

Received March 21, 1939

The experiments described herein were undertaken originally with the intention of locating by comparison methods the phenolic hydroxyl group in the oestrone molecule. In the intervening time, the synthesis of 7-methoxy-1,2-cyclopentenophenanthrene, the dehydrogenation product of oestrone, has been accomplished by Cohen, Cook, Hewett, and Girard[1], proving the position of the hydroxyl group at C_3 of the oestrone molecule, as suggested previously by Butenandt, Weidlich, and Thompson[2]. Also, the 7-hydroxy-1,2-dimethylphenanthrene obtained by the German authors has been synthesized by Haworth and Sheldrick[3]. Our method aimed at the synthesis of the latter substance, too, and our results may still be of interest, as they provide a route to the direct preparation of compounds of the 1,2-dimethylphenanthrene type, which are interesting analogs of the corresponding cyclopenteno- or benzophenanthrene derivatives[4].

The starting material for our synthesis was 2,3-dimethyl-2-cyclohexen-1-one (I)[5]. On reaction with phenethylmagnesium chloride and *m*-methoxyphenethylmagnesium chloride, it gave II and III, respectively. (See p. 267.) It is characteristic of this method, that the position of the double bond created by the Grignard reaction is unambiguous, in spite of the asymmetry of the ketone molecule, since no allene system is capable of existence in a six-membered ring. Therefore the direction of the subsequent cycloisomerisation, which was carried out by means of stannic chloride, is also fixed *a priori*; in addition, the cyclization product (V) is more unsaturated than in the usual syntheses, which facilitates the final dehydrogena-

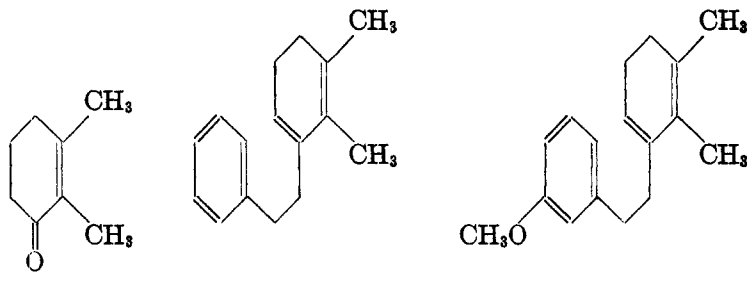
[1] COHEN, COOK, HEWETT, AND GIRARD, *J. Chem. Soc.*, **1934**, 653.

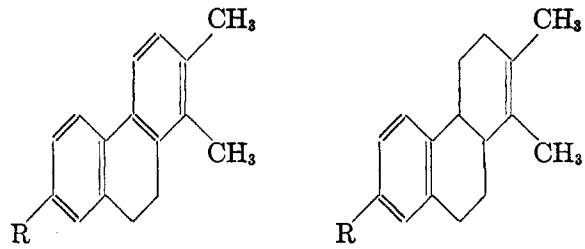
[2] BUTENANDT, WEIDLICH, AND THOMPSON, *Ber.*, **66**, 601 (1933).

[3] HAWORTH AND SHELDRICK, *J. Chem. Soc.*, **1934**, 864.

[4] 1,2-Dimethylphenanthrene, *e.g.*, gives mixed crystals with the 1,2-cyclopentenocompound. For comparison of carcinogenic properties of such pairs, see, *e.g.*: COOK *et al.*, *Proc. Roy. Soc. London*, **111B**, 455 (1922). FIESER AND NEWMAN, *J. Am. Chem. Soc.*, **58**, 2376 (1936); NEWMAN, *ibid.*, **59**, 1003 (1937); BARRY, COOK *et al.*, *Proc. Roy. Soc. London*, **117B**, 318 (1935).

[5] KOETZ, AND CO-WORKERS, *Ann.*, **400**, 83 (1913).





tion process. This reaction, however, proved difficult, as along with the desired phenanthrenes, on dehydrogenation, dihydro derivatives, most probably the 9,10-dihydrogenated substances (IV) were obtained. The separation of (IV) and the phenanthrenes was easy, as only the latter form picrates. In this way, 1,2-dimethylphenanthrene, previously described by Haworth, Mavin, and Sheldrick[6], and 7-methoxy-1,2-dimethylphenanthrene picrate were obtained. The latter compound corresponds to the substance prepared previously by Haworth and Sheldrick[3].

EXPERIMENTAL

The necessary *dimethylcyclohexenone* was prepared as follows. The crude condensation product (270 g.) from ethyl acetoacetate (260 g.) and trioxymethylene (30 g.) was heated with a solution of sodium (23 g.) in alcohol (800 cc.) for 2 hours to 85–115°. After removal of the alcohol, the residue, dissolved in water, was treated with acetic acid until the evolution of carbon dioxide ceased, and ethyl 3-methyl-2-cyclohexen-1-one-4-carboxylate was isolated and fractionated; b.p. 160–165°/35 mm., 108°/1 mm.; yield 130 g.

Anal. Calc'd for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7.
Found: C, 65.2; H, 8.3.

This ester (62 g.) was added to a solution of sodium (7.8 g.) in methanol (120 cc.) and methylated with methyl iodide (48.3 g.). After 2 hours' boiling, the solvent was evaporated, water and ether added and the methylation product, ethyl 2,3-dimethyl-2-cyclohexen-1-one-4-carboxylate was isolated; b.p. 158–161°/21 mm.,

[6] HAWORTH, MAVIN, AND SHELDRICK, *J. Chem. Soc.*, **1934**, 454.

104–110°/1 mm.; yield, 39–42 g. It was converted into (I) by heating (20 g.) for 8 hours with 10% alcoholic potash solution (60 cc.). The fraction 53–65°/1.5 mm. was used.

Anal. Calc'd for $C_8H_{12}O$: C, 77.4; H, 9.7.
Found: C, 77.2; H, 10.1.

1,2-Dimethyl-3-phenethyl-1,3-cyclohexadiene (II).—To a Grignard solution, prepared from phenethyl chloride[7] (14.2 g.) and magnesium (2.3 g.), dimethylcyclohexenone (12.5 g.) was added. The reaction product was isolated as usual; b.p. 155°/6 mm.; yield, 6.g.

Anal. Calc'd for $C_{16}H_{20}$: C, 90.6; H, 9.4.
Found: C, 90.9; H, 9.1.

1,2-Dimethyl-,3,4,9,10,11,12-hexahydrophenanthrene (V, R = H)—The solution of the above diene (4 g.) in benzene (60 cc.) was saturated with gaseous hydrogen chloride, and, after addition of stannic chloride (2 cc.), was kept at 0° for several days. The red mass was decomposed with ice and concentrated hydrochloric acid, and the product was isolated by distillation; b.p. 105–107°/0.02 mm., 150–160°/29 mm.; yield, 3.3 g.

Anal. Calc'd for $C_{16}H_{20}$: C, 90.6; H, 9.4.
Found: C, 90.3; H, 9.3.

1,2-Dimethylphenanthrene was obtained by heating the foregoing product with an equal amount of selenium to 330° for 20 hours. The product was isolated by extraction with ether and distillation in a good vacuum. The leaflets obtained were identified by the melting point of a mixture with authentic 1,2-dimethylphenanthrene (m.p. 142–143°). In another experiment, the picrate, m.p. 156°, was isolated. The oily mother liquors were distilled again; they had the boiling point 115–120°/2 mm., and according to the analysis consisted of 2,3-dimethyl-9,10-dihydrophenanthrene (IV, R = H).

Anal. Calc'd for $C_{16}H_{16}$: C, 92.3; H, 7.7.
Found: C, 92.2, 92.2; H, 7.5, 7.8.

m-*Methoxyphenethyl alcohol.*—*m*-Methoxyphenylmagnesium bromide solution (from 2.4 g. magnesium and 18.7 g. *m*-bromoanisole) reacted violently with ethylene oxide (5.5 g.) at 0°, a yellow precipitate being formed. The reaction was completed by boiling the mixture for 1 hour. The reaction product had the boiling point 105–110°/1 mm.; yield, 7 g.[8]

Anal. Calc'd for $C_9H_{12}O_2$: C, 71.0; H, 7.9.
Found: C, 70.9, 70.9; H, 8.1, 7.9.

m-*Methoxyphenethyl chloride.*—(*a*) The alcohol (8 g.) in dimethylaniline (10 g.) reacted violently with thionyl chloride (10 g.) at 0°. After heating for 30 minutes at 100°, the mass was kept at room temperature for 12 hours, was decomposed with cold dilute sulfuric acid, and the chloride was isolated by distillation; b.p. 85–87°/1.5 mm., 128–130°/14 mm.; yield, 6 g.

Anal. Calc'd for $C_9H_{11}OCl$: C, 63.5; H, 6.5.
Found: C, 63.1, 63.0; H, 6.4, 6.7.

The use of pyridine instead of dimethylaniline gave inconstant results.

(*b*) According to the procedure described by Higginbottom and Hill[9] the Grignard compound from *m*-bromoanisole (38 g.) and magnesium (4.8 g.) was treated with β-chloroethyl *p*-toluenesulfonate (47 g.). The sluggish reaction, occurring at

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[7] Schlenk and Bergmann, *Ann.*, **479**, 83 (1930).

[8] Hewett, *J. Chem. Soc.*, **1936**, 50.

[9] Higginbottom and Hill, *J. Chem. Soc.*, **1937**, 264.

55°, was completed by 8 hours' boiling, and the *m*-methoxyphenethyl chloride was isolated as usual; b.p. 90–95°/0.7 mm.; yield, 10.5 g.

Anal. Calc'd for $C_9H_{11}OCl$: C, 63.5; H, 6.5.
Found: C, 62.9; H, 6.8.

1,2-Dimethyl-3-(m-methoxyphenethyl)-1,3-cyclohexadiene (*III*). — (*m*-Methoxyphenethylmagnesium chloride (prepared from 1.55 g. of magnesium and 11 g. of the above chloride) reacted with dimethylcyclohexenone (I) (9.2 g.) as above. The resulting product had the boiling point 145–147°/0.8 mm.; yield, 7.5 g.

Anal. Cale'd for $C_{17}H_{22}$; C, 84.3; H, 9.1.
Found: C, 83.3, 83.6; H, 9.6, 9.8.

Cyclization was carried through as above, yielding *1,2-dimethyl-7-methoxy-3,4,9,10,11,12-hexahydrophenanthrene* (V, R = OCH_3). It boiled at 135°/0.07 mm.; yield; 3.5 g. (from 7 g. of III).

Anal. Calc'd for $C_{17}H_{22}O$: C, 84.3; H, 9.1.
Found: C, 83.4; H, 9.4.

7-Methoxy-1,2-dimethylphenanthrene.—The hydro derivative (1.5 g.) was heated with selenium (3.5 g.) in a sealed tube at 320° for 24 hours. The dehydrogenation product was isolated by vacuum distillation and treated with picric acid in alcoholic solution. The picrate, after recrystallization from methyl alcohol, had m.p. 149° and analyzed well for the picrate of the desired substance.

Anal. Calc'd for $C_{17}H_{16}O + C_6H_3N_3O_7 = C_{23}H_{19}N_3O_8$: C, 59.4; H, 4.1; OCH_3, 6.7.
Found: C, 59.4, 60.0; H, 3.8, 4.3; OCH_3, 6.9.

From the mother liquor, *2,3-dimethyl-7-methoxy-9,10-dihydrophenanthrene* (IV, R = OCH_3) was isolated by distillation. It boiled at about 150°/1 mm. as a colorless liquid.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6.
Found: C, 85.8; H, 7.9.

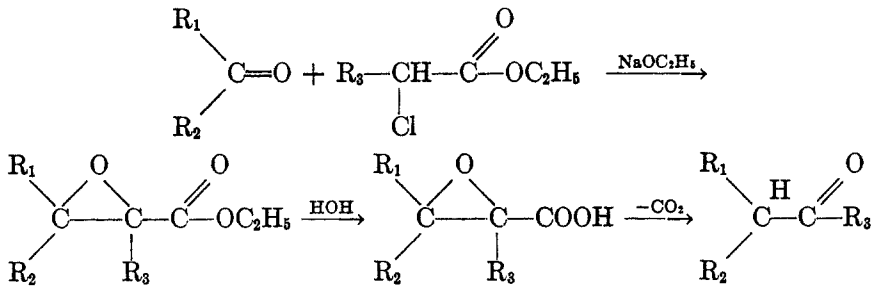
[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, PRINCETON, NEW JERSEY]

THE SYNTHESIS OF CERTAIN SUBSTITUTED ALICYCLIC METHYL KETONES. I

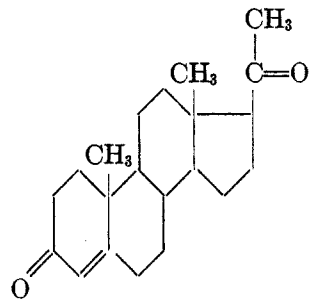
WILLIS AARON YARNALL* AND EVERETT S. WALLIS

Received March 24, 1938

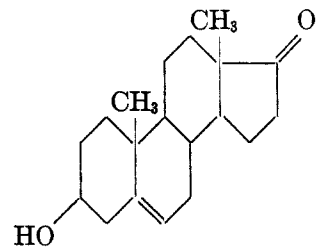
It is well known that a condensation reaction[1] takes place between a ketone or an aldehyde, and an α-halogenated ester in the presence of sodium ethylate. The resulting glycidic ester on saponification yields an acid which, with the loss of a molecule of carbon dioxide, rearranges into a ketone or an aldehyde (R_3=H), as the case may be.



In search for a new and convenient method for the preparation of progesterone (II) from the more plentiful sterol cholesterol the authors of



Progesterone
II



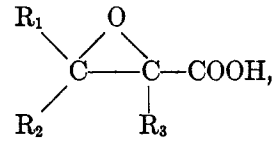
Dehydroandrosterone
I

* Research Assistant on special funds from Merck and Co., Inc., Rahway, New Jersey.

[1] DARZENS AND CO-WORKERS, *Compt. rend.*, (*a*) **139**, 1214 (1905); (*b*) **141**, 766 (1906); (*c*) **142**, 714 (1906); (*d*) **144**, 1123 (1907); (*e*) **145**, 1342 (1908); (*f*) **150**, 1243 (1910); (*g*) **151**, 758 (1911); (*h*) **152**, 1105 (1911); (*i*) **154**, 1812 (1912); (*j*) **195**, 884 (1932).

the present paper investigated the applicability of the above reaction, known as the Darzens condensation, to the steroid ketone, dehydro androsterone (I). Some time ago the results[2] of the preliminary qualitative studies of this problem were published. It was soon found however that the reaction itself needed a more detailed study, and in view of the costly materials involved when working with steroid compounds, experiments were first carried out on such model substances as cyclohexanone, cyclopentanone, etc.

It should be noted in this connection that previous work by other investigators on compounds of this type had revealed certain facts which were pertinent to this problem. Darzens and his co-workers[1] have reported that while the reaction is fairly general for ketones it cannot be extended always to aldehydes. In their hands aliphatic and alicyclic ketones gave better yields of the glycidic ester than semi-aromatic ketones. They observed also that better yields of the glycidic ester can be obtained by substituting ethyl α-chloropropionate for ethyl chloroacetate. The α-methyl glycidic acids,



so formed were observed also to decompose to the corresponding methyl ketones more readily. In some instances the sodium salts, which as a rule are more stable than the corresponding acids, decomposed at the temperatures of the boiling alkaline solutions.

Although Darzens claimed good yields for the decomposition of these glycidic acids to aldehydes and ketones, in no case did he give definite figures. This made it necessary for us to study the effect of various factors, such as temperature, solvent, excess of one or of the other reactants, etc., which, we observed at an early stage in our investigations, greatly influenced the yield of the desired products. It seems pertinent at this time to record some of our more important observations made during the course of these studies.

During the addition of powdered sodium ethoxide, which brings about the condensation, it was noticed that by cooling to $-80°$ the mixture so produced was practically devoid of the brown coloration always noticed when Darzens' procedure was followed. Yields of the glycidic acid ester (65–69 per cent.) were also increased when the mixture was allowed to stand several hours at room temperature before heating on the water

[2] YARNALL AND WALLIS, *J. Am. Chem. Soc.*, **59**, 951 (1937).

bath. When, however, ethyl α-bromopropionate was substituted for ethyl α-chloropropionate in the condensation with cyclohexanone a lower yield (44 per cent.) of the glycidic ester was always obtained.

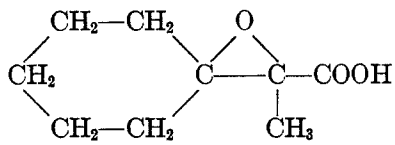
Solvents appear to have some influence on the yield. The effect of benzene, of ether, and of a mixture of benzene and diisopropyl ether on the condensation was studied.

Other important facts influencing the condensation were observed. An increase in the yield of the glycidic ester was always noted when a large excess of the α-halogen ester and of sodium ethoxide was used. In one experiment, in which a large excess of ethyl α-bromopropionate and of sodium ethoxide, with ether as the diluent, was used, a yield of 66 per cent. was obtained as compared with 44 per cent. when the bromo ester was used without any solvent.

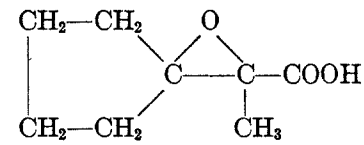
The order of the addition of the reactants appears to have an appreciable effect on the condensation. In one experiment when ethyl α-chloropropionate was added to the mixture of the ketone and sodium ethoxide in ether a conversion of only 25 per cent. was observed. This result can be interpreted as supporting the view of Scheibler[3] who believes that in this condensation the sodium ethoxide forms an enolate with the ester and not with the ketone.

In our experiments it was also observed that lower yields of the glycidic ester were obtained when cyclopentanone was used in the condensation instead of cyclohexanone. We were unable to obtain yields greater than 35 per cent. Large amounts of high-boiling products were always formed, the exact nature of which was not determined.

The results of our experiments show that the yields of the ketones obtained from the corresponding glycidic esters by saponification and rearrangement are also sensitive to the conditions employed. Excellent yields of the corresponding glycidic acids III and IV were obtained from the glycidic esters when alcoholic sodium hydroxide was used. It was also



III



IV

observed, that if the free glycidic acids were allowed to stand in weakly acidic solutions for certain periods of time before their isolation, decomposition took place and small amounts of ketones were produced.

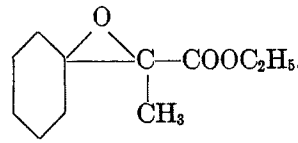
In certain experiments the sodium salts of the glycidic acids were

[3] SCHEIBLER AND TUTUNDZITSCH, *Ber.*, **64B**, 2916 (1931).

obtained in good yields by allowing them to crystallize from the cooled alcoholic solution in which the saponification process had taken place.

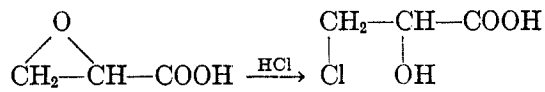
In the present work on the decomposition and rearrangement of the glycidic acids it was found that the pyrolysis of the glycidic acids both at ordinary and at reduced pressures gave low yields of ketones. Thus, methyl cyclohexyl ketone was formed in 27–45 per cent. yield, and methyl cyclopentyl ketone in 10–16 per cent. yield. In all our pyrolysis experiments appreciable amounts of resinous material always remained, and are probably formed as a result of secondary condensations of the carboxyl group with the oxide bridge of the glycidic acid. Because of these facts, a study was made of other possible ways of bringing about the rearrangement. As a result, two new methods were developed for the conversion of glycidic acids to ketones.

It had previously been observed by Darzens[1f] that certain β-chloro-α-hydroxy esters on treatment with aqueous alkali rearrange to aldehydes or ketones. This reaction was therefore studied with ethyl α-(1-chloro-1-cyclohexyl)-α-hydroxypropionate, a compound obtained by saturating a cold ether solution of the glycidic ester with dry hydrogen chloride. Results obtained by the treatment of this product with one equivalent of sodium hydroxide in either water or alcohol indicated that the reaction leading to the reformation of the glycidic ester is faster than the hydrolysis of the ester and its subsequent rearrangement. Thus, the main product of the reaction was the glycidic ester,



Only traces of methylcyclohexanone were formed. Thus it became evident that better results should be obtained if hydrogen chloride were allowed to react with the free glycidic acid.

Consultation of the literature showed that glycidic acids add hydrogen chloride to give β-chloro-α-hydroxy acids[1]:



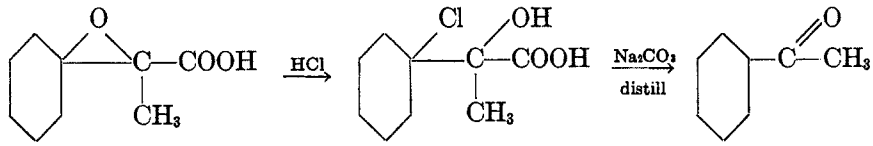
Erlenmeyer[4] had also observed that an aqueous solution of the sodium salt of such an acid on warming gave acetaldehyde, sodium chloride and carbon dioxide. It has also been reported by Melikow[5] that similar treat-

[4] Erlenmeyer, *ibid.*, **13**, 307 (1880).

[5] Melikow and Petrenko-Kritschenko, *J. Russ. Phys. Ges.*, **21**, 396; see also Beilstein, 4th Ed. III, 305, 317.

ment of β-chloro-α-hydroxybutyric and -isobutyric acids gives propionaldehyde and acetone respectively.

With these facts in mind a study was made of the action of hydrogen chloride on the free glycidic acids obtained from cyclohexanone and cyclopentanone. The results so obtained are of interest. With α-1-oxido-α-cyclohexylpropionic acid (V) hydrogen chloride gave a halogen derivative which, when dissolved in a solution of sodium carbonate and steam-distilled, gave methyl cyclohexyl ketone (VI) in 29 per cent. yield and a mixture of acids.

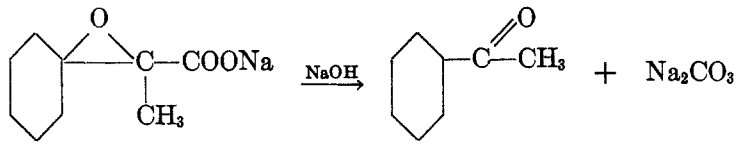


(V) (VI)

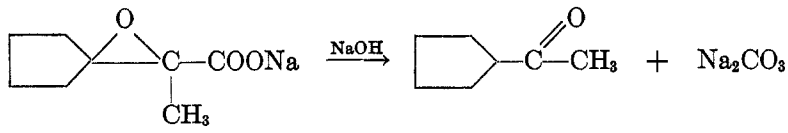
Pyrolysis of this mixture also yielded some of the ketone VI.

Much better yields were obtained when the chlorohydroxy acid was dissolved in pyridine. With α-1-oxido-α-cyclohexylpropionic acid yields of 75 per cent. of the ketone were obtained. With α-1-oxido-α-cyclopentylpropionic acids the yield of ketone was somewhat low (25 per cent.), although much better than when the acid was pyrolyzed.

Since it was observed that pyrolysis of the free glycidic acids led to the formation of much resinous material it seemed desirable to study the pyrolysis of their sodium salts. Theoretically, such a pyrolysis should lead to the desired ketones for it involves a reaction analogous to the preparation of hydrocarbons. Accordingly, the sodium salts VII and VIII were prepared in a pure state and heated with equivalent quantities of sodium hydroxide.



VII



VIII

Yields of 45–56 per cent. of the ketones were produced depending on the conditions of the experiment. Thus both of these new methods are improvements over the known method of production of methyl alicyclic ketones from glycidic acids by pyrolysis.

The condensation with dehydroandrosterone.—The information obtained from the above experiments was utilized in the condensation with dehydroandrosterone. The details of the work will be found in the experimental part of this paper. The results may be briefly summarized as follows. The condensations were carried out under various conditions of temperature, concentrations of reactants, solvent, stirring, etc. The products isolated were mainly unchanged dehydroandrosterone, the glycidic ester, androstenediol, and traces of the sodium glycidate. Twelve different condensations were run. The poorest yields (10 per cent.) were obtained by permitting the ether solution of equivalent amounts of the reactants to stand at room temperature. When an excess of the chloroester and of the condensing agent was employed (10–100 per cent.), and the ether solution was shaken at room temperature, and then refluxed in an atmosphere of nitrogen for a period of two and a half to four days, the per cent. conversion was increased (23 to 40 per cent.). When large excesses of sodium ethoxide and the chloro ester dissolved in ether were employed, and the mixture was shaken and refluxed several days the conversion was practically complete (90–93 per cent.)

Attempts to crystallize the glycidic ester were unsuccessful. In all probability this is due to the fact that the ester is produced in more than one enantiomorphic form, made possible by the introduction into the molecule of new asymmetric carbon atoms. However, on saponification an acid melting at 160–163° was isolated. Experiments showed that this acid was a mixture of several isomers.[6] By crystallization methods one isomer which melted at 183–185° was obtained. The presence of a second acid of much higher melting point, 240–244°, was also noted. Undoubtedly this compound is an isomer. Other isomers may be present in the mother liquors. Indications of the presence of at least one such acid were observed.

The isolation of androstenediol-3,17 and the isomeric pregnenolones was carried out in the following manner. The condensation mixture was usually diluted with ether and thoroughly washed to remove sodium salts.

[6] Since this work was done a paper by MIESCHER AND KAGI [*Helv. Chim. Acta*, **22**, 184 (1939)] has appeared in which they have described the results of certain investigations on the condensation of dehydroandrosterone with α, α-dihalogenated esters in the presence of magnesium amalgam along lines similar to those previously outlined by us [*J. Am. Chem. Soc.*, **59**, 951 (1937)]. Their results strongly show that all four possible isomers of this acid are present.

The residue obtained from the ether solution was heated at 50–70° in a high vacuum to remove any propionates. The unchanged dehydroandrosterone was then removed in the form of its semicarbazone. The residue, which contains the glycidic ester and androstenediol, was saponified with alcoholic alkali. The ether extract from the saponification mixture gave a residue which was treated with semicarbazide hydrochloride in the usual manner. Small amounts of the semicarbazones of Δ^5-pregnenolone and Δ^5-isopregnonolone were obtained. This semicarbazone mixture melted at 215–223°. When the above saponification mixture was acetylated before the treatment with semicarbazide hydrochloride a mixture of semicarbazone acetate was obtained which melted at 240–244° with decomposition. Hydrolysis of these semicarbazones gave a product, which, on purification by high vacuum distillation and recrystallization, melted at 153–159° and gave a correct analysis for pregnenolone, $C_{21}H_{32}O_2$. The separation of the two isomers was accomplished by precipitating the normal pregnenolone with digitonin by a method essentially described by Butenandt and Fleischer[7]. The pregnenolone so obtained melted at 189°. Small amounts of isopregnenolone were also isolated. From the ether extract of the semicarbazones of the pregnenolones, androstenediol was obtained in yields of 4–21 per cent. based on the amount of hormone which entered into the reaction. The isolation of this diol as a reduction product causes one to recall the ketyl theory of Rutovski and Daev[8] for aromatic ketones which undergo the Darzens condensation.

Studies were made in an attempt to increase the yields of Δ^5-pregnenolone. In most instances they were unsuccessful because of the stability of the free glycidic acid. When pyrolysis was conducted in a high vacuum only resinous material was obtained. The sodium salt in boiling alkali was also found to be too stable to give good yields of the rearranged products. Heating the free acid with pyridine or quinoline did give in each case small amounts of neutral products, which on purification were found to contain Δ^5-pregnenolone, and small amounts of another ketone whose structure is still somewhat uncertain.

When the free glycidic acid in dry ether solution was treated with dry hydrogen chloride, a halogen derivative was obtained, which, when boiled with pyridine, was more easily decarboxylated. Much better yields of ketonic material were produced when this method of decarboxylation was used. The ketones were isolated in the form of their semicarbazones. Hydrolysis of these semicarbazones gave a crystalline product which melted at 110–114°. When an acetic acid solution of this mixture of ketones was brominated, oxidized with chromic acid, and debrominated

[7] BUTENANDT AND FLEISCHER, *Ber.*, **70**, 96 (1937).
[8] RUTOVSKI AND DAEV, *ibid.*, **64B**, 693 (1931).

according to the usual methods, a crystalline product was isolated, which, upon purification by crystallization, was found to be identical with a sample of progesterone prepared from stigmasterol.

Since the glycidic acid from dehydroandrosterone can also add hydrogen chloride at the double bond as well as at the oxide bridge, it seemed wise to determine if in the subsequent treatment with pyridine the double bond is shifted to the 4–5 position, thereby producing an allo type of compound. Because of this possibility, the effect of heating cholesterol hydrochloride with moist pyridine was studied. Results were obtained which showed conclusively that on treatment with pyridine, cholesterol hydrochloride yields both cholesterol and allocholesterol. Thus, reasoning by analogy, one of the pregnenolones which we would expect to be present in the ketone mixtures described above would be Δ^4-pregnenolone. At the present writing this particular ketone has not been isolated in a pure state from the neutral ketone fraction. It should be noted however that its presence is not bothersome since in this case also, bromination, oxidation, and debromination would yield the desired progesterone.

EXPERIMENTAL

Preparation of sodium ethoxide.—The dry, powdered sodium ethoxide used in the condensation experiments was always freshly prepared. A weighed amount of sodium was dissolved in 20–25 times its weight of absolute alcohol. After solution the excess alcohol was rapidly distilled. The solid sodium ethoxide was baked at 160–180° and 15 mm. for fifteen minutes. On cooling to room temperature it was carefully powdered, and used immediately.

The condensation of cyclohexanone with ethyl α-chloropropionate.—*A.* The method of Darzens. To a mixture of 5.0 g. (5.26 cc.) of pure cyclohexanone and 6.97 g. (6.4 cc.) of ethyl α-chloropropionate there was added the powdered sodium ethoxide made from 1.2 g. of sodium. Yield of glycidic ester 5.5 g. (54% of the calculated amount); b.p. 126–128/19 mm.

Anal. Calc'd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15.
Found: C, 66.5; H, 9.26.

B. Modifications of the above method showing effect of temperature, concentration, solvent, etc.

1. A mixture of 10.5 cc. of cyclohexanone and 12.8 cc. of ethyl α-chloropropionate was cooled to −80° in a glass-stoppered flask, and to this was added in 0.1-mole portions with shaking, powdered sodium ethoxide made from 2.35 g. of sodium. The mixture was allowed to stand for ten minutes and then was brought to room temperature and left overnight. After warming on a steam bath for two and a half hours (moisture excluded) the mixture was poured into ice water and ether, and was thoroughly shaken. The ether layer was washed with a 5% solution of sodium carbonate, and dried over sodium sulfate. Evaporation of the ether solution left a residue which on distillation gave 13.6 g. of the glycidic ester; b.p. 126–127°/20 mm.; yield, 68% of the calculated amount.

2. The above experiment was repeated with 50 cc. of dry ether as the solvent. The reaction mixture was shaken 24 hours at room temperature and then refluxed for another 24 hours; yield of glycidic ester, 34% of the theoretical.

3. The experiment was similar to No. 1 except that 25 cc. of anhydrous benzene was used as the solvent. The mixture was allowed to stand overnight, and was then refluxed for eight hours. Yield of glycidic ester, 47%.

4. Same as in No. 3, with benzene-petroleum ether (1:1) instead of ether as the solvent. Yield of glycidic ester, 54%.

5. Same as in No. 2 with the use of a 10% excess of both ethyl α-chloropropionate and sodium ethoxide. Shaken for four days at room temperature. Yield of glycidic ester 37% of the calculated amount.

6. Same as No. 1, with 0.1 mole of ethyl α-bromopropionate instead of ethyl α-chloropropionate. Yield of glycidic ester, 44%.

7. In this experiment a reversal was made in the order of mixing the reagents. Sodium ethoxide (0.1 mole) was added to 0.1 mole of cyclohexanone dissolved in 20 cc. of dry ether. The mixture was cooled to 0°, and 0.1 mole of ethyl α-chloropropionate was slowly added. A rise in temperature was noted. The contents of the flask were shaken for 24 hours and worked up in the usual manner. Yield of glycidic ester, 25%.

Condensation of cyclopentanone with ethyl α-chloropropionate.—The condensation was carried out by the method No. 1 for cyclohexanone described above. Yield of glycidic ester, b.p. 128°/25 mm., 35%.

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.7.
Found: C, 65.0; H, 8.9.

A higher-boiling material was also obtained, but was not further investigated.

Experiments on the hydrolysis of the glycidic esters.—1. Preparation of sodium α-1-oxido-α-cyclohexylpropionate. Ten grams of the corresponding glycidic ester described in the above experiments was dissolved in 50 cc. of an alcoholic solution of sodium hydroxide which contained 6 g. of sodium hydroxide. The solution was refluxed for two hours and allowed to cool. On standing overnight, crystals separated in plates. Recrystallization from 95% alcohol gave 6.5 g. of the pure sodium salt; yield, 63%.

Neutralization equivalent.—A 0.741-g. sample of the sodium salt required 38.9 cc. of 0.6969 *N* hydrochloric acid. Equiv. wt. for $C_9H_{13}NaO_5$: calc'd, 192.2; found, 196.

2. Preparation of sodium α-1-oxido-α-cyclopentyl propionate. The method used was essentially the same as that described above. Essentially the same yields were obtained.

Neutralization equivalent.—A 0.804-g. sample of the sodium salt required 47.2 cc. of 0.969 *N* hydrochloric acid. Equiv. wt. for $C_8H_{11}NaO_3$: calc'd, 178.2; found, 176.

3. Preparation of α-1-oxido-α-cyclohexylpropionic acid. Twelve grams of the corresponding glycidic ester were hydrolyzed in the manner already described. The alcoholic solution was diluted with water and extracted with ether. The aqueous layer was acidified with 10% hydrochloric acid to Congo red, and then 2 cc. of 10% hydrochloric acid was added. The oil so produced was worked up in the usual way; yield of acid, 9.1 g.; 88% of the theoretical.

4. Preparation of α-1-oxido-α-cyclopentylpropionic acid. The preparation was carried out as described in No. 3. Yield of acid, b.p. 128°/25 mm.; 91% of the theoretical.

Preparation of the alicyclic methyl ketones.—1. Preparation of methyl cyclohexyl ketone by pyrolysis of α-1-oxido-α-cyclohexylpropionic acid under reduced pressure. Four and four-tenths grams of the glycidic acid was used in this experiment. At 120° and 15 mm. carbon dioxide evolution began. Pyrolysis was continued for fifteen minutes at 130°. The temperature of the bath was then raised to 160° for the distillation of the ketone. Yield 0.88 g.; 27% of the calculated amount. The

ketone was converted into its semicarbazone in the usual manner. Recrystallization from dilute alcohol gave a product which melted at 177°. (Beilstein records m.p. 175°; Darzens, m.p. 177°.)

2. Pyrolysis at atmospheric pressure. Four and seven-tenths grams of the glycidic acid gave 1.4 g. of methyl cyclohexyl ketone. Yield, 41% of the theoretical.

3. Pyrolysis of the sodium salt of the glycidic acid. The sodium salt (1.6 g.) prepared as described above was heated with 0.35 g. of sodium hydroxide. An intimate mixture was made by the addition of 1 cc. of alcohol, which was subsequently removed. After removal of the solvent the bath temperature was raised to 300° and kept at that temperature for 45 minutes. Most of the material distilled at this temperature. Decomposition was completed at 400°. Yield of ketone in form of its semicarbazone, m.p. 176°, 45% of the theoretical.

4. Rearrangement of α-(1-chloro-1-cyclohexyl)-α-hydroxypropionic acid. Eleven grams of an impure α-(1-chloro-1-cyclohexyl)-α-hydroxypropionic acid, prepared from the above glycidic acid by saturation with dry hydrogen chloride, was dissolved in 35 cc. of pyridine, to which had been added 5 g. of semicarbazide hydrochloride dissolved in the minimum amount of water. The solution was refluxed for 30 minutes. On working up the product, 5 g. of a semicarbazone was obtained. Recrystallization gave 3.8 g., which melted at 175–176°. This is equivalent to 2.5 g. of methyl cyclohexyl ketone. Yield, 75% of the calculated amount.

5. Preparation of methyl cyclopentyl ketone. Pyrolysis of the corresponding glycidic acid gave the ketone, whose semicarbazone melted at 141°. Yield, 16% of the theoretical. When the sodium salt of the glycidic acid was pyrolyzed as described above for the corresponding cyclohexyl derivative the yield was increased to 56 per cent. Rearrangement of an impure α-(1-chloro-1-cyclopentyl)-α-hydroxypropionic acid gave a semicarbazone, m.p. 141, in a yield of 25%.

Condensations of dehydroandrosterone with ethyl α-chloropropionate.—The dehydroandrosterone used in these experiments was prepared from cholesterol by well-known methods. Many condensations were carried out. However, only four typical experiments will be given in detail.

Experiment 1. In this experiment a 10% excess of the chloro ester, and of sodium ethoxide was used. The dehydroandrosterone (0.401 g.) was dissolved in 30 cc. of dry ether in a 50-cc. glass-stoppered Erlenmeyer flask. After cooling to −80°, 0.19 cc. of ethyl α-chloropropionate and 0.10 g. of powdered sodium ethoxide were added. The mixture was then allowed to come to room temperature, and shaken for four days in a shaking machine. It was finally refluxed for one day in an atmosphere of dry nitrogen. The product was diluted with ether and extracted with a 5% solution of sodium bicarbonate. The water extract gave but a slight cloudiness on acidification. The ether layer was worked up in the usual manner, and the residue was subjected to a high vacuum (0.02 mm.) for one-half hour to remove any α-chloro-, or α-ethoxypropionic acid esters which might have been present.

The residue was treated in the usual manner with semicarbazide hydrochloride (0.7 g.) and sodium acetate (2 g.) dissolved in 50 cc. of alcohol. The mixture was refluxed for two hours and then worked up. After it had stood overnight a semicarbazone separated between the water-ether layers. This product was separated by filtration and dried *in vacuo*, m.p. 247–250°. The weight of product was 0.34 g., corresponding to 0.12 g. of dehydroandrosterone; amount of dehydroandrosterone which entered into reaction, 70%.

The semicarbazone was hydrolyzed in the usual manner, and the dehydroandrosterone obtained from it was recovered.

Experiment 2. In this experiment a 65% excess of ethyl α-chloropropionate was used. The amount of sodium ethoxide employed was three and one-half times the theoretical quantity.

A solution of 1.60 g. of dehydroandrosterone and 1.18 cc. of ethyl α-chloropropionate in 150 cc. of dry ether was cooled to −80° and to it was added the powdered sodium ethoxide from 0.584 g. of sodium. After the mixture had come to room temperature, it was refluxed for 60 hours in an atmosphere of nitrogen. The ether was then evaporated, and the residue was refluxed for two hours with a solution of 120 cc. of 90% alcohol which contained 4 g. of sodium hydroxide. The cold solution was diluted with water and extracted with ether. The alkaline water layer was acidified with dilute acid and again extracted with ether. This latter ether extract was worked up in the usual manner and gave 0.91 g. of a glycidic acid. Melting point 160–163°. This corresponds to a 46% conversion of the dehydroandrosterone.

Anal. Calc'd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.96.
Found: C, 73.20; H, 9.10.

Crystallization of this crude acid from a variety of solvents finally gave a product which melted at 183–185°. Another acid was isolated from the mother liquors which melted at 240–244°.

The first ether extract which contained the unchanged dehydroandrosterone was worked up, and the dehydroandrosterone was recovered as the semicarbazone. It also contained some androstenediol. A description of the recovery of this substance will be given later.

Experiment 3. In this experiment, twenty times the equivalent amounts of ethyl α-chloropropionate were used. One gram of the hormone and 8.7 cc. of the α-chloro ester was dissolved in 10 cc. of ether. The solution was cooled to −80°, and finely powdered sodium ethoxide from 1.60 g. of sodium was added. The resulting mixture was allowed to stand one day at room temperature and then shaken for one day. It was then worked up essentially as described in Experiment 1. The amount of the semicarbazone of dehydroandrosterone recovered was 0.11 g. The amount of ketone therefore which reacted was 91%.

Experiment 4. In this experiment a mixture of benzene and diïsopropyl ether was used as the solvent. Therefore, a higher temperature of refluxing was obtained. Three grams of dehydroandrosterone and 1.31 cc. (1 mole) of ethyl α-chloropropionate were dissolved in a mixture of 20 cc. of dry benzene and 20 cc. of diïsopropyl ether. The solution was cooled to −80° and one mole of powdered sodium ethoxide was added (from 0.27 g. of sodium). The mixture was allowed to stand overnight at room temperature and then refluxed for four hours. Another equivalent of the α-chloro ester and of sodium ethoxide was then added, and heating under reflux was continued for an additional four hours. The product was then worked up as described in Experiment 2. The amount of free glycidic acid obtained indicated a 58% conversion. The ether layer, containing the unchanged dehydroandrosterone, neutral products of rearrangement, and androstenediol, gave a residue which weighed 1.55 g.

Recovery of unchanged dehydroandrosterone.—In all experiments the unchanged dehydroandrosterone was recovered as the semicarbazone during some stage of the procedure. Thus, in Experiment 4 above, the excess hormone was separated from androstenediol in this way. The crude semicarbazone was hydrolyzed in the usual manner. The ketone was sublimed in a high vacuum and recrystallized; m.p. 146–148°.

Isolation of androstenediol.—In the earlier stages of this research attempts to purify the excess dehydroandrosterone by simple recrystallization failed. In this

way it was found that the products of the reaction were contaminated with another material, androstenediol. It was isolated in the following manner. The residue (containing the neutral products) from the ether extract of the alkaline solution from the saponification of the products of condensation, Experiment 2, was refluxed for two hours with an alcoholic solution of semicarbazide acetate. After separation of the semicarbazone of dehydroandrosterone and other ketones, the ether extract was dried and evaporated, and the residue was sublimed in a high vacuum at 140–150°. The sublimate, wt. 35 mg., was crystallized from acetone. Crystals were obtained which melted at 170–173°. The melting point of a mixture with an authentic specimen of androstenediol (m.p. 172°) was not depressed.

The semicarbazone fraction (wt. 0.51 g.) was hydrolyzed as usual, and the product was recrystallized from benzene and petroleum ether three times without obtaining a pure compound. Other ketones (pregnenolones) besides dehydroandrosterone were found to be present. The following experiments show how they were isolated.

Isolation of the pregnenolones.—(*A*) A solution of 0.71 g. of dehydroandrosterone in dry ether was boiled under reflux with 0.57 g. (1.75 mole) of ethyl α-chloropropionate and the sodium ethoxide from 0.11 g. (1.9 mole) of sodium for 56 hours. Water and ether were then added, and after the ether layer was washed free of alkali, it was dried over sodium sulfate and evaporated. The excess dehydroandrosterone was then removed as the semicarbazone as in Experiment 1. In this manner 0.05 g. of the semicarbazone was obtained, showing the conversion to have been practically complete.

The ether extract from the semicarbazone was dried and evaporated, and the residue was taken up in acetone. As crystals did not form quickly, the acetone was evaporated, and the residue was taken up in alcohol and boiled under reflux with an excess of 2 *N* sodium hydroxide for two hours. The solution was then diluted, and extracted with ether. The aqueous layer was acidified, and the free unrearranged glycidic acid was recovered. The amorphous residue from the dried ether extract was partially crystallized. It was taken up in alcohol and treated with sodium acetate and semicarbazide hydrochloride as usual. A semicarbazone was obtained which melted at 215–223°; yield, 50 mg.

This semicarbazone was hydrolyzed in the usual manner. The mixture of ketones so obtained melted at 120–124°. Distillation in a high vacuum (115–125°) gave a product which on recrystallization from acetone melted at 153–159° (uncorr.); yield, 12 mg.

Anal. Calc'd for $C_{21}H_{32}O_2$: C, 79.73; H, 10.18.
Found, C, 79.69; H, 10.60; 10.4.

(*B*) The ether solution containing the materials from which the dehydroandrosterone semicarbazone had been removed (Experiment 1) was evaporated and warmed for 20 minutes with about 15 cc. of alcohol containing 0.5 g. of sodium. The solution was diluted, and extracted with ether. The ether solution was dried and evaporated. A residue was obtained which was acetylated.

The acetic anhydride solution was then poured into water and ether. The ether solution was extracted with a 10% solution of sodium carbonate and then worked up in the usual manner. The residue was dissolved in alcohol and treated with semicarbazide hydrochloride and sodium acetate. On working up the products, 40 mg. of a semicarbazone acetate, m.p. 241–243°, was obtained.

This semicarbazone was hydrolyzed in the usual way and gave a ketonic material which was sublimed in a high vacuum. The product so obtained was recrystallized from dilute alcohol (70%). Crystals were obtained which melted at 124–130°; yield, 15 mg.

This material was united with that obtained in *A* and the same material from two other experiments. Since it was regarded as a mixture of isomeric pregnenolones, it was treated according to the method of Butenandt and Fleischer[7] for the separation of these isomers. The pregnenolone so obtained melted at 189°, and gave no melting point depression with an authentic specimen. Small amounts of Δ^5-iso-pregnenolone were also isolated. Other ketonic material also seemed to be present.

Action of hydrogen chloride on the glycidic acid.—As stated in the general discussion, many attempts were made to increase the yields of the pregnenolones formed by the rearrangement. They were generally unsuccessful. The action of hydrogen chloride on the acid, however, is of interest, and the details of the experiments follow.

Experiment *A*. A solution of one gram of the glycidic acid in 25 cc. of anhydrous ether was saturated with dry hydrogen chloride at 0° and allowed to stand overnight at room temperature. The ether was partially evaporated to remove the major portion of the excess hydrogen chloride. The solution was then diluted with ether and washed repeatedly with distilled water until the washings were free of chloride ion. The dried ether solution yielded, on evaporation, a non-crystalline residue which gave a strong Beilstein test for halogen.

This crude chloro acid was heated on the steam bath for one hour with 15 cc. of pyridine which contained two grams of semicarbazide hydrochloride dissolved in 5 cc. of water. Addition of ether and water gave an insoluble material. The water solution was made acid to extract the pyridine, and the precipitate was filtered and dried. Recrystallization from alcohol gave crystals melting at 227° (uncorr.); weight of crude semicarbazone, 420 mg.

The semicarbazone was dissolved in 10 cc. of alcohol which contained 5 cc. of 5 *N* sulfuric acid, and boiled under reflux for three hours. From an ether extract of the resulting mixture, 300 mg. of neutral non-crystalline material was obtained. This was sublimed in a high vacuum, giving at 110–130° about 150 mg. of a mixture of crystals and oil. The crystals, on treatment with petroleum ether and drying, melted at 110–114°.

Experiment *B*. In this experiment, performed for us by Dr. E. Gilmore Ford, the crude chlorohydroxy acid obtained as in *A* was dissolved in pyridine and refluxed for approximately two hours. The pyridine was removed by vacuum distillation, and the residue was treated with semicarbazide hydrochloride in the usual manner. A semicarbazone was obtained which melted at 226–235°. The ether solution from the semicarbazone was evaporated and found to contain free glycidic acid. Thus, the velocity of reformation of the glycidic acid is comparable to the velocity of decarboxylation and rearrangement.

Preparation of progesterone.—The mixture of ketones obtained by hydrolysis from 0.5 g. of the semicarbazone described above was dissolved in 20 cc. of glacial acetic acid, treated with bromine in the usual manner and oxidized at room temperature for seventeen hours with chromic acid (one gram of chromic oxide in 1 cc. of water and 5 cc. of glacial acetic acid.) The organic material was precipitated with water, and after solution in acetic acid, was debrominated with zinc. Recrystallization of the crude ketone so produced gave a product which melted at 126–128°.

Action of pyridine on cholesterol hydrochloride.—(This experiment was performed by Dr. E. Gilmore Ford.) A solution of 6 g. of cholesterol hydrochloride (m.p. 164°) in 30 cc. of pyridine and 6 cc. of water was refluxed for one hour. The solution was then worked up in the usual manner, and the product so obtained was systematically recrystallized from alcohol. After many recrystallizations three crops of crystals were obtained which were identified as (*1*) cholesterol, (*2*) the molecular compound of cholesterol and allocholesterol, and (*3*) allocholesterol.

We wish to take this opportunity to express our thanks to Merck and Company, Inc., Rahway, New Jersey, for certain analyses and for a grant-in-aid for this work, and to Dr. E. Gilmore Ford of this laboratory for certain experiments herein described.

SUMMARY

A study has been made of the Darzens condensation of ethyl α-chloropropionate with cyclohexanone, cyclopentanone, and dehydroandrosterone.

Yields of the corresponding glycidic ester produced in this condensation are increased by using an excess of the α-halogenated ester and of the condensing agent; ethyl α-chloropropionate is more efficient than the α-bromo ester in this condensation.

A modified procedure, giving good yields in the Darzens condensation in a shorter time than previously used has been developed.

Two new methods for the rearrangement of glycidic acids have been developed.

The Darzens condensation has been applied for the first time to cyclopentanone and to dehydroandrosterone. A part of the latter ketone is reduced to androstenediol by the action of the condensing agent. Rearrangement of the condensation product under suitable conditions gives low yields of pregnenolone and other isomeric ketones.

Dehydroandrosterone behaves like an aromatic aldehyde in respect to the stability of its glycidic acid, and like an aromatic ketone in that it is partially reduced to androstenediol.

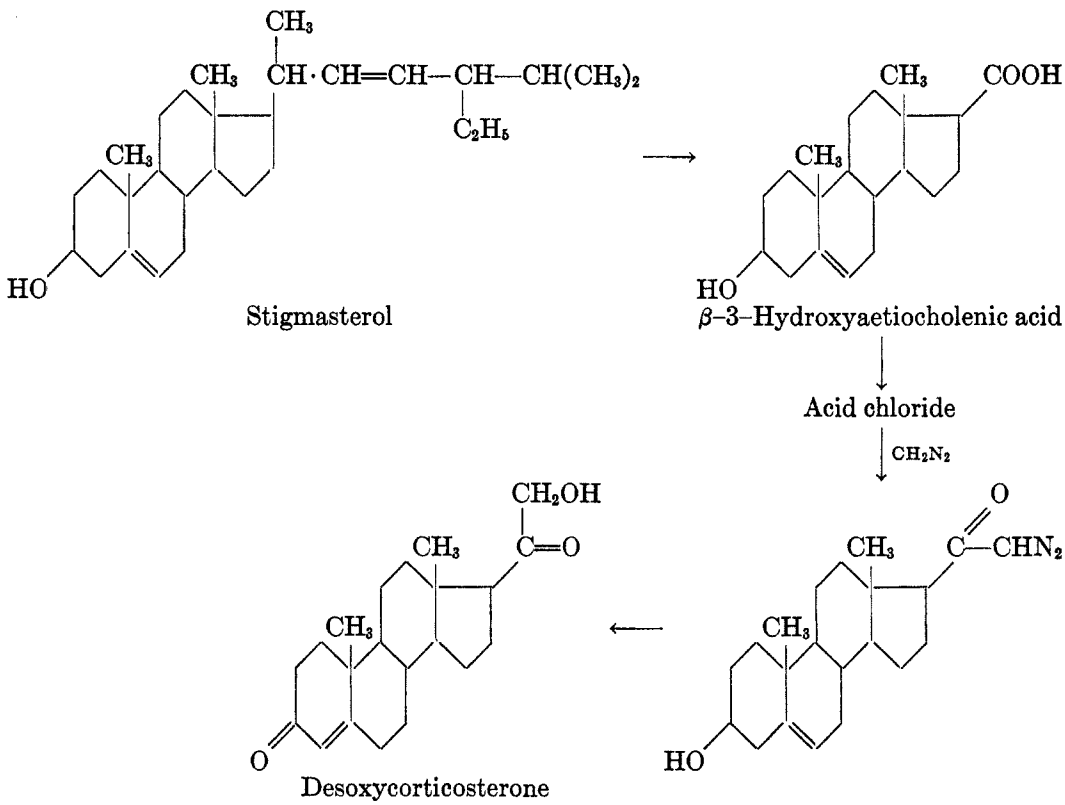
[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, PRINCETON, NEW JERSEY]

THE SYNTHESIS OF CERTAIN SUBSTITUTED ALICYCLIC METHYL KETONES. II. HYDROXYMETHYL KETONES

WILLIS AARON YARNALL* AND EVERETT S. WALLIS

Received March 24, 1939

For some time past work has been in progress in this laboratory on the preparation of steroid compounds with a side-chain of the structure, —CH(—C(=O)—CH$_2$OH), the characteristic side-chain of corticosterone. Recently, Reichstein[1] has obtained desoxycorticosterone by the following series of reactions:



* Research Assistant on special funds from Merck and Company, Inc., Rahway, N. J.

[1] STEIGER AND REICHSTEIN, *Helv. Chim. Acta*, **20**, 1040, 1164 (1937).

Since β-3-hydroxyaetiocholenic acid is an extremely expensive compound it would be both interesting and useful if a synthesis of desoxycorticosterone using dehydroandrosterone as the starting material could be developed. In a preliminary study of this problem, the results of which are described in this paper, certain condensations with more simple alicyclic compounds have been investigated.

In our first experiments, condensations of the Darzens type were attempted using cyclohexanone and α,β-substituted esters. When the reaction was carried out with ethyl α,β-dichloropropionate, ethyl α-chloroacrylate was found to be the main product of the reaction. Under all the conditions studied, hydrogen chloride was split out by the condensing agent.

$$CH_2Cl—CHCl—COOC_2H_5 \xrightarrow{NaOC_2H_5} CH_2{=}CCl—COOC_2H_5$$

With the corresponding β-hydroxy-α-chloro ester, practically no condensation took place. The cyclohexanone was recovered almost quantitatively, and this method was abandoned.

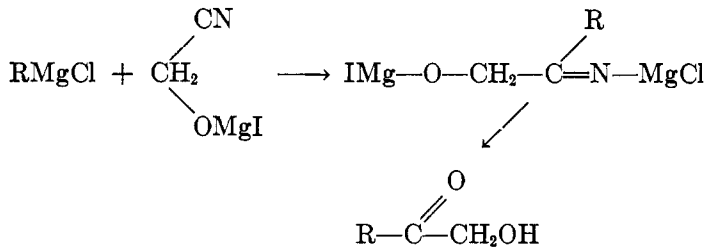
In the course of this work, however, an excellent procedure was developed for the preparation of α,β-dichloropropionic acid. The chlorination of acrolein was studied, and the dichloro aldehyde so obtained was oxidized with nitric acid. A search of the literature revealed that acrolein had been chlorinated in carbon bisulfide to give the corresponding dichloride[2] in a yield of 74 per cent. We observed that when the chlorination was carried out without a solvent, and the compound so formed was immediately oxidized with nitric acid, excellent yields (85 per cent.) of pure α,β-dichloropropionic acid were obtained.

Our next experiments involved a study of the action of Grignard reagents on formaldehyde cyanohydrin. This reaction is of special interest in this connection. In his preparation of α-ketols Gautier[3] applied the Blaise reaction to hydroxy nitriles.

$$CH_3CH(OH)CN + 2C_2H_5MgBr \longrightarrow CH_3CH(OMgBr)—C(=N—MgBr)—C_2H_5 \longrightarrow CH_3CH(OH)—C(=O)—C_2H_5$$

[2] Moureau and Boismann, *Ann. Chim.*, **15**, 158 (1921).
[3] Gautier, *Compt. rend.*, **152**, 1100, 1259 (1911).

Two other compounds of this type were also prepared by him. Other investigators have likewise studied this reaction. Asahina[4] has prepared benzoïn, isobenzfuroïn, *o*- and *p*-methoxybenzoïn, etc. by the action of phenylmagnesium bromide on cyanohydrins. Guerden[5] has studied the action of Grignard reagents of methyl, ethyl, phenyl, and benzyl bromides on keto cyanohydrins, and reports that tertiary alcohols are produced almost exclusively. In his studies on the preparation of certain benzoïns Weissberger[6] also has carried out this reaction. Other experimental results on this problem have been described by J. A. Smith.[7] As far as can be ascertained, however, this condensation has not been applied to alicyclic halides. Therefore a study of this type of reaction was made. For this purpose cyclohexyl, cyclopentyl, and 2-methylcyclopentyl chlorides were chosen. Glycollic acid nitrile was the cyanohydrin employed. In all of our experiments the hydroxyl group of the cyanohydrin was protected by the addition of one equivalent of methylmagnesium iodide. The cyclic chlorides were obtained



in good yields by the method employed by Hartman[8] for the preparation of cyclohexyl chloride. It is to be noted that cyclopentyl chloride has not been previously prepared by this method, and that 2-methylcyclopentyl chloride is a new compound.

It was observed that very little reaction took place when an ether solution of one mole of cyclohexylmagnesium chloride and one mole of the Grignard compound, I—Mg—O—CH_2—CN, was allowed to stand overnight. The procedure, therefore, had to be modified. The ether was evaporated, and dry benzene added to insure a higher reflux temperature. The keto alcohols were isolated in the form of their dinitrobenzoates, the physical properties of which are to be found in the experimental part of this paper. Yields varying from 8–19 per cent. were obtained. The most plausible reason for these low yields is that the Grignard reagents decom-

[4] Asahina and Terasaka, *J. Pharm. Soc. Japan*, **494**, 19 (1923).
[5] Guerden, *Bull. Acad. Roy. Belg.*, [5], **11**, 701 (1925).
[6] Weissberger, Strasser, Mainz, and Schwartze, *Ann.*, **478**, 112 (1930).
[7] Smith, *Ber.*, **64**, 427 (1931).
[8] *Organic Syntheses*, Coll. Vol. I, p. 183.

pose the hydroxy nitrile to formaldehyde, and then react with this aldehyde to give ethyl alcohol or (and) the alicyclic carbinol.

EXPERIMENTAL

Preparation of α,β-dichloropropionic acid, CH_2Cl-$CHCl$-$COOH$.—(*a*) From allyl alcohol: one hundred nineteen grams of dry allyl alcohol was chlorinated, and the resulting dichlorohydrin was oxidized with nitric acid. Fifty-two grams of dichloropropionic acid was produced; b.p. 119–128°/21 mm.; yield, 18%. (*b*) From acrolein: two hundred grams of acrolein was kept below a temperature of −5° and stirred while dry chlorine gas was passed in until a slight excess was present. When no more chlorine was absorbed, the product was immediately placed in a dropping funnel and slowly added to a mixture of 400 g. of fuming nitric acid and 800 g. of concentrated nitric acid. The temperature was maintained at 40–50°. To insure complete oxidation the mixture was finally heated on a steam bath for one hour. The nitric acid was then removed by vacuum distillation. The residue was distilled at 15 mm. pressure. The main portion distilled constantly at 118°/15 mm. giving 345 g. of an acid which solidified to beautiful crystals of melting point 49–50°. Yield, 85%, for the two steps of the reaction.

Preparation of ethyl α,β-dichloropropionate, CH_2Cl-$CHClCOOC_2H_5$.—This ester was prepared by saturating a cold absolute alcohol solution of the above acid with dry hydrogen chloride at 0°, and allowing it to stand overnight. In this manner the ester was obtained in yields of 74–78%: b.p. 76–77°/15 mm.

Preparation of cyclopentyl chloride.—The cyclopentanone used in these experiments was prepared from adipic acid.[9] One hundred fifty-six grams of the ketone was obtained from 400 g. of adipic acid; yield, 68%.

The cyclopentanol was prepared by the reduction of 60 g. of cyclopentanone with sodium;[10] yield, 28 g.

Twenty-five grams of cyclopentanol was refluxed for three hours, with stirring, with twice its volume of concentrated hydrochloric acid and 20 g. of anhydrous calcium chloride; yield, 13.9 g.; b.p. 113.5–114.5°/752 mm.

Preparation of 2-methylcyclopentyl chloride.—2-Methylcyclopentanone was prepared by the method of Cornubert and Borrel.[11] The ketone (36 g.) was reduced with sodium. Twenty-six grams of 2-methylcyclopentanol was obtained. This material was then converted into the corresponding chloride in the usual manner. The halide so obtained boiled at 122–124° at atmospheric pressure, and tended to decompose. It was, therefore, again distilled at reduced pressure.

Anal.. Calc'd for $C_6H_{11}Cl$: C, 60.75; H, 9.36.
Found: C, 60.70, 60.97; H, 9.29, 9.48.

The condensation of cyclohexyl chloride with glycollic acid nitrile.—Glycollic acid nitrile was prepared according to the method of Polstorff and Meyer[12] by the addition of potassium cyanide to a solution of formalin. The yields were about 15%.

Cyclohexyl chloride was prepared according to the method of Hartman.[8] It was found that about two hours of stirring on a water bath under a reflux condenser, protected by a drying tube, gave excellent results.

An ether solution of methylmagnesium iodide was prepared by gradually adding 4.8 cc. of methyl iodide in 40 cc. of dry ether to about 3 g. of bright magnesium turn-

[9] *Organic Syntheses*, Coll. Vol. I, p. 187.
[10] *Chem. Abstr.* **27**, 1329 (1933).
[11] CORNUBERT AND BORREL, *Bull. soc. chim.*, [4], **47**, 302 (1930).
[12] POLSTORFF AND MEYER, *Ber.*, **45**, 1911 (1912).

ings. This Grignard solution was then slowly added with stirring to a solution of 4.0 cc. of glycollic acid nitrile in 100 cc. of anhydrous ether. Throughout the reaction a temperature of 0–5° was maintained. Methane was evolved, and a white, flocculent precipitate of the reaction product was formed. In a separate flask a Grignard reagent was prepared from 9.2 cc. of cyclohexyl chloride. This reagent was added slowly to the ether suspension of the magnesium compound, $CH_2(CN)$-O-MgI, described above. The mixture so produced was warmed on a water bath, and after the ether was refluxing well the condenser was removed, and the ether was allowed to evaporate. When the ether was nearly gone 100 cc. of warm, dry benzene were added, and the reflux condenser was replaced. The suspension in benzene was then refluxed for two and a half hours. At the end of this time 12 g. of 3-5-dinitrobenzoyl chloride was added, followed by an addition of 50 cc. of dry pyridine. A heavy precipitate was produced. After warming on the steam bath for one-half hour the product was worked up in the usual manner. The crude crystalline dinitrobenzoate so obtained (7.8 g.) was dissolved in ether and decolorized with charcoal. Recrystallization from alcohol gave 5.1 g. of needle-like crystals which melted at 110–111°.

Anal. Calc'd for $C_{15}H_{16}N_2O_7$: C, 53.57; H, 4.80; N, 8.33.
Found: C, 53.55; H, 5.10; N, 8.5

Preparation of the 3,5-dinitrobenzoate of hydroxymethyl cyclopentyl ketone.—This compound was prepared in a manner essentially the same as the one described for the dinitrobenzoate of hydroxymethyl cyclohexyl ketone. One-tenth mole portions were used. A crystalline dinitrobenzoate was obtained which melted at 100°; yield, 3.8 g.

Anal. Calc'd for $C_{14}H_{14}N_2O_7$: C, 52.17; H, 4.38; N, 8.69.
Found: C, 52.40; H, 4.40; N, 8.77.

Preparation of the 3,5-dinitrobenzoate of hydroxymethyl 2-methylcyclopentyl ketone.—2-Methylcyclopentyl chloride was used in this preparation. The method, essentially the same as that described above, gave a crystalline product which melted at 103°. The compound reduced an ammoniacal alcoholic silver nitrate solution.

Anal. Calc'd for $C_{15}H_{16}N_2O_7$: C, 53.53; H, 4.80.
Found: C, 53.59, 53.27; H, 4.83, 4.89.

We wish to take this opportunity to express our thanks to Merck and Company, Inc., Rahway, N. J. for a grant-in-aid for this work, for certain analyses which are published herein.

SUMMARY

The action of certain Grignard reagents on formaldehyde cyanohydrin has been studied.

The following new compounds have been prepared and characterized: 2-methylcyclopentyl chloride, and the 3,5-dinitrobenzoates of cyclohexyl, cyclopentyl, and 2-methylcyclopentylhydroxymethyl ketones.

In our hands the Darzens condensation for the preparation of these compounds, involving the use of either α,β-dichloro or α-chloro-β-hydroxy esters was unsuccessful.

An excellent method for the preparation of α,β-dichloropropionic acid in large-scale laboratory runs has been developed.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

ALLOSTROPHANTHIDIN

EDITH BLOCH* AND ROBERT C. ELDERFIELD

Received March 28, 1939

During recent years the chemical structures of a large number of cardiac drugs of both plant and animal origin have been elucidated. The former occur as glycosides and the latter as conjugations of an "aglycone" with suberylarginine. The majority of aglycones of plant origin have been shown to contain the cyclopentanophenanthrene ring system, hydroxylated in varying degrees and carrying a characteristic $\Delta^{\beta\text{-}\gamma}$-unsaturated lactone group as the side-chain in position 17. Glycosides of such aglycones, containing one to three sugar residues have been isolated.[1]

It is well known that digitalis preparations lose part of their cardiac activity on storage. While no exact information concerning the cause or nature of this loss of activity is available, various empirical stabilizing measures have been employed, such as buffering of aqueous tinctures or storage of the carefully dried leaves *in vacuo*.

A possible cause for such inactivation may be found in two observations. Jacobs, in a study of the action of enzymes present in *Strophanthus kombé* seeds on the glycosides of the seeds found that at least three enzymes are present. The first two[2] act as glucoside-splitting enzymes and remove one or more of the glucose residues from the original glycoside. The third enzyme[3] accomplishes a stereochemical isomerization of the aglycone portion of the glycoside molecule with resultant marked loss of physiological activity. Thus, 4 mg. of isomerized cymarin (allocymarin) failed to kill a 25-g. frog, whereas 0.015 mg. of cymarin is lethal to such an animal. Jacobs clearly showed that isomerization involved the aglycone portion of the cymarin molecule, since the same sugar, cymarose, was obtained from both the active and the inactive glycosides. Further, this change in the aglycone is purely stereochemical, as the same functional groups are present in both aglycones.

In a later study on the glycosides of *Strophanthus eminii*, Jacobs and

* This work was carried out during tenure of the Hernheim fellowship by one of us (E. B.).

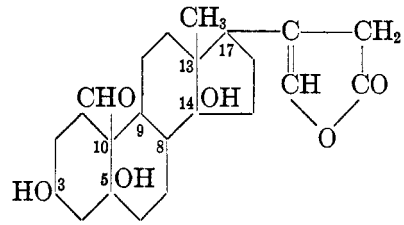
[1] ELDERFIELD, *Chem. Rev.*, **17**, 187 (1935); TSCHESCHE, *Erg. Physiol.*, **38**, 31 (1936).

[2] JACOBS AND HOFFMANN, *J. Biol. Chem.*, **57**, 569 (1923); **67**, 609 (1926); **69**, 153 (1926); STOLL, RENZ, AND KREIS, *Helv. Chim. Acta*, **20**, 1484 (1937).

[3] JACOBS, *J. Biol. Chem.*, **88**, 519 (1930).

Bigelow[4] found that a similar isomerization occurred. An aglycone, presumably isomeric with periplogenin, was isolated as its trianhydro derivative from the hydrolysis products of a comparatively inactive bioside. This trianhydro derivative was different from the corresponding substance prepared from active periplogenin. Lamb and Smith[5] confirmed these observations, and succeeded in isolating several additional glycosides. Among these were the above allocymarin and a substance called by them alloemicymarin. The latter name is unfortunate, since the glycoside presumably is one of alloperiplogenin and digitalose. Inasmuch as both of these inactive allo derivatives were found either after digestion of the seeds in aqueous suspension or after prolonged storage of the seeds themselves, it is obvious that a further study of the changes in the aglycone molecule which take place on allomerization would throw considerable light on the changes occurring during the deterioration of pharmaceutical preparations of similar drugs.

Since the change to allostrophanthidin is purely one involving the stereochemistry of the aglycone, eight possible centers of asymmetry can be considered as being involved, namely carbon atoms 3, 5, 8, 9, 10, 13, 14, and 17 (I). However it seems reasonable to assume that those bearing no functional group, namely carbon atoms, 8, 9, and 13 may be eliminated



I

from consideration in this respect on the basis of current theories of enzyme action. Furthermore, by adopting the conventional practice of regarding the substituent on carbon atom 10 as projecting out from the plane of the molecule, this center may also be eliminated by being chosen as a fixed point of reference. Moreover, since a similar change occurs both in strophanthidin, which carries an aldehyde group in this position, and in periplogenin, which carries a similarly located methyl group, inversion at carbon atom 10 seems excluded.

It is known from the observations of Tschesche and Bohle[6] and Chen, Chen, and Anderson[7], that changes in the relative configurations of carbon

[4] Jacobs and Bigelow, *ibid.*, **99**, 521 (1933).
[5] Lamb and Smith, *J. Chem. Soc.*, 1936, 442.
[6] Tschesche and Bohle, *Ber.*, **69**, 2368, 2443 (1936).
[7] Chen, Chen, and Anderson, *J. Am. Pharm. Assoc.*, **25**, 579 (1936).

atoms 3, 5, and 10 in certain cardiac aglycones produce marked changes in physiological activity (Table I). From this it is obvious, that uzarin at least approaches allocymarin in lack of activity, and further, that the asymmetric centers at carbon atoms 3 and 5 become distinct possibilities as sources of the allomerization process.

Information at present available indicates a *cis* arrangement of the aldehyde group on carbon atom 10 and the hydroxyl group on carbon atom 3 in strophanthidin. This conclusion is based on the ready formation of oxidic bridges between these two groups. In addition, deductions of Tschesche and Bohle[6] from observations of Jacobs and Elderfield[8] on the cyanohydrins from dihydrostrophanthidin indicate a *cis* linkage of rings I and II. A possible inversion at carbon atom 5 in allocymarin would then bring its physiological properties in line with those of uzarin.

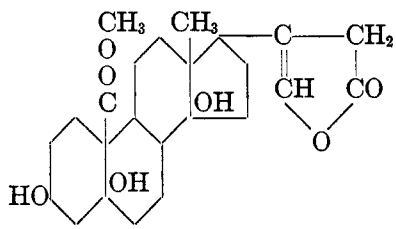
Neither strophanthidin nor allostrophanthidin give precipitates with digitonin, either in 90 per cent. alcoholic or 50 per cent. methyl alcoholic

TABLE I

CONFIGURATION AND PHYSIOLOGICAL ACTIVITY

STEREOMER	STEREOCHEMICAL ARRANGEMENT RELATIVE TO C_{10}	MIN. SYSTOLIC DOSE	
		Cat	Frog
Digitoxin	*trans* 3, *cis* 5	0.33 mg./kg.	0.0080 mg./g.
Thevetin	*cis* 3, *cis* 5	0.92 mg./kg.	0.0045 mg./g.
Uzarin	*cis* 3, *trans* 5	5.08 mg./kg.	1.5000 mg./g.

solution. However, too much weight cannot be placed on this observation, since the influence of the aldehyde group on the digitonin reaction is unknown. Therefore successive destruction of the asymmetric centers on carbon atoms 3 and 5 was carried out, starting from both strophanthidinic acid methyl ester and the corresponding allo derivative. If either of these two centers is exclusively involved in the allomerization, identical compounds should be obtained at some stage of this series of reactions.



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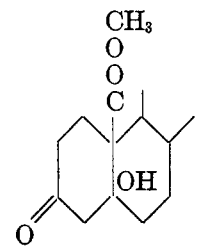
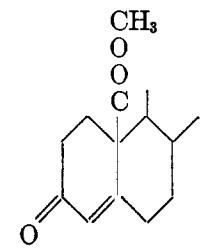


III

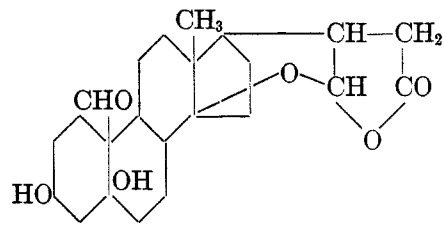


IV

[8] JACOBS AND ELDERFIELD, *J. Biol. Chem.*, **113**, 625 (1936).

Strophanthidinic acid methyl ester (II) has already been prepared by Jacobs[9] and has been converted to strophanthidonic acid methyl ester (III) and anhydrostrophanthidonic acid methyl ester (IV) by Jacobs and Gustus[10]. We have carried out similar transformations, starting with allostrophanthidin. Neither allostrophanthidonic acid methyl ester, nor its anhydro derivative is identical with the corresponding compound from strophanthidin. Therefore carbon atoms 3 and 5 may be definitely eliminated from further discussion.

Jacobs[3] observed that allostrophanthidin failed to undergo isomerization under the influence of alkali with the formation of an isoaglycone—a reaction highly characteristic of the physiologically active aglycones[1] as well as of the comparatively inactive uzarin[11] and adynerin[12]. Tschesche and Bohle[12] also observed a similar failure of Lamb and Smith's alloemicymarigenin to undergo iso-compound formation. If it be assumed, as a study of the atomic model indicates, that a *cis* configuration of the hydroxyl group on carbon atom 14 relative to the side-chain on carbon atom 17 is necessary for the formation of the oxidic bridge in the iso compound (V)[13], then the failure of the alloaglycones to form iso compounds must be attributable to a *trans*-configuration of these two groups. Such an



V

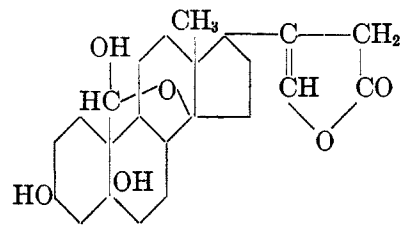
arrangement would then be due either to inversion at carbon atom 14 or 17 during the allomerization. Tschesche and Bohle[12] prefer the latter, although no new experimental evidence is offered.

In order to make a decision between these two remaining alternatives it was planned to attempt the conversion of allostrophanthidin into its trianhydro derivative, the side-chain of which could then be degraded in a manner similar to that described by Jacobs and Gustus[14] with eventual destruction of the asymmetric center at carbon atom 17. Jacobs[3] reported

[9] JACOBS, *ibid.*, **57**, 553 (1923).
[10] JACOBS AND GUSTUS, *ibid.*, **74**, 795 (1927).
[11] TSCHESCHE AND BOHLE, *Ber.*, **68**, 2252 (1935).
[12] TSCHESCHE AND BOHLE, *ibid.*, **71**, 654, 1927 (1938).
[13] JACOBS AND ELDERFIELD, *J. Biol. Chem.*, **108**, 497 (1935).
[14] JACOBS AND GUSTUS, *ibid.*, **74**, 805 (1927).

that, when the preparation of trianhydroallostrophanthidin from the dianhydro compound was attempted a chlorine-containing substance was formed, for which no satisfactory analytical figures could be obtained. We have checked this. When dianhydroallostrophanthidin is dissolved in concentrated hydrochloric acid, rapid crystallization of the chloro derivative occurs. However, on recrystallization, or on prolonged exposure to the air, the substance loses chlorine to yield the original dianhydroallostrophanthidin. Likewise all attempts to obtain the desired trianhydro derivative by the use of hot hydrochloric acid or saturated alcoholic hydrogen chloride failed.

However, a study of the action of concentrated hydrochloric acid on allostrophanthidin itself furnished information that is significant. Jacobs and Collins[15] obtained pseudostrophanthidin (VI) in 10 to 15 per cent. yield on similar treatment of strophanthidin. This substance did not



VI

form an oxime, and gave a non-crystalline benzoate, which was not further characterized. Hence it was assigned a stable oxidic ring structure, which is possible only if the hydroxyl group on carbon atom 14 and the aldehyde group on carbon atom 10 bear a *cis* relationship to each other. When allostrophanthidin is dissolved in concentrated hydrochloric acid, a nearly quantitative yield of a chloro derivative is obtained. Like the chloro derivative from dianhydroallostrophanthidin this is unstable, but in contrast to the latter, the present compound yields an anhydro derivative of allostrophanthidin on recrystallization from dilute acetone or on treatment with dilute ammonia. The anhydro derivative forms both on oxime and a monobenzoate, indicating retention of both the aldehyde group on carbon atom 10 and the secondary hydroxyl group on carbon atom 3. No trace of a pseudoallostrophanthidin was found in the products of the above reaction. Therefore, it seems probable that in allostrophanthidin the hydroxyl group on carbon atom 14 has undergone a reversal, so that it is now *trans* to the aldehyde group on carbon atom 10 and to the side-chain

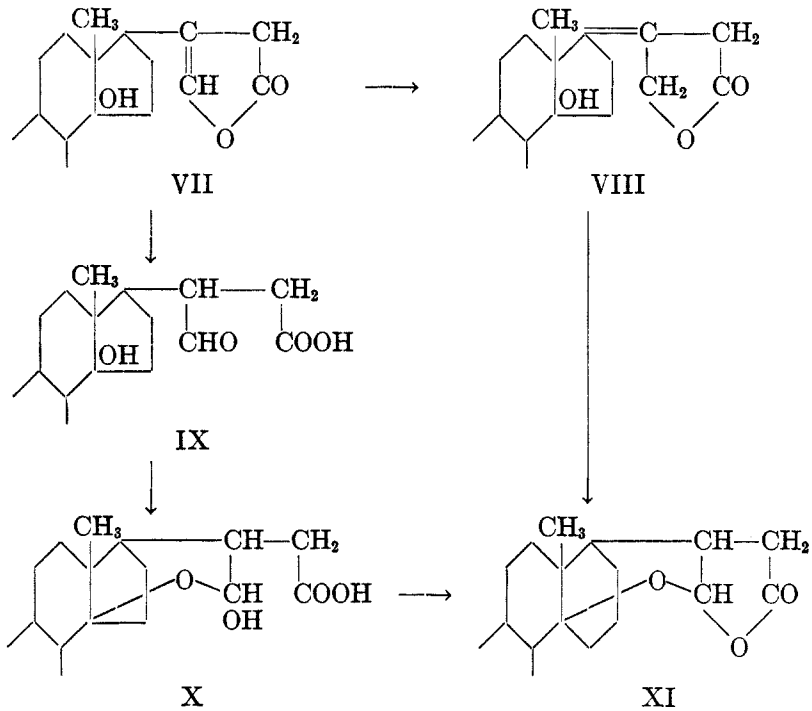
[15] JACOBS AND COLLINS, *ibid.*, **63**, 123 (1925); **65**, 491 (1926); JACOBS AND ELDERFIELD, *ibid.*, **108**, 693 (1935).

on carbon atom 17, an arrangement which would not permit the formation of the stable oxidic bridge which is present in pseudostrophanthidin.

Finally, we have reëxamined the action of alkali on allostrophanthidin and, in common with Jacobs[3], have found that, although the substance is changed, no crystalline products could be isolated even after using a variety of procedures. Likewise, oxidation of saponified allostrophanthidin with hypobromite failed to yield crystalline derivatives.

From the above discussion, it can be concluded that the isomerization involved in the allomerization of cymarin consists in an inversion of one of the asymmetric centers of the strophanthidin molecule, located at carbon atom 14 or 17. We are inclined to favor carbon atom 14 as the seat of this inversion, although carbon atom 17 cannot be excluded. A parallel for such an isomerization on carbon atom 14 is found in the observations of Hirschmann and Wintersteiner[16] on isoequilin. Against this view must be cited the more numerous cases of stereoisomerism in natural steroids in which carbon atom 17 is involved.[17]

The inability of substances containing a *trans* configuration of carbon



[16] HIRSCHMANN AND WINTERSTEINER, *ibid.*, **126**, 735 (1938).
[17] REICHSTEIN AND GAETZI, *Helv. Chim. Acta*, **21**, 1185 (1938).

atoms 14 and 17 to form iso derivatives is difficult to understand, if one accepts the mechanism for iso-compound formation suggested by Jacobs and Elderfield[18] (VII, VIII, XI). It would be expected that the formation of iso compounds would proceed at least to a certain extent, irrespective of the configuration originally present. However the failure of aglycones of the allo series to undergo iso-compound formation can be rationalized on the basis of the mechanism for the formation of such derivatives originally put forward by Jacobs and Gustus[18] (VII, IX, X, XI). This was subsequently withdrawn on the basis of the observation that preliminary saponification of the lactone group is presumably not necessary for iso-compound formation[19]. It is possible that a change in one asymmetric center of the aglycone molecule may profoundly affect the chemical behavior of substituents on some other asymmetric center in a manner at present obscure.

We wish to express our appreciation to S. B. Penick and Company, New York City, who generously contributed the strophanthus seeds used in this investigation.

EXPERIMENTAL

Allostrophanthidinic acid.—Two and one-half grams of finely-powdered allostrophanthidin was suspended in 100 cc. of dry acetone (distilled from potassium permanganate), the mixture was chilled to about 5°, and 1.25 g. of finely-powdered potassium permanganate was added. The mixture was stirred mechanically and kept at 5° for 8 hrs. with strict exclusion of moisture. The precipitated salts were filtered, washed with acetone, and thoroughly extracted with water. The aqueous extract was concentrated to about 20 cc. and then carefully acidified with acetic acid. On long standing in the refrigerator the acid slowly crystallized. The yield varied from 0.3 to 0.5 g. After recrystallization by careful dilution of a concentrated solution in acetone, the acid formed fine white needles which melted at 247°; $[\alpha]_D^{22}$ 39.2° (c = 0.976 in methanol).

Anal. Calc'd for $C_{23}H_{32}O_7$: C, 65.7; H, 7.7.
Found: C, 65.7; H, 7.8.

From the mother liquors, on addition of about 4 volumes of saturated ammonium sulfate solution, a gummy precipitate appeared. By recrystallization from acetone, a small additional amount of acid could be obtained.

The original acetone filtrate was concentrated to dryness *in vacuo*. The residue was extracted several times with hot chloroform from which about 800 mg. of allostrophanthidin could be recovered.

Allostrophanthidinic acid methyl ester.—The above acid was esterified in acetone solution with diazomethane. After recrystallization by careful dilution of its acetone solution with absolute ether, the ester melted at 263–265°.

Anal. Calc'd for $C_{24}H_{34}O_7$: C, 66.3; H, 7.9.
Found: C, 66.4; H 7.9.

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[18] JACOBS AND GUSTUS, *J. Biol. Chem.*, **74**, 811 (1927).
[19] JACOBS AND COLLINS, *ibid.* **61**, 387 (1924).

Allostrophanthidonic acid methyl ester.—Two hundred fifty milligrams of allostrophanthidinic methyl ester was dissolved in 3 cc. of glacial acetic acid, and, after chilling to about 15°, 0.9 cc. of Kiliani's chromic acid solution was added. After standing for 30 minutes at room temperature, the mixture was diluted to about 50 cc. and then saturated with ammonium sulfate. On rubbing, the keto acid gradually crystallized. After several recrystallizations by careful dilution of its solution in methyl alcohol, it melted at 255–260°. A somewhat purer product was obtained by extraction of the oxidation products with chloroform. The extracts were washed with sodium carbonate solution and with water. The residue, after removal of the chloroform, was taken up in methyl alcohol, and the hot solution was diluted with an equal volume of water. On slow cooling, the substance crystallized in stout prisms, which melted at 258°; $[\alpha]_D^{26}$ 20.1° (c = 0.749 in pyridine).

Strophanthidonic acid methyl ester melts at 161–162° and shows $[\alpha]_D$ 26° in pyridine[10].

Anal. Calc'd for $C_{24}H_{32}O_7$: C, 66.6; H, 7.5.
Found: C, 66.2; H, 7.5.

Monoanhydroallostrophanthidonic Acid Methyl Ester.—One hundred fifty milligrams of crude allostrophanthidonic methyl ester was refluxed for 15 minutes with 2.5 cc. of a mixture of 20 cc. of methyl alcohol and 5 cc. of 10 per cent hydrochloric acid. No crystallization occurred on dilution and saturation with ammonium sulfate. The mixture was therefore extracted exhaustively with chloroform, the extracts were washed and dried, and the solvent was evaporated *in vacuo*. The residue was taken up in acetone, the solution was concentrated *in vacuo* to about 1 cc., and carefully diluted with 5 volumes of anhydrous ether. On rubbing and standing in the refrigerator, the substance slowly crystallized; yield 90 mg. After recrystallization from acetone-ether, the substance formed long rectangular prisms which melted at 138–145°. It is easily soluble in alcohol, acetone, and chloroform; less so in ether and petroleum ether; $[\alpha]_D^{20}$ 118° (c = 0.693 in pyridine).

Monoanhydrostrophanthidonic methyl ester melts between 203° and 213° and shows $[\alpha]_D$ 123° in pyridine[10].

Anal. Calc'd for $C_{24}H_{30}O_6$: C, 69.5; H, 7.3.
Found: C, 69.3; H, 7.3.

Dianhydroallostrophanthidin.—One and four tenths gram of the oxidoethylal of dianhydroallostrophanthidin[3] was refluxed for 30 minutes with 75 cc. of alcoholic hydrochloric acid (5 cc. of concentrated hydrochloric acid in 45 cc. of water and 50 cc. of ethyl alcohol). Solution occurred at once. After cooling, the solution was diluted with 75 cc. of ice water. A crystalline precipitate appeared and was collected by filtration after standing overnight in the refrigerator. The yield was 1.2 g. of fine needles of m.p. 170°. After recrystallization from 95 per cent alcohol, the substance formed clusters of heavy prisms which melted at 172–175°; $[\alpha]_D^{20}$ −123.1° (c = 1.202 in pyridine).

Anal. Calc'd for $C_{23}H_{28}O_4$: C, 75.0; H, 7.7.
Found: C, 75.0; H, 7.8.

When 1 g. of this substance was treated with 10 cc. of concentrated hydrochloric acid, solution occurred at once, but after 15 sec. crystallization started. After 30 minutes, the substance was filtered through a sintered glass funnel and washed several times with ice water; yield about 1 g. The substance contained chlorine and formed fine white needles which melted at 165°.

One hundred milligrams of the above chloro derivative was refluxed for 10 minutes with 2 cc. of alcohol containing 2 drops of 10 per cent ammonia. On cooling, a mass of heavy prisms separated. After 2 recrystallizations from dilute alcohol, the

product was free from chlorine and melted at 173°. The melting point of a mixture with dianhydroallostrophanthidin was 172–175°.

Anal. Calc'd for $C_{23}H_{26}O_3$: C, 78.8; H, 7.5.
Calc'd for $C_{23}H_{28}O_4$: C, 75.0; H, 7.7.
Found: C, 74.8; H, 8.1.

Anhydroallostrophanthidin.—Four and three-tenths grams of allostrophanthidin was dissolved in 20 cc. of hydrochloric acid (sp. gr. 1.19) at 0°. The substance dissolved at once, forming a light-yellow solution. After standing for about 30 min. in the refrigerator, crystallization started. After 2 hours, the crystals were collected on a sintered glass funnel and washed twice with ice water. The yield was 4 g. After recrystallization from dilute acetone, the substance formed fine needles and plates which melted at 175°. It contained chlorine.

Anal. Calc'd for $C_{23}H_{31}ClO_5$: C, 63.4; H, 7.4.
Found: C, 64.5; H, 7.5.

Apparently partial decomposition of the chloro derivative had taken place during recrystallization.

After dilution of the hydrochloric acid mother liquors, an amorphous precipitate slowly deposited. This material, anhydroallostrophanthidin, was recrystallized several times from dilute acetone and from methanol. It formed shining plates and melted at 209°; $[\alpha]_D^{20}$ 119° (c = 0.630 in methanol).

Anal. Calc'd for $C_{23}H_{32}O_6$: C, 68.3; H, 7.9.
Calc'd for $C_{23}H_{30}O_5$: C, 71.5; H, 7.8.
Found: C, 71.5; H, 8.2.

The chlorine-containing product was warmed for 10 minutes in alcohol containing a few drops of ammonia. On cooling and dilution, anhydroallostrophanthidin crystallized in thin plates which melted at 205°; $[\alpha]_D^{20}$ 119° (c=0.257 in alcohol).

Anal. Found: C, 71.8; H, 8.0.

3-Benzoylanhydroallostrophanthidin.—A solution of 0.1 g. of anhydroallostrophanthidin and 0.1 cc. of benzoyl chloride in 2 cc. of pyridine was allowed to stand 24 hours at room temperature, and was then poured onto cracked ice and dilute sulfuric acid. After extraction with chloroform, the benzoate was recrystallized from methanol, and formed thin prisms which melted at 252°.

Anal. Calc'd for $C_{30}H_{34}O_6$: C, 73.4; H, 7.0.
Found: C, 73.8; H, 7.3.

Oxime of anhydroallostrophanthidin.—This was prepared by refluxing anhydroallostrophanthidin with a slight excess of hydroxylamine in alcohol for 4 hours. After concentration and dilution the oxime crystallized. It melted at 182° after recrystallization from alcohol.

Anal. Calc'd for $C_{23}H_{31}NO_5$: N, 3.5. Found: N, 3.4.

The analyses here reported were made by Mr. Saul Gottlieb of these laboratories.

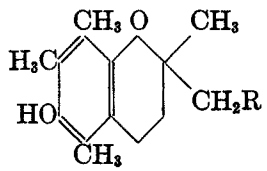
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. IV. THE SYNTHESIS OF TOCOPHEROLS[1,*]

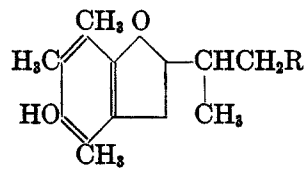
LEE IRVIN SMITH AND HERBERT E. UNGNADE

March 31, 1939

The first recorded synthesis of *dl*-α-tocopherol (I, R = 3,7,11-trimethyldodecyl-1), was that of Karrer, Fritzsche, Ringier, and Salomon.[2]



I



II

These authors, by heating trimethylhydroquinone, phytyl bromide and anhydrous zinc chloride in petroleum ether, obtained the product "in almost quantitative yields."† After chromatographing twice, the substance was a light-yellow oil which had the proper composition, and which was biologically active 100 per cent in 6 mg. doses.

A second synthesis of α-tocopherol was achieved by Bergel, Jacob, Todd, and Work[3] who first used phytol, trimethylhydroquinone, and zinc chloride, and then later modified the synthesis by adding decalin as the solvent.

In our work, we found that much better results were obtained by conducting the condensation in the absence of any catalyst or solvent. Under

[1] Papers I, II, III: *Science*, **88**, 37, 38, 40 (1938).

* Presented (in part) at the 96th meeting of the American Chemical Society, Milwaukee, Sept. 5–9, 1938.

[2] KARRER, FRITZSCHE, RINGIER, AND SALOMON, *Helv. Chim. Acta*, **21**, 520 (1938).

† The nomenclature of derivatives of phytol does not follow accepted rules. Thus the unsaturated alcohol $C_{20}H_{40}O$ from chlorophyll, is called phytol; the saturated hydrocarbon, $C_{20}H_{42}$ is phytane; the diene $C_{20}H_{38}$ is phytadiene. The name phytyl should properly belong to the alkyl group $C_{20}H_{41}$ corresponding to phytane, while the radical $C_{20}H_{39}$ should be called phytenyl and the alcohol $C_{20}H_{40}O$, phytenol. It appears to be accepted practice in this field to use phytol for $C_{20}H_{40}O$; phytyl for the corresponding radical $C_{20}H_{39}$; hydrophytyl or phytanyl for the radical $C_{20}H_{41}$ corresponding to hydrophytyl alcohol or phytanol, $C_{20}H_{42}O$, while the names phytane, phytene, and phytadiene are used for the saturated, ethylenic, and diethylenic hydrocarbons respectively.

[3] (*a*) BERGEL, JACOB, TODD, AND WORK, *Nature*, **142**, 36 (1938); (*b*) *J. Chem. Soc.*, **1938**, 1382.

these circumstances, excellent yields of a fairly pure product are obtained, and what is more important, this product can be purified by high-vacuum distillation alone. This avoids the chromatographic adsorption, which our earlier experiments had shown to give a distinctly inferior product and to entail much loss. Recently Isler[4] has also stressed this point; he found, as we have, that synthetic *dl*-α-tocopherol is very susceptible to oxidation by the air. But Isler also discovered this susceptibility to be increased markedly when the substance is spread over a large surface as it is in the chromatograph tube, or when it is mixed with powders of any sort.

TABLE I

PREPARATION OF PHYTYL BROMIDE

EXPT. NO.	PHYTOL (G.)	Na_2SO_4 (G.)	HBr ABSORBED (G.)	YIELD OF BROMIDE (G.)
1	5.35	0.5	1.94	6
2	5.36	0.5	2.16	6.5
3	10.80	1.8	4.91	13.0

TABLE II

SYNTHESIS OF TOCOPHEROLS

HYDROQUINONE,	G.	PHYTYL BROMIDE (G.)	TEMP., °C.	TIME (HRS.)	PRODUCT (G.)
Trimethyl-	2.0	5.0	125	4	2.44
Trimethyl-	4.0	12.0	105	5	6.0
Trimethyl-	5.0	13.0	105	5	3.0[a]
p-Xylo-	2.0	6.0	105	2.5	None
p-Xylo-	2.0	6.0	150	5	[b]
m-Xylo	2.0	6.5	120	3	[b]

[a] Two grams of hydroquinone was recovered.

[b] The products from these reactions could not be weighed as the material was collected in several small ampoules. Judging from the appearance, the yields were quite good.

Since the beginning of the work on the tocopherols, two structural formulas have been under discussion. The difference between these formulas lies in the size of the hetero ring. In his earlier work, Karrer[2,5] although mentioning both structures, chose II (R = 3,7,11-trimethyldodecyl-1) as the most likely, basing his choice upon the fact that allyl phenol actually does cyclize to a coumaran. But as will be shown in a later paper, allyl bromide itself and γ,γ-disubstituted allyl bromides behave entirely differently in these condensations, the latter giving chromans; hence the

[4] ISLER, *Helv. Chim. Acta*, **21**, 1756 (1938).

[5] KARRER, SALOMON, AND FRITZSCHE, *ibid.*, **21**, 309 (1938).

correct substance to use as an analogue of phytyl bromide is not allyl bromide itself, but a γ,γ-disubstituted allyl bomide. That α-tocopherol is a chroman (I) was first suggested seriously by Fernholz, and that it actually has this structure has been amply shown by the beautiful oxidation experiments of Fernholz[6] and by the elegant degradative experiments of W. John and his collaborators.[7] Recently Karrer[8] reported what appeared to be convincing evidence that trimethylhydroquinone and crotyl bromide condensed to give a chroman, while allyl bromide and the hydroquinone gave a coumaran. This evidence was based upon the fact that both compounds, on gentle oxidation, gave tetrasubstituted quinones, and these quinones, in turn, both gave positive iodoform reactions, indicating that both had, in a side-chain, the group—$CHOHCH_3$. Later[9] when it was discovered that duroquinone itself gave a positive iodoform reaction, this evidence became of no value in deciding between the chroman and coumaran structures. Very recently, however, Karrer and Escher on the basis of the results of a careful oxidation of this compound, have concluded that it is definitely a chroman.[10]

The English workers likewise, while recognizing the possibility of structure II, have preferred structure I, and have considered the analogy between allyl bromide and phytyl bromide to be invalid.[3, 11]

Five different tocopherols have reported in the literature, known as α-, β-, γ-, cumo-, and neo-tocopherols. Cumo-tocopherol, reported by John[12] was later shown by him[13] to be identical with β-tocopherol. Karrer's neo-tocopherol was also found to be identical with β-tocopherol.[5] There remain, then, only three natural tocopherols definitely established as chemical entities, namely, α-, β-, and γ-tocopherols. Of these, α-tocopherol has the composition $C_{29}H_{50}O_2$, while β- and γ-tocopherols are isomers and have the composition $C_{28}H_{48}O_2$. Emerson[14] using the degradative method of Fernholz[6] has shown that the same oxidation products are obtained from all three tocopherols. This work establishes that the hetero ring and the aliphatic side-chains are the same in all three toco-

[6] FERNHOLZ, *J. Am. Chem. Soc.*, **60**, 700 (1938); see also EMERSON, *Science*, **88**, 40 (1938).

[7] JOHN, *Z. physiol. Chem.*, **252**, (*a*) 208, (*b*) 222 (1938).

[8] KARRER, ESCHER, FRITZSCHE, KELLER, RINGIER, AND SALOMON, *Helv. Chim. Acta*, **21**, 939 (1938).

[9] KARRER AND JENSEN, *ibid.*, **21**, 1622 (1938).

[10] KARRER AND ESCHER, *ibid.*, **22**, 264 (1939).

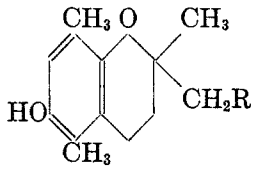
[11] (*a*) BERGEL, TODD, AND WORK, *J. Chem. Soc.*, **1938**, 253; (*b*) BERGEL, JACOB, TODD, AND WORK, *Nature*, **141**, 646 (1938).

[12] JOHN, *Z. physiol. Chem.*, **250**, 11 (1937).

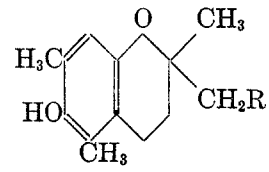
[13] JOHN, *Ibid.*, **252**, 201 (1938).

[14] EMERSON, *J. Am. Chem. Soc.*, **60**, 1741 (1938).

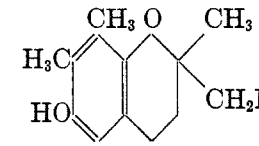
pherols; the difference then must lie in the number and position of the methyl groups in the benzene ring. Theoretically there could exist three "xylo-tocopherols", III, IV, and V. (R as in I and II) β-Tocopherol gave



III



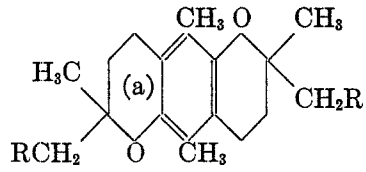
IV



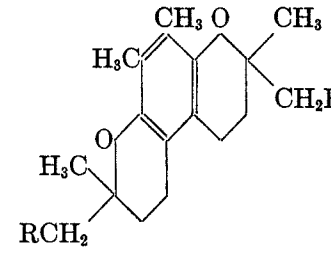
V

trimethylhydroquinone on pyrolysis, and 2,5-dimethylphenol on treatment with hydriodic acid.[7a] This establishes the structure of β-tocopherol as III; that there is one free position in the benzene ring in β-tocopherol is shown also by the fact that it can be allylated.[15] γ-Tocopherol must then have the structure IV or V; at the present time it is not possible to decide this point.

The reaction between phytyl bromide and *p*- and *m*-xylohydroquinones leads to mixtures. This was rather to be expected, because of the high reactivities of the allylic halide, phytyl bromide, and of the ring in the polymethyl hydroquinones. In Karrer's experiments[15, 16] the condensation of phytyl bromide with *p*- and *o*-xylohydroquinones gave rise to difficultly separable mixtures which consisted for the most part of the double chromans VI and VII (R as in I and II), respectively, although the tocopherols III and IV were present.



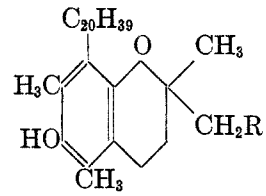
VI



VII

Although *m*-xylohydroquinone cannot give a double chroman, the vacant position in the ring can readily be attacked by such an active halide as phytyl bromide. The two products from this hydroquinone then, are the tocopherol IV and its phytyl derivative VIII.

[15] KARRER, FRITZSCHE, RINGIER, AND SALOMON, *Helv. Chim. Acta*, **21**, 820 (1938).
[16] KARRER AND FRITZSCHE, *ibid.*, **21**, 1234 (1938).



VIII

Moreover, there is the possibility also of the formation of substances analogous to VIII in the case of *p*- and *o*-xylohydroquinones. This would probably be the case when *p*-xylohydroquinone is used, for in the double chroman VI it is not possible to distribute the double bonds so that the two chroman rings are alike, and some of the evidence from a study of the Mills-Nixon effect indicates that a 6-membered ring, such as (a) in VI, is subject to considerable strain whereas a similarly constructed 5-membered ring is nearly strainless. It may well be that this effect is sufficient to overcome the tendency of the γ,γ-disubstituted allyl group to give a chroman, and that ring (a) in VI is actually part of a coumaran system, or that there is a resistance to the closing of the second ring, whatever its size, so that analogs of VIII result.‡

In our work, two xylohydroquinones, para and meta, were used. Condensation of phytyl bromide with *p*-xylohydroquinone gave a product which boiled at 145–150° in a molecular still (10^{-6} mm.) and which was noticeably more viscous than α-tocopherol. The product is almost insoluble in cold concentrated sulfuric acid although a red color develops in the oil and at the interphase, while α-tocopherol is soluble in sulfuric acid, giving a characteristic yellowish-green solution. The product gave a positive phenol reaction (Folin test). The substance was not obtained completely pure, but the analysis agreed better with the composition $C_{28}H_{48}O_2$ (III) than with $C_{48}H_{86}O_2$ (VI). When pyrolyzed, according to the procedure of Fernholz[6] a sublimate was obtained which consisted of a mixture of hydroquinones and which began to melt at about 130°. We conclude from these results that the product consisted of a mixture of III and VI.

When condensed with phytyl bromide, *m*-xylohydroquinone gave a product which boiled slightly lower than α-tocopherol. The low boiling point does not indicate that two phytyl groups have reacted, but rather only one, and that the product is essentially IV. Work on this product is still in progress and will be reported in a later paper. The product is biologically active, however, in 20- and 100-mg. doses.

‡ Dr. R. T. Arnold, of this laboratory, has had under way for some time a comprehensive investigation of the Mills-Nixon effect as it applies to heterocyclic compounds, and publications in this field will appear soon.

EXPERIMENTAL

Preparation of phytyl bromide.—Phytol was mixed with one-tenth of its weight of anhydrous sodium sulfate, and the mixture was cooled and saturated at 0° with dry hydrogen bromide. After standing overnight at 0°, the mixture was shaken with water and ether. The ether layer was separated, washed with water until the washings were neutral to litmus, then dried over sodium sulfate. The drying agent was removed, and the solvent was evaporated under reduced pressure. The product was used at once since it decomposes on standing, even at room temperature.

Anal. Calc'd for $C_{20}H_{39}Br$: C, 66.79; H, 10.96.

Found: (expt. 1) C, 65.32; H, 10.81; (expt. 2) C, 66.38; H, 9.10.

It is not possible to distil phytyl bromide, even under high vacuum, because it decomposes largely even at 75° to give phytadiene. A sample of such a distillate was analyzed: found C, 80.0; H, 12.88: calc'd for $C_{20}H_{38}$: C, 86.33; H, 13.66.

Synthesis of tocopherols.—The preparation of α-tocopherol will be described, and the results of other experiments will be given in tabular form. For small amounts of materials, trimethylhydroquinone and a slight excess of phytyl bromide are placed in the bottom of a Pyrex tube and intimately mixed. The tube is sealed and carefully heated in an upright position. After cooling, the tube is opened carefully with a torch, as there is considerable pressure of hydrogen bromide. The product is washed out with ether (peroxide-free) and dried over sodium sulfate. After removal of the drying agent, the solvent is evaporated and the residue is distilled under high vacuum (10^{-6} mm.) in a molecular pot still. In the distillation, after degassing, unchanged hydroquinone sublimes at first; thereafter it is necessary to lower the temperature somewhat in order to prevent superheating. Between 115 and 125° most of the phytadiene distills; at 135 to 140° small amounts of impure material distil, and then the pure α-tocopherol comes over at 140° (10^{-6} mm.).

For large amounts of material, the reaction was carried out in a bomb with a glass liner, under a pressure of 1100 lbs. of hydrogen, at 105° for 5 hours.

Racemic α-tocopherol.—The substance is a pale, straw-colored liquid, fairly viscous. It oxidizes quite readily when exposed to air; the oxidation becomes quite apparent if hydroquinone is present, for the material turns red and darkens quickly wherever it touches a crystal of hydroquinone in the distilling apparatus.

Anal. Calc'd for $C_{29}H_{50}O_2$: C, 80.85; H, 11.71.

Found: C, 80.75, 80.91; H, 11.69, 11.82.

The substance formed an allophanate which melted at 168–170° and which, when mixed with natural α-tocopherol allophanate (m.p. 157–160) melted between the two. The yield of allophanate was not good.

Anal. Calc'd for $C_{31}H_{52}N_2O_4$: C, 72.03; H, 10.15.

Found: C, 72.09, 72.28; H, 10.00, 10.00.§

The substance gives a positive phenol test (Folin); rapidly reduces silver nitrate in methanol; gives a bright greenish-yellow color when it dissolves in cold sulfuric acid. Biologically, the substance was active in single doses of 3 and 7 mg.**

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§ The analysis of α-tocopherol, and the preparation and analysis of the allophanate were carried out by Messrs. Emerson and Hayman in the Laboratories of Merck & Co., Inc., Rahway, N. J.

** All of the bio assays connected with this work were carried out by Dr. H. M. Evans of the University of California.

The absorption spectrum of this product was practically indistinguishable from that of natural α-tocopherol.††

p-*Xylotocopherol.*—The product boiled at 145–150° in the molecular still, was light yellow and very viscous. It was insoluble in cold, concentrated sulfuric acid, and a red color developed at the interphase. The substance gave a positive phenol test (Folin) and reduced silver nitrate in methanol. It was not completely soluble in Claisen's alkali.

Anal. Calc'd for $C_{28}H_{48}O_2$: C, 80.69; H, 11.62.
Found: C, 79.49; H, 11.84.

A small amount of the material was pyrolyzed by heating it to 355–360° under carbon dioxide for several hours. A crystalline sublimate and a red liquid were obtained. The white sublimate after washing with petroleum ether, melted over a wide range, beginning at 130°. It was undoubtedly a mixture of hydroquinones.

m-*Xylotocopherol.*—The crude product was extracted with ether, and unchanged hydroquinone was washed out with 1% potassium hydroxide. The ether layer was then washed with water and dried over sodium sulfate. The solvent was removed, and the residue distilled in the molecular still. It boiled at 120–130° (10^{-6} mm.). The pale-yellow oil gave a positive phenol test (Folin), reduced silver nitrate in methanol, and gave a yellow to red color with sulfuric acid. Although this product was biologically active in 100-mg. doses, it was not analytically pure and contained phytadiene.

SUMMARY

1. This paper contains a description of a synthesis of certain tocopherols having vitamin E activity.

2. The nature of the byproducts formed in these syntheses is discussed.

†† These curves were determined by Dr. T. J. Webb, in the Laboratories of Merck & Co., Inc. and will form the subject of a later communication.

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

THE CHEMISTRY OF VITAMIN E. V. THE DIRECT ALLYLATION OF PHENOLS AND HYDROQUINONES[1,*]

LEE IRVIN SMITH, HERBERT E. UNGNADE, HARVEY H. HOEHN, AND STANLEY WAWZONEK

Received March 31, 1939

Coumarans and chromans have been reported by Claisen[2] as cyclization products of *o*-allylic phenols. In the presence of alkali and a non-dissociating solvent, direct allylation of phenols gives largely allylic phenols, with small amounts of phenyl ethers as byproducts. Some of the allylic halides, however, are so active that a reaction occurs in the cold, with liberation of heat. Whenever this exothermic reaction occurs—as a rule with γ,γ-disubstituted allylic halides—coumarans or chromans will be present in the reaction product. Claisen also discovered that these very reactive allylic halides would react spontaneously and exothermally, with phenols in the absence of alkali. He considered this reaction to be a direct C-allylation, and the ease with which it occurred was found to depend upon the reactivities of both the phenol and the halide. Claisen found that hydroquinone and its monomethyl ether would not react, even with the most active halides, under the conditions used by him.[2b]

In the present work, the reaction has been extended to the polyalkyl phenols and to hydroquinones. Four allylic bromides have been used, namely allyl, γ,γ-dimethylallyl geranyl and phytyl bromides. Of these, allyl bromide itself is the least reactive; it does not react with trimethylhydroquinone at all unless the reaction mixture is heated or a catalyst is used. Geranyl bromide is the most reactive of the four bromides, reacting rapidly in the cold. Unfortunately it also underwent side reactions to the greatest extent, giving a product that was very difficult to separate from the terpene-like byproducts. Allyl, γ,γ-dimethylallyl, and phytyl bromides all reacted with the hydroquinone in a sealed tube at temperatures between 100 and 150°, without solvent or catalyst. Nevertheless, a catalyst can be used, and of these zinc chloride appears to be the most effective. Similarly, a solvent—benzene, petroleum ether, etc.—can be used. But

[1] Paper IV: J. ORG. CHEM., **4**, 000 (1939).

[*] Presented (in part) at the 96th meeting of the American Chemical Society, Milwaukee, Sept. 5–9, 1938.

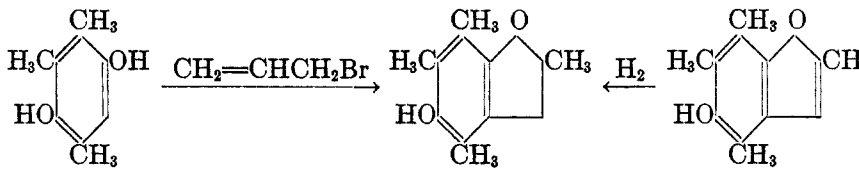
[2] (*a*) *Ann.*, **401**, 26 (1913); (*b*) *ibid.*, **442**, 210 (1925); (*c*) *Ber.*, **58**, 279 (1925).

neither the yield nor the quality of the product appears to be improved by using catalyst or solvent.

The optimum temperature range lies between 100 and 150°, and for good yields and a fairly pure product it is important that the reactants be pure and thoroughly stirred to a paste, and that the tube be heated in a vertical position, especially with the more viscous halides. Otherwise the halide will be converted to the diene more rapidly than it reacts with the hydroquinone, and the product will be contaminated with large amounts of high-boiling material, presumably diene polymers.

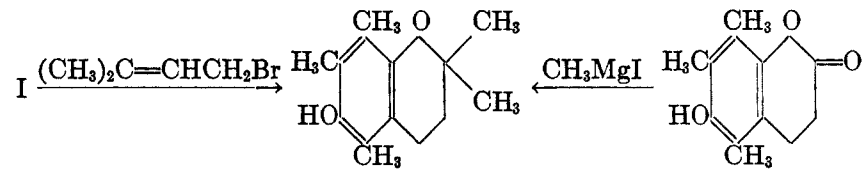
In all of this work, whenever it was possible to prove the structure of the product independently, it was found that no rearrangements of the allylic groups had occurred. Likewise, in every case in which a γ,γ-disubstituted allylic halide was used, the product was a chroman. Only in the case of allyl bromide itself did a coumaran result.

Trimethylhydroquinone (I) and allyl bromide gave 2,4,6,7-tetramethyl-5-hydroxycoumaran (II), m.p. 129–130°, which was identical with the product obtained by reduction of the corresponding coumaron (III) prepared some time ago from trimethylquinone and acetoacetic ester.[3]



I II III

The hydroquinone I and γ,γ-dimethylallyl bromide gave 2,2,5,7,8-pentamethyl-6-hydroxycoumaran (IV), m.p. 94–94.5°, identical with the product obtained by the action of methylmagnesium iodide upon 5,7,8-trimethyl-6-hydroxy-3,4-dihydrocoumarin (V).[4]



IV V

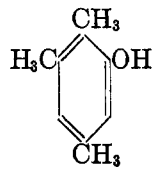
The reaction between I and phytyl bromide, leading to racemic α-tocopherol, has been discussed in the previous paper.[1]

When hydroquinones and phenols which contained one or more open

[3] SMITH AND MACMULLEN, *J. Am. Chem. Soc.*, **58**, 629 (1936).

[4] SMITH AND DENYES, *ibid.*, **58**, 304 (1936).

positions were used, these reactive halides gave mixtures. Presumably these consist of the chroman or coumaran, together with the allylated derivative and the hydrobromic acid addition product of the allylated derivative, since the product contained aliphatic halogen. Thus, from 2,3,5-trimethylphenol (VI) and allyl bromide, the three products VII, VIII, and IX may be derived.



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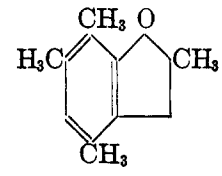

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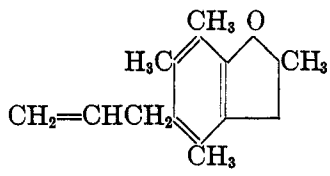

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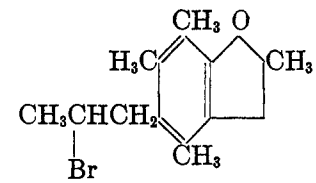
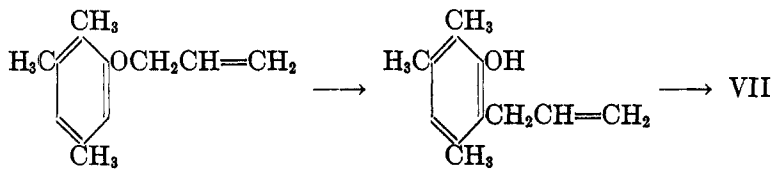


IX

The coumaran VII, however, was made from the phenol VI by preparing the allyl ether of the phenol, rearranging this to trimethylallylphenol and then closing the ring by the action of hydrobromic acid in acetic acid.



X XI

EXPERIMENTAL

The general procedure for carrying out the allylations was essentially the same as that described in the previous paper[1] for the preparation of tocopherols. Hence the results of this work will be given in tabular form only; the only variation introduced into the procedure was to reflux in certain cases. These cases are indicated in the table. In the last five examples in the table products were formed which contained aliphatic halogen; in these cases the yields were poor except for the last case in which zinc chloride was used. Otherwise the yields were excellent whenever a reaction occurred.

2,4,5,7-Tetramethyl-5-hydroxycoumaran (II).—This substance was first reported by Bergel, Todd, Jacob, and Work,[5] who gave the melting point as 124–125°; later

[5] Bergel, Todd, Jacob, and Work, *Nature*, **141**, 646 (1938).

TABLE I

RESULTS OF ALLYLATION OF PHENOLS AND HYDROQUINONES

PHENOL	(G.)	BROMIDE	(CC.)	CATALYST	SOLVENT	TEMP., °C.	TIME	PRODUCT
Trimethylhydroquinone	1	Allyl	10	None	None	155	4.5 hrs.	II, m.p. 100–110°
Trimethylhydroquinone	1	Allyl	2	$AlCl_3$	None	Refluxed	5 min.	None
Trimethylhydroquinone	1	Allyl	10	$AlCl_3$	None	Refluxed	30 min.	None
Trimethylhydroquinone	1	Allyl	5	$ZnCl_2$	Acetic acid	Refluxed	30 min.	None
Trimethylhydroquinone	0.1	Allyl	0.5	None	None	115	4 hrs.	II, m.p. 121°
Trimethylhydroquinone	0.1	Allyl	0.1	None	None	110	5 hrs.	II, m.p. 105–109°
Trimethylhydroquinone	5	Allyl	20	None	None	115	4 hrs.	II, m.p. 118°
Trimethylhydroquinone	1	Geranyl	1.4	None	None	115	1 hr.	Mixture
Trimethylhydroquinone	1	Geranyl	1.5	None	None	115	4.5 hrs.	Mixture
Trimethylhydroquinone	1	Geranyl	1.3	None	None	110	4 hrs.	Mixture
Trimethylhydroquinone	1	Dimethylallyl	3	None	None	140	4 hrs.	IV, m.p. 89–90°
m-Xylohydroquinone	6.9	Allyl	6.05	$ZnCl_2$, 6 g.	Benzene, 75 cc.	Refluxed	3.5 hrs.	Dark oil
	6.9	Allyl	4.4	$ZnCl_2$, 3 g.	Ligroïn, 80 cc.	Refluxed	18 hrs.	Dark oil
Phenol	10	Allyl	12	None	None	150	12 hrs.	Tar
p-Nitrophenol	1	Allyl	3	None	None	125	3 hrs.	None
2,3,5-Trimethylphenol	3	Allyl	5	None	None	130	3 hrs.	2 products
2,5-Dimethylphenol	3	Allyl	5	None	None	130	3 hrs.	2 products
3,5-Dimethylphenol	3	Allyl	5	None	None	150	3 hrs.	2 products
4-Methoxyphenol	5	Allyl	7	None	None	150	3 hrs.	2 products
2,3,5-Trimethylphenol	10	Allyl	15	$ZnCl_2$	None	130	2.5 hrs.	2 products

by Smith, Ungnade, and Prichard[6], who gave the melting point as 123–123.5°; and by Karrer, Fritzsche, Ringier, and Salomon[7], who gave 127°. Our value for the melting point represents the highest obtainable with the use of alcohol and water as solvents, but if the substance is steam-distilled and then crystallized from petroleum ether, the melting point rises at once to 130.5–131.5°.

Anal.† Calc'd for $C_{12}H_{16}O_3$: C, 75.00; H, 8.33.
Found: C, 75.18; H, 7.92.

Preparation by reduction of the coumaron.—2,4,6,7-Tetramethyl-5-hydroxycoumaron (III) (5 g.) was dissolved in alcohol and reduced at 200° with hydrogen and Raney nickel under a pressure of 2600 lbs. The product was steam-distilled, and the coumaran (II) was isolated from the distillate and crystallized from petroleum ether; m.p. and mixture m.p. 129–130°. The acetate, prepared from the coumaran and acetic anhydride and crystallized from dilute alcohol, melted at 72.5–73.5°.

Anal. Calc'd for $C_{14}H_{18}O_3$: C, 71.80; H, 7.69.
Found: C, 71.92; H, 7.84.

2,2,5,7,8-Pentamethyl-6-hydroxychroman (IV).—The dihydrocoumarin (V) (1.33 g.) was dissolved in a little benzene and added to the Grignard solution from methyl iodide (4 g.) and magnesium (0.62 g.). The ether was distilled, more benzene was added, and the mixture was refluxed for two hours. The crude product, isolated in the usual way, was only partially cyclized. It was accordingly cyclized and acetylated by boiling it in acetic anhydride containing a drop of sulfuric acid, when it gave the acetate of IV. Crystallized from ethanol several times, this melted at 91.5–92° and showed no depression in melting point when mixed with an authentic sample of the acetate. The chroman IV, prepared by refluxing the hydroquinone (10 g.), isoprene (10 g.), and zinc chloride (1 g.) in acetic acid (100 cc.) for one hour, melts at 94–94.5° after three crystallizations from ethanol; yield 7 g.

Anal. Calc'd for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09.
Found: C, 76.57; H, 9.45.

The acetate, prepared in the usual way from acetic anhydride, was white and melted at 92.5–93.5° after several crystallizations from petroleum ether followed by dilute methanol.

Anal. Calc'd for $C_{16}H_{12}O_3$: C, 73.28; H, 8.39.
Found: C, 72.84; H, 8.43.

2,3,5-Trimethylphenyl allyl ether (X).—The general procedure used was that of Hurd.[8] 2,3,5-Trimethylphenol (68 g.) was dissolved in acetone (100 cc.) in which potassium carbonate (69 g.) was suspended. With stirring, allyl bromide (60 g.) was slowly dropped in, after which the mixture was refluxed for 8 hours. Water (800 cc.) was added, the oil was separated, and the aqueous layer was extracted three times with ether. The oil was combined with the ether extractions and the whole was washed with Claisen's alkali, followed by water. After drying, and removal of the ether, the residue was distilled at 0.1 mm. through a Hickman still. There resulted 37.7 g. of a colorless oil boiling at 59.2°.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.77; H, 9.15.
Found: C, 80.91; H, 9.20.

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[6] Smith, Ungnade, and Prichard, *Science*, **88**, 37 (1938).

[7] Karrer, Fritzsche, Ringier, and Salomon, *Helv. Chim. Acta*, **21**, 820 (1938).

† Analyses by J. W. Opie and C. O. Guss.

[8] Hurd, *J. Am. Chem. Soc.*, **52**, 1702 (1930).

2,3,5-Trimethyl-6-allylphenol (XI).—The ether (44 g.) was refluxed at atmospheric pressure for one hour, the temperature (thermometer in the liquid) rising from 250° to 262°. The product was taken up in ether, and extracted thoroughly with Claisen's alkali. The alkali solutions were diluted with water, acidified with dilute sulfuric acid and extracted with ether. After drying over sodium sulfate, the ether was removed and the residue was fractionated under 2–3 mm. The middle fraction, boiling at 105–112°, weighed 19.6 g. and solidified on cooling. After crystallization from dilute alcohol, the substance formed white needles which melted at 49.5–50.5°.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.77; H, 9.15.
Found: C, 81.08; H, 9.25.

2,4,6,7-Tetramethylcoumaran (VII).—The allylphenol (XI) (40 g.) was dissolved in acetic acid (125 cc.) aqueous hydrobromic acid (40%, 56 cc.) was added, and the solution was refluxed for 3 hours. More acetic acid (175 cc.) and hydrobromic acid (25 cc.) were then added, and refluxing was continued for an hour longer. The cooled solution was diluted with water and extracted with low-boiling petroleum ether. The ether extract was dried over calcium chloride, the solvent was removed, and the residue was distilled under 29 mm. pressure. The product (20.5 g.) was a colorless oil boiling at 142–144°.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.77; H, 9.15.
Found: C, 81.41; H, 8.96.

SUMMARY

1. Hydroquinones and phenols have been directly allylated.

2. The allylation apparently occurs in one step and does not involve a phenyl allyl ether as an intermediate.

3. The products are chromans and coumarans, and the structures of certain of these have been proved. No rearrangements in the allyl groups have been found.

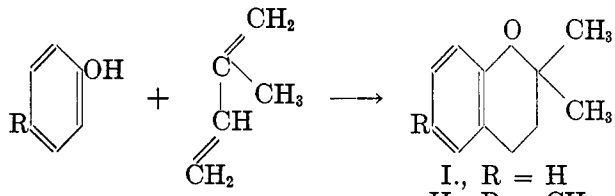
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. VI. THE ADDITION OF DIENES TO PHENOLS AND HYDROQUINONES[1, *]

LEE IRVIN SMITH, HERBERT E. UNGNADE, HARVEY H. HOEHN, AND STANLEY WAWZONEK

Received March 31, 1939

According to Claisen[2] dienes can be condensed with phenols in the presence of acid catalysts to give chromans. Thus when isoprene and phenol or *p*-cresol are dissolved in acetic acid and subjected to the action of dry hydrochloric acid or of zinc chloride, the chromans I and II respectively, are formed.



I., R = H
II., R = CH_3

Claisen proved the structure of the chroman I by synthesizing it from coumarin.

We were interested in extending this reaction to polymethylated phenols and to hydroquinones and their mono ethers, having in view a possible synthesis of tocopherols from appropriate hydroquinones and phytadiene. It was found that, with certain modifications of Claisen's conditions, the reaction was fairly generally applicable to methylated hydroquinones and their mono ethers, as well as to polymethylated phenols. The reaction, however, is quite difficult[3], and the conditions must be very carefully controlled if good yields are to be obtained with hydroquinones and their derivatives. Using Claisen's procedure and dry hydrochloric acid as the condensing agent, 2,3,5-trimethylphenol gave a mixture of three different products. These were the chroman III, m.p. 40–41°, the phenol IV*a* or

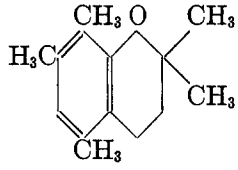
[1] Paper V: J. ORG. CHEM., **4**, 305 (1939).

[*] Presented (in part) at the 96th meeting of the American Chemical Society, Milwaukee, Sept. 5–9, 1938.

[2] CLAISEN, *Ber.*, **54**, 200 (1921).

[3] SPÄTH, *Ber.*, **70**, 2276 (1937), has also experienced considerable difficulty in applying the reaction to derivatives of dihydric phenols. Thus from 7-hydroxycoumarin and isoprene, he obtained only 1–2 per cent yield of condensation product.

IV*b*, m.p. 84–86°, and the chroman V, a liquid. The structure of IV is not certain, although we favor IV*b* because of the ready solubility of the sub-



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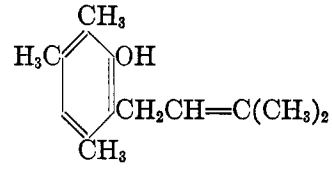
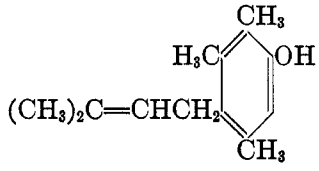


IVa



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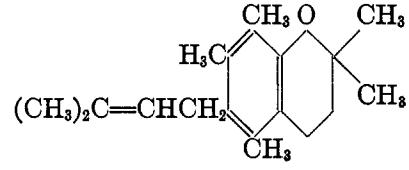

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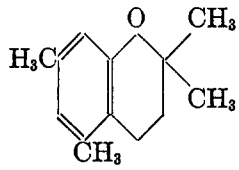

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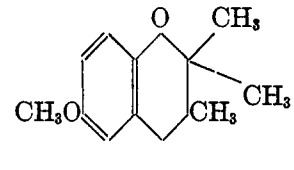
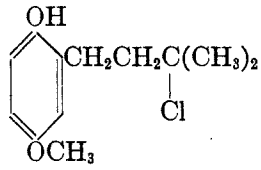


VII

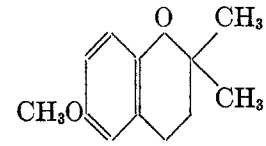
stance in alkali. Substance V was obtained as an oil which, because of lack of material, could not be purified sufficiently for detailed examination. When the condensation between this phenol and isoprene was carried out in acetic acid using zinc chloride instead of hydrochloric acid, a good yield of the chroman III was obtained. Mercuric chloride was also found to be a good catalyst, although the yields of chroman when it was used were not as good as those produced by zinc chloride. In a similar manner, with the use of zinc chloride as the catalyst, 2,2,5,7-tetramethylchroman (VI) was produced from 3,5-dimethylphenol and isoprene.

Hydroquinone itself was found to be inactive toward dienes under practically all of the conditions used by Claisen. The inactivity may be due partly to adverse solubility relationships, necessitating such high dilutions for solution that the reaction does not occur, but in any event the temperature necessary for a reaction to occur under any of the conditions tried by us is apparently above the decomposition points of the reactants. The mono methyl ether of hydroquinone, however, reacts readily with dimethylbutadiene in acetic and hydrochloric acids to give 2,2,3-trimethyl-6-methoxychroman (VII), and with isoprene to give first the

halogen compound VIII, which can readily be cyclized to 2,2-dimethyl-6-methoxychroman (IX) with alcoholic potassium acetate.

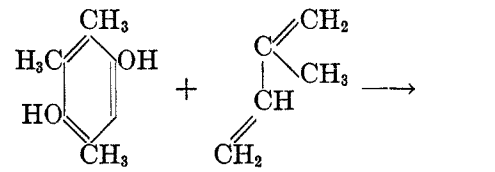


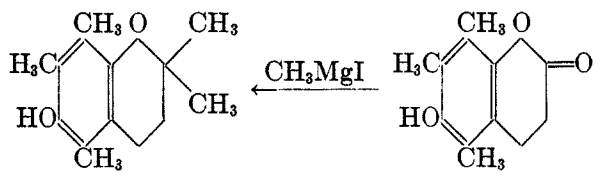
VIII



IX

The reluctance to react with dienes extends to the methylated hydroquinones, although to a considerably lesser degree than is the case with hydroquinone itself. Thus trimethylhydroquinone, the most reactive of the hydroquinones examined, reacts well with isoprene but only in boiling acetic acid containing zinc chloride and sulfuric acid, and the reaction between hydroquinones and dienes in general appears to require high concentrations of the components and an active catalyst. Under these circumstances, 2,2,5,7,8-pentamethyl-6-hydroxychroman (X) is produced in good yields. The structure of this substance was proved by synthesizing it from 5,7,8-trimethyl-6-hydroxy-3,4-dihydrocoumarin (XI)[4] and methylmagnesium iodide.





X XI

Trimethylhydroquinone also was found to react with phytadiene to give *dl*-α-tocopherol, and although the product was not obtained absolutely pure, the analysis and melting point of the allophanate (155°, poor yield) indicate that the substance was about as pure as specimens obtained by other methods.

The reaction between 2,5-dimethylhydroquinone and isoprene under

[4] SMITH AND DENYES, *J. Am. Chem. Soc.*, **58**, 304 (1936).

all the conditions tried gave only viscous oils having no definite boiling points and which could not be crystallized. Some hydroquinone was recovered in most of the experiments, but the products were mixtures which we have not, as yet, been able to separate.

EXPERIMENTAL

Reaction between 2,3,5-trimethylphenol and isoprene.—The phenol (30 g.) and isoprene (13 g.) were dissolved in acetic acid (32 g.), and the solution was saturated with dry hydrogen chloride at 0°. (3 hours), after which the mixture was allowed to stand in the ice box for 36 hours. More isoprene (5 g.) was then added, and dry hydrogen chloride was passed in for 12 hours longer. At this stage most of the phenol had dissolved. The mixture stood at room temperature for 12 hours, and was then warmed on the steam bath for one hour. An excess of 40% potassium hydroxide solution was added and the solution was extracted thoroughly with ether. The ether layer was washed several times with water and then extracted, first with 40% potassium hydroxide and then with 2% sodium hydroxide. The ether solution was washed with water, and dried over calcium chloride. The solvent was removed, and the residue was fractionated through a Hickman still under 0.1 mm. pressure. The distillate, which came over at 81–124°, weighed 24.1 g. and gave a strong positive halogen test (Beilstein). The material was refluxed under the vacuum of the water pump for 5 hours, when it was halogen-free. It was then fractionated under 0.1 mm. pressure. Fractions were taken as follows: *A*, b.p. 58°, 5.13 g.; *B*, 68–108°, 6.2 g.; *C*, 108–113°, 9.1 g. *A* was 2,2,5,7,8-pentamethylchroman (III) (see below). *B* solidified completely, and *C* partially, on cooling. The solid in *C* was found by its melting point to be the same as *B*; accordingly *C* was filtered, and the solid was combined with *B*. Recrystallization twice from petroleum ether gave white needles; m.p. 84–86°. The substance was soluble in aqueous potassium hydroxide, and Claisen's alkali.

Anal.† Calc'd for $C_{14}H_{20}O$ (IV*a* or IV*b*): C, 82.24; H, 9.87.
Found: C, 82.26; H, 9.87.

The oil remaining after the solid was removed from fraction *C* was very small in amount. It could not be crystallized and there was not enough of it to distill.

2,2,5,7,8-Pentamethylchroman (III).—The trimethylphenol (34 g.), fused zinc chloride (4 g.), and isoprene (17 g.) were shaken with acetic acid (30 cc.) for one hour, when the phenol all dissolved. The mixture was allowed to stand at room temperature for 12 hours and then was refluxed for 7 hours. The mixture was diluted with twice its volume of water, the oily layer was removed and the aqueous layer was extracted three times with petroleum ether. The oil and the extracts were combined and extracted three times with Claisen's alkali to remove any unchanged phenol. After washing with water, the organic layer was dried over calcium chloride, the solvent was removed, and the residue was distilled under 2–3 mm. pressure. The chroman thus obtained boiled at 104–110° and weighed 22 g. It crystallized from methyl alcohol as a white solid melting at 40–41°.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.24; H, 9.87.
Found: C, 82.14; H, 9.88.

In a similar experiment, the phenol (5 g.), isoprene (2.5 g.), and mercuric chloride (0.37 g.) were heated under an efficient reflux condenser on the steam bath for 6 hours

† Micro analyses by J. W. Opie and C. O. Guss.

and then brought to a temperature of 240°. The chroman (III), isolated and purified as above, weighed 2 g. and boiled at 152–154° under 27 mm. pressure.

2,2,3-Trimethyl-6-methoxychroman (VII).—Hydroquinone mono methyl ether (12.4 g.) and dimethylbutadiene (8.2 g.) were dissolved in acetic acid (10 g.) and the solution was saturated with dry hydrogen chloride acid at 0°. After standing for 18 hours, the mixture was warmed on the steam bath. Water was added and the product was removed by ether extraction. The ether solution was washed thoroughly with 10% sodium hydroxide, then with water, and was dried over calcium chloride. The solvent was removed, and the product was distilled under high vacuum (10^{-6} mm.) in a molecular still. The yield was about 4 g.; b.p. 50–55°; n_D^{20} 1.5263.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.73.
Found: C, 75.97; H, 8.72.

*2,2-Dimethyl-6-methoxychroman (IX) and 1-[o-hydroxy-*m*-methoxyphenyl]-3-chlorobutane (IX).*—Hydroquinone mono methyl ether (18 g.) and isoprene (11 g.) were dissolved in acetic acid (25 cc.), and the solution was saturated at 0° with dry hydrogen chloride. The mixture, after standing in the ice box for 12 hours, was warmed on the steam bath for 30 minutes. After cooling, an excess of 40% potassium hydroxide was added, and the solution was thoroughly extracted with ether. The ether layer was washed with water several times and then dried over calcium chloride. After removal of the ether, the residue was fractionated in a Hickman still under 0.1 mm. pressure. Two fractions were collected: *A*, b.p. 74–80° (3.94 g.); *B*, b.p. 105–107°, (3.38 g.). Fraction *A* had $n_D^{22.5} = 1.5276$, reacted with alcoholic silver nitrate only very slowly, and gave a slightly positive phenol test (Folin) and a light-orange color with cold concentrated sulfuric acid. It was undoubtedly the methoxychroman (IX), but it was possible, with one distillation, to separate it in a pure state.

Fraction *B* was the chloro compound VIII. It had $n_D^{23} = 1.5310$, gave a precipitate rapidly with cold alcoholic silver nitrate; the phenol test was strongly positive, and the color with cold concentrated sulfuric acid was deep-red. It was not analyzed, however, but was converted directly to the chroman IX by boiling for one hour with excess potassium acetate in methanol. The mixture was evaporated to dryness, and the residue was taken up in ether and water. The ether was removed, the solvent was evaporated, and residue was distilled under 0.1 mm. in a Hickman still. The distillate, which boiled at 83–90°, weighed 2 g. and was the chroman IX. It had $n_D^{25} = 1.5323$, gave no precipitate with alcoholic silver nitrate, and produced an orange color with cold concentrated sulfuric acid.

Anal. Calc'd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33.
Found: C, 74.48; H, 8.45.

2,2,5,7,8-Pentamethyl-6-hydroxychroman (X).—Trimethylhydroquinone (10 g.) and zinc chloride (1 g.) were dissolved in acetic acid (100 cc.). The solution was heated to 100° under an *efficient* reflux condenser, and isoprene (10 g.) was slowly added. The mixture was allowed to stand for an hour, and then was refluxed for an hour. One drop of sulfuric acid was added, and the mixture refluxed for an hour longer. The cooled mixture was poured into water, and the white solid was removed. It weighed 7 g. After three crystallizations from dilute ethanol, it melted at 94–94.5°.

Anal. Calc'd for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09.
Found: C, 76.57; H, 9.45.

The substance formed an acetate which melted at 92.5–93.5°. The preparation of X, m.p. 94–94.5° and its acetate, m.p. 92.5–93.5°, from the coumarin and methylmagnesium iodide is described in the previous paper.[1]

The allophanate of the hydroxychroman melted at 209–211.5° with decomposition. W. John[5] who also prepared this allophanate, reported it to melt at 230°.

Anal. Calc'd for $C_{16}H_{22}O_4N_2$: C, 62.74; H, 7.19.
Found: C, 62.78; H, 7.28.

Phytadiene.—In an attempt to purify phytyl bromide by distillation under high vacuum, it was found that the distillate consisted largely of phytadiene.[6] The distillate and residue were therefore combined (9 g.) and heated on the steam bath for 45 minutes with potassium hydroxide (10 g.) in methanol (30 cc.). After cooling, ether and water were added, the ether layer was separated, washed with water, and dried. The solvent was removed, and the residue was distilled. It boiled at 186–188° under 14 mm. pressure, and weighed 2.5 g.

α-Tocopherol.—A mixture of trimethylhydroquinone (1.3 g.), phytadiene (2.5 g.), absolute formic acid (5 g.), and acetic acid (2 g.) was refluxed for 3 hours. After cooling, ether was added, and the solution was washed thoroughly with water. The ether solution was dried over sodium sulfate, the solvent was removed, and the residue was distilled in a molecular still (5×10^{-6} mm.). About 0.1 g. of unchanged hydroquinone sublimed first. This was followed by the oily distillate, which was collected in five fractions, although all of it boiled at 140–145°. The first two fractions were dark, due to some of the liquid in the still bumping over, but the last three fractions consisted of a pale-yellow oil with a slight blue fluorescence. The estimated yield was 1.5–2 g.

Anal. Calc'd for $C_{29}H_{50}O_2$: C, 80.86; H, 11.71.
Found: C, 81.65, 81.62, 80.85; H, 12.03, 12.00, 11.95.

The substance formed an allophanate which melted at 155°, although the yield was poor, and the tocopherol was apparently contaminated with a high-boiling oil, insoluble in methanol.‡

One of the later fractions was adsorbed on Brockman's alumina. The tocopherol layer could be distinguished in ultra-violet light. It was extracted with a mixture of methanol and ether. The residue after removal of the solvents reduced silver nitrate in methanol, and gave an orange-yellow color with cold concentrated sulfuric acid. Attempts to prepare the dinitrobenzoate from a small amount of the material were unsuccessful.

Reaction between 2,5-dimethylhydroquinone and isoprene.—The hydroquinone (13.8 g.) was dissolved in acetic acid (70 cc.) and ether (15 cc., absolute), and the solution was cooled to 0°. Isoprene (6.8 g.) was added, and the solution was saturated with dry hydrogen chloride. The mixture, after standing in an ice box for one week and then at room temperature for 24 hours, was poured into water and extracted with ether. Extraction of the ether with alkali removed some hydroquinone and left a dark, viscous oil which could not be crystallized nor distilled.

An experiment analogous to that used for the preparation of VIII above, involving 2,5-dimethylhydroquinone (9 g.), zinc chloride (1 g.), acetic acid (70 cc.), and

[5] JOHN, *Ber.*, **71**, 2646 (1938).

[6] Paper IV, J. ORG. CHEM., **4**, 298 (1939).

‡ The analysis of the tocopherol and preparation of the allophanate, were carried out by Messrs. Emerson and Hayman in the laboratories of Merck & Co., Inc., Rahway, N. J.

isoprene (10 g.) also gave only a dark oil which could neither be crystallized nor distilled.

SUMMARY

1. The condensation between dienes and phenols leading to chromans, has been extended to certain hydroquinones and to hydroquinone mono methyl ether.

2. Under proper conditions, these substances give good yields of chromans, but unless the conditions are carefully regulated, mixtures will result.

3. Hydroquinone itself does not react under any of the conditions tried, but its mono methyl ether reacts readily. Trimethylhydroquinone reacts well, but 2,5-dimethylhydroquinone does not.

4. α-Tocopherol has been synthesized in this way from trimethylhydroquinone and phytadiene.

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

THE CHEMISTRY OF VITAMIN E. VII. PREPARATION OF QUINONES FROM METHYLPHENOLS[1]

LEE IRVIN SMITH, J. W. OPIE, STANLEY WAWZONEK, AND W. W. PRICHARD

Received March 31, 1939

In connection with the synthesis of tocopherols and the many simpler compounds related to them, large amounts of methylated quinones were required. The preparation of a kilogram of trimethylquinone by the method used in previous work[2] would represent a truly formidable task, even if the necessary starting material, pseudocumidine-5, were available in quantity. Consequently, before undertaking to prepare large amounts of the quinone by this method, we sought to find other, less laborious methods of preparation, and especially those which did not require the expensive and rare amine. In pseudocumene, however, the first point of attack by a reagent is usually at the 5-position, therefore, in any synthesis of trimethylquinone from pseudocumene, the molecule must first be modified in some way which avoids attack at this point.

Pseudocumene is converted by direct bromination into a mixture of the 5- and 3-bromo derivatives, the former predominating. But Smith and Moyle[3] have shown that 5-bromopseudocumene undergoes the Jacobsen reaction giving the 3-bromo compound in good yield, and that the mixture of bromo compounds obtained from pseudocumene can in this way serve as a good source for the pure 3-bromo isomer. Previous experiments upon the conversion of bromopolymethylbenzenes to polymethylphenols[4] had shown that good results could be obtained by heating the bromo compounds with alkali and copper in a bomb at 250–300°. Applied to 3-bromopseudocumene, this method gave pseudocumenol-3 (I) in fair overall yield from pseudocumene, and most important, the method appeared to be feasible on a large scale—4 or 5 moles.

Since preliminary experiments had shown that duroquinone could be prepared from durenol in about 50 per cent. yields by direct oxidation with dichromate, this method was applied to pseudocumenol-3, and

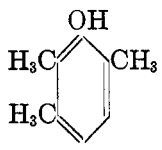
[1] Paper VI: J. ORG. CHEM., **4**, 311 (1939).

[2] SMITH, *J. Am. Chem. Soc.*, **56**, 472 (1934).

[3] SMITH AND MOYLE, *ibid.*, **58**, 1 (1936).

[4] A. C. KEYL, Unpublished work, this laboratory.

with about the same results, for trimethylquinone was produced in about 50 per cent. yields on small-scale runs.



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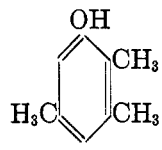

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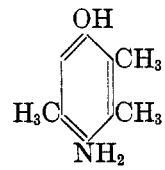

III

Our work was at this point when Dr. E. C. Williams of the Shell Development Company informed us that he had available pilot-plant quantities of pseudocumenol-6 (II) and durenol, and he very kindly sent us a most generous supply of each of these phenols.* To our astonishment, however, we were unable to obtain more than traces of trimethylquinone by direct oxidation of the phenol II. Under all of the conditions tried by us, the product was either unchanged phenol, or a dark oily material from which no pure products could be obtained, and which gave no quinone when it was steam-distilled.

We then decided to try converting the phenol to the quinone by coupling it with a diazonium compound as the first step. Although the phenol is open to attack at two points, ortho and para, respectively, to the hydroxyl group, it was thought that conditions might be found under which the coupling would occur largely or entirely in the para position. Using the method described by Fieser[5] diazotized sulfanilic acid was coupled with the phenol in strongly alkaline solution. There was produced an excellent yield of the *para* hydroxyazo compound, which was readily cleaved by stannous chloride and hydrochloric acid to give the *p*-aminophenol (III). The aminophenol was converted to the quinone without isolation. After the reduction, excess ferric chloride was added, the mixture was *at once* steam-distilled, and the quinone was isolated from the distillate. The overall yields of quinone, based upon the phenol II were always 90 per cent. and often were over 95 per cent. At least a kilogram of the quinone has been prepared in this way, and the conspicuous success of this method led us to apply it to other phenols, several of which are now available commercially in a very pure state. By this procedure 3,5-dimethylphenol was converted

*We wish at this point to thank Dr. Williams and the Shell Development Company for this magnificent gift. It is not exaggerating to say that this gift made it possible for us to do many times as much experimentation in the time at our disposal as would have been the case otherwise, and that the successful outcome of our researches so far has in no small measure been due to this aid.

[5] FIESER, *Organic Syntheses* **17**, 9. John Wiley & Sons, Inc., New York, **1937**.

into *m*-xyloquinone in 74 per cent. yield; 2,5-dimethylphenol was converted into *p*-xyloquinone in 55 per cent. yield, and durenol into duroquinone in in 60 per cent. yield. Only traces of toluoquinone could be obtained by this method, starting with either *o*- or *m*-cresol. We believe that the method represents the most rapid and efficient procedure known at present for preparation of the polymethylquinones in quantity.

While other diazonium salts may be used, that derived from sulfanilic acid has given the best results in our hands. Diazotized aniline couples well with the phenols, but reduction of the azo compounds so obtained either produces aniline which may later react with the quinones, or else reduction of the azo compounds in the strongly acid solution causes a rearrangement of the semidine type. In any event, when aniline is used, the yields of quinones are at best only about half as much as when sulfanilic acid is used. When sodium hydrosulfite instead of stannous chloride was used for reduction of the azo compounds derived from aniline, no quinone was obtained. Catalytic reduction of the azo compounds followed by the usual oxidation, gave as a maximum a 43 per cent. yield of trimethylquinone. In this connection, the azo compounds derived from sulfanilic acid cannot be reduced catalytically because of the sulfonic acid group[6] although those derived from aniline are easily attacked, even at moderate temperatures, provided high pressure of hydrogen is used, an much ammonia usually results.

EXPERIMENTAL

Pseudocumenol-3 (*I*).—3-Bromopseudocumene (50 g.), cuprous oxide (7.5 g.), and copper powder (2.5 g.) were placed in a bomb, and aqueous sodium hydroxide solution (50 g. in 500 cc.) was added. The bomb was closed and heated at 275° for 3 hours. After cooling, the mixture was filtered and the filtrate was acidified with sulfuric acid (30%) and steam distilled. The phenol (28 g., 82%) which crystallized from the cooled distillate melted at 55–56°.

Oxidations.—The phenol I (5 g.) was dissolved in a mixture of concentrated sulfuric acid (75 g.) and water (7.5 g.). The hot solution was allowed to stand for a few minutes and was then cooled to 5°. Sodium dichromate (12.5 g.) in water (50 cc.) was added at such a rate that the temperature was maintained between 10–20°. After the addition was complete, the mixture was heated to 40° for 15 minutes, then cooled and extracted with ether. Removal of the ether left *trimethylquinone* as a liquid; yield, 50%.

A similar oxidation of *durenol* (5 g.) produced duroquinone, m.p., 110–111°, in 50% yield.

Pseudocumenol-6 (*II*), when similarly oxidized, gave no quinone. A part of the phenol was recovered, and the rest was converted into a dark tar. Addition of solid sodium dichromate to a solution of the phenol in concentrated sulfuric acid at 5°, or at −5°, produced no better result. Chromic oxide in acetic acid, ferric chloride,

[6] Private communication from Dr. R. T. Major, Rahway, New Jersey.

potassium ferricyanide, and mercuric oxide were all tried as oxidizing agents, but no quinone could be obtained by the use of any of them.

Trimethylquinone from the azo compound.—Sulfanilic acid (105 g.) was dissolved in water (500 cc.) containing sodium carbonate (26.5 g.) by warming. The solution was cooled to 15° and a solution of sodium nitrite (37 g.) in water (100 cc.) was added and the mixture was immediately poured into ice (600 g.) and hydrochloric acid (106 cc.), and allowed to stand for 20–30 minutes. The diazonium solution was poured slowly into a well-stirred solution of pseudocumenol-6 (63 g.) in water (300 cc.) containing sodium hydroxide (75 g.) *An excess of alkali at this point is very important.* The mixture was allowed to stand for at least 2 hours—*best over night*—allowing the ice to melt and the temperature to rise to that of the room. The solution was made strongly acid with hydrochloric acid (200–250 cc.). Without removal of the red azo compound, stannous chloride (164 g.) in hydrochloric acid (200 cc.) was added, and solution was heated almost to boiling until the solution cleared and the color became orange-brown. The mixture was transferred to a steam-distillation flask, excess ferric chloride (about 800 g.) was added, and the mixture was *at once* steam-distilled. In the case of trimethylquinone it is particularly important that the steam distilla-

TABLE

PREPARATION OF QUINONES

PHENOL	(G.)	QUINONE	(G.)	M.P., °C.	YIELD, %
3,5-Dimethyl-	(27)	*m*-Xylo	(32.2)	73–75[7]	74.5
2,5-Dimethyl-	(27)	*p*-Xylo	(15)	123.5–125[8]	50
Trimethyl-	(63)	Trimethyl	(72)	26[2]	95
Tetramethyl-	(10)	Duro-	(6.5)	111–112[9]	60†

[7] NOELTING AND BAUMANN, *Ber.*, **18**, 1151 (1885), give the m.p. as 72–73°.

[8] NIETZKI, *Ann.*, **215**, 168 (1882), gives the m.p. as 125°.

[9] SMITH AND DOBROVOLNY, *J. Am. Chem. Soc.*, **48**, 1422 (1926); m.p. 111°.

† This quinone was not steam-distilled but was merely filtered from the cold reaction mixture.

tion be performed at once to avoid formation of trimethylchloroquinone. The quinone was removed from the distillate by ether extraction which *must be continued* until the aqueous layer is colorless as this quinone is fairly soluble in the large volume of water. The combined ether solutions were dried over sodium sulfate, and the solvent was removed by *distilling it through a short packed column.* The residue which weighed 72 g. (95%) solidified in an ice bath and then melted at 26°. Although this melting point is a few degrees low (Smith[2], m.p. 29–30) the quinone does not need to be purified further for most purposes. For purification it is best distilled: b.p., 98° under 10 mm., 108° under 18 mm.

The other quinones were prepared by the same method, using 0.2 molar quantities of materials. The results are given in the accompanying table. It must be emphasized again that the coupling reaction must be allowed plenty of time for completion. Thus in one run in which durenol (69.6 g.) was used, and in which coupling was allowed to proceed for only an hour and a half, there resulted 25.4 g. of a product which melted at 91.5–108°, and which was a mixture of the quinone and unchanged phenol. A similar run, in which 3,5-dimethylphenol was used, and in which only an hour and a half was allowed for the coupling, gave only a red oil as the product.

If any unchanged phenols are present when the quinones are produced, red phenoquinones are apparently formed. These substances are extremely difficult to separate from the quinones, either by crystallization or by distillation. About the only feasible separation is to dissolve the mixture in petroleum ether and remove the phenol by extraction with Claisen's alkali, and since some of the quinones, especially trimethylquinone, are extremely sensitive to alkali, this method often involves great losses.

Coupling with aniline.—Aniline (112 g.) was diazotized in the usual manner in sulfuric acid solution; volume of the solution 2400 cc. The diazonium compound was coupled with trimethylphenol (126 g.) as described above. After acidification, the red azo compound was collected by filtration and dried. It weighed 218 g. (98%).

Reduction of the azo compound (20 g.) by stannous chloride (50 g.), and subsequent oxidation as outlined above, produced 2.5 g. of trimethylquinone (20.8%).

Reduction of the azo compound (10 g.) by boiling in sodium hydroxide (15 g.) and water (100 cc.) with sodium hydrosulfite (18 g.) in water (100 cc.) for 2 hours at 100°, followed by acidification and subsequent oxidation as before produced no quinone.

Catalytic reduction.—The azo compound (49 g.) was suspended in alcohol (100 cc.), and about 0.2 g. of Raney nickel catalyst was added. The mixture was reduced in a bomb at 120° for 2 hours with hydrogen under 2000 lbs. initial pressure. The mixture which smelled strongly of ammonia, was acidified, excess ferric chloride was added, and the quinone was removed by steam distillation; yield 13 g. (43%); b.p., 98–103° under 11 mm. In a similar experiment, with water (150 cc.) substituted for the alcohol, 20 g. of the azo compound gave 5 g. (41%) of quinone which boiled at 99–101° under 12 mm. Although these reductions were carried out at 120°, the reaction started even at room temperature under the high pressure of hydrogen; in a low pressure apparatus (40 lbs.), however, no reduction occurred in 15 hours.

SUMMARY

1. This paper contains the description of a convenient and rapid method for preparing polymethylquinones in quantity starting with polymethylphenols.

2. The method comprises coupling the phenol with diazotized sulfanilic acid, reductive cleavage of the azo compound, and oxidation of the aminophenol, followed by removal of the quinone by steam-distillation or filtration. The quinones are obtained quite pure if certain precautions are taken during the preparation.

3. Duroquinone, pseudocumoquinone, *o*- and *p*-xyloquinones have been prepared in overall yields of from 50 to over 90 per cent. by the method, which fails, however, when applied to the preparation of toluoquinone.

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

THE CHEMISTRY OF VITAMIN E. VIII. THE CHLOROMETHYLATION OF POLYMETHYLHYDROQUINONES AND THEIR DERIVATIVES: CLEAVAGE OF HYDROQUINONE ETHERS[1]

LEE IRVIN SMITH, HERBERT E. UNGNADE, J. W. OPIE, W. W. PRICHARD R. B. CARLIN, AND E. W. KAISER

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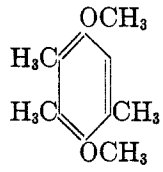
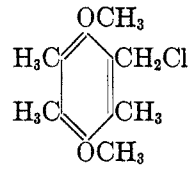
Many syntheses may be devised for the preparation of *p*-hydroxychromans and coumarans, in which the starting materials are hydroquinones and in which the proper side-chain is built stepwise into the hydroquinone molecule, with ring closure as the final step. However, for the α-mono- and disubstituted ring compounds, it is not possible to introduce the whole of the necessary side-chain into the hydroquinone in one step, and the gradual building up of the side-chain requires that the hydroquinone and its derivatives be subjected to conditions such as those encountered in the Grignard reaction, alkaline alkylations and hydrolyses and the like. The polymethylhydroquinones are extremely unstable in the presence of alkali, and the hydroxyl groups, of course, react at once with Grignard reagents, giving magnesium derivatives which are only sparingly soluble and which therefore react only slowly with the reagents at other points in the molecule. Moreover, the reaction at the two hydroxyl groups destroys two molecules of the Grignard reagent, a result which becomes a limiting factor when the reagent has been derived from complicated and difficultly accessible halogen compounds, as is the case in any synthesis of this type the aim of which is the production of α-substituted chromans and coumarans at all closely related to the tocopherols. For these reasons, it is necessary to protect the hydroxyl groups of the hydroquinones as the first step in syntheses of this type. The protecting group, however, must be one which will withstand the reagents and reaction conditions to be used in the synthesis, and which, at the same time, can be removed cleanly and without too much difficulty, so that the rest of the molecule will not be disturbed during the removal of the protecting group. As will be seen from the discussion which follows, it is not easy to select a protecting group which fulfils adequately all of the necessary requirements.

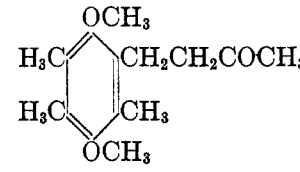
Our first experiments started with the dimethyl ether of trimethylhydro-

[1] Paper VII: J. ORG. CHEM., **4**, 318 (1939).

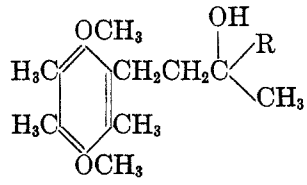
quinone (I), a substance made some time ago by one of us[2], and of which we had a supply on hand. This was readily converted to the chloro-

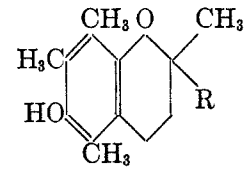

I


II


III

methyl derivative (II)[3] in nearly quantitative yield, which in turn reacted well with sodium acetoacetic ester to give, after hydrolysis, the ketone III, again in nearly quantitative yields. It was planned to complete the synthesis of V from III by adding an appropriate Grignard reagent, demethylating the resulting carbinol IV, and then closing the ring to V, but before carrying out these reactions, experiments were performed on the demeth-


IV

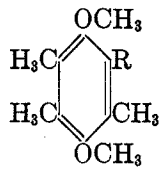

V

ylation of the ketone III. It was not found possible, by any of the methods tried, to demethylate this ketone unless at the same time deep-seated decompositions occurred. Aluminum chloride in boiling benzene, or at 100° without a solvent, was without action; fusion of III with zinc chloride at 120–140° for one hour gave a product which was not phenolic. Hydriodic acid removed the methyl groups, but caused at the same time secondary reactions, most likely of the type discovered by John, Dietzel, and Gunther[4] in the case of the tocopherols. Aqueous hydrobromic acid (40 per cent) and hydrogen bromide in acetic acid were both tried. Some cleavage was apparently produced, for the product gave a positive phenol test. However, we have been so far unable to purify the products. The ketone was also fused with aniline hydrobromide, but this procedure gave products which were not phenolic.

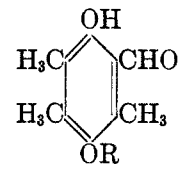
Attention was next turned to the aldehyde VIII as a possible starting material. This aldehyde can be made from I by the action of zinc cyanide,

[2] SMITH, *J. Am. Chem. Soc.*, **56**, 473 (1934).
[3] SMITH AND MACMULLEN, *ibid.*, **58**, 634 (1936).
[4] JOHN, DIETZEL, AND GUNTHER, *Z. physiol. Chem.*, **252**, 208 (1938).

aluminum chloride, and hydrochloric acid[2], but the yield is not good. Far better results were achieved by starting with II, converting this, via the acetate VI to the carbinol VII, and oxidizing the carbinol to the aldehyde. In this way overall yields of 60–70 per cent. of VIII were obtained, based upon the ether I.



VI., R = CH_2OAc
VII., R = CH_2OH
VIII., R = CHO



IX., R = CH_3
X., R = H

Two attempts to employ the Sommelet reaction and oxidize the chloride with hexamethylenetetramine[5] gave only the alcohol. Experiments showed that VIII could be demethylated by heating it carefully with aluminum chloride. The product, however, was always a mixture of VIII, the monomethyl ether IX, and the hydroquinone aldehyde X. These could be separated, but the total yield of product was poor. Apparently the action of the aluminum chloride was not confined to demethylation, and the prolonged action of the reagent at the temperatures required for complete removal of the methyl groups destroyed a great deal of the product.

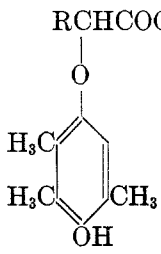
Since the methyl ethers were cleaved with such difficulty, the series of analogous ethyl ethers, consisting of XI, XII, XIII, XIV and the aldehyde XV (respectively formulas I, II, VI, VII, VIII with OCH_3 replaced by OC_2H_5) was made. But the cleavage of the ethoxyl groups in the aldehyde XV presented even more difficulties than were encountered with the methoxyaldehyde VIII. The action of aluminum chloride gave a mixture of products, in poor yield; boiling acetic acid saturated with hydrogen bromide reacted extremely slowly; and 35 per cent. hydriodic acid (with just enough acetic acid to dissolve the aldehyde) was without action on boiling for an hour and a half.

It became obvious that if hydroquinone ethers were to be used as starting materials in syntheses of the type outlined, it would be necessary to find a group which could be removed from the oxygen far more readily than methyl or ethyl. The benzyl group fitted this requirement, for it is known that benzyl ethers are cleaved by boiling hydrochloric acid[6] or by high-

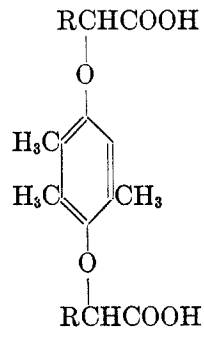
[5] MAYER AND SIEGLITZ, *Ber.*, **55**, 1837 (1922).
[6] REICHSTEIN, *Helv. Chim. Acta*, **18**, 819 (1935).

pressure hydrogenolysis.[7] The difficulty here, however, lies in the preparation of the ethers, for the benzyl halides are so reactive that the benzylation, even more than allylation, takes place predominantly on carbon instead of oxygen.[6] The action of benzyl chloride upon the hydroquinone in pyridine, or in the presence of alkali, or upon the bromomagnesium salt of the hydroquinone in ether gave in every case a difficultly separable mixture which consisted for the most part of the C-benzyl derivative and unchanged hydroquinone. Only in one case, by the action of benzyl chloride upon an alcoholic solution of hydroquinone in the presence of carbonate was it possible to obtain any of the dibenzyl ether, and then only in small amounts. Nor was the action of phenyldiazomethane upon the hydroquinone attended with any better success. Aside from the difficulties involved in the preparation of the diazo compound, the reaction between it and the hydroquinone was very slow and produced a mixture which could not be separated.

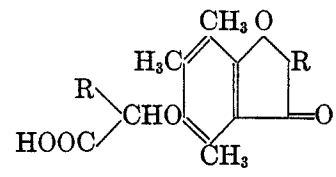
Although it was known[8] that the aryl oxy acids were cleaved with difficulty, some experiments were carried out on the action of bromoacetic ester, α-bromopropionic ester and alkali upon the hydroquinone. If this reaction could be confined to the hydroxyl group adjacent to the vacant position in the hydroquinone, the resulting aryl oxy acid could be cyclized to a coumaranone which then could be further manipulated. It was found, however, that treatment of the hydroquinone with one mole of alkali and one mole of the bromo ester gave, not the mono ether XVI, but a mixture of the di ether XVII and unchanged hydroquinone. Although



XVI



XVII



XVIII

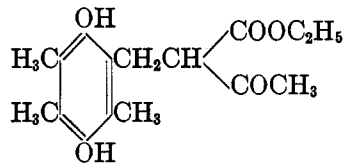
XVII could be readily cyclized to the coumaranone XVIII, the product could not be "dealkylated". Moreover, the fact that two stereoisomers of XVII were possible[8] introduced additional complications, for it rendered

[7] ADKINS AND VAN DUZEE, *J. Am. Chem. Soc.*, **57**, 147 (1935).

[8] BISCHOFF, *Ber.*, **33**, 1689 (1900).

the purification of XVII so difficult that the synthesis had to be abandoned. Certain points were discovered regarding the cyclization of these acids to coumaranones, however. The acid chloride of XVII (R=H) was readily prepared from the acid and thionyl chloride, but the chloride did not cyclize readily. However, when the *acid* was heated to 100° with 85–95 per cent. sulfuric acid, the coumaranone XVIII (R=H) was easily obtained.

It appeared, then, that any synthesis in which the hydroxyl groups were protected as ether groups was attended with so much difficulty as to be impracticable, and we turned our attention to the use of esters as protecting groups. The hydroquinone readily forms a diacetate XIX and although the conditions must be very carefully controlled, this can be chloromethylated to give XX (formulas I and II, respectively, with OCH_3 replaced by OAc). Alkylation of acetoacetic ester by XX gave the *hydroquinone* ester (XXI) in fair yield (40 per cent.). With this sub-



XXI

stance available, the route to the corresponding ketone (III, OCH_3 replaced by OH) is clear, and from this ketone, to alcohols and chromans analogous to IV and V. These experiments will be reported in a later paper.

It is interesting in this connection that while the diacetate of the hydroquinone readily undergoes the chloromethylation reaction at 0°, the dibenzoate is completely inert under the same conditions and is recovered quantitatively even after prolonged action of hydrochloric acid and formalin at 40°.

EXPERIMENTAL

3,6-Dimethoxy-2,4,5-trimethylbenzylchloride (II) was prepared from the dimethyl ether of trimethylhydroquinone in quantitative yields by the procedure of Smith and MacMullen.[3] The melting point of the product, previously reported as 63–63.5°, was 67–68° when very pure (solid) starting material was used.

1-(3,6-Dimethoxy-2,4,5-trimethylphenyl)butanone-3 (III).—Acetoacetic ester (12 g.) was added to a solution of sodium (2.12 g.) in absolute ethanol (100 cc.). The mixture was well shaken while a solution of the chloride II (21 g.) in absolute ethanol (100 cc.) was slowly added. After standing for 3 hours, the mixture was warmed on the steam bath for 30 minutes. It was then neutral to wet litmus. Water was added, the solution was made slightly acid with dilute sulfuric acid, and most of the

alcohol was removed under reduced pressure. The aqueous solution was extracted with ether, and the ether was evaporated. The residue was stirred with an excess of 5% aqueous sodium hydroxide for 4 hours at room temperature, then ethanol (50 cc.) was added, and the mixture was refluxed for 30 minutes. Water (50 cc.) was added, the solution was made acid to Congo Red with 30% sulfuric acid and warmed and shaken until all the solid was melted. After cooling, the solid (22 g., m.p., 63–64°) was removed and crystallized several times from aqueous alcohol, when it melted at 78–78.5°.

Anal. Calc'd for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80.
Found: C, 71.75; H, 8.63.

The *semicarbazone*, prepared in the usual way and crystallized from aqueous ethanol, melted at 108–109°.

Anal. Calc'd for $C_{16}H_{25}N_3O_3$: C, 62.54; H, 8.22.
Found: C, 62.54; H, 8.62.

The haloform reaction on the ketone gave, not the expected acid, but a bromo acid which melted at 155–157°, and which was not further investigated.

Demethylation experiments.—(*a*) The ketone (1 g.) was fused with aniline hydrobromide (2 g.) at 225–227° for 15 minutes. The cooled mixture was poured into hydrochloric acid and the solid was removed. The crude product melted at 115–120°; the filtrate, on standing, deposited a small amount of solid which melted at 130–130.5°. Neither product was phenolic (very weak Folin test); they were not investigated further.

(*b*) The ketone (2 g.) was boiled with hydriodic acid (20 cc., d., 1.50) and acetic acid (8 cc.) for five minutes. The product was an oily material which contained a substance giving a blue solution. The oil could not be purified.

(*c*) The ketone (0.5 g.) was heated with hydrobromic acid (10 cc., 40%) for 3.5 hours at 150°. The product was a small amount of yellow oil which gave a positive phenol test.

(*d*) The ketone (1 g.) was heated with 10 cc. of a saturated solution of hydrobromic acid in acetic acid. The product was an oil which gave a positive phenol test but which could not be purified.

3,6-Dimethoxy-2,4,5-trimethylbenzyl acetate (*VI*).—The chloride (II) (6 g.) and potassium acetate (12 g.) were refluxed for one hour in acetic acid (100 cc.). The mixture was poured over ice, neutralized with ammonia, and the solid was collected by filtration. The yield was 6.25 g. (95%). The substance melts at 65–66°.[9]

3,6-Dimethoxy-2,4,5-trimethylbenzyl alcohol (*VII*).—The crude acetate (6.5 g.) was boiled for one hour with ethanol (50 cc.) and potassium hydroxide (70 cc., 20% aqueous). The product was poured into water, and the solid was removed. The yield was 95%. A sample of the alcohol melted at 120–121° after several crystallizations from dilute acetone (*cf.*, Smith and Dobrovolny[9], m.p. 115–116°).

3,6-Dimethoxy-2,4,5-trimethylbenzaldehyde (*VIII*).—The alcohol (18.7 g., .089 moles) was dissolved in acetic acid (250 cc.) and water (20 cc.). The solution was maintained at a temperature of 45–50° while a solution of chromic oxide (6.23 g., 5% excess) in acetic acid (150 cc.) and water (20 cc.) was slowly added (1 hour). The mixture was poured over ice, and the solid (12 g., m.p. 78–79°) was removed by filtration. The filtrate, when neutralized with ammonia, deposited an additional 3.3 g. of the aldehyde which melted at 78–79°. The total yield was 83%. When pure, the aldehyde melts at 83.5–84.5°.[2]

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[9] SMITH AND DOBROVOLNY, *J. Am. Chem. Soc.*, **48**, 1709 (1926).

Sommelet reaction on the chloride.—The chloride II (1 g.) in alcohol (20 cc.) and water (15 cc.) was refluxed for 12 hours with hexamethylenetetramine (0.6 g.). The alcohol was distilled, water (50 cc.) was added to the residue, and the mixture was extracted with ether. After drying over calcium chloride, the ether was removed. The residue (0.85 g., 88%) was a waxy solid which melted at 104–107°. When mixed with the alcohol VII (sample melting at 115–116°), the substance melted at 107–108°.

Demethylation of the aldehyde.—The dimethoxyaldehyde (5 g.) was dissolved in purified petroleum ether (100 cc., b.p., 90–100°) and refluxed for 70 minutes with aluminum chloride (5 g.). The mixture was cooled, and the solvent was decanted from the solid, which was washed with hot petroleum ether (20 cc.). Ice and water were added, and the greenish solid reacted vigorously to give a yellow solution containing some yellow solid. The mixture was extracted with ether, and the brown oil left after evaporation of the ether was boiled with water and filtered while hot. From the cooled filtrate, yellow crystals (about 0.25 g.) were obtained. These melted at 135–136°, gave a positive phenol test, but no color with ferric chloride. It was probably the dihydroxyaldehyde (X), for when mixed with the product made (in very poor yield) from the hydroquinone, zinc cyanide, and hydrochloric acid (m.p. 147–148°), it melted at 139–141°.

The brown oil, which was not water-soluble, was leached from the filter paper with alcohol, taken up in ether and extracted thoroughly with 20% potassium hydroxide. The alkaline layer was acidified and extracted with ether, and the ether was evaporated. The product, crystallized from ethanol, melted at 88–89°, gave an emerald-green color with ferric chloride, and a positive phenol test. It was the aldehyde IX; yield 50%.

Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.00; H, 7.26.
Found: C, 67.76; H, 7.16.

3,6-Dihydroxy-2,4,5-trimethylbenzaldehyde (*X*).—At room temperature, dry hydrogen chloride was passed for 5 hours into a well-stirred solution of trimethylhydroquinone (4 g., 0.0286 moles) and ether (60 cc.) in which was suspended zinc cyanide (6 g., 0.051 moles). The solvent was decanted, and the pasty orange-colored solid was boiled with water (100 cc.) and filtered while hot. The filtrate on cooling, deposited a solid, which was removed and the filtrate was used to extract the pasty solid again. In this way there was obtained 3.07 g. of a solid which melted at 163–168°; the residue from these extractions was unchanged hydroquinone. After crystallization from dilute ethanol, it weighed 0.44 g. and melted at 168–170°. The solid which melted at 163–168° was a mixture of hydroquinone and the aldehyde X. Most of the hydroquinone was removed by boiling the mixture with benzene (65 cc.) and petroleum ether (65 cc.), cooling and filtering the cold suspension. The filtrate was evaporated to dryness and the yellow residue was crystallized four times from petroleum ether (90–100°). The product at this point was a few mg. of a *yellow* solid, which melted at 129–131°. Two more crystallizations from dilute ethanol gave an *orange* product melting at 147–148°.

Anal. Calc'd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67.
Found: C, 66.61; H, 6.70.

Some indication was obtained that this aldehyde exists in two crystalline forms with different melting points, one yellow and one orange, for when a portion of the analytical sample was recrystallized from petroleum ether, a *yellow* product melting at 131–138° was obtained, which, when mixed with the analytical sample, melted at 138–144°.

3,6-Diethoxypseudocumene: Pseudocumohydroquinone diethyl ether (*XI*).—The hydroquinone (7.6 g., 0.05 moles) and ethyl sulfate (45 g.) were heated to boiling in methanol (50 cc.). To this was added potassium hydroxide (60 g.) in hot methanol (300 cc.). After the vigorous reaction subsided, the mixture was refluxed for 30 minutes, and was then steam-distilled. The distillate was extracted thoroughly with ether, the ether was *distilled* through a short (2″) packed column, and the residue was distilled under 2 mm. pressure. The diethoxy compound boiled at 102–103° (2 mm.) and melted, after crystallization from alcohol, at 34–35°. The yield was 80%.

Anal. Calc'd for $C_{13}H_{20}O_2$: C, 75.00; H, 9.61.
Found: C, 74.89; H, 9.65.

3,6-Diethoxy-2,4,5-trimethylbenzyl chloride (*XII*), prepared in nearly quantitative yields as described above for the dimethoxy compound, was crystallized twice from ether, when it melted at 86–87°.

Anal. Calc'd for $C_{14}H_{21}ClO_2$: C, 65.50; H, 8.19.
Found: C, 65.31; H, 8.04.

3,6-Diethoxy-2,4,5-trimethylbenzyl acetate (*XIII*), prepared as described above for the dimethoxy compound, melted at 113.5–114.5° after two crystallizations from dilute acetone.

Anal. Calc'd for $C_{16}H_{24}O_4$: C, 68.57; H, 8.57.
Found: C, 68.84; H, 8.68.

3,6-Diethoxy-2,4,5-trimethylbenzyl alcohol (*XIV*), prepared by hydrolysis of the acetate, melted at 112–113° after crystallization from dilute acetone.

Anal. Calc'd for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24.
Found: C, 71.20; H, 9.32.

The overall yield of XIV in this series, based upon the chloro compound XII, was 91%.

3,6-Diethoxy-2,4,5-trimethylbenzaldehyde (*XV*) was prepared from the alcohol (5.56 g.) by oxidation at 50° in acetic acid (100 cc.) and water (10 cc.) by chromic oxide (1.56 g.) in acetic acid (50 cc.) and water (5 cc.). When the oxidation (which is rather slow at 50°) was complete, water was added, and the solid (m.p. 93–95°) was removed and crystallized from ethanol. It then melted at 99–100°; the yield was 60%.

Anal. Calc'd for $C_{14}H_{20}O_3$: C, 71.19; H, 8.47.
Found: C, 71.57; H, 8.71.

This aldehyde showed the same phototropic effect as the dimethoxyaldehyde—the crystalline product was white when freshly prepared, but turned bright-yellow on exposure to light.

Dealkylation experiments.—These were duplicates of the experiments performed on the dimethoxy compound, but the results were much poorer. The monoethoxyaldehyde was never obtained pure, and in general, the ethoxy compounds proved to be much less suitable than the methoxy compounds for the purpose in view.

3,6-Dibenzyloxypseudocumene: Pseudocumohydroquinone dibenzyl ether.—Potassium carbonate (7.3 g., 0.052 moles) was suspended in a solution of the hydroquinone (4 g., 0.0263 moles) in acetone (30 cc.). To this was added slowly (4 hours) benzyl chloride (8 g., 0.0634 moles, freshly distilled). The mixture was then refluxed for 8 hours. The acetone was distilled, and water (100 cc.) was added to the residue. The product was extracted with ether, the ethereal solution was dried over sodium sulfate, and the ether was removed. On standing in the ice box, the residual oil deposited 1.4 g. of a solid (*A*), m.p. 137–150°, which was collected by filtration and

washed with a small amount of petroleum ether (b.p. 40–70°). The oily filtrate and washings from the solid were combined, the solvent was removed, and the residue was distilled under 13 mm. pressure. The distillate (*B*) weighed 2.35 g. and boiled at 75–76°. The semi-solid residue was then distilled in a molecular still, giving 2.10 g. of distillate b.p. 153–160° (10^{-6} mm.) which solidified on cooling (*C*). This product was crystallized from dilute alcohol, then from low-boiling petroleum ether, and again from dilute alcohol. It then melted at 72.5–73.5°. *A* was impure hydroquinone, *B* was benzyl chloride, and *C* was the dibenzyl ether. Based upon the amount of hydroquinone taken, the yield was 24%; when corrected for the hydroquinone recovered (*A*), the yield was 37%. The substance gave a negative phenol test (Folin).

Anal. Calc'd for $C_{28}H_{24}O_2$: C, 83.13; H, 7.23.
Found: C, 82.40; H, 7.83.

A suspension of the hydroquinone (5 g., 0.0329 moles) in dry ether was added to ethylmagnesium bromide (0.068 moles). The ether was removed and replaced by benzene. After refluxing for an hour, benzyl chloride (8.6 g.) was added and the solution was allowed to stand for 12 hours. Dilute sulfuric acid and ice were added, and the mixture was extracted with ether. The ether solution was extracted thoroughly with 10% potassium hydroxide. Removal of the ether left 12 g. of semi-solid oil; the solid was removed and crystallized from ether and petroleum ether. It melted at 141–142°, and was strongly phenolic (Folin). Since it was not the dibenzyl ether, it was not examined further.

The hydroquinone (5 g.) was dissolved in pyridine (15 g.), and benzyl chloride (9 g.) was added dropwise, with cooling. The deep-red solution was warmed on the steam bath for 3 hours, then poured over iced hydrochloric acid. The salmon-colored solid was removed and dried. It melted at 158–164° and weighed 4.8 g. It was impure hydroquinone.

A solution of phenyldiazomethane (from 25 g. of benzylurethane)[6] was filtered into a suspension of the hydroquinone (2.429 g.) in ether (50 cc.). The suspension turned green, and then brown. It was allowed to stand in the ice box for 12 hours, protected from moisture. The mixture was then warmed and made acid with acetic acid. The ethereal solution was washed twice with water and dried over sodium sulfate. Removal of the ether left an oil which could not be crystallized.

A similar experiment (5 g. of hydroquinone) in which a solution of phenyldiazomethane prepared from 9 g. of benzalhydrazone[10] was used gave a product which contained over 4 g. of impure hydroquinone besides a small amount of oil.

Dicarboxy methyl ether of pseudocumohydroquinone (*XVII*, *R* = *H*).—Sodium ethoxide (0.0197 moles) was prepared from sodium (0.454 g.) and alcohol (20 cc.) under nitrogen, and the hydroquinone (3 g., 0.0197 moles) was added. When traces of oxygen were rigidly excluded, the hydroquinone dissolved to give a red solution; otherwise the solution was purple. Bromoacetic ester (3.4 g., 0.0197 moles) was added, and the solution was refluxed for 2 hours. The mixture was poured onto ice, and the oily product was removed by ether extraction. The ether was evaporated, and the residue was refluxed for an hour with aqueous potassium hydroxide (20 cc., 10%). The cooled solution, when poured onto ice, gave a small amount of a dark, tarry, precipitate, together with a red solution. The precipitate was removed by filtration and discarded. The red filtrate was extracted thoroughly with ether, and the ether was evaporated. A red viscous oil remained, which solidified when

[10] STAUDINGER, *Ber.*, **49**, 1906 (1916).

rubbed with a little petroleum ether. The product when recrystallized from ether or petroleum ether was gummy, but it crystallized well from water after decolorization of the hot solution with bone black and removal of the insoluble tarry impurity. The white product melted at 205–206°, gave a very weak phenol test, and was completely soluble in carbonate. It was not analyzed.

The acid (0.3 g.) was refluxed with thionyl chloride (10 cc.) for a few minutes. The excess reagent was pumped off, and the solid residue was dissolved in dry benzene and refluxed for 30 minutes with a small amount of aluminum chloride. There was no evolution of hydrochloric acid, and the original acid (m.p. 205–206°) was recovered by pouring the reaction mixture into water, separating the benzene layer, and evaporating the solvent.

5-Carbomethoxy-4,6,7-trimethylcoumaranone (*XVIII R = H*).—The acid (0.6 g.) was dissolved in sulfuric acid (5 cc., 95%) and warmed gently. After 45 minutes, ice was added, and the solid product (2 g.) was collected by filtration and crystallized from dilute acetic acid. It melted at 211–213° (m.p. of mixture with the starting material, 193°), and was soluble in carbonate.

Anal. Calc'd for $C_{11}H_{12}O_3$ (hydroxycoumaranone): C, 68.75; H, 6.11.
Calc'd for $C_{13}H_{14}O_5$ (XVIII, R = H): C, 62.45; H, 5.60.
Found: C, 62.50; H, 6.20.

The product is therefore XVIII (R = H), and the action of bromoacetic ester upon the hydroquinone produced a di ether, XVII (R = H).

The dipropionic acid ether (*XVII, R = CH_3*).—The hydroquinone (5 g.) was converted to the disodium salt as above, and two equivalents of α-bromopropionic ester were added. After refluxing for 2 hours, the mixture was poured over ice and extracted with ether. The solvent was removed, and unchanged bromo ester was pumped off. The residue was taken up in ether and washed with potassium hydroxide (10%) until the washings were colorless. The light-yellow ethereal solution was then washed with water and dried. Removal of the ether left a yellow oil (8 g.), which was refluxed with potassium hydroxide (10%) for 1.5 hours. Most of the oil dissolved, and the solution was purple. The cooled solution was extracted with ether, and the aqueous layer was bone-blacked and filtered. Acidification of the filtrate produced a red oil which resisted all attempts to crystallize it. The oil was completely soluble in carbonate, but acidification produced only the oil, and no solid could be obtained from it.

3,6-Diacetoxy-2,4,5-trimethylbenzyl chloride (*XX*) (*II, OCH_3 replaced by OAc*).—The diacetate of pseudocumohydroquinone (5 g.),[2] which must be pure (m.p. at least 108°), formalin (15 cc., 40%) and hydrochloric acid (20 cc.) were stirred vigorously and *maintained* at 10–20° while a fairly rapid stream of dry hydrogen chloride was passed in. After about one hour, the reaction mixture set to a paste; it was warmed to 25° and hydrogen chloride was passed in for 2 hours longer. The mixture was poured onto a *large* volume of ice, and the solid was immediately collected by filtration, washed with water and dried at room temperature while on the funnel. The product weighed 4.3 g (73%) and melted 138–142°. A small amount was dissolved in low-boiling petroleum ether, the solution was decolorized with charcoal, and the product was crystallized from the filtrate. It melted at 150–151° and gave a negative phenol test.

Anal. Calc'd for $C_{14}H_{17}ClO_4$: C, 59.05; H, 5.98.
Found: C, 59.63; H, 6.45.

Often the chloride is accompanied by a high-melting byproduct (225–227°) which is insoluble in ether, and if the temperatures are not carefully controlled, the product

is oily, very difficult to purify and the yield is low. It is best not to run this preparation on larger amounts than 5 g. of the acetate.

(3,6-Dihydroxy-2,4,5-trimethylbenzyl) acetoacetic ester (XXI).—A suspension of sodium acetoacetic ester in benzene was prepared as follows: sodium (0.5 g.) was dissolved in absolute ethanol (10 cc.), and acetoacetic ester (2.6 g.) was added. Benzene (50 cc., pure, thiophene free) was added, and half of the liquid was removed by distillation. The residual material was brought back to its original volume by addition of benzene and again half of the liquid was distilled. This process was repeated twice more—four times in all. To the well-stirred suspension was added during 5 minutes, a solution of the benzyl chloride XX (5 g., m.p. 138–141°) in benzene (50 cc.). Within 10 minutes all of the suspended solids dissolved. The mixture was allowed to stand for 1.5 hours, after which it was refluxed for 2 hours. The cooled solution was washed twice with dilute hydrochloric acid (3 cc. in 100 cc. of water each time), then once with water. The benzene was removed under reduced pressure at room temperature, and the residue, a brown pasty mass, was crystallized from ether-petroleum ether. The product separated in the form of white plates which melted at 135–136° with decomposition and which gave a strong phenol test (Folin). The yield was 2 g. (40%).

Anal. Calc'd for $C_{16}H_{22}O_5$: C, 65.23; H, 7.59.
Found: C, 65.17; H, 7.29.

SUMMARY

1. The dimethyl ether of trimethylhydroquinone has been chloromethylated, and an excellent yield of the substituted benzyl chloride resulted. This chloride, in turn, gave an excellent yield of ketone via the acetoacetic ester synthesis, but the ketone could not be demethylated to the hydroquinone ketone.

2. The dimethoxytrimethylbenzaldehyde was made from the ether in excellent overall yields. While the aldehyde could be demethylated, the product was a mixture, and the yields were poor.

3. Analogous reactions were carried out with the diethyl ether of the hydroquinone, but removal of the ethyl groups was even more difficult than demethylation.

4. The dibenzyl ether of the hydroquinone could not be prepared in quantity because nuclear benzylation occurred simultaneously.

5. "Alkylation" of the hydroquinone by α-bromo esters produced only the di ether, no mono ether resulting under any of the conditions tried.

6. The diacetate of the hydroquinone was chloromethylated, and a good yield of the benzyl chloride resulted. This in turn gave a good yield of dihydroxytrimethylbenzylacetoacetic ester.

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

THE CHEMISTRY OF VITAMIN E. IX. PREPARATION OF LONG CHAIN HALIDES AND KETONES CONTAINING ISOPENTANE UNITS[1]

LEE IRVIN SMITH, HERBERT E. UNGNADE, F. L. AUSTIN, W. W. PRICHARD, AND J. W. OPIE

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In connection with several projected syntheses of tocopherols, their coumaran isomers and lower "prenologs"[2] halides of types I and II, as well as ketones of types III, were required (n = 1 or 2)

$$(CH_3)_2CHCH_2CH_2[CH_2CH(CH_3)CH_2CH_2]_nX \quad (I)$$

$$(CH_3)_2CHCH_2CH_2[CH_2CH(CH_3)CH_2CH_2]_nCH_2X \quad (II)$$

$$(CH_3)_2CHCH_2CH_2[CH_2CH(CH_3)CH_2CH_2]_nCH_2COCH_3 \quad (III)$$

This paper contains a description of the synthesis of such compounds, together with some observations on the cleavage of aliphatic ethers, formation of long-chain halides, alkylations of acetoacetic ester and acetonedicarboxylic ester with these halides, and hydrolysis of the resulting keto esters to ketones.

There are two readily available substances, both alcohols, which contain a chain composed of two isoprene units, geraniol (IV) and citronellol (V), and

$$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH_2OH \quad (IV)$$

$$(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)CH_2CH_2OH \quad (V)$$

our syntheses therefore started with these substances. The general plan is shown in the following diagram:

$$\left.\begin{matrix}\text{IV}\\ \text{V}\end{matrix}\right\}\rightarrow (CH_3)_2CHCH_2CH_2CH_2CH(CH_3)CH_2CH_2OH \text{ (VI)} \quad (1)$$

$$\text{VI} \rightarrow \text{I}(n = 1, \text{X} = \text{Br or Cl}) \quad (2)$$

$$\text{I} \rightarrow RCH\begin{matrix}\diagup COCH_3\\ \diagdown COOC_2H_5\end{matrix} \text{ (VII)} \quad (3)$$

[1] Paper VIII. J. ORG. CHEM., **4**, 323 (1939).

[2] SPÄTH AND BRUCK, *Ber.*, **71**, 2708 (1938).

$$\text{VII} \rightarrow \text{RCH}_2\text{COCH}_3 \text{ (III, n = 1)} \quad (4)$$

$$\text{I} \rightarrow \underset{\substack{\text{CO}\\|\\\text{CH}_2\text{COOC}_2\text{H}_5}}{\text{RCHCOOC}_2\text{H}_5} \xrightarrow{\text{BrCH}_2\text{CH}_2\text{OR}'} \underset{\substack{\text{CO}\\|\\\text{CHCOOC}_2\text{H}_5\\|\\\text{CH}_2\text{CH}_2\text{OR}'}}{\text{RCHCOOC}_2\text{H}_5} \rightarrow \underset{\substack{\text{CO}\\|\\\text{CH}_2\\|\\\text{CH}_2\text{CH}_2\text{OR}'}}{\text{RCH}_2} \quad (5)$$

VIII IX ($R' = C_2H_5$) X

$$\text{I} \rightarrow \text{RMgX} \xrightarrow{\text{ClCH}_2\text{OCH}_3} \text{RCH}_2\text{OCH}_3 \text{ (XI)} \rightarrow \text{RCH}_2\text{X (II, } n = 1, \text{X} = \text{Br}) \quad (6)$$

Reduction of the unsaturated alcohols (reaction 1).—There is a marked difference in the ease with which the two unsaturated alcohols are reduced catalytically, and in the quality of the product from the two. Geraniol (IV), with two double bonds, one of them allylic, begins to absorb hydrogen in the presence of Raney nickel at 100° (pressure 2000 lbs.). When the reduction was allowed to proceed at 125° until no more hydrogen was absorbed, the product was found to be still unsaturated. Reduction was continued at 150°; again the product was still unsaturated after absorption ceased. The temperature was then raised to 200° (pressure 2550 lbs.) and at this point reduction was complete and the product was saturated. The reduction curve showed that the reaction occurred in two well-defined stages. Since allylic carbinols apparently required high temperatures and pressures for reduction,[3] it was postulated that the first, rather easy stage in the reduction involved the non-allylic double bond and on this basis it was predicted that citronellol (V) would reduce completely under much milder conditions than those required in the case of geraniol. This was found to be the case; under 1900 lbs. of hydrogen, citronellol reduced completely at 125° in the presence of Raney nickel, giving VI in quantitative yield and in high purity—so pure that distillation was quite unnecessary. In agreement with these results, farnesol, $(CH_3)_2C{=}CHCH_2CH_2{-}C(CH_3){=}CHCH_2CH_2C(CH_3){=}CHCH_2OH$ (XII) was found to require a temperature of 200° and a pressure of 2700 lbs. of hydrogen for complete reduction.*

It follows from these results in the preparation of alcohols of type VI by catalytic reduction of unsaturated alcohols, an alcohol of type V rather than of type VI should be chosen as the starting material whenever possible.

[3] Adkins, Diwoky, and Broderick, *J. Am. Chem. Soc.*, **51**, 3418 (1929).

* The authors are greatly indebted to Dr. R. T. Major and to Merck & Co., Inc., for a generous supply of farnesol.

Conversion of the alcohols to halides (reaction 2).—Various methods were used for the preparation of halides from saturated and unsaturated alcohols, but of these, only two were found to be useful in the case of the compounds under investigation. Both of these methods involved the use of the dry hydrogen halide. For allylic alcohols, good yields are obtained when the alcohol is saturated with dry hydrogen bromide or hydrogen chloride, preferably in the presence of a drying agent, and allowed to stand in the cold, while the higher saturated alcohols give the best yields of halides (bromides) by subjecting them to the action of a current of dry

TABLE

CONVERSION OF ALCOHOLS TO HALIDES[4]

ALCOHOL	(G.)	CONDITIONS	YIELD (G.)	B.P., °C.	n_D^{20}
VI	(38)	8 cc. H_2SO_4, 38 g. HBr 48%; reflux 5 hrs.	16	89–90 (8 mm.)	1.4543
VI	(30)	42 g. PBr_3, cold; 2 hrs.	25	95 (9 mm.)	1.4549
VI	(101.5)	142 g. PBr_3, cold; 1 hr.	65	101–102 (12 mm.)	
VI	(95)	80 g. Pyridine, 143 g. $SOCl_2$, 115°	77	87–88 (12 mm.)	
VI	(30)	42 g. PBr_3 in 100 cc. petr. ether, cold	15	101–103 (12 mm.)	
VI	(79)	Gaseous HBr, 140–150°; 2 hrs.	103.5 (4%)	109–110 (18 mm.)	1.4538
VI	(259.5)	Gaseous HBr, 140–150°; 7 hrs.	304 (84%)	109–110 (18 mm.)	1.4545
IV†	(30)	30 g. PBr_3, 100 cc. petr. ether, −7°; 1 hr.	8.5	46–47 (0.1 mm.)	1.5053
Hexahydro-farnesol	(20)	Gaseous HBr, 130°; 2 hrs.	16.8	124–140 (10 mm.)[5]	1.4560

[4] For the conversion of phytol to phytyl bromide, see paper IV, J. ORG. CHEM., **4**, 298 (1939).

† This experiment was carried out by Mr. Paul Sanders.

[5] FISCHER, (*a*) *Ann.*, **475**, 183 (1929); (*b*) *ibid.*, **464**, 90 (1928).

hydrogen bromide at 150° without a solvent. Aqueous hydrobromic acid cannot be used to convert allylic alcohols to bromides, for in the presence of water, the acid also adds to the double bond and dihalides constitute the main products. The following table summarizes the results obtained by several methods.

Alkylation of acetoacetic ester by perhydrogeranyl bromide (reaction 3).—At first, the method of F. G. Fischer[5a] was employed, in which reaction mixture is diluted with petroleum ether during the alkylation. The yield of VII in these experiments was about 45 per cent. Although the rather complicated procedure of Fischer appears to be of advantage when allylic

halides are involved, it is unnecessary when the saturated halides are used, and the more standard procedure as exemplified in *Organic Syntheses*[6] gave much better results. When followed by high-temperature hydrolysis, this method of alkylation gave the ketone III (n = 1) in 61 per cent. overall yields based on the bromide used. Alkylation of acetoacetic ester by perhydrofarnesyl bromide by the procedure of Fischer gave approximately the yield reported by him.

Hydrolysis of the acetoacetic ester VII to the ketone III (reaction 4).—Hydrolysis of the ester VII by aqueous (5 per cent.) alkali to which ethanol was added produced the ketone in poor yields (28 per cent.). The method of Fischer[5a] in which dilute (3 per cent.) alkali in methanol is used also gave very poor results and produced large amounts of an acidic substance. But the method of Connor and Adkins[7] in which the ester was hydrolyzed with water alone at 200° under a high pressure of hydrogen, proved to be excellent, and gave the ketone III in good yield.

Alkylation of acetone dicarboxylic ester (reaction 5).—These alkylations were uniformly disappointing. The ester was alkylated with β-ethoxy ethyl chloride, bromide, and iodide,‡ and with perhydrogeranyl bromide, but the yields in every case were low. Of the ethoxyethyl halides, the chloride failed to react at all, while the other two halides never gave more than 30 per cent. yield of product. The product from alkylation with the bromide was the most satisfactory, for it was more readily isolated and purified than was the case when the iodide was used. Alkylation of acetonedicarboxylic ester by perhydrogeranyl bromide gave very poor results; hence in most of the experiments alkylation with the ethoxyethyl halide was carried out first. But the maximum yield of IX ever obtained, by any of the methods tried, was 26 per cent.

Conversion of the C_{10}-halides to C_{11}-halides (reaction 6).—For increasing the carbon chain of the C_{10}-halide, the most promising method appeared to be the sequence given in reaction 6. Both of the halides (I, n = 1, X = Cl or Br) reacted with magnesium in an atmosphere of nitrogen under the usual Grignard conditions to give the RMgX compounds. The Grignard reagents, in turn, reacted well with chloromethyl ether. Although the chloride reacted with magnesium much more slowly than did the bromide, the yield of ether (XI) from the chloride (70 per cent.) was much better than that from the bromide (56 per cent.). Cleavage of XI to II was not successful using 48 per cent. aqueous hydrobromic acid

[6] *Organic Syntheses*, Collective Volume I, p. 243. John Wiley & Sons, Inc., New York, **1932**.

[7] CONNOR AND ADKINS, *J. Am. Chem. Soc.*, **54**, 3424 (1932).

‡ We are indebted to Dr. G. H. Reid and the Carbide & Carbon Chemicals Corp. for some of the materials used in these experiments.

(XI is not soluble in the hot reagent to any appreciable extent); when 48 per cent. hydrobromic acid was combined with enough acetic acid and acetic anhydride to give a homogeneous solution, cleavage occurred, but the product contained a considerable amount of the acetate of the C_{11}-alcohol. But dry hydrogen bromide at 135° converted the ether XI to the bromide II in good yield. This method of cleaving aliphatic ethers is generally applicable and is very efficient when the ether and the bromide have fairly high boiling points so that little or no material is swept out by the current of hot gas. Since most aliphatic ethers require relatively high temperatures for cleavage by gaseous hydrogen bromide, the method is attended with considerable difficulty in order to prevent great losses when the ether and bromide have boiling points much below 150° unless a bomb is used.

EXPERIMENTAL

Reduction of unsaturated alcohols.—Citronellol was hydrogenated in amounts ranging from 50 g. to 600 g. Raney nickel catalyst (0.5–1.0 g.) was used in all the experiments. Although the reduction started at 80–85° under an initial hydrogen pressure of about 2000 lbs., the temperature was raised to 120–125° and held there until the absorption of hydrogen ceased. The yield was practically quantitative. After removal of the catalyst, the product, which did not reduce permanganate, was quite pure and could be used directly for preparation of the bromide.

Geraniol and farnesol required temperatures around 200° for complete reduction and at these temperatures there was some hydrogenolysis. The catalyst was removed, and the product was distilled. Geraniol was reduced in amounts ranging from 30 g. to 100 g.; farnesol was reduced in 25-g. lots. Perhydrogeraniol boiled at 98–99° under 9 mm.; n_D^{20} 1.4379. The yield from geraniol was 90%. Perhydrofarnesol was not distilled; n_D^{22} 1.4422; yield 90%. The farnesol which was reduced had n_D^{20} 1.4728 as compared with the literature value of 1.4899; however, the value for the perhydrofarnesol prepared from this checked well with the value in the literature (n_D^{20} 1.4452)[8].

Conversion of the alcohols to halides.—Most of the necessary experimental data are tabulated. The physical constants of the pure bromides are as follows: perhydrogeranyl bromide: b.p. 89–90° under 8 mm., 95–96° under 9 mm., 101–102° under 12 mm. n_D^{20} 1.4543, 1.4549 (for two different preparations); geranyl bromide: b.p. 45–46 in a Hickman still (0.05 mm.); n_D^{20} 1.5031; perhydrogeranyl chloride: b.p., 88–89° under 12 mm.

Alkylations, α-perhydrogeranyl acetoacetic ester (VII) and perhydrogeranylacetone (hexahydropseudoionone) (III).—The ester VII was prepared by Fischer[5] and by Ishisaka[9] but was not isolated by them. We were able to isolate it by distilling the product in a Hickman "boiling-point" still, as a colorless oil boiling at 95–96° under 0.1 mm. pressure; n_D^{20} 1.4427.

Anal. Calc'd for $C_{16}H_{30}O_3$: C, 71.11; H, 11.11.
Found: C, 70.65; H, 11.21.

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[8] SCHIMMEL & Co., *Chem. Zentr.*, **1914**, I, 1654.

[9] ISHISAKA, *Ber.*, **47**, 2455 (1914).

Much loss of material was avoided, and much time saved, however, by omitting the isolation of the acetoacetic ester, hydrolyzing the product directly to the ketone. After many experiments, the following was found to be the best procedure. Acetoacetic ester (162.5 g., 1.25 mole) was added to a solution of sodium (28.75 g., 1.25 mole) in absolute ethanol (750 cc.). The mixture was refluxed gently on the steam bath, and perhydrogeranyl bromide (300 g., 1.35 mole) was slowly added. Refluxing was continued until the solution was neutral to litmus (10 hrs.). After cooling, the liquid was decanted, and the solid sodium bromide (120 g., theory 129 g.) was washed with a little alcohol. The alcoholic solutions were combined and the alcohol was removed on the steam bath. The residue weighed 382 g. It was hydrolyzed in two portions under slightly different conditions. (*a*) The residue (106 g.) and water (92 cc.) were placed in the bomb under hydrogen (1600 lbs.), and the temperature was raised to 200° and held at this point for 8 hours (pressure 3150 lbs.). The product was extracted with ether and the ethereal solution was washed with water, and dried over calcium chloride. After removal of the solvent, 41 g. of the *ketone III*, boiling at 120–123 under 10 mm., was obtained; $n_D^{25.5}$ 1.4320. (*b*) The remainder of the residue (276 g.), water (240 cc.), and sodium hydroxide (4 g.) were heated in the bomb under the same conditions as those used in (*a*). The ketone, isolated as above, had the same boiling point, and weighed 110 g. Thus the addition of the small amount of sodium hydroxide had no effect on the yield of ketone. The total overall yield of 151 g. is 61%.

Anal. Calc'd for $C_{13}H_{26}O$: C, 78.78; H, 13.13.
Found: C, 78.50; H, 12.96.

β-Ethoxyethyl chloride was prepared from ethyl cellosolve (2 moles), thionyl chloride (3 moles), and pyridine (3 moles) according to the procedure of Darzens[10]. The product which boiled at 106–109° was obtained in 20% yields.

β-Ethoxyethyl bromide.—Phosphorus tribromide (400 g.) was slowly (one drop per second) dropped into well-stirred and cooled (0°) cellosolve (106 g.). After the addition, the mixture was allowed to come to room temperature and was then heated to 60° for two hours. The product was poured over ice and steam-distilled. The bromide was removed from the distillate by ether extraction; the ether solution was washed with water and dried over Drierite. The ether was removed, and the residue was distilled. The yield was 71 g. (44.6%) of a product which boiled at 126–127° under 739 mm.

β-Ethoxyethyl iodide.—The chloride (27 g.) and sodium iodide (40 g.) were refluxed in acetone (300 cc.) for 15 hours. The acetone was distilled, the residue was poured into water, and the product was taken up in ether. The ethereal solution was washed with carbonate, then with water, and dried over sodium sulfate. After removal of the solvent, 6 g. of a product boiling at 151–154° was obtained.

Ethoxyethyl acetonedicarboxylic ester.—Acetonedicarboxylic ester (1 mole) was added to a cooled solution of sodium (1 mole) in excess absolute ethanol. After standing for a short time, the halide (1 mole) was added, and the mixture was refluxed for 3 days. The reaction mixture was poured over ice, made slightly acid to litmus, and thoroughly extracted with ether. The ether solution was washed with water and dried over Drierite. The ether was removed, and the product was distilled. It boiled at 108–114° under 17 mm. The alkylation was carried out three times with the iodide, once with the bromide, and once with the chloride, using

[10] DARZENS, *Compt. rend.*, **152**, 1601 (1911).

0.25 molar quantities. The chloride failed to react at all, and the yields from the bromide and iodide were 25–30%.

Anal. Calc'd for $C_{13}H_{22}O_6$: C, 56.93; H, 8.03.
Found: C, 57.07; H, 8.34.

Perhydrogeranyl acetonedicarboxylic ester (VIII).—Acetonedicarboxylic ester (30 g.) was alkylated as above with perhydrogeranyl bromide (35.8 g.). The product (14 g.) was a yellow oil boiling at 145–155 under 0.1 mm. pressure; n_D^{20} 1.4441.

Alkylation of ethoxyethyl acetonedicarboxylic ester (30 g.) with perhydrogeranyl bromide (24 g.) gave about 30% yields of a product which was a mixture that could not be separated into pure compounds. The boiling point was never constant, but two fractions were taken, boiling at 91–116° (5 g.) and 116–160° respectively, under 0.1 mm. The first fraction, (n_D^{20} 1.4350) was the alkylation product IX.

Anal. Calc'd for $C_{23}H_{42}O_6$: C, 66.62; H, 10.21.
Found: C, 67.23; H, 10.72.

Conversion of the C_{10}-halides to C_{11}-halides.—Tetrahydrogeranyl bromide (11.5 g.) was added to magnesium (2.4 g.) in dry ether under an atmosphere of purified nitrogen. The reaction, which started readily, was completed by refluxing for 45 minutes after addition of the bromide. Chloromethyl ether (5 g., 20% excess) was slowly dropped into the Grignard solution. The reaction was strongly exothermic, and a white precipitate formed. After standing for 30 minutes, the mixture was poured into water and the product was removed by extraction with ether.

4,8-Dimethyl-1-methoxynonane, methyl 4,8-dimethylnonyl ether (XI), was thus obtained in 60% yield. The boiling point was 94–94.5° under 14.5 mm.; n_D^{20} 1.4240.

Anal. Calc'd for $C_{12}H_{26}O$: C, 77.42; H, 13.98.
Found: C, 77.62; H, 14.33.

When tetrahydrogeranyl chloride was used in the above procedure, the Grignard reaction took place much more slowly. Ethyl bromide (1 cc.) was added to start the reaction; the mixture was allowed to stand for 16 hours before addition of the chloromethyl ether. However the yield of product, identical with that above, was 70%.

Cleavage of the ether.—Perhydrogeranylcarbinyl bromide (II). The ether (20.5 g.) was refluxed for 6 hours with hydrobromic acid (80 g., 48%), acetic acid (35 g.), and acetic anhydride (5 g.). The mixture was poured over ice, and the product was removed by ether extraction. The ether solution was washed with carbonate and dried. Fractionation of the residue under 14.5 mm. after removal of the ether gave four products: *A*, (3.7 g.) b.p., 106–112°; n_D^{20} 1.4347; *B*, (1.87 g.), b.p., 112–115°, n_D^{20} 1.4408; *C*, (4.1 g.), b.p., 117–119°, n_D^{20} 1.4400; *D*, (9.04 g.), b.p., 120–121°, n_D^{20} 1.4368. *A* was largely unchanged ether; *D* was largely the acetate of the eleven-carbon alcohol, while most of the bromide was in *B* and *C*. The fractions were combined and subjected to the action of a current of dry hydrogen bromide at 135° for 2 hours. Distillation of this product under 14.5 mm. gave three fractions: *E* (1.23 g.), b.p., 111–115°, n_D^{20} 1.4400; *F* (4.93 g.), b.p., 115–117°, n_D^{20} 1.4425; *G* (9.88 g.), b.p., 117–121°, n_D^{20} 1.4405. The high refractive index indicated that *F* was the purest sample of the bromide, while *E* contained unchanged ether, and *G* contained unchanged acetate.

SUMMARY

1. The reduction of geraniol and citronellol to the saturated alcohol has been described.

2. The conversion of saturated and unsaturated C_{10} - and C_{15}-alcohols to bromides has been discussed.

3. A method has been developed for the alkylation of acetoacetic ester by perhydrogeranyl bromide, and for the preparation of perhydrogeranyl acetone (hexahydropseudoionone) in good yields.

4. Certain experiments upon the alkylation of acetonedicarboxylic ester have been described.

5. The C_{10} -halide has been converted to the C_{11}-bromide by coupling the Grignard reagent with chloromethyl ether, followed by cleavage of the ether.

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

THE CHEMISTRY OF VITAMIN E. X. THE REACTION BETWEEN QUINONES AND METALLIC ENOLATES. IX[1]. *

LEE IRVIN SMITH AND W. W. PRICHARD

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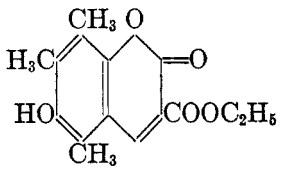
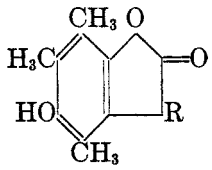
* Abstracted from a thesis by W. W. Prichard, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree.

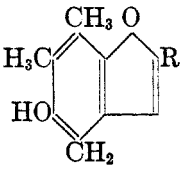
Coumarones, coumarans, and their derivatives are of particular interest in connection with the chemistry of vitamin E, because although the tocopherols are chromans, several of the 5-membered ring analogs are biologically active[2] and the absorption spectra[3] of the 5- and 6- membered heterocycles are strikingly similar. Moreover, in many of the syntheses of these ring systems, there is the possibility of interconversion so that, for structure proof, it is advisable to investigate for both types of heterocycles a large number of syntheses which are unequivocal or as nearly so as possible. One type of synthesis which seemed particularly promising for the 5- and 6-membered oxygen heterocycles was the reaction between metallic enolates and alkylated quinones, a study of which was begun by one of us with Dobrovolny several years ago[4] with a study of the reaction between duroquinone and sodium malonic ester, which gave a 6-hydroxycoumarin derivative (I). In 1936, this reaction was applied to trimethyl-



I



II



III

quinone[5] which had one unsubstituted position in the quinone ring. The product of the reaction between this quinone and sodium malonic ester

[1] Paper IX on Vitamin E: J. ORG. CHEM., **4**, 334 (1939). Paper VIII on Quinones and Enolates, *J. Am. Chem. Soc.*, **60**, 676 (1938).

[2] Paper XIII on Vitamin E: J. ORG. CHEM., **4**, in press (1939).

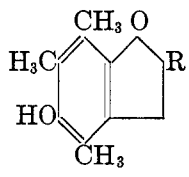
[3] Paper XIV on Vitamin E: J. ORG. CHEM., **4**, in press (1939).

[4] SMITH AND DOBROVOLNY, *J. Am. Chem. Soc.*, **48**, 1693 (1926).

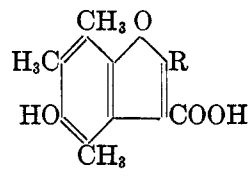
[5] SMITH AND MACMULLEN, *ibid.*, **58**, 629 (1936).

was the isocoumaronone II, a 5-membered oxygen heterocycle. When sodium acetoacetic ester was used, two products resulted; one was the isocoumaranone II (R = H) and the other was the coumarone III (R = CH_3). These two products were the result of 1,4 addition of acetoacetic ester to the quinone, followed by the two types of cleavages shown by β-keto esters with subsequent ring closure.

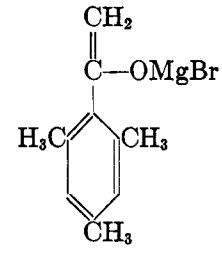
This reaction was applied recently by Bergel, Jacob, Todd, and Work[6] for the synthesis of coumarans (IV). Starting with stearoyl acetic ester and trimethylquinone, three products were obtained: the isocoumaronone



IV



V

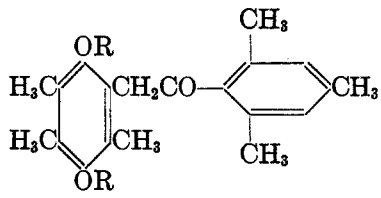


VI

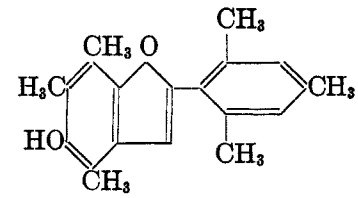
(II, R = $COC_{17}H_{35}$), the coumarone (III, R = $C_{17}H_{35}$) and the acid V (R = $C_{17}H_{35}$). The majority of the product was II, obtained in good yield, with smaller amounts of III and V. Analogous compounds were obtained using palmitoylacetic ester. Both II and V were converted to III in good yields by the action of hydrochloric acid in acetic acid, a reaction which, from II, involved ring opening, loss of carbon dioxide, and ring closure to III. Catalytic reduction of III then gave the coumaran IV (R = $C_{17}H_{35}$).

In extending this reaction, our first experiments involved the bromomagnesium enolate of acetomesitylene VI, a substance easily prepared from the ketone and any Grignard reagent.[7] Enolates of this type seemed likely to react particularly well with trimethylquinone, because they are not strongly basic in the sense that sodium enolates are, and thus the destructive action of the stronger bases upon the very sensitive quinone might be avoided. The reaction between trimethylquinone and the enolate VI was rapid and complete, and the product, VII, was formed in good yield. The hydroquinone VII gave a diacetate, VIII, but no carbonyl derivatives.

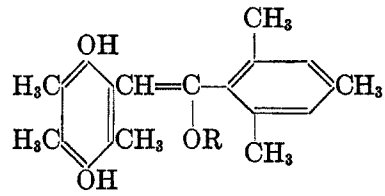
[6] Bergel, Jacob, Todd, and Work, *J. Chem. Soc.*, **1938**, 1375.
[7] Kohler and Baltzly, *J. Am. Chem. Soc.*, **54**, 4015 (1932).



VII, R = H
VIII, R = Ac.



IX



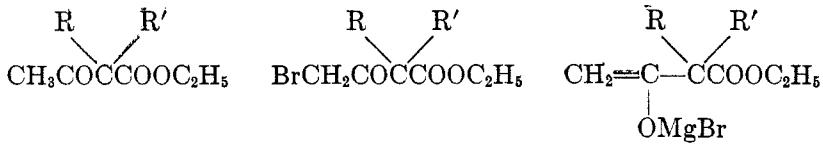
IXa., R = CH_3
IXb., R = C_2H_5
IXc., R = Ac.

This was to be expected in view of the hindrance exerted by the mesityl group. It was not possible, however, to convert the ketone VII into the coumaron IX by elimination of water. When refluxed with hydrochloric acid, in methanol, ethanol, or acetic acid, VII was converted into compounds which appear to be the enolic derivatives IX*a*, *b* and *c*, and the nature of the product varied with the solvent used. When warmed with sulfuric acid, the ketone VII gave only tarry products from which no solids could be isolated. These enol derivatives resembled somewhat those obtained recently by Fuson and his co-workers[8] in that they were extremely difficult to purify, possibly because the crude products consisted of mixtures of stereoisomers. These products were not investigated further, since none of the coumaron IX could be obtained from any of them.

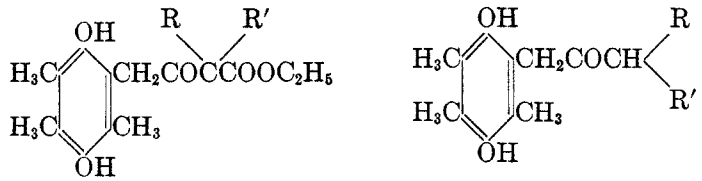
Having thus established that the essentially neutral enolates of the type of VI would add readily to the quinone and give good yields of products, we next turned our attention to enolates derived from α,α-disubstituted acetoacetic esters. In view of the elegant work of Kohler and his students[9] on the enolization of α-bromo ketones by Grignard reagents, the sequence X to XV appeared to be a most promising route to coumarones and coumarans with branched α substituents, with no possibility of closing any other type of hetero ring. The γ-bromoacetoacetic ester (XI) was readily prepared, but it could not be converted to the

[8] FUSON, ULLYOT, AND HICKSON, *ibid.*, **61**, 410 (1939).

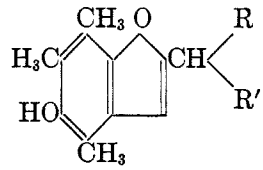
[9] KOHLER AND TISHLER, *ibid.*, (*a*) **54**, 1594 (1932); (*b*) *ibid.*, **57**, 217 (1935); (*c*) KOHLER AND SONNICHSEN, *ibid.*, **60**, 2650 (1938).



X XI XII



XIII XIV



XV

enolate XII with any of several reagents tried. These included phenylmagnesium bromide, mesitylmagnesium bromide, and phenylcadmium chloride. In every case the bromo ester (XI), after treatment with the enolizing agent, failed to condense with the quinone.

It then seemed advisable to activate the γ hydrogen atoms in the ester X and thus facilitate the formation of enolates at this point in the molecule. For this purpose XVI and XVII were prepared.

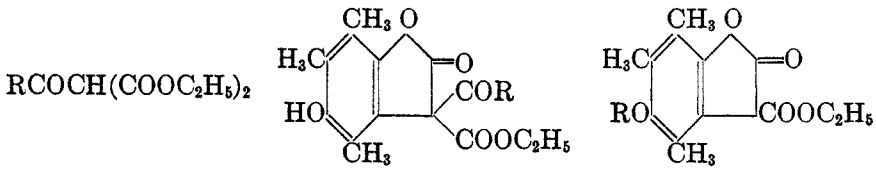
$CH_2(COOC_2H_5)COC(CH_3)_2COOC_2H_5$ $CH_2(CN)COC(CH_3)_2COOC_2H$[5]

XVI XVII

Attempts were made to condense the di ester XVI with trimethylquinone in the presence of magnesium methoxide, but no condensation product could be isolated. The ester XVI was subjected to the action of powdered sodium, and, although it reacted with the metal, the product gave only a red oil with the quinone. The cyano compound XVII gave a crystalline enolate with magnesium methoxide, but this enolate, with the quinone, gave only a red, viscous material which could not be crystallized, and from which no pure products were obtained.

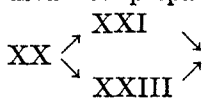
With the failure of these enolates to react well, attention was next turned to acylmalonic esters (XVIII), for it was thought that these might be converted to enolates readily and if so that the latter would condense with the quinone to give typical isocoumaranones (XIX) which could, in

turn, be converted to coumarones (III) by the procedure of Bergel, Jacob, Todd and, Work[6]. Isobutyrylmalonic ester (XVIII, R = i-C_3H_7)

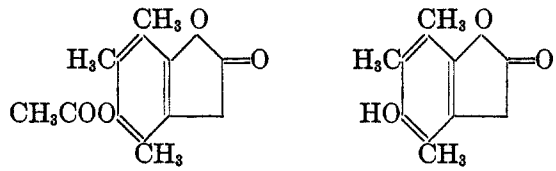


XVIII XIX XX, R = H
XXI, R = Ac.

reacted readily with the quinone in the presence of sodium ethoxide or magnesium ethoxide but the product was the isocoumaranone ester XX, the isobutyryl group having been eliminated in the reaction. The structure of XX was proved by a synthesis from the quinone and malonic ester, under somewhat different conditions from those used by Smith and MacMullen[5] and by the fact that the acetate of XX (XXI), when hydrolyzed carefully, gave the acetate of the isocoumarone itself (XXII), identical with the acetate prepared from the isocoumaronone of Smith and MacMullen. Moreover, the ester XX, when hydrolyzed gave the isocoumaranone (XXIII) of Smith and MacMullen. The two methods used for preparing XX, and the relationships shown by the series



XXII, leave no doubt as to the structures of all the compounds involved.



XXII XXIII

The isocoumaranone ester XX is still a malonic ester derivative, and if it were possible to acylate it to give XIX, the projected synthesis of III might still be achieved. Acylation of XX attacked the molecule only at the hydroxyl group, however, producing substances of the type of XXI. Attempts were made to acylate XXI, but the product was always XXII. The ester (XXII) was recovered unchanged after treatment with acetyl chloride and aluminum chloride in boiling petroleum ether (110–120°), and the action upon XXII, of ethylmagnesium bromide followed by acetyl chloride gave a mixture which melted over a wide range (20°),

and which could not be separated into pure products by any of the methods tried.

EXPERIMENTAL

3,6-Dihydroxy-2,4,5-trimethylphenylacetomesitylene (VII).—To a well-stirred ethereal solution of ethylmagnesium bromide (0.026 mole) was added acetomesitylene (4.0 g., 0.0263 mole) in ether (20 cc.). The crystalline enolate separated with evolution of heat. Stirring was continued for 40 minutes after the addition of the ketone, and then a solution of trimethylquinone (1.95 g., 0.013 mole) in ether (15 cc.) was added. The mixture became bluish-green. After standing for 12 hours, iced hydrochloric acid was added, and the product was isolated in the usual way as an oil which rapidly solidified. The product was crystallized, first from benzene and then from dilute acetic acid. It formed glistening white needles which melted at 148–148.5°; yield 90%.

Anal. Calc'd for $C_{20}H_{24}O_3$: C, 76.9; H, 7.69.
Found: C, 76.85; H, 7.71.

The *diacetate* (VIII) was prepared from VII and acetic anhydride containing a drop of sulfuric acid. Crystallized from ether-petroleum ether, it melted at 169–170° and gave a negative phenol test (Folin).

Anal. Calc'd for $C_{24}H_{28}O_5$: C, 72.72; H, 7.07.
Found: C, 71.83; H, 7.12.

Enol derivatives of VII.—The hydroquinone VII (0.5 g.) was refluxed for 30 minutes with a saturated solution of hydrogen chloride in ethanol (15 cc.). Addition of water produced a light-yellow oil which rapidly solidified. When recrystallized several times from petroleum ether, the white solid IX*b*, melted at 160–161.5°. When mixed with VII, it melted at 130–140°.

Anal. Calc'd for $C_{22}H_{28}O_3$: C, 77.69; H, 8.24.
Found: C, 77.98; H, 8.41.

The *methyl ether IX*a, prepared similarly in methanol and crystallized several times from petroleum ether, melted at 158–159°. When mixed with the ethyl ether IX*b*, it melted at 148–152°; when mixed with VII, it melted at 137–140°.

Anal. Calc'd for $C_{21}H_{26}O_3$: C, 77.30; H, 7.97.
Found: C, 76.86; H, 7.32.

The *acetate IX*c, prepared similarly in acetic acid and crystallized several times from petroleum ether, melted at 149.5–150.5°. When mixed with VIII, it melted at 139–148°; when mixed with IX*b*, it melted at 140–144°; when mixed with VII it melted at 131–139°.

Anal. Calc'd for $C_{22}H_{26}O_4$: C, 74.60; H, 7.35.
Found: C, 73.58; H, 7.10.

When the ethyl ether IX*b* (0.1 g.) was boiled for one hour with dioxan (2.5 cc.) and hydrochloric acid (2.5 cc.) no change occurred; the starting material was recovered quantitatively. When the methyl ether IX*a* (0.1 g.) was allowed to stand for 15 minutes in sulfuric acid (5 cc., 80%)[8], a green solution was formed. When this was poured onto ice, the product was a dark tar which could not be crystallized.

Experiments with γ-bromo-α, α-dimethylacetoacetic ester (XI).—A solution of the bromo ester (7.11 g., 0.3 mole) in dry ether (10 cc.) was added to an ethereal solution (50 cc.) of mesitylmagnesium bromide (0.03 mole). After 30 minutes, trimethylquinone (2.25 g., 0.015 mole) in ether (10 cc.) was added. The reaction mixture, which was blue, was allowed to stand for 12 hours and then was acidified and the product isolated in the usual way. It was a reddish-brown oil, which deposited

black crystals of the quinhydrone. These were removed and identified by steam-distilling it and reducing the quinone in the distillate—both distillate and residue then gave trimethylhydroquinone. The filtrate from the quinhydrone was steam-distilled. Neither the distillate nor the residue could be crystallized.

A solution of phenylcadmium chloride[10] (0.03 mole) in ether (25 cc.) was prepared, and to it was added the bromo ester (0.03 mole) in ether (10 cc.). After 20 minutes, trimethylquinone (0.0135 mole) in ether (10 cc.) was added, and the reaction mixture was allowed to stand for 16 hours. Acid was added, and the mixture was steam distilled. The distillate contained quinone and ester, and the residue, which was very small (0.5 cc.) could not be crystallized.

Ethyl-α, α-dimethyl-β-keto glutarate (*XVI*) was prepared according to the method of Perkin and Smith[11]. The yield was about 10% of a yellow oil which boiled at 146–149° under 24 mm.

Condensation with magnesium methoxide.—The ester XVI (7.61 g., 0.033 mole) was added to a solution of magnesium methoxide (from 1.59 g., 0.066 mole of Mg) in dry methanol (100 cc.), and the mixture was allowed to stand for 45 minutes, during which a gelatinous solid separated out. Trimethylquinone (4.96 g., 0.033 mole) in methanol (5 cc.) was then added. A dark-brown color developed. After standing for 2 hours, the mixture was poured into iced hydrochloric acid. A black gummy material precipitated, which was removed and steam-distilled. The distillate contained quinone and the ester XVI; the residue was a black tar from which no pure product could be obtained.

Condensation with powdered sodium.—The ester XVI 3.88 g., (0.0169 mole) was added to a suspension of powdered sodium (0.388 g., 0.0169 mole) in benzene (10 cc.). There was a vigorous reaction, and the metal dissolved giving a clear orange solution. To the cooled (20°) solution there was added trimethylquinone (1.268 g., 0.00845 mole) in benzene (5 cc.). A dark-green color developed. After standing for 12 hours, ice and hydrochloric acid were added and the benzene layer was separated. The solvent was pumped off and the residue, a red oil which could not be crystallized, was steam-distilled. It was almost completely volatile with steam but the distillate contained only starting materials, while the residue consisted of a small amount of dark tar.

γ-Cyano-α, α-dimethylacetoacetic ester (*XVII*) was prepared by the method of Lawrence[12]. The yield was 52% in 0.1 molar runs; b.p., 122–123° under 22 mm.

Condensation with magnesium methoxide.—The cyano ester XVII (3.66 g., 0.02 mole) was added to a solution of magnesium (0.24 g., 0.01 mole) in methanol (20 cc.). About half the methanol was distilled from the pink solution. Addition of dry ether (30 cc.) precipitated a salmon-colored solid, which was filtered off and suspended in ether (20 cc.). Trimethylquinone (1.5 g., 0.01 mole) in ether (5 cc.) was added to this suspension, which rapidly became red and then brown. After standing for 12 hours, the mixture was poured into iced hydrochloric acid, and extracted with ether. The ether solution was washed free from acids and dried over sodium sulfate. Removal of the ether left a red oil which could not be crystallized. Steam-distillation of this oil gave a distillate which contained quinone and the cyano ester, and a very small residue which was black and tarry. Repetition of the condensation

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[10] GILMAN, *Rec. trav. chim.*, **55**, 518 (1936).

[11] PERKIN AND SMITH, *J. Chem. Soc.*, **83**, 12 (1903).

[12] LAWRENCE, *ibid.*, **75**, 418 (1899).

without isolation of the magnesium enolate, and without the addition of ether, gave essentially the same results.

Isobutyryl malonic ester (*XVIII*, R = i-C_3H_7) was prepared from isobutyryl chloride and sodium malonic ester according to the method of Knoevenagel[13]. The product boiled at 141–142° under 18 mm.; yield 25% in 0.5 molar runs.

2-Carbethoxy-4,6,7-trimethyl-5-hydroxyisocoumaranone (*XX*).—Isobutyrylmalonic ester (5 g., 0.0217 mole), was dissolved in a solution of sodium ethoxide (0.46 g., 0.02 mole sodium in 10 cc. of ethanol) and to this solution trimethylquinone (1.5 g., 0.01 mole) in alcohol (5 cc.) was added. The reaction mixture became purple, and after 2 hours a white sodium derivative (1.6 g.) separated. This was removed, washed with ether, and suspended in cold dilute hydrochloric acid under a layer of ether. After the salt dissolved, the yellow ether layer was removed and dried over sodium sulfate, and the ether was evaporated. The residue, a white solid (1.4 g.) was crystallized twice from ether-petroleum ether. It melted at 111–112°. The same product resulted when powdered sodium suspended in ether was used in place of sodium ethoxide in the above procedure, and also when magnesium methoxide was used, although in the last case the condensation was very slow and required 5 days for complete precipitation of the metallic derivative.

Anal. Calc'd for $C_{14}H_{16}O_5$: C, 63.60; H, 6.07.
Found: C, 63.56; H, 6.08.

Acetate (*XXI*).—A small amount of the isocoumaranone (XX) was gently warmed in acetic anhydride containing a drop of sulfuric acid. The product, isolated in the usual way and crystallized from ether-petroleum ether, melted at 101–103° (m.p. of mixture with the isocoumaranone, 84–110°).

Anal. Calc'd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.88.
Found: C, 62.90; H, 6.11.

4,6,7-Trimethyl-5-hydroxyisocoumaranone (*XXIII*).—The carbethoxy compound (XX), was heated with acetic acid saturated with hydrochloric acid, and the solution was poured into water. The white solid was removed and crystallized from dilute acetic acid. It melted at 195–196°.[5]

Anal. Calc'd for $C_{11}H_{12}O_3$: C, 68.8; H, 6.26.
Found: C, 68.76; H, 6.57.

The *acetate* (XXII), prepared from XXIII in the usual way and crystallized from dilute acetic acid, melted at 166–167°.

Anal. Calc'd for $C_{13}H_{14}O_4$: C, 66.67; H, 5.98.
Found: C, 67.49; H, 6.20.

Substance XX, m.p. and mixture m.p., 111–112°, was also prepared in good yield by adding trimethylquinone (3.38 g., 0.0225 mole) to a solution of malonic ester (3.7 g., 0.0227 mole) in alcoholic sodium ethoxide (0.518 g. sodium, 10 cc. ethanol) at 0°. After standing for 12 hours at room temperature the solid sodium derivative (88% yield) was removed and decomposed as described above.

The sodium derivative of XX (0.5 g.) was shaken with excess acetyl chloride. After 15 hours, the mixture was poured into water and extracted with ether. The ether was removed, and the residue was crystallized from ether-petroleum ether. It melted at 101–103° and was the acetate XXI; mixed m.p., 101–103°.

Attempts to acylate XX using acetyl chloride and pyridine gave only yellow oils which could not be crystallized. When these yellow oils were shaken with hydro-

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[13] KNOEVENAGEL, *Ber.*, **31**, 2770 (1898).

chloric acid, the product was the acetate XXII, m.p., 162–163°. It is possible that the yellow oils contain an *O*-acetate of XX.

The acetate XXII (0.4 g.) was dissolved in petroleum ether (b.p., 110–120°) and aluminum chloride (0.45 g., 2 equivalents) was added, followed by excess acetyl chloride. There was a vigorous reaction. The mixture was refluxed for 20 minutes and then decomposed by iced hydrochloric acid. The white, insoluble solid was removed and taken up in benzene. Addition of petroleum ether precipitated XXII; m.p. and mixture m.p., 167–168°.

The acetate XXII (0.815 g., 0.00348 mole) in dry ether (5 cc.) was added to ethylmagnesium bromide (0.007 mole) in ether (10 cc.). A white precipitate formed immediately. After standing for 10 minutes, excess acetyl chloride (3 g.) was added, the mixture was refluxed for a few minutes, and then poured onto iced hydrochloric acid. The gummy solid was removed and crystallized from petroleum ether. The solid was brown, and melted at 103–140°. Several crystallizations from ether, petroleum ether, and dilute acetic acid did not give a product with a sharper melting point. Since the product might have consisted of a mixture of an acetate and the hydroxy compound, all of the solid was combined and boiled with a saturated solution of hydrogen chloride in ethanol (10 cc.). Again a gummy solid was obtained which, after crystallization from ether-petroleum ether melted at 150–170°. Repeated crystallization failed to give a product with a sharper melting point.

SUMMARY

1. The magnesium enolate of acetomesitylene adds to trimethylquinone to give a dihydroxytrimethylphenylacetomesitylene in good yield. This product could not be cyclized, however, to give the corresponding coumarone; instead compounds resulted which are apparently derivatives of the enol form of the ketone.

2. The condensation between this quinone and enolates derived from α,α-disubstituted acetoacetic esters could not be effected, nor were such condensations successful even when the γ hydrogen atoms in the acetoacetic ester were activated by cyano- or carbethoxyl groups.

3. Acylmalonic esters condensed with the quinone, but the acyl group was lost in the process, and the primary product was a carbethoxyisocoumaranone, which in turn could not be acylated. Certain relationships between this condensation and that carried out in earlier papers of this series are shown, and the structures of the compounds involved have been proved.

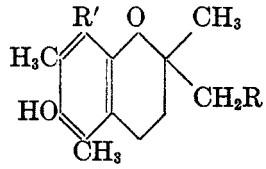
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. XI. INTRODUCTION OF THE *p*-HYDROXYL GROUP INTO CHROMANS AND COUMARANS[1,*]

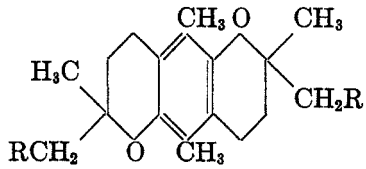
LEE IRVIN SMITH, HARVEY H. HOEHN, AND HERBERT E. UNGNADE

Received March 31, 1939

Previous papers have dealt with the synthesis of tocopherols from phytyl bromide and appropriate hydroquinones,[2] the direct introduction of allyl groups into phenols and hydroquinones[3] and with the addition of dienes to phenols and hydroquinones.[4] In the case of trimethylhydroquinone, the reaction with dienes and with allylic halides gave good yields of products which were readily purified, but when more than one position of the hydroquinone molecule was vacant, these reactions led to complications, and mixtures were produced with both allylic halides and dienes. This is due to the ease with which the nucleus of the polymethylated hydroquinone is substituted, and it is especially troublesome when the halides are used. Thus when *m*-xylohydroquinone reacts with phytyl bromide, there is produced not only the tocopherol I, but also the phytyl derivative of this, II (R = 3,7,11-trimethyldodecyl-l).



I., R′ = H
II., R′ = $C_{20}H_{39}$



III

With the *o*- and *p*-xylohydroquinones, the complexities are still greater, because in these cases the second phytyl group enters a position adjacent to a hydroxyl group, and the phytyl derivatives, analogous to II, may undergo ring closure leading to double chromans, such as III.

* Presented (in part) at the 96th meeting of the American Chemical Society, Milwaukee, Sept. 5–9, 1938.

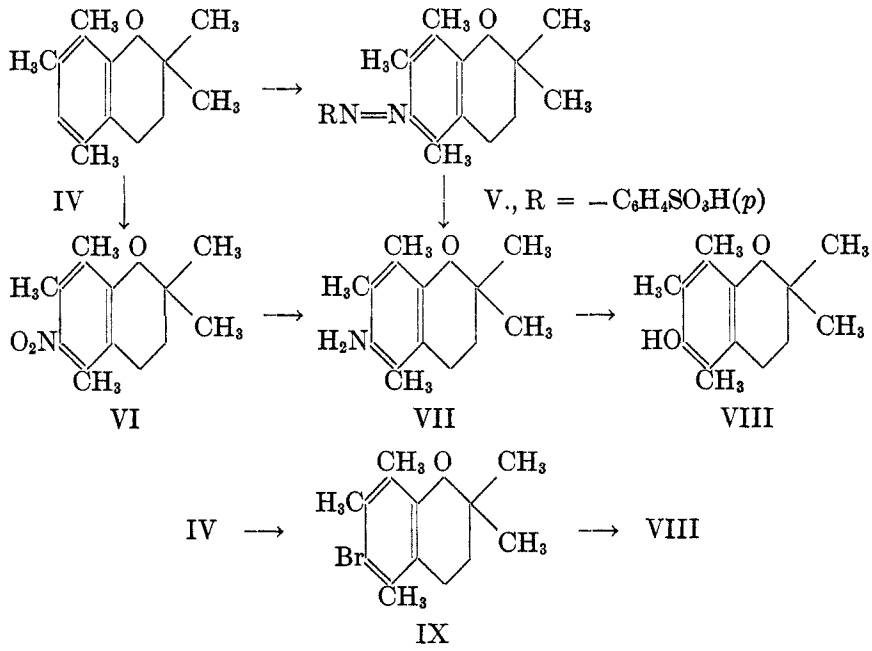
[1] Paper X: J. ORG. CHEM., **4**, 342 (1939).

[2] Paper IV: J. ORG. CHEM., **4**, 298 (1939).

[3] Paper V: J. ORG. CHEM., **4**, 305 (1939).

[4] Paper VI: J. ORG. CHEM., **4**, 311 (1939).

Since phenols are much less troublesome than hydroquinones as far as these byproducts are concerned, we have explored the possibility of synthesizing *p*-hydroxychromans and coumarans from phenols by first closing the heterocyclic ring and then, in the final step, introducing the hydroxyl group para to the bridge oxygen atom. For the model experiments, which are reported in this paper, we selected 2,3,5-trimethylphenol,† which was condensed with isoprene[4] to give the chroman IV m.p. 40–41° in good yield. For the introduction of the hydroxyl group into position 6, three methods were investigated. In the first two of these, the aim was the introduction of an amino group, to give VII, either by nitration, or by coupling with a diazonium compound, followed by reduction of the respective intermediates VI and V. It was then planned to convert the aminochroman VII to the hydroxychroman VIII by mild oxidation to the quinone, followed by reduction and recyclization.[5,6] In the third method, the aim was to introduce the hydroxyl group via the bromo compound IX, either by oxidation of the Grignard reagent produced from IX, or by hydrolysis of the bromo compound with hot alkali under pressure.



† We are greatly indebted to Dr. E. C. Williams of the Shell Development Company for a most generous supply of this phenol.

[5] JOHN, *Z. physiol. Chem.*, **252**, 222 (1938).

[6] KARRER, ESCHER, FRITZSCHE, RINGIER, AND SALOMON, *Helv. Chim. Acta.*, **21**, 939 (1938).

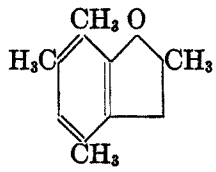
While the chroman IV developed a color with diazotized sulfanilic acid, coupling was extremely slow, and it was not possible to obtain more than traces of the azo compound V under the conditions used. Nitration of the chroman produced in good yield a mono nitro compound having the composition of VI, but this nitro compound was extremely inert—so much so that the ordinary qualitative tests for nitrogen failed completely and it was only after nitrogen was determined quantitatively (micro Dumas) that we could be certain that the substance actually was a nitro compound. The substance was recovered unchanged after the action of tin and hydrochloric acid, and also after being subjected to the action of hydrogen (45 lbs.) in the presence of a platinum catalyst. The nitro compound was attacked by sodium and butanol, but the product was an oil which gave a strong phenol test, but which could not be crystallized. These two routes to VIII therefore were abandoned temporarily.

The route to VIII via the bromo compound IX was more successful. Bromination of the chroman IV in carbon tetrachloride gave a good yield of IX, and the bromo compound was converted into the Grignard reagent by the method of entrainment. Oxidation of the Grignard reagent by tank oxygen, followed by hydrolysis of the metallic derivative, produced the hydroxychroman VIII, m.p. 94–94.5°, although in poor yield. The bomb hydrolysis of the bromochroman IX was not tried, but in view of the results obtained when this method was applied to the analogous bromocoumaran, it is unlikely that the hydroxychroman would have been produced.

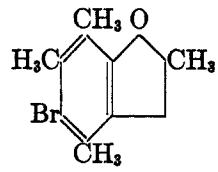
For the experiments in the coumaran series, the tetramethylcoumaran X was prepared from the phenol by rearranging the allyl ether to the *o*-allylphenol and cyclizing the latter.[3] The coumaran was readily brominated in carbon tetrachloride, giving a good yield of a mono bromo compound XI,[7] which gave no precipitate with alcoholic silver nitrate and which was inert to further action of bromine. Action of oxygen upon the Grignard reagent obtained from this bromo compound, gave a phenolic compound. Although this product was obtained only in very small amounts, it melted at 115–118° without recrystallization, and when mixed with the known 2,4,6,7-tetramethyl-5-hydroxycoumaran (m.p. 129–130°) it melted at 120–122°. Hence in the coumaran series also, it is possible to introduce the *p*-hydroxyl group by this method, although the yields in both series—chromans and coumarans—are very small.

When the bromo compound XI was heated to 300° in a bomb with 10% sodium hydroxide, the product was a solid which melted at 87–88°, and

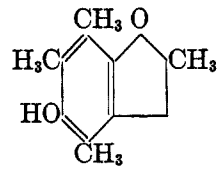
[7] ADAMS AND RINDFUSZ, *J. Am. Chem. Soc.*, **41**, 648 (1919), have been, so far, the only ones to investigate the action of bromine on coumarans. They obtained 5-bromo-2-methylcoumaran by bromination of 2-methylcoumaran.



X



XI



XII

after crystallization, at 93–94°. The substance was strongly phenolic (Folin test), and was soluble in 5% sodium hydroxide and in dilute sodium carbonate, but not in bicarbonate. Since the hydroxycoumaran XII melts at 129–130°, it was at first thought that the product was more likely trimethylallylhydroquinone, but it could not be cyclized by heating it with pyridinium chloride; moreover, the analysis did not check for any simple substance containing two oxygen atoms. When brominated, the substance formed a solid dibromo compound melting at 147–148°. The melting points and analyses of the substance and its dibromo derivative[8] were sufficient to identify the hydrolysis product of the bromocoumaran XI as 2,3,5-trimethylphenol. Hence, the action of alkali at high temperatures upon the bromocoumaran XI consists in elimination of the heterocyclic ring completely, and replacement of the bromine by hydrogen. This effect of "positive" halogen has been known to us for some time[9] in connection with the dibromotetramethylbenzenes. Thus, dibromodurene under high-temperature alkaline hydrolysis gives, not durohydroquinone, but durenol. In a recent study, Suter and Smith[10] have observed the same sort of reaction when certain dibromobiphenyls were heated with potassium benzoate in boiling benzoic acid, the products being the benzoates of monohydroxylated biphenyls. The simultaneous cleavage of a side-chain at the nucleus, however, has been observed by John, Dietzel, and Gunther[11] in connection with the tocopherols, which give polymethylated phenols, and certain mono ethers of hydroduroquinone, which give, along with durenol, some 2,3,5-trimethylphenol. But in these cases the reagent was hydriodic acid, and not alkali. We have under way further investigation of this interesting reaction, a report of which will be made in a later paper.

[8] (*a*) EDLER, *Ber.*, **18**, 630 (1885), and (*b*) JACOBSEN, *ibid.*, **19**, 1220 (1886), both give the m.p. of 4,6-dibromo-2,3,5-trimethylphenol as 152°.

[9] Unpublished work by Mr. A. C. Keyl of this Laboratory.

[10] SUTER AND SMITH, *J. Am. Chem. Soc.*, **61**, 166 (1939); other references to this effect are also given.

[11] JOHN, DIETZEL, AND GUNTHER, *Z. physiol. Chem.*, **252**, 208 (1938).

EXPERIMENTAL

Coupling reaction of the chroman IV.—In this experiment, the procedure of Meyer and Lenhardt[12] for coupling of resorcinol dimethyl ether was followed, because the chroman is, in effect, a phenol ether. Sulfanilic acid dihydrate (5.25 g.) was diazotized in the usual manner and the white precipitate of the diazonium compound was collected by filtration and at once dissolved in cold acetic acid (60 cc.). The solution was added to a cold solution of the chroman IV (5.1 g.) and sodium acetate (2.05 g.) in acetic acid (60 cc.). The reaction mixture was kept in the ice box for one week, with occasional shaking. A bright-red color developed, and a small amount of pink solid was deposited. This was found to consist largely of unchanged diazonium compound together with traces of a red substance, presumed to be the azo compound. No further precipitate was deposited even on long standing, or when the solution was diluted with water.

2,2,5,7,8-Pentamethyl-6-nitrochroman (VI).—A solution of pentamethyl chroman IV (1 g.) in acetic acid (5 cc.) was cooled to 0° and nitric acid (0.3 cc.) in acetic acid (5 cc.) was added. After standing for one hour, the reaction mixture was diluted with water and extracted with ether. The ether was removed and replaced by alcohol. On cooling, the nitrochroman crystallized in light-yellow plates which after crystallization from ethanol melted at 125–125.5°; yield 0.7 g.

Anal. Calc'd for $C_{14}H_{19}NO_3$: C, 67.43; H, 7.69; N, 5.62.
Found: C, 67.12; H, 7.71; N, 6.38.

The substance gave a negative phenol test (Folin) and was insoluble in aqueous sodium carbonate, sodium hydroxide (even on boiling), and in Claisen's alkali. It gave an olive-brown color with cold sulfuric acid, and no reaction with bromine in carbon tetrachloride.

Reduction experiments (A).—The substance (100 mg.) was dissolved in ethanol (25 cc.), platinum oxide catalyst (.01 g.) was added, and the mixture was shaken under hydrogen at 45 lbs. pressure. The nitro compound (m.p. 124–125°) was recovered unchanged. (*B*) The nitro compound (100 mg.) was boiled with excess tin and concentrated hydrochloric acid for 2 hours. Ether extraction of the cooled mixture removed unchanged material, m.p., 123.5–125°. (*C*) The nitro compound (100 mg.) was dissolved in butanol (50 cc.), sodium (0.7 g.) was added, and the solution was refluxed for 2 hours. Some of the butanol was removed by distillation, water was added and the mixture was acidified with 30% sulfuric acid and extracted with ether. The ether solution was steam distilled to remove the ether and the last traces of butanol. The residue was a strongly phenolic oil which could not be crystallized.

2,2,5,7,8-Pentamethyl-6-bromochroman (IX).—Bromine (2 cc.) in carbon tetrachloride (10 cc.) was added to a solution of the chroman IV (5 g.) in the same solvent (10 cc.). The reaction mixture was allowed to stand until no more hydrobromic acid was evolved (20–30 minutes). Excess bromine was removed by shaking with a little aqueous sodium bisulfite, ether was added and the ether-carbon tetrachloride layer was removed. The solvents were pumped off, and the solid residue was crystallized from dilute alcohol several times. It weighed 6.2 g., and melted at 69–70°.

Anal. Calc'd for $C_{14}H_{19}OBr$: C, 59.35; H, 6.77.
Found: C, 59.34; H, 6.76.

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[12] MEYER AND LENHARDT, *Ann.*, **398**, 74 (1913).

2,2,5,7,8-Pentamethyl-6-hydroxychroman (VIII).—The bromochroman (4 g.) and ethyl bromide (1.54 g.) in ether (12 cc.) were dropped slowly (1 hour) onto magnesium (688 mg.). After disappearance of any further visible reaction, the mixture was refluxed for an hour. Oxygen from a tank was then bubbled through for 2 hours. Iced hydrochloric acid was added, and the mixture was thoroughly extracted with ether. The ether was removed under vacuum, but the residual oil could not be crystallized. It was taken up in petroleum ether and thoroughly extracted with Claisen's alkali. The alkaline extract was diluted with water, acidified, and extracted with ether. Removal of the ether left an oil which deposited crystals when its solution in dilute alcohol was cooled. The solid was removed and crystallized from petroleum ether. It formed large white crystals which weighed 250 mg. and which melted at 94–94.5° alone and when mixed with an authentic specimen.

2,4,6,7-Tetramethyl-5-bromocoumaran (XI).—The coumaran X (5 g.) in carbon tetrachloride (10 cc.) was brominated by addition of bromine (1.55 cc.) in the same solvent (10 cc.). The solution was washed with bisulfite, ether was added, and the organic layer was removed. The solvents were evaporated under reduced pressure, and the residue, a white solid, was crystallized from alcohol. The product weighed 4.9 g., and melted at 76–77°.

Anal. Calc'd for $C_{12}H_{14}OBr$: C, 56.46; H, 5.93.
Found: C, 55.93, 55.92; H, 5.90, 5.89.

The substance gave a strong positive test for halogen (Beilstein), was inert toward bromine, and gave no precipitate with alcoholic silver nitrate.

2,4,6,7-Tetramethyl-5-hydroxycoumaran (XII).—A Grignard reagent was prepared from magnesium (0.3 g.), ethyl bromide (1 g.) and the bromocoumaran (0.7 g.) in ether (25 cc.). The ether was replaced by benzene and the mixture was refluxed for an hour. Then oxygen was passed through for an hour. The product, isolated in the usual way, was a semi-solid from which some starting material was isolated. The remainder was extracted with Claisen's alkali and the alkaline extracts were manipulated as described under the preparation of the chroman VIII. The product, only a few milligrams, was a white solid which melted at 115–118°. When mixed with an authentic sample of XII (m.p. 129–30°), it melted at 120–122°. The substance gave a positive phenol test.

Bomb hydrolysis of the bromo coumaran.—The bromo compound XI, (4.3 g.) was suspended in sodium hydroxide (5 g.) and water (40 cc.) in a small hydrogenation bomb. Cuprous oxide (0.75 g.) and copper powder (3 g.) were added, the bomb was closed and heated to 200° for 5 hours. At this temperature there was no reaction, and the bromo compound was recovered unchanged. The experiment (4.8 g. of bromo compound) was repeated at a higher temperature (300°) for 5 hours. The copper and copper oxide were removed by filtration, and the filtrate was extracted with ether. The alkaline aqueous layer was acidified and again extracted with ether. Removal of the ether left an oil (*ca.* 2.5 g.) which after much manipulation, involving great losses, was finally separated from the tar by distillation in a sausage flask under reduced pressure. The nearly colorless distillate (0.8 g.) solidified on cooling (m.p. 87–88°). The solid was crystallized from petroleum ether, then from ethanol after the solution was decolorized with charcoal, and finally from petroleum ether. It then melted at 93–94°. When mixed with known 2,3,5-trimethylphenol (m.p., 95°), the substance melted at 93.5–94.5°. It was insoluble in aqueous sodium bicarbonate, but soluble in carbonate and in sodium hydroxide (5%). The phenol test was strongly positive; the iodoform test was negative, and silver nitrate in methanol was reduced only very slowly. The product was halogenfree. Heated with pyridin-

ium chloride (1 g.) for 1 hour at 210°, the substance (0.35 g.) was recovered practically unchanged (m.p., 86–88°).

Anal. Calc'd for $C_9H_{12}O$: C, 79.41; H, 8.82.
Found: C, 79.30; H, 9.27.

The substance was further identified as 2,3,5-trimethylphenol by preparation of the dibromo derivative. After crystallization from ethanol, this melted at 147–148 (literature[9], m.p. 152°).

Anal. Calc'd for $C_9H_{10}Br_2O$: C, 36.93; H, 3.40.
Found: C, 36.90; H, 3.40.

SUMMARY

1. The introduction of a hydroxyl group para to the bridge oxygen in 2,2,5,7,8-pentamethylchroman and in 2,4,6,7-tetramethylcoumaran has been accomplished by brominating these substances and oxidizing the Grignard reagents formed from the resulting para bromo compounds.

2. Diazotized sulfanilic acid coupled extremely slowly with the chroman under the conditions used.

3. The chroman formed a very stable and inert mono nitro compound, which could not be reduced, by any of the methods tried.

4. The bromocoumaran is cleaved by alkali at 300° to give 2,3,5-trimethylphenol, an interesting example of the "positive" bromine effect, and a reaction which parallels the reaction of hot hydriodic acid upon the tocopherols.

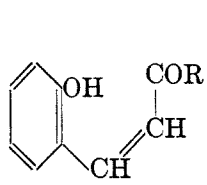
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. XII. PREPARATION OF CHROMANS BY ACTION OF GRIGNARD REAGENTS UPON DIHYDROCOUMARINS[1,*]

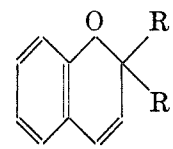
LEE IRVIN SMITH, HERBERT E. UNGNADE, AND W. W. PRICHARD

Received March 31, 1939

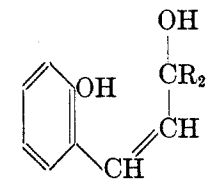
The action of Grignard reagents upon coumarins has been studied by a number of investigators. Decker and Fellenberg[2] reported that coumarin reacted with phenylmagnesium bromide to give 2-phenylphenopyrrylium salts; Houben[3] reported that coumarin, with benzylmagnesium chloride gave as the first product the hydroxy ketone (I, R = benzyl), but that the usual products of the Grignard reaction were 2,2-disubstituted Δ^3-chromenes (II), presumably via the carbinols (III) as intermediates, although



I



II



III

these could not be isolated, at least when methyl and ethyl Grignard reagents were used. When phenylmagnesium bromide was used, Heilbron and Hill[4] found that a 2,2-diphenylchromene (II, R = phenyl) resulted only when the 4-position in the coumarin was occupied by a substituent such as methyl or methoxyl. More recently, Bergel, Jacob, Todd, and Work[5] have also found that a Δ^3-chromene resulted when the 4 position of the coumarin was occupied; they obtained 2,2,4-trimethyl-6-hydroxy-Δ^3-chromene when 4-methyl-6-acetoxycoumarin reacted with methylmagnesium iodide. Heilbron and Hill also found, in agreement with the work

[1] Paper XI: J. ORG. CHEM., **4**, 351 (1939).

[*] Presented (in part) at the 96th meeting of the American Chemical Society, Milwaukee, Sept. 5–9, 1938.

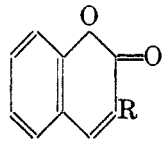
[2] DECKER AND FELLENBERG, *Ann.*, **356**, 300 (1907); *Ber.*, **40**, 3816 (1907).

[3] HOUBEN, *Ber.*, **37**, 489 (1904).

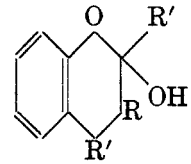
[4] HEILBRON AND HILL, *J. Chem. Soc.*, **1927**, 2005; see also HEILBRON, HILL AND WALLS, *ibid.*, **1931**, 1701; HILL, *Chem. Rev.*, **19**, 35 (1936).

[5] BERGEL, JACOB, TODD, AND WORK, *J. Chem. Soc.*, **1938**, 1375.

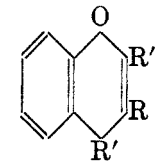
of Lowenbein[6] that when phenylmagnesium bromide reacted with coumarin or a 3-substituted coumarin, (IV) the reaction was quite complex, and the coumarin was attacked in both the 2 and the 4 positions. The chief products were the chromanol (V) and the Δ^2-chromene (VI) derived from it.



IV

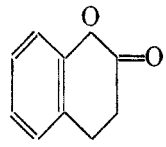


V, R′ = C_6H_5 or $C_{10}H_7$

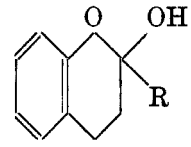


VI

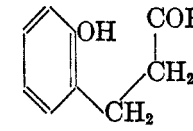
It is evident that the complications connected with these reactions of coumarins are in large part due to the effect of the conjugated system. To avoid this, we decided to eliminate the double bond by reduction, and to start our experiments with dihydrocoumarins. While our work is still incomplete, we are publishing our results now in view of the recent paper by John, Gunther, and Schmeil[7] which parallel, to some extent, the work reported here. Prior to our own experiments[8] and those of John, Gunther, and Schmeil, Grignard reagents do not appear to have been added to dihydrocoumarins. In analogy with the work of Houben[3] on the saturated lactones, the reaction between hydrocoumarins (VII) and Grignard reagents would be expected to lead ultimately to phenolic carbinols (IX) and to 2,2-disubstituted chromans (X) presumably via the intermediate VIII*a*



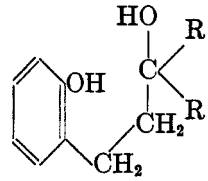
VII



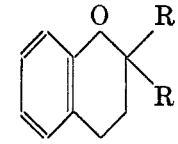
VIII *a*



VIII *b*



IX



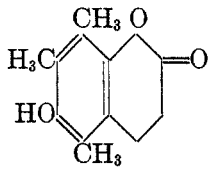
X

[6] LOWENBEIN, *Ber.*, **57**, 1519 (1924).
[7] JOHN, GUNTHER, AND SCHMEIL, *ibid.*, **71**, 2637 (1938).
[8] Paper I: *Science*, **88**, 37 (1938).

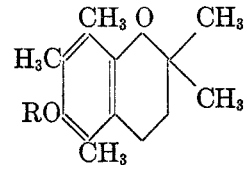
or *b*. In any event, the attack would be entirely at the carbonyl group, and by modifying the conditions we hoped to stop the reaction at the first stage and isolate the intermediate ketones (VIII*b*). This was necessary if the method were to be used as a synthesis of tocopherols and their analogs, since in the tocopherols two different groups occupy the α positions in the chroman ring.

It was not found possible, however, under any of the conditions used, to isolate the ketone. The first isolable product of the reaction was the carbinol (IX), which was usually accompanied by and readily cyclized to, the chroman (X). Thus when a solution of dihydrocoumarin (VII) was added to ethylmagnesium bromide, there resulted in good yield a solid melting at 71–72° the analysis of which corresponded to IX (R = C_2H_5). This substance, when boiled for a short time with acetic acid and 20 per cent. sulfuric acid, gave the chroman X (R = C_2H_5), a liquid boiling at 128.5–128.9° under 12 mm. No ketone whatever was obtained. Similar results were obtained when *n*-propylmagnesium chloride was used; the carbinol and the chroman, but no ketone, were obtained. Claisen[9] prepared the chroman X (R = CH_3) by the action of methylmagnesium iodide upon the ethyl ester of dihydrocoumaric acid, obtaining the intermediate carbinol IX (R = CH_3) which was then cyclized to the chroman. We have prepared this chroman (X, R = CH_3) from phenol and isoprene; the properties of the product agreed with those reported by Claisen.

Since the chroman system in α-tocopherol is substituted by an hydroxyl group in position 6 and by methyl groups in positions 5, 7, and 8, to obtain by means of this Grignard reaction true analogs and homologs of toco-



XI



XII

pherol, it is necessary to start with 5,7,8-trimethyl-6-hydroxy-3,4-dihydrocoumarin (XI), a substance made by Smith and Denyes.[10] When XI was added to methylmagnesium iodide, the product was a solid which, before recrystallization, melted sharply at 151–152°. Recrystallization of this substance resulted in a product with a lower melting point, which indicated that the original product was the carbinol, and that it was undergoing cyclization during recrystallization, for it was known that the

[9] CLAISEN, *Ber.*, **54**, 200 (1921).
[10] DENYES, *J. Am. Chem. Soc.*, **58**, 304 (1936).

chroman (XII, R = H) melted at 94–94.5°. Accordingly this product was cyclized and acetylated by warming it in acetic acid containing a little sulfuric acid. The acetate of the hydroxychroman (XII, R = Ac), m.p., 87–88°, resulted, identical with a specimen of the acetate prepared in another way.

Hence in the case of the highly-substituted dihydrocoumarin (XI) it appears that the Grignard reaction can be stopped at the carbinol stage, but not at the ketone stage. John, Gunther, and Schmeil[7] reported that only the chroman could be obtained from this reaction, and that if only one mole of the Grignard reagent were used, the product was a mixture of the chroman XII (R = H) and starting material (XI). In general, their results parallel ours, but they reported no evidence indicating the presence of the carbinol. However, by the very neat experimental procedure of adding the hydrocoumarin (XI) to a mixture of the two different Grignard reagents, they were able to obtain a 10–15 per cent. yield of 2-dodecyl-2,5,7,8-tetramethyl-6-hydroxychroman, which indicates that a ketone such as VIII must be one of the intermediates.

Further work upon this reaction is in progress and will be reported in a later paper.

EXPERIMENTAL

5-(o-Hydroxyphenyl)-3-ethylpentanol-3 (*IX*, *R* = C_2H_5).—Dihydrocoumarin (5 g., m.p., 25°) in ether (30 cc.) was added to the Grignard solution prepared from magnesium (1.6 g.) and ethyl bromide (7.4 g.). The reaction was completed by refluxing for one hour. The mixture was decomposed by adding ice and 30% sulfuric acid, and the product was removed by ether extraction. After drying over calcium chloride, and removal of the ether, there remained 6 g. of a white solid. When crystallized from petroleum ether it melted at 71–72°.

Anal. Calc'd for $C_{13}H_{20}O_2$: C, 75.00; H, 9.61.
Found: C, 74.84; H, 9.60.

2,2-Diethylchroman (*X*, *R* = C_2H_5).—The carbinol IX (R = C_2H_5) (4.5 g.) was cyclized by boiling it for 30 minutes in acetic acid (25 cc.) and sulfuric acid (20%, 10 cc.). The reaction mixture was diluted with water and extracted with ether. The ethereal solution was extracted thoroughly with 10% aqueous sodium hydroxide. After drying over calcium chloride, the ether was removed and the product distilled. There resulted 3.14 g. of a colorless oil which boiled at 128.5–128.9° under 12 mm.

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.11; H, 9.47.
Found: C, 82.03; H, 9.77.

*2,2-Di-*n*-propylchroman* (*X*, *R* = n-C_3H_7).—Dihydrocoumarin (5 g.) in ether (25 cc.) was added to the Grignard solution prepared from magnesium (2.4 g.) and *n*-propyl chloride (7.8 g.) in ether (50 cc.). The product, isolated as described above, was an oil (6.15 g.) which could not be crystallized, but which gave a strongly positive phenol test. This oil was dissolved in acetic acid (15 cc.), 30% sulfuric acid (5 cc.) was added and the solution was refluxed for 30 minutes. The product was isolated as described above except that potassium carbonate was used as the drying agent. The oily product still gave a positive phenol test. Accordingly, a drop of sulfuric

acid was added, and the oil was distilled under reduced pressure. The distillate, which gave a negative phenol test, was taken up in ether, washed with water and dried over calcium chloride. The solvent was removed, and the residue was distilled. The distillate was a clear, colorless oil which weighed 3.0 g. and which boiled at 153–154° under 15 mm.

Anal. Calc'd for $C_{15}H_{22}O$: C, 82.57; H, 10.04.
Found: C, 82.23; H, 10.19.

2,2,5,7,8-Pentamethyl-6-hydroxychroman (XII).—The hydrocoumarin (XI) (1.33 g.) in benzene (50 cc.) was added to a Grignard solution prepared from magnesium (0.62 g., 4 moles) and a slight excess of methyl iodide in ether (50 cc.). The preparation of the reagent and addition were carried out under nitrogen. As the coumarin solution was added, ether was distilled off at about the same rate so that when the addition was complete, the solvent was practically all benzene in which the gelatinous reaction product was suspended. The mixture was refluxed for two hours, then poured into ice and 30% sulfuric acid. The layers were separated and the aqueous layer was extracted twice with benzene (25 cc.) then with ether (25 cc.) and finally again with benzene (25 cc.). The combined organic extracts deposited a white crystalline precipitate (*A*) which was removed. The filtrate was evaporated, leaving an oil which soon solidified (*B*). (*A*) after washing with a little benzene weighed 0.4 g. and melted at 127–129°. (*B*) was slightly purple, and after washing with a little benzene it weighed 0.4 g. and melted at 151–152° to a red liquid. The benzene washings from *A* and *B* were evaporated on the steam bath, leaving a red oil (0.5 g.) which was not investigated further. *A* and *B* were separately recrystallized from benzene. *A* then melted at 125–127°; *B* at 146–149°; when mixed, they melted at 131–138°. It was concluded from these data that *A* and *B* were mixtures of the chroman and the intermediate carbinol. A small amount of *B* was set aside for later examination; the remainder of *B* was combined with *A* (total weight 0.45 g.), dissolved in acetic acid (5 cc.) and a drop of sulfuric acid and refluxed for an hour. The red solution was poured into water and extracted with ether. The ethereal solution was washed thoroughly with aqueous sodium carbonate (5%), and the ether was evaporated. The residual brown oil solidified after addition of a few drops of ethanol. The product weighed 0.33 g. and melted at 82–83°. After recrystallization from dilute ethanol, the product formed flat plates melting at 87–88° and was the acetate of XII; m.p. of mixture with an authentic specimen (m.p. 91–91.5), 87–88°. The melting point of a mixture with an authentic specimen of XII (m.p. 94°) was 69–86°†.

SUMMARY

1. Grignard reagents have been added to dihydrocoumarin, and to 5,7,8-trimethyl-6-hydroxy-3,4-dihydrocoumarin.

2. The final products are 2,2-disubstituted chromans, but the intermediate carbinols are first formed, and in one case this was isolated as a crystalline solid.

3. It was not possible to isolate the ketones which are first products of the reaction; hence this reaction cannot well be used as a synthesis of 2,2-disubstituted chromans in which the two substituents differ.

† The preparation by another method, of the chroman and its acetate, and the analyses, are given in paper VI: J. Org. Chem., **4**, 311 (1939).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF BUFFALO]

STUDIES IN SILICO-ORGANIC COMPOUNDS. I. THE PREPARATION OF SILICON ANALOGUES OF CERTAIN ALIPHATIC ORTHO ESTERS

HOWARD W. POST AND CHARLES H. HOFRICHTER, JR.

Received March 25, 1939

The purpose of this investigation was to prepare certain aliphatic orthosilicopropionates, -valerates, and -benzoates. This was accomplished by refluxing ethyl orthosilicate with a Grignard reagent, according to procedures already published[1,2], and treating the product with an aliphatic alcohol, for example:

$$Si(OC_2H_5)_4 + C_2H_5MgBr \rightarrow C_2H_5OMgBr + C_2H_5Si(OC_2H_5)_3$$
$$C_2H_5Si(OC_2H_5)_3 + 3C_3H_7OH \rightleftarrows 3C_2H_5OH + C_2H_5Si(OC_3H_7)_3$$

In one instance, however, the desired ortho ester was prepared by the action of the Grignard reagent on silicon tetrachloride and subsequent refluxing with *n*-propyl alcohol, a modification of Ladenburg's procedure[3]. This type of reaction is also covered by patents[4].

EXPERIMENTAL

Ethyl orthosilicopropionate was prepared as outlined by Andrianov and Gribanova[1] save that the extraction with acetic acid was omitted. B.p. 158°–160° (found), 158° (literature[1]); d_4^{22} 0 928 (found), 0.9204 (literature[1]); n_D^{22} 1.3853 (found); Mol. Wt. 187 (found, cryoscopic in benzene), 192 (theoretical); Yield 83.7%. The column used in this work was of the Claisen type; one inch in diameter, 15.5 inches long, and 3.5 inches from top to orifice. The top was fitted with an adjustable cold-point condenser which was 6 inches overall and 4.5 inches from side-arm to end. The column was packed with 0.25-inch copper Lessing rings, and the outside was wound with two lengths of Nichrome No. 22 wire, six turns to the inch. Each of these resistances could be used independently, or both in series. Over the wire was placed 0.5 inch of asbestos, packed while wet. This column was found serviceable for the distillation of materials boiling up to 170° (760 mm.).

n-*Propyl orthosilicopropionate.*—Ethyl orthosilicopropionate was refluxed with six molar quantities of normal propyl alcohol. The interchange of radicals was slow, refluxing being continued for ninety-six hours. Product b.p. 202°–204° (760

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[1] ANDRIANOV AND GRIBANOVA, *J. Gen. Chem., U.S.S.R.*, **8**, 552 (1938).
[2] KHOTINSKY AND SEREGENKOFF, *Ber.*, **41**, 2946 (1908).
[3] LADENBURG, *Ann.*, **173**, 151 (1874).
[4] KAUFMANN, *Chem. Abstr.*, **25**, 5177 (1931); **31**, 6416 (1938).

mm.); d_4^{23} 0.896; n_D^{23} 1.4017; n_D^{10} 1.4060; Mol. wt. (as above) 228 (found), 223 (theoretical). Si 11.99, 11.88 (found), 11.98 (theoretical).

The following orthoesters were prepared as was the *n*-propyl orthosilicopropionate:

n-*Butyl orthosilicopropionate.*—B.p. 235°–238° (760 mm.); $d_4^{2.4}$ 0.878; n_D^{24} 1.4128, n_D^{10} 1.4174; Mol. wt. (as above) 268 (found), 272 (theoretical); Si 9.99, 10.09 (found), 10.15 (theoretical). Yield 71.3%.

n-*Amyl orthosilicopropionate.*—B.p. 285° (760 mm.); d_4 0.891; Mol. wt. (as above) 303 (found), 318 (theoretical); n_D^{23} 1.4210, n_D^{10} 1.4262, Si 8.90, 8.83 (found), 8.81 (theoretical).

i-*Amyl orthosilicopropionate.*—B.p. 266°–269° (760 mm.), d_4 0.891; Mol. wt. (as above) 312 (found), 318 (theoretical); n_D^{24} 1.4170, n_D^{10} 1.4222, Si 8.88, 8.68 (found), 8.81 (theoretical).

Ethyl orthosilicobutyrate.—Ethyl orthosilicate was refluxed with propylmagnesium bromide. B.p. 179–180° (760 mm.); n_D^{20} 1.4076; Si, 13.81, 13.55 (found), 13.60 (theoretical); mol. wt. (cryoscopic in benzene) 204, (theoretical) 206; d_4^{20} 0.852.

Ethyl orthosilicobenzoate.—Prepared by the action of phenylmagnesium bromide on ethyl orthosilicate as outlined for ethyl orthosilicopropionate. B.p. 235°–238° (760 mm.) (found), 235° (literature[3]), 232° (literature[2]); d^{10} 1.0055 (found and literature[3]).

n-*Propyl orthosilicobenzoate.*—Phenylmagnesium bromide was allowed to react with silicon tetrachloride, and the resulting silicobenzotrichloride was treated with propyl alcohol. d_4^{20} 1.036; n_D^{20} 1.5025; Mol. wt. 298 (cryoscopic from benzene) 302 (theoretical); b.p. 192° (7 mm.), Si 9.86, 9.90 (found), 9.94 (theoretical).

n-*Heptyl orthosilicate.*—Silicon tetrachloride was allowed to react, under reflux with *n*-heptyl achohol.

$$SiCl_4 + 4C_7H_{15}OH \longrightarrow 4HCl + Si(OC_7H_{15})_4$$

n_D^{29} 1.4300; d_4^{29} 0.876; mol. wt. (cryoscopic in benzene) 472 (theoretical) 488; b.p. 213.5 (4 mm.); Si, 5.80, 5.75 (found), 5.74 (theoretical); yield 53.5%.

Normal amyl orthosilicopropionate always distilled slightly yellow in color. Its physical constants also indicate slight contamination. Normal butyl orthosilicovalerate could not be found among the products of the reaction between normal butyl alcohol and ethyl orthosilicovalerate. Ethyl alcohol produced in exchange reactions was collected and identified by the iodoform reaction.

SUMMARY

1. Revised methods have been presented for the preparation of ethyl orthosilicopropionate and ethyl orthosilicobenzoate.

2. Methods for the preparation of *n*-propyl, *n*-butyl, *n*-amyl, and *i*-amyl orthosilicopropionates, ethyl orthosilicobutyrate, *n*-heptyl orthosilicate, and *n*-propyl orthosilicobenzoate, have been described, and data are given covering their simple physical properties.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

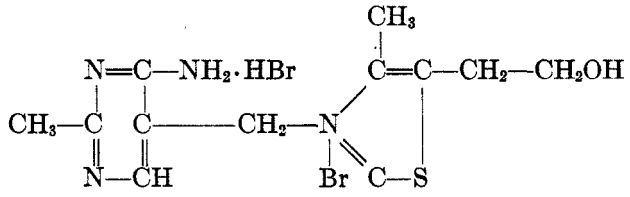
STUDIES IN THE PYRIDINE SERIES. I. AN IMPROVED SYNTHESIS OF 2,3-DIMETHYLPYRIDINE AND THE CONVERSION OF THE LATTER INTO AN ANALOG OF THIAMINE

JACOB FINKELSTEIN AND ROBERT C. ELDERFIELD

Received April 3, 1939

The striking similarity in physical and chemical properties between members of the benzene and thiophene series has often been noted. In 1933 Erlenmeyer, Berger, and Leo[1] offered the theory that such similarity could be explained on the basis of the fact that divalent sulfur contains a shell of orbit electrons similar to that of the "pseudo-atom: —CH=CH—. For this similarity they suggested the term "isosterism." At the same time they added the observation to the scattered cases on record of similar pharmacological action of such pairs[2] that certain pairs of isosteric compounds could not be differentiated by the precipitin reaction. In later work[3] Erlenmeyer and von Meyenburg substituted a ring sulfur atom for the —CO·NH— and —CO·NH·R— group in dialkyl barbituric acids and obtained compounds with hypnotic action similar to that of the parent barbiturates. Wohmann noted that the diethylamide of thiazolecarboxylic acid showed qualitatively the same analeptic action as the corresponding pyridine diethylamide (coramine)[4].

As a result of the investigations of Williams and co-workers[5] and of Windaus and co-workers the structure of vitamin B_1, or thiamine, is now recognized as being represented by I:



I

[1] ERLENMEYER, BERGER, AND LEO, *Helv. Chim. Acta*, **16**, 733 (1933); ERLENMEYER AND LEO, *ibid.*, **16**, 1381 (1933).

[2] HARTMANN AND WYBERT, *ibid.*, **2**, 60 (1919); STEINKOPF AND OHSE, *Ann.*, **437**, 14 (1924), *inter alia*.

[3] ERLENMEYER AND VON MEYENBURG, *Helv. Chim. Acta*, **20**, 1388 (1937).

[4] WOHMANN, *Ann.*, **259**, 277 (1890).

[5] WILLIAMS AND SPIES, "Vitamin B_1," MacMillan, New York, **1938**.

While a considerable number of homologs and variants of this structure have been synthesized in an effort to arrive at some relationship between the structure and physiological activity of thiamine,[5] these have been largely confined to variations of the pyrimidine component of the molecule and to the preparation of substances homologous with respect to the various side-chains. Inspection of the thiazole portion of the thiamine molecule shows that application of Erlenmeyer's theory of isosterism by substitution of an ethylene unit for the sulfur atom can be accomplished by using an appropriately substituted pyridine, namely 3-(2-hydroxyethyl)-2-picoline, in place of the thiazole. A study of the physiological properties of such a substance should be not without interest.

The investigation thus resolved itself into the development of a suitable synthesis for 2,3-disubstituted pyridines. A survey of the literature revealed a surprising lack of satisfactory methods for the preparation of such compounds. Attention therefore was directed toward the synthesis of 2,3-dimethylpyridine. By taking advantage of the activity of the hydrogen atoms in the 2-methyl group, it should be possible to condense this substance with formaldehyde to yield 2-(2-hydroxyethyl)-3-picoline. The synthesis of the latter substance and its condensation with the pyrimidine portion of the thiamine molecule forms the basis of this report. The synthesis of the true pyridine analog of thiamine is under way and will be described in another paper.

2,3-Dimethylpyridine, apparently the only 2,3-dialkylpyridine reported, was first described by Garrett and Smythe[6], who isolated it from Scottish shale oil. Ahrens[7] isolated it from the products of the dry distillation of coal. Several years later, Lipp and Widnmann[8] obtained it by zinc dust distillation of 2,3-dimethyl-Δ^2-tetrahydropyridine, and identified it by its picrate, and by oxidation to quinolinic acid. The key compound for the synthesis thus becomes the tetrahydro derivative, which has been prepared by a number of workers, although none of the recorded syntheses is satisfactory. Sachs[9] condensed sodio ethyl α-methylacetoacetate with trimethylene bromide. Eighty per cent. of the resulting compound was ethyl α,α'-dimethyl-α,α'-diacetopimelate. Hydrolysis of the twenty per cent. of the desired compound gave 3-methylhexan-6-ol-2-one, a compound which easily passed to the dihydropyran if the slightest amount of impurity was present. Conversion of the keto alcohol to the bromide, and interaction of the latter with ammonia gave the desired tetrahydropyridine. Other workers attempted to avoid the difficulties inherent in Sachs' synthesis.

[6] GARRETT AND SMYTHE, *J. Chem. Soc.*, **83**, 764 (1903).
[7] AHRENS, *Chem. Zentr.*, **1906**, I, 510.
[8] LIPP AND WIDNMANN, *Ann.*, **409**, 79 (1915); LIPP, *ibid.*, **289**, 173 (1896).
[9] SACHS, *Ber.*, **32**, 62 (1899).

Bently, Haworth, and Perkin[10] used halohydrins in the condensation, with unfavorable results for the most part. Likewise Perkin and Sprankling[11] and Bogert and Slocum[12] were unable to repeat Fittig and Chanlaroff's[13] synthesis of γ-hydroxybutyric acid by condensation of ethylene chlorohydrin with acetoacetic ester and hydrolysis of the resulting product. Bogert and Slocum also attempted the condensation of γ-iodopropyl acetate with acetoacetic ester, but this was abandoned since, on hydrolysis, the dihydropyran would be formed in the same manner as in Sachs' synthesis. Lipp and Widnmann[8] attempted to improve Sachs' method by using the Gabriel amine synthesis, but their reactions were complicated by the formation of an excessive number of by-products. Further, no intermediates were isolated or characterized by them.

It seemed probable that if a halide containing only one reactive group could be found, the difficulties inherent in the general Sachs method could be avoided. Such a substance has been found in γ-bromopropyl ethyl ether (II). This condensed smoothly with sodio ethyl α-methylacetoacetate in alcoholic solution. However, instead of the expected disubstituted acetoacetic ester, ethyl α-methyl-δ-ethoxyvalerate (III) was obtained. Such catalytic splitting of the disubstituted acetoacetic ester first formed under the influence of sodium ethoxide is not unusual. Dieckmann[14] and Vavon and Horeau[15], among others, have noted a similar behavior of such esters. The undesirable reaction was avoided by carrying out the condensation in dry dioxane, and a good yield of ethyl α-methyl-α-(γ-ethoxypropyl)acetoacetate (IV) resulted, although even in this medium a slight amount of valeric ester was formed. Hydrolysis of this substance by the method of Adkins and Connor[16] led to a 75 per cent. yield of 3-methyl-6-ethoxyhexan-2-one (V). The latter on heating with a saturated solution of hydrogen bromide in glacial acetic acid gave 3-methyl-6-bromohexan-2-one (VI), which after standing with alcoholic ammonia gave 2,3-dimethyl-Δ^2-tetrahydropyridine (VII).

Dehydrogenation of hydrogenated pyridines to pyridines by distillation with zinc dust has been successfully used in the past, and was at first applied to the dehydrogenation of the above dimethyltetrahydropyridine. A poor yield of crude 2,3-dimethylpyridine (VIII) was thus obtained. Attention was then directed to possible improvements in the dehydrogenation process. In a model experiment based on the observation of Orechoff

[10] Bently, Haworth, and Perkin, *J. Chem. Soc.*, **69**, 162 (1896).
[11] Perkin and Sprankling, *J. Chem. Soc.*, **75**, 11 (1899).
[12] Bogert and Slocum, *Am. Perf.*, **18**, 621 (1924).
[13] Fittig and Chanlaroff, *Ann.*, **226**, 326 (1884).
[14] Dieckmann, *ibid.*, **317**, 27 (1901).
[15] Vavon and Horeau, *Bull. soc. chim.*, [5], **1**, 1710 (1934).
[16] Adkins and Connor, *J. Am. Chem. Soc.*, **54**, 3420 (1932).

and Menschikoff[17] that dipyridyl results when anabasine is heated with silver acetate in acetic acid at 180°, 2-picoline was similarly treated in order to determine the stability of substituent alkyl groups under such conditions. The product of the reaction furnished a picrate which agreed in properties with pyridine picrate, thus showing that the 2-methyl group had been removed during the reaction. The possibility of catalytic dehydrogenation with retention of the alkyl groups was next explored. Pyridine is smoothly hydrogenated to piperidine over palladized asbestos at 150°; at 250° the reverse reaction takes place[18]. Various workers have successfully dehydrogenated piperidine derivatives carrying substituents on one or both of the 2 or 4 positions[19] but no information is at hand concerning retention of substituents in the 3 position during such treatment. Therefore copellidine (2-methyl-5-ethylpiperidine), prepared by catalytic reduction of aldehyde collidine with Adams and Shriner's catalyst, was slowly passed over palladized asbestos at 275°. An excellent yield of aldehyde collidine with retention of both substituents resulted. 2,3-Dimethyltetrahydropyridine when similarly treated gave the desired 2,3-dimethylpyridine (VIII).

Condensation of 2,3-dimethylpyridine with formaldehyde according to Koenigs and Bernhart[20] or Oparina[21] resulted in a poor yield of the expected 2-(2-hydroxyethyl)-3-picoline (IX) which was exceedingly difficult to separate from the di- and trimethylol derivatives simultaneously formed. The observation of Bergmann and Rosenthal[22] that the reactive hydrogen of the methyl group of 2-picoline may be replaced by lithium and that the resulting picolyllithium may then be treated with benzaldehyde to give phenylpyridylcarbinol formed the basis for a radical improvement in the preparation of the monomethylol derivative. Bearing in mind the abnormal reaction of formaldehyde with benzyl Grignard reagents, which leads to *o*-tolylcarbinol, an orienting experiment was performed using 2-picoline. 2-Picolyllithium reacts smoothly with formaldehyde to give a superior yield of 2-(2-hydroxyethyl)pyridine. Oxidation of the latter to picolinic acid showed that 2-methyl-3-hydroxymethylpyridine was not formed during the reaction. When the same procedure was applied to 2,3-dimethylpyridine, 2-(2-hydroxyethyl)-3-picoline (IX) resulted.

[17] ORECHOFF AND MENSCHIKOFF, *Ber.*, **64**, 272 (1931); TAFEL, *ibid.*, **25**, 1619 (1892).

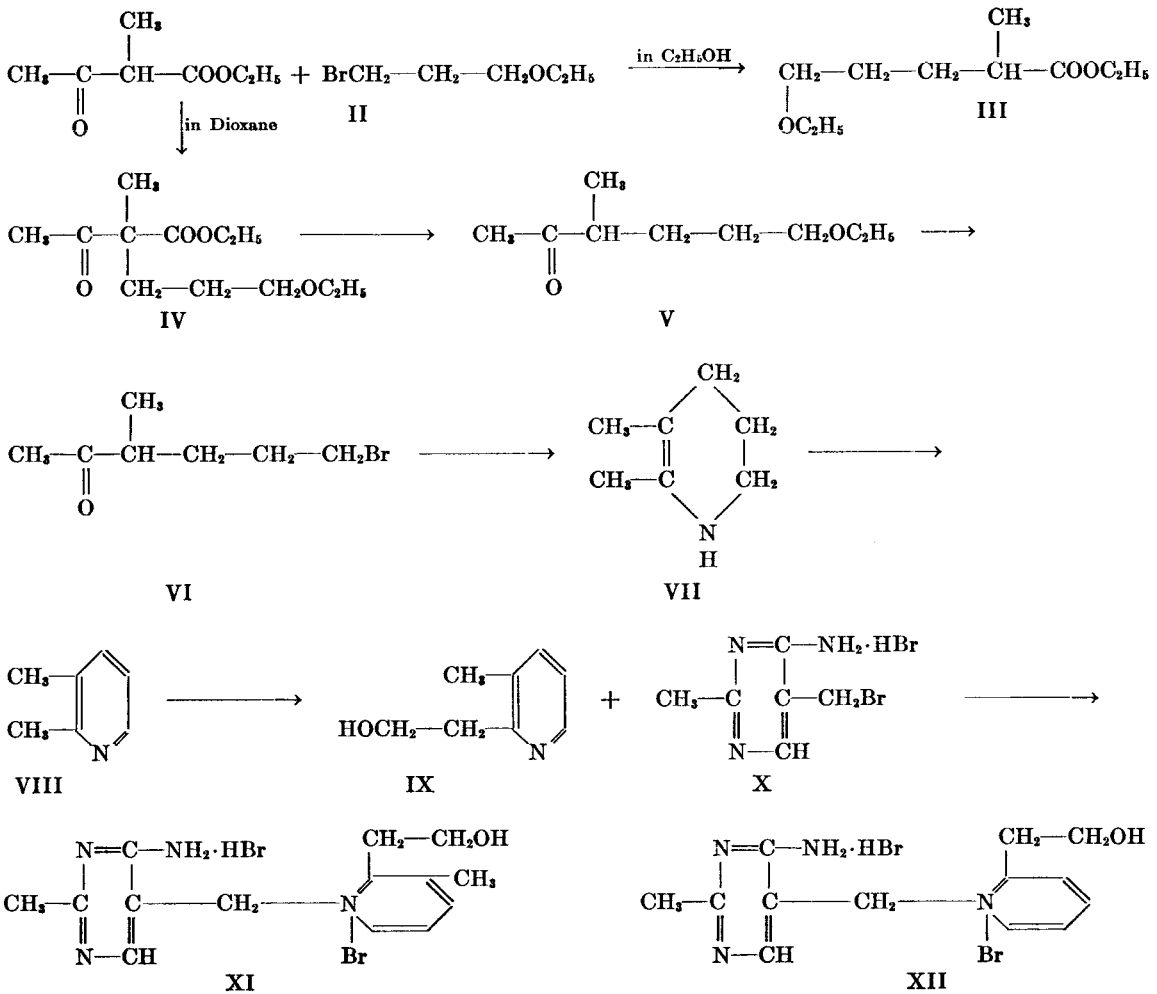
[18] ELLIS, "Hydrogenation of Organic Substances," 3rd Ed. Van Nostrand, New York, **1930**, p. 286.

[19] EHRENSTEIN, *Ber.*, **64**, 1137 (1931); SPÄTH AND GALINOVSKY, *ibid.*, **69**, 2059 (1936).

[20] KOENIGS AND BERNHART, *ibid.*, **38**, 3049 (1905).

[21] OPARINA, *ibid.*, **64**, 569 (1931).

[22] BERGMANN AND ROSENTHAL, *J. prakt. Chem.*, **135**, 277 (1932).


in C2H5OH
in Dioxane
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII

The final condensation of IX with 2-methyl-4-amino-5-bromomethylpyrimidine (X) took place readily on heating the two in light petrolatum, and yielded 1-[(4-amino-2-methyl)-5-pyrimidylmethyl]-2-(2-hydroxyethyl)-3-picolinium bromide hydrobromide (XI). This compound closely resembles the corresponding derivative of thiamine in its behavior on heating, and in other general properties. At the same time 2-(2-hydroxyethyl)pyridine was similarly condensed with X, giving 1-[(4-amino-2-methyl)-5-pyrimidylmethyl]-2-(2-hydroxyethyl)pyridinium bromide hydrobromide (XII).

Neither XI nor XII showed thiamine activity when assayed on polyneuritic rats at a dose level of 100γ per rat. The same substances were tested by the yeast fermentation method developed in the Fleischmann laboratories[23] at levels equivalent to 1γ and 2γ of 4-aminopyrimidine. As controls, 2γ and 4γ of thiamine (containing approximately 1γ and 2γ of pyrimidine respectively) were run at the same time. The results, expressed on a pyrimidine basis, are shown in Table I.

TABLE I

SUBSTANCE (EXPRESSED AS PYRIMIDINE EQUIVALENT)	CC. OF CO_2 EVOLVED IN 3 HRS.
1γ pyrimidine (either XI or XII)	320
2γ thiamine	319
2γ pyrimidine (either XI or XII)	366
4γ thiamine	372

We are indebted to Dr. R. T. Major of Merck & Company, Rahway, N. J. for the generous gift of the pyrimidine derivative used in this research, as well as for placing at our disposal the necessary high-pressure equipment. We also desire to express our appreciation to Dr. W. L. Sampson, of the Merck Therapeutic Institute, who graciously performed the biological tests here reported.

EXPERIMENTAL

Ethyl α-methyl-α-(γ-ethoxypropyl)acetoacetate (IV).—Sodium sand (57.5 g.) was prepared in 4 l. of dioxane, which had been distilled from sodium, contained in a 5-l. 3-necked flask equipped with a dropping funnel, a reflux condenser and a very efficient mechanical stirrer. Three hundred sixty grams of ethyl α-methylacetoacetate[24] was then added with vigorous stirring, at such a rate that the temperature of the mixture was kept just below the melting point of sodium. After all the ester had been added, the mixture was allowed to stand overnight, when all the sodium

[23] SCHULTZ, ATKIN, AND FREY, *J. Am. Chem. Soc.*, **59**, 2457 (1937).
[24] MICHAEL, *Ber.*, **38**, 2091 (1903).

had reacted. Four hundred eighteen grams of γ-bromopropylethylether[25] was then added slowly, and the mixture was refluxed with stirring for 60 hrs. until it was neutral to phenolphthalein. After cooling, the sodium bromide was centrifuged and thoroughly washed with dioxane, the washings being added to the main decantate. The residue, after removal of the solvent, was fractionally distilled at 16 mm. pressure. The fraction up to 90° was unchanged bromide; that boiling from 90–110° was chiefly ethyl α-methyl-δ-ethoxyvalerate, and weighed 50 g.; the main fraction, ethyl α-methyl-α-(γ-ethoxypropyl)acetoacetate, boiled at 141–143°, and weighed 220 g.

Anal. Calc'd for $C_{12}H_{22}O_4$: C, 62.6; H, 9.6.
Found: C, 61.7; H, 9.9.

Similar difficulty in securing satisfactory analytical figures for disubstituted acetoacetic esters has been commonly encountered[26].

After removal of the above products, the residue in the flask was distilled at 0.5 mm., and 32 g. of material distilled up to 140°. This was redistilled at 0.5 mm., and boiled at 128–130°. It gave the following analytical figures:

Anal. Found: C, 63.5; H, 9.5; OC_2H_5, 32.5.

The substance was not investigated further.

Ethyl α-methyl-δ-ethoxyvalerate (III).—Forty grams of γ-bromopropyl ethyl ether was added dropwise to a solution of sodio α-methylacetoacetic ester from 34.5 g. of the ester in 80 cc. of absolute alcohol. After refluxing for 6 hrs. the alcohol was distilled off, and sufficient water was added to the residue to dissolve the sodium bromide. The oily layer was drawn off, and the aqueous layer was extracted with ether. Fractionation of the product at 13 mm. gave 25 g. of ethyl α-methyl-δ-ethoxyvalerate boiling at 96–97°; n_D^{25} 1.4168. None of the above disubstituted acetoacetic ester was obtained.

Anal. Calc'd for $C_{10}H_{20}O_3$: C, 63.8; H, 10.7.
Found: C, 63.8; H, 10.9.

α-Methyl-δ-ethoxyvaleric acid.—Saponification of the above ester gave the parent acid, which boiled at 137–139° at 11 mm.; n_D^{25} 1.4289. Neutralization equivalent: calc'd, 160.8; found, 160.2.

Anal. Calc'd for $C_8H_{16}O_3$: C, 60.0; H, 10.1.
Found: C, 60.0; H, 10.2.

3-Methyl-6-ethoxyhexan-2-one (V).—A solution of 6.8 g. of sodium hydroxide in 33 cc. of water was added to a solution of 33 g. of ethyl α-methyl-α-(γ-ethoxypropyl)-acetoacetate in 30 cc. of alcohol. The mixture, contained in a copper-lined Aminco bomb, was placed under 1000 lbs. per sq. in. hydrogen pressure and heated at 250° for 8 hrs. After cooling, the solution was acidified with sulfuric acid and warmed on the steam bath to expel carbon dioxide. It was then extracted with ether. The product was fractionated at 17 mm., and the fraction boiling at 96–99° was collected as 2-methyl-6-ethoxyhexan-2-one. The yield was 16.5 g.

Anal. Calc'd for $C_9H_{18}O_2$: C, 68.3; H, 11.5.
Found: C, 68.2; H, 11.5.

In addition to the above ketone, 5 g. of material boiling at 141–143° at 17 mm. was obtained. At first this was believed to be unreacted ester. However, it was unchanged by further heating in the bomb.

Anal. Found: C, 64.6; H, 10.6.

The substance was not investigated further.

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[25] NOYES, *Am. Chem. J.*, **19**, 766 (1897).

[26] JAMES, *Ann.*, **226**, 208 (1884).

3-Methyl-6-bromohexan-2-one (*VI*).—A mixture of 11 g. of 3-methyl-6-ethoxyhexan-2-one and 80 cc. of glacial acetic acid which had been previously saturated with hydrogen bromide at 0° was warmed on the steam bath for 2 hours. After cooling, the brown reaction mixture was poured onto 300 cc. of cracked ice and water. The heavy oil was extracted with chloroform. After being washed free from acid, the product was distilled at 1.5 mm.; 6 g. of 3-methyl-6-bromohexan-2-one, boiling at 70–74° was obtained. Sachs[9], who also apparently prepared this compound, gave no physical constants nor analysis.

Anal. Calc'd for $C_7H_{13}BrO$: C, 43.5; H, 6.7.
Found: C, 43.4; H, 6.8.

When the above reaction was carried out in sealed tubes at 100° the same bromoketone was obtained, but the yield was lower.

2,3-Dimethyltetrahydropyridine (*VII*).—A solution of 20 g. of 3-methyl-6-bromohexan-2-one in 200 cc. of 10% absolute alcoholic ammonia was allowed to stand at room temperature for 48 hours, and was then neutralized with hydrochloric acid. After cooling, the salts which had separated were removed by filtration, and the alcohol was removed from the filtrate by concentration at reduced pressure. The salts were then added to this concentrate together with sufficient water to dissolve them completely, and the solution was made strongly alkaline with potassium hydroxide. It was then steam-distilled until the distillate was free from basic odor. The distillate was saturated with potassium hydroxide and repeatedly extracted with ether. After drying with solid potassium hydroxide, the product was distilled, and boiled constantly at 154–157°. This agrees with the boiling point for 2,3-dimethyltetrahydropyridine reported by Sachs[9], and by Lipp and Widnmann[8]. The yield was 7.5 g. The compound is so hygroscopic that satisfactory analyses could not be obtained even after distillation from sodium. The picrate, prepared in ether and recrystallized from alcohol, melted at 154–155°, in agreement with Lipp and Widnmann[8], and was analyzed.

Anal. Calc'd for $C_{13}H_{16}N_4O_7$: C, 45.9; H, 4.7; N, 16.5.
Found: C, 45.7; H, 4.8; N, 16.5.

Action of silver acetate on 2-picoline.—One gram of 2-picoline was heated in a sealed tube with 12 cc. of 10% acetic acid and 14 g. of silver acetate at 180° for 8 hrs. The tube opened with considerable pressure, and a heavy precipitate of metallic silver had deposited. This was removed by filtration, and the filtrate was saturated with potassium hydroxide and extracted with ether. Ethereal picric acid was added to the extract. The picrate thus obtained melted at 164° and showed no depression when mixed with pyridine picrate. Since the methyl group of 2-picoline is thus removed, experiments with silver acetate were discontinued.

2-Methyl-5-ethylpiperidine (*Copellidine*).—A solution of 22 g. of aldehyde collidine, prepared according to Graf[27], in 50 cc. of acetic acid was shaken with Adams and Shriner's platinum oxide catalyst under 3 atmospheres of hydrogen. Fresh catalyst was added after 5 hrs., and again after 16 hrs. The required amount of hydrogen was absorbed in 36 hrs. The filtrate from the catalyst was diluted with water, and the base was isolated as in the preceding case; 18 g. of copellidine, boiling at 160°, was obtained. The platinum salt was prepared for analysis, and melted at 145–147°. These constants agree with those of Ladenburg and Dürkoff[28], who prepared copellidine by reduction of aldehyde collidine with sodium and alcohol. The picrate was oily.

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[27] GRAF AND LANGER, *J. prakt. Chem.*, **150**, 155 (1938).
[28] LADENBURG AND DURKOFF, *Ann.*, **247**, 90 (1888).

Anal. Calc'd for $(C_8H_{17}N \cdot HCl)_2 \cdot PtCl_4$: C, 29.0; H, 5.4.
Found: C, 29.0; H, 5.4.

Dehydrogenation of copellidine with palladized asbestos.—The catalyst was prepared by shaking a suspension of 1 g. of acid- and alkali-washed and ignited asbestos fiber in 130 cc. of 0.46% palladium chloride solution under hydrogen at 3 atmospheres. After the palladized asbestos had been washed until neutral it was dried at 100°.

The apparatus which was used in this and subsequent dehydrogenations is shown in Figure I. The trap, *A*, was chilled in a dry-ice bath, and served to dry the gases used in sweeping. *B* is the vaporizer in which was placed the material to be dehydrogenated. *C* is the catalyst chamber, which was made of 8-mm. Pyrex tubing, and packed with a 7.5-cm. length of palladized asbestos. *D* is a second dry-ice trap which served to condense the products of the reaction. *E* is a mercury safety valve the presence of which is vital, since the dry ice traps show a tendency to plug as solid condensate accumulates. Copper wire projecting into the bath which heated the

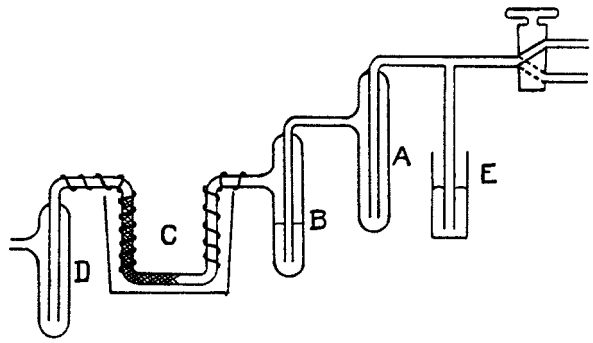

FIGURE 1

catalyst chamber and wound around the ends of the catalyst tube aided in transporting the vapor.

Five grams of copellidine was placed in the vaporizer, and a slow stream of nitrogen was admitted through the 3-way stop-cock until all the air in the train had been displaced. The catalyst tube was meanwhile heated to 270–280° by means of a sodium-potassium nitrate bath. A slow stream of hydrogen was then substituted for the nitrogen, and the temperature of the vaporizer was raised to 90° by immersion in an oil bath. The passage of the gas was continued for 9 hrs., when all the copellidine in the vaporizer had been driven over. From the trap, *D*, 4.5 g. of aldehyde collidine, boiling at 177–178° was obtained. The picrate melted at 164–165°. These values agree with those of Graf[27] and of Fichter and Labhardt[29].

Anal. Calc'd for $C_{14}H_{14}N_4O_7$: C, 48.1; H, 4.0; N, 16.0.
Found: C, 47.8; H, 3.8; N, 16.1.

2,3-Dimethylpyridine (VIII).—2,3-Dimethyltetrahydropyridine was dehydrogenated in exactly the same manner as was copellidine. The yield was 90% of material boiling at 162–164°. Since the usual difficulty was experienced in obtaining satisfactory analytical figures for carbon and hydrogen on the free base, the picrate was prepared. This melted at 187–188°, after recrystallization from alcohol. Ahrens[7], and Lipp[85] report 183–184°.

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[29] FICHTER AND LABHARDT, *Ber.*, **42**, 4714 (1909).

Anal. Calc'd for $C_{13}H_{12}N_4O_7$: C, 46.5; H: 3.6; N, 16.7.
Found: C, 46.6; H, 3.8; N, 17.0.

2,3-Dimethylpyridine by zinc dust distillation.—Dehydrogenation of the tetrahydro compound according to the general method of Lipp and Widnmann[8] gave a 20% yield of material boiling at 162–164°. The picrate melted at 182–184°, but gave poor analytical figures. Inasmuch as purification was difficult the method was abandoned in view of the more favorable results with the catalytic method.

2-(2-Hydroxyethyl)pyridine.—A 500-cc. three-necked flask was equipped with a dropping funnel, reflux condenser, mechanical stirrer, and a gas inlet tube for sweeping with dry nitrogen. One and eight-tenths gram of very fine, freshly cut lithium was suspended in 200 cc. of anhydrous ether after the air had been displaced with nitrogen; 20.7 g. of freshly distilled bromobenzene was then added at such a rate that the ether was maintained at a gentle reflux. Stirring was continued for 30 min. after the addition of the last of the bromobenzene, when all the lithium had dissolved. Twelve grams of 2-picoline, dried over barium oxide, was then added to the phenyllithium solution over 15 min., during which the color of the mixture changed from black to red. After 45 min. the flask was immersed in a freezing mixture, and the dropping funnel was replaced by the side-arm of a distilling flask which contained 6.5 g. of paraformaldehyde dried over phosphorus pentoxide. The side-arm of the flask was about 12 mm. in diameter and reached just to the surface of the ether. The paraformaldehyde was heated at 180–190° until it had been completely depolymerized and driven over into the reaction flask. The mixture was then stirred for 45 min. at room temperature and refluxed for an additional 45 min. After decomposition with ice and hydrochloric acid, the ether layer was separated, and the aqueous layer was extracted with ether, and then made alkaline with potassium hydroxide. The 2-(2-hydroxyethyl)pyridine was extracted with chloroform, and, after drying with fused potassium carbonate, boiled at 88–90° at 2 mm. The yield was 8 g.

Anal. Calc'd for C_7H_9NO: C, 68.3; H, 7.4.
Found: C, 67.9; H, 7.5.

The chloroplatinate of the above base melted at 176° with decomposition, in agreement with Ladenburg and Dürkoff[28].

Anal. Calc'd for $(C_7H_9NO \cdot HCl)_2PtCl_4$: C, 25.6; H, 3.1; N, 4.3; Pt, 29.9.
Found: C, 25.5; H, 3.1; N, 4.3; Pt, 29.9.

Oxidation of 2-(2-hydroxyethyl)pyridine to picolinic acid.—To a boiling solution of 1.2 g. of the above pyridine in 40 cc. of water containing 2.5 g. of potassium carbonate, 6 g. of potassium permanganate dissolved in 120 cc. of water was added gradually. The mixture was refluxed for 7 hrs., cooled, and filtered from manganese dioxide. Excess of hot copper acetate solution was added to the boiling filtrate after acidification with hydrochloric acid. On cooling, the copper salt of picolinic acid crystallized. This was suspended in dilute hydrochloric acid and decomposed with hydrogen sulfide. The filtrate from the copper sulfide was concentrated to dryness and the residue was recrystallized from alcohol. The substance melted at 216°. Meyer[30] gives 210–212° as the melting point for picolinic acid hydrochloride.

Anal. Calc'd for $C_6H_6ClNO_2$: C, 45.2; H, 3.8; N, 8.8; Cl, 22.2.
Found: C, 44.9; H, 4.1; N, 9.1; Cl, 22.0.

2-(2-Hydroxyethyl)-3-picoline (IX).—This was prepared in exactly the same manner as was 2-(2-hydroxyethyl)pyridine using 1.05 g. of lithium, 12 g. of bromobenzene, 8 g. of 2,3-dimethylpyridine and 5 g. of paraformaldehyde. Distillation of the product of the reaction gave 4 g. of unreacted 2,3-dimethylpyridine and 2.5 g. of

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[30] MEYER, *Monatsh.*, **15**, 164 (1894).

2-(2-hydroxyethyl)-3-picoline, which boiled at 94–95° at 1 mm. The picrate was prepared in ether and crystallized from alcohol for analysis. It formed yellow-orange needles and melted at 137–138°.

Anal. Calc'd for $C_{14}H_{14}N_4O_8$: C, 45.9; H, 3.9; N, 15.3.
Found: C, 46.1; H, 3.8; N, 15.4.

1-[(4-Amino-2-methyl)-5-pyrimidylmethyl]-2-(2-hydroxyethyl)pyridinium bromide hydrobromide (XII).—To a suspension of 100 mg. of 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide in 10 cc. of light petrolatum (Merck) which was heated in a boiling water bath was added a 10 per cent. excess of 2-(2-hydroxyethyl)-pyridine with constant stirring. The crystalline pyrimidine salt promptly disappeared, and a yellow semi-solid, which gradually became solid, separated. Heating was continued for 1 hr. with constant stirring. After cooling, the solid material was centrifuged, washed with "Skellysolve D" and purified by solution in absolute alcohol and careful precipitation by addition of ether. The substance melted at 240–245° with decomposition. On attempted drying at 100° and 10 mm. it turned brown and showed obvious signs of decomposition. It was dried at room temperature *in vacuo* over phosphorus pentoxide for analysis. It still obviously contained water of crystallization[31].

Anal. Calc'd for $C_{13}H_{18}Br_2N_4O$: C, 38.4; H, 4.5; Br, 39.4.
Calc'd for $C_{13}H_{18}Br_2N_4O \cdot H_2O$: C, 36.9; H, 4.8; Br, 37.6.
Found: C, 37.9; H, 4.6; Br, 37.0.

1-[(4-Amino-2-methyl)-5-pyrimidylmethyl]-2-(2-hydroxyethyl)-3-picolinium bromide hydrobromide (XI).—This was prepared exactly as in the case of the preceding compound. It was purified by crystallization from *n*-butyl alcohol. The substance was filtered, washed with cold *n*-butyl alcohol, then with ether, and dried over phosphorus pentoxide. It melted at 240–242° with decomposition.

Anal. Calc'd for $C_{14}H_{20}Br_2N_4O$: C, 40.0; H, 4.8; Br, 38.1.
Calc'd for $C_{14}H_{20}Br_2N_4O \cdot H_2O$: C, 38.4; H, 5.1; Br, 36.5.
Calc'd for $C_{14}H_{20}Br_2N_4O \cdot 2H_2O$: C, 36.8; H, 5.3; Br, 35.1.
Found: C, 37.0; H, 5.3; Br, 35.8.

The microanalyses here reported were performed by Mr. Saul Gottlieb of this laboratory.

SUMMARY

1. A satisfactory synthesis for 2,3-dimethyltetrahydropyridine, which should be applicable to the synthesis of other 2,3-dialkylpyridines, has been developed.

2. The palladium dehydrogenation of partially hydrogenated alkylpyridines has been extended to cover those carrying substituents in the 3 position.

3. An improved method for preparing the monomethylol derivative of 2-picoline and its derivatives has been developed.

4. Two pyridine derivatives have been condensed with the pyrimidine of thiamine. The resulting substances showed no antipolyneuritic activity, but approximated the activity of thiamine as measured by carbon dioxide evolution in the yeast test.

[31] BASTEDO, TRENNER, AND WEBB, *J. Am. Chem. Soc.*, **60**, 2303 (1938).

[JOINT CONTRIBUTION FROM THE INSTITUTE OF EXPERIMENTAL BIOLOGY, UNIVERSITY OF CALIFORNIA, AND THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. XIII. SPECIFICITY AND RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND VITAMIN E ACTIVITY[1, *]

H. M. EVANS, O. H. EMERSON, G. A. EMERSON, LEE IRVIN SMITH, HERBERT E. UNGNADE, W. W. PRICHARD, F. L. AUSTIN, H. H. HOEHN, J. W. OPIE, AND S. WAWZONEK

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With the synthesis of α-tocopherol, the most active of the vitamin E constituents, successfully accomplished in three laboratories[2] the attention of the various workers in the field has turned to an investigation of synthetic compounds in which part of the tocopherol nucleus has been modified in the hope of obtaining information which would uncover some regularity of relationship between chemical structure and vitamin E activity. That more than one substance can show this activity has been known for some time for all three of the tocopherols, α-, β-, and γ-, possess potent vitamin E activities.

Since the publication of the first paper[3] of this series upon the biological assays of compounds related to the tocopherols, many more substances have been tested. The total number of compounds investigated for vitamin E activity is now well over 60; among these are many which are active and which are quite simple in structure. Moreover, these are distributed among more than half a dozen different classes structurally.

α-Tocopherol possesses the structure I*a* and is the most potent of all substances so far discovered in its activity. This structure may be modified in several different ways, by changing: (*a*) the nature of the groups in the 2 position, and especially the length and structure of the long aliphatic side-chain; (*b*) the kind, number, and position of the alkyl groups in the benzene ring; (*c*) the *p*-hydroxyl group which may be modified by converting it to ethers or esters, or even omitting it; (*d*) the degree of satura-

[1] Paper XII: J. ORG. CHEM., **4**, 358 (1939).

[*] Presented (in part) at the 96th meeting of the American Chemical Society, Milwaukee, September 5–9, 1938.

[2] (*a*) KARRER, FRITZSCHE, RINGIER, AND SALOMON, *Helv. Chim. Acta.*, **21**, 520 (1938); (*b*) SMITH, UNGNADE, AND PRICHARD, *Science*, **88**, 37 (1938); J. ORG. CHEM., **4**, 298 (1939); (*c*) BERGEL, JACOB, TODD, AND WORK, *Nature*, **142**, 36 (1938); *J. Chem. Soc.*, **1938**, 1382.

[3] Paper II: EVANS, EMERSON, AND EMERSON, *Science*, **88**, 38 (1938).

TABLE**

COMPOUNDS TESTED FOR VITAMIN E ACTIVITY

COMPOUND TESTED	DOSE, MG.	REFERENCE	EFFECT
(*1*) *Chromans, Tocopherols, and Derivatives*			
(*a*) Chroman	100	16	+
(*b*) 2,2-Dimethylchroman	100	*	−
(*c*) 2,2-Diethylchroman	100	*	+
	100	*	+
(*d*) 2,2-Dipropylchroman	50	*	−
	100	*	−
(*e*) 2,4 Me Et chroman (mixture)	50	*	−
(*f*) 2,2,3-Trimethylchroman	50	*	−
(*g*) 2,2,5,7-Tetramethylchroman	50	*	−
(*h*) 2,5,7,8-Tetramethylchroman	30	16	+
(*i*) 2,5,7,8-Tetramethyl-6-hydroxy chroman	30	16	−
	100	16	−
(*j*) 2,2,5,7,8-Pentamethylchroman	50	*	−
(*k*) 2,2,3-Trimethyl-6-methoxychroman	100	*	−
(*l*) 2,5,7,8-Tetramethyl-6-hydroxychroman	50	6	−
	30	4	−
(*m*) 2,2,5,7,8-Pentamethyl-6-hydroxy-chroman	50	6	−
	50	*	−
	100	*	−
	100	*	−
	100	*	+
(*n*) 2,3,5,7,8-Pentamethyl-6-hydroxy-chroman	50	6	−
(*o*) 2,5,7,8-Tetramethyl-2[4′,8′-dimethyl-nonyl]-6-hydroxychroman	20	4	−
(*p*) 2,5,7,8-Tetramethyl-6-acetoxychromone	50	16	+
(*q*) 6-Desoxy-*dl*-α-tocopherol	100	16	−
(*r*) *dl*-α-Tocopherol (synthetic)	1	16	−
	2	16	−
	3	16	+
	7.5	16	++
	15	16	++
(*s*) α-Tocopherol (synthetic)	1	*	−
	2	15	+
	3	*	++
	6	12	+
	7.5	*	++
(*t*) α-Tocopherol (natural)	1–3	9	+
	2	15	+
(*u*) β- and γ-Tocopherols (natural)	6–8	11	+
(*v*) *o*-, *m*-, *p*-Xylotocopherols	8–10	14	+
(*w*) *m*-Xylotocopherol	20	*	+
	100	*	++

* Prepared at Minnesota; activity determined at California.

TABLE—*Continued*

COMPOUND TESTED	DOSE, MG.	REFERENCE	EFFECT
(*1*) *Chromans, Tocopherols, and Derivatives—Con.*			
(*x*) Toluotocopherols (mixture)	40	14	−
(*y*) Acetate and benzoate of α-tocopherol	3(?)	10	+
(*z*) Acetate of natural α-tocopherol	2	15	+
	1	15	+
	0.3	15	−
(*aa*) Acetate of synthetic *dl*-α-tocopherol	2	15	+
(*bb*) Propionate of synthetic *dl*-α-tocopherol	5	15	+
	2	15	+
	1	15	+
(*cc*) Butyrate of synthetic *dl*-α-tocopherol	4	15	+
	2	15	+
	1	15	+
(*dd*) Caproate of synthetic *dl*-α-tocopherol	5	15	+
	2	15	+
(*ee*) Stearate of synthetic *dl*-α-tocopherol	10	15	+
	5	15	+
(*ff*) Succinate of synthetic *dl*-α-tocopherol	5	15	+
	2	15	−
(*gg*) Benzoate of synthetic *dl*-α-tocopherol	5	15	+
	2	15	+
(*hh*) Anthrone	100	*	−
(*2*) *Coumarans*			
(*a*) Coumaran	100	16	−
(*b*) 2-Methylcoumaran	25	*	−
	50	*	−
	50	*	++
	100	*	−
(*c*) 3-Methylcoumaran	100	*	−
(*d*) 2,2,7-Trimethylcoumaran	100	†	+
(*e*) 2,4,6,7-Tetramethylcoumaran	50	*	−
	100	*	−
(*f*) 2,4,6,7-Tetramethyl-5-hydroxycoumaran	25	*	−
	30	16	−
	50	*	−
	100	*	−
	100	16	−
(*g*) 5-Hydroxy-4,6,7-trimethyl-2-*n*-heptadecylcoumaran	50	5	−
	100	5	−
(*3*) *Coumarins*			
(*a*) Coumarin	100	*	Toxic
	50	*	−
(*b*) 5,7,8-Trimethyl-6-hydroxy-3-4-dihydrocoumarin	100	*	−
(*c*) 3-Carbethoxy-5,7,8-trimethyl-6-hydroxycoumarin	50	*	+
	20	*	+

† Prepared by Dr. Q. R. Bartz at Illinois; activity determined at California.

TABLE—*Continued*

COMPOUND TESTED	DOSE, MG.	REFERENCE	EFFECT
(3) *Coumarins—Con.*			
(*d*) Dihydrocoumarin	100	*	−
(*e*) 3-Carboxy-5,7,8-trimethyl-6-hydroxy-coumarin	21	*	−
(*f*) Isoamyl-5,7,8-trimethyl-6-hydroxy-coumarin-3-carboxylate	28	*	−
(4) *Coumarons*			
(*a*) 2,4,6,7-Tetramethyl-5-hydroxycoumarone	25	*	−
	30	16	−
	100	*	+
(5) *Phenols*			
(*a*) *o*-Allylphenol	25	*	−
	50	*	++
(*b*) *o*-Propenylphenol	100	*	−
	50	*	−
(*c*) *o*-α-Methylallylphenol	50	*	−
(*d*) *o*-Hexenylphenol (mixture)	100	*	−
	85	*	−
	50	*	−
(*e*) *o,o*-Dihexenylphenol (mixture)	50	*	+
	25	*	−
(*f*) 2,3,5-Trimethyl-6-allylphenol	100	*	−
(6) *Quinones, hydroquinones, and esters of hydroquinones*			
(*a*) Hydroquinone	100	3	−
(*b*) 2,3-Dimethylhydroquinone	100	7	+
(*c*) *m*-Xylohydroquinone	50, 100	*, 16	−, −
(*d*) *p*-Xylohydroquinone	50, 100	*, 16	−, +
(*e*) Pseudocumohydroquinone	50	*	−
	100	*	−
	100	16	+
(*f*) Pseudocumohydroquinone monobenzoate	100	16	+
(*g*) Pseudocumohydroquinone bis-β-iodopropionate	100	16	−
(*h*) Durohydroquinone	50	*	−
	100	*	+
	100	16	+
	500	3	++
(*i*) Durohydroquinone diacetate	50	*	−
(*j*) 5-Acetopseudocumohydroquinone	50	16	−
(*k*) Trimethylethylhydroquinone	50	16	−
(*l*) Duroquinone	50	3	−
	100	7, 3	+
(*m*) 1,4-Dioxy-2,3-dimethyl-5,6,7,8-tetrahydronaphthalene	100	7	+
(*n*) 1,4-Naphthoquinone	50	16	Toxic
	100	16	Toxic

TABLE—*Continued*

COMPOUND TESTED	DOSE, MG.	REFERENCE	EFFECT
(6) *Quinones, hydroquinones, and esters of hydroquinones—Con.*			
(*o*) 2,3-Dimethylnaphthoquinone	50, 100	*, 16	−, −
(*p*) Quinone oxidation product of α-tocopherol	4	9	+
(*q*) α-Tocopherylquinone	20, 20	16, 17	−, −
	5	16	−
(*r*) Thymoquinone	100	*	Toxic
(*s*) Trimethylethylquinone	50	*	−
(*t*) 2-Methylnaphthoquinone	50	*	−
(*u*) Anthraquinone	50	*	−
(*v*) β-Methylanthraquinone	50	*	−
(*w*) 2-Hydroxy-1,4-naphthoquinone	30	*	−
(*x*) 2-Methoxy-1,4-naphthoquinone	50	*	−
(7) *Alcohols*			
(*a*) Phytol	50	*	−
(*b*) Mixture of phytol and cumohydroquinone	(10 mg. each)	*	−
(8) *Ethers of phenols and hydroquinones*			
(*a*) Phenyl hexenyl ether	50	*	−
(*b*) 4-(2,5-Dimethoxy-3,4,6-trimethyl)butanone-2	7.5	*	−
(*b*2) *p*-Carboxyphenyl allyl ether	100	*	−
(*b*3) Cinnamyl phenyl ether	100	*	−
(*c*) Durohydroquinone mono-*n*-butyl ether	100	7	+
(*d*) Durohydroquinone di-*n*-butyl ether	100	7	+
(*e*) Durohydroquinone di-*n*-hexyl ether	100	7	+
(*f*) Durohydroquinone mono-*n*-hexyl ether	100	7	+
(*g*) Durohydroquinone mono-*n*-heptyl ether	100	7	−
(*h*) Durohydroquinone di-*n*-heptyl ether	100	7	+
(*i*) Durohydroquinone di-*n*-octyl ether	100	7	+
(*j*) Durohydroquinone mono-*n*-octyl ether	100	7	+
(*k*) Durohydroquinone mono-cetyl ether	50	3, 13	+
	100	3, 13	+
	100	3, 13	−
(*l*) Durohydroquinone di-*n*-dodecyl ether	100	7	−
(*m*) Durohydroquinone mono-*n*-dodecyl ether propionate	100	7	−
(*n*) Durohydroquinone mono-*n*-dodecyl ether	100	3, 13	+
	250	3, 13	+
	100	7	+
(*o*) Durohydroquinone mono-*n*-dodecyl ether palmitate	50	7	+
(*p*) Durohydroquinone mono-dihydrophytyl ether	100	7	+
(*q*) Durohydroquinone mono-*n*-octadecyl ether	50	3, 13	−
	250	3, 13	+
(*r*) Durohydroquinone mono-*n*-nonadecyl-2-ether	100	3, 13	+
	250	3, 13	+

TABLE—*Concluded*

COMPOUND TESTED	DOSE, MG.	REFERENCE	EFFECT
(*8*) *Ethers of phenols and hydroquinones—Con.*			
(*s*) Durohydroquinone mono-2-methyloctadecyl ether	250	3, 13	−
(*t*) Durohydroquinone mono-*n*-nonadecyl ether	100	16	+
(*u*) Durohydroquinone di-*n*-nonadecyl ether	100	16	−
(*v*) Durohydroquinone 3-methyl-5-(1′,1′,3′-trimethyl-2′-cyclohexyl)pentyl-1 monoether	50	16	−
(*w*) Durohydroquinone mono-dihydrochaulmoogryl ether	100	7	+
(*x*) Durohydroquinone mono-benzyl ether	100	7	+
(*y*) Durohydroquinone dibenzyl ether	100	7	−
(*z*) Pseudocumohydroquinone mono-*n*-hexyl ether	100	7	+
(*aa*) Pseudocumohydroquinone mono-*n*-dodecyl ether	100	7	+
(*bb*) Pseudocumohydroquinone mono-*n*-dodecyl ether acetate	100	7	+
(*cc*) Pseudocumohydroquinone mono-dihydrochaulmoogryl ether	50	7	+
(*dd*) Dimethyltetrahydronaphthohydroquinone mono-*n*-dodecyl ether	60–80	8	+
(*ee*) Pseudocumohydroquinone di-*n*-dodecyl ether	100	7	−

** Since this paper was submitted to the Journal, several additional substances have been tested for vitamin E activity. These are given here as an appendix to the table.

COMPOUND TESTED	DOSE, MG.	REFERENCE	EFFECT
(*1*) *Chromans, Tocopherols, and Derivatives*			
(*b′*) 2,2-Dimethylchromene	100	*	−
(*c′*) 2,2-Diethylchromene	100	*	−
(*d′*) 2,2-Di-*n*-butylchroman	100	*	+
(*d″*) 2,2-Di-*n*-butylchromene	100	*	−
(*j′*) 2,5,7,8 -Tetramethyl - 2 - dodecyl - 6 - hydroxychroman	60	18*c*	−
(*o*) 2,5,7,8-Tetramethyl-21-(4′,8′-dimethylnonyl)-6-hydroxychroman	40	18*c*	−
(*o′*) 2,5,7,8 - Tetramethyl - 2 - isohexyl - 6 - hydroxychroman (?)	50	*	−
(*s′*) *dl*-α-Tocopherol from synthetic phytol	5	18*a*	+(100%)
	3	18*a*	+(80%)
(*t′*) 5,7-Dimethyl-8-ethyltocol	16	18*b*	+(100%)

APPENDIX—*Concluded*

COMPOUND TESTED	DOSE, MG.	REFERENCE	EFFECT
(*e*) *Coumarans*			
(*f'*) 2,3,4,6,7 - Pentamethyl - 5 - hydroxy-coumaran	50	*	+
(*5*) *Phenols*			
(*g*) *p*-Caprylphenol	50	*	−
(*h*) *p-tert.*-Octylphenol	50	*	−
(*i*) 1 - (*o* - Hydroxyphenyl) - 3 - *n* - butyl-heptan-3-ol	65	*	−
(*j*) *o*-Allyl-*p*-carboxyphenol	100	*	−
(*k*) *o*-Allyl-*p*-carbethoxyphenol	100	*	−
(*l*) β-(*o*-Hydroxystyryl)-diethylcarbinol	100	*	−
(*m*) *p*-Amino-*o*-allylphenol	50	*	+
(*6*) *Quinones, Hydroquinones, and Esters of Hydroquinones*			
(*n'*) 1,2-Naphthoquinone	50	*	Toxic
(*p'*) Red oxidation product of α-tocopherol (*o*-quinone)	3	*	−
	6	*	−
	12	*	+
(*s'*) Tetraethylquinone	50	*	Toxic

Additional references:

[18a] KARRER AND RINGIER, *Helv. Chim. Acta*, **22**, 610 (1939).

[18b] KARRER AND HOFFMANN, *ibid.*, **22**, 654 (1939).

[18c] JOHN, *Angew. Chem.*, **52**, 418 (1939).

[5] BERGEL, JACOB, TODD, AND WORK, *J. Chem. Soc.*, **1938**, 1375.

[7] V. WERDER AND MOLL. *Z. physiol. Chem.*, **254**, 39 (1938).

[8] JOHN AND GUNTHER, *ibid.*, **254**, 51 (1938).

[11] EMERSON, EMERSON, MOHAMMAD, AND EVANS, *J. Biol. Chem.*, **122**, 991 (1937).

[12] KARRER, FRITZSCHE, RINGIER, AND SALOMON, *Helv. Chim. Acta*, **21**, 821 (1938).

[13] FERNHOLZ AND FINKELSTEIN, *J. Am. Chem. Soc.*, **60**, 2402 (1938).

[14] KARRER AND FRITZSCHE, *Helv. Chim. Acta.*, **22**, 260 (1939).

[15] DEMOLE, ISLER, RINGIER, SALOMON, AND KARRER, *ibid.*, **22**, 65 (1939).

[16] V. WERDER, MOLL, AND JUNG, *Z. physiol. Chem.*, **257**, 129 (1939).

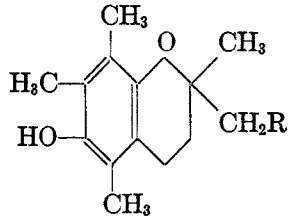
tion of the two rings. Moreover, this *p*-hydroxy chroman may be regarded as a hydroquinone mono-ether of a special kind, in that the ether linkage can be broken without disrupting the molecule completely. Hence such derivatives of chromans must be considered. Since the products to be expected by hydrolytic cleavage of the heterocyclic ring are hydroquinones with a hydroxyl group in the side-chain, the substances derived from them by oxidation and dehydration become of interest, and along with these, the isomeric heterocycles with a 5-membered ring, the coumarans, must always be considered. The structure of α-tocopherol has been modified in practically all of the ways mentioned, and yet no regularity connecting

structure with activity has appeared. Each modification has produced classes of compounds which contain both active and inactive substances, although with but one or two exceptions, these substances do not approach the tocopherols in potency. One difficulty which hampers research in this field is the length of time required for the assays, but even more of a disadvantage is the fact that the dosage is arbitrarily determined and as yet, no such thing as "minimum effective doses" can be determined for any considerable number of compounds without enormous labor and an expenditure of test animals quite beyond question.

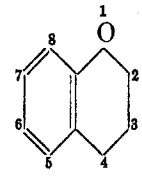
The accompanying table contains a list of compounds tested, grouped by classes. This table has been made complete and at the date of writing it contains a reference to every compound either tested by us or which has been reported in the literature as having been tested for vitamin E activity. Results obtained by us are designated "positive at level fed (++)"; "weakly positive at level fed (+)"; and "negative at level fed (−)". Results obtained by others are reported simply as "positive (+)" or "negative (−)" at the levels fed.

DISCUSSION

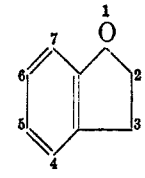
From the results shown in this table, it is possible to discuss in a qualitative way the effects on the activity obtained by modifying the structure of α-tocopherol (I*a*) in the various ways outlined above. The compounds are grouped into classes, as follows and the parent ring structures are shown in the formulas: (1) chromans (I), including tocopherols; (2) coumarans (II); (3) coumarins (III); (4) coumarones (IV); (5) *o*-allylic phenols (V); (6) quinones and hydroquinones; (7) alcohols; (8) ethers of phenols and hydroquinones.



I*a*, R = 3,7,11-Trimethyldodecyl-1
I*b*, R = 3,7-Dimethyloctyl-1



I



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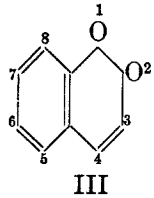

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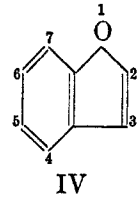
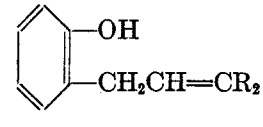


IV



V

1. *Chromans.*—Of the ten representatives of this class other than the tocopherols which have so far been tested, only one, 2,2-diethylchroman, has been found active. The compounds include a considerable variety of substituted chromans, running all the way from the simple 2,2-disubstituted chromans to those which have several methyl groups, with or without the hydroxyl group, in the benzene ring, and including the next lower prenolog of α-tocopherol itself (I*b*), recently synthesized by Karrer.[4] The inactivity of this close relative of α-tocopherol, and the activity of the much simpler 2,2-diethylchroman, present a strange and perplexing contrast, and while it is certainly true, as Karrer says, that the activity of the tocopherols depends greatly upon the nature of the long aliphatic side-chain, the explanation cannot be so simple as this, and other factors must also play a part.

2. *Coumarans.*—Of the five members of this class which have been assayed, two, 2-methyl- and 2,2,7-trimethylcoumaran, have been found active. Again these are the simplest of their class and they do not approach the tocopherol system nearly as much in structure as the next three compounds listed. Compounds *d* and *e* have three methyl groups in the benzene ring and they have the *p*-hydroxyl group in place; compound *e* is even an isomer of β-tocopherol and it has a long aliphatic side chain. The contrast between 2- (active) and 3- (inactive) methylcoumarans is striking. The former substance was assayed twice; in the first assay, the substance was active, but in the second, it was definitely negative.

3. *Coumarins.*—Of the three members of this class, two—coumarin itself and 5,7,8-trimethyl-6-hydroxy-3,4-dihydrocoumarin—are inactive, but the third, which differs from the second only by having the double bond and the carbethoxyl group in the heterocyclic ring, is active. In this compound there is no side-chain at all in the 2 position of the hetero ring, and the ring itself is not saturated; the benzene ring is substituted in exactly the same manner as it is in α-tocopherol.

4. *Coumarones.*—The one member of this class which has been investigated is active. Here again the benzene ring is substituted in the same manner as the one in α-tocopherol, but the hetero ring is unsaturated. It is interesting that the reduction product of this coumarone is inactive, while the simple 2-methylcoumaran, with no substituents in the benzene ring, is active.

5. *Allylic phenols.*—Of these, two have been found active, namely *o*-allylphenol and a di-*o*-hexenylphenol mixture. These allyl phenols can be converted to coumarans and chromans; *o*-allylphenol (active) on cyclization gives 2-methylcoumaran (also active), while *o*-hexenylphenol (mix-

[4] KARRER AND JENSEN, *Helv. Chim. Acta.*, **21**, 1622 (1938).

ture), and its cyclization product (mixture) are both inactive. The di-*o*-hexenylphenol mixture was not cyclized.

6. *Quinones and hydroquinones.*—These substances have no heterocyclic ring at all, yet among them occurs the largest percentage of active compounds. Hydroquinone itself, and trimethylhydroquinone, are inactive, but duroquinone and its hydroquinone, as well as *o*-xylohydroquinone and 2,3-dimethyl-5,6,7,8-tetrahydro-α-naphthohydroquinone, are active. This last compound may be regarded as a derivative of either durohydroquinone or of *o*-xylohydroquinone. In this group also is found the most active substance known outside of α-tocopherol and its acetate and benzoate[10], namely the quinone VI obtained by mild oxidation of α-tocopherol[9].

7. The only *alcohol* which has been fed is phytol. Since trimethylhydroquinone (inactive) and phytol can be used in the synthesis of α-tocopherol, it was of interest to determine if a biological synthesis from these two substances would take place. Phytol is inactive, either alone or when fed with the hydroquinone. Thus biologically a synthesis of α-tocopherol from these two components, which involves only elimination of the elements of water and ring closure, does not occur. Even the ring closure would be unnecessary for activity: merely transference of the elements of water and an easy dehydrogenation would be sufficient to give the quinone VI which is as active as α-tocopherol.

8. A considerable number of hydroquinone mono-ethers and di-ethers have been fed, and included in this group are two phenol ethers, both of them inactive. But among the hydroquinone ethers, many are active. These are derived from two hydroquinones, one of which (tetramethyl-) is active, and the other (trimethyl-) is inactive. Among the active ethers are found those with short as well as long chains, and in case of the dihydrochaulmoogryl ethers, a long chain with an isocyclic ring.

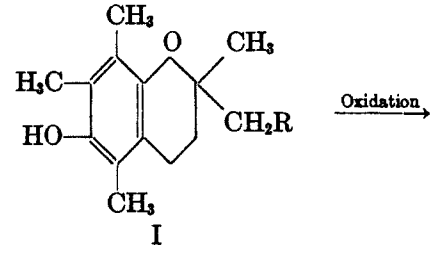
If one assumes that certain minimum structural factors are required for vitamin E activity, and that the compound must be one which has the proper fat solubility so that it can be absorbed and delivered in the body to the proper place, the results in the table, which are in themselves very confusing, can be reconciled into an harmonious whole. The *structural* factor necessary is a system capable of being readily transformed into an oxidation-reduction system.§ For certain of the active compounds in the

[10] ISLER, *Helv. Chim. Acta*, **21**, 1756 (1938).

[9] EVANS, EMERSON AND EMERSON, *J. Biol. Chem.*, **113**, 322 (1936).

§ In view of the recent findings of John and his collaborators (ref. 17) that α-tocopherylquinone (VI, R = $C_{15}H_{31}$) is devoid of vitamin E activity, it may be necessary to abandon or to modify considerably the hypothesis that a reversible red-ox system as such is responsible, even in part, for biological activity. This, however, does not affect the main hypothesis that easy oxidation *in situ* may have a great deal to do with the mechanism of vitamin E activity. See also on this point the recent paper by KARRER, *Helv. Chim. Acta.*, **22**, 349 (1939).

table this is readily accomplished in the laboratory, thus for all of the *p*-hydroxy compounds:



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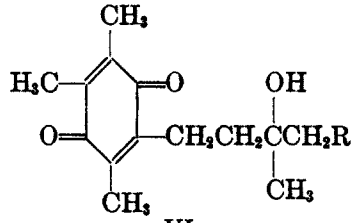
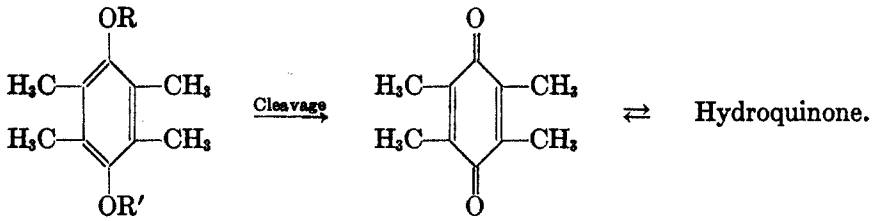


⇄ Hydroquinone.

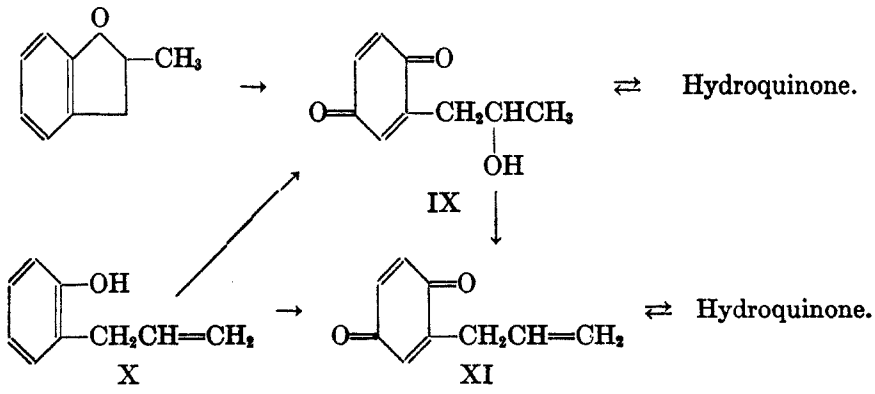
VI



⇄ Hydroquinone.

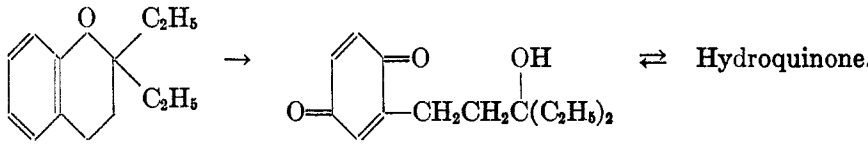
VIII. R′ = H, acyl, alkyl
R = alkyl

For those compounds which do not possess the *p*-hydroxyl group, it is necessary to assume that, once delivered to the proper place in the body, these compounds can be hydroxylated biologically and so transformed into



⇄ Hydroquinone.

⇄ Hydroquinone.



XII XIII

an oxidation-reduction system. In each of these cases, the alcoholic side-chain of the quinone may become dehydrated (or hydrated) as is shown by the arrows connecting IX, X, and XI: in this way many chromans and coumarans could lead to the same oxidation-reduction system.

The function of the auxiliary part of the molecule—the side-chains—would be that of a carrier, to confer upon the compounds definite solubility relationships enabling the body to transport the substances to the place where they are to be used. In the case of some of the inactive compounds, notably the mono- and di-ethers of the hydroquinones, it might be assumed that the differences are due to the inability of the organism to cleave certain of these compounds and open the way to a true hydroquinone. If this asssumption is made, however, the results in group *8* are indeed difficult to explain, for one is faced with the inactivity of a mono-ether (*8-g*) and the activity of the di-ether (*8-h*), and *vice versa*, with the activity of a mono-ether (*8-o*) and the inactivity of the di-ether (*8-m*).

It seems to us, therefore, that the requirements necessary for a compound to show vitamin E activity are more likely that (*a*) a certain structural skeleton must be present, an important function of which is to provide for a ready conversion of the substance into an oxidation-reduction system with a potential within certain limits; (*b*) accessory groups of such a nature that the compound has the solubility properties enabling it to be absorbed and transported to the place where it is to be used; and (*c*) it must be assumed that the organism can carry out the necessary chemical transformation involved. But since these transformations all come within a few groups of well known biological transformations—cleavages, hydrolyses, dehydrations, hydrations, dehydrogenations, reductions and the like—there is nothing new or unusual in such an assumption.

With this theory in mind, then, the way toward further research on the nature of vitamin E activity is clear. We have had under way for some time the determination of the surface tension and parachors of the substances we have prepared, and a comprehensive polarographic investigation of the potentials involved when these compounds are oxidized. These results will be reported in later papers. In their recent papers, John and co-workers[6,17] have expressed views similar to ours and have remarked that

[6] JOHN, GUNTHER, AND SCHMEIL, *Ber.*, **71**, 2637 (1938).
[17] JOHN, DIETZEL, AND EMTE, *ibid.*, **257**, 173 (1939).

neither part of the tocopherol molecule—the one capable of giving rise to the oxidation-reduction system, the other which may act as the carrier—seems to be strongly specific as far as structure is concerned. We are in complete accord with their views and we believe that an explanation such as the one outlined or one very similar to it, offers the only possibility of explaining such diverse results as are given in our table.§

SUMMARY

This paper contains a list of all of the compounds so far tested for vitamin E activity, a discussion of the structural and other factors which influence this property, and the outline of a tentative theory to account for these influences.

[JOINT CONTRIBUTION FROM THE LABORATORIES OF MERCK & CO., INC., AND THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. XIV.

ABSORPTION SPECTRA OF TOCOPHEROLS, CHROMANS, COUMARANS, AND RELATED COMPOUNDS.[1,2]

T. J. WEBB, LEE IRVIN SMITH, W. A. BASTEDO, JR., HERBERT E. UNGNADE, W. W. PRICHARD, HARVEY H. HOEHN, S. WAWZONEK, J. W. OPIE, AND F. L. AUSTIN

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Early in the vitamin E investigations, ultraviolet absorption spectrum measurements on concentrates from cottonseed and wheat-germ oils indicated that there was present in these concentrates a substance having a strong absorption band in the spectral region between 2900Å and 3000Å.[3,4,5,6,7] As the isolation and purification of the vitamin progressed, it became increasingly evident that this absorption band was a reliable guide to the identity of the compound sought. In fact, absorption spectrum measurements and melting points of the allophanate constituted almost the only physical methods of comparing various preparations. The problem of comparing various preparations was complicated by the fact that there are present in such natural preparations, several compounds closely related chemically, showing biological activity in varying degrees. Compounds of this group were called tocopherols, the most active receiving the designation *alpha*. In connection with these studies there has grown up a body of absorption spectra information, which has served to show the characteristic absorption bands of α-tocopherol, its allophanate and methyl ether,[6a,8,9,10,11,12] β-tocopherol and its

[1] Paper XIII, J. ORG. CHEM., **4**, 376 (1939).

[2] Presented (in part) at the 96th Meeting of the American Chemical Society, Milwaukee, Sept. 5–9, 1938.

[3] MARTIN, MOORE, SCHMIDT, AND BOWDEN, *Nature*, **134**, 214 (1934).

[4] OLCOTT, (*a*) *J. Biol. Chem.*, **107**, 471 (1934); (*b*) *ibid.*, **110**, 695 (1935).

[5] DRUMMOND, SINGER, AND MACWALTER, *Biochem. J.*, **29**, 456 (1935).

[6] EMERSON, EMERSON, MOHAMMAD, AND EVANS, *J. Biol. Chem.*, **122**, 99 (1937).

[6a] *Loc. cit.* (*6*), curve determined by Hogness and Zscheile.

[7] DRUMMOND AND HOOVER, *J. Soc. Chem. Ind.*, **56**, 553 (1937).

[8] JOHN, *Naturwiss*, **26**, 453 (1938).

[9] JOHN, DIETZEL, AND GÜNTHER, *Z. physiol. Chem.*, **252**, 208 (1938).

[10] JOHN, DIETZEL, GÜNTHER, AND EMTE, *Naturwiss.*, **26**, 366 (1938).

[11] KARRER, FRITZSCHE, RINGIER, AND SALOMON, *Helv. Chim. Acta.*, **21**, 520 (1938).

[12] FERNHOLZ, *J. Am. Chem. Soc.*, **60**, 700 (1938).

derivatives [8, 9, 10, 13, 14, 15] as well as various synthetic tocopherols.[10, 11, 16, 24] The products obtained by pyrolysis of α-tocopherol[17] led to the erroneous supposition that α-tocopherol was a mono ether of durohydroquinone. For the purpose of deciding this point, absorption spectra of various hydroquinones and certain of their derivatives were determined. The majority of these were derivatives of durohydroquinone[8, 9, 12, 14a, 15] but included among them were isoamylhydroquinone, toluhydroquinone, mono ethers of trimethylhydroquinone, and their allophanates,[9] the allophanate of the monophytol ether of durohydroquinone,[15] the very interesting monodecyl ether of dimethyltetrahydronaphthohydroquinone,[18] the product, now known to be a quinone, obtained by mild oxidation of α-tocopherol[19, 20] and 5-acetotrimethylhydroquinone as well as its monoacetate.[21]

With the publication of Fernholz[12] who proposed the chroman structure for α-tocopherol, and that of Karrer[15] in which the alternative coumaran structure was favored, workers in various laboratories were generally agreed that α-tocopherol was best represented as a *p*-hydroxy-*bz*-trimethylchroman or -coumaran with a long aliphatic side-chain, consisting of isopentane units, in the 2 position. Chroman and coumaran analogues were synthesized and examined spectroscopically in an attempt to decide between the two alternative structures. In the chroman series, absorption data have been reported for 6-methoxychroman[16]; 2,2,4-trimethyl-6-hydroxychroman and its allophanate[14c]; 2,5,7,8-tetramethyl-6-hydroxychroman,[22, 23] 2,3,5,7,8-pentamethyl-6-hydroxychroman[8, 10]; and the allophanate of the chroman obtained by condensing trimethylhydroquinone with geranyl bromide.[16] In the coumaran series absorption data have been reported for 2-methyl-5-hydroxycoumaran[15] and its allophanate[11]; 2,4,6,7-tetramethyl-5-hydroxycoumaran[10, 14a, 14c, 23] and 4,6,7-trimethyl-5-hydroxy-2-heptadecylcoumaran[14a, 14c] and its allophanate.[14c] The absorption curves in the two series of compounds are very similar qualitatively

[13] JOHN, *Z. Physiol. Chem.*, **252**, 201 (1938).

[14] BERGEL, JACOB, TODD, AND WORK, (*a*) *Nature*, **141**, 646 (1938); (*b*) *J. Chem. Soc.*, **1938**, 253; (*c*) *ibid.*, **1938**, 1375.

[15] KARRER, SALMON, AND FRITZSCHE, *Helv. Chim. Acta*, **21**, 309 (1938).

[16] KARRER, FRITZSCHE, RINGIER, AND SALOMON, *ibid.*, **21**, 820 (1938).

[17] FERNHOLZ, *J. Am. Chem. Soc.*, **59**, 1154 (1937).

[18] JOHN AND GÜNTHER, *Z. physiol. Chem.*, **254**, 52 (1938).

[19] EVANS, EMERSON, AND EMERSON, *J. Biol. Chem.*, **113**, 319 (1936).

[20] JOHN, *Z. physiol. Chem.*, **252**, 222 (1938).

[21] V. WERDER AND JUNG, *Ber.*, **71**, 2650 (1938).

[22] KARRER, ESCHER, FRITZSCHE, KELLER, RINGIER, AND SALOMON, *Helv. Chim. Acta*, **21**, 939 (1938).

[23] V. WERDER, MOLL, AND JUNG, *Z. physiol. Chem.*, **257**, 129 (1939).

as well as quantitatively, and it is generally agreed that absorption studies cannot afford a means of deciding between the two alternative structures.[24] However, recent work[25] indicates that a distinction between the two ring systems may be made if the allophanates are used instead of the parent substances themselves. Naturally this would apply only to those substances capable of forming allophanates—*i.e.*, those chromans and coumarans hydroxylated in the benzene ring.

In the previous papers[1] it has been pointed out that vitamin E activity is not confined to one compound or to one class of compounds, but that members of several different classes of compounds,—notably hydroquinones, quinones, coumarans, chromans, and allylic phenols—in addition to the tocopherols—show varying degrees of biological activity. In connection with our work upon the relationship between structure and vitamin E activity, the absorption spectra of a number of representative compounds have been measured, and the purpose of this paper is to supplement the existing information with graphs for fifteen compounds that have been significant in our studies in this field. These graphs appear in groups of three in Figures 1–5. Hexane was used as solvent for all these compounds with the exception of 5,7,8-trimethyl-6-hydroxy-3-carbethoxycoumarin. Ethyl alcohol was used in this case. The ordinates for the graphs represent the values of the millimolecular extinction coefficient ϵ_m, defined as follows:

$$\frac{I}{I_0} = 10^{-\epsilon_m cl}$$

I_0, I being the intensities of incident and emergent light, c the concentration in millimols per liter, and l the length in centimeters. The abscissae represent wave-lengths in Ångstrom units. The experimental uncertainty in the determination of ϵ_m is estimated to be approximately 3 per cent. Measurements were made with a Hilger spectrograph and Spekker photometer. The source of light was a high-voltage spark between tungsten-steel electrodes.

The structural formulae of the fourteen compounds represented in Figures 1–5 are given below.

The compounds here represented have been grouped so as to bring out the degree of correlation which may be expected to exist between chemical

[24] BERGEL, JACOB, TODD, AND WORK, *Nature*, **142**, 36 (1938), have discussed this point and state that 6-hydroxychromans, 5-hydroxycoumarans, α- and β-tocopherols are nearly identical as regards absorption spectra, reducing properties, and the effect of esterification upon absorption spectra; see also refs. 10 and 25.

[25] JOHN, DIETZEL, AND EMTE, *Z. physiol. Chem.*, **257**, 173 (1939).

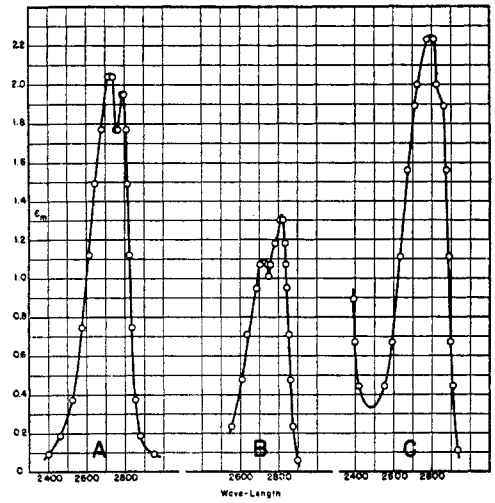
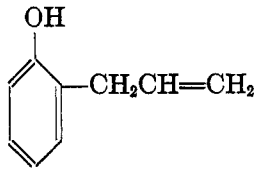


FIGURE 1



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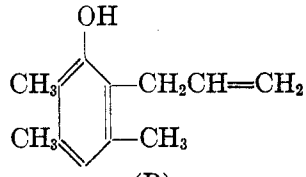

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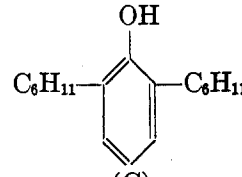


(C)

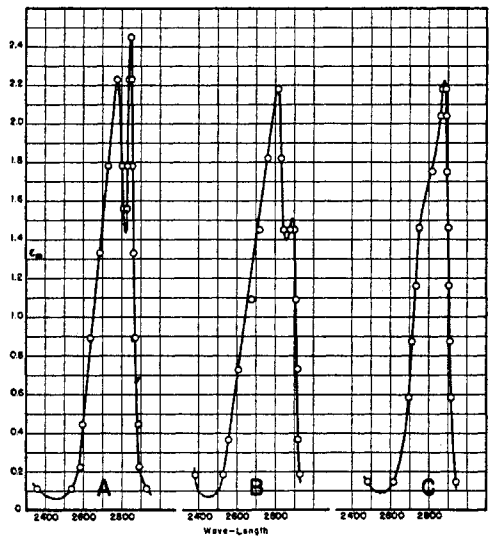
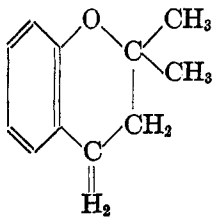
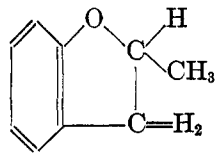


FIGURE 2



(A)



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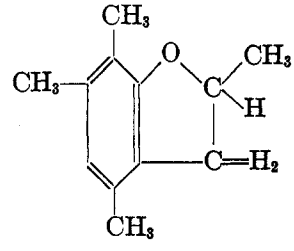

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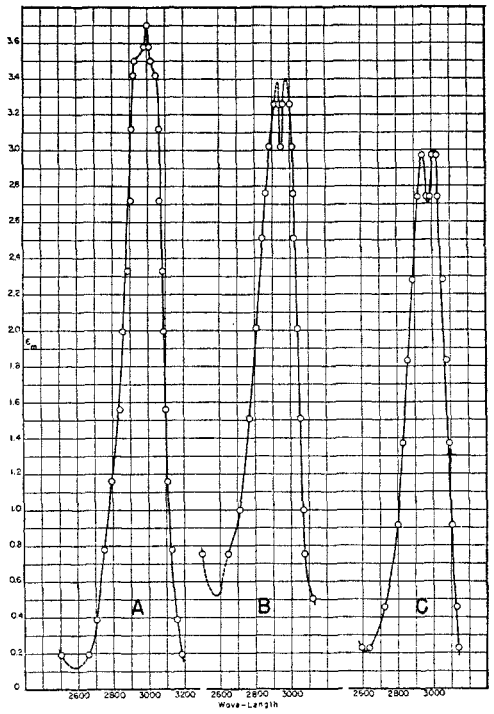
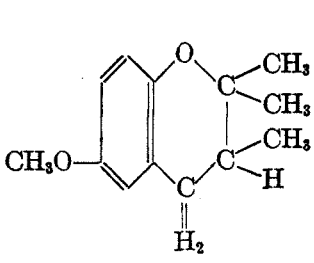
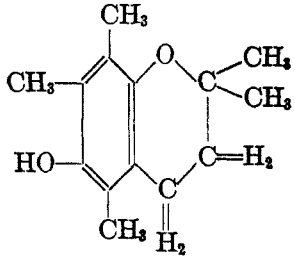


FIGURE 3



(A)



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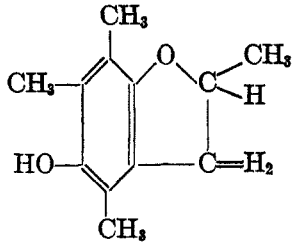

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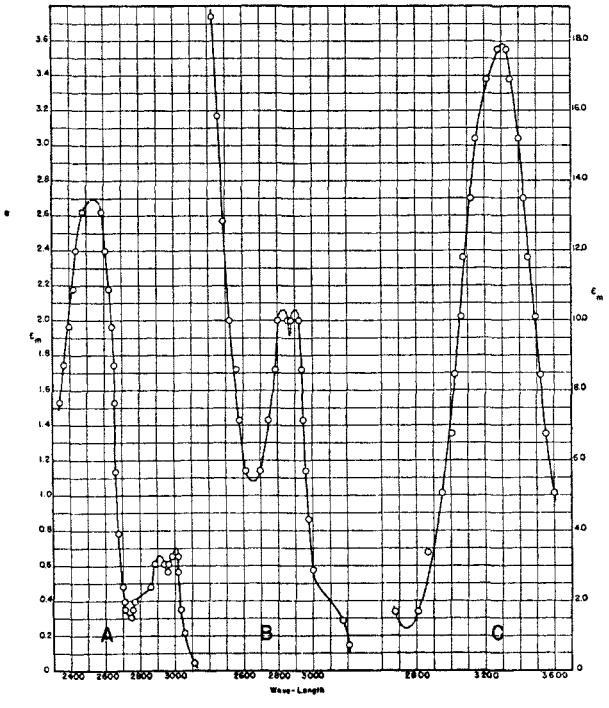
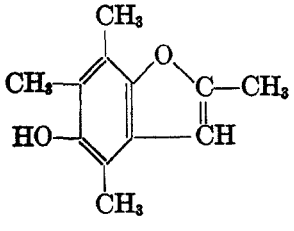
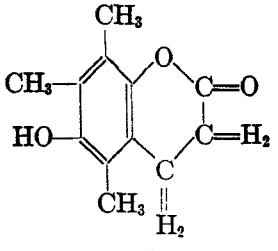


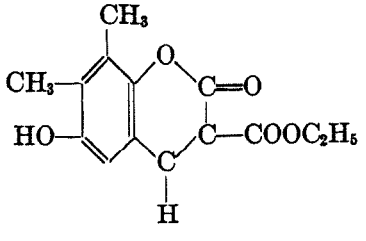
FIGURE 4



(A)



(B)



(C)

structure and ultraviolet absorption. For example, in passing from the three compounds (chromans and coumarans) shown in Figure 2 to those in Figure 3 containing hydroxyl (or methoxyl) in corresponding positions, strikingly similar alterations in the absorption curves are to be noted.

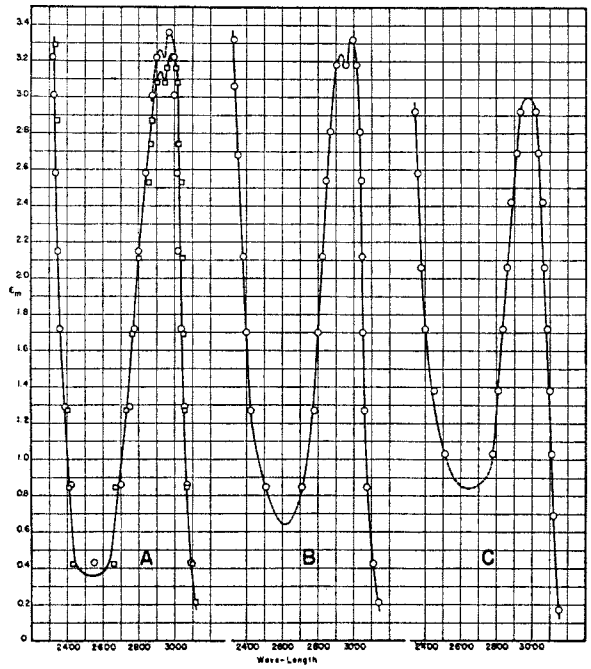
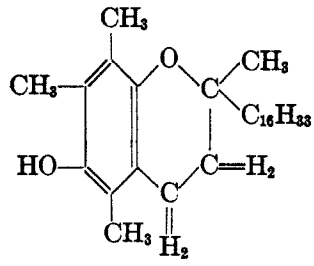
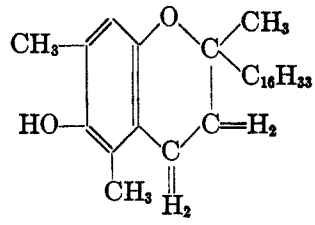


FIGURE 5



(A) (B)



(C)

Concomitant with the introduction of the hydroxyl (or methoxyl)—in the benzene ring, para to the oxygen of the heteroring—, the intensity of maximum absorption shows a marked increase and shifts in the direction of longer wave-lengths. These alterations in the absorption are to be observed also in the tocopherols illustrated in Figure 5, being similarly

but more highly substituted than the compounds in Figure 3. The radical changes in the absorption resulting from the presence of double bonds in the hetero ring are to be observed in Figure 4 (A) and (C) in contrast to (B) for example. The three substituted phenols (Figure 1) all show the maximum of absorption in the spectral region from 2700–2800 Å. With compounds differing as widely in their substituents as do these, considerable variation in the intensity of absorption is not unexpected.

SUMMARY

Ultraviolet absorption spectra of tocopherols, chromans, coumarans, and other compounds significant in vitamin E studies are discussed. Fifteen absorption spectra graphs are presented.

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

THE CHEMISTRY OF VITAMIN E. XV
AN EXTENSION OF THE ANALYTICAL METHOD OF FURTER AND MEYER[1]

HERBERT E. UNGNADE AND LEE I. SMITH

Received April 24, 1939

In a recent paper, Furter and Meyer[2] have described an elegant analytical method for the determination of tocopherols which in simplicity and exactness leaves little to be desired. The method consists essentially in treating an alcoholic solution of the substance with nitric acid under definite conditions, whereby a red color is produced. This red color is then measured quantitatively by means of a photometer or colorimeter, and from the extinction coefficient at the maximum wavelength (4670Å), the amount of tocopherol can be calculated, since the solution obeys Beer's Law. The whole procedure requires only about 30 minutes, and the accuracy of the method, as checked against the potentiometric method of Karrer and his collaborators[3] is well within 3 per cent., with a sensitivity of 0.2 mg. of tocopherol in 4 cc. of solution.

Furter and Meyer found that the method was highly specific in that the red color was given by tocopherols (α- and β-) alone among the substances investigated. These substances were hydroquinones, phytol, and phytyl bromide (possible impurities in synthetic tocopherols); phenols and phenolic acids, sterols, tyrosine, β-carotin, and ascorbic acid (possible contaminants in tocopherols from natural sources); glucose, starch, lactose (possible diluents present in tablets containing tocopherols); and various oils (possible vehicles for liquid preparations containing tocopherols). Of the oils, only wheat-germ oil gave a red color; all the other substances gave a yellow color or else no color at all. Acetyltocopherol produced at first a yellow color, and gave the red color only as it was gradually hydrolyzed. The method, however, does not distinguish between α- and β-tocopherols, for these two substances give the same values. Since α- and β-tocopherols differ markedly in biological action, the method cannot be used generally as a substitute for the bio-assay of tocopherols from unknown substances.

We were interested in extending the method to some simple analogs of

[1] Paper XIV: J. ORG. CHEM., **4**, 389 (1939).
[2] FURTER AND MEYER, *Helv. Chim. Acta*, **22**, 240 (1939).
[3] KARRER *et al.*, *ibid.*, **21**, 939, 1161 (1938).

the tocopherols and compounds related to them, to determine whether or not the reaction was limited to the tocopherols specifically, or was characteristic rather of the ring system present in the tocopherols. We have found the latter to be true; the method appears to be specific for 6-hydroxy chromans and 3-hydroxy coumarans. Our results are given in the following table, which shows only the value of E at the maximum wavelength.

The detailed curves for five of these substances which showed a red color are given in Figures 1 and 2. Figure 1 shows the curves obtained from known 6-hydroxy chromans, including the tocopherols, and includes for comparison, the curve which Furter and Meyer obtained with synthetic

TABLE

RESULTS OF THE FURTER AND MEYER REACTION UPON VARIOUS SUBSTANCES

SUBSTANCE	COLOR	E
α-Tocopherol (impure)	Red	773
γ-Tocopherol	Red	588
2,2,5,7,8-Pentamethyl-6-hydroxychroman	Red	850
2-Ethyl-5,7,8-trimethyl-6-hydroxychroman*	Red	
Reduced condensation product of geraniol and cumohydroquinone*	Red	
2,4,6,7-Tetramethyl-5-hydroxycoumaran	Red	684
2,4,6,7-Tetramethyl-3-ethyl-5-hydroxycoumaran	Red	
2,3,4,6,7-Pentamethyl-5-hydroxycoumaran	Red	650
2,4,6,7-Tetramethylcoumaran	Yellow-pink	113
2,2,5,7-Tetramethylchroman	Yellow	
2,2,5,7,8-Pentamethylchroman	Yellow	
2,2,5,7,8-Pentamethyl-6-nitrochroman	Yellow	
2,4,6,7-Tetramethyl-5-hydroxycoumarone	Yellow	
2-Methylcoumaran	Yellow	
3-Carbethoxy-5,7,8-trimethyl-6-hydroxycoumarin	Yellow	
Coumarin	Colorless	
4-(2,5-dimethoxy-3,4,6-trimethylphenyl)butanone-2	Colorless	

* Structure not fully determined.

dl-α-tocopherol. Figure 2 shows the curves obtained from known coumarans.

Our α-tocopherol was a synthetic product, distilled only once and not particularly pure. This no doubt accounts for the rather low value of E which we obtained. The γ-tocopherol was a sample isolated from corn oil by Dr. O. H. Emerson.‡ While this specimen of γ-tocopherol showed a maximum at 4670Å, identical with those of α- and β-tocopherols, the value of E for our γ-tocopherol was somewhat low. Our work does not enable us to say whether this is characteristic of γ-tocopherol, or is due to

‡ We wish to thank Dr. Emerson for the specimens of γ-tocopherol used in these experiments.

lack of purity in the sample. A sample of γ-tocopherol from cottonseed oil also showed a maximum at 4670Å, and thus all three of the tocopherols, α-, β-, and γ-, show this same maximum.

It is surprising how closely the curve for 2,2,5,7,8-pentamethyl-6-hydroxychroman follows the curve of Furter and Meyer for α-tocopherol—in fact, the agreement between the two curves is better than the experimental error of the method. This suggests at once that the method may be applied to 6-hydroxy chromans in general and leads one to suspect strongly that this chroman and α-tocopherol, when subjected to the action

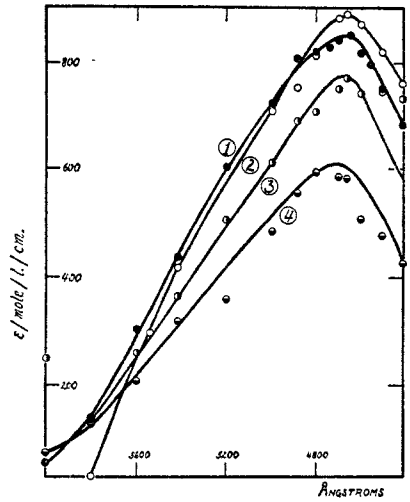


FIGURE 1

① 2,2,5,7,8-Pentamethyl-6-hydroxychroman
③ α-Tocopherol (Furter)
③ α-Tocopherol, once distilled (impure)
④ γ-Tocopherol (impure?)

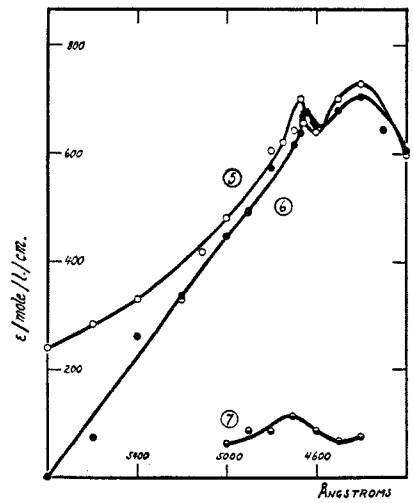


FIGURE 2

⑤ 2,3,4,6,7-Pentamethyl-5-hydroxycoumaran
⑥ 2,4,6,7-Tetramethyl-5-hydroxycoumaran
⑦ 2,4,6,7-Tetramethylcoumaran

of nitric acid under the conditions used in the method give very similar compounds indeed.

A red color was obtained from both 2,4,6,7-tetramethyl-5-hydroxy- and 2,3,4,6,7-pentamethyl-5-hydroxycoumarans. This red color, however, contains a great deal more yellow than that produced by the corresponding 6-hydroxy chromans. This difference is clearly apparent from the curves shown in Figures 1 and 2. The maximum at 4670Å is still present, but E is reduced to 650–700 while a new maximum at 4400Å (E 750–800) has appeared. Thus the colorimetric method is still applicable to these compounds, but by determining the values of E at 4670Å and 4400Å it appears possible to distinguish between isomeric coumarans and chromans.

Coumarans and chromans without the hydroxyl group para to the bridge oxygen atom give a yellow color which may have a tinge of pink in it, as is the case with 2,4,6,7-tetramethylcoumaran. The value of E at 4670Å is however, extremely low. Moreover, the high specificity of the reaction, which Furter and Meyer have pointed out in other connections, is also apparent from the fact that 2,4,6,7-tetramethyl-6-hydroxycoumaron gives a yellow color with no trace of red.

Our results lead us to the conclusion that the method of Furter and Meyer is not only the best so far developed for rapid determination of tocopherols, but that it is also a very promising method indeed for distinguishing between chromans and coumarans hydroxylated para to the bridge oxygen. Much more work will of course be necessary in order to determine the limits of the method; Dr. Furter has such studies already under way.

We are very grateful to Dr. Furter, who most generously invited us to carry out and to publish our work upon the new method.

EXPERIMENTAL

The apparatus used was a Bausch and Lomb spectrometer equipped with a Martens type photometer. The determinations were carried out as follows. The substance (1–5 mg.) was weighed into a 25-cc. volumetric flask and dissolved in exactly 5 cc. of absolute ethanol. To this solution was added with shaking exactly 1 cc. of concentrated nitric acid (from a burette). A small piece of porous tile was added and a cooling "finger" was placed loosely in the neck of the flask. The solution was heated to boiling on the steam bath and then refluxed for exactly 3 minutes, after which it was removed and allowed to cool for 15 minutes on the laboratory table. The solution was then placed in the photometer cell and covered with a slide. The compensating liquid was a mixture of absolute ethanol (83.5 vol. %) and nitric acid (16.5 vol. %). The readings were taken usually within an hour or two after the solutions were prepared, but little change occurs during the first 24 hours.

The values for the extinction coefficient were calculated using the formula,

$$E = \frac{\log \frac{\tan \theta^1}{\tan \theta^2}}{c \times l},$$

where c = concentration in moles per liter, and l = length of the cell in centimeters.

SUMMARY

1. The colorimetric method of Furter and Meyer for determination of tocopherols has been extended to several simple chromans and coumarans. The method appears to be specific not only for all of the tocopherols, but also for 6-hydroxy chromans generally. By means of this procedure, it appears possible to distinguish clearly between 6-hydroxy chromans and 5-hydroxy coumarans.

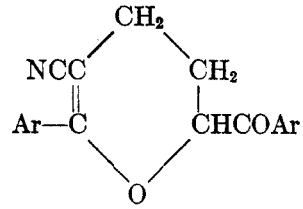
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

DIHYDRO-1,4-PYRANS. VI.[1] OPENING AND CLOSING THE RING

REYNOLD C. FUSON, R. E. CHRIST,* AND C. K. BRADSHER**

Received April 15, 1939

Dihydro-1,4-pyrans (I) are cyclic enol ethers of aldehydes or ketones. In view of their somewhat peculiar structure these substances might be expected to behave as vinyl ethers. In particular the opening of the ring by acidic reagents should offer no difficulty. Although this expectation was fully realized in the simple types studied by Perkin,[2] by Fargher and Perkin[3], and by Lipp[4], the more complex derivatives encountered in this laboratory[1] have proved refractory. The latter are of type I in which Ar = phenyl, *p*-tolyl or *p*-anisyl.



I

However, by the introduction of suitable groups into the molecule we have succeeded in synthesizing a dihydro-1,4-pyran of a more tractable type. It is 2-mesityl-5,6-dihydro-1,4-pyran-6-carboxylic acid (II) as shown on p. 402. This dihydro-1,4-pyran has properties very similar to those of type I but can also undergo ring opening. When it is treated with sulfuric acid in the presence of methyl alcohol the methyl ester of α-hydroxy-(2,4,6-trimethylbenzoyl) valeric acid (III) is formed. Heat reconverts the open-chain acid to the cyclic compound with the loss of water.

[1] For the preceding paper in this series see HULLY, BROCK, AND FUSON, *J. Am. Chem. Soc.*, **58**, 2634 (1936).

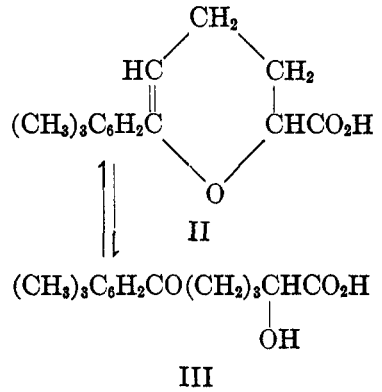
* du Pont Post-Doctorate Fellow, 1935–1937.

** Röhm and Haas Post-Doctorate Fellow, 1937–1938; du Pont Post-Doctorate Fellow, 1938–1939.

[2] PERKIN, *J. Chem. Soc.*, **51**, 702 (1887).

[3] FARGHER AND PERKIN, *ibid.*, **105**, 1353 (1914).

[4] LIPP, *Ann.*, **289**, 173 (1896).

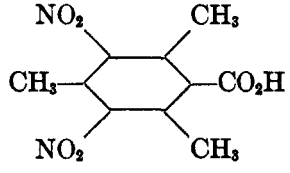


II

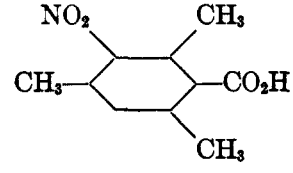
III

The hydroxy acid (III) was obtained by an interesting reaction. Ethyl α-hydroxy-γ-(2,4,6-trimethylbenzoyl) sorbate (VII), prepared by the method of Fuson, Christ, and Whitman,[5] was hydrogenated in the presence of Raney nickel.† The presence of the hydroxy acid (III) in the crude reaction mixture was demonstrated by treating the impure material with α-naphthyl isocyanate and isolating the corresponding urethan. Purification of the hydroxy acid by distillation was impossible; this process gave instead the cyclic acid (II).

The hydroxy acid (III) was best obtained by hydrolysis of the methyl ester, which was obtained from the cyclic acid by ring opening. Permanganate oxidation of the hydroxy acid gave an oil, which, upon nitration, yielded 3,5-dinitro-2,4,6-trimethylbenzoic acid. Treatment of the methyl ester with fuming nitric acid gave 3-nitro-2,4,6-trimethylbenzoic acid (VI).



V



VI

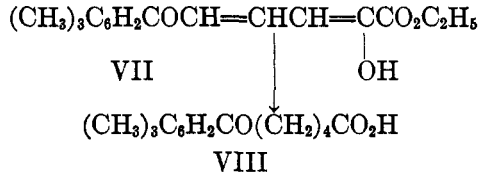
The use of a mixture of concentrated nitric and sulfuric acids produced the methyl ester of the trinitro acid (IV) to be discussed later.

Mention should be made of two other compounds which were found among the hydrogenation products. These were obtained in considerable

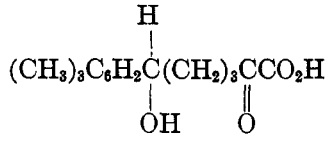
[5] FUSON, CHRIST, AND WHITMAN, *J. Am. Chem. Soc.*, **58**, 2450 (1936).

† Attempts to hydrogenate the benzoate of the sorbic ester did not give promising results and were abandoned.

quantities when the hydrogenation was carried out with Adams' catalyst[6] in acidic absolute alcohol.



VII VIII



IX

One of the acids, δ-trimethylbenzoylvaleric acid (VIII), was isolated as the *p*-phenylphenacyl ester. The structure assigned was established by synthesis. An authentic specimen of the acid was obtained by condensation of mesitylene with adipic anhydride. Its *p*-phenylphenacyl ester was shown by the mixture melting point method to be identical with that from the hydrogenation product (VIII). The keto acid gave a monobromo derivative which was converted by permanganate oxidation into a mixture of 2,4,6-trimethylbenzoic acid and succinic acid.

By fractional distillation of the liquid mixture of esters and saponification of the highest-boiling fraction there was obtained a third hydrogenation product, melting at 81°. It yielded a phenylhydrazone, and therefore is a keto acid. Since the ε-keto group cannot yield a phenylhydrazone on account of steric hindrance, this substance must be an α-keto acid. It may have the structure IX or that of the corresponding diketo acid. Its analysis corresponds to that expected on the basis of formula IX.

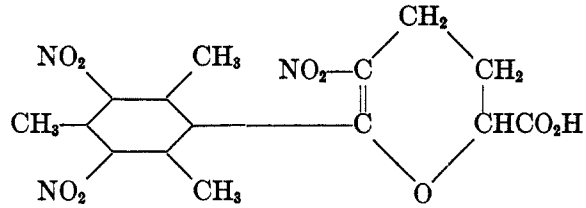
The new dihydro-1,4-pyran (II) reacted with a variety of reagents. Hydrogenation, however, could not be effected catalytically or with sodium amalgam. Treatment with hydrogen iodide and red phosphorus apparently failed also to reduce the ethylenic linkage. However, it cleaved the molecule to give adipic acid.‡

Bromination converted the cyclic acid into a monobromo derivative. Oxidation with ozone or dilute nitric acid gave 2,4,6-trimethylbenzoic acid, as would be expected. The most interesting result was obtained by

[6] ADAMS, VORHEES, AND SHRINER, *Organic Syntheses*, Coll. Vol. I, 452 John Wiley and Sons, Inc., New York, **1932**.

‡ This type of cleavage is characteristic of mesityl ketones [KLAGES AND LICKROTH, *Ber.*, **32**, 1549 (1899)].

nitration. A trinitro derivative was formed which very probably has the structure represented by IV.



IV

The dihydro-1,4-pyran ring evidently undergoes nitration after the fashion of true aromatic compounds.

EXPERIMENTAL

Reactions of Ethyl α-Hydroxy-δ-(2,4,6-trimethylbenzoyl)sorbate

1. Benzoylation.—To a solution of 0.23 g. of sodium in 10 cc. of absolute alcohol was added 50 cc. of dry ether. To the resulting solution were added 3.26 g. of the ester and 1.7 g. of benzoyl chloride. The mixture was allowed to stand overnight. Water was added, and the ethereal solution, after being washed several times with 2.5% potassium hydroxide solution, and then with water, was dried and concentrated. Addition of petroleum ether caused the benzoate to separate in the form of lemon yellow prisms; m.p. 109°; yield, 2.7 g.

Anal. Calc'd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16.
Found: C, 73.46; H, 5.97.

2. Hydrogenation.—In a typical experiment 69 g. of the ester was hydrogenated in three equal portions. The portions were each suspended in 100 cc. of ethanol, about one gram of Raney nickel catalyst was added, and the mixture was hydrogenated at a pressure of approximately 40 lbs. per sq. in. At the end of about five hours all the yellow solid had dissolved and the solution had absorbed nearly two moles of hydrogen. The three solutions were combined, evaporated to a small volume, and the residual oil was suspended in 700 cc. of a 10% solution of sodium carbonate, and refluxed for twelve hours. At the conclusion of this period the solution was cooled, and unchanged ester was extracted with ether. Upon acidification of the water layer the free hydroxy acid was obtained as a yellow oil, which was extracted with ether, dried, concentrated, and the residue was distilled under a pressure of 20 mm. The resulting crystalline mass was recrystallized from benzene-ligroïn as white prisms; m.p. 147–149°; yield 25 g. By addition of more ligroïn to the solution another gram of material may be obtained, making the total yield 44% of the theoretical. The 2-mesityl-5,6-dihydro-1,4-pyran-6-carboxylic acid obtained in this way was pure enough for most reactions; however, upon recrystallization it melted at 149–150°.

Anal. Calc'd for $C_{18}H_{18}O_3$: C, 73.13; H, 7.37; neutr. equiv., 246.1; mol. wt. 246.1.
Found: C, 73.42, 73.21; H, 7.30, 7.36; neutr. equiv., 245.7, 249.7, 246.4; mol. wt. (in boiling acetone), 251, 254.

The acid is readily soluble in a solution of sodium bicarbonate.

Reaction of the Cyclic Acid with Reducing Agents

1. Catalytic hydrogenation.—The acid (4.5 g.) was dissolved in absolute alcohol (50 cc.) and hydrochloric acid (0.5 cc.), and platinum oxide (0.2 g.) was added. After three days' treatment with hydrogen the starting material was recovered. Other unsuccessful attempts were made using as catalysts nickel, palladium, and platinum oxide at 70°.

2. Sodium amalgam.—One-half gram of the acid was dissolved in 0.5*N* sodium hydroxide solution, and 40 g. of 2% sodium amalgam added. After fourteen hours the solution was decanted from the mercury and acidified. The recovered product melted at 149°, and was shown by a mixture melting-point determination to be the starting material.

3. Red phosphorus and hydriodic acid.—One-half gram of the acid was refluxed for four hours with a mixture of 0.5 g. of red phosphorus and 10 cc. of constant-boiling hydriodic acid. At the end of this period the mixture was diluted with water, and filtered through a sintered glass funnel. The phosphorus was washed thoroughly with ether. The filtrate was extracted with ether, the extract was washed with water and with a solution of sodium thiosulfate, dried, and concentrated. Upon addition of petroleum ether white crystals were obtained; m.p. 150° (previous softening); melting-point of mixture with starting material, 130–137°. The yield was 0.1 g. It was shown by a mixture melting-point determination to be adipic acid.

Anal. Calc'd for $C_6H_{10}O_4$: C, 49.32; H, 6.90.
Found: C, 49.73; H, 6.60.

Reaction of the Cyclic Acid with Oxidizing Agents

1. Alkaline hydrogen peroxide.—The acid (0.2 g.) was dissolved in 5 cc. of 2*N* sodium hydroxide solution and 1 cc. of 30% hydrogen peroxide was added. After standing overnight, the solution was acidified with acetic acid, and the solid was collected; m.p. 148°. It was shown by a mixture melting point determination to be the starting material.

2. Ozone.—One gram of pure crystalline acid was dissolved in 50 cc. of dry carbon tetrachloride. Ozone was led through the solution for a period of four hours. The ozonized product was insoluble and separated on the surface of the solution as a viscous mass. It was decomposed by adding water directly to the carbon tetrachloride solution and warmed slightly on the steam bath to insure complete decomposition. The solvent was then evaporated. The viscous residue was distilled at low pressure and solidified after standing for a short period. Recrystallization from benzene gave 0.3 g. of colorless crystals; m.p. 152°. The melting point of a mixture with 2,4,6-trimethylbenzoic acid showed no depression.

3. Dilute nitric acid.—One-half gram of the cyclic acid was suspended in 20 cc. of water containing 5 cc. of concentrated nitric acid. The mixture was refluxed for about thirty minutes; the oil which formed at first gradually solidified. The mixture was cooled, and the product was collected; yield, 0.3 g.; m.p. 151°. A mixture melting-point determination showed the compound to be 2,4,6-trimethylbenzoic acid.

Bromination of the cyclic acid.—The acid (0.35 g.) was dissolved in carbon tetrachloride (10 cc.) and cooled in ice water while a solution of bromine (0.23 g.) in carbon tetrachloride (5 cc.) was added with shaking. A copious evolution of hydrogen bromide was observed. When about nine-tenths of the calculated quantity of

bromine had been added the rate of bromination appeared to slow up appreciably and the reaction was stopped. The solution was concentrated to a small volume, and petroleum ether was added. The slightly pink crystals of the bromo acid were collected; yield, 0.30 g. The compound melted at 139°. Recrystallization from chloroform-petroleum ether gave colorless needles; m.p. 139°. The Beilstein test for halogen was positive.

Anal. Calc'd for $C_{15}H_{17}BrO_8$: C, 55.41; H, 5.27.
Found: C, 55.58; H, 5.07.

Nitration of the cyclic acid.—One-half gram of the acid was dissolved in 5 cc. of concentrated sulfuric acid, and concentrated nitric acid was added dropwise until the further addition of acid seemed to produce no change in the color. The mixture was poured on ice, and the yellow product was collected and washed with water. Upon crystallization from dilute alcohol the 2-(3,5-dinitromesityl)-3-nitro-5,6-dihydro-1,4-pyran-6-carboxylic acid was obtained as yellow needles; m.p. 250°, with decomposition; yield, 0.5 g. These crystals contained water of hydration which could be removed from the product only by repeated crystallization from benzene. The product so purified melted at 255°.

Anal. Calc'd for $C_{15}H_{15}N_3O_9$: C, 47.26; H, 3.96; N, 11.01.
Found: C, 47.60; H, 4.10; N, 10.81.

The *methyl ester* of the nitro acid was prepared by refluxing with a mixture of methyl alcohol and concentrated sulfuric acid. The product was obtained from methyl alcohol as stout yellow prisms; m.p. 162–163°.

Anal. Calc'd for $C_{16}H_{17}N_3O_9$: C, 48.62; H, 4.33; N, 10.62.
Found: C, 48.66; H, 4.20; N, 10.70.

Esterification and ring-opening of the acid.—Ten grams of the cyclic acid was dissolved in 200 cc. of methyl alcohol, and 7 cc. of concentrated sulfuric acid was added. The mixture was refluxed for four hours, after which the solution was concentrated at room temperature under reduced pressure. When the volume had been reduced to about one-fifth, the mixture was poured into water, and the product was taken up in ether. The ethereal extract was washed with bicarbonate solution and with calcium chloride solution and dried over calcium chloride. Upon concentration of the solution and the addition of petroleum ether the methyl α-hydroxy-δ-(2,4,6-trimethylbenzoyl)valerate separated as an oil, but crystallized upon standing in the ice-chest; yield, 6.5 g.; m.p. 43–44°. A further quantity of ester (1.3 g.) can be recovered by further concentration of the solution. The ester can be distilled unchanged under reduced pressure.

Anal. Calc'd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97.
Found: C, 69.24; H, 7.75.

Reactions of α-Hydroxy Ester

1. Saponification.—The crude uncrystallized ester obtained from 0.5 g. of the cyclic acid was saponified by boiling for three hours with 10 cc. of 10% sodium hydroxide. Upon acidification of the alkaline solution, a yellow oil was obtained. This was taken up in ether, dried, and the ether was evaporated. The resulting oil was placed in a test-tube with 1 cc. of α-naphthyl isocyanate and heated at 100° for fifteen minutes. The resulting solid was taken up in ether and extracted with sodium bicarbonate. The bicarbonate solution was acidified, and the acid liberated

was taken up in ether, dried, and concentrated. After addition of petroleum ether the solution was allowed to stand; 0.15 g. of white crystals was obtained. After repeated crystallization from ether-petroleum ether the urethan melted at 145–146°.

Anal. Calc'd for $C_{26}H_{27}NO_5$: C, 72.04; H, 6.13; N, 3.23.
Found: C, 72.00; H, 6.23; N, 3.40.

The liquid acid obtained by the saponification of the α-hydroxy ester can be distilled under reduced pressure practically without residue. Under these conditions it is converted to the cyclic acid; m.p. 149–150°.

2. Oxidation.—(*a*) *Alkaline permanganate.*—One gram of pure crystalline ester was saponified by boiling for two hours with 10 cc. of 10% sodium hydroxide solution. The solution was diluted to 100 cc., cooled in ice, and 0.76 g. of potassium permanganate was added in 50 cc. of water. After twelve hours sulfur dioxide was passed in to dissolve the manganese dioxide. The acidified solution was extracted with ether, and the ethereal extract was dried, concentrated, and the residue was distilled under reduced pressure. The yellow oil obtained could not be crystallized, so it was dissolved in 3 cc. of concentrated sulfuric acid and nitrated by the addition of about 0.5 cc. of concentrated nitric acid. After standing for three hours the mixture was poured on ice, and the product was twice crystallized from benzene. The 3,5-dinitro-2,4,6-trimethylbenzoic acid melted at 230–231° and was identified by a mixture melting-point determination.

(*b*) *Fuming nitric acid.*—One gram of the ester was powdered and added to 50 cc. of fuming nitric acid, and the mixture was stirred for twenty-four hours. The mixture was poured on ice, the product collected, and recrystallized from benzene-ligroïn; m.p. 181–182°. This was shown by a mixture melting-point determination to be 3-nitro-2,4,6-trimethylbenzoic acid.

3. Nitration.—One-half gram of crude crystalline ester was dissolved in 5 cc. of concentrated sulfuric acid and concentrated nitric acid added to constant color. The solution was poured on ice; the yellow, crystalline product was collected, and recrystallized from methyl alcohol; m.p. 162–163°. By a mixture melting-point determination this was shown to be identical with the methyl ester of the trinitro cyclic acid.

4. Reaction with phenylmagnesium bromide.—A solution of phenylmagnesium bromide prepared from 7.9 g. of bromobenzene and 1.33 g. of magnesium turnings in 100 cc. of dry ether was concentrated by distillation of 75 cc. of the ether. Then 75 cc. of dry benzene was added. The resulting mixture was refluxed on a hot plate while 2.8 g. of the ester in 25 cc. of dry benzene was added; the mixture was then refluxed for three hours and poured on 200 g. of ice containing 2 cc. of concentrated sulfuric acid. The mixture was separated, and the benzene layer was washed with water, dried, and concentrated to a small volume. Upon addition of ligroïn 1.3 g. of needles was obtained, which upon repeated crystallization melted at 134–135°. Evaporation of the mother liquor left an oil which was not identified.

Anal. Calc'd for $C_{27}H_{30}O_3$: C, 80.54; H, 7.53.
Found: C, 80.61; H, 7.72.

5. *Reaction with liquid ammonia.*—One gram of the pure solid ester was dissolved in 10–15 cc. of liquid ammonia in a stout Pyrex tube, and the tube was sealed. After being allowed to stand at room temperature for four days the tube was opened, the contents were poured out, and the excess ammonia was allowed to evaporate. Upon addition of a small quantity of ether the amide crystallized, and was collected. It

melted at 111.5–112.5°, and the melting point was not raised by repeated recrystallizations from toluene. The yield was nearly quantitative.

Anal. Calc'd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.02; N, 5.32.
Found: C, 68.54; H, 8.10; N, 5.39.

Hydrogenation of ethyl α-hydroxy-δ-(2,4,6-trimethylbenzoyl)sorbate by the Adams method.[6]—When the hydrogenation was carried out with Adams' catalyst in acidic absolute alcohol there resulted a yield of 10–15% of the cyclic acid and an oil.

Four grams of this oil was dissolved in a solution of 0.8 g. of sodium carbonate in 15 cc. of water. The solution was made faintly acidic with hydrochloric acid, 4.4 g. of *p*-phenylphenacyl bromide in 30 cc. of ethyl alcohol was added, and the mixture was refluxed for one hour. The oil precipitated by the addition of water was taken up in ether and dried. The solution was concentrated, and petroleum ether was added; 0.5 g. of slightly colored crystals were obtained. These were twice recrystallized from ethyl alcohol; m.p. 79°. By a mixture melting-point determination the compound was identified as the *p*-phenylphenacyl ester of δ-(2,4,6-trimethylbenzoyl)valeric acid.

Anal. Calc'd for $C_{29}H_{30}O_4$: C, 78.71; H, 6.83.
Found: C, 78.51; H, 6.95.

In another experiment the reduced ester was fractionally distilled and the highest boiling fraction saponified separately with 10% potassium hydroxide solution. The mixture was acidified, extracted with ether, and the ethereal extract was dried and distilled. The distillate upon crystallization from ether-petroleum ether gave white crystals; m.p. 74–78°; yield, 0.6 g. When pure the keto acid melted at 81°.

Anal. Calc'd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.63.
Found: C, 68.30; H, 7.77.

The *phenylhydrazone*, once recrystallized from benzene, melted at 103–104°.

δ-(2,4,6-Trimethylbenzoyl)valeric acid.—This acid was prepared by a modification of the method used by Hill[4] for the preparation of δ-benzoylvaleric acid.[7]

Seventy-three grams of adipic acid was refluxed for six hours with 200 cc. of acetic anhydride. The excess acetic anhydride and the acetic acid formed in the reaction were removed by distilling the mixture under a pressure of 18 mm. until the temperature of the heating bath reached 120°. The residual adipic anhydride was dissolved in 200 cc. of nitrobenzene.

Aluminum chloride (150 g.) was dissolved in a mixture of nitrobenzene (350 cc.), carbon disulfide (200 cc.) and mesitylene (140 cc.). This mixture was cooled to 10°, and the solution of anhydride was added slowly. The mixture was stirred mechanically for fourteen hours without further addition of ice to the cooling bath. After addition of ice and hydrochloric acid to the mixture the solvents were removed by steam distillation. The brown residual oil was taken up in ether, washed with hydrochloric acid and finally extracted with 5% potassium hydroxide solution. The alkaline solution was acidified and extracted with ether. Upon concentration of the ethereal solution and addition of petroleum ether the trimethylbenzoylvaleric acid was obtained as needles melting at 59°; yield, 35 g. Recrystallization gave colorless needles; m.p. 60°.§

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[7] HILL, *J. Am. Chem. Soc.*, **54**, 4105 (1932).

§ This compound was prepared previously by Borsche [*Ber.*, **52**, 2080 (1919)] who failed to report either the melting point or analysis.

Anal. Calc'd for $C_{15}H_{20}O_3$: C, 72.6; H, 8.07.
Found: C, 72.4; H, 8.13.

Evaporation of the ether solution containing the alkali-insoluble material gave a solid which when recrystallized from alcohol gave 18 g. of *1,4-di-(2,4,6-trimethylbenzoyl)butane*[8]; m.p. 106°.

p-*Phenylphenacyl ester of δ-(2,4,6-trimethylbenzoyl)valeric acid.*—The ester was prepared in the usual manner by the action of *p*-phenylphenacyl bromide on the sodium salt of δ-(2,4,6-trimethylbenzoyl)valeric acid. The product after repeated crystallization from ethyl or methyl alcohol melted at 79°.

Anal. Calc'd for $C_{29}H_{30}O_4$: C, 78.71; H, 6.83.
Found: C, 79.61; H, 6.87.

Bromination of δ-(2,4,6-trimethylbenzoyl)valeric acid.—The acid (2.48 g.; 0.01 mole) was dissolved in carbon tetrachloride and bromine (1.60 g.; 0.01 mole) was added to the solution at 0°. A lowering in the reaction rate was observed when about nine-tenths of the bromine had been added, and the addition was discontinued. The solution was evaporated to a small volume, and ligroïn was added. Upon cooling crystals melting at 90–92° were obtained. Upon recrystallization from chloroform-petroleum ether the compound was obtained as colorless needles; m.p. 90–92°.

Anal. Calc'd for $C_{15}H_{19}BrO_3$: C, 55.07; H, 5.86.
Found: C, 55.34; H, 6.07.

Oxidation of δ-bromo-δ-(2,4,6-trimethylbenzoyl)valeric acid.—One gram of the brominated acid was dissolved in 100 cc. of 1% potassium hydroxide solution and potassium permanganate solution added at room temperature until a permanent purple color was reached. Sulfur dioxide was passed in to dissolve the precipitated manganese dioxide and the organic acids were separated from water solution by continuous extraction with ether. Upon concentration of the ethereal solution and fractional crystallization of the solid obtained, both succinic acid (m.p. 182°) and mesitylglyoxylic acid (m.p. 117°) were obtained; both were identified by mixture melting-point determinations.

SUMMARY

A new dihydro-1,4-pyran has been isolated from the hydrogenation products of ethyl α-hydroxy-δ-(2,4,6-trimethylbenzoyl)-sorbate (II). This compound, 2-mesityl-5,6-dihydro-1,4-pyran-6-carboxylic acid (IV), undergoes ring opening to yield the corresponding open-chain acid. Dehydration of the latter regenerates the dihydro-1,4-pyran.

[8] Kao, *J. Chinese Chem. Soc.*, **3**, 355 (1935); See also BORSCHE, *loc. cit.*

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

A KINETIC STUDY OF THE FORMATION OF *d*-GLUCOSE PHENYLHYDRAZONE*

A. ORNING AND G. H. STEMPEL, JR.

Received April 17, 1939

Although phenylhydrazine has been extensively used in the characterization of sugars, little is known concerning the mechanism of the formation of sugar hydrazones or the conditions under which further reaction leads to osazones. Kinetic studies in buffered solutions have not conclusively demonstrated whether the buffer exerts a catalytic effect, or whether the free phenylhydrazine base or the corresponding ammonium type ion, $\phi \cdot NH \cdot NH_3^+$, hereafter referred to as BH^+, is the active reagent.[1] Studies on the mutarotation and hydrolysis of α-*d*-glucose phenylhydrazone have failed to indicate any correlation between its structure and that of the isomeric *d*-glucoses.[2]

The use of buffered solutions in studying a reaction which may be subject to general acid-base catalysis is a complication which should be avoided if possible. The favorable pH range for the reaction between *d*-glucose and phenylhydrazine includes that in which phenylhydrazine and its salt with a strong acid may be used as a buffer. This makes it possible to avoid the introduction of buffer acids and bases other than those which are essential to the reaction itself. It has the further advantage that the concentration of BH^+ will remain practically constant while that of the free base will be reduced in proportion to the degree of reaction. The kinetics of the reaction should be distinctly different depending upon which of these substances is the active form of the reagent.

Preliminary investigations not only showed that *d*-glucose would react with a mixture of the free base and its hydrochloride in the absence of any other buffer, but also indicated that the formation of osazone could be prevented[2] by careful elimination of all oxidizing agents, including oxygen dissolved in the solutions. A portion of a reaction mixture left in an open

* Abstracted from a thesis submitted by A. Orning to the Committee on Graduate Instruction in partial fulfillment of the requirements for the degree of Doctor of Science.

[1] ARDAGH AND RUTHERFORD, *J. Am. Chem. Soc.*, **57**, 1085-8 (1935).

[2] STEMPEL, *J. Am. Chem. Soc.*, **56**, 1351-5 (1934).

beaker formed a brown precipitate within a few hours while that in a sealed polarimeter tube remained clear.

Reagents.—Phenylhydrazine hydrochloride was purified by dissolving it in a minimum amount of hot water, boiling with decolorizing charcoal, filtering, and precipitating by cooling and addition of concentrated hydrochloric acid. This was repeated until the product was completely free of any red color. It was stored in a desiccator over pellet sodium hydroxide.

The dissolved oxygen was removed from water by placing boiling water under a vacuum. As soon as the violent boiling stopped, the flask was cooled in an ice bath while purified nitrogen was bubbled through the water until the vacuum was relieved. This water was used in making all solutions.

Barium hydroxide solutions were made from material which had been recrystallized from water to remove any carbonate. These solutions were stored in a flask

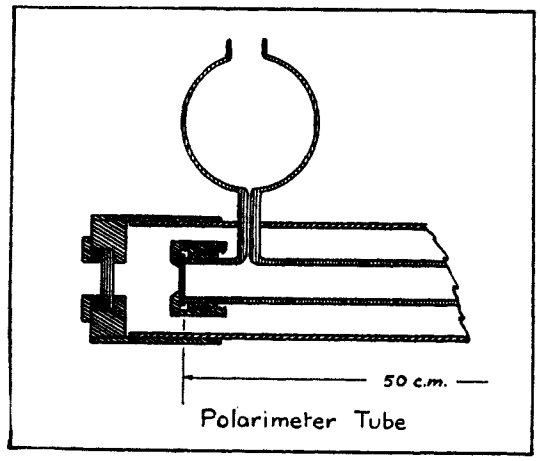


FIGURE 1

mounted on a portable burette stand so that the solution could be forced into the burette by increasing the nitrogen pressure over the solution.

The mutarotation constant, as determined in a 5-dm. polarimeter tube at 30°, of the α-*d*-glucose used to prepare sugar solutions was 0.0166, and the specific rotation at equilibrium was $[\alpha]_D^{30}$ 52.55°. These solutions were prepared in advance, so that the mutarotation equilibrium had been reached, and were stored in the same manner as the barium hydroxide solutions.

Polarimeter tube.—The reaction was followed by measuring the optical rotation using a specially designed 5-dm. polarimeter tube, Figure 1. This tube was fitted with a 3-mm. side-arm at one end and a capillary tube with a 100-cc. filling flask at the other. The water jacket was a 5-cm. micarta tube provided with brass end caps. The jacket completely enclosed the polarimeter tube; a zero check was always made with water in circulation in order to detect any error due to leakage of solutions into the circulating system. Since manipulation of the tube in a crowded space made bulky insulation impractical, it was necessary to keep the polarimeter room at

not less than 29° in order to hold a temperature of 30° with less than 0.1° difference between inlet and outlet.

Procedure.—Nitrogen was passed through the polarimeter tube to remove oxygen. After a weighed amount of phenylhydrazine hydrochloride had been placed in the filling flask, a slow stream of nitrogen was used to provide stirring and prevent flow of solutions through the capillary. Addition of less than the equivalent amount of barium hydroxide produced a solution containing the free base in amount equivalent to the barium ion, and the ionized base in amount equivalent to the excess of phenylhydrazine hydrochloride. The zero time was taken as the time of half-addition of sugar solution to this reagent. With a maximum delivery time of 30 seconds this could not have introduced any serious error. As soon as mixing was complete, the nitrogen pressure was removed, and the solution flowed into the polarimeter tube. The first reading was usually taken between the third and fourth minutes, and subsequent readings at convenient intervals. Readings were accurate within ± 0.01°

TABLE I

TIME (MINUTES)	ROTATION (DEGREES)
0.00	1.89
3.33	1.65
4.75	1.56
7.58	1.39
10.25	1.25
12.92	1.13
19.00	0.90
25.00	0.69
31.92	0.53
38.83	0.40
46.58	0.33
57.25	0.22
Inf.	0.18

$a = 0.0404\ M$
$b = 0.0200\ M$
$c = 0.0492\ M$

except for the first few minutes during which the operator's eye was becoming accustomed to the low light intensity.

Experimental results.—The record of a typical run is given in Table I. Initial concentrations of *d*-glucose, free base, and BH^+ are denoted by *a*, *b*, and *c* respectively. Since the molecular rotatory powers of *d*-glucose and its phenylhydrazone are $\delta = 9{,}460$ and $\gamma = -14{,}180$ respectively for the sodium D line, it is evident that the reaction did not go to completion. On the assumption that the rotatory power is an additive function of the concentration of the solutes, the rotation at time *t* may be converted into concentrations:

$$r = 5\,\delta(a - x) + 5\,\gamma\,x,$$

or,

$$x = (r_0 - r)/5(\delta - \gamma),$$

where x is the concentration of the hydrazone at time t. The equilibrium constant,

$$K = x_\infty/(a - x_\infty)\ (b - x_\infty),$$

was found to be independent of the concentration of the ionized base. Of the various simple rate equations consistent with the equilibrium expression the only one which fitted the experimental results was:

$$dx/dt = k^0(a - x) - k'x/(b - x).$$

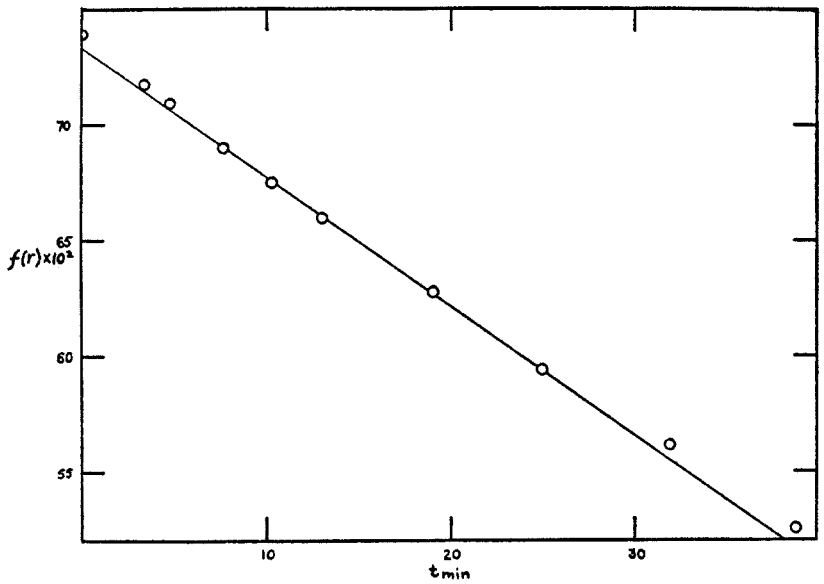


FIGURE 2

Formal integration of this equation gives:

$$\frac{b - x_\infty}{\frac{ab}{x_\infty} - x_\infty} \log (x_\infty - x) + \frac{\frac{ab}{x_\infty} - b}{\frac{ab}{x_\infty} - x_\infty} \log \left(\frac{ab}{x_\infty} - x\right) = -k^0 t + C.$$

Figure 2 is a plot of the left hand member of the integrated rate equation against time for the run given in Table I. The slope of the best straight line drawn through the points gives the value of k^0. Since the argument of the first logarithmic term becomes zero at the equilibrium point while the probable error remains constant, the fit is well within the limits of

experimental accuracy. Within these limits no deviations from straight lines were found for any of the runs.

Table II is a summary of the various runs. The value of k^0 was found to depend only upon the concentration of BH^+, indicating that the reactive form of the phenylhydrazine is the ion, $\phi \cdot NH \cdot NH_3^+$. The curve in

TABLE II

$a \times 10^2$ (MOLARITY)	$b \times 10^2$ (MOLARITY)	$c \times 10^2$ (MOLARITY)	IONIC STRENGTH	K	$k^\circ \times 10^3$ SEC.$^{-1}$
4.04	2.00	4.92	0.0992	104.8	5.57
4.04	2.00	1.99	0.0993	101.8	3.38
3.41	2.56	3.41	0.0981	98.5	4.74
1.95	1.68	2.26	0.0646	102.2	3.67
1.95	1.68	2.28	0.0646	102.2	3.81
1.95	1.68	2.28	0.143	102.8	3.59
1.95	1.68	10.18	0.144	102.8	8.56
1.20	2.15	0.80	0.0618	109.0	1.66
1.19	2.17	7.77	0.132	101.0	7.22
3.96	2.59	1.38	0.0786	100.8	2.55
4.00	2.58	1.37	0.174	95.8	2.49
4.12	2.53	5.36	0.112	96.8	6.16

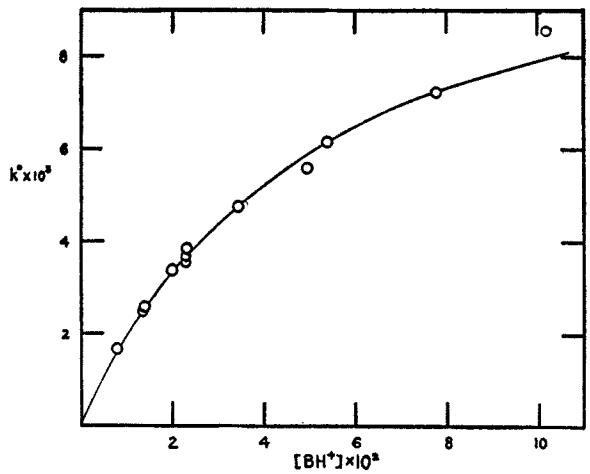


FIGURE 3

Figure 3, obtained by plotting k^0 against the concentration of BH^+, shows the relation between k^0 and the concentration of the ionized base, and the shape of this curve indicates that the process involves consecutive reactions. Since it does not appear in the equilibrium expression, this dependence

must be a common factor in k^0 and k'. There may be a slight negative salt effect, but the evidence is not conclusive.

The proposed mechanism.—The rate of production of hydrazone is proportional to the concentration of BH^+ for low concentrations but appears to approach a maximum at high concentrations. This is exactly what we should expect if the reaction were with a minor constituent of the *d*-glucose equilibrium. As long as the rate is low, the concentration of this constituent will not be appreciably disturbed but with higher rates its concentration will be reduced until its rate of formation controls the rate of production of hydrazone. In order to account for the fact that even with the highest rates there was no apparent disturbance due to the mutarotation reaction it is necessary to assume that this minor constituent is symmetrically related to the major constituents of the *d*-glucose equilibrium.

In order to account for these facts, the following reaction scheme is proposed:

$$\alpha \underset{4}{\overset{1}{\rightleftharpoons}} \epsilon \underset{2}{\overset{5}{\rightleftharpoons}} \beta$$
$$6 \downarrow \uparrow 3$$
$$\gamma$$

The symbols α, β, γ, and ϵ represent α- and β-*d*-glucose, the hydrazone, and the proposed intermediate whose concentrations are x_1, x_2, x_3, and x_4 respectively. Reaction 3 is assumed to be acid-catalyzed and therefore proportional to the ratio of the concentrations of BH^+ and the free base. Reaction 6 is assumed to be a second-order reaction with BH^+. All other reactions are considered as apparent first-order reactions. The simultaneous equations corresponding to this scheme are:

$$\begin{aligned} dx_1/dt + k_1x_1 &= k_4x_4, \\ dx_2/dt + k_2x_2 &= k_5x_4, \\ dx_3/dt + k_3x_3c/(b - x_3) &= k_6cx_4, \\ dx_1/dt + dx_2/dt + dx_3/dt &= 0. \end{aligned}$$

In these equations the assumption is made that x_4 is smaller and that dx_4/dt is negligible. This will be true provided both k_1 and k_2 are negligible in comparison with either k_4 or k_5. It may also be shown that, if k_1 and k_2 are equal, the addition to the system in equilibrium of any reagent, and in particular the phenylhydrazine reagent, which will react with ϵ will not disturb the ratio of x_1 to x_2. This is just the condition which is necessary to explain the fact that mutarotation did not appear to be present in any

of the runs. It is also the condition which makes it possible to obtain a simple solution of the simultaneous solutions.

If c is set equal to zero, the system should represent the mutarotation reaction. In fact with the assumptions given, it may be shown that,

$$x_1 = Ae^{-k_1 t} + k_2 k_4 a/(k_4 + k_5).$$

Together with a similar equation for x_2 and with a suitable choice for the integration constant, A, this is exactly the form which is known to fit the mutarotation reaction.

Elimination of x_4, dx_1/dt, and dx_2/dt from the simultaneous equations gives:

$$(k_4 + k_5 + k_6 c)\, dx_3/dt = k_1 k_6 c(a - x_3) - k_3 c(k_4 + k_5)x_3/(b - x_3).$$

A comparison of this equation with the experimentally found rate equation shows that:

$$k^0 = k_1 k_6 c/(k_4 + k_5 + k_6 c),$$

and

$$k' = k_3 c(k_4 + k_5)/(k_4 + k_5 + k_6 c).$$

The curve drawn in Figure 3 corresponds to the values:

$$k_1 = 0.0120$$

and

$$(k_4 + k_5)/k_6 = 0.0514.$$

For any assumed value of one of these two, the best value of the other is easily found, but the best pair is subject to considerable error.

According to the proposed scheme k_1 should also equal the mutarotation constant. The failure to agree with the accepted value, 0.0167 at 30°, is probably beyond the experimental error. This may mean that k_1 and k_2 are not quite equal but it is more probable that the difference is due to the existence of other parallel mechanisms for the mutarotation reaction. The mutarotation is known to be catalyzed by both acids and bases, and there is no reason to believe that only one intermediate substance is involved in both forms of catalysis. Since the principal mode of catalysis of the mutarotation reaction in the solutions used is probably basic catalysis by the solvent, it is probable that the intermediate substance involved in the hydrazone formation is the glucosate ion, $C_6H_{11}O_6^-$.

Conclusions.—The formation of *d*-glucose phenylhydrazone is due to a reaction between BH^+ and an intermediate substance which is symmetrically related to the isomeric forms of *d*-glucose. The reverse reaction is an acid-catalyzed hydrolysis. The exact details of the proposed mechanism, and in particular the values of the derived constants, are subject to some doubt. A study of the combined mutarotation reaction and hydrazone formation by starting with the crystalline sugars might settle this doubt. However, this would require a change in technique and would involve a serious difficulty in mathematical analysis. The set of simultaneous differential equations involves a non-linear term which makes

formal solution difficult if not impossible except for the special case given here.

SUMMARY

1. The reaction between equilibrium *d*-glucose and a mixture of phenylhydrazine and its hydrochloride has been followed in aqueous solution at 30°.

2. If all oxidizing agents, including dissolved oxygen, are eliminated, there is no evidence of osazone formation.

3. The forward reaction is between BH^+ and an intermediate substance symmetrically related to the isomeric forms of *d*-glucose.

4. The reverse reaction is acid-catalyzed.

[CONTRIBUTION FROM THE DEPARTMENT OF MEDICAL CHEMISTRY OF THE UNIVERSITY OF EDINBURGH AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF GLASGOW]

THE ALKALOIDS OF *MITRAGYNA ROTUNDIFOLIA*. I

GEORGE BARGER†, ELIZABETH DYER*, AND LEWIS J. SARGENT‡

Received April 18, 1939

The present investigation describes two crystalline alkaloids of empirical formulas $C_{22}H_{28}N_2O_4$ and $C_{22}H_{26}N_2O_5$, which were obtained from the leaves of *Mitragyna rotundifolia* (Roxb.) O. Kuntze (*M. diversifolia*, Hook, f.). The genus Mitragyna occurs in the natural order Rubiaceae, which has in the past yielded the important alkaloids of the cinchona group and yohimbine. The first Mitragyna alkaloids to be studied chemically were mitragynine ($C_{22}H_{31}NO_5$) from the leaves of *M. speciosa*, and mitraversine ($C_{22}H_{26}N_2O_4$) from the leaves of *M. diversifolia*.[1] Mitraphylline ($C_{21}H_{26}N_2O_4$) was isolated from the bark of *M. macrophylla* by Michiels[2a] and mitrinermine ($C_{22}H_{28}N_2O_4$) was obtained by Raymond-Hamet and Millat[3] from the bark of both *M. inermis* and *M. stipulosa*. From the bark of *M. diversifolia* Raymond-Hamet[4] obtained an alkaloid, the physical properties of which are reminiscent of mitraphylline.

The alkaloid $C_{22}H_{28}N_2O_4$, isolated in the present investigation from *M. rotundifolia*, differs from the first three alkaloids mentioned above, both in formula and in number and type of constituent groups (*cf.* table). On the other hand, it is identical with mitrinermine as shown by a mixture melting-point determination with a sample kindly supplied by Dr. Raymond-Hamet. In addition, the alkaloid has been proved identical with rhynchophylline, which Kondo[5] isolated from *Ouronparia rhynchophylla* (N. O. Rubiaceae). We are indebted to Professor Kondo for supplying a specimen for a mixture melting point.

† This paper was submitted by the junior authors after the death of Professor Barger.

* Fellow of the American Association of University Women, 1937–1938. Present address: Women's College, University of Delaware.

‡ Present address: Cobb Chemical Laboratory, University of Virginia.

[1] FIELD, *J. Chem. Soc.*, **119**, 887 (1921).

[2a] MICHIELS, *J. pharm. Belg.*, **13**, 719 (1931); *Chem. Abstr.*, **26**, 3070 (1932).

[2b] RAYMOND-HAMET AND MILLAT, *Bull. sci. pharmacol.*, **42**, 602 (1935); *Chem. Abstr.*, **30**, 1379 (1936).

[3] RAYMOND-HAMET AND MILLAT, *Compt. rend.*, **199**, 587 (1934).

[4] RAYMOND-HAMET AND MILLAT, *J. pharm. chim.*, **25**, 391 (1937).

[5] KONDO, FUKUDA, AND TOMITA, *J. Pharm. Soc. Japan*, **48**, 321 (1928); *Chem. Abstr.*, **22**, 3166 (1928).

TABLE

SUMMARY OF PREVIOUS WORK ON MITRAGYNA ALKALOIDS

NAME	SOURCE	FORMULA	MELTING POINT	GROUPS PRESENT
Mitragynine[1]	*M. speciosa* (leaves)	$C_{22}H_{31}NO_5$	102–106°	3 —OCH_3, 2 —$COOCH_3$, indole
Mitraversine[1]	*M. rotundifolia* (leaves)	$C_{22}H_{26}N_2O_4$	237°	2 —OCH_3, phenolic —OH
Mitraphylline[2a,b]	*M. macrophylla* *M. stipulosa* (bark)	$C_{21}H_{26}N_2O_4$	262–263°[2a] 258–267°[2b]	1 —OCH_3
Mitrinermine[3]	*M. inermis* *M. stipulosa* (bark)	$C_{22}H_{28}N_2O_4$	215–216°	2 —OCH_3
Alkaloid[4] (not named)	*M. diversifolia* (bark)	Not given	263.5–264.5° (*cf.* mitraphylline)	1 —OCH_3
Rhynchophylline[5]	*Ouronparia rhynchophylla*	$C_{22}H_{28}N_2O_4$	216°	$C_{19}H_{21}O$ { —OCH_3, —$COOCH_3$, =NH, 
Rubradinine[13]	*Adina rubrostipulata*	$C_{24}H_{28}N_2O_4$	306°	Not given

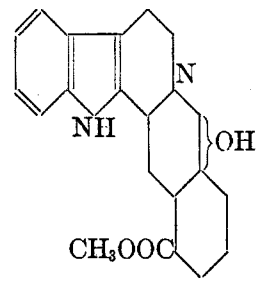
[13] DENIS, *Bull. classe sci., Acad. roy. Belg.*, **23**, 174 (1937); *Chem. Abstr.*, **31**, 3928 (1937).

The second alkaloid isolated in this investigation, $C_{22}H_{26}N_2O_5$, is unlike any previously recorded crystalline Mitragyna alkaloid; for this substance the name *rotundifoline* is suggested.

From the mother liquors of the crystalline alkaloids, an amorphous material was obtained which gave evidence of being a mixture of the above two.

Rhynchophylline.—We have confirmed Kondo's observations that the alkaloid contains two methoxyl groups (one of which is present as a methyl ester), and that it does not contain a methylenedioxy group. Of the two nitrogen atoms, one is basic and tertiary, while the other belongs to an indole ring. Analysis for $=NCH_3$ gave negative results, whereas Kondo reported a value indicating $\frac{1}{2}$ an $=NCH_3$ group. Three of the four oxygen atoms are accounted for by the carbomethoxyl and the methoxyl groups; the nature of the fourth oxygen is as yet unknown, since tests for hydroxylic, enolic, and carbonyl oxygen proved negative. The Zerewitinoff method indicated 0.8 of an active hydrogen atom, which, in view of the foregoing evidence, may be ascribed to the imino group of the indole nucleus.

It has been suggested[5] that rhynchophylline may be a methoxy derivative of yohimbine because of its composition and certain parallel color reactions.



Yohimbine[6], $C_{21}H_{26}N_2O_3$

Evidence bearing on this view has been obtained by a comparison of the ultra-violet absorption spectra of these two substances (see figure). The difference between the absorption curves appears to be greater than would be expected to result from a constitutional difference of only one methoxyl group. Chemical evidence (as outlined below) also indicates that the two substances are less closely related than suggested.

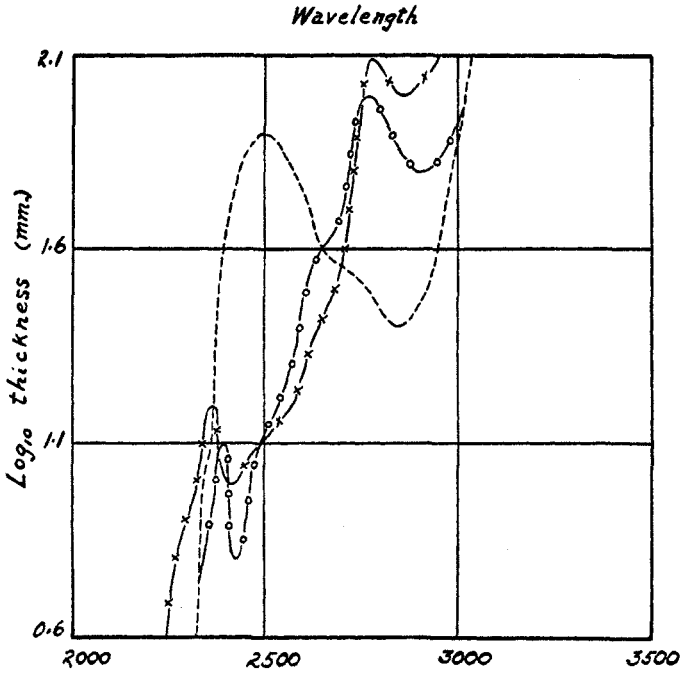
Rhynchophylline was hydrolyzed to the amphoteric rhynchophyllic acid. Dry distillation of this acid with calcium oxide yielded a neutral substance of formula $C_{10}H_9NO$ which gave no indole reaction and did not contain methoxyl. The substance was soluble in boiling alkali, a fact

[6] BARGER AND SCHOLZ, *Helv. Chim. Act.*, **16**, 1343 (1933); *Ber.*, **67B**, 1124 (1934).

which indicates the possibility of an enolic hydroxyl. By heating with zinc dust, it yielded a substance which gave a positive Ehrlich reaction. It is conceivable that the compound is a methyl derivative of carbostyril, in accordance with the fact that carbostyril is known[7] to yield indole by fusion with potash.

Degradation of rhynchophylline by heating with soda-lime yielded a mixture of oxygenated indoles, ammonia, and a pyridine-like base of probable formula C_8H_9NO or $C_8H_{11}NO$.

By boiling rhynchophylline with 30 per cent. sulfuric acid, carbon



dioxide was split off, and a residue was obtained which resembled in its insolubility that formed by the action of acids on mitragynine.[1]

Rotundifoline.—Like rhynchophylline this alkaloid contains two methoxyls (one of which is present as a methyl ester); similarly methylenedioxy and $=NCH_3$ groups were found to be absent. The alkaloid shows 1.4 atoms of active hydrogen, part of which may be ascribed to an enolic hydroxyl, since with ferric chloride in non-hydroxylic solvents a deep-red coloration is produced. (This test was negative in the case of rhynchophylline.) Of the five oxygen atoms present, three are accounted for by

[7] MORGAN, *Chem. News*, **36**, 269 (1877).

the carbomethoxy and methoxyl groups; the nature of the other two is as yet uncertain since the base yielded no definite acetylation product, and no semicarbazone could be obtained. One of the nitrogen atoms is basic and tertiary; the other is a member of an indole ring.

Rotundifoline was hydrolyzed to the corresponding rotundifolic acid, which, like rhynchophyllic acid, was amorphous and amphoteric. The acid was decarboxylated by heating with calcium oxide with the formation of the base $C_{20}H_{24}N_2O_3$. Degradation of the alkaloid with soda-lime yielded a mixture of indoles, ammonia, and pyridine-like bases. Carbon dioxide was eliminated by boiling rotundifoline with 30 per cent. sulfuric acid, and the residue was similar in properties to that obtained from rhynchophylline under the same conditions. From a selenium dehydrogenation of the alkaloid a mixture of bases was obtained, from which a pyridine-like base of formula $C_9H_{13}N$ was separated.

Amorphous fraction.—A quantity of amorphous alkaloid was isolated, the composition of which, after purification, was found to be similar to that of the crystalline alkaloids. Moreover, its corresponding acid, on distillation with calcium oxide, gave the same neutral substance $C_{10}H_9NO$, as obtained from rhynchophyllic acid and also, on selenium dehydrogenation, yielded the base $C_9H_{13}N$, identical with that obtained from rotundifoline.

EXPERIMENTAL

Isolation and separation of alkaloids.—Ninety kilograms of air-dried leaves of *M. rotundifolia*, from the Philippines, was percolated with cold 95% alcohol, which yielded a tarry extract (*ca.* 5.5 kg.). In view of the presence of large amounts of chlorophyll, the extract was worked up in quantities of 500 g. at a time. The following is a typical procedure. The crude extract (500 g.) was dissolved in the minimum quantity of warm glacial acetic acid, and the dark-green syrup was poured into a large volume (*ca.* 6 l.) of cold water with rapid stirring. After standing overnight, the precipitated chlorophyll and other neutral products were filtered at the pump, collected and dispersed in 10% acetic acid (1 l.). After 12 hours the suspension was filtered, and the precipitate was once again digested with acetic acid, after which it was discarded.

The combined filtrates were made basic with ammonia and shaken with ether from which the total alkaloids were removed by 10% oxalic acid. The acid extract was slightly diluted with water (to prevent the separation of ammonium oxalate), made basic with ammonia and exhausted with ether, from which an amorphous phenolic fraction (not yet investigated) was removed by normal sodium hydroxide.

After some preliminary experiments, the non-phenolic alkaloids were separated in the following way. Thirty-four cubic centimeters of 1.15 *N* hydrochloric acid was diluted to 500 cc., and the solution divided into 5 equal portions; the ethereal solution of the alkaloids was then extracted with each portion in turn. Frequently a sixth extraction (using 13.4 cc. of 1.15 *N* hydrochloric acid in 100 cc. of solution) was necessary in order to remove completely the remaining alkaloidal material. Each acid extract was made basic with ammonia and shaken with ether; upon concentration, rhynchophylline crystallized from fractions I and II; III and IV yielded small

amounts of a crystalline mixture, while V and VI gave rise to practically pure rotundifoline. With fractions I–III, it was found advisable to decant the deeply-colored mother liquors after a few hours in order to prevent contamination of the crystalline material; on the other hand, fractions IV–VI could be left in contact with their mother liquors over-night. Evaporation of the various mother liquors yielded syrups; these on being dried, formed amorphous solids which apparently were mixtures of the two alkaloids. The average yields (from 500 g. extract) were: rhynchophylline, 2.4 g.; rotundifoline, 4.4 g.; and amorphous alkaloids, 10.4 g.

Rhynchophylline is readily soluble in chloroform, moderately in acetone, alcohol, and in benzene, sparingly in ether and in ethyl acetate, and insoluble in petroleum ether. It crystallizes in minute prisms from acetone, m.p. 208–209°.

Anal. Calc'd for $C_{22}H_{28}N_2O_4$ [= $C_{19}H_{21}ON(NH)(OCH_3)(COOCH_3)$]: C, 68.8; H, 7.3; N, 7.3; —OCH_3, 16.1

Found: C, 68.6, 68.5; H, 7.3, 7.2; N, 7.3, 7.4; —OCH_3, 15.9, 16.1; —NCH_3, 0.0; active H, 0.21%; $[\alpha]_D^{15°}$, −14.5° § (c = 2.5, in chloroform).

The alkaloid is stable to permanganate in neutral solution; on the other hand it rapidly decolorizes bromine in chloroform. In agreement with Kondo's observations, a methylenedioxy group was found absent by Gaebel's method[8]; and no coloration was produced with ethereal ferric chloride in non-hydroxylic solvents. No =NCH_3 group was detected.

When rhynchophylline in dilute acetic acid was treated with sodium nitrite (either 1 or 2 moles) no precipitate was produced, and the solution remained colorless. However, with a very large excess of sodium nitrite, an oily nitroso derivative was formed which gave a positive Liebermann reaction; the indole nitrogen was probably involved.

Rhynchophyllic acid.—When rhynchophylline was hydrolyzed with boiling alcoholic 2*N* potassium hydroxide, according to the method of Field (*loc. cit.*), the product obtained on adding water to the neutralized, alcohol-free syrup consisted of an amorphous, amphoteric acid which sintered at 140° and decomposed gradually above 150°; yield 70%. The substance was easily soluble in cold dilute acids, bases, and organic solvents, and, unlike yohimbic acid[9], could not be crystallized. For analysis it was dissolved in acid and reprecipitated by ammonia.

Anal. Calc'd for $C_{21}H_{26}N_2O_4$: C, 68.1; H, 7.1; —OCH_3, 8.4.

Found (after drying at 70–100°): C, 67.2; H, 7.1; —OCH_3, 10.0.

Distillation of rhynchophyllic acid with calcium oxide.—Rhynchophyllic acid (0.5 g.) was ground with dry calcium oxide (3.0 g.), and the mixture was heated in a distilling bulb at a pressure of 1 to 2 mm. After 45 minutes, when the temperature had reached 180°, traces of a solid sublimate appeared, and at 210–230° a yellow oil distilled. The crystalline sublimate was separated from the oil by cautious washing with cold ether, in which the oil was more soluble. The solid, after recrystallization from a small volume of ether, yielded 2.0 mg. of hexagonal plates, which sintered at 180° and melted at 182–184° to a clear oil.

Anal. Calc'd for $C_{10}H_9NO$: C, 75.4; H, 5.7; N, 8.8; molecular weight, 159.

Found: C, 75.2; H, 5.5; N, 8.9; —OCH_3, 0.0; molecular weight (Rast), 173.

This substance was insoluble in cold acid and alkali, but was soluble in boiling sodium hydroxide. It did not give a positive Ehrlich nor pine splint reaction. When heated with zinc dust, a white sublimate was obtained which had a strong indole odor and gave a positive Ehrlich reaction in the cold.

§ Kondo reported $[\alpha]_D^{13°}$ −14.7° in chloroform.[5]

[8] GAEBEL, *Arch. Pharm.*, **248**, 207 (1910).

[9] SPIEGEL, *Ber.*, **36**, 169 (1903).

The yellow, oily distillate was basic material, unidentified.

Degradation of rhynchophylline with soda-lime.—Rhynchophylline (2 g.) was ground with soda-lime (20 g.), and the mixture heated in an apparatus similar to that used by Jacobs and Craig[10], except that a trap of ethereal picric acid replaced their acid traps. While dry nitrogen was passed through the reaction tube, the temperature was slowly raised from 220° to 355° over a period of 5 hours, and then maintained at that point for 1.5 hour.

In the picric acid trap a precipitate of ammonium picrate was formed, identified by its failure to melt and its analysis.

Anal. Calc'd for $C_6H_6N_4O_7$: C, 29.3; H, 2.4.
Found: C, 29.4; H, 1.6.

The contents of the reaction bulb were washed thoroughly with ether, and the washings added to the oily distillate present in the exit arm of the reaction tube and the following U-trap. The combined ethereal solution was separated into acidic, neutral, and basic fractions as usual.

(*1*) The acidic (or phenolic) fraction was negligible.

(*2*) The neutral fraction, on distillation at 13 mm., yielded: (*a*) a small quantity of a pale-yellow oil which distilled with the bath at 110–120°, (*b*) about 180 mg. of a yellow oil which distilled at 120–165°, and (*c*) a negligible amount of dark higher-boiling material. The oil *a* was the principal product in previous degradations which were conducted at lower temperatures. Both *a* and *b* resembled skatole in odor, in the pine-splint reaction, and in their behavior toward Ehrlich's reagent in the cold. But on the addition of nitrous acid to the red solution produced with Ehrlich's reagent, these substances were bleached to a tan, whereas with skatole derivatives a blue color is formed.[11] With picric acid in various solvents a red color was obtained, but no crystalline picrate. The oil *a* slowly decolorized an acetone solution of potassium permanganate, and rapidly reduced Tollens' solution. Analysis of *a* and *b* after redistillation, (*a*) bath 110–120° and (*b*) bath 145–155° at 13 mm., clearly showed the presence of oxygen in both cases, though the results are not in agreement with any single indole.

Anal. Calc'd for $C_{10}H_{11}NO$: C, 74.5; H, 6.9; N, 8.7.
$C_{11}H_{13}NO$: C, 75.4; H, 7.5; N, 8.0
Found for *a*: C, 75.6, 75.3; H, 6.8, 6.8; N, 9.2, 8.7; —OCH_3, 0.0; —NCH_3, 0.0
Calc'd for $C_{12}H_{13}NO$: C, 77.0; H, 7.0; N, 7.5.
$C_{13}H_{15}NO$: C, 77.6; H, 7.5; N, 7.0
Found for *b*: C, 77.5; H, 7.1; N, 7.9; —OCH_3, 0.0; —NCH_3, 0.0

Reduction of 100 mg. of the indole fraction *b* with zinc dust and hydrochloric acid in alcohol solution according to the procedure of Schlieper[12] yielded a basic fraction with an indole odor, which distilled at 75–85° (bath temperature) at 13 mm., and which gave a yellow picrate from benzene. After recrystallization from benzene, long yellow needles (5 mg.) were obtained, which sintered above 135°, and melted to a dark oil at 140–142°.

Anal. Calc'd for $C_{16}H_{14}N_4O_8$: C, 49.2; H, 3.6
Found: C, 49.5; H, 3.8.

The residual neutral fraction from the reduction of the indolic material still gave a positive Ehrlich and pine-splint test, and was therefore reduced exhaustively until

[10] JACOBS AND CRAIG, *J. Biol. Chem.*, **119**, 141 (1937).
[11] BLAIKIE AND PERKIN, *J. Chem. Soc.*, **125**, 296 (1924).
[12] SCHLIEPER, *Ann.*, **239**, 229 (1887).

the purified neutral oil was entirely negative in both of these reactions. This neutral oil distilled at 100–138° (bath temperature) at 13 mm. It still contained nitrogen. (Found: N, 7.2%.)

(*3*) The basic fraction from the original soda-lime degradation consisted of a volatile oil which turned dark in the air, showed unsaturation toward permanganate, gave an oily methiodide and picrate, was unreactive toward nitrous acid, and had an odor resembling that of pyridine. It was advantageous to hydrogenate this oil at once in alcoholic solution, using the Adams platinum oxide catalyst. After filtration of the platinum, the solution was made acid with sulfuric acid, and the alcohol was evaporated *in vacuo* at 60°. The residue, after basification and extraction with ether, yielded as the principal fraction a colorless oil, which on redistillation came over at 85–95° (bath temperature) at 13 mm. Since analysis showed that this oil was not homogeneous, it was converted to the picrate for purification. The picrate (formed in ether solution) had a constant, though not sharp melting-point after three crystallizations from benzene (sinters above 115°, liquefies to a red oil at 123–125°).

Anal. Calc'd for $C_{14}H_{12}N_4O_8$: C, 46.1; H, 3.3; N, 15.4.
$C_{14}H_{14}N_4O_8$: C, 45.9; H, 3.9; N, 15.3.
Found: C, 46.2; H, 3.5; N, 15.7.

The base corresponding to this picrate would have the formula C_8H_9NO or $C_8H_{11}NO$. The oxygen present is not phenolic, nor enolic (no color with ferric chloride in ether).

Rotundifoline is easily soluble in chloroform, moderately in acetone, alcohol, and in benzene, sparingly in ether and in ethyl acetate, and insoluble in petroleum ether. It forms slender, glistening prisms from methyl alcohol, m.p. 233–234°.

Anal. Calc'd for $C_{22}H_{26}N_2O_5$ [$=C_{19}H_{19}O_2N(NH)(OCH_3)(COOCH_3)$]: C, 66.3; H, 6.6; N, 7.0; $-OCH_3$, 15.6.

Found: C, 66.1, 66.1; H, 6.7, 6.6; N, 7.4, 7.0; $-OCH_3$, 15.8; $-NCH_3$, 0.0; active H, 0.35, $[\alpha]_D^{15°}$ +124° (c = 2.14, in chloroform).

The alkaloid is stable to permanganate in neutral solution, but rapidly decolorizes bromine in chloroform. The base shows neither an $=NCH_3$ nor a methylenedioxy group. With ferric chloride is non-hydroxylic solvents, a deep garnet-red coloration is produced, which suggests the presence of an enolic hydroxyl; however, no derivative of such a group has as yet been obtained. Moreover, no reaction with semicarbazide was observed.

When an acetic acid solution of the base was treated with either one or two moles of sodium nitrite, no precipitate was formed, but a deep orange-red color was produced almost immediately (*cf.* rhynchophylline, which undergoes no change in color). The alkaloid yielded no definite acetylation product with acetic anhydride at 100° or at the boiling temperature; in addition to resinous products, large quantities of unchanged alkaloid were recovered in both cases.

Rotundifolic acid.—When rotundifoline was hydrolyzed with alcoholic potassium hydroxide in the manner described above for rhynchophylline, an amorphous, amphoteric acid was obtained which softened at 160°, effervesced above 165°, and became brown by 170°; yield 78%. This acid resembled rhynchophyllic acid in its solubilities, failure to crystallize, and difficulty of purification by reprecipitation.

Anal. Calc'd for $C_{21}H_{24}N_2O_5$: C, 65.6; H, 6.3; $-OCH_3$, 8.1.
Found: C, 64.0; H, 6.3; $-OCH_3$, 8.6.

Distillation of rotundifolic acid with calcium oxide.—When a mixture of 0.6 g. of rotundifolic acid and 4.0 g. of calcium oxide was heated as described for rhynchophyllic acid, the principal product was a glassy resin which distilled at 200–250°

(bath temperature) at 1–2 mm. After crystallization from a small volume of ether, this substance separated as fine needles, which sintered at 198° and melted at 200–202°; yield 10 mg. The product was a base, which gave a positive Mayer's reaction and was easily soluble in organic solvents except petroleum ether.

Anal. Calc'd for $C_{20}H_{24}N_2O_3$: C, 70.6; H, 7.1; N, 8.2.
Found: C, 70.4; H, 7.4; N, 8.1.

Degradation of rotundifoline with soda-lime.—The products obtained were similar to those resulting from analogous treatment of rhynchophylline. Ammonia was given off, identified as its picrate, a neutral fraction was obtained containing a mixture of indoles qualitatively resembling those from rhynchophylline though somewhat higher in boiling point, and a basic fraction was separated which contained tertiary bases, resembling pyridine in odor and showing a tendency to form a crystalline picrate after hydrogenation.

Selenium dehydrogenation of rotundifoline.—An intimate mixture of the base (6 g.) and selenium (4.5 g.), contained in a small distilling flask was heated in a metal bath for ½ hour at 300°. During this interval, a small quantity of orange-colored oil distilled, and was added to the benzene extract (see below). After cooling, the flask was broken, and the contents were ground to a fine powder which was mixed with sand and extracted for 16 hours with benzene (Soxhlet); the benzene was then replaced by absolute alcohol, and the extraction was continued for another 12 hours. The cooled extracts, after 48 hours, deposited small quantities of dark-colored amorphous material which could neither be distilled nor sublimed. After concentration to a small volume (*in vacuo*), the respective extracts were separated into basic and neutral fractions as usual, and these were taken up in ether and dried.

Basic fraction (benzene extract).—After removal of the ether, the remaining dark-brown oil when distilled under a pressure of 14 mm. yielded the following fractions: (I) 85–135°; (II) 150–175°; (III) 180–210°. By slow redistillation of I, a colorless, strong-smelling oil was obtained at 85–100°, which was alkaline to litmus. At atmospheric pressure, the b.p. was *ca.* 195–200°. The picrate formed long, yellow needles (from methyl alcohol), m.p. 134–135°.

Anal. Calc'd for $C_9H_{13}N \cdot C_6H_3N_3O_7$: C, 49.4; H, 4.4; N, 15.4.
Found: C, 48.9, 48.8; H, 4.4, 4.3; N, 15.8.

The oil is optically inactive and forms no nitroso derivative; it does, however, form an oily methiodide. The higher-boiling, basic fractions are mixtures which have not yet been completely investigated.

The neutral fractions from both the benzene and alcoholic extracts contained selenium in chemical combination, and have not been examined.

The base $C_9H_{13}N$ was also derived from a selenium dehydrogentation of the amphoteric acid obtained by hydrolysis of the amorphous alkaloid. The melting point of its picrate (130–131°) was not depressed when admixed with the above picrate (m.p. 134°).

Ultra-violet absorption measurements.—A Hilger medium quartz spectrograph was used, and the substances examined were purified by several recrystallizations and dissolved in 98% ethyl alcohol. Solutions of $M/10{,}000$ in a Baly tube were exposed to an iron arc for 15 seconds, the thickness of the solution varying from 0–160 mm. Ilford special rapid plates were used.

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SUMMARY

Two crystalline, non-phenolic alkaloids, of formulas $C_{22}H_{28}N_2O_4$ and $C_{22}H_{26}N_2O_5$ respectively, have been isolated from the leaves of *Mitragyna rotundifolia*. The former is identical with rhynchophylline of Kondo and mitrinermine of Raymond-Hamet, while the latter appears to be new and is named rotundifoline.

Both alkaloids are methyl esters, and each contains in addition a methyl ether grouping; methylenedioxy and $=NCH_3$ groups were found to be absent. In rhynchophylline three of the oxygen atoms are accounted for; the nature of the fourth is unknown. Similarly in rotundifoline, the function of only three of the five oxygen atoms has been determined.

The absorption spectra of rhynchophylline and rotundifoline have been compared with that of yohimbine.

Distillation of rhynchophyllic acid with calcium oxide yielded a neutral substance of formula $C_{10}H_9NO$. Rotundifolic acid, on the other hand, was merely decarboxylated under these conditions with the formation of a crystalline base, $C_{20}H_{24}N_2O_3$.

Degradation of rhynchophylline and rotundifoline with soda-lime gave mixtures of oxygenated indoles and pyridine-like bases, from which, in the case of rhynchophylline, a base of probable formula C_8H_9NO, was isolated.

From selenium dehydrogenation of rotundifoline, a base resembling pyridine, of formula $C_9H_{13}N$, was obtained.

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

THE PEROXIDE EFFECT IN THE ADDITION OF REAGENTS TO UNSATURATED COMPOUNDS. XXI. "NORMAL" AND "ABNORMAL" ADDITIONS OF HYDROGEN BROMIDE

M. S. KHARASCH, SARAH C. KLEIGER, AND FRANK R. MAYO

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Previous work from this laboratory has shown that in each case either of two possible products may be obtained by the addition of hydrogen bromide to propylene[1], isobutylene[2], 1-butene[3], 1-pentene[4], allyl bromide[5], allyl chloride[6], 2-bromopropene[7], 2-chloropropene[7], vinyl chloride[8], vinyl bromide[9], and neopentylethylene[10]. The products formed when the reaction is carried out in the absence of oxygen and/or peroxides (in the presence or absence of an antioxidant) have been regarded as the "normal" addition products, while those formed in the presence of oxygen or peroxides have been designated the "abnormal" addition products. This paper discusses the difficulty of designating as "normal" or "abnormal" any given addition product of hydrogen bromide to trichloroethylene, 1-chloropropene, or 1-bromopropene, and proposes a solution of these and similar problems.

Trichloroethylene[11] does not react with hydrogen bromide in the presence of an antioxidant, even in the course of several days at 100°. In the presence of anhydrous ferric or aluminum chloride, the unsymmetrical tetrahalide is formed readily, while in the presence of benzoyl peroxide, or of air and light, the symmetrical tetrahalide is obtained. The definition of the "normal" addition product may be open to some question in this

[1] KHARASCH, MCNAB, AND MAYO, *J. Am. Chem. Soc.*, **55**, 2531 (1933); **56**, 1425 (1934).
[2] KHARASCH AND HINCKLEY, *ibid.*, **56**, 1243 (1934).
[3] KHARASCH AND HINCKLEY, *ibid.*, **56**, 1212 (1934).
[4] KHARASCH, HINCKLEY, AND GLADSTONE, *ibid.*, **56**, 1642 (1934).
[5] KHARASCH AND MAYO, *ibid.*, **55**, 2468 (1933).
[6] SHANE, Ph.D. Thesis, The University of Chicago, **1935**.
[7] KHARASCH, ENGELMANN, AND MAYO, J. ORG. CHEM., **2**, 288 (1937).
[8] KHARASCH AND HANNUM, *J. Am. Chem. Soc.*, **56**, 712 (1934).
[9] KHARASCH, MCNAB, AND MAYO, *ibid.*, **55**, 2521 (1933).
[10] KHARASCH, HANNUM, AND GLADSTONE, *ibid.*, **56**, 244 (1934).
[11] KHARASCH, NORTON, AND MAYO, J. ORG. CHEM., **3**, 48 (1938).

instance because no uncatalyzed addition of hydrogen bromide to this molecule has been observed.

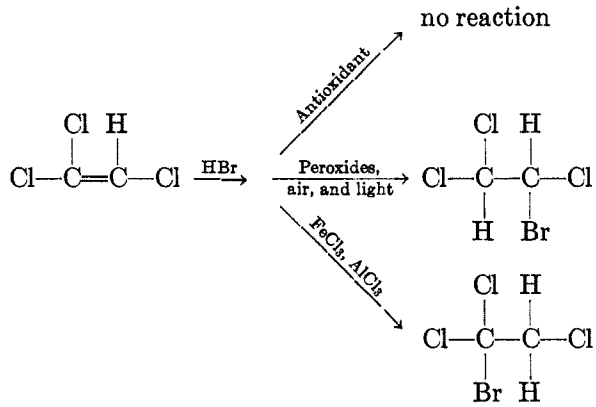


TABLE I

ADDITION OF HYDROGEN BROMIDE TO THE 1-HALOPROPENES

HALOGEN ACID ADDED	CONDITIONS	% 1,2-DIHALIDE FROM 1-HALOPROPENE	
		Chloro	Bromo
HBr.....	Peroxides and/or air	100	100
HBr.....	Air absent, antioxidant present	40–80	90–100
HBr.....	Air absent, $FeCl_3$ catalyst	0–10	67

Previous work on the addition of hydrogen bromide to the 1-halopropenes[7] is summarized in Table I. These results show that the 1,2-dihalides, exclusively, are formed in the presence of air or peroxides. The other data show that a smaller proportion of 1,2-dihalide is formed in the presence of an antioxidant, and still less in the presence of ferric chloride, a powerful catalyst for the "normal" addition reaction. The remainder of the addition product in each case is the isomeric 1,1-dihalide. The greater effectiveness of ferric chloride over the usual antioxidants in this case is of some importance, for in all previously-investigated cases they could be used interchangeably (with respect to directive influence), except that the rate of reaction was greater with ferric chloride.

Our tentative assumption was, therefore, that products formed by the addition of hydrogen bromide to the 1-halopropenes in the presence of ferric chloride represent the "normal" addition products. This conclusion was further tested by experiments in which hydrogen chloride was added

TABLE II

ADDITION OF HYDROGEN BROMIDE AND HYDROGEN CHLORIDE TO OLEFINS

REF.	EXPT. NO.	OLEFIN	HALOGEN ACID[a]	$FeCl_3$[a]	REACTION[b]		% YIELD[c]		PRODUCT[d]
					Time, Hrs.	Temp., °C.	Min.	Max.	
	50	Propene	HBr, 1.5	None	2	0	89	98	2-Bromopropane
	49	Propene	HBr, 1.2	.001	.25	−80	91	98	2-Bromopropane
	5	Propene	HCl, 1.5	None	144	0	48	65	2-Chloropropane
	15	Propene	HCl, 1.4	.001	48	−80	40	90	2-Chloropropane
	46	Propene	HCl, 1.5	.001	48	−80	60	97	2-Chloropropane
					24	0			
2		Isobutylene*	HBr, 1.5	Not given			90		*tert.*-Butyl bromide
	51	Isobutylene	HCl, 1.0	.001	.08	−80	97	100	*tert.*-Butyl chloride
	52	Isobutylene	HCl, 1.5	None	6	−80	88	94	*tert.*-Butyl chloride
5		Allyl bromide*	HBr, 1.5	Trace	18	Room		29	94% 1,2-Dibromopropane[e]
5		Allyl bromide*	HBr, 1.5	.007	6	Room		100	1,2-Dibromopropane
5		Allyl bromide*	HBr, 1.5	.007	17	Room		100	1,2-Dibromopropane
	31	Allyl bromide	HBr, 1.5	.001	16	0	44	65	1,2-Dibromopropane[f]
	41	Allyl bromide	HBr, 1.5	.001 ($FeBr_3$)	72	0	59	71	1,2-Dibromopropane[f]
	28	Allyl bromide	HBr, 1.4	.001	5	Room	47	51	1,2-Dibromopropane[f]
5		Allyl bromide*	HCl, 1.5	None	1426	Room		<10	1-Bromo-2-chloropropane
	12	Allyl chloride	HCl, 1.5	None	1488	Room		<10	1,2-Dichloropropane
	17	Allyl chloride	HCl, 2.5	None[g]	48	0	33		1,2-Dichloropropane
					432	Room			
	6	Allyl chloride	HCl, 1.5	.001	72	0	79	83	1,2-Dichloropropane
					144	Room			
	11	Allyl chloride	HCl, 1.4	.001	168	Room	85	89	1,2-Dichloropropane

	30	2-Bromopropene	HBr, 1.5	.001	48	Room	94	94	2,2-Dibromopropane
	40	2-Bromopropene	HBr, 1.6	.001 ($FeBr_3$)	72	0	94	98	2,2-Dibromopropane
	8	2-Bromopropene	HCl, 1.6	None	1826	Room	63	70	2-Bromo-2-chloropropane
	39	2-Bromopropene	HCl, 1.5	None	2640	Room	68	75	2-Bromo-2-chloropropane
	25	2-Bromopropene	HCl, 1.5	.001	72	0	65	74	2-Bromo-2-chloropropane
	26	2-Chloropropene	HCl, 1.5	.001	48	0	77	94	2,2-Dichloropropane
					120	Room			
9		Vinyl bromide*	HBr, 1.6	.019	24	Room	88		1,1-Dibromoethane
	54	Vinyl bromide	HCl, 1.5	None	1296	Room		<10[A]	
	53	Vinyl bromide	HCl, 1.5	.001	1	Room		>60[A]	
	29	Vinyl chloride	HBr, 1.4	.001	24	0	77	93	1-Chloro-1-bromoethane
					48	Room			
	45	Vinyl chloride	HBr, 1.4	.001	48	0	86	95	1-Chloro-1-bromoethane
					24	Room			
	3	Vinyl chloride	HCl, 1.5	None	504	Room		<10	1,1-Dichloroethane
	1	Vinyl chloride	HCl, 1.3	.001	48	0	57	62	1,1-Dichloroethane
					148	Room			
	13	Vinyl chloride	HCl, 1.4	.001	120	Room	59	77	1,1-Dichloroethane
	18	Vinyl chloride	HCl, 1.4	.001	72	Room	71	84	1,1-Dichloroethane
	19	Vinyl chloride	HCl, 1.5	.001	72	Room	71	82	1,1-Dichloroethane
11		Trichloroethylene*	HBr, 1.5	.005	24	Room	73		1,1,2-Trichloro-1-bromoethane
11		Trichloroethylene*	HBr, 1.1	.004	24	Room	81		1,1,2-Trichloro-1-bromoethane
11		Trichloroethylene*	HCl, 1.6	.003	144	Room	49		1,1,1,2-Tetrachloroethane

TABLE II—*Concluded*

REF.	EXPT. NO.	OLEFIN	HALOGEN ACID[a]	$FeCl_3$[a]	REACTION[b]		% YIELD[c]		PRODUCT[d]
					Time, Hrs.	Temp., °C.	Min.	Max.	
	37	1-Bromopropene*	HBr, 1.8	.003	1.4	0	96		59% 1,2-Dibromopropane
7		1-Bromopropene*	HBr, 1.6	.006	2	0	90		67% 1,2-Dibromopropane
7		1-Bromopropene*	HBr, 1.6	.01	.75[i]	0	91		67% 1,2-Dibromopropane
7		1-Bromopropene*	HCl, 1.6	.016	15	0	61		65% 1-Bromo-2-chloropropane
	35	1-Bromopropene*	HCl, 1.5	.003	24	0	75	85	64% 1-Bromo-2-chloropropane
7		1-Chloropropene*	HBr, 1.6	.006	2	0	83		1-Chloro-1-bromopropane
7		1-Chloropropene*	HBr, 1.6	.003	2	0	15		1-Chloro-1-bromopropane
7		1-Chloropropene*	HBr, 1.6	.018	13[i]	0	91		1-Chloro-1-bromopropane
	22	1-Chloropropene	HCl, 1.5	.001	72	Room	55	61	1,1-Dichloropropane
7		1-Chloropropene	HCl, 2.0	.04	48	Room		90	1,1-Dichloropropane

* Indicates experiments in which the vacuum technique of Kharasch and Mayo[5] was employed. Pressures of 10^{-3}–10^{-4} mm. were used.

[a] Expressed in moles per mole of olefin. In all cases 0.1 mole of ethylene derivative was used.

[b] All reactions were carried out in the dark.

[c] The "minimum" yield is calculated from the weight of pure dihalide isolated after the final distillation. Low yields are often due to loses from incomplete condensation in vacuum distillation. "Maximum yields" are calculated on the basis of the crude reaction product after removal of solvent, catalyst, hydrogen halide and unchanged olefin.

[d] These products are the "normal" addition products. In those cases where percentages are given, the remainder was the other possible addition product.

[e] Percentage of 1,2-dihalide was recalculated on the basis of the corrected index of refraction: 1.5200.

[f] Large amounts of tar formed during the reaction account for the low yields.

[g] One and one half moles of nitromethane were used as solvent in this experiment. It is of interest to note that addition is accelerated by the presence of a solvent of high dielectric constant.

[h] All attempts to add hydrogen chloride to vinyl bromide yielded products having no sharp boiling point, an indication that halogen exchange had taken place.

[i] Complete in five minutes.

to the 1-halopropenes in the presence of anhydrous ferric chloride. Under such conditions both halogen acids added in the same manner.

The addition of hydrogen chloride is not complicated by an oxygen or peroxide effect,[12, 13, 14, 15] but this reagent adds very slowly to many ethylene derivatives unless ferric chloride is used as a catalyst. (Aluminum chloride has the same effect as ferric chloride but often causes more tar formation.) In order that hydrogen chloride additions might be used as a standard for a "normal" addition, it therefore remained to be shown (1) that ferric chloride does not effect the direction of addition of either hydrogen chloride or hydrogen bromide, and (2) that the "normal" addition of hydrogen bromide corresponds to the addition of hydrogen chloride.

This work has now been completed and we can state with certainty that ferric chloride affects only the rate, but not the course, of "normal" addition of hydrogen bromide and hydrogen chloride, both of which give corresponding products. It is our conclusion, therefore, that the addition of hydrogen chloride with or without ferric chloride, and the addition of hydrogen bromide with a ferric halide catalyst, are altogether equivalent to the "normal" uncatalyzed addition of hydrogen bromide. We have been unable to find any exceptions to this principle in our laboratory or in the literature.

DISCUSSION OF RESULTS

It has already been mentioned that oxygen and peroxides have no observable effect on the direction of addition of hydrogen chloride to double bonds. The product formed in each case must therefore be the "normal" addition product. Table II shows that ferric chloride affects only the rate, and not the direction, of addition of hydrogen chloride to propene, isobutylene, allyl chloride, 2-bromopropene, and 2-chloropropene. We conclude, therefore, that the "normal" addition products are obtained when hydrogen chloride is added to vinyl bromide, 1-chloropropene, 1-bromopropene, and trichloroethylene in the presence of ferric chloride. Furthermore, these data indicate that addition of hydrogen chloride to any ethylene derivative, with or without ferric chloride, gives only the "normal" addition product.

Table II also summarizes the results of the addition of hydrogen bromide to nine ethylene derivatives in the presence of ferric halides. In all cases, except those of 1-chloro- and 1-bromopropenes and of trichloroethylene,

[12] KHARASCH AND MAYO, unpublished work.

[13] ABRAHAM AND SMITH, *J. Chem. Soc.*, **1936**, 1605.

[14] RUDKOVSKIĬ AND TRIFEL, *Org. Chem. Ind.* (U. S. S. R.), **2**, 203 (1936); *C. A.*, **31**, 1004 (1937).

[15] SCHJÅNBERG, *Ber.*, **70B**, 2385 (1937).

the addition products were identical with those obtained in the presence of antioxidants. Since, in all cases where comparisons are possible, these hydrogen bromide addition products also correspond to the hydrogen chloride addition products, they must necessarily be the "normal" addition products. Ferric salts must, therefore, catalyze the "normal" addition of hydrogen bromide as well as of hydrogen chloride.

Table I summarizes previous work with the 1-halopropenes, which gave different proportions of addition products in the presence of antioxidants and ferric halides. Table II indicates that in the presence of ferric chloride, hydrogen bromide and hydrogen chloride add in the same manner to each halopropene. It is our belief, therefore, that in this instance, the addition products obtained in the presence of ferric chloride, rather than in the presence of antioxidants, represent the "normal" addition of halogen acids to these ethylene derivatives. In short, it now appears evident that in such addition reactions antioxidants and metallic halides are negative and positive catalysts respectively, and that their concordant influence upon direction of addition is adequately elucidated by the facts that the former retard or suppress the "abnormal" addition reaction, whereas the latter accelerate the "normal" reaction. The previous conclusions of Kharasch, Engelmann, and Mayo[7] are thus confirmed and extended. Similar reasoning leads to the conclusion that the unsymmetrical halide obtained from trichloroethylene in the presence of ferric halides must be the "normal" addition product, although no uncatalyzed addition has yet been observed.

EXPERIMENTAL

All experiments except numbers 35 and 37 were performed in the presence of air. The anhydrous ferric chloride was weighed in the bomb tube, the olefin was added, and the halogen acid was passed in at $-80°$ until a sufficient quantity had been absorbed. The bomb was then sealed off and allowed to stand in the dark until the reaction was complete. The bombs were shaken at intervals to insure contact of their contents with the ferric chloride.

When the reaction was complete, the bomb was cooled to $-80°$ and opened. The excess hydrogen halide was allowed to escape, and the reaction products were distilled from the catalyst and tar at 15–25 mm., the distillate being collected at $-80°$. The halides were then dried over anhydrous potassium carbonate and fractionally distilled through an efficient column. The composition of the addition products was determined by their boiling points and refractive indices, most of which had been recorded previously in papers from this laboratory. Attempts to add hydrogen chloride to allyl bromide or hydrogen bromide to allyl chloride, in the presence of ferric chloride, led to halogen exchange and the formation of mixtures which could not be separated.

Runs number 35 and 37 were carried out according to the vacuum technique of Kharasch and Mayo[5], pressures of 10^{-3}–10^{-4} mm. of mercury being used.

SUMMARY

1. The addition of hydrogen bromide and hydrogen chloride to several ethylene derivatives has been studied in the presence and absence of ferric chloride as catalyst.

2. The direction of addition of hydrogen chloride is the same as that of the "normal" addition of hydrogen bromide.

3. Ferric halides greatly accelerate the rate but do not change the "normal" direction of addition of both halogen acids.

4. It is suggested that the "normal" addition of hydrogen bromide be defined as that corresponding to the following equivalent addition reactions: the addition of hydrogen chloride, with or without ferric chloride, and the addition of hydrogen bromide in the presence of ferric chloride.

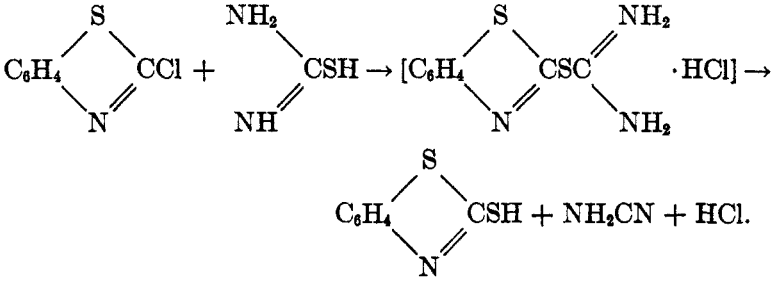
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GOODYEAR TIRE & RUBBER CO. AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

REACTIONS IN THE THIAZOLE SERIES. II. THE REACTION OF 2-CHLOROBENZOTHIAZOLE WITH THIOUREA IN AQUEOUS MEDIA

GEORGE W. WATT

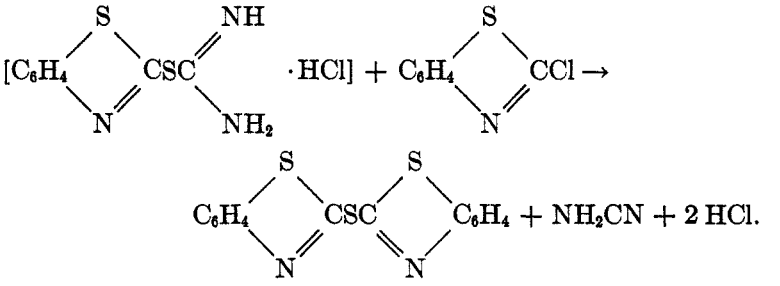
Received April 24, 1939

It has been shown previously[1] that reactions between organic halides and thiourea lead to the formation of stable addition compounds, mercaptans, sulfides, or disulfides. It was shown that 2-chlorobenzothiazole and thiourea react quantitatively in alcoholic solution to form 2-mercaptobenzothiazole,



(1)

Further study has shown that when these substances react in aqueous media (in which the chloro compound is practically insoluble), there is obtained both 2-mercaptobenzothiazole and 2,2′-dibenzothiazyl sulfide. The formation of the latter may be explained by assuming that the intermediate addition compound postulated in equation 1 reacts with another molecule of the 2-chloro compound:[2]



(2)

[1] SCOTT AND WATT, J. ORG. CHEM., **2**, 148–56 (1937).

[2] *Cf.*, ROSENHAUER, HOFFMAN, AND HEUSER, *Ber.*, **62B**, 2730–6 (1929).

By altering the experimental conditions, it was found possible to cause the formation of either the mercaptan or sulfide to predominate. A somewhat detailed study was made of the influence of concentration, time, temperature, and the nature of the reaction medium upon the course of this reaction.

No evidence of the formation of either mercaptan or sulfide was obtained when 2-chlorobenzothiazole and thiourea were brought together in liquid ammonia at $-33.5°$ or at room temperature either in the presence or absence of ammonium bromide (an acid in liquid ammonia). However, it was found that both thiourea and the thiazole enter into reaction with the solvent at room temperature. These reactions are being studied in more detail.

EXPERIMENTAL

Materials.—2-Chlorobenzothiazole was prepared and purified as previously described.[1] The thiourea used was a commercial product purified by repeated recrystallization from water.

Procedure.—One-tenth mole each of 2-chlorobenzothiazole (17 g.) and thiourea (7.6 g.) and 50 cc. of water contained in a 250 cc. flask* were stirred rapidly and continuously for 80 hours by means of an air-driven stirrer. The resulting white precipitate was filtered and washed twice with small portions of water. (In all cases involving the use of mixtures of water and organic solvents, the reaction mixture was diluted with 200 cc. of cold water and allowed to stand for one-half hour prior to filtration.) The solid product was extracted twice with 50 cc. portions of cold 10 per cent sodium hydroxide solution and filtered. The alkali-insoluble solid was washed twice on the filter with small portions of petroleum ether to remove any unchanged 2-chlorobenzothiazole. When dry, this product weighed 5.8 g. Recrystallization from alcohol gave fine needle-like crystals of 2,2′-dibenzothiazyl sulfide, m.p. 98.7–99.1° (corr.). The melting point of a mixture with a sample of the sulfide prepared by an independent method gave no depression.

Anal., Calc'd for $C_{14}H_8N_2S_3$: N, 9.33; S, 32.00.
Found: N, 9.48; S, 32.13.

The combined alkaline extracts and washings were extracted with ether, following which the aqueous layer was acidified with dilute hydrochloric acid. The precipitated 2-mercaptobenzothiazole was filtered, washed with cold water, dried, and found to weigh 0.55 g. The mercaptan thus obtained was of a high degree of purity and melted at 179.2–180° (corr.). The melting point of this product was not depressed by mixing with a specimen of the mercaptan prepared by another method.

In Table I are presented data obtained as described above. Data given in Table II relate to reactions which occurred in acid media,† while results obtained using water-alcohol and water-acetone mixtures are given in Table III. Unless otherwise specified, each experiment involved reaction at room temperature between one-tenth mole each of 2-chlorobenzothiazole and thiourea in the indicated volume of solvent

* Reactions effected above room temperature were carried out in a 3-necked flask equipped with an air-driven stirrer, a thermometer, and a reflux condenser.

† No reaction occurs between 2-chlorobenzothiazole and thiourea in the presence of aqueous alkali at room temperature.

and over the given period of time. Repeated experiments under representative sets of experimental conditions showed that the yield data are subject to variation within the range, ± 4 per cent.

DISCUSSION

The experimental data presented in Table I show: (1) that the yields of both mercaptan and sulfide are decreased with decrease in concentration; (2) that at any particular concentration the yields increase with increase in time of reaction; and (3) that the rate at which these reactions approach completion is increased by the presence of an excess of either thiourea or of

TABLE I

REACTIONS IN WATER AT 25°

EXPT. NO.	VOL. (CC.)	TIME (HRS.)	YIELD (%)	
			Sulfide	Mercaptan
13	50	52	—	9
30[a]	50	52	39	19
48	25	80	65	28
10	50	80	39	3
42[b]	50	112	8	92
49	75	80	—	5
12	75	112	35	1
11	75	148	70	24
51	50	112	42	44
28[c]	50	112	56	35
34[d]	50	112	19	73
52	50	148	33	50
7[e]	50	4	32	66

[a] Reaction in presence of 0.05 mole of 2-mercaptobenzothiazole.
[b] Reaction in presence of excess thiourea (0.1 mole).
[c] Reaction in presence of 0.1 mole of 2-mecaptobenzothiazole.
[d] Reaction in presence of excess thiourea (0.05 mole).
[e] Reaction at 95°.

2-mercaptobenzothiazole. The influence of temperature upon the velocity of the reactions is shown by the data of experiment 7.

Preliminary experiments showed that the sulfide is not formed by the direct interaction of 2-chlorobenzothiazole and 2-mercaptobenzothiazole either in alcohol at its boiling point or in water at room temperature. Hence, some intermediate substance must be involved in the formation of the sulfide. The earlier work of Rosenhauer, Hoffman, and Heuser[2] on the reactions of chloroquinolines with thiourea demonstrated that either sulfide or mercaptan may be formed from addition compounds of the type postulated as an intermediate in equation 1. They obtained addition

compounds which were sufficiently stable to permit isolation. However, in the case of the reactions presently under consideration, all attempts to

TABLE II

REACTIONS IN SULFURIC AND HYDROCHLORIC ACIDS AT 25°

EXPT. NO.	REACTION MEDIUM[a]	TIME (HRS.)	YIELD (%)	
			Sulfide	Mercaptan
	Sulfuric acid:			
38	0.01*N*	88	—	48
39	0.1*N*	40	—	25
37	0.5*N*	16	—	41
44	2.0*N*	3	—	92
	Hydrochloric acid:			
41	0.05*N*	49	57	12
5	0.5*N*	24	73	6
6[b]	0.5*N*	4	19	73
8[c]	0.5*N*	4	36	61
43	2.0*N*	3	2	89

[a] Fifty cubic centimeters used in all cases.
[b] Reaction at 60°.
[c] Reaction at 95°.

TABLE III

REACTIONS IN WATER-ALCOHOL AND WATER-ACETONE MIXTURES AT 25°

EXPT. NO.	REACTION MEDIUM[a]	TIME (HRS.)	YIELD (%)	
			Sulfide	Mercaptan
	Aqueous alcohol:[b]			
21	12.5%	112	30	54
55	25.0	40	—	18
20	25.0	90	26	44
18	50.0	16	—	19
54	50.0	24	—	51
16	50.0	40	—	59
25	50.0	112	4	90
	Aqueous acetone:[b]			
27	25.0%	80	19	75
22	50.0	24	—	38
23	50.0	40	9	56
53	50.0	80	11	89

[a] Fifty cubic centimeters used in all cases.
[b] Concentration of organic solvent given in per cent. by volume.

isolate such compounds met with failure. Whether mercaptan or sulfide is formed in any given case appears to be dependent upon the stability of

either the addition compound or of its dissociation products. If the addition compound itself is relatively unstable, it should be expected to decompose rapidly, yielding mercaptan in accordance with equation 1. A more stable addition compound, or a stable ion formed therefrom, however, might be expected to react as shown by equation 2, yielding the sulfide. The greater stability required in the formation of sulfide is probably due to the fact that the reaction involved occurs only very slowly.

The data of Table II show that the rate of conversion of the chloro compound to either the mercaptan or sulfide is increased markedly with increase in hydrogen-ion concentration. This increase in rate of reaction is probably due to the influence of the acids upon the solubility of the chloro compound, since thiazoles are known to be soluble in mineral acids by virtue of salt formation on the nitrogen atom in the thiazole ring.[3] It is of interest to note that all reactions involving the use of sulfuric acid led to the formation of mercaptan almost exclusively.‡ When hydrochloric acid was used, the product predominating was dependent upon the temperature at which the reaction was effected. The marked increase in reaction velocity observed in reactions carried out at elevated temperatures and the predominance of mercaptan over sulfide in the product are probably due to the effect of temperature upon the stability of the addition compound. Earlier work has shown that compounds of this type are unstable under comparable conditions.[2, 4]

The manner in which the formation of the observed products may be determined by the ionization of the addition compound must also be considered. Goldschmidt and co-workers[5] have measured the conductance of a large number of addition compounds of alkyl halides with thiourea and substituted thioureas. They have shown that the degree of ionization in aqueous solutions is such that these substances may be considered as being relatively strong electrolytes. In alcoholic solutions, however, the degree of ionization is low, but is progressively increased by the addition of water.

The data of Table III indicate that the formation of sulfide is dependent upon the ionization of the addition compound. The formation of sulfide in water-alcohol and water-acetone mixtures occurs only when a low percentage of organic solvent is present or in reactions allowed to proceed over long periods of time. Hence it appears that the degree of ionization

[3] HOFMANN, *Ber.*, **13**, 15 (1880).

‡ Although no yield data for sulfide are given, traces of this product were formed in nearly every case.

[4] CLAUS, *ibid.*, **8**, 41–4 (1875).

[5] GOLDSCHMIDT AND GRINI, *Z. Elektrochem.*, **19**, 226–34 (1913). GOLDSCHMIDT AND HOUGEN, *ibid.*, **22**, 339–49 (1916).

of the addition compound is decreased as the percentage of organic solvent is increased and this results in the formation of mercaptan rather than sulfide.

The foregoing evidence, although not wholly conclusive, indicates that the formation of 2,2′-dibenzothiazyl sulfide from 2-chlorobenzothiazole and thiourea may occur only in a medium which permits the 2-chlorobenzothiazole-thiourea addition compound to ionize to form an ion which is more stable than the addition compound itself and which is capable of reacting with 2-chlorobenzothiazole in a relatively slow reaction in which the sulfide is formed.

SUMMARY

1. The reaction between 2-chlorobenzothiazole and thiourea in aqueous media has been shown to result in the formation of 2-mercaptobenzothiazole and 2,2′-dibenzothiazyl sulfide.

2. It has been shown that the formation of the sulfide is dependent upon the formation and ionization of an intermediate addition compound.

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

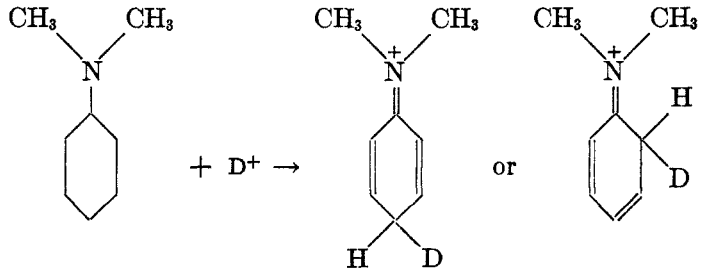
EXCHANGE REACTIONS IN DEUTEROALCOHOL. II.

WELDON G. BROWN, M. S. KHARASCH, AND W. R. SPROWLS

Received April 28, 1939

In the first paper of[1] this series we reported the results of a preliminary investigation of hydrogen-deuterium exchange reactions involving organic substances of various types and deuteroalcohol as the solvent and donor of deuterium. The experiments included representatives of two different types of exchange reaction which could be differentiated on the basis of catalytic influences. One class comprises the base-catalyzed exchange reactions of substances of inherent acidic properties, such as fluorene, *o*- and *p*-nitrotoluene, and sym-trinitrobenzene. The second type of exchange reaction exhibits acid catalysis, as in the case of dimethylaniline,* and, since the reaction is initiated by acids, the lability of hydrogen is clearly a consequence of the molecule having functioned as a base. The survey has been continued in various directions, but with particular emphasis on reactions of the second type, that is, the acid-catalyzed exchange reactions of dimethylaniline and related substances.

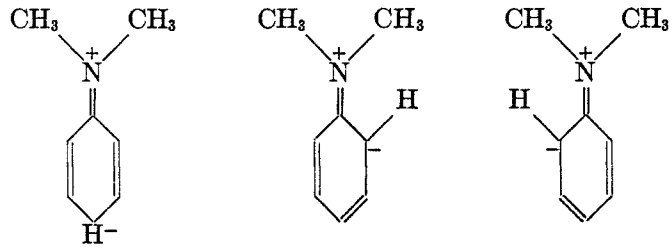
The mechanism of the dimethylaniline exchange reaction was briefly discussed in our first paper and it was pointed out that while the normal reaction of dimethylaniline with a dilute acid would be the formation of an ammonium salt, this salt would not necessarily be an intermediate in the exchange reaction. In fact, having in mind the deactivating effect of salt formation in nuclear substitution reactions, mechanisms involving the normal ammonium salt as an intermediate seemed somewhat less probable than one involving the direct addition of protons at the nuclear positions, giving rise to tautomeric forms of the salt, as follows:



[1] KHARASCH, BROWN, AND MCNAB, *J. Org. Chem.*, **2**, 36 (1937).

* The acid-catalyzed hydrogen exchange reaction of dimethylaniline in aqueous

This mechanism is suggested by the interpretation of the structure of the free base as a resonance hybrid of the normal aromatic resonance forms together with three zwitterion forms shown below:



The free base is to be regarded, of course, as a single composite structure, but the fact that the pair of electrons normally available for salt formation on the nitrogen atoms may be shared with the two ortho positions and the para position makes more plausible the assumption that the molecule may accept a proton at any one of these points. The products formed would no longer be resonance forms but tautomeric forms, and it will be evident that dissociation of the quinoid forms of the salt, but not of the normal form, will give rise to hydrogen exchange.

The two hypotheses would seem to be experimentally distinguishable if the influence of base strength on the ease of hydrogen exchange is considered. If the normal ammonium salt is an intermediate in the exchange reaction, then structural changes which decrease the basicity of the molecule should also inhibit the exchange reaction. If, however, the structural change decreases the basic strength mainly by increasing the number or the stability of the zwitterion resonance forms, and if the salts derived from these forms are the intermediates, the exchange reaction should be facilitated. Thus we should expect triphenylamine to be capable of exchanging hydrogen at a rate of about the same order of magnitude as for dimethylaniline, despite the tremendous disparity in base strength, since the effect of substituting phenyl groups for methyl groups will be to increase the number of resonance structures and so to increase the number of points at which a proton may become attached.

The experimental results which have been obtained for a number of substances in this category are, on the whole, in accord with the hypothesis that quinoid forms of the salts act as intermediates. Unfortunately, rate

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solution was reported prior to the publication of our first paper by INGOLD, RAISIN, AND WILSON (*J. Chem. Soc.*, **1936**, 1636), who also supposed that the reaction is limited to the ortho and parahydrogens. These authors were also the first to consider a mechanism of direct introduction of deuterium into the aromatic nucleus, and the mechanism which was given in our first paper (Ref. 1, p. 43, footnote) should be credited to them. It will be noted, however, that the mechanism proposed in the present paper presents a number of distinctly new features.

data which could be handled in rigorous kinetic fashion are not yet readily available, as the experimental procedure is still too cumbersome, and with our present methods rate studies would be too costly in materials.

The behavior of dimethylaniline has been carefully re-investigated in view of the rather peculiar results which were reported previously. Those results, while they demonstrated an acid-catalyzed exchange reaction involving three hydrogens, indicated also an exchange reaction to the extent of about 0.5 hydrogen in both neutral and alkaline solution. Since this reaction appeared not to be inhibited by alkali, it was felt that the experimental results must be in error, perhaps as a consequence of the presence of some dimethylaniline in the samples of alcohol which were analyzed for deuterium. It is now found, after repeating the experiments and exercising greater care in the separation of the mixtures, that dimethylaniline does not exchange hydrogen appreciably in the absence of acid. This result has been checked repeatedly.

Diphenylamine exchanges one hydrogen, presumably the *N*-hydrogen, in the absence of acid, while in the presence of acid the exchange number rises to six. The most probable value for the number of exchangeable hydrogen atoms, consistent with the value of six for the exchange number, is seven, and it is therefore likely that the exchange reaction in the presence of acid involves the ortho and para positions in each ring in addition to the hydrogen attached to nitrogen. Triphenylamine behaves similarly, the observed exchange number, 7.9, corresponding to the exchange of nine hydrogens. There is, therefore, no marked diminution in the ability of the nuclear hydrogens to exchange which would parallel the very great decrease in basicity in the series, dimethylaniline, diphenylamine, and triphenylamine, and these results provide convincing evidence against the normal salt (or ion) as an intermediate in the exchange reaction.

The nitro derivatives of dimethylaniline exhibit very striking differences in the lability of the nuclear hydrogens. The theoretical limit for the number of exchangeable hydrogens, assuming that only the hydrogens ortho and para to the dimethylamino group are labile, would be two for *o*- and *p*-nitrodimethylaniline, and three for the meta compound. Actually the ortho compound exhibits no exchange at all under the experimental conditions we have adopted. The hydrogen exchange of the para compound under the influence of acid is practically complete, and the exchange of the meta compound under the same conditions, while greater in absolute amount than for the para compound, falls short of the theoretical limit, and the meta compound is therefore to be regarded as intermediate in reactivity.

The failure of *o*-nitrodimethylaniline to exchange is to be correlated

with the observations[2] that this compound does not form a nitroso derivative with nitrous acid, does not couple with diazo compounds, and does not condense with aldehydes as is characteristic not only of dimethylaniline itself but also of *m*-nitrodimethylaniline. The deactivating effect is not however specific for the nitro group; dimethyl-*o*-toluidine[3] and *o*-chlorodimethylaniline[2] likewise fail to react with nitrous acid and to couple with diazonium salts, and it has been postulated by Karrer[4] that the effect is due to steric hindrance. Because of these effects, Karrer was led to suppose that the initial point of attack by the reagent in coupling and nitrosation reactions is the nitrogen atom, which in turn necessitates a rearrangement to obtain the final product.

In the present instance, at least, it would not appear to be necessary to assume that the initial point of attack is the nitrogen atom in order to see how steric effects might arise. Both the orthoquinoid and the paraquinoid forms of the aryldimethylammonium salts, which in our hypothesis act as intermediates in the exchange reactions, will possess a configuration such that the methyl groups are confined to the plane of the ring as a consequence, based on classical theory, of the presence of the nitrogen-carbon double bond. The steric effect of an ortho substituent could then consist in a tendency to prevent the alkyl groups from assuming this configuration, the result of which would be to increase the energy of activation required for the formation of the reaction intermediate which is now a form of higher energy (lower stability). Since the contribution to the activation energy arising from this source need be relatively small in order to account for the observed results, it is by no means necessary to assume that rotation of the dialkylamino group is entirely prevented or that the hindrance would necessarily be sufficient to introduce optical isomerism in the case where the dialkylamino group is unsymmetrical. Otherwise the type of optical isomerism discovered by Mills and Kelham[5] in the case of *N*-acetyl-*N*-methyl-*p*-toluidine-3-sulfonic acid would be more commonly encountered. An effect amounting to between five and ten kilocalories in the energy of activation would appear to be sufficient to account for the phenomenon, little more, for example, than the estimated energy of rotation about the C—C bond in ethylene chloride. An interaction energy of this magnitude in the present instances appears not to be unreasonable, but that it could be of such significance for the chemistry of the substance is at first sight surprising.

[2] FRIEDLÄNDER, *Monatsh.*, **19**, 638 (1898).
[3] WURSTER AND RIEDEL, *Ber.*, **12**, 1796 (1879).
[4] KARRER, *ibid.*, **48**, 1398 (1915).
[5] MILLS AND KELHAM, *J. Chem. Soc.*, **1937**, 274.

The steric effect which we suppose to originate in the tautomeric forms of the dimethylaniline salts is in certain respects similar to, and is probably supplemented by, an effect manifesting itself in the free base which is known as damped resonance. The effect is similar in that the quinoid resonance forms of the free base, from which the tautomeric forms of the cation may be considered as derived, are rendered less stable by the presence of an ortho substituent, which tends to prevent a planar arrangement, with the result that these forms contribute less to the actual structure of the molecule. This idea was introduced by Birtles and Hampson[6] who believed that the abnormally large dipole moment of *p*-nitrodimethylaniline is due to the contribution of a quinoid resonance form and who predicted correctly that the substitution of four methyl groups in the nuclear positions would restore the dipole moment to a normal value. Further evidence has been accumulating rapidly. The effect of damped resonance in the free base will be to decrease the enhancement of nuclear reactivity which has its origin in resonance involving the nitrogen atom, and, insofar as exchange reactions are concerned, will be indistinguishable from the analogous steric effects in the cation forms. However, there appears to be a possibility of securing independent experimental evidence for the effect of damped resonance in molecules of the type under consideration in an examination of the relative base strengths of ortho and para isomers; the effect should be manifested by an increase in the base strength of the ortho isomer.*

It is our belief that the essential ideas underlying this interpretation of the exchange reactions can be extended profitably to other reactions in which ortho effects appear, and we are therefore continuing the investigation not only with the aid of exchange reactions but with regard to some other types of substitution as well. However, in suggesting that this type of steric hindrance is of general significance in connection with ortho effects in nuclear substitutions, we do so while recognizing that in indi-

[6] BIRTLES AND HAMPSON, *ibid.*, **1937**, 10. Since this article was submitted for publication a second paper, which deals with chemical applications of the principle of damped resonance has appeared [INGHAM AND HAMPSON, *J. Chem. Soc.*, **1939**, 981.]

* Since this paper was written our attention has been drawn to the fact that there are several known instances in which the base strength of ortho-substituted tertiary bases is greater than that of the corresponding meta- and para-substituted bases, whereas, in accordance with the interpretation on the basis of damped resonance, no such ortho effect manifests itself in the base strength of primary and secondary amines [for experimental data, see DAVIES AND ADDIS, *J. Chem. Soc.*, **1937**, 1622; WALKER, *Z. phys. Chem.*, **57**, 608 (1906)]. Further manifestations of the effect of damped resonance are to be seen in the refractivities and ultraviolet absorption spectra of ortho-substituted tertiary bases as will be shown more fully in a subsequent paper.

vidual cases the purely steric factor may be only one of several factors influencing nuclear reactivity and that in special circumstances it may be altogether absent.

The alkali-catalyzed exchange reaction of the hydrocarbon, fluorene, is representative of a distinctly different type of hydrogen lability, namely, a type in which the labile hydrogen is acidic. That fluorene is readily capable of reacting as a proton donor is well known from its condensation reactions and the formation of salts with the alkali metals, and its strength as an acid has been determined by Conant and Wheland[7]. The fact that triphenylmethane, which is also capable of salt formation, did not exchange hydrogen under the same experimental conditions is in accord with the relative positions of fluorene and triphenylmethane in the acidity series established by these authors. Further evidence for the existence of a relationship between the ability of such substances to exchange hydrogen and their acid strength was provided by Heuse[8] who showed that xanthane, which occupies an intermediate position in the acidity series, is also intermediate in its rate of hydrogen exchange. He found also that indene and 9-phenylfluorene, which, according to Conant and Wheland, are both somewhat stronger as acids than fluorene, exhibited hydrogen exchange under the influence of alkali at least as readily as fluorene.

It is clearly evident from these results that the origin of the extraordinary lability of hydrogen in indene and in fluorene derivatives is to be sought in the cyclopentadiene nucleus, and we may note, as others have done, that the formation of an anion by the loss of a proton would convert the cyclopentadiene nucleus to a structure in which various possibilities for resonance are present. The stabilization effect of resonance in the anion would result in a lowering of the energy of electrolytic dissociation and thus in an increase in acid strength. The assumption of such electronic mobility in the anions seems necessary also in order to account for rearrangements of a prototropic type which occur when certain indene derivatives are treated with alkali. In the case of indene itself we could predict the exchange of three hydrogens under the influence of alkali if we are to assume a resonating anion as an intermediate. This anion would certainly be electronically symmetrical about the *beta* carbon atom, and in the reformation of the indene molecule by proton capture, the incoming proton could enter at either alpha position. The repetition of the processes of dissociation and recombination would then give rise ultimately to the exchange of three hydrogens. Heuse, in his work on the exchange of indene catalyzed by sodium hydroxide, obtained values for the exchange

[7] CONANT AND WHELAND, *J. Am. Chem. Soc.*, **54**, 1212 (1932).
[8] HEUSE, Master's Dissertation, University of Chicago, **1937**.

TABLE I

EXCHANGE REACTIONS OF DIMETHYLANILINE AND RELATED SUBSTANCES

REF. NO.	SUBSTANCE	MMOLES. SUBSTANCE	MMOLES. ALCOHOL	CATALYST	TEMP., °C.	TIME, HRS.	INITIAL D_2O	FINAL D_2O	EXCHAGE NUMBER
1	Dimethylaniline	39.3	85.8	—	110	96	3.43	3.35	0.06
4	Dimethylaniline	39.3	85.8	—	110	96	3.43	3.35	0.06
80	Dimethylaniline	39.3	85.8	—	110	112	3.17	3.06	0.08
12	Dimethylaniline	39.3	85.8	NaOH, 2 mg.	110	137	3.43	3.37	0.04
2	Dimethylaniline	39.3	85.8	H_2SO_4, 140 mg.	110	96	3.43	1.56	2.55
41	Dimethylaniline	39.3	85.8	H_2SO_4, 140 mg.	25	24	3.10	2.97	0.13
7	Diphenylamine	29.6	85.8	—	110	115	3.43	2.47	1.13
14	Diphenylamine	29.6	85.8	NaOH, 2 mg.	110	115	3.43	2.46	1.14
10	Diphenylamine	29.6	85.8	H_2SO_4, 140 gm.	110	96	3.43	1.12	5.98
17	Triphenylmethane	20.4	85.8	—	110	98	3.43	3.36	0.09
22	Triphenylmethane	20.4	85.8	NaOH, 2 mg.	110	115	3.43	3.41	0.03
19	Triphenylmethane	20.4	85.8	H_2SO_4, 140 mg.	110	105	3.43	1.19	7.93
37	Triphenylmethane	8.2	85.8	H_2SO_4, 100 mg.	25	115	3.10	3.07	
28	*p*-Nitrodimethylaniline	9.1	85.8	—	110	101	3.10	3.09	0.03
27	*p*-Nitrodimethylaniline	9.7	85.8	NaOH, 2 mg.	110	97	3.10	3.08	0.06
26	*p*-Nitrodimethylaniline	12.0	85.8	H_2SO_4, 100 mg.	110	96	3.10	2.48	1.62
35	*m*-Nitrodimethylaniline	12.0	85.8	—	110	96	3.10	3.08	0.04
34	*m*-Nitrodimethylaniline	12.0	85.8	NaOH, 2 mg.	110	96	3.10	3.07	0.07
33	*m*-Nitrodimethylaniline	12.0	85.8	H_2SO_4, 100 mg.	110	96	3.10	2.44	2.08
54	*m*-Bromodimethylaniline	6.8	85.8	—	110	120	3.10	2.75	1.21
75	*m*-Bromodimethylaniline	6.8	85.8	—	110	98	3.17	2.99	0.76
53	*m*-Bromodimethylaniline	13.7	85.8	NaOH, 2 mg.	110	96	3.10	3.06	0.08
49	*m*-Bromodimethylaniline	13.7	85.8	H_2SO_4, 100 mg.	110	96	3.10	2.20	2.41
92	*o*-Nitrodimethylaniline	27.6	85.8	—	110	111	3.17	3.22	
94	*o*-Nitrodimethylaniline	27.6	85.8	NaOH, 2 mg.	110	98	3.17	3.20	
98	*o*-Nitrodimethylaniline	27.6	85.8	H_2SO_4, 140 mg.	110	99	3.17	2.86	0.24

TABLE II

EXCHANGE REACTIONS OF FLUORENE AND RELATED SUBSTANCES

REF. NO.	SUBSTANCE	M-MOLES.	CATALYST	TEMP., °C.	TIME, HRS.	INITIAL D_2O	FINAL D_2O	EXCHANGE NUMBER	REMARKS
3	Fluorene	30.1	NaOH, 2 mg.	110	69	3.43	2.16	1.70	2 H's exchange
40	9-Fluorenol	8.8	—	110	108	3.10	2.80	1.12	Exchange of OH hydrogen
38	9-Fluorenol	9.4	NaOH, 2 mg.	110	96	3.10	2.58	1.84	2 H's exchange
76	9-Fluorenol	9.1	NaOH, 1 mg.	25	1226	3.17	2.80	1.25	Exchange of 2nd H incomplete
93	9-Fluorenol	11.0	NaOH, 439 mg.	25	12	3.17	2.69		Decomposition
83	9-Fluorenol	4.2	Na_2CO_3, 450 mg.	25	43	3.17	2.84	1.19	
39	9-Fluorenol	9.6	H_2SO_4, 100 mg.	110	119	3.10			Decomposition
77	9-Methoxyfluorene	15.3	—	110	95	3.17	3.14	0.05	No exchange
78	9-Methoxyfluorene	15.3	NaOH, 2 mg.	110	116	3.17	3.15	0.04	No exchange
79	9-Methoxyfluorene	15.3	H_2SO_4, 100 mg.	110	116	3.17	3.03		Decomposition
57	9-Aminofluorene	8.3		110	96	3.10	2.58		Decomposition
58	9-Aminofluorene	11.0	NaOH, 2 mg.	110	115	3.10	2.30		Decomposition
59	9-Aminofluorene	8.3	H_2SO_4, 70 mg.	110	97	3.10	2.55		Decomposition
69	9-Dimethylaminofluorene	9.5	—	110	97	3.17	2.46		Decomposition
70	9-Dimethylaminofluorene	9.5	NaOH, 1 mg.	110	97	3.17	2.64		Decomposition
71	9-Dimethylaminofluorene	9.5	H_2SO_4, 70 mg.	110	96	3.17	2.45		Decomposition

number ranging from 1.9 to 2.0, and which were therefore not quite decisive on the question as to whether two or three hydrogens are involved. The exchange of indene has been reinvestigated by Eberly,[9] working with indene samples which have been more highly purified and with sodium ethylate as a catalyst, and he has obtained the value 2.5 for the exchange number, which is in accord with a value of three for the number of exchangeable hydrogen atoms.

Our study of compounds of this type has been extended to include a number of derivatives of fluorene in which the substituents occupy the 9 position. The results are tabulated in Table II. 9-Fluorenol, as might be expected, exchanges one hydrogen in neutral solution. In alkaline solution a second hydrogen atom exchanges, presumably the hydrogen atom at the 9 position. In acid solutions of comparable strength the compound decomposes rapidly, forming dibiphenyleneethylene. 9-Methoxyfluorene also decomposes in acid solution, but, in contrast to the behavior of 9-fluorenol, no exchange was observed in either neutral or alkaline solution. Thus, while the presence of a hydroxyl group appears to have no very marked effect on the lability of the remaining hydrogen atom on the 9 position, a methoxy group has a very pronounced inhibiting effect. The corresponding 9-amino and 9-dimethylamino compounds were investigated but it was found that these substances decomposed in both neutral and alkaline solutions, as well as in acid solution, the decomposition product being in each instance dibiphenyleneethane.

In connection with the supposed steric hindrance in the reactions of acetomesitylene, we have been interested in comparing the hydrogen exchange of this substance with acetophenone. It is to be expected that the exchange reactions of these ketones, like enolization reactions, would be subject to catalysis by both acids and bases. This type of behavior has been observed previously in the exchange reactions of acetone and cyclohexanone. The experimental results for acetophenone and acetomesitylene are included in Table II, and it is evident that these reactions are also subject to catalysis by both acids and bases. The exchange reaction of mesitylene takes place to a greater extent than the corresponding reaction of acetophenone, the difference being particularly noticeable in neutral solution where, under the experimental conditions adopted, the acetomesitylene exchange is about 50 per cent. complete while the exchange of acetophenone is about 5 per cent. complete. These results indicate that the process of enolization in acetomesitylene, whether acid- or base-catalyzed, is appreciably faster than in acetophenone. Kohler and Baltzly[10], in a study of the reactions of acetomesitylene, came to the con-

[9] EBERLEY, Doctor's Dissertation, University of Chicago, **1938.**

[10] KOHLER AND BALTZLY, *J. Am. Chem. Soc.*, **54,** 4015 (1932).

clusion that the failure of this substance to exhibit the normal addition reactions of ketones is due to steric hindrance and not to a greater tendency toward enolization for which they could find no evidence. Our results do not necessarily invalidate their conclusion, but we prefer to regard the lower reactivity of acetomesitylene in carbonyl addition reactions, as well as its greater tendency toward enolization, as an effect due, in part at least, to the higher electronegativity of the mesityl radical as compared with the phenyl radical.

We include also in this report some further experiments on quinaldine. It was previously reported[1] that at 110° for 60 hours this substance exhibited exchange almost to the extent of three hydrogens. The lability of the methyl hydrogens in quinoline and related compounds is well known, and it could be anticipated on general chemical grounds that these hydrogens would be exchangeable under the influence of either acidic or basic catalysts. The occurrence of exchange without an added catalyst might indicate either that the base strength of quinoline is sufficient for a self-catalyzed exchange reaction or, in view of the probable high sensitivity of the substance to acid catalysis that the reaction mixture contained sufficient acid as an impurity to promote the reaction. On repeating the experiment with the latter possibility in mind, we have confirmed the previous result with regard to the occurrence of a reaction without added catalyst, but not with regard to the extent of the reaction. The exchange now observed at 110° for 106 hours corresponds to the exchange of somewhat less than one hydrogen. That the reaction is subject to acid catalysis is shown by the results from experiments carried out at room temperature. Here in the absence of added catalyst no exchange occurs, but when a relatively small amount of sulfuric acid is added exchange takes place.

EXPERIMENTAL RESULTS

The experimental procedure has been, as before, to prepare mixtures of the substance under investigation, deuteroalcohol, and the catalyst, in evacuated tubes which were then sealed and placed in a thermostat for a specified period of time. At the end of this period the tubes were re-attached to the vacuum line, the break-seals opened, and the alcohol recovered from the mixtures by vacuum distillation. The deuterium content of the alcohol samples was determined by density measurements on water formed in the combustion of the alcohol.

Some improvements have been made in the analytical procedure, particularly in the procedure for the combustion of the alcohol samples. The combustion was originally carried out using a small alcohol lamp operating in a stream of dry air and adjusted to give a blue flame. The resulting gas was passed over a heated copper oxide catalyst to complete the combustion and then through a cooled trap where the water was collected. In

the present work the alcohol lamp was retained, but with the substitution of a sintered glass wick for the original asbestos wick, and the copper oxide catalyst was replaced by a platinum catalyst supported on a granular fused quartz. These changes were made with a view toward reducing errors caused by contamination of the sample by adsorbed water. The sequence of operations in the purification of the water samples has been altered by including a period of heating with freshly precipitated silver oxide subsequent to distillation from alkaline permanganate. As a result of these changes it has been possible to reduce the analytical errors to about half their former magnitude. The errors have been rendered still less signifi-

TABLE III

EXCHANGE REACTIONS OF ADDITIONAL SUBSTANCES

REF. NO.	SUBSTANCE	M-MOLES.	CATALYST	TEMP., °C.	TIME HRS.	INITIAL D_2O	FINAL D_2O	EXCH. NO.
109	Acetophenone	42.6		110	97	3.00	2.81	0.14
114	Acetophenone	42.6	NaOH, 2 mg.	110	96	3.00	1.45	2.15
111	Acetophenone	42.6	H_2SO_4, 140 mg.	110	112	3.00	1.64	1.63
88	Acetomesitylene	29.8		110	96	3.17	2.24	1.20
89[a]	Acetomesitylene	29.8	NaOH, 2 mg.	110	97	3.17	1.70	2.49
91	Acetomesitylene	29.8	H_2SO_4, 140 mg.	110	97	3.17	1.80	2.10
16	Quinaldine	36.3		110	96	3.43	2.67	0.67
36	Quinaldine	36.3		25	24	3.10	2.98	0.09
50	Quinaldine	36.3		25	167	3.10	3.01	0.07
51	Quinaldine	36.3	H_2SO_4, 140 mg.	25	24	3.10	2.68	0.29
66[b]	Styrene	45.2		110	100	3.17	2.39	0.62
67[c]	Styrene	45.2	NaOH, 2 mg.	110	97	3.17	2.67	0.28
65[c]	Styrene	45.2	H_2SO_4, 140 mg.	110	106	3.17	2.83	0.17

[a] Exchange 3H's.

[b] Some polymerization.

[c] Extensive polymerization.

cant by the use of alcohol of higher deuterium content. In the determination of the deuterium content of water samples by the float-temperature method, the floating temperature was observed with a thermometer reading directly to 0.1° and permitting estimation to within 0.01°.

The extent of the exchange reaction is indicated in the tables of results (Tables I–III) under the heading of "exchange number." This is calculated from the experimental data by means of the following equation:

$$n = \frac{a}{s}\left(\frac{D_1}{D_2} - 1\right)$$

where n is the exchange number, s is the number of moles of substance, a is the number of moles of alcohol, and D_1 and D_2 represent the initial and final concentrations of deuterium in the alcohol.

In an idealized case, namely one in which equilibrium has been established, and in which the partition coefficient for the distribution of deuterium is equal to unity, the exchange number, as defined by the above equation, would be equal to the number of hydrogen atoms per molecule taking part in the exchange reaction. Actually the distribution of deuterium is not a purely statistical one, and fractional values for the exchange numbers are to be expected. In exchange reactions involving C—H hydrogens the deviations are such that the deuterium shows a slight preference for the alcoholic linkage and in such cases the observed exchange numbers are less than the theoretical values for the number of exchangeable hydrogen atoms. These effects can be interpreted, qualitatively at least, on the basis of the differences in zero-point energies of vibration.

In the tables of results the deuterium concentrations given are the concentrations of deuterium in the water samples (as D_2O, in mole per cent.) formed in the combustions. The values were obtained directly from the calibration curve for the quartz float, and since only the ratio of initial to final concentrations enters into the calculation of the exchange number it is not necessary to convert the D_2O concentrations to C_2H_5OD concentrations.

Small corrections were applied in the calculation of the exchange numbers for the exchange reactions of dimethylaniline derivatives catalyzed by sulfuric acid, the correction being necessitated by the dilution of the deuteroalcohol by the light hydrogen of the sulfuric acid. These corrections were not applied to the corresponding data for diphenylamine and triphenylamine, as some uncertainty existed as to whether it should be applied. In the former cases the alcohol recovered from the reaction mixtures was treated with phosphorous pentoxide, primarily to remove traces of amines, but this treatment also served to remove water. In the experiments on diphenylamine and triphenylamine the alcohol was not so treated and could have contained an amount of water equivalent to the amount of sulfuric acid originally added. This would result in an increased concentration of deuterium in the water of combustion and hence introduce an error opposite in direction to that caused by the dilution of the deuteroalcohol with sulfuric acid.

MATERIALS

Deuteroalcohol.—Deuteroalcohol was prepared, as in the previous work by means of the rapid exchange reaction between ethyl alcohol and deuterium oxide. After mixing absolute alcohol and the desired quantity of deuterium oxide, the alcohol was dried by repeated treatments with freshly ignited calcium oxide. The proportions of alcohol to deuterium oxide were chosen so as to yield a product containing approximately 20 mole per cent. C_2H_5OD.

Dimethylaniline.—Commercial dimethylaniline was twice distilled over sodium, a fraction, b.p. 190–192°, being collected on the second distillation.

Diphenylamine.—Recrystallized from ethyl acetate, decolorized in hot alcoholic solution with Norite, distilled three times at 6 mm. pressure, m.p. 54°–55°.

Triphenylamine.—Purified by vacuum distillation, m.p. 126.5°.

p-*Nitrodimethylaniline.*—From *p*-nitroaniline on methylation with dimethyl sulfate. Product purified according to the method of Davies[11] m.p. 162°.

m-*Nitrodimethylaniline.*—By the nitration of dimethylaniline according to the method of Nölting and Faurneau[12]. Purified by vacuum distillation and recrystallizations from alcohol, yielding a product of constant melting point, 61° (literature, 66°).

m-*Bromodimethylaniline.*—This compound was prepared in 15% yield by the action of dimethyl sulfate on *m*-bromoaniline[13]. The product reacted very slightly with acetyl chloride and may therefore have been contaminated with the monomethyl derivative. The erratic experimental results for the hydrogen exchange in neutral solution likewise indicate that the compound was not of satisfactory purity, but these results could not be accounted for by the presence of the monomethyl compound. The fact that no exchange occurred when a small amount of sodium hydroxide had been added (expt. 53) suggests that the observed exchange in neutral solution (expts. 54, 75) was a result of catalysis by an acidic impurity.

o-*Nitrodimethylaniline.*—Samples prepared by the methylation of *o*-nitroaniline with dimethyl sulfate were unsatisfactory because of contamination by the monomethyl derivative. A satisfactory product was obtained by the action of dimethylamine on *o*-chloronitrobenzene[14]. Red oil; b.p. 157–158°/20 mm.

Fluorene.—Purified by repeated recrystallization from alcohol, m.p. 112°.

9-Fluorenol.—Prepared from fluorenone by reduction with zinc dust and ammonia[15]. The product was isolated from the reaction mixture by extraction with alcohol, and after several recrystallizations from alcohol was sublimed *in vacuo*, m.p. 152°.

The decomposition of fluorenol under the influence of sulfuric acid (expt. no. 39) resulted in the formation of an orange solid, m.p. 186–191°, probably dibiphenyleneethylene (m.p. 189–190°). In expt. 93, in which fluorenol was treated in solution in deuteroalcohol with a relatively large amount of sodium hydroxide (1 mole) the solution became deep red in color, and from it was isolated a pale yellow solid, m.p. 116°, probably fluorene.

9-Methoxyfluorene.—From 9-chlorofluorene on treatment with silver nitrate in methyl alcohol solution. After separation of the silver chloride precipitate by filtration, the alcohol was evaporated, and the product taken up in ligroïn, from which it was obtained in large yellow crystals, m.p. 41° (literature, 43°); mol. wt. (in cyclopentadecanone), found 192, calc'd 196. The color of this material was probably due to traces of dibiphenyleneethylene. In the exchange experiments on this substance, no decomposition occurred in neutral or alkaline solution, but extensive decomposition occurred in acid solution. The product was a solid insoluble in alcohol and in ligroïn; it decomposes gradually on heating above 145°.

9-Aminofluorene.—By reduction of fluorenone oxime by zinc dust in acetic acid[16].

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[11] DAVIES, *Bull. soc. chim.*, [5], **2**, 295–96 (1935).

[12] NÖLTING AND FOURNEAU, *Ber.*, **30**, 2931 (1897).

[13] KHARASCH AND PICCARD, *J. Am. Chem. Soc.*, **42**, 1855 (1920).

[14] LEFEVRE, *J. Chem. Soc.*, **1930**, 149.

[15] WERNER AND GROB, *Ber.*, **37**, 2895 (1904).

[16] INGOLD AND WILSON, *J. Chem. Soc.*, **1933**, 1499.

The product was purified by extraction with ligroïn in a closed system, and was obtained on evaporation of the ligroïn as light-brown crystals, m.p. 63°.

The product of the decomposition of α-aminofluorene in neutral solution was a colorless solid, m.p. 231–235°; mol. wt. found 335, calc'd for dibiphenyleneethane, 330. *Anal.*: found, C, 94, 21; H, 6.06; calc'd for dibiphenyleneethane, C, 94.6; H, 5.4. The decomposition in acid solution (expt. 59) yielded a similar product, m.p. 240°, while the decomposition in the presence of alkali (expt. 58) yielded an impure material, m.p. 175–185°.

9-Dimethylaminofluorene.—From 9-aminofluorene hydrochloride on treatment with methyl alcohol at 115° for 96 hours in sealed tubes. Recrystallized from ligroïn, m.p. 54°; recorded melting point 49°. The crystals, originally colorless, became greenish on keeping. The materials recovered from the exchange reaction mixtures were similar to those obtained with 9-aminofluorene and probably consisted chiefly of dibiphenyleneethane.

Acetomesitylene.—From mesitylene and acetyl chloride[17]; b.p. 156°/53 mm.

Quinaldine.—Purified by multiple vacuum distillation; b.p. 244.5°.

ACKNOWLEDGMENT

The authors wish to acknowledge many helpful discussions of the theory of the ortho effect with Drs. G. W. Wheland and F. H. Westheimer of this department.

SUMMARY

1. Previous discussion of the probable mechanism of certain hydrogen-deuterium exchange reactions has been amplified and extended.

2. Preliminary experimental results previously reported have been re-checked and supplemented.

3. Further experimental implications of the mechanism postulated have been pointed out.

4. The results of additional experiments are reported and are shown to be consistent with the mechanism proposed.

5. An ortho effect appears in the hydrogen-deuterium exchange reactions of ortho-substituted dimethylanilines. A tentative explanation has been advanced.

[17] GILMAN, "Organic Syntheses," Coll. vol. I., John Wiley and Sons, **1925**, p. 334.

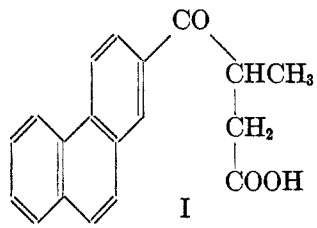
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE SYNTHESIS OF DERIVATIVES OF CHRYSENE

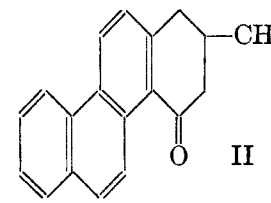
W. E. BACHMANN AND W. S. STRUVE*

Received April 29, 1939

Three years ago[1] we described the preparation of β-(2-phenanthroyl)-butyric acid (I), which we prepared from 2-propionylphenanthrene as an intermediate in the synthesis of 2-methylchrysene (IV)†. We have now completed the projected synthesis, using the well-known steps of the



I



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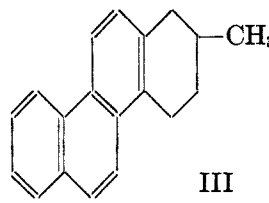
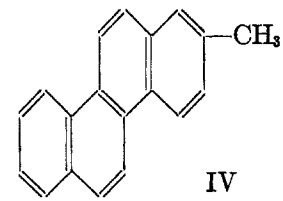


III



IV

Haworth method.[2] Clemmensen reduction of the acid yielded γ-(2-phenanthryl)-β-methylbutyric acid, which was cyclized in the form of its acid chloride by means of stannic chloride. Under the conditions employed cyclization took place nearly entirely from the 2 to the 1 position with the formation of 2-methyl-4-keto-1,2,3,4-tetrahydrochyrsene (II), although there appeared to be present some of the cyclic ketone formed by cyclization to the 3 position. 2-Methyltetrahydrochrysene (III) was obtained from the cyclic ketone by Clemmensen reduction, and the resulting hydrocarbon was dehydrogenated smoothly to 2-methylchrysene by palladium on charcoal. The 2- and 3-propionylphenanthrenes, which we

* From the Ph.D. dissertation of W. S. Struve.

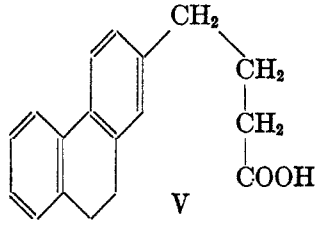
† The numbering system for the chrysene molecule is that used in the index of *Chemical Abstracts*.

[1] BACHMANN AND STRUVE, *J. Am. Chem. Soc.*, **58**, 1659 (1936).

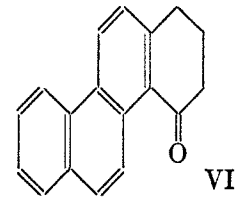
[2] HAWORTH, *J. Chem. Soc.*, **1932**, 1125.

had prepared from phenanthrene and propionyl chloride, have now been reduced by the Clemmensen method to the corresponding 2-*n*-propylphenanthrene and 3-*n*-propylphenanthrene.

We have also prepared 4-methylchrysene (VIII) from the cyclic ketone, 4-keto-1,2,3,4-tetrahydrochrysene (VI). The latter compound was made by Haworth[3] from 2-acetylphenanthrene. We have made use of the γ-[2-(9,10-dihydrophenanthryl)]-butyric acid (V) of Burger and Mosettig,[4,5] which is readily obtained by Clemmensen reduction of the corresponding keto acid, which in turn can be prepared in excellent yields by interaction of 9,10-dihydrophenanthrene and succinic anhydride. The dihydrophenan-



V



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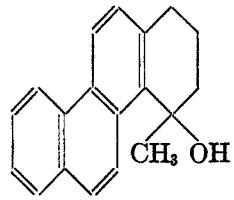
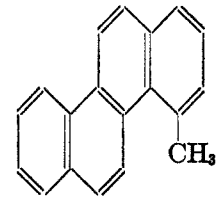


VII



VIII

thrylbutyric acid was dehydrogenated in the form of its methyl ester with palladium on charcoal at a relatively low temperature (240–260°) in excellent yields (90–95 per cent.). At this temperature the hydrogen was eliminated rapidly and the yield was much higher than was the case when the free acid or its methyl ester was dehydrogenated at a higher temperature (300–320°), the yield under these conditions being only 20–40 per cent.

The γ-(2-phenanthryl)butyric acid was cyclized by treating the acid chloride in benzene solution in the cold with stannic chloride. This procedure gives the 4-keto-1,2,3,4-tetrahydrochrysene in better yields than the Haworth[3] method of cyclization with sulfuric acid and does not require repeated recrystallizations in order to obtain the cyclic ketone in a pure form. When the cyclization was carried out at room temperature, a

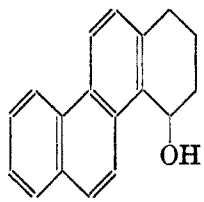
[3] HAWORTH AND MAVIN, *ibid.*, **1933**, 1013.
[4] BURGER AND MOSETTIG, *J. Am. Chem. Soc.*, **59**, 1302 (1937).
[5] FIESER AND JOHNSON, *ibid.*, **61**, 168 (1939).

mixture of cyclic ketones was obtained which probably contained the isomeric compound formed by cyclization to the 3 position, although no attempt was made to isolate the product. Clemmensen reduction of the 4-ketotetrahydrochrysene yielded a crystalline tetrahydrochrysene, which could be dehydrogenated to chrysene by palladium on charcoal at a temperature of 300–320°.

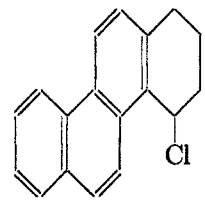
4-Methyl-4-hydroxy-1,2,3,4-tetrahydrochrysene (VII) was prepared by interaction of the cyclic ketone with methylmagnesium iodide. The crystalline carbinol was simultaneously dehydrated and dehydrogenated to 4-methylchrysene in 92 per cent. yield by the action of palladium on charcoal, the method used successfully by Bachmann and Wilds[6] on a number of carbinols. Unlike the parent hydrocarbon, 4-methylchrysene forms a relatively stable picrate in alcohol. The 4-methylchrysene is being tested for carcinogenic activity.

1,2-Dihydrochrysene (XI) was obtained in two ways. 4-Ketotetrahydrochrysene was heated with an excess of aluminum isopropoxide in *n*-propyl alcohol according to the procedure of Lund,[7] but under these conditions no reduction took place. When the reaction was carried out in boiling toluene solution the corresponding carbinol, 4-hydroxy-1,2,3,4-tetrahydrochrysene (IX), was obtained in good yield. When xylene was substituted for toluene, the carbinol was obtained in two runs; in six other runs the product was 1,2-dihydrochrysene. It appears that prolonged heating at the temperature of the boiling xylene resulted in the splitting off of basic aluminum isopropoxide with the formation of the dihydrochrysene.

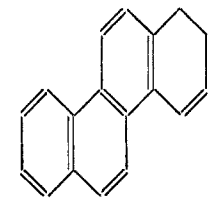
The 4-hydroxytetrahydrochrysene readily forms a methyl ether by the action of methanol containing a small amount of sulfuric acid and gives an acetate with acetic anhydride in pyridine. By treatment of a benzene solution of the carbinol with hydrogen chloride gas the carbinol yielded 4-chlorotetrahydrochrysene (X). 1,2-Dihydrochrysene can be obtained from the chloride by treatment with pyridine at the boiling point of the solution.



IX



X



XI

[6] BACHMANN AND WILDS, *ibid.*, **60**, 624 (1938).

[7] LUND, *Ber.*, **70**, 1520 (1937).

As was expected, the dihydrochrysene is readily dehydrogenated to chrysene.

Experiments are in progress on the condensation of the 4-chlorotetrahydrochrysene with sodio-malonic ester. With the acetic acid group in the 4 position it should be possible to prepare derivatives of 3,4-benzpyrene by cyclization of the acid and treatment of the cyclic ketone with various reagents.

EXPERIMENTAL

γ-(2-Phenanthryl)-β-methylbutyric acid.—A mixture of 2 g. of β-(2-phenanthroyl)-butyric acid (I), 5 g. of amalgamated zinc, 7.5 cc. of acetic acid, 7.5 cc. of concentrated hydrochloric acid, and 4 cc. of toluene was refluxed for thirty six hours. An additional 10 cc. of concentrated hydrochloric acid was added in portions over this time. The toluene layer was separated, the toluene was evaporated, and the oily residue was sublimed at 250° and 0.4 mm. The sublimate was crystallized from benzene-petroleum ether (b. p. 60–75°), as fine colorless prisms; weight, 0.96 g. (50%); m. p. 120–125°. After two further crystallizations from benzene-petroleum ether the melting point was raised to 127.5–129°.

Anal. Calc'd for $C_{19}H_{18}O_2$; C, 82.0; H, 6.5.
Found: C, 82.3; H, 6.7.

2-Methyl-4-keto-1,2,3,4-tetrahydrochrysene (II).—Four-tenths gram of γ-(2-phenanthryl)-β-methylbutyric acid was suspended in a mixture of 5 cc. of absolute ether and 1 drop of pyridine. When 1 cc. of thionyl chloride was added, the acid rapidly went into solution. After the solution had stood for a half-hour at room temperature, the ether and thionyl chloride were removed under reduced pressure. The acid chloride was dissolved in 5 cc. of dry benzene, the solution was cooled to 0°, and 0.75 cc. of stannic chloride was then added with swirling. After standing for fifteen minutes in the cold, the complex was hydrolyzed with ice and dilute hydrochloric acid. The benzene layer was washed with water, dilute ammonium hydroxide, and again with water. The benzene was evaporated, and the keto compound was crystallized from alcohol-acetone; weight, 0.32 g. (86%); m. p. 129–133°. After two recrystallizations from benzene-petroleum ether the melting point was 141–142°.

Anal. Calc'd for $C_{19}H_{16}O$: C, 87.7; H, 6.2.
Found: C, 87.3; H, 6.2.

2-Methyl-1,2,3,4-tetrahydrochrysene (III).—A mixture of 0.23 g. of 2-methyl-4-keto-1,2,3,4-tetrahydrochrysene, 5 g. of amalgamated zinc, 7.5 cc. of acetic acid, 7.5 cc. of concentrated hydrochloric acid, and 2 cc. of toluene was refluxed for twenty-four hours. The toluene layer was separated, the toluene was evaporated, and the residue was sublimed at 200° and 0.4 mm.; weight 0.18 g. (83%); m. p. 137–140°. After two crystallizations from acetone-alcohol the hydrocarbon melted at 141.5–142°. It first comes down as very thin leaflets which turn to thin prisms on standing in contact with the mother liquor. Both forms appear to have the same melting point.

Anal. Calc'd for $C_{19}H_{18}$: C, 92.7; H, 7.3.
Found: C, 92.3; H, 7.3.

The *hemi-picrate* crystallizes from alcohol-acetone as reddish-orange needles; m. p. 145–5–146°.

Anal. Calc'd for $2C_{19}H_{18}\cdot C_6H_3N_3O_7$: N, 5.8. Found: N, 6.0.

2-Methylchrysene (*IV*).—A mixture of 0.18 g. of 2-methyl-1,2,3,4-tetrahydrochrysene and 0.03 g. of palladium-charcoal catalyst[3] was heated at 300–320° for one hour. The mixture was taken up in hot benzene and filtered. The benzene was evaporated, and the residue was crystallized from alcohol-acetone; weight, 0.16 g. (90%); m. p. 224–225°. Two further crystallizations gave colorless leaflets from benzene-alcohol; m. p. 224.5–225.5° (229–230° corr.).

Anal. Calc'd for $C_{19}H_{14}$: C, 94.2; H, 5.8.
Found: C, 94.5; H, 5.9.

The rather unstable *picrate* crystallizes from alcohol in the form of golden-yellow needles; m. p. 143–146°.

Anal. Calc'd for $C_{19}H_{14}\cdot C_6H_3N_3O_7$: N, 8.9. Found: N, 9.1.

2-n-Propylphenanthrene.—A mixture of 2 g. of 2-propionylphenanthrene, 4 g. of amalgamated zinc, 6 cc. of acetic acid, 6 cc. of concentrated hydrochloric acid, and 4 cc. of toluene was refluxed for twenty-four hours. An additional 5 cc. of concentrated hydrochloric acid was added over that time. The toluene layer was separated, and the toluene was evaporated. The oily residue, which did not crystallize, was dissolved in alcohol, and 3 g. of picric acid was added. On cooling, 3.2 g. of 2-*n*-propylphenanthrene picrate deposited; yield, 83%; m. p. 84–88°. The picrate was recrystallized twice from alcohol and then decomposed with dilute sodium hydroxide solution. The oil formed was taken up in benzene, the benzene layer was separated, the benzene was evaporated, and the residue was sublimed. The sublimate crystallized from alcohol-acetone in colorless leaflets; m. p. 35–36°.

Anal. Calc'd for $C_{17}H_{16}$: C, 92.7; H, 7.3.
Found: C, 92.6; H, 7.4.

The *picrate* crystallizes from alcohol in yellow needles; m. p. 92–93°.

Anal. Calc'd for $C_{17}H_{16}\cdot C_6H_3N_3O_7$: N, 9.4. Found: N, 9.4.

3-n-Propylphenanthrene.—Two grams of 3-propionylphenanthrene was reduced and worked up in the same way as the 2-propionylphenanthrene; weight of picrate, 2.98 g. (77%); m. p. 104–107°. By hydrolysis of the pure picrate, the 3-*n*-propylphenanthrene was obtained as a colorless oil which failed to crystallize, even when cooled to a low temperature.

Anal. Calc'd for $C_{17}H_{16}$: C, 92.7; H, 7.3.
Found: C, 93.1; H, 7.4.

The *picrate* crystallizes from alcohol as clusters of orange needles; m. p. 107–108°.

Anal. Calc'd for $C_{17}H_{16}\cdot C_6H_3N_3O_7$: N, 9.4. Found: N, 9.5.

γ-[2-(9,10-Dihydrophenanthryl)] butyric acid (*V*).—A mixture of 48 g. of β-[2-(9,10-dihydrophenanthroyl)]propionic acid, 100 g. of amalgamated zinc, 150 cc. of acetic acid, 150 cc. of concentrated hydrochloric acid, and 80 cc. of toluene was refluxed for twenty hours. An additional 100 cc. of concentrated hydrochloric acid was added in portions over this time. The toluene layer was separated, the toluene was evaporated, and the residue was distilled in a vacuum. The distillate crystallized from dilute alcohol in colorless needles; yield, 42 g. (92%); m. p. 91–92°. This yield is somewhat higher than that reported by Burger and Mosettig[4] who employed slightly different conditions.

γ-(2-Phenanthryl)butyric acid.—A stream of dry hydrogen chloride gas was passed into an ice-cold solution of 10 g. of γ-[2-(9,10-dihydrophenanthryl)] butyric acid in 300 cc. of methanol for a half hour. The solution was refluxed for an hour, and dry hydrogen chloride was again passed in the cooled solution for a half hour. After refluxing the solution again for an hour, most of the methanol was distilled, and

[3] ZELINSKY AND TUROWA-POLLAK, *ibid.*, **58**, 1295 (1925).

benzene was added. The benzene solution of the methyl ester was washed twice with water, and the benzene was distilled. The oily residue was dehydrogenated with 1 g. of palladium-charcoal catalyst at 240–260° for two hours. The mixture was taken up in benzene, and the catalyst was removed by filtration. The benzene was evaporated, and the ester was hydrolyzed with hot 40% potassium hydroxide solution. The hydrolysis mixture was diluted and acidified with concentrated hydrochloric acid. The precipitated acid was collected by filtration and crystallized from benzene as colorless plates; weight, 9.0–9.5 g. (90–95%, based on the dihydro acid); m. p. 133–134°. Haworth and Mavin[3] report the melting point of this acid to be 134–135°. The recovered catalyst can be used for the dehydrogenation of a second run of ester with no apparent decrease in activity.

4-Keto-1,2,3,4-tetrahydrochrysene (VI).—To a suspension of 13.5 g. of γ-(2-phenanthryl)butyric acid in 100 cc. of dry ether and 5 drops of pyridine was added 30 cc. of thionyl chloride. The mixture was swirled until the acid had gone into solution, and was then allowed to stand at room temperature for a half-hour. The ether and thionyl chloride were evaporated under reduced pressure, and the acid chloride was dissolved in 100 cc. of benzene. The benzene solution was cooled to 0° and 22 cc. of stannic chloride was added with swirling. After standing for fifteen minutes in the cold, the complex was decomposed with ice and dilute hydrochloric acid. The benzene layer was washed with water, dilute ammonium hydroxide, and again with water. The benzene was evaporated, and the keto compound was crystallized from alcohol as light tan prisms; yield, 9.36 g. (74%); m. p. 122–124°. After two crystallizations and treatment with activated alumina, colorless prisms, m. p. 125–126°, were obtained. Haworth and Mavin[3] report the melting point of this compound as 124–125°.

4-Methyl-4-hydroxy-1,2,3,4-tetrahydrochrysene (VII).—To a Grignard reagent made from 0.25 g. of magnesium, 0.75 cc. of methyl iodide, and 10 cc. of absolute ether were added 1 g. of 4-keto-1,2,3,4-tetrahydrochrysene and 10 cc. of dry benzene. The mixture was allowed to stand in the cold for twelve hours and was then decomposed with ice and ammonium chloride solution. The benzene-ether layer was separated, filtered, and then allowed to evaporate in an evaporating dish at room temperature. The methyl carbinol crystallized upon evaporation of the solvent as colorless prisms; weight, 0.87 g. (82%); m. p. 123.5–125°. After two recrystallizations from benzene-petroleum ether, the carbinol melted at 124–125°.

Anal. Calc'd for $C_{19}H_{18}O$: C, 87.0; H, 6.9.
Found: C, 87.5; H, 7.0.

4-Methylchrysene (VIII).—Six-tenths gram of 4-methyl-4-hydroxy-1,2,3,4-tetrahydrochrysene was heated with 0.06 g. of palladium-charcoal catalyst at 300–320° for one hour. The mixture was taken up in hot benzene and filtered. The hydrocarbon obtained from the residue crystallized from benzene-petroleum ether as colorless leaflets; weight, 0.51 g. (92%); m. p. 146–148°. After two recrystallizations from benzene-petroleum ether the melting point was 149–149.5° (151–151.5° corr.).

Anal. Calc'd for $C_{19}H_{14}$: C, 94.2; H, 5.8.
Found: C, 94.0; H, 5.6.

The *picrate* crystallizes from alcohol as bright-red needles; m. p. 134–135°.

Anal. Calc'd for $C_{19}H_{14}\cdot C_6H_3N_3O_7$: N, 8.9. Found: N, 9.0.

4-Hydroxy-1,2,3,4-tetrahydrochrysene (IX).—A solution of aluminum isopropoxide was prepared by refluxing a mixture of 1 g. of aluminum wire, 25 cc. of dry isopropyl alcohol, 5 drops of carbon tetrachloride, and a pinch of mercuric chloride. After the aluminum had dissolved, the isopropyl alcohol was distilled, and 2.75 g. of 4-keto-

1,2,3,4-tetrahydrochrysene and 25 cc. of toluene were added. The mixture was refluxed for four hours, 25 cc. of isopropyl alcohol was added and then distilled from the mixture. The toluene solution was cooled, and the aluminum salt was decomposed with cold 10% sulfuric acid. The toluene layer was separated, washed with dilute ammonium hydroxide, and evaporated in the cold. The carbinol separates as colorless silky needles; yield, 2.10 g. (76%); m. p. 156–158°. Two recrystallizations from benzene-petroleum ether raised the melting point to 160–162°. The carbinol gives a black color with sulfuric acid.

Anal. Calc'd for $C_{18}H_{16}O$: C, 87.1; H, 6.5.
Found: C, 87.5; H, 6.3.

4-Methoxy-1,2,3,4-tetrahydrochrysene.—To a solution of 0.05 cc. of concentrated sulfuric acid in 5 cc. of methanol was added 0.3 g. of 4-hydroxy-1,2,3,4-tetrahydrochrysene. The mixture was shaken occasionally, and after about a half-hour all the carbinol had gone into solution. The solution was allowed to stand overnight, then poured into a mixture of benzene and aqueous sodium carbonate. The benzene layer was separated, washed with water, filtered, and evaporated. The methyl ether crystallizes from methanol in colorless rhombic prisms; weight, 0.27 g. (86%); m. p. 79–80.5°.

Anal. Calc'd for $C_{19}H_{18}O$: C, 87.0; H, 6.9.
Found: C, 87.0; H, 6.8.

4-Acetoxy-1,2,3,4-tetrahydrochrysene.—Three-tenths gram of 4-hydroxy-1,2,3,4-tetrahydrochrysene was added to a solution of 0.3 cc. of pyridine and 0.6 cc. of acetic anhydride, and the mixture was heated on a steam bath for one hour. The acetic anhydride and the pyridine were then evaporated on a steam bath in a current of air, and the residue was dissolved in benzene. The benzene solution was washed with dilute ammonium hydroxide, water, dilute hydrochloric acid, and again with water. The acetate obtained from the benzene solution crystallized from petroleum ether in leaflets; yield, 0.30 g. (86%); m. p. 119–120.5°.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 82.8; H, 6.2.
Found: C, 83.2; H, 6.4.

4-Chloro-1,2,3,4-tetrahydrochrysene (*X*).—A stream of dry hydrogen chloride gas was passed into a cold solution of 0.2 g. of 4-hydroxyl-1,2,3,4-tetrahydrochrysene in 10 cc. of dry benzene with 0.5 g. of calcium chloride suspended in it. The mixture turned cloudy almost immediately. After hydrogen chloride had been passed in for ten minutes the mixture was allowed to stand at room temperature for one hour, by which time the solution had again become clear. Evaporation of the benzene left a crystalline residue of the chloride. The latter crystallizes from benzene-petroleum ether in colorless, diamond-shaped prisms; yield, 0.17 g. (80%); it melts at 115–117° with decomposition, evolving hydrogen chloride. The melt solidifies and remelts at 174–178°.

Anal. Calc'd for $C_{18}H_{15}Cl$: Cl, 13.3. Found: Cl, 13.1.

1,2-Dihydrochrysene (*XI*).—A solution of 0.1 g. of 4-chloro-1,2,3,4-tetrahydrochrysene and 3 cc. of pyridine was refluxed for fifteen minutes; benzene and dilute hydrochloric acid were then added. The benzene solution was separated, washed with water, and the benzene was evaporated. The residue was sublimed at 200° and 0.4 mm. pressure; weight, 0.05 g. (58%); m. p. 181.5–183.5°. After two crystallizations from benzene-petroleum ether the colorless plates which were obtained melted at 182.5–184.5°.

Anal. Calc'd for $C_{18}H_{14}$: C, 93.9; H, 6.1.
Found: C, 93.4; H, 6.3.

The *picrate* forms bright-red needles from alcohol-acetone; m. p. 155–156°.

Anal. Calc'd for $C_{18}H_{14}\cdot C_6H_3N_3O_7$: N, 9.1. Found: N, 9.2.

1,2,3,4-Tetrahydrochrysene.—A mixture of 1 g. of 4-keto-1,2,3,4-tetrahydrochrysene, 4 g. of amalgamated zinc, 7 cc. of acetic acid, 7 cc. of concentrated hydrochloric acid, and 3 cc. of toluene was refluxed for twenty-four hours. An additional 5 cc. of concentrated hydrochloric acid was added in portions over this period. The toluene layer was separated, and the toluene was evaporated. The residue was sublimed at 200° and 0.4 mm.; weight, 0.56 g. (60%); m. p. 173–178°. After two crystallizations from benzene-petroleum ether, the hydrocarbon formed colorless leaflets; m. p. 180.5–181.5°.

Anal. Calc'd for $C_{18}H_{16}$: C, 93.1; H, 6.9.
Found: C, 92.9; H, 6.8.

The *picrate* formed orange needles from benzene containing an excess of picric acid; m. p. 134–135.5°.

Anal. Calc'd for $C_{18}H_{16}\cdot C_6H_3N_3O_7$: N, 9.3. Found: N, 9.1.

Chrysene.—(*a*) *From dihydrochrysene.*—A mixture of 0.43 g. of dihydrochrysene and 0.05 g. of palladium-charcoal catalyst was heated in a nitrogen atmosphere at 300–320° for one hour. The chrysene was taken up in benzene, and the solution was filtered to remove the catalyst. The benzene was evaporated, and the residue was crystallized from benzene, giving colorless, glistening leaflets; weight, 0.4 g. (93%); m. p. 247–249°. The hydrocarbon was also identified by means of its quinone.

(*b*) *From tetrahydrochrysene.*—A mixture of 0.32 g. of 1,2,3,4-tetrahydrochrysene and 0.04 g. of palladium-charcoal catalyst was treated as in part *a*; colorless, glistening leaflets; weight, 0.28 g. (87%); m. p. 247–249°.

SUMMARY

A number of new chrysene derivatives have been prepared from phenanthrene.

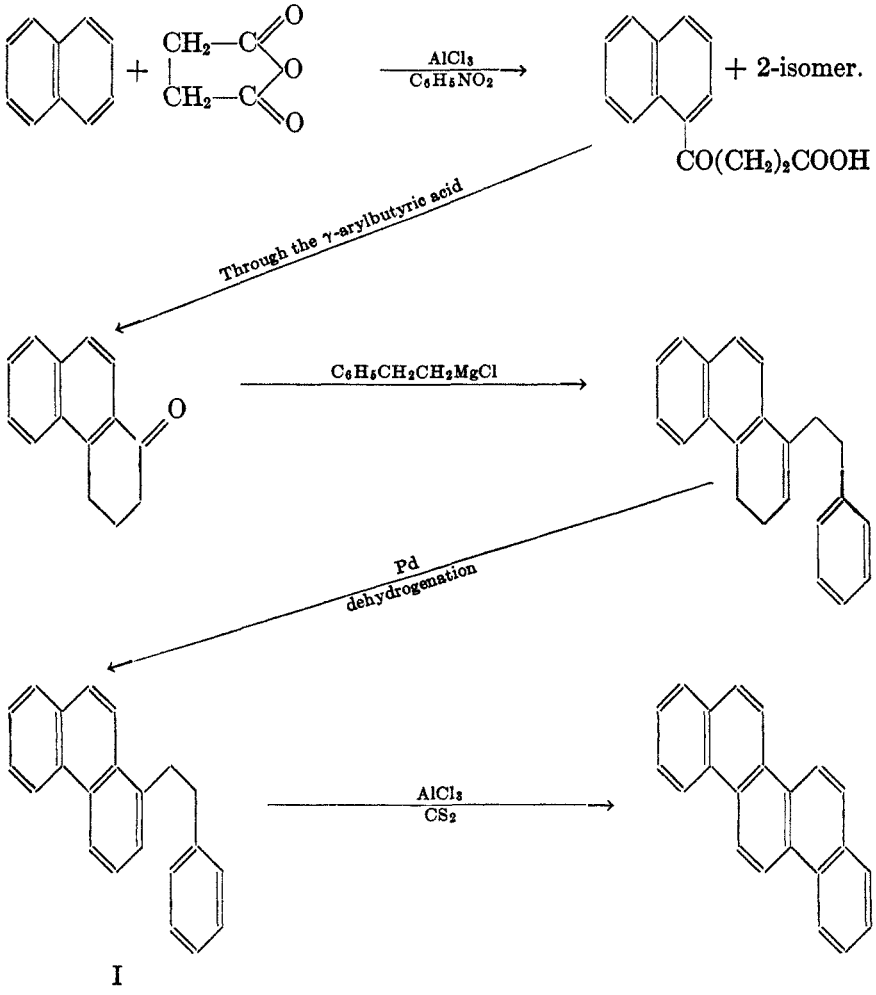
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MARYLAND]

A NEW SYNTHESIS OF PICENE*

NATHAN L. DRAKE AND WARREN C. McVEY

Received May 8, 1939

The occurrence of alkylated picenes among the products of dehydrogenation of many triterpenoids makes the synthesis of picene homologues of

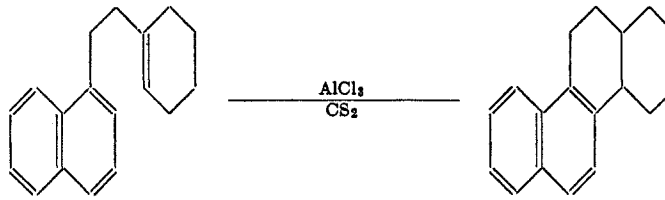


I

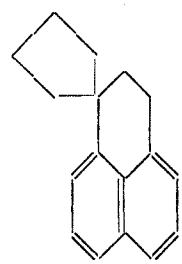
* Taken in part from the Ph.D. Dissertation of Warren C. McVey.

considerable interest. Certain polymethylated picenes have been synthesized by L. Ruzicka and co-workers[1] and 1,8-dimethylpicene has also been synthesized in our own laboratories[2]. The work to be described was undertaken with the object of devising a new picene synthesis which might prove useful in the preparation of alkylated picenes, and the method which we planned to employ can be summarized by the preceding formulas. However, when I, dissolved in carbon disulfide, was treated with anhydrous aluminum chloride in an attempt to bring about cyclization, only a tarry product was obtained, and no picene could be isolated.

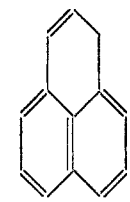
The method of cyclization depicted above, involving a compound containing only aromatic rings is not the one most frequently employed, but such a method has been employed successfully in the synthesis of 1,8-dimethylpicene[1, 2]. The more common procedure in syntheses of this general nature is to effect ring closure involving the unsaturation of a hydroaromatic ring and the hydrogen of an aromatic ring in the fashion set forth by the formulas:[3]



In carrying out the synthesis formulated above, Cook and Hewett observed the formation of a considerable quantity of a substance corresponding to the spirocyclopentane which they had earlier isolated during the synthesis of 1,2-cyclopentanophenanthrene, and which they considered to be 7,8-dihydrophenalyl-7-spirocyclopentane (II),



II



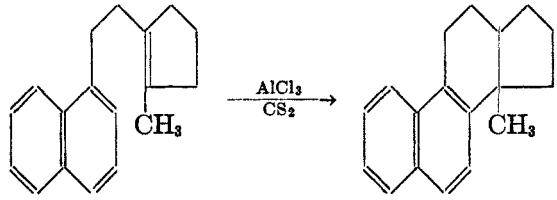
III

[1] RUZICKA AND HÖSLI, *Helv. Chim. Acta*, **17**, 470, (1934); RUZICKA AND MORGELI, *ibid.*, **19**, 377, (1936); RUZICKA AND HOFMANN, *ibid.*, **20**, 1155, (1937); **22**, 126, (1939).

[2] F. HOWARD, Thesis, University of Maryland, **1938**.

[3] COOK AND HEWETT, *J. Chem. Soc.*, **145**, 365 (1934).

a derivative of a substance to which Mayer and Seiglitz[4] had given the name "phenalene" (III). The presence of an alkyl group on the hydroaromatic ring where cyclization was expected to occur was shown by Cohen, Cook, Hewett, and Girard[5] to repress spirane formation to such an extent that a 97 per cent. yield was obtained in the cyclization (IV→V):

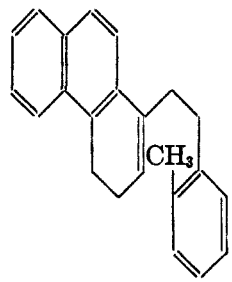


IV V

whereas the cyclization of 1-(β-1′-naphthylethyl)-Δ^1-cyclopentene[3] led to the formation of a mixture of products from which the pure picrate of 7,8-dihydrophenalylspirocyclopentane was isolated in 28 per cent. yield.

Inasmuch as we were unsuccessful in cyclizing I, we next turned to an examination of the behavior of 3,4-dihydro-1-phenethylphenanthrene when treated in carbon disulfide solution with aluminum chloride. Judging from the work of Cohen, Cook, Hewett, and Girard[5] one would expect considerable spirane formation in this reaction, and we found that the product was a viscous oil from which no pure substance could be isolated. However, from the products of dehydrogenation of the oil, picene could be obtained (yield 1 per cent.); the remainder of the oil was apparently not affected by the dehydrogenation (bath temperature 390–400°).

When 3,4-dihydro-1-(β-2′-tolylethyl)phenanthrene (VI)



VI

was treated in carbon disulfide with aluminum chloride, and the resultant product was dehydrogenated, only picene could be isolated from the

[4] Mayer and Seiglitz, *Ber.*, **55**, 1837 (1922).

[5] Cohen, Cook, Hewett, and Girard, *J. Chem. Soc.*, **145**, 655 (1934).

reaction products, but the yield was about four and a half times as great as that obtainable from 3,4-dihydro-1-phenethylphenanthrene. It should be noted that the cyclization of VI is a different sort of process from that studied by Cook *et al*[5] when they noted the improvement of yield caused by a methyl group *in the hydroaromatic ring* at the point where a new bond was to be established. In our case cyclization might have been expected to take place at 6′ with the formation of a product which would yield 10-methylpicene on dehydrogenation. However, the picene obtained showed no depression of melting point when mixed with the substance prepared from unmethylated intermediate, and Ruzicka[6] has shown that, in those cases which he investigated, methylated picenes, if they are unlike, do show a depression in the mixture melting point determination. The loss of an alkyl group from an aromatic hydrocarbon in the presence of aluminum chloride is a well-known process, but that this loss should be attended by cyclization at the point vacated by the alkyl is extremely interesting and worthy of further study.

Attempts to produce 8-methylpicene by dehydrogenating the product obtained from the treatment of 3,4-dihydro-1-(β-4′-tolylethyl)phenanthrene with aluminum chloride in carbon disulfide failed. We have not yet examined the behavior of 3,4-dihydro-1-(β-3′-tolylethyl)phenanthrene, but it seems reasonable that this substance should cyclize smoothly, and that 9-methylpicene could be made from it.

EXPERIMENTAL

β-1-Naphthoylpropionic acid.—The method used in this synthesis was a modification of the one described by Fieser and Peters.[7] The modifications which we have introduced were concerned principally with the separation of the 1-, and 2-isomers; consequently that part of the preparation starting with the crude mixture of β-1- and β-2-naphthoylpropionic acids, produced by the reaction of succinic anhydride on naphthalene in nitrobenzene solution in the presence of aluminum chloride, alone will be described.

Sixty-eight grams of finely pulverized crude acids was suspended in 1500 ml. of warm water, and 50 ml. of 2*N* sodium hydroxide was added (1/3 the amount necessary for complete neutralization). The mixture was held at 50–60° for several hours, preferably overnight, with occasional shaking, and was then cooled to room temperature and filtered. The filtrate was acidified, and the resulting β-1-naphthoylpropionic acid was filtered and recrystallized several times from 20% acetic acid. The product melted at 132–3°. The residue of undissolved acids was returned to the flask, treated with another 50-ml. portion of 2*N* sodium hydroxide, filtered, and the filtrate was acidified as before. The product so obtained was a mixture of both isomers, free from tarry material, and was added to the next batch of crude acid. The residue undissolved by the two treatments with alkali consisted almost exclusively of β-2-naphthoylpropionic acid contaminated with tarry material.

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[6] RUZICKA AND HOFMANN, *Helv. Chim. Acta*, **22**, 127 (1939).

[7] FIESER AND PETERS, *J. Am. Chem. Soc.*, **54**, 4350 (1932).

γ-1-Naphthylbutyric acid.—This acid was prepared by use of the modified Clemmensen procedure described by Martin[8]. The product melted at 107.5–108.5°.

1-Keto-1,2,3,4-tetrahydrophenanthrene.—Fifty grams of γ-1-naphthylbutyric acid was suspended in 500 ml. of dry benzene in a three-necked flask provided with a mercury-sealed stirrer, a reflux condenser, and a trap for hydrogen chloride. Phosphorus pentachloride (50 g.) was added, and stirring was commenced. The acid dissolved within a few minutes, whereupon the mixture was heated under reflux for an hour and a half.

The solution was next cooled to 0–5° by means of an ice bath, and maintained at this temperature during the addition of 34 g. of pulverized anhydrous aluminum chloride over a period of about 30 minutes. The mixture was then allowed to warm to room temperature, and was kept at this temperature overnight without stirring. The mixture was then heated under reflux for two and one-half hours, and, after cooling, was poured upon ice and hydrochloric acid. The precipitated 1-keto-1,2,3,4-tetrahydrophenanthrene was extracted with benzene, washed carefully with sodium carbonate and water, and finally distilled in vacuum. The yield of product distilling at 145–150° at 1 mm. was 37 g. (81%). After crystallization from methanol the product melted at 95–6°.

Anal. Calc'd for $C_{14}H_{12}O$: C, 85.67; H, 6.17.
Found: C, 85.49; H, 6.13.

The 2,4-dinitrophenylhydrazone of the ketone, prepared in the usual manner, and recrystallized from pyridine, melted at 283–5° with decomposition.

Anal. Calc'd for $C_{20}H_{16}N_4O_4$: N, 14.89. Found: N, 14.80, 14.62.

2-(β-Hydroxyethyl)toluene.—This alcohol was prepared from *o*-bromotoluene and ethylene oxide by the Grignard reaction. The method employed was similar to one earlier described for the preparation of *n*-hexyl alcohol.[9] The yield of product distilling at 99–105° under 1 mm. pressure was 62%; d_{20}^{20} 1.0195; n_D^{20} 1.5349.

Anal. Calc'd for $C_9H_{12}O$: C, 79.37; H, 8.88.
Found: C, 79.14, 79.20; H, 8.95, 8.77.

β-2'-Tolylethyl 3,5-dinitrobenzoate.—Prepared from 3,5-dinitrobenzoyl chloride in the usual manner, and recrystallized from ethanol, this ester melted at 126–128°.

Anal. Calc'd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27.
Found: C, 58.38, 58.41; H, 4.34, 4.18.

4-(β-Hydroxyethyl)toluene.—This substance was prepared from *p*-bromotoluene by a method similar to that used for 2-(β-hydroxyethyl)toluene, described above. The yield was 53% based on the aryl halide. The product distilled at 100–106° under 1 mm. pressure, and at 235° at atmospheric pressure; d_{20}^{20} 1.0008; n_D^{20} 1.5282.

Anal. Calc'd for $C_9H_{12}O$: C, 79.37; H, 8.88.
Found: C, 79.29; H, 9.02.

β-4'-Tolyethyl 3,5-dinitrobenzoate.—Prepared in the usual way, and recrystallized from ethanol, this ester formed yellowish needles which melted at 147–9°.

Anal. Calc'd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27.
Found: C, 58.32, 58.28; H, 4.31, 4.25.

2-(β-Chloroethyl)toluene.—2-(β-Hydroxyethyl)toluene (34 g.) was mixed with dry dimethylaniline (61 g.). The mixture was cooled in an ice and salt bath, and 60 g. of thionyl chloride was added. The resultant black, viscous solution was allowed to stand overnight at room temperature and was then heated on the steam bath for an

[8] MARTIN, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

[9] *Organic Syntheses*, John Wiley and Sons, Inc., New York, Vol. 6, page 54 (1926).

hour. The mixture was then poured into water, the halide was extracted with ether, washed with 5% sodium carbonate solution, and with water, and finally dried and distilled in vacuum. The 2-(β-chloroethyl)toluene boiled at 80–84° under 1 mm. pressure, and at 223° at atmospheric pressure; d_{20}^{20} 1.0553; n_D^{20} 1.5313. The yield was 85%.

Anal. Calc'd for $C_9H_{11}Cl$: Cl, 22.93. Found: Cl, 22.73, 23.07.

4-(β-Chloroethyl)toluene.—This halide was prepared as described directly above; yield 85%. The substance boiled at 81–85° under 1 mm. pressure, and at 222° at atmospheric pressure; d_{20}^{20} 1.0370; n_D^{20} 1.5251.

Anal. Calc'd for $C_9H_{11}Cl$: Cl, 22.93. Found: Cl, 22.96, 22.85.

3,4-Dihydro-1-phenethylphenanthrene.—To a cooled, stirred ethereal solution of the Grignard reagent prepared from 6.0 g. of magnesium and 37 g. of phenethyl bromide was added slowly 32.0 g. of 1-keto-1,2,3,4-tetrahydrophenanthrene dissolved in 200 ml. of a solvent consisting of one part of anhydrous ether and one part of anhydrous benzene. After the addition of the solution of ketone was complete, the cooling bath (ice water) was removed, and the mixture was refluxed for one hour. Ether was then distilled until the temperature *of the solution* reached 75°, whereupon refluxing was continued for five hours longer. The addition complex was then decomposed with ice and hydrochloric acid, and the product was extracted, dried, and distilled in vacuum; during this treatment the tertiary alcohol originally produced underwent dehydration. The yield of 3,4-dihydro-1-phenethylphenanthrene, boiling at 185–187° under 0.5–1 mm. pressure, was 24.0 g. Some unchanged ketone was recovered from the fore-run, so that the yield, based on the ketone not recovered was 69%. The product was difficult to crystallize; best results were obtained by the use of 95% ethanol, from which the product formed colorless hexagonal plates which melted at 62–3°.

Anal. Calc'd for $C_{22}H_{20}$: C, 92.91; H, 7.09.
Found: C, 93.01, 92.60; H, 6.97, 7.24.

The trinitrobenzenate of this hydrocarbon, prepared from equimolar quantities of s-trinitrobenzene and the phenanthrene dissolved in a small quantity of hot 95% alcohol, separated in orange needles which melted at 91–2°.

Anal. Calc'd for $C_{28}H_{23}N_3O_6$: C, 67.60; H, 4.66.
Found: C, 67.81; H, 4.71.

3,4-Dihydro-1-(β-2'-tolylethyl)phenanthrene.—This substance was prepared by a method quite similar to that described for the preparation of 3,4-dihydro-1-phenethylphenanthrene. The yield was 79% on the basis of the ketone consumed. The product distilled at 190–195° under 0.5–1 mm. pressure, and crystallized readily from 95% ethanol, from which it formed colorless well-defined plates which melted at 57–8°.

Anal. Calc'd for $C_{23}H_{22}$: C, 92.57; H, 7.43.
Found: C, 92.83, 92.58; H, 7.43, 7.34.

The trinitrobenzenate of this hydrocarbon, prepared in the usual way, formed orange laths from ethanol, and melted at 101.5–102.5°. This compound shows slightly oblique extinction.

Anal. Calc'd for $C_{29}H_{25}N_3O_6$: C, 68.09; H, 4.93.
Found: C, 68.29; H, 4.85.

3,4-Dihydro-1-(β-4'-tolylethyl)phenanthrene.—A method of preparation similar to that described above for 3,4-dihydro-1-phenethylphenanthrene gave a yield of 63% of the phenanthrene based on ketone consumed. The product distilled at 200–205° under 0.5–1.0 mm. pressure, and formed a viscous liquid which solidified on standing,

and after several recrystallizations from ethanol, from which it forms quadrilateral plates which show symmetrical extinction, melted at 79.5–81°.

Anal. Calc'd for $C_{28}H_{22}$: C, 92.57; H, 7.43.
Found: C, 92.66, 92.59; H, 7.29, 7.46.

The picrate was prepared by dissolving the reactants in a small volume of hot 95% ethanol. After several recrystallizations from ethanol, the picrate melted at 101–102°; it forms brick-red laths from ethanol.

Anal. Calc'd for $C_{29}H_{25}N_3O_7$: C, 66.02; H, 4.78.
Found: C, 66.08; H, 4.98.

1-Phenethylphenanthrene.—Thirteen grams of 3,4-dihydro-1-phenethylphenanthrene was intimately mixed with 5 g. of palladium-charcoal catalyst,[10] and heated in a flask connected to a vertical section of large-bore glass tubing about 2 feet in length, provided with a bubble counter at the top. During the dehydrogenation the temperature of the bath was raised slowly from 270° at the beginning to 300° by the end of the first hour, and to 320° by the end of the second hour. After cooling, the contents of the flask were extracted with successive portions of boiling ethanol. Upon concentrating the combined filtrates, crude yellow 1-phenethylphenanthrene separated. The crude material was dissolved in petroleum ether, and the solution was passed through a 9-inch column packed with ground alumina ("Hydralo" ground to 100–200 mesh and activated by heating it at 250° *in vacuo*). The column was washed with successive portions of hot petroleum ether until a portion of the filtrate, on evaporation, showed no residue. Almost all of the yellow impurity remained in the first few centimeters of the alumina at the top of the column. After several recrystallizations from methanol, from which it separates in the form of colorless plates, the product melted at 86.5–89.5°. The yield of purified material was 9.2 g. from 10.8 g. of crude dehydrogenation product.

Anal. Calc'd for $C_{22}H_{18}$: C, 93.57; H, 6.43.
Found: C, 93.38, 93.34; H, 6.50, 6.49.

1-Phenethylphenanthrene forms a sparingly soluble trinitrobenzenate which contains two moles of nitro compound, and separates from ethanol in narrow yellow laths which melt at 149–151°.

Anal. Calc'd for $C_{34}H_{24}N_6O_{12}$: C, 57.63; H, 3.41.
Found: C, 57.67, 57.96, 57.83, 57.79; H, 3.66, 3.57, 3.58, 3.62.

All attempts to cyclize 1-phenethylphenanthrene by treatment in carbon disulfide with aluminum chloride under reflux and at lower temperatures, yielded tarry material from which no picene could be obtained by high-vacuum sublimation.

Cyclization and dehydrogenation of 3,4-Dihydro-1-phenethylphenanthrene.—A solution of 3.7 g. of 3,4-dihydro-1-phenethylphenanthrene in 37 ml. of carbon disulfide was cooled to 0° by means of an ice and salt bath, and 3.7 g. of pulverized anhydrous aluminum chloride was added in small portions, with shaking, over a period of 30 minutes. The mixture was allowed to stand overnight at 5°, and was then poured on ice and hydrochloric acid. When the carbon disulfide had been removed by steam distillation, the viscous red oil which remained was taken up in ether, washed first with concentrated hydrochloric acid, then with sodium hydroxide solution (20%), and finally with water. After the ethereal solution had been dried, the ether was removed by distillation, and the residual oil was distilled in vacuum. The distillate (2.9 g.) was an extremely viscous oil which distilled at 205–215° under 0.5–1.0 mm. pressure. After several weeks of standing the substance became opaque,

[10] DIELS AND GÄDKE, *Ber.*, **58**, 1232 (1925).

and finally solidified to a pasty mass. Repeated attempts to recrystallize the product were unsuccessful, as were also attempts to prepare a picrate or a trinitrobenzenate.

The viscous yellow oil (2.4 g.) was mixed with 1.2 g. of palladium-charcoal catalyst and heated in the apparatus described above; the bath temperature was maintained at 390–400° for two hours. When the mixture had cooled, it was leached with ether until no more colored material was extracted, then placed in a Soxhlet extractor and extracted with chloroform for 20 hrs. The chloroform solution was evaporated to dryness, and the residue was again leached with ether. The brown ether-insoluble residue was then heated in a sublimer in high vacuum at 270–290°. The sublimate was dissolved in hot chloroform, in which it was but slightly soluble; upon cooling picene separated in glistening white plates. The yield was 29.5 mg., m.p. 367–368.5°.

Anal. Calc'd for $C_{22}H_{14}$: C, 94.93; H, 5.07.

Found: C, 94.72, 94.74; H, 5.08, 5.29.

Cyclization of 3,4-dihydro-1-(β-2′-tolylethyl)phenanthrene and dehydrogenation of the cyclized product.—This cyclization was carried out by a procedure like that described for 3,4-dihydro-1-phenethylphenanthrene. The product was a viscous yellow oil which boiled at 205–10° under 0.5–1 mm. pressure (7.5 g. from 9.7 g. starting material), and which did not show any evidence of crystallization after standing for several months. The oil formed no picrate or trinitrobenzenate; d_{20}^{20} 1.097; n_D^{20} 1.6440.

A mixture of 5.4 g. of this oil and 2.7 g. of palladium-charcoal catalyst was heated in the dehydrogenation apparatus for two hours (bath temperature, 380–400°), and then worked up as described above. The yield of sublimed and recrystallized picene from 5.4 g. of cyclized product was 230 mg.; the product melted at 367–369°.

Anal. Calc'd for $C_{22}H_{14}$: C, 94.93; H, 5.07.

Found: C, 94.76, 94.93; H, 5.25, 5.24.

This product and that obtained from 3,4-dihydro-1-phenethylphenathrene showed no depression of melting point when mixed.

Attempts to cyclize 3,4-dihydro-1-(β-4′-tolylethyl)phenanthrene, and to dehydrogenate the product.—Under conditions similar to those described above 3,4-dihydro-1-(β-4′-tolylethyl)phenanthrene yielded an exceedingly viscous oil (b. p. 210–220° under 0.5–1.0 mm. pressure) when treated in carbon disulfide with anhydrous aluminum chloride. The product solidified slowly to a pasty mass from which it proved impossible to separate any pure compounds. Dehydrogenation of this product by the method previously described yielded no picene.

SUMMARY

1. Picene has been synthesized from 3,4-dihydro-1-phenethylphenanthrene and from 3,4-dihydro-1-(β-2′-tolylethyl)phenanthrene.

2. No picene or methylpicene was obtained from 3,4-dihydro-1-(β-4′-tolylethyl)phenanthrene.

3. Attempts to cyclize 1-phenethylphenanthrene failed.

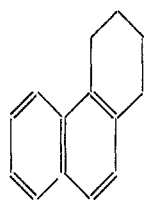
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

REACTIONS OF TETRAHYDROPHENANTHRENE. THE SYNTHESIS OF TRIPHENYLENE AND METHYLTRIPHENYLENE*

W. E. BACHMANN AND W. S. STRUVE

Received May 8, 1939

In the Friedel-Crafts reaction phenanthrene is usually substituted in the 3 position and to a lesser extent in the 2 position. In order to obtain



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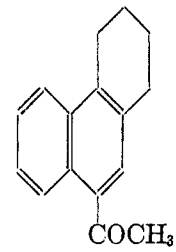

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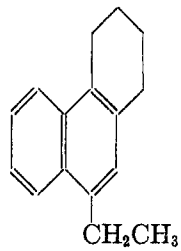

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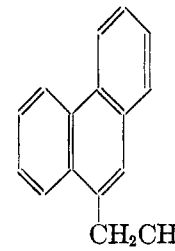

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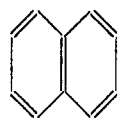

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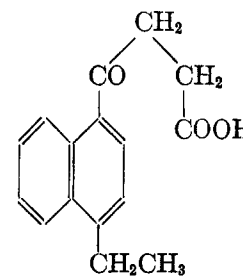


VI

* From the Ph.D. dissertation of W. S. Struve.

substituents in other positions, partially hydrogenated phenanthrene has been used. Although *as*-octahydrophenanthrene is attacked in the 3 position[1], the *sym*-octahydrophenanthrene can yield only 9-substituted derivatives in the Friedel-Crafts reaction[2]. An excellent method of securing 2-substituted derivatives of phenanthrene exclusively in this reaction consists in the use of 9,10-dihydrophenanthrene[3, 4]. We have undertaken a study of the reactions of 1,2,3,4-tetrahydrophenanthrene (I), and in this paper report the results obtained in the Friedel-Crafts reaction with acetyl chloride and with succinic anhydride. In the experimental section directions are given for the convenient preparation of tetrahydrophenanthrene from naphthalene, employing the Haworth method.

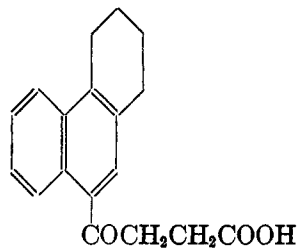
Acetyl chloride reacts with 1,2,3,4-tetrahydrophenanthrene in the 9 position to give 9-acetyltetrahydrophenanthrene (II). That the acetyl group was either in the 9 or the 10 position was shown by the formation of the known 9-acetylphenanthrene on dehydrogenation of the ketone by sulfur. Proof that the group is actually in the 9 position was obtained by reducing II by the Clemmensen method to 9-ethyl-1,2,3,4-tetrahydrophenanthrene (III), which proved to be identical with the compound prepared by a method which fixed the position of the ethyl group. In the latter synthesis, 1-ethylnaphthalene (V) was condensed with succinic anhydride; by analogy with the behavior of 1-methylnaphthalene, which reacts in the 4 position under the same conditions[5], the product is probably VI. By the usual reduction, cyclization, and reduction of the cyclic ketone, 9-ethyltetrahydrophenanthrene (III) was obtained. The tetrahydro compound is smoothly dehydrogenated to 9-ethylphenanthrene (IV) by palladium on charcoal.

Tetrahydrophenanthrene reacts with succinic anhydride chiefly in the 9 position to give β-[9-(1,2,3,4-tetrahydrophenanthroyl)]propionic acid (VII); there was some evidence of the presence of an isomeric acid in the mixture, but this compound has not yet been obtained in a pure state. The structure of the acid was proved by its synthesis from 9-acetyltetrahydrophenanthrene (II), through the bromo ketone VIII, by means of the malonic ester synthesis.

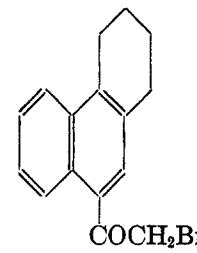
By Clemmensen reduction of the tetrahydrophenanthroylpropionic acid (VII) the corresponding tetrahydrophenanthrylbutyric acid was obtained, and was cyclized, through its acid chloride, by stannic chloride to the ketoöctahydrotriphenylene (IX). Clemmensen reduction of this cyclic

[1] COOK AND HASLEWOOD, *J. Chem. Soc.*, **1935**, 767.
[2] VAN DE KAMP AND MOSETTIG, *J. Am. Chem. Soc.*, **57**, 1107 (1935).
[3] BURGER AND MOSETTIG, *ibid.*, **57**, 2731 (1935).
[4] BURGER AND MOSETTIG, *ibid.*, **59**, 1302 (1937).
[5] HAWORTH AND MAVIN, *J. Chem. Soc.*, **1932**, 2720.

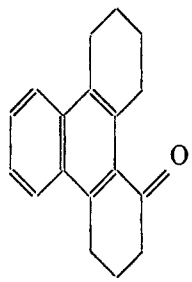
ketone yielded 1,2,3,4,5,6,7,8-octahydrotriphenylene (X), which was smoothly dehydrogenated to triphenylene by palladium on charcoal. Triphenylene has been synthesized recently by Bergmann and Blum-Bergmann[6] from phenanthrene. By the action of methylmagnesium iodide on the cyclic ketone IX, the methyl carbinol was formed; the latter was converted to 1-methyltriphenylene (XII) by the action of the palladium-charcoal catalyst.



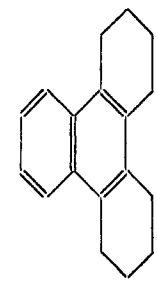
VII



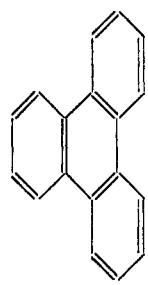
VIII



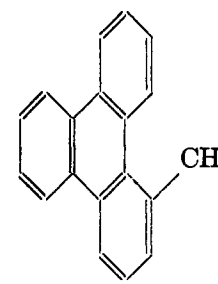
IX



X



XI



XII

EXPERIMENTAL

γ-(1- and 2-Naphthyl)butyric acids.—In the manner prescribed by Haworth's directions,[7] 52 g. of a mixture of β-(1- and 2-naphthoyl)propionic acids was obtained

[6] BERGMANN AND BLUM-BERGMANN, *J. Am. Chem. Soc.*, **59**, 1441 (1937).
[7] HAWORTH, *J. Chem. Soc.*, **1932**, 1125.

from 25 g. of succinic anhydride, 50 g. of naphthalene and 69 g. of aluminum chloride in 190 cc. of nitrobenzene. The mixture of acids, without recrystallization, was heated with 100 g. of amalgamated zinc, 75 cc. of water, 175 cc. of concentrated hydrochloric acid, 100 cc. of toluene and 5 cc. of acetic acid for twenty-four hours, an additional 150 cc. of concentrated hydrochloric acid being added in portions over this period. The toluene layer was separated, the toluene was evaporated, and the residue was distilled in a vacuum; yield, 38 g. (78%). The acids so obtained were used directly in the next step.

Mixture of 1- and 4-keto-1,2,3,4-tetrahydrophenanthrenes.—To a solution of 38 g. of a mixture of γ-(1- and 2-naphthyl)butyric acids in 200 cc. of absolute ether and 5 drops of pyridine was added 40 cc. of thionyl chloride. After standing at room temperature for a half hour the ether and thionyl chloride were evaporated under reduced pressure. The oily acid chloride was dissolved in 200 cc. of dry benzene and cooled in an ice bath. Then 30 cc. of stannic chloride was added, and the mixture allowed to stand in the ice water for fifteen minutes. The complex was hydrolyzed with ice and dilute hydrochloric acid, the benzene layer was separated, washed with water and dilute ammonium hydroxide solution, the benzene was evaporated, and the residue was distilled under reduced pressure (0.4 mm.), yielding a colorless liquid; weight, 26 g. (75%).

1,2,3,4-Tetrahydrophenanthrene (I).—Twenty-six grams of the mixture of 1- and 4-keto-1,2,3,4-tetrahydrophenanthrene, 100 g. of amalgamated zinc, 150 cc. of acetic acid, 150 cc. of concentrated hydrochloric acid, and 100 cc. of toluene was refluxed for twenty-four hours, an additional 75 cc. of concentrated hydrochloric acid being added in portions over this time. Vacuum distillation of the residue obtained from the toluene layer gave tetrahydrophenanthrene as a colorless liquid; yield, 16.5 g. (69%). In one run the distillate from 23 g. of starting material was dissolved in alcohol, and an excess of picric acid was added. The solution deposited 33 g. of picrate; m. p. 110–112°, corresponding to a 68 per cent. yield of tetrahydrophenanthrene. The melting point of pure tetrahydrophenanthrene picrate is 111°[8]. The picrate was decomposed with dilute ammonium hydroxide, and the oil so obtained was crystallized from methanol, giving colorless plates; m. p. 32.5–33.5°. It is not necessary however to purify the tetrahydrophenanthrene through the picrate in order to crystallize it. In another run 26 g. of distillate from 37.5 g. of starting material was crystallized from methanol, giving about 22 g. of crystalline product; m. p. 32–33°. Because of the large solubility of the tetrahydrophenanthrene in methanol there is some loss upon crystallization and it has been found that either the liquid or solid tetrahydrophenanthrene can be used in the following experiments.

9-Acetyl-1,2,3,4-tetrahydrophenanthrene (II).—To a solution of 13.5 g. of aluminum chloride and 4.5 g. of acetyl chloride in 42 cc. of dinitrobenzene cooled to −10° was added 10 g. of 1,2,3,4-tetrahydrophenanthrene. The mixture was kept in a refrigerator for twenty-four hours. After two hours the reaction mixture had solidified. The mixture was hydrolyzed with ice and dilute hydrochloric acid, the solution was washed with water, and the nitrobenzene was removed by steam distillation. The residue crystallized on cooling; yield, 11.7 g. (95%); m. p. 45–50°. The crude mixture was distilled in a vacuum, giving 10.5 g. of distillate, which crystallized from methanol-alcohol as slightly yellow prisms; weight, 7.9 g. (75% of the distilled product); m. p. 56–58°. The second crop (1.33 g.) melted at 40–52°. Two recrystallizations of the first crop from alcohol-methanol gave colorless prisms of 9-acetyl-1,2,3,4-tetrahydrophenanthrene; m. p. 56.5–58°.

[8] SCHROETER, MÜLLER, AND HUANG, *Ber.*, **62B**, 653 (1929).

Anal. Calc'd for $C_{16}H_{16}O$: C, 85.7; H, 7.1.
Found: C, 86.0; H, 7.1.

9-Acetylphenanthrene.—A mixture of 0.5 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene and 0.17 g. of sulfur was heated for three hours at 210–220°. A small amount of powdered copper was then added, and the heating was continued for ten minutes more. The mixture was extracted with benzene, the benzene solution was filtered, and the benzene was evaporated. The residue was sublimed at 220° and 0.4 mm., and the sublimate was crystallized from alcohol; yield, 0.22 g. (46%); m. p. 70–73°. The melting point of a mixture with authentic 9-acetylphenanthrene (m. p. 72.5–73°) prepared from 9-cyanophenanthrene and methylmagnesium iodide[9] was 71–73°.

β-[1-(4-Ethylnaphthoyl)]propionic acid (VI).—To a cold solution of 3.5 g. of succinic anhydride and 8.5 g. of anhydrous aluminum chloride in 27 cc. of nitrobenzene was added 5.4 g. of 1-ethylnaphthalene (V), and the mixture was kept at 0° for fifteen hours. The complex was hydrolyzed with ice and dilute hydrochloric acid, the nitrobenzene solution was washed with water, and the nitrobenzene was removed by steam distillation. The residue was dissolved in a solution of 5 g. of sodium hydroxide in 200 cc. of water, the solution treated with charcoal, filtered, and acidified. The precipitated acid weighed 6.5 g. (74%); m. p. 122–127°. Crystallization from benzene gave colorless needles; m. p. 127–131°; two further crystallizations from benzene raised the melting point to 129.5–131°.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3.
Found: C, 74.8; H, 6.2.

γ-[1-(4-Ethylnaphthyl)]butyric acid.—A mixture of 4 g. of β-[1-(4-ethylnaphthoyl)]-propionic acid, 10 g. of amalgamated zinc, 15 cc. of acetic acid, 15 cc. of concentrated hydrochloric acid, and 8 cc. of toluene was refluxed for twenty-four hours. An additional 15 cc. of concentrated hydrochloric acid was added in portions over this period. The toluene layer was separated, the toluene was evaporated, and the residue was crystallized from benzene; weight, 3.54 g. (94%); m. p. 113–116°. Two further crystallizations from benzene gave clusters of colorless needles; m. p. 115–116.5°.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.4.
Found: C, 79.2; H, 7.4.

1-Keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene.—To a solution of 2 g. of γ-[1-(4-ethylnaphthyl)]butyric acid in 20 cc. of absolute ether and 5 drops of pyridine was added 4 cc. of thionyl chloride. The mixture was allowed to stand at room temperature for a half-hour, and then the ether and thionyl chloride were removed under reduced pressure. An ice-cold solution of the acid chloride in 20 cc. of benzene was treated with 3 cc. of stannic chloride, and the solution was kept cold for a half-hour. The complex was hydrolyzed with ice and dilute hydrochloric acid, the benzene layer was separated, washed with water and dilute ammonium hydroxide, and the benzene was evaporated. The residue crystallized from dilute alcohol as colorless needles; yield, 1.42 g. (77%); m. p. 51–53°. Two further crystallizations raised the melting point to 52–53°.

Anal. Calc'd for $C_{16}H_{16}O$: C, 85.7; H, 7.1.
Found: C, 85.3; H, 7.3.

9-Ethyl-1,2,3,4-tetrahydrophenanthrene (III).—*(a) From 9-acetyl-1,2,3,4-tetrahydrophenanthrene.*—A mixture of 1 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene, 5 g. of amalgamated zinc, 10 cc. of acetic acid, 10 cc. of concentrated hydrochloric acid, and 4 cc. of toluene was refluxed for twenty-four hours, an additional 6 cc. of

[9] BACHMANN AND BOATNER, *J. Am. Chem. Soc.*, **58**, 2098 (1936).

concentrated hydrochloric acid being added in portions over this period. The toluene layer was separated, the toluene was evaporated, and the residue was sublimed at 200° and 0.4 mm. The sublimate was crystallized from alcohol-acetone; weight, 0.51 g.; m. p. 22–24°. To the filtrate from the crystallization was added 0.7 g. of picric acid. A bright orange picrate crystallized; weight, 0.64 g.; m. p. 124–126°. Total yield, 0.82 g. (88%).

(*b*) *From 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene.*—One gram of this ketone was reduced in exactly the same way as the 9-acetyl-1,2,3,4-tetrahydrophenanthrene; weight, 0.27 g.; m. p. 23–25°. The melting point of a mixture with the material obtained in part *a* was 22–24.5°. The picrate obtained from the filtrate from the crystallization weighed 0.84 g.; m. p. 124–126°. The melting point of a mixture with the picrate obtained in part *a* was 124–126°.

After two recrystallizations of the hydrocarbon from alcohol-acetone, colorless needles with unchanged melting point were obtained.

Anal. Calc'd for $C_{16}H_{18}$: C, 91.4; H, 8.6.
Found: C, 91.3; H, 8.8.

The pure *picrate* crystallizes from alcohol as clusters of fine, bright-orange needles; m. p. 125.5–126.5°.

Anal. Calc'd for $C_{16}H_{18}\cdot C_6H_3N_3O_7$: N, 9.6. Found: N, 9.7.

9-Ethylphenanthrene (IV).—A mixture of 0.27 g. of 9-ethyl-1,2,3,4-tetrahydrophenanthrene and 0.04 g. of palladium-charcoal catalyst[10] was heated for one hour at 300–320°. The mixture was taken up in benzene, the solution was filtered to remove the catalyst, the benzene was evaporated, and the residue was crystallized from alcohol, giving colorless needles; weight, 0.20 g. (75%); m. p. 63.5–64.5°. The picrate melted at 120.5–122.5°. Mosettig and van de Kamp[11] give 62.5–63° and 123–124° for the melting points of the hydrocarbon and the picrate respectively.

ω-Bromo-9-acetyl-1,2,3,4-tetrahydrophenanthrene (VIII).—A solution of 1.48 g. of bromine in 40 cc. of absolute ether was added to a solution of 2 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene in 80 cc. of absolute ether cooled in an ice-salt mixture. An orange precipitate formed which dissolved as the solution decolorized, the decolorization taking twenty minutes. After standing another half hour the ether was evaporated, and the residue was crystallized from methanol; yield, 1.95 g. (72%); m. p. 90–91°. Two further crystallizations from methanol gave colorless needles; m. p. 90.5–91.5°.

Anal. Calc'd for $C_{16}H_{15}BrO$: Br, 26.4. Found: Br, 26.3.

β-[9-(1,2,3,4-Tetrahydrophenanthroyl)]propionic acid (VII).—(*a*) A mixture of 0.05 g. of sodium, 0.5 cc. of malonic ester, and 10 cc. of benzene was refluxed for twelve hours, 0.39 g. of ω-bromo-9-acetyl-1,2,3,4-tetrahydrophenanthrene was then added, and the whole was refluxed for twenty-four hours. The benzene solution was washed with cold dilute hydrochloric acid, and the benzene was evaporated. The residue was heated with 3 cc. of 40% potassium hydroxide solution for a half-hour, water was added to dissolve the potassium salts formed, and the solution was filtered and acidified. The dry dicarboxylic acid was heated at 160–180° for a half-hour. It was then taken up in benzene, the acid was extracted with dilute potassium hydroxide, and the solution of the potassium salt was filtered. Acidification gave 0.24 g. (66%) of the desired acid; m. p. 160–163°. Two crystallizations from acetic acid gave colorless rectangular prisms; m. p. 167–169°.

(*b*) To a cooled solution of 2.2 g. of succinic anhydride and 5.4 g. of aluminum

[10] Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

[11] Mosettig and van de Kamp, *J. Am. Chem. Soc.*, **55**, 3442 (1933).

chloride in 17 cc. of nitrobenzene was added 4 g. of tetrahydrophenanthrene. The mixture was kept cold for twelve hours, and was then hydrolyzed with ice and dilute hydrochloric acid. The nitrobenzene solution was washed with water, steam distilled to remove the nitrobenzene, and the residue was dissolved in hot dilute sodium hydroxide solution. Acidification of the filtered solution gave 4.83 g. (78%) of the acids; m. p. 137–155°. After one recrystallization from benzene-petroleum ether, 3.32 g. of acid melting at 161–165° was obtained. After two further recrystallizations from toluene-acetic acid the acid was obtained as colorless, rectangular prisms; m. p. 167.5–169°, alone and when mixed with the acid prepared in part *a*.

Anal. Calc'd for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4.
Found: C, 76.7; H, 6.5.

γ-[9-(1,2,3,4-Tetrahydrophenanthryl)]butyric acid.—A mixture of 1.49 g. of β-[9-(1,2,3,4-tetrahydrophenanthroyl)]propionic acid, 3.0 g. of amalgamated zinc, 4.8 cc. of acetic acid, 4.8 cc. of concentrated hydrochloric acid, and 2 cc. of toluene was refluxed for twenty-four hours, an additional 5 cc. of concentrated hydrochloric acid being added over this time. The toluene layer was separated, the toluene was evaporated, and the residue was crystallized from benzene; yield, 1.37 g. (96%); m. p. 132.5–134°. After two recrystallizations it separated as colorless prisms; m. p. 133–134°.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5.
Found: C, 81.1; H, 7.6.

γ-(9-Phenanthryl)butyric acid.—A mixture of the methyl ester obtained from 1 g. of γ-[9-(1,2,3,4-tetrahydrophenanthryl)]butyric acid by means of diazomethane and 0.1 g. of palladium-charcoal catalyst was heated for two hours at 250–270°. The mixture was taken up in benzene, and the catalyst was removed by filtration. The benzene was evaporated, and the ester was hydrolyzed with hot 40% potassium hydroxide solution. Acidification of the diluted hydrolysis mixture gave 0.89 g. (90%) of the acid; m. p. 167–170°. After two crystallizations from benzene the acid gave colorless needles; m. p. 171–172°. Bergmann and Blum-Bergmann[6] give 176° for the melting point of γ-(9-phenanthryl)butyric acid, which they prepared by reduction of the keto acid obtained by interaction of 9-phenanthrylmagnesium bromide and succinic anhydride.

1-Keto-1,2,3,4,9,10,11,12-octahydrotriphenylene (IX).—To a solution of 1.55 g. of γ-[9-(1,2,3,4-tetrahydrophenanthryl)]butyric acid in 15 cc. of absolute ether and 5 drops of pyridine was added 3 cc. of thionyl chloride. The solution was allowed to stand for a half-hour, and the ether and thionyl chloride were then evaporated under reduced pressure. The acid chloride was dissolved in 15 cc. of dry benzene, the solution was cooled in ice water, and 2.5 cc. of stannic chloride was added with swirling. The mixture was allowed to stand for ten minutes in the cold, and then the complex was decomposed with ice and dilute hydrochloric acid. The benzene layer was washed with dilute ammonium hydroxide, the benzene was evaporated, and the residue was crystallized from alcohol-acetone; weight, 1.37 g. (95%); m. p. 121–121.5°. After two recrystallizations from alcohol-acetone, the compound formed colorless needles; m. p. 121–122°.

Anal. Calc'd for $C_{18}H_{18}O$: C, 86.4; H, 7.2.
Found: C, 86.5; H, 7.1.

1,2,3,4,5,6,7,8-octahydrotriphenylene (X).—A mixture of 0.78 g. of the aforementioned cyclic ketone, 3 g. of amalgamated zinc, 5 cc. of acetic acid, 5 cc. of concentrated hydrochloric acid and 2 cc. of toluene was refluxed for twenty-four hours; an additional 5 cc. of concentrated hydrochloric acid was added over this period.

The product obtained from the toluene layer was sublimed at 200° and 0.4 mm., and the sublimate was crystallized from alcohol-acetone; yield, 0.54 g. (74%); m. p. 117.5–119.5°. Two further crystallizations gave colorless prisms; m. p. 120.5–122°.

Anal. Calc'd for $C_{18}H_{20}$: C, 91.5; H, 8.5.
Found: C, 91.3; H, 8.3.

The *picrate* crystallizes from alcohol-acetone as red needles; m. p. 193–195°.

Anal. Calc'd for $C_{18}H_{20}\cdot C_6H_3N_3O_7$: N, 9.0. Found: N, 9.0.

Triphenylene (XI).—A mixture of 0.13 g. of the octahydrotriphenylene and 0.02 g. of palladium-charcoal catalyst was heated for one hour at 300–320°. The mixture was taken up in benzene, and filtered to remove the catalyst; the benzene was evaporated, and the residue was crystallized from acetone-alcohol, giving colorless needles; yield, 0.095 g. (75%); m. p. 196.5–197.5°. The compound gave no depression of melting point when mixed with authentic triphenylene. The mixture melting point of the picrates also gave no depression.

1-Methyl-1-hydroxy-1,2,3,4,9,10,11,12-octahydrotriphenylene.—An ice-cold solution of a Grignard reagent made from 0.56 cc. of methyl iodide, 0.19 g. of magnesium, and 10 cc. of ether was treated with a cold solution of 0.75 g. of 1-keto-1,2,3,4,9,10,-11,12-octahydrotriphenylene in 10 cc. of dry benzene. The mixture was allowed to stand in the cold overnight, and then hydrolyzed with ice and dilute ammonium chloride solution. Evaporation of the benzene-ether layer in an open vessel gave colorless crystals of the methyl carbinol; yield, 0.43 g. (54%); m. p. 102–105°. After two crystallizations from benzene-petroleum ether the methyl carbinol melted at 104–105°.

Anal. Calc'd for $C_{19}H_{22}O$: C, 85.7; H, 8.3.
Found: C, 85.5; H, 8.5.

1-Methyltriphenylene (XII).—A mixture of 0.43 g. of the aforementioned carbinol and 0.05 g. of palladium charcoal catalyst was heated for two hours at 300–320°. The mixture was taken up in benzene, filtered, and the benzene was evaporated. The residue crystallized from alcohol-acetone in the form of colorless needles; yield, 0.35 g. (90%); m. p. 89–90°. Two recrystallizations raised the melting point to 93–94°.

Anal. Calc'd for $C_{19}H_{14}$: C, 94.2; H, 5.8.
Found: C, 94.2; H, 5.8.

The *picrate* crystallizes from alcohol as golden-yellow needles; m. p. 172.5–174°.

Anal. Calc'd for $C_{19}H_{14}\cdot C_6H_3N_3O_7$: N, 8.9. Found: N, 9.0.

SUMMARY

The reactions of 1,2,3,4-tetrahydrophenanthrene with succinic anhydride and with acetyl chloride have been investigated. In both cases the substituent group enters the 9 position of the tetrahydrophenanthrene.

The syntheses of triphenylene and of 1-methyltriphenylene are described.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

THE ACYLATION OF ALDOXIMES. II.* THE INVERSION OF CONFIGURATION IN THE PREPARATION OF CARBANILINO ALDOXIMES FROM PHENYL ISOCYANATE AND *syn*-ALDOXIMES†

A. E. RAINSFORD AND CHARLES R. HAUSER

Received May 11, 1939

The purpose of this series of papers is to study the reactions of *syn* and *anti* aldoximes with various acylating reagents, and to investigate the action of bases on the acyl derivatives thus formed. These reactions are of interest in themselves, and are of especial importance in connection with the geometrical isomerism of this series of compounds.

In spite of the rather extensive literature[1] on the acylation of aldoximes, there are still a number of unsolved problems; in fact, a perusal of the literature gives one the impression that the uncertainties outweigh the certainties in this field. In this connection Brady and McHugh[1a] have pointed out that the following problems should be considered: "(*1*) How far it is justifiable to assume that all acyl derivatives which on alkaline hydrolysis give the nitrile have a similar configuration? (*2*) If the above assumption is correct, why one reagent, *e.g.*, ethyl chloroformate, brings about inversion of some oximes but not of others, whereas another similar reagent, diphenylcarbamyl chloride, always brings about inversion, and a third, benzoyl chloride, never. (*3*) Why phenylcarbimide causes inversion, but α-naphthylcarbimide does not do so . . . ." It is hoped that with the aid of more recent results some light might be thrown on these and related problems.

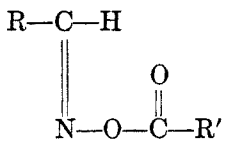
At the time (1925) of the above quotation it was generally believed that of a pair of geometrically isomeric acyl aldoximes, (I and II), only the β, or *anti* isomer (II)‡ reacts with alkali to give nitrile.

* The paper on carbethoxy aldoximes by HAUSER, JORDAN, AND O'CONNER, *J. Am. Chem. Soc.*, **57**, 2456 (1935), is regarded as the first paper of this series.

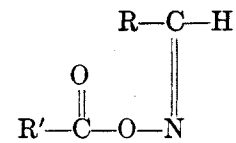
† This paper is from a portion of a thesis presented by A. E. Rainsford in partial fulfilment of the requirements for the Ph.D. degree at Duke University.

[1] See especially, (*a*) BRADY AND MCHUGH, *J. Chem. Soc.*, **127**, 2417 (1925); (*b*) FREUDENBERG, "Stereochemie", **7**, 996–9 (1933).

‡ For a discussion of the evidence supporting these configurations for α, and β aldoximes and their acyl derivatives see especially, FREUDENBERG, "Stereochemie", **7**, 974–981; GILMAN, "Organic Chemistry", John Wiley and Sons, New York, N. Y.,



(I) *syn* (α)



(II) *anti* (β)

This assumption then seemed plausible because with the acetyl, and carbanilino aldoximes (the most widely studied acyl derivatives) only the *anti* isomers give mainly nitrile when treated with alkali; most of the α, or *syn* isomers‡ of these derivatives give with this reagent almost entirely the corresponding α, or *syn* aldoxime.[2] We now know however, that, although all acyl *anti* aldoximes (II) probably always form nitrile more readily than the isomeric acyl *syn* derivatives (I), certain of the latter also react with hot alkali to give partly or even largely nitrile. Consequently, in certain cases in which the isomeric *anti* derivatives cannot be isolated for comparison, acyl *syn* derivatives that give considerable nitrile with alkali might easily be mistaken for *anti* isomers. This has happened with certain carbethoxy, and diphenylcarbamyl derivatives which have been isolated in only one isomeric form.

The carbethoxy derivatives, prepared from ethyl chloroformate and *syn* aldoximes in alkaline solution, were formerly assigned[1a] the *anti* configuration because when heated with alkali they gave considerable nitrile or corresponding acid. We now know however, that these derivatives must have the *syn* configuration because when treated with cold alkali* or with *n*-butylamine,[3] they give almost quantitative yields of the original *syn* aldoximes. The isomeric carbethoxy *anti* derivatives are formed presumably when *anti* aldoximes in alkaline solution are treated with ethyl chloroformate, but they are decomposed immediately by the alkali to give nitrile which is the product isolated.

The diphenylcarbamyl derivatives also are prepared from the sodium salts of *syn* aldoximes, and in a paper to be published shortly it will be shown that they likewise very probably are *syn* derivatives.

Thus, contrary to the assumption stated in (*2*) of the above quotation, no inversion of configuration occurs in the reactions of *syn* aldoximes (as sodium salts) with either ethyl chloroformate or diphenylcarbamyl chloride.

1938, p. 386. Since these configurations are now commonly accepted it seems justified to use the terms, "*syn*" and "*anti*", which have more significance than the symbols, α and β.

[2] See HAUSER AND JORDAN, *J. Am. Chem. Soc.*, **57**, 2450 (1935).

[3] HAUSER AND JORDAN, *ibid.*, **58**, 1772 (1936).

The reaction of phenyl isocyanate (phenylcarbimide) with aldoximes, mentioned in (*3*) of the above quotation, is somewhat different. Unlike the reactions with ethyl chloroformate and with diphenylcarbamyl chloride, which were carried out with the salts of oximes, the reaction with phenyl isocyanate has been carried out with the free oximes in ether solution. Brady and co-workers[4] showed that under these conditions *syn* aldoximes with phenyl isocyanate give carbanilino *anti* aldoximes or mixtures of *syn*, and *anti* derivatives; *anti* aldoximes with this reagent also give *anti* derivatives. The carbanilino *syn* aldoximes were generally obtained by heating the *anti* derivatives in alcoholic solution. Since it is possible to isolate certain carbanilino derivatives in two isomeric forms, their configurations are readily determined.

In this paper we have confirmed Brady's conclusions that in reaction with *syn* aldoximes phenyl isocyanate is capable of causing inversion of configuration while α-naphthyl isocyanate apparently is not. Also, we have made a further study of the phenomenon of inversion and of its prevention.

In Table I are given the melting points and probable configurations of the products obtained from the reactions of phenyl isocyanate with certain *syn*, and *anti* aldoximes in ether solution. In cases in which a similar product has been prepared previously the melting points recorded in the literature are given. The relative amounts of ether used, and the approximate time that elapsed before precipitation began are indicated also, since these factors should be considered in certain cases. In Table II are given the yields of products (with melting points in parentheses) obtained from certain pure carbanilino *syn*, and carbanilino *anti* derivatives with pyridine and with *n*-butylamine.

It can be seen from Table I that the product which precipitated within a few seconds when phenyl isocyanate was added to *syn*-3,4-methylenedioxybenzaldoxime in a minimum of ether (expt. 1) melted within a few degrees of the melting point of the product obtained from the isomeric *anti* aldoxime (expt. 2). In agreement with Brady and McHugh[1a], we believe that the product from the *syn* aldoxime consisted mostly of the carbanilino *anti* derivative since with hot alkali it gave mostly 3,4-methylenedioxybenzoic acid; the derivative from the *anti* aldoxime appeared to consist entirely of the *anti* derivative, giving with hot alkali only 3,4-methylenedioxybenzoic acid. This conclusion is supported by our pyridine-*n*-butylamine test[3] for configuration; however, the results of this test with the crude carbanilino derivatives were not very satisfactory, and attempts to recrystallize the crude derivatives always resulted in

[4] BRADY AND DUNN, *J. Chem. Soc.*, **109**, 650 (1916); also reference 1 *a*.

TABLE I

PRODUCTS OBTAINED FROM PHENYL ISOCYANATE AND SUBSTITUTED BENZALDOXIMES IN ETHER SOLUTION

EXPT.	CONFIG.	SUBSTITUENT	AMT. OF ETHER USED	TIME OF PRECIPITATION	M. P. CRUDE PRODUCT			M. P. RECRYST. PRODUCT		
					Found	Lit.	Config.	Found	Lit.	Config.
1	*syn*	3,4-CH_2O_2	Minimum	5–15 sec.	78–80	78	*anti* + (*syn*)[a]	Dec.	Dec.	—
2	*anti*	3,4-CH_2O_2	Minimum	Instantly	82–84	84	*anti*	Dec.	Dec.	—
3	*syn*	3,4-CH_2O_2	2 × minimum	1–2 min.	80–82	—	*anti* + (*syn*)[a]	—	—	—
4	*syn*	3,4-CH_2O_2	4 × minimum	1 hr.	112–115	—	*syn* + (*anti*)[a]	127	—	*syn*
5	*syn*	3,4-CH_2O_2	5 × minimum	Several hrs.[b]	123–125	—	*syn*	127	—	*syn*
6	*syn*	4-OCH_3	—	1–2 min.	78–80	74	*anti* + *syn*	—	—	—
7	*anti*	4-OCH_3	—	Instantly	74	74	*anti*	—	—	—
8	*syn*	4-OCH_3	—	10–15 min.	100–103	—	*syn* + (*anti*)[a]	110	103	*syn*
9	*syn*	3-NO_2	—	3–7 min.	114–120	105	*syn* + *anti*	148	148	*syn*
10	*anti*	3-NO_2	—	Instantly	88–90	94	*anti*	94	94	*anti*
11	*syn*	4-$N(CH_3)_2$	—	2 sec.–20 min.	114–116	—	*anti*	118	117	*anti*

[a] The parenthesis indicates that the isomer is probably present in relatively small amounts.

[b] In this experiment the precipitate was obtained only after cooling the reaction mixture.

TABLE II

YIELDS OF PRODUCTS[a] FROM PURE CARBANILINO DERIVATIVES OF SUBSTITUTED BENZALDOXIMES WITH PYRIDINE AND *n*-BUTYLAMINE

CARBANILINO DERIV.		WITH PYRIDINE		With *n*-BUTYLAMINE	
Config.	Substituent	% Nitrile	% Orig. Deriv. Recov.	% Nitrile[b]	% *syn*-Oxime
syn	3,4-CH_2O_2		93 (m.p. 126°)		70 (m.p. 110°)
syn	3-NO_2		93 (m.p. 140°)		90 (m.p. 118°)
anti	3-NO_2	82 (m.p. 114°)		93 (m.p. 110–112°)	
syn	4-$(CH_3)_2N$		93 (m.p. 154°)		90 (m.p. 140°)
anti	4-$(CH_3)_2N$	80 (m.p. 70–72°)		88 (m.p. 72–74°)	

[a] The melting points of the products on which these yields are based are given in parentheses; after recrystallization of the products, their melting points agreed with those reported in the literature.

[b] The addition of *n*-butylamine to most *anti* derivatives generates considerable heat.

decomposition. The crude derivatives (from expts. 1 and 2) were decomposed by pyridine to give nitrile but only a low yield of this product could be isolated. With *n*-butylamine, the reaction was not vigorous as is generally the case with pure carbanilino-anti-derivatives, and a small amount of *anti* oxime** was obtained instead of nitrile. It can be seen from Table II that recrystallized (pure) *anti* derivatives with pyridine or *n*-butylamine (hot) give high yields of nitrile.

The product that precipitated within two minutes when phenyl isocyanate was added to *syn*-3,4-methylenedioxybenzaldoxime in about twice the minimum of ether (expt. 3) also probably consisted mostly of the *anti* derivative, but the products that precipitated after an hour or more when four or five times the minimum of ether was used (expts. 4 and 5) undoubtedly consisted mostly if not entirely of the *syn* derivative. Recrystallization of these products gave pure carbanilino-*syn*-3,4-methylenedioxybenzaldoxime, melting at 127°. Brady and co-workers did not obtain this product, having carried out the reaction only in a minimum of ether. They reported that the *syn* derivative (m.p. 104°) was obtained on heating the *anti* derivative in alcohol. We were able to isolate a similar product (m.p. 107–109°) in very small yield but it was not the pure *syn* derivative. That our product melting at 127° is the pure *syn* derivative is shown by analysis and by the fact that it is stable in pyridine but is decomposed by *n*-butylamine or hot alkali to give the original *syn* aldoxime. (See Table II.)

Similar results have been obtained with phenyl isocyanate and the other aldoximes studied. The precipitate that formed within about a minute from *syn*-4-methoxybenzaldoxime (expt. 6) probably consisted mostly of the *anti* derivative, since Brady and McHugh[1c] have shown that a similar product (m.p. 74°) is decomposed by alkali to give nitrile. The precipitate that formed after 10–15 minutes (expt. 8), however, very likely consisted almost entirely of the *syn* derivative, which was obtained in the pure condition on recrystallization.

The crude product from *syn*-3-nitrobenzaldoxime (expt. 9), although melting somewhat higher than the product obtained by Brady and Dunn,[4] probably consisted of a mixture of the *syn*, and *anti* derivative; the pure *syn* derivative was obtained on recrystallizing the product from hot alcohol.

** The addition of *n*-butylamine to pure *anti* derivatives generates sufficient heat to give nitrile; see reference 3. Crude carbanilino-*anti*-3,4-methylenedioxybenzaldoxime apparently does not generate enough heat when treated with *n*-butylamine to give an appreciable amount of nitrile and *anti* oxime is obtained instead. In this connection it should be noted that when *n*-butylamine is added to an acetyl *anti* aldoxime and the reaction mixture cooled, the anti aldoxime is the main product. See HAUSER AND JORDAN, *J. Am. Chem. Soc.*, **58**, 1419 (1936).

The reaction of phenyl isocyanate with *anti*-3-nitrobenzaldoxime (expt. 10) gave a crude product which on recrystallization from cold acetone gave the pure *anti* derivative. The configurations of these derivatives is established by their reactions with pyridine and *n*-butylamine (See Table II), and with alkali.[4]

The reaction with *syn*-4-dimethylaminobenzaldoxime (expt. 11) is of especial interest. Although the isomeric *anti* aldoxime has never been isolated, the carbanilino *anti* derivative is readily obtained by the action of phenyl isocyanate on *syn*-4-dimethylaminobenzaldoxime, even when the precipitation is retarded for half an hour by the use of a relatively large amount of ether. In fact, of the *syn* aldoximes studies by us, this is the only one that gave pure *anti* derivative. The latter was obtained by recrystallization of the crude product from cold acetone. When heated

TABLE III

PRODUCTS[a] FROM α-NAPHTHYLCARBANILINO DERIVATIVES OF SUBSTITUTED BENZALDOXIMES WITH PYRIDINE AND *n*-BUTYLAMINE

BENZALDOXIME USED TO PREPARE DERIVATIVE		PRODUCT FROM DERIVATIVE WITH PYRIDINE		PRODUCT FROM DERIVATIVE WITH *n*-BUTYLAMINE	
Config.	Substituent	% Nitrile	% Deriv. recov.	% Nitrile	% α-Oxime
syn	3,4-CH_2O_2		80 (m.p. 225)		75 (m.p. 110)
syn	4-OCH_3		89 (m.p. 160)		38 (m.p. 64)
syn	4-$N(CH_3)_2$		70 (m.p. 141–144)		—
anti	3,4-CH_2O_2	88 (m.p. 92)		78 (m.p. 91)	
anti	3-NO_2	46 (m.p. 114)		25 (m.p. 117)	

[a] The melting points of the products on which these yields are based are given in parentheses.

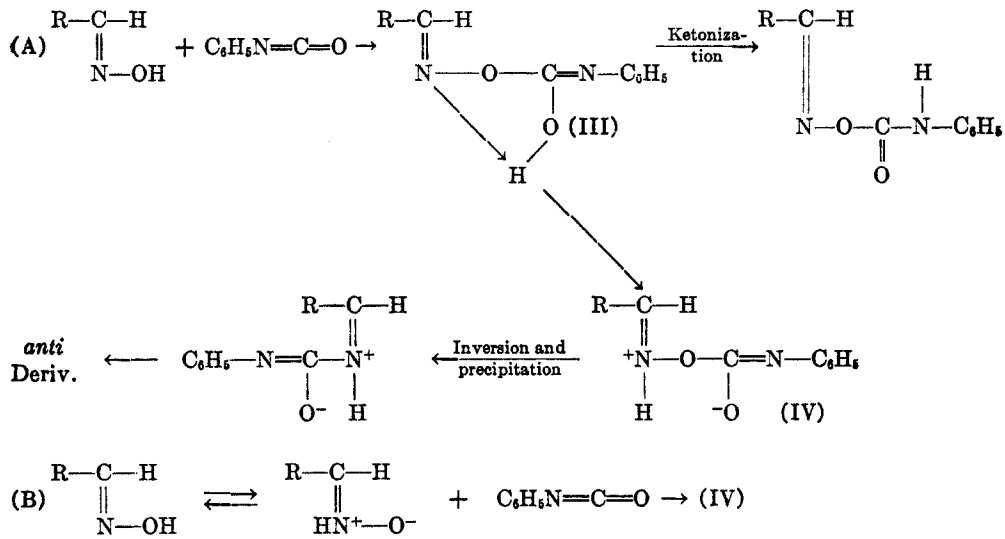
in alcohol this *anti* derivative is converted into the *syn* isomer as reported by Brady. The configurations of these isomeric derivatives seems well established; the *syn* derivative may be recovered unchanged from pyridine, but is decomposed by *n*-butylamine or hot alkali[4] to give the original *syn* aldoxime, whereas the *anti* isomer is decomposed by pyridine, *n*-butylamine (hot) or alkali[4] to give nitrile (See Table II).

In confirming Brady's conclusion that α-naphthyl isocyanate is apparently not capable of causing inversion of configuration, we have prepared derivatives from this reagent and certain representative *syn*, and *anti* aldoximes in a minimum of ether. The melting points of the derivatives prepared by us agreed essentially with those reported in the literature. From a study of the reactions with alkali Brady and co-workers[5] concluded

[5] BRADY AND RIDGE, *J. Chem. Soc.*, **123**, 2163 (1923); also reference 1*a*.

that the derivatives obtained from *syn* aldoximes have the *syn* configuration and that those from *anti* oximes, the *anti* configuration. We have confirmed this conclusion by means of our pyridine-*n*-butylamine test for configuration. It can be seen from Table III that the derivatives obtained from *syn* aldoximes are recovered unchanged from pyridine but are aminolyzed by *n*-butylamine to regenerate the original *syn* aldoxime, the derivatives from *anti* aldoximes are decomposed by pyridine or *n*-butylamine (hot) to give nitrile. The rather low yields of nitrile and oxime obtained in certain cases is due at least in part to the difficulty of isolating these products.

The mechanism for the inversion of configuration brought about by the action of phenylisocyanate on *syn* aldoximes is not entirely clear, but certain suggestions can be made in this connection. Since *syn* aldoximes are commonly converted into their *anti* isomers through the intermediate formation of their hydrochloride salts, it seems possible that the inversion effected by phenyl isocyanate likewise involves the formation of a "salt-like" intermediate with a positive charge on the nitrogen atom. Such a substance might be formed by the reaction of either tautomeric form of the aldoxime with phenylisocyanate as represented by A and B.



In A the addition of the oxime to the carbon-oxygen double bond of the isocyanate†† would give an acid (III), which might either undergo ketoni-

†† The addition of other hydroxy compounds to phenyl isocyanate has been formulated in this way. See ALLEN AND BLATT, Gilman's "Organic Chemistry", John Wiley and Sons, New York, N. Y., **1938**, p. 574.

zation to give the *syn* derivative, or form the "inner" salt (IV). The tendency for chelation (hydrogen bond formation), involving the acid hydrogen and the free pair of electrons on the oxime nitrogen, should facilitate the formation of (IV). As represented by B, IV might result from the direct action of the nitrone (amine oxide) form of the oxime with phenyl isocyanate. Also, it is possible, as suggested by Brady and Dunn,[4] that the nitrone form of the *syn* oxime itself undergoes inversion to the nitrone form of the *anti* oxime which then reacts with phenyl isocyanate.

In connection with this explanation two questions arise. First, why with *syn*-3,4-methylenedioxybenzaldoxime, phenyl isocyanate causes inversion in a minimum of ether but not in several times the minimum of ether; and second, why phenyl isocyanate is capable of causing inversion, whereas α-naphthyl isocyanate is apparently not. At first sight it might appear that inversion occurs also in the relatively dilute solution, but before the *anti* derivative precipitates it isomerizes, giving the *syn* derivative. While this is a possible explanation of the result, it is also possible that in the relatively dilute solution, an appreciable amount of *anti* derivative is never formed, because under these conditions the concentration of the acid (III) and salt (IV) is never sufficiently great to bring about appreciable inversion. The failure of α-naphthyl isocyanate to cause inversion might be explained in a similar manner; that is, the intermediate salt corresponding to IV might never be formed in sufficient concentration to cause inversion. In this connection it should be mentioned that α-naphthyl isocyanate appears to be less active than phenyl isocyanate towards *syn* aldoximes; in no case were we able to cause a derivative of the former to precipitate within less than eight minutes, whereas with phenyl isocyanate under similar conditions the derivative generally precipitated within a few seconds.

On the basis of the ideas discussed above it was predicted that no inversion should occur if the reaction of *syn* aldoximes with phenyl isocyanate were carried out in the presence of a base of sufficient strength to prevent the formation of an intermediate with a positive charge on the nitrogen atom; and, in agreement with this, it has been found that no inversion occurs when the reaction is carried out in the presence of triethylamine or tri-*n*-propylamine.

In Table IV are given the melting points and configurations of the derivatives obtained from *syn* aldoximes and phenyl isocyanate in the presence of approximately equivalent amounts of certain tertiary amines and a minimum of ether; the approximate time of precipitation is also given in this table. Except for the presence of the amines (and slightly less ether) these experiments were carried out under essentially the same conditions as those used in the experiments represented in Table I.

It can be seen from Table IV that in the presence of triethylamine or tri-*n*-butylamine (expts. 1–7), the four *syn* benzaldoximes studied in this work reacted with phenyl isocyanate to give high yields of the corresponding carbanilino *syn* derivative. With *syn*-3,4-methylenedioxybenzaldoxime, practically pure *syn* derivative was obtained directly, even in the presence of only one-fourth of an equivalent of triethylamine (expt. 2). With the other three *syn* benzaldoximes, the precipitates melted within a few degrees of the melting points recorded for the *syn* derivatives; the pure *syn* derivatives were obtained on recrystallization of the precipitates.

TABLE IV

PRODUCTS OBTAINED FROM PHENYL ISOCYANATE AND SUBSTITUTED *syn*-BENZALDOXIMES IN PRESENCE OF TERTIARY AMINES AND MINIMUM OF ETHER

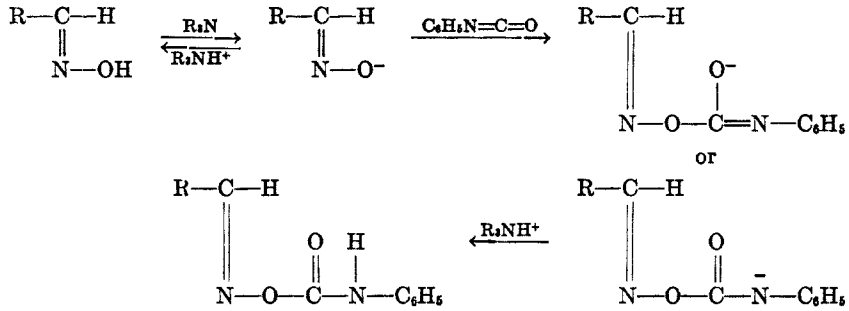
EXPT.	SUBSTITUENT IN *syn*-BENZALDOXIME	TERTIARY AMINE USED	TIME OF PRECIPITATION	M.P. OF PRODUCT	CONFIGURATION OF PRODUCT
1	3,4-CH_2O_2	Triethylamine	5–15 sec.	126–127	*syn*
2	3,4-CH_2O_2	Triethylamine[a]	5–15 sec.	123–124	*syn*
3	4-CH_3O	Triethylamine	10 min.	103–105	*syn*
4	3-NO_2	Triethylamine	3 min.	135–137	*syn*
5	4-$N(CH_3)_2$	Triethylamine	10 sec.	144–148	*syn*
6	3,4-CH_2O_2	Tri-*n*-propylamine	50 sec.	126–127	*syn*
7	4-$N(CH_3)_2$	Tri-*n*-propylamine	20 min.	145–148	*syn*
8	3,4-CH_2O_2	Dimethylaminobenzaldehyde	20–50 sec.	82	*anti*
9	3,4-CH_2O_2	Dimethylaniline	20–30 min.	125–126	*syn*
10	4-$N(CH_3)_2$	Dimethylaniline	1–2 min.	114–117	*anti* + (*syn*)
11	4-$N(CH_3)_2$	Dimethylaniline[b]	8–9 min.	142–144	*syn*
12	4-$N(CH_3)_2$	Pyridine	1–3 min.	108–110	*anti*
13	3,4-CH_2O_2	Pyridine	—	—	*anti* ?

[a] In this experiment only one-fourth equivalent of triethylamine was used.

[b] In this experiment approximately thirteen times the equivalent of dimethylaniline was used.

It should be noted that in the presence of these amines, the *syn* derivative has been precipitated in most cases within the time in which the *anti* derivative was obtained in the absence of these bases (compare Table I). Thus it can hardly be argued that the *anti* derivative was also obtained first in the presence of the amine, and then isomerized to the *syn* derivative; this becomes still more unlikely when one considers that the *anti* derivatives are readily decomposed by tertiary amines to form nitriles. There seems little doubt therefore that, in the presence of these tertiary amines, phenyl isocyanate reacts with *syn* aldoximes to form the corresponding *syn* deriva-

tive directly. In this connection it should be pointed out that in the presence of these bases, the anion of the *syn* aldoxime, rather than the free oxime, may react with phenyl isocyanate; the reaction may be represented as follows:



Experiments 8 to 13 of Table IV were carried out in the presence of tertiary amines that are much less basic than triethylamine or tri-*n*-propylamine. It can be seen from the table that dimethylaminobenzaldehyde (expt. 8) and pyridine (expt. 13) are apparently not sufficiently basic to prevent inversion when *syn*-3,4-methylenedioxybenzaldoxime is treated with phenyl isocyanate. In the presence of pyridine no pure derivative was obtained, but since nitrile was isolated from the reaction mixture, the *anti* derivative was apparently formed and then decomposed.

The reaction of *syn*-3,4-methylenedioxybenzaldoxime with phenyl isocyanate in the presence of dimethylaniline (expt. 9) gave the *syn* derivative, but in this case, it was not possible to cause precipitation within less than twenty minutes and in this time the *syn* derivative might have been obtained even in the absence of the amine.

The reaction of *syn*-4-dimethylaminobenzaldoxime with phenyl isocyanate in the presence of an equivalent of dimethylaniline (expt. 10) or of pyridine (expt. 12) gave products that appeared to consist mostly of the *anti* derivative, since on dissolving them in pyridine they were decomposed to give partly nitrile; a little of the *syn* derivative was also isolated from the product of experiment 10. It is of interest to note that in the presence of a relatively large amount of dimethylaniline, (expt. 11), the product obtained consisted apparently only of the *syn* derivative which could be recovered unchanged from pyridine; after recrystallization practically pure *syn* derivative (m.p. 150–152°) was obtained.

Thus, although certain tertiary amines prevent inversion of configuration in the reaction of phenyl isocyanate with *syn* aldoximes, certain weaker bases do not; apparently, inversion is prevented only when the

medium is sufficiently basic to prevent the formation of a "salt-like" intermediate with a positive charge on the nitrogen atom.

Finally, it should be pointed out that the results presented in this paper are in agreement with the view held in this laboratory that the acylation of *syn* aldoximes in sufficiently basic solution involves no inversion of configuration.

Acknowledgment.—The writers wish to thank Miss Mildred Patterson and Miss Gertrude Vermillion for checking certain of the results reported in this paper.

EXPERIMENTAL

Reactions of syn, *and* anti *aldoximes with phenyl isocyanate.*—(See Table I). To 2 g. of *syn*-3,4-methylenedioxybenzaldoxime in a minimum of dry ether (approx. 10 cc.) was added 2 cc. of phenyl isocyanate according to the method of Brady and McHugh.[1a] The precipitate that formed within a few seconds was collected by filtration, washed with dry ether, and pressed on a porous plate. Attempts to recrystallize the crude carbanilino derivative (m.p. 78–80°) from several types of solvents resulted in decomposition. The crude derivative, on heating with 2*N* sodium hydroxide gave an 80% yield of 3,4-methylenedioxybenzoic acid. Treatment of the crude derivative with pyridine according to the general directions given below, gave a mixture of products from which only a 10–15% yield of nitrile could be isolated. Addition of *n*-butylamine to the crude derivative failed to generate much heat, and it was difficult to isolate a pure substance from the products; however, a small amount of *anti* aldoxime (m.p. 136–140°) was isolated.

The addition of phenyl isocyanate to *anti*-3,4-methylenedioxybenzaldoxime in dry ether gave a precipitate instantaneously. Attempts to recrystallize the crude carbanilino derivative (m.p. 82–84°) resulted in decomposition. The crude derivative, on heating with alkali gave a 90% yield of 3,4-methylenedioxybenzoic acid. Treatment of the crude carbanilino derivative with pyridine gave a mixture of products (apparently diphenylurea and nitrile) from which a 20–25% yield of pure nitrile was isolated. The high yield of nitrile reported previously[2] for this reaction was based apparently on the crude product. Addition of *n*-butylamine to the crude carbanilino derivative at room temperature failed to generate much heat, and, contrary to an earlier report[2], no appreciable amount of nitrile could be isolated. On working up the mixture (involving an acid extraction of the amine) a 30% yield of the *syn* aldoxime (m.p. 110°) was isolated. The *anti* aldoxime was probably first formed in the reaction with *n*-butylamine, but was converted to the *syn* isomer during the acid extraction.

The reaction of *syn*-3,4-methylenedioxybenzaldoxime with phenyl isocyanate has been carried out also in the presence of excess ether. In the presence of about twice the minimum of ether the product was similar to that obtained with less ether, but in the presence of four or five times the minimum of ether, the precipitate formed much more slowly and apparently consisted mostly if not entirely of the *syn* derivative. On recrystallization from alcohol pure carbanilino-*syn*-3,4-methylenedioxybenzaldoxime, melting at 127°, was obtained. Since this substance has apparently not been isolated previously in the pure state, it was analyzed.

Anal. Calc'd for $C_{15}H_{10}N_2O_4$: N, 9.86. Found: N, 9.84.

The reactions of certain other *syn*, and *anti* aldoximes with phenyl isocyanate

were carried out in a similar manner. The results are summarized in Table I. In experiment 6 of this table, 10 cc. of ether to 1 g. of *syn*-4-methoxybenzaldoxime was used; this is more than the minimum of ether required for solution of the oxime. In experiment 11, *syn*-4-dimethylaminobenzaldoxime was dissolved in a minimum of ether, but the same product has been obtained using several times the minimum of ether.

Reactions of syn *aldoximes with phenyl isocyanate in the presence of certain tertiary amines.*—(See Table IV). Except for the presence of the amines, these experiments were carried out in essentially the same manner as those described above with the corresponding *syn* aldoxime in a minimum of ether. It seemed to make no difference whether the tertiary amine was mixed with the phenyl isocyanate and the mixture added to the oxime in ether, or the amine dissolved in the ether solution of the oxime and the phenylisocyanate added to this solution; in all cases the corresponding carbanilino *syn* derivative was obtained. The presence of the amine appeared to retard the precipitation of the derivative. However, by using less ether in these experiments than was used in corresponding experiments in the absence of the amine it was possible in most cases to cause precipitation of the *syn* derivative in the presence of the amine within the time required for precipitation of the *anti* derivative in the absence of this base. A typical experiment was carried out as follows. Two grams of *syn*-3,4-methylenedioxybenzaldoxime was dissolved in a warm mixture of approximately 7 cc. of ether and 1 cc. of triethylamine. After the solution had cooled to room temperature 2 cc. of phenyl isocyanate was added, and the solution was cooled slightly with cold water. The *syn* derivative began to precipitate within ten seconds; the precipitation was complete within one minute. A summary of results with other *syn* aldoximes is given in Table IV.

*The pyridine-*n*-butylamine test for configuration.*—One-gram samples of the derivative to be tested were placed in each of two 50-cc. Erlenmeyer flasks and 4–5 cc. of pyridine added to one, and the same amount of normal butylamine added to the other in ½-cc. portions from a medicine dropper. Addition of butylamine to *anti* compounds was usually accompanied by an evolution of considerable heat. The flasks were stoppered and allowed to stand overnight at room temperature. The solutions were poured into about 40 cc. of crushed ice and water and the mixture was filtered. The *anti* derivative with both pyridine and *n*-butylamine gave nitrile, while *syn* derivatives with pyridine gave unchanged derivative, and with *n*-butylamine gave *syn* aldoxime. In the case of *syn* derivatives with butylamine, high yields of *N*-phenyl-*N'*-*n*-butylurea were also obtained. In these cases the precipitated mixture was thoroughly washed in the crucible with 2*N* sodium hydroxide, and the oxime was isolated from the washings in the usual manner by acidifying with carbon dioxide. In certain instances when yields at first appeared to be low, both from pyridine and butylamine solutions, the filtrates from the original precipitate were extracted with 50 cc. of ether. The ether layer was washed with water and evaporated, yielding additional quantities of products. The results obtained from these reactions with pure carbanilino derivatives are shown in Table II.

Reactions of syn, *and* anti *aldoximes with α-naphthyl isocyanate.*—The reaction of certain *syn*, and *anti* aldoximes with α-naphthyl isocyanate were carried out essentially as described by Brady and Ridge.[5] The melting points of the derivatives obtained agreed essentially with those reported by these earlier workers.

The results of the reactions of these derivatives with pyridine and *n*-butylamine are summarized in Table III. These reactions were carried out essentially as described above with the carbanilino derivatives, except that in isolating the nitrile, it was necessary to dissolve α-naphthylamine in hydrochloric acid.

SUMMARY

1. Brady's conclusion that phenyl isocyanate is capable of converting certain *syn* aldoximes into carbanilino *anti* derivatives has been confirmed. An explanation is suggested for this inversion of configuration.

2. We have shown that inversion does not occur when *syn* aldoximes are treated with phenyl isocyanate in the presence of certain tertiary amines. This supports the hypothesis that there is no inversion of configuration during the preparation of acyl derivatives when the reaction is carried out in solution in the presence of a sufficiently strong base.

3. Carbanilino-*syn*-3,4-methylenedioxybenzaldoxime has been prepared in the pure condition for the first time.

4. Further results on the reactions of carbanilino *syn*, and carbanilino *anti* aldoximes with pyridine and with *n*-butylamine are reported.

5. Brady's conclusion that there is no inversion of configuration when *syn* aldoximes are treated with α-naphthyl isocyanate has been confirmed. It has been shown that α-naphthylcarbanilino *syn* aldoximes may be recovered unchanged from pyridine, but are decomposed by *n*-butylamine to give *syn* aldoximes; the corresponding *anti* isomers with pyridine or *n*-butylamine give nitrile.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE EASTMAN KODAK COMPANY]

DIETHYL METHYLENEMALONATE

G. B. BACHMAN AND H. A. TANNER

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The reaction of formaldehyde with malonic ester has been studied frequently. A number of different products have been isolated and identified, but the formation of diethyl methylenemalonate was first demonstrated by W. H. Perkin, Jr.[1] In later publications Perkin describes methods of obtaining this substance in larger quantities, but despite continued work by him and by others, no reliable method giving satisfactory yields has yet been made available. An alternative procedure involving the reaction of methylene chloride or iodide with disodium malonic ester was developed by Tanatar,[3] but this method also is not very satisfactory. No other practicable methods have been proposed, although it should be mentioned that diethyl methylenemalonate is formed when ethyl pentanehexacarboxylate is treated with methylene iodide and sodium ethylate.[2]

A few of the reactions which may occur when formaldehyde and diethyl malonate are brought together are illustrated below:

A. $CH_2O + CH_2(COOEt)_2 \rightarrow HOCH_2CH(COOEt)_2 \rightarrow CH_2{=}C(COOEt)_2 + H_2O$

(I) (II)

B. $2CH_2O + CH_2(COOEt)_2 \rightarrow (HOCH_2)_2C(COOEt)_2$

(III)

C. $HOCH_2CH(COOEt)_2 + CH_2(COOEt)_2 \rightarrow (EtOOC)_2CHCH_2CH(COOEt)_2$

(I) (IV)

D. $(HOCH_2)_2C(COOEt)_2 + 2CH_2(COOEt)_2 \rightarrow$

(III)

$(EtOOC)_2CHCH_2C(COOEt)_2CH\ CH(COOEt)_2$

(V)

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[1] (*a*) PERKIN, *Ber.* **19**, 1053 (1886).

Others who have prepared methylenemalonic ester by this same method, or by slight variations of it, include:

(*b*) KNOEVENAGEL, *ibid.*, **27**, 2345 (1894).

(*c*) KOMPPA, *Chem. Zentr.* **1898**, II, 1169.

(*d*) GAULT, *Bull. soc. chim.*, **11**, 381 (1912).

(*e*) MEERWEIN AND SCHURMAN, *Ann.*, **398**, 214 (1913).

Obviously still further condensations can take place, and more complex products make their appearance. It is difficult to deduce conditions which would favor the formation of the desired product exclusively. However, it is known that a catalyst is needed to promote any reaction at all. Acetic anhydride was first used,[1a] but basic substances such as dilute sodium hydroxide, diethylamine and piperidine appear to be more satisfactory. A reaction medium of pH 9 has been recommended.[1f] Various temperatures and combinations of temperatures ranging from 0° to the boiling point of acetic anhydride have been suggested as suitable for the reaction. There is no indication that the formation of methylenemalonic ester is favored by one temperature any more than another. Antipolymerization catalysts have not been used, although their presence would seem desirable. The effect of the solvent on the course of the reaction has not as yet been investigated. Alcohol has been used frequently.

THE PREPARATION OF DIETHYL METHYLENEMALONATE

In our attempts to repeat the work of the earlier investigators yields of from 0 to 20 per cent. were obtained. Occasionally, with conditions apparently the same as in successful experiments, none of the desired product was obtained. As a first variation we attempted to carry out the reaction in the vapor phase, where it was hoped the shorter times of contact with the catalyst would hinder secondary reactions leading to high-molecular-weight by-products.

In general, the reactants were passed over various catalysts packed in a glass tube mounted vertically in an electric resistance furnace. The formaldehyde and malonic ester were introduced from above (*1*) separately, as 40 per cent. formalin and malonic ester, (*2*) separately, as solid paraformaldehyde and malonic ester, or (*3*) as a solution of formaldehyde gas in malonic ester. The materials were introduced as nearly as possible at equimolecular rates. The temperature in the reaction chamber was measured by means of a thermocouple. The conditions employed in some of the experiments and the results obtained are summarized in Table I. It is obvious that the yields are comparable to those obtained previously.

(*f*) WELCH, *J. Chem. Soc.*, **1930**, 259; **1931**, 673.

(*g*) ZELINSKY, *Ber.*, **22**, 3295 (1889).

(*h*) WOJCIK AND ADKINS, *J. Am. Chem. Soc.*, **56**, 2424 (1934).

[2] Most authors have failed to mention yields at all, but BOTTOMLEY AND PERKIN, *J. Chem. Soc.*, **77**, 294 (1900), make the following statement: "The best yield obtained this way was 22 g. of the crude dry product (from 96 g. of diethyl malonate—a 21% yield—Authors) . . . , but for some reason the yield varies very much in different operations, although the greatest care may be taken to reproduce in each case the same conditions."

[3] TANATAR, *Ann.*, **273**, 48 (1893).

Returning to a study of the preparation in the liquid phase, a large number of experiments were run in which the ratio of formaldehyde to malonic ester and the natures and amounts of both the solvent and the catalyst were varied. Eventually a procedure was developed which enabled us to obtain methylene malonic ester in yields of 40–45 per cent. consistently. Some of the more significant experiments are shown in Table II. The final procedure, which was repeated many times with satisfactory results, is given in the experimental part. It is believed that the use of an acid medium, of copper salts, of potassium salts and of two moles of formaldehyde are all important. The excess of formaldehyde

TABLE I

VAPOR PHASE REACTION OF FORMALDEHYDE AND MALONIC ESTER

MALONIC ESTER WITH:	YIELD PER 100 G. MALONIC ESTER[b]				
	Catalyst[a]	Temp., °C.	Recov. Ester, g.	Product, g.	High-Boiling, g.
40% Formalin	$AlPO_4$	300	30	6	25
40% Formalin	"	420	25	17	—
Paraformaldehyde	"	420	52	9	—
40% Formalin + 5% piperidine	Glass wool	380	0	17	14
CH_2O gas	$AlPO_4$	400	27	10	40
CH_2O dissolved	Soda lime	380	20	8	28
CH_2O dissolved	Al_2O_3	400	16	5	23
CH_2O dissolved + 3% piperidine	Al_2O_3	350	22	6	27
CH_2O dissolved	Na_3PO_4	350	25	4	25
40% Formalin	Na_2HPO_4	320	30	6	33
40% Formalin	Na_2HPO_4	250	18	11	—
40% Formalin	$Cu_3(PO_4)_2$	300	7	15	20

[a] The $AlPO_4$ and Al_2O_3 were supported on glass wool, the $Cu_3(PO_4)_2$ on copper turnings.

[b] The high-boiling material was chiefly ethyl propane-1,1,3,3-tetracarboxylate. The products not otherwise accounted for consisted of undistillable residues.

serves to eliminate completely all malonic ester from the reaction mixture. This is desirable, since malonic ester combines with methylenemalonic ester to form ethyl propanetetracarboxylate.[1f] Sodium acetate in place of potassium acetate gives a considerably slower reaction. The yields in the absence of copper salts are irregularly lower.

THE POLYMERIZATION OF DIETHYL METHYLENEMALONATE

Diethyl methylenemalonate may be regarded as ethylene with two negative substituents unsymmetrically placed. Compounds having the structure of ethylene with one negative substituent are known to poly-

TABLE II

LIQUID-PHASE REACTION OF FORMALDEHYDE AND MALONIC ESTER

RUN NO.	MOL RATIO CH_2O/ MALONIC ESTER	SOLVENT, G./MOLE MALONIC ESTER	CATALYST, G./MOLE MALONIC ESTER	CO-CATALYSTS, G./MOLE MALONIC ESTER	RECOV. ESTER, G.	METHYLENE MALONIC ESTER, G.	HIGH-BOILING FRACTION, G.	RESIDUE, G.
1	1:1	Acetic acid, 400 g.	Potassium acetate, 6 g.	None	9	10	40	30
2	2:1	Acetic acid, 400 g.	Potassium acetate, 6 g.	Hydroquinone, 1 g.	16	28	12	30
3	2:1	Acetic acid, 400 g.	Potassium acetate, 10 g.	Copper acetate, 10 g.	21	46	11	15
4	2:1	Acetic acid, 400 g.	Potassium acetate, 10 g.	Ferric acetate, 14 g.	11	23	33	30
5	2:1	Formic acid, 400 g.	Potassium acetate, 10 g.	Copper formate, 10 g.	—	9	51	30
6	2:1	Methyl alcohol, 400 g.	Potassium acetate, 10 g.	Copper chloride, 10 g.	8	25	31	30
7	2:1	Methyl alcohol, 400 g.	Piperidine, 10 g.	Copper chloride, 10 g.	9	8	22	50
8	2:1	Acetic acid, 200 g.	None	Copper chloride, 10 g.	14	41	11	30
9	1.3:1	Acetic acid, 400 g.	Potassium acetate, 10 g.	Copper chloride, 10 g.	19	31	24	20
10	2:1	Propionic acid, 400 g.	Potassium acetate, 10 g.	Copper acetate, 10 g.	—	41	—	—
11	2:1	Acetic acid, 200 g. Acetic anhydride, 200 g.	Potassium acetate, 10 g.	Copper acetate, 10 g.	30	15	30	20
12	2:1	Acetic acid, 70 g.	Potassium acetate, 5 g.	Copper acetate, 16 g.	6	15	8	60

merize readily to form resinous products. Examples of such compounds are acrylic acid and its derivatives, vinyl chloride, vinyl acetate, styrene, etc. Compounds having the structure of ethylene with two negative substituents also polymerize, although less readily, and the polymers generally have lower molecular weights. However, certain such substances, notably maleic anhydride, co-polymerize with great ease to give products of relatively high molecular weight. It was hoped that methylenemalonic acid derivatives which are position isomers of the corresponding maleic acid derivatives would copolymerize equally easily. Since this is not the case, and since symmetrically disubstituted derivatives are less active than unsymmetrically disubstituted derivatives, it may be inferred that the structure, possibly the five-membered ring structure, of maleic anhydride is in some way uniquely suited for co-polymerizations.

Two polymeric forms of diethyl methylenemalonate are described in the literature.[2] The newly prepared monomer forms the so-called para-diethyl methylenemalonate, a white wax-like solid. This product melts at 154–156°, and on stronger heating decomposes to the monomer. Meta-diethyl methylenemalonate is described as a horny material of limited solubility. It melts at 225° and decomposes at 240–250°, forming the monomer.

Various samples of diethyl methylenemalonate prepared in this laboratory formed the waxy para polymer in from a few hours to several weeks. The variation in speed of polymerization is probably due to differences in the purity of the material.

Actually the first distillate of methylene diethylmalonate forms the waxy polymer very readily. Further purification by distillation yields a product which may polymerize only with considerable difficulty and be quite inert towards the usual polymerization catalysts or to ultra-violet light or heat. If, however, distillation is continued, and a fraction boiling over a narrow range, say 209–11°, is taken, it will be found that the product polymerizes readily in an hour or so on the steam bath. It is evident that impure diethyl methylenemalonate polymerizes only with difficulty. The ease with which the newly-prepared ester polymerizes is probably due to the presence in it of acrylic acid or ethyl acrylate, both of which polymerize with great east and are capable of initiating the polymerization of diethyl methylenemalonate. These substances are probably formed in small amounts by hydrolysis and partial decarboxylation of methylenemalonic ester or its precursor, diethyl hydroxymethylmalonate (Compound I, Equation A). The potassium acetate present serves as a catalyst for this hydrolysis, while heat alone is sufficient to decarboxylate the malonic acid derivative.

[4] DREHER, *Kunstastoffe*, **8**, 220 (1937).

The polymer obtained from highly purified methylenemalonic ester is a colorless transparent glass which changes rapidly to a hard but brittle porcelain-like solid. It dissolves slowly in acetic acid, acetone and ethyl alcohol and may be precipitated from these as a white, granular powder by pouring into water or petroleum ether. It decomposes on heating to 230–240° to form the monomer and higher-boiling products. In this respect it resembles polymethacrylic esters rather than polyacrylic esters which do not depolymerize readily to the corresponding monomers.

Purified diethyl methylenemalonate will also co-polymerize with a number of substances. In the table (Table III) are shown the co-polymers studied and the results obtained. In each case the materials were heated

TABLE IV

REACTIONS OF METHYLENEMALONIC ESTER WITH CONJUGATED DIENES

DIENE	G. DIENE / G. ESTER	SOLVENT, CC.	TEMP., °C.	TIME, HRS.	% YIELD (ON ESTER)	B.P. °C. (MM. PRESS.)	n_D^{25}	d_4^{25}	ANALYSES	
									Calc'd	Found
Butadiene	22/22	C_6H_6, 200	−70	24	38	117 (6)	1.452	1.020	C 63.72	63.36
	20/20	None	25	24	80				H 7.96	8.06
2-Methyl-butadiene	20/44	C_6H_6, 250	80	18	35	127 (6)	1.456	1.030	C 65.00	64.79
	20/30	None	100	3	86				H 8.33	8.11
2,3-Di-methyl-butadiene	31/65	C_6H_6, 400	80	3	73	136 (6)	1.460	1.038	C 66.14	65.89
	20/30	None	100	3	91				H 8.66	8.64
Anthracene	21/25	None	220	6	54	126–7 (m.p.)			C 75.43	75.82
									H 6.29	6.37

together on the steam bath (under a reflux condenser when necessary) until reaction ceased. The percentage yields were calculated on the basis of the amounts of material obtained when the polymerized products were dissolved in acetone, precipitated in water and dried at 60° overnight. The percentages of co-polymerizing material, when this was vinyl acetate, were determined by acetyl determinations similar to those in general use for the analysis of cellulose acetates.

Methylenemalonic ester does not resemble maleic anhydride either in the ease or completeness of its co-polymerization with other olefin derivatives. There is also no apparent tendency to form co-polymers in a definite ratio with other unsaturated substances, as is generally the case with maleic anhydride. Maleic anhydride does not, however, polymerize by itself as readily as does methylenemalonic ester.

TABLE III

CO-POLYMERIZING MATERIAL	% OF CO-POLYMERIZING MATERIAL IN REACTION MIXTURE	CATALYST	REACTION RATE	% YIELD	% OF CO-POLYMERIZING MATERIAL IN PRODUCT	NATURE OF FILM COATED FROM ACETONE
Vinyl acetate	33	Benzoyl peroxide	Rapid	44	21	Hard, brittle, clear
Vinyl acetate[a]	33	Benzoyl peroxide	Slow	35	30	Hard, brittle, clear
Vinyl acetate[b]	50	Benzoyl peroxide	Rapid	50	62	Hard, brittle, reticulated
Vinyl acetate[c]	66	Benzoyl peroxide	Rapid	50	76	Tacky, reticulated
Vinyl acetate	75	Benzoyl peroxide	Rapid	79	74	Rather brittle, reticulated
Vinyl acetate	80	Benzoyl peroxide	Rapid	86	84	Hard, sl. brittle, clear
Vinyl acetate	90	Benzoyl peroxide	Rapid	90	93	Tough and clear
Methyl methacrylate	35	Benzoyl peroxide	Moderate	68	—	Hard, brittle, clear
Methyl methacrylate	75	Benzoyl peroxide	Moderate	80	—	Hard, brittle, clear
Dimethyl itaconate	50	Benzoyl peroxide	Slow	40	37	Very brittle
Maleic anhydride	35	Benzoyl peroxide	No reaction		—	
Methyl isopropenyl ketone	50	Benzoyl peroxide	No reaction		—	
Styrene	60	Benzoyl peroxide	Moderate		—	(Rubbery solid—not homogeneous—insoluble)
Vinyl ethyl ether	29	Benzoyl peroxide	No reaction		—	

[a] The vinyl acetate used in this polymerization was distilled from a 1% formic acid solution containing a little boron trifluoride.

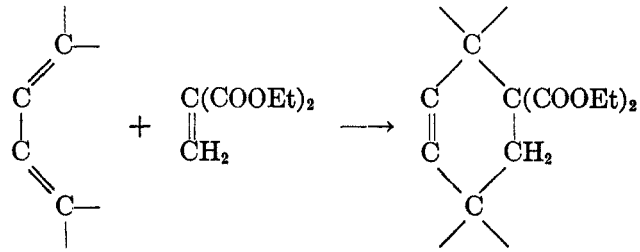
[b] The diethyl methylene malonate used in this polymerization was prepared by the reaction of methylene chloride and sodium malonic ester.

[c] A second portion of catalyst had to be added.

REACTIONS OF METHYLENEMALONIC ESTER WITH DIENES

In the past ten years the reactions of certain olefin derivatives with conjugated dienes[5] has been developed into an extraordinarily useful tool for the organic chemist. Substances like acrolein, acrylic acid, vinyl ketones etc. react readily with dienes. Substances like maleic anhydride, quinones, and acetylenedicarboxylic acid esters may react violently at room temperatures with simple dienes unless sufficiently diluted with inert solvent.

Up to the present, no disubstituted olefin with two carbonyl groups unsymmetrically placed has been condensed with dienes. Diethyl methylenemalonate is a compound of this type. Diethyl methylenemalonate was found to combine readily with butadiene, isoprene, 2,3-dimethylbutadiene, and anthracene according to the following type reaction:



Reaction occurred slowly at room temperature (except with anthracene), more rapidly at elevated temperatures, and the yields in general were good. However, diethyl methylenemalonate does not seem to combine with dienes quite as readily as does maleic anhydride. In no case was a diluent essential to prevent violent reaction. With furane, polymerization rather than condensation occurred. In Table IV are shown the conditions and results of these experiments.

The 2,3-dimethylbutadiene-methylenemalonic ester adduct was readily hydrolyzed to the corresponding dicarboxylic acid by alcoholic potassium hydroxide. This compound lost carbon dioxide quantitatively at 200° and was converted into the corresponding monocarboxylic acid, 3,4-dimethylcyclohexene-3-carboxylic acid.

EXPERIMENTAL

Diethyl methylene malonate.—To 200 g. of glacial acetic acid were added 30 g. of paraformaldehyde, 80 g. of malonic ester, 5 g. of copper acetate and 5 g. of potassium acetate. The mixture was heated on the steam bath until clear (about an hour) and for an hour longer. It was then distilled under diminished pressure until the b.p. reached 130° at 35 mm. At this point the contents of the distilling flask began

[5] DIELS AND ALDER, *Ann.*, **460**, 98 (1928).

to thicken to a paste. The receiver was changed, and the distillation continued. The blue-colored paste seemed to foam up and decompose, the product being evolved during the decomposition. When the distillation temperature reached 200° and the paste had turned dark-brown distillation was stopped. The greenish-yellow distillate solidified on standing to the waxy polymer. It was, however, impure. Redistillation yielded a fraction boiling at 205–215° which was nearly pure diethyl methylene malonate and suitable for the preparation of co-polymers or diene adducts. Yield 36.8 g. or 46% theoretical (based on malonic ester). By repeated fractionation, or by distillation through a column under diminished pressure a very pure product was obtained, although the losses at each step were considerable. The purest sample showed the following constants: b.p. 210° at 760 mm.; n_D^{25} 1.432; d_4^{25} 1.052.

Anal. Calc'd. for $C_8H_{12}O_4$: C, 55.82; H, 6.98.
Found: C, 55.88; H, 7.01.

1,1-Dicarboxy-3,4-dimethylcyclohex-3-ene.—To the solution made by adding 30 g. of sodium to 600 g. of absolute ethyl alcohol were added 94 g. of diethyl 1,1-dicarboxy-3,4-dimethylcyclohexene-3 (obtained by adding 2,3-dimethylbutadiene to diethyl methylenemalonate). The mixture was refluxed on the steam bath for 5 hours, cooled, and filtered. The sodium salt collected in this way was dissolved in 250 cc. of water, and acidified with dilute hydrochloric acid. The white precipitate was collected, dried, and recrystallized twice from 50% ethanol. Yield 59.7 g., or 86% theoretical; m.p. 186.5–188.0°, with evolution of carbon dioxide.

Anal. Calc'd. for $C_{10}H_{14}O_4$: C, 60.61; H, 7.07.
Found: C, 60.77; H, 7.27.

3,4-Dimethylcyclohex-3-ene-1-carboxylic acid.—A test-tube containing 4.0 g. of 1,1-dicarboxy-3,4-dimethylcyclohexene-3 was heated in an oil bath at 205° until the evolution of carbon dioxide had ceased. The product was recrystallized twice from a 50% methanol-water mixture. There were obtained 2.6 g. (85% theoretical) of white needles of m.p. 80–81°.

Anal. Calc'd for $C_9H_{14}O_2$; C, 70.13; H, 9.09.
Found: C, 70.25; H, 9.38.

SUMMARY

The preparation of diethyl methylenemalonate has been studied extensively, and the yields of this product obtainable have been considerably improved. The polymerization of diethyl methylenemalonate, alone and with other polymerizable olefin derivatives, has been described. Compounds resulting from the addition of diethyl methylenemalonate to certain dienes have been isolated and characterized.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY, CHICAGO, ILLINOIS]

ESTERS OF ALIPHATIC THIO ACIDS OF HIGH MOLECULAR WEIGHT

A. W. RALSTON, E. W. SEGEBRECHT, AND S. T. BAUER

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Previous work upon the preparation of thio esters has been confined to the thio esters of aromatic acids or of the aliphatic acids of low molecular weight. Muhler[1] prepared ethyl thioacetate by the action of acetyl chloride upon ethyl mercaptan. Wallach and Bleibtreu[2] reported the formation of several thioacetates by the hydrolysis of thioacetanilides. Obermeyer[3] prepared methyl thioacetate and thioisobutyrate by the action of the acid chlorides upon lead mercaptides. Later Wheeler[4] prepared ethyl thiobenzoate by the action of ethyl bromide upon potassium thiobenzoate. Reid[5] reported the preparation of ethyl thiobenzoate by the esterification of benzoic acid with ethyl mercaptan. Pratt and Reid,[6] in a study of the equilibrium reactions between methyl, ethyl, and propyl mercaptans with benzoic acid, stated that the stability of the esters decreased with increase in molecular weight. In a study of the methyl, ethyl, propyl, isobutyl, and isoamyl esters of thioacetic and thiopropionic acids Faber and Reid[7] restated this conclusion. The preparation of ethyl thioacetate from acetyl chloride and ethyl mercaptan as reported by Muhler[1] was later repeated by Baker and Reid[8].

This earlier work casts some doubt upon the stability of the higher members of the aliphatic series. Because of this question and the fact that no attempt to prepare these higher members has been reported previously, the author have undertaken the synthesis of some representative esters of this type. After several alternate methods for their preparation were investigated the method chosen was the action of the acid chlorides upon the respective mercaptans. The methyl, ethyl, *n*-propyl, and *n*-butyl esters of thiolauric, thiomyristic, thiopalmitic, and thiostearic acids and

[1] MUHLER, *Ann.*, **176**, 182 (1875).
[2] WALLACH AND BLEIBTREU, *Ber.*, **12**, 1061 (1879).
[3] OBERMEYER, *ibid.*, **20**, 2918 (1887).
[4] WHEELER, *Am. Chem. J.*, **24**, 69 (1900).
[5] REID, *ibid.*, **43**, 489 (1910).
[6] PRATT AND REID, *J. Am. Chem. Soc.*, **37**, 1934 (1915).
[7] FABER AND REID, *ibid.*, **39**, 1930 (1917).
[8] BAKER AND REID, *ibid.*, **51**, 1567 (1929).

the *n*-propyl ester of thioöleic acid have been prepared. These are stable compounds which can be distilled under reduced pressure without decomposition.

EXPERIMENTAL

Preparation of the acid chlorides.—Stearic acid (586 g., 2 moles) m.p. 67–70°, was placed in a three-necked flask fitted with a dropping funnel, reflux condenser, mechanical stirrer, and thermometer. Thionyl chloride (285.5 g., 2.4 moles) was then added over a period of two and one-half hours, and the mixture heated at 75° for two hours. The temperature was then increased to 90°, and heating was continued for an additional two hours. The excess thionyl chloride was then removed under a vacuum, and the product was fractionally distilled. An 81% yield of stearyl chloride boiling at 200–215° at 1 mm. was obtained.

The acid chlorides of lauric, myristic, palmitic, and oleic acids were prepared in a similar manner. Approximately 80% yields were obtained with the following boiling ranges: lauryl chloride, 146–150° at 16–17 mm.; myristyl chloride, 175–176° at 16–17 mm.; palmityl chloride, 191–194° at 14–15 mm.; and oleyl chloride, 184–186° at 12–13 mm.

Preparation of methyl thiolaurate.—Tri-*n*-butylamine (18.5 g., 0.1 mole) was weighed into a 125-cc. stoppered distilling flask, and the flask and contents were cooled to −30° in an acetone-carbon dioxide bath. Chilled methyl mercaptan (5.8 g., 0.12 mole) was then added, and the flask was shaken to insure a uniform solution. Lauryl chloride (21.9 g., 0.1 mole) was then added dropwise over a period of thirty minutes. The acid chloride must be added in such a manner that it does not come in contact with the walls of the reaction vessel and solidify. The reaction mixture was then kept at a temperature of −15° for twelve hours and was then held in an ice bath at 4° for twenty-four hours. It was then removed from the ice bath and held at room temperature for an additional twenty-four hours.

The reaction mixture was then dissolved in 50 cc. of ether, and the ether solution was washed with water until the washings were neutral to litmus. The ether solution was then dried with anhydrous sodium sulfate, filtered, and the ether was removed under a vacuum. The crude ester was then purified by fractional distillation and 20.5 g. retained.

The methyl esters of thiomyristic, thiopalmitic, and thiostearic acids were prepared in a similar manner. The methyl thiostearate was purified by crystallization to a constant melting point from a 1:1 acetone-alcohol mixture.

Preparation of n-*butyl thiolaurate.*—*n*-Butyl mercaptan (10 g., 1.1 mole) and lauryl chloride (21.9 g., 0.1 mole) were weighed into a 50-cc. flask. The flask was then fitted with a reflux condenser; the contents were cooled to 20°, and then mixed by shaking the flask. When the evolution of hydrogen chloride was first observed the mixture was cooled immediately to 0° and maintained at this temperature until the generation of hydrogen chloride had subsided. The mixture was then heated slowly to 50° and held at this temperature for one hour, after which it was heated to 80° for one-half hour. Dry nitrogen was then passed through the mixture for two hours at 60°. The product was then treated in a manner similar to that described for the methyl thiolaurate; 27.5 g. of *n*-butyl thiolaurate was obtained.

The ethyl, *n*-propyl, and *n*-butyl esters of thiolauric, thiomyristic, thiopalmitic, and thiostearic acids, and the *n*-propyl ester of thioöleic acid, were prepared by a similar procedure.

TABLE

PROPERTIES OF ESTERS OF ALIPHATIC THIO ACIDS

COMPOUND	M.P. OR B.P., °C.	SULFUR ANALYSIS		REFRACTIVE INDICES		DENSITY, 60°C.	MOLECULAR REFRACTION	
		Calc'd	Found	n_D^{25}	n_D^{60}		Obs	Calc'd
Methyl thiolaurate	112–115 at 1 mm.	13.91	13.78	1.4642	1.4496	0.8734	70.84	70.22
Ethyl thiolaurate	115–117 at 1 mm.	13.11	12.84	1.4626	1.4478	0.8645	75.66	74.83
n-Propyl thiolaurate	126–128 at 1 mm.	12.40	12.09	1.4628	1.4478	0.8610	80.32	79.45
n-Butyl thiolaurate	133–135 at 1 mm.	11.76	11.77	1.4640	1.4493	0.8595	85.08	84.07
Methyl thiomyristate	34–35	12.40	11.98	—	1.4507	0.8668	80.23	79.45
Ethyl thiomyristate	134–136 at 1 mm.	11.76	11.65	1.4632	1.4488	0.8609	84.86	84.07
n-Propyl thiomyristate	148–150 at 1 mm.	11.19	11.21	1.4627	1.4485	0.8568	89.61	88.69
n-Butyl thiomyristate	149–151 at 1 mm.	10.66	10.55	1.4642	1.4501	0.8570	94.26	93.31
Methyl thiopalmitate	44–45	11.19	10.85	—	1.4521	0.8644	89.44	88.69
Ethyl thiopalmitate	172–175 at 1 mm.	10.66	10.81	1.4648	1.4513	0.8547	94.74	93.31
n-Propyl thiopalmitate	27–28	10.19	10.33	1.4642	1.4507	0.8559	98.90	97.92
n-Butyl thiopalmitate	29–30	9.75	10.26	1.4646	1.4505	0.8579	103.02	102.54
Methyl thiostearate	50–51	10.19	10.31	—	1.4526	0.8624	98.51	97.92
Ethyl thiostearate	38–39	9.75	9.46	—	1.4514	0.8550	103.56	102.54
n-Propyl thiostearate	34–35.5	9.35	9.58	—	1.4509	0.8508	108.41	107.16
n-Butyl thiostearate	31–32	9.00	9.38	—	1.4529	0.8534	112.89	111.78
n-Propyl thiooleate	175–178 at 1 mm.	9.41	9.62	1.4713	1.4577	0.8643	107.46	106.69

The following table shows the melting or boiling points, sulfur analyses, refractive indices, densities, and molecular refractions of these thio esters.

It will be noted that the densities at 60° of the methyl esters are higher than those of the ethyl, *n*-propyl, and *n*-butyl esters of the corresponding acids. The observed molecular refractions are, without exception, somewhat higher than the calculated values.

Acknowledgment.—The authors wish to acknowledge their indebtedness to M. R. McCorkle who checked several of the syntheses, and to E. J. Hoffman who determined the refractive indices and densities of the esters.

SUMMARY

The methyl, ethyl, *n*-propyl, and *n*-butyl esters of thiolauric, thiomyristic, thiopalmitic, and thiostearic acids, and *n*-propyl thioöleate have been prepared, and their refractive indices, densities, and molecular refractions have been determined.

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INVESTIGATIONS ON STEROIDS
I. 6-OXOPROGESTERONE AND THE STEREOCHEMICAL CONFIGURATION OF SEVERAL 3,5,6-TRIOLS*

MAXIMILIAN EHRENSTEIN

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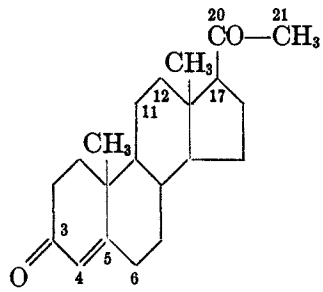
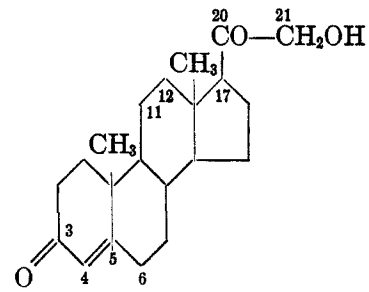
The physiologically active compounds of the adrenal cortex are chemically derived from progesterone (I). Recently progesterone has also been found in the adrenal cortex[1]. It has been stated and confirmed in the recent physiological literature that it possesses, at least to a limited extent, the life-maintaining property of the "cortin" compounds. Desoxycorticosterone (II) is at present in many respects the most potent crystalline hormone[2] with "cortin" activity. It manifests to a certain degree also a progestational action[3]. It therefore follows that the introduction in the side-chain of progesterone (I) of an alcoholic hydroxyl group, such as appears in the structure of desoxycorticosterone (21-hydroxyprogesterone) (II), is connected with a great reduction of progestational activity and a considerable increase of "cortin" action.



I. Progesterone



II. Desoxycorticosterone (21-Hydroxyprogesterone)

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[1] BEALL AND REICHSTEIN, *Nature*, **142**, 479 (1938).

[2] REICHSTEIN AND V. EUW, *Helv. Chim. Act.*, **21**, 1197 (1938).

[3] VAN HEUVERSWYN, COLLINS, WILLIAMS, AND GARDNER, *Proc. Soc. Exptl. Biol. Medicine*, **41**, 552 (1939) (contains other references).

There occur other active compounds in the adrenal cortex which contain, besides the fundamental structure of desoxycorticosterone, additional oxygen atoms in the nucleus at carbon atom 11 or carbon atoms 11 and 17. In all these compounds, however, the characteristic ketol arrangement of the side-chain is present. No systematic attempts have been made to investigate compounds which represent progesterones oxygenated only in the ring system and therefore containing an intact methyl ketone side-chain. Reference was recently made in a brief report[4] of 12-hydroxyprogesterone, which was obtained from desoxycholic acid. This compound is said to possess no remarkable progestational activity. Apparently it has not been examined for "cortin" action.

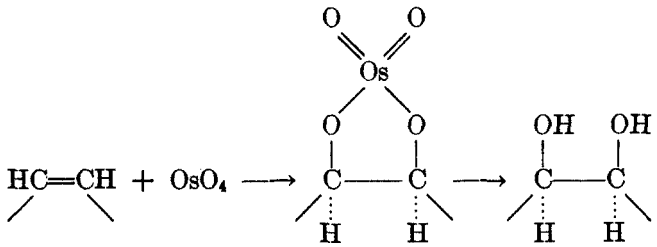
With the idea of preparing for physiological examination a series of progesterones which are oxygenated in the nucleus, it was decided to undertake the preparation of 6-oxoprogesterone (XIV) which has not yet been described in the literature. Analogous experiments have been carried out, however, in the androstane series. Utilizing a method which was developed by Mauthner and Suida[5] on cholesterol, Butenandt and Riegel[6] prepared 6-oxotestosterone acetate and 4-androstene-3,6,17-trione (V) by oxidizing 5-androstene-3,17-diol 17-monoacetate and dehydroisoandrosterone (III) respectively with chromic acid in glacial acetic acid. Their yields of these compounds, which crystallize in yellow prisms, were 20 per cent. and 25 per cent. respectively. Both yellow compounds show an absorption maximum at 252 mμ which agrees with that of 4-cholestene-3,6-dione. The physiological examination of these two substances with oxo groups at carbon atom 6 indicated oestrogenic activity, whereas they possessed practically no androgenic property. This demonstrated that the introduction of a second oxo group in conjugation with the double bond may greatly change the physiological character of compounds of this type. Besides these yellow substances, Butenandt and Riegel obtained in each instance traces of a white crystalline substance which they considered to be a hydrate of the respective 6-oxo compound (as in formula VI). A definite proof for the structure of these hydrates was not given.

Ouchakov and Lutenberg[7] subjected dehydroisoandrosterone (III) to a series of transformations at the end of which they arrived at a compound which is presumably identical with Butenandt and Riegel's 4-androstene-3,6,17-trione (V). The melting point of one of the intermediates of this preparation indicated that it was probably identical with the by-product (VI) which was obtained by Butenandt and Riegel when they subjected

[4] Ehrhart, Ruschig, and Aumüller, *Angewandte Chemie*, **52**, 363 (1939).
[5] Mauthner and Suida, *Monatsh*, **17**, 584 (1896).
[6] Butenandt and Riegel, *Ber.*, **69**, 1163 (1936).
[7] Ouchakov and Lutenberg, *Bull. soc. chim.*, [5], **4**, 1394 (1937).

dehydroisoandrosterone (III) to a chromic acid oxidation. A direct comparison was not made, however. Since the data of the paper of Ouchakov and Lutenberg are not complete, a re-investigation of the various oxidations of dehydroisoandrosterone was made. In agreement with Butenandt and Riegel's statements, the white by-product (VI) of the chromic acid oxidation of dehydroisoandrosterone was easily isolated. The same compound could be obtained by first treating dehydroisoandrosterone acetate (IV) with 30 per cent. hydrogen peroxide according to Miescher and Fischer[8], and then oxidizing the 3,5,6-triol (VII) with chromic acid according to Ouchakov and Lutenberg[9]. The melting point of a mixture showed no depression; in addition, the optical rotation of Ouchakov and Lutenberg's substance was in fair agreement with that given by Butenandt and Riegel. The identity of the two substances is therefore definitely established.

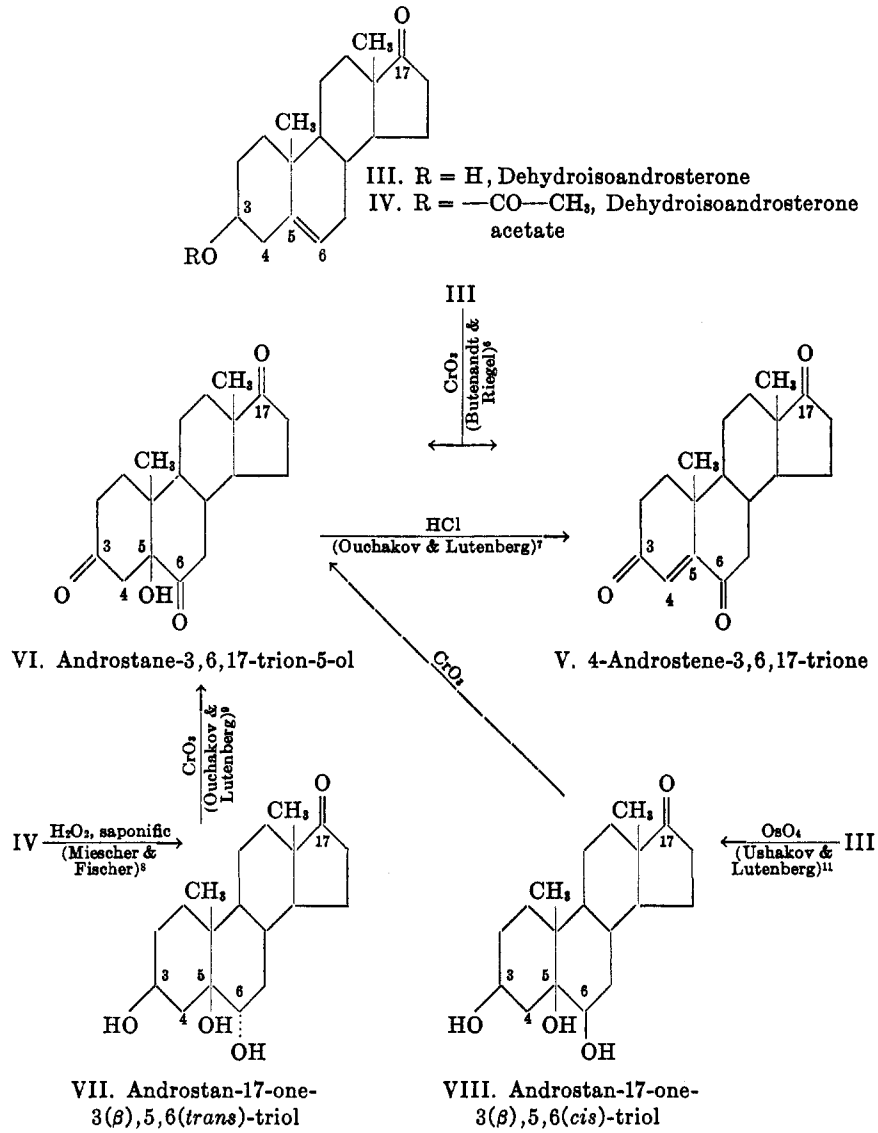
When two hydroxyl groups are added to an alicyclic double bond by means of Criegee's osmic acid method[10] the intermediary formation of a cyclic ester of osmic acid fixes the hydroxyl groups in the *cis* position:



In a brief communication[11] without experimental details Ushakov and Lutenberg stated that they subjected dehydroisoandrosterone (III) to this treatment and obtained a 3,5,6-triol (VIII) which is different from the above-mentioned compound which would therefore appear to be the 5,6-*trans* compound (VII).

It was interesting to determine in the 5,6-*cis* and 5,6-*trans* forms the actual configuration of the hydroxyl groups at carbon atoms 5 and 6. It was established that the configuration at carbon atom 5 is the same in both triols because the chromic acid oxidations of both substances (VII and VIII) furnished the identical androstane-3,6,17-trion-5-ol (VI).

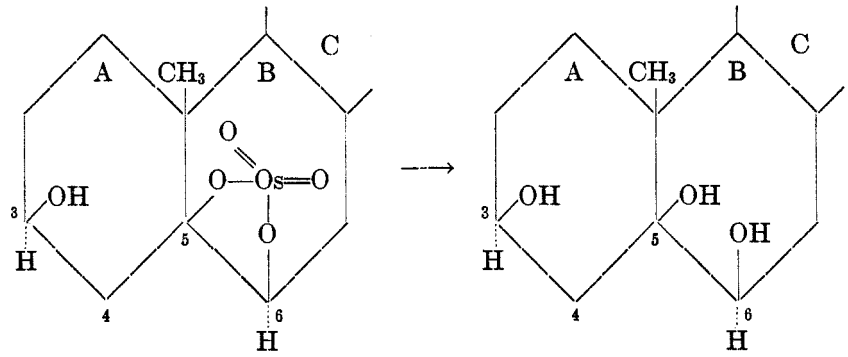
[8] MIESCHER AND FISCHER, *Helv. Chim. Acta*, **21**, 353 (1938).
[9] OUCHAKOV AND LUTENBERG, *Bull. soc. chim.*, [5], **4**, 1397 (1937).
[10] CRIEGEE, *Ann.*, **522**, 75 (1936).
[11] USHAKOV AND LUTENBERG, *Nature*, **140**, 466 (1937).



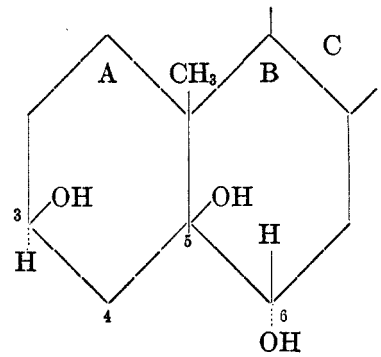
The assignment of a definite configuration to these compounds at carbon atom 5 would automatically fix the configuration at carbon atom 6. In this respect observations of Butenandt, Schmidt-Thomé, and Paul[12] and of Westphal, Wang, and Hellmann[13] should be mentioned. In those

[12] Butenandt, Schmidt-Thomé, and Paul, *Ber.*, **72**, 1114 (1939).
[13] Westphal, Wang and Hellman, *Ber.*, **72**, 1235 (1939).

derivatives of dehydroisoandrosterone in which the hydroxyl group at carbon atom 3 is esterified (for instance acetylated), the 5:6-double bond is inert to the addition of osmic acid. Since the hydroxyl group at carbon atom 3 in these compounds is in the β position, esterification of this hydroxyl group should sterically hinder the addition of osmic acid provided the latter leads to a *cis* linkage of rings A and B.



In the case of the 5,6-*trans* compound the following configuration might be assigned:

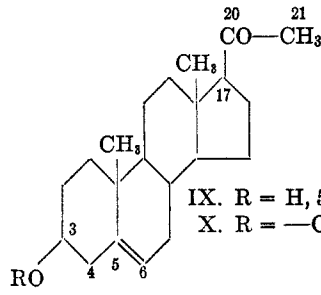


Since the configuration of these compounds at carbon atom 5 cannot be considered finally proven, their present nomenclature as androstane derivatives will not be changed. If the configuration is actually that of the above scheme, all compounds of this series ought to be labeled as etiocholane derivatives.

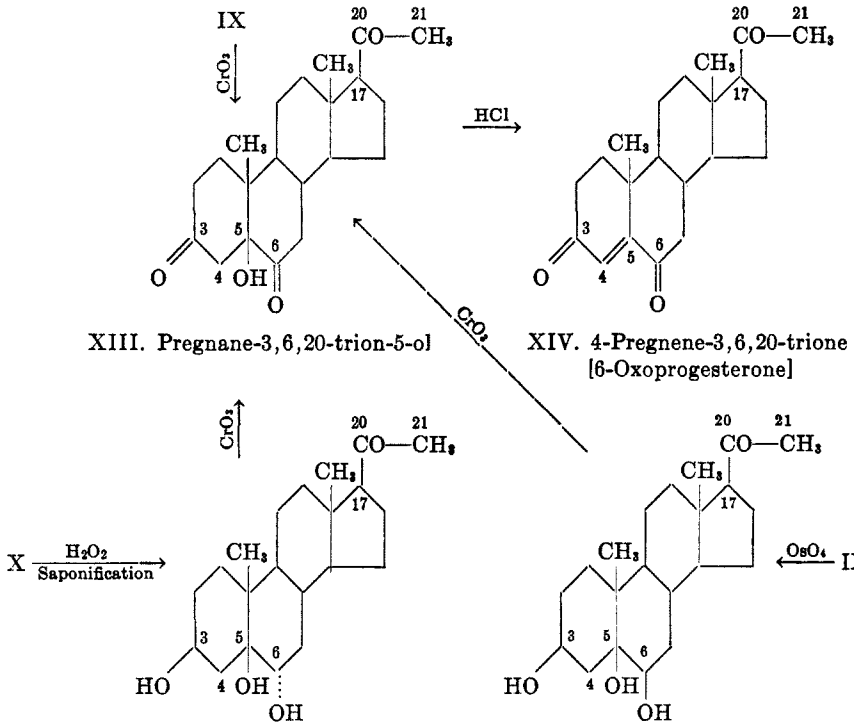
Analogous experiments, as described above, have been performed on 4-pregnen-20-on-3-ol (IX). This compound gave with chromic acid in glacial acetic acid a fair yield of a white substance which proved to be pregnane-3,6,20-trion-5-ol (XIII)**. The 6-oxoprogesterone may per-

** This name is used for a *cis* linkage of rings A and B. A proof of a different configuration at carbon atom 5 would change the names of the compounds of this group only in that the prefix "allo" would have to be added.

haps be present in the yellow mother liquors; thus far it has not been possible to secure from the latter the desired substance. The hydrogen peroxide oxidation of the acetate of 5-pregnen-20-on-3-ol (X) leads to a



IX. R = H, 5-Pregnen-20-on-3-ol
X. R = —CO—CH_3, 5-Pregnen-20-on-3-ol acetate



XIII. Pregnane-3,6,20-trion-5-ol

XIV. 4-Pregnene-3,6,20-trione [6-Oxoprogesterone]

XI. Pregnan-20-one-3(β),5,6(*trans*)-triol

XII. Pregnan-20-one-3(β),5,6(*cis*)-triol

pregnan-20-one-3,5,6-triol (XI) with the hydroxyl groups at carbon atoms 5 and 6 in *trans* position. On the other hand, when 5-pregnen-20-on-3-ol (IX) was treated with osmic acid the corresponding pregnan-20-one-3,5,6-triol (XII) with the hydroxyl groups at carbon atoms 5 and 6 in *cis* position

was obtained. Both 3,5,6-triols yielded the same pregnane-3,6,20-trion-5-ol (XIII) when they were subjected to a chromic acid oxidation. The trione (XIII) also proved to be identical with the compound obtained by directly oxidizing 5-pregnen-20-on-3-ol (IX) with chromic acid. The production of an identical trione from either XI or XII proves that the two triols have the identical configuration at carbon atom 5. Since 5-pregnen-20-on-3-ol (IX) has the same β configuration at carbon atom 3 as dehydroisoandrosterone it was interesting to learn whether its acetate was also inert towards osmic acid. It was, indeed, not possible to isolate any pregnan-20-one-3,5,6-triol; the reaction product seemed to consist

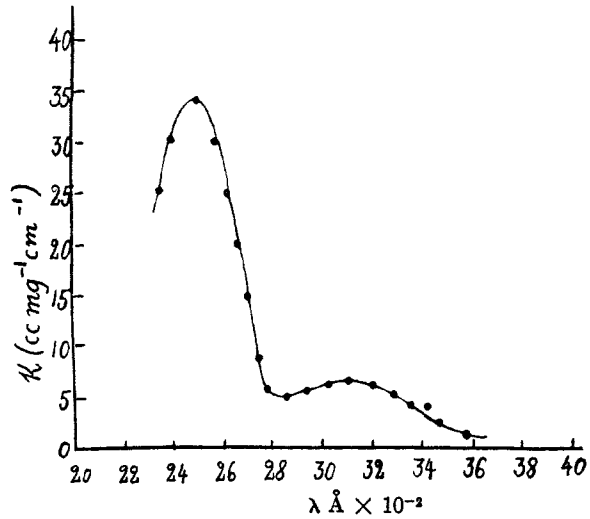


FIG. 1. ABSORPTION CURVE OF 6-OXOPROGESTERONE (IN ABSOLUTE ALCOHOL)

$$\log\left(\frac{i_0}{i}\right) = Kcl$$

i_0, incident light intensity; i transmitted light intensity; K, specific extinction coefficient; c, concentration; l, cell length.

to a large extent of unchanged starting material. This is another instance[12, 13] in which the esterification of a hydroxyl group in the β position at carbon atom 3 makes the double bond between carbon atoms 5 and 6 inert to the addition of osmic acid. The same steric considerations outlined above with the androstan-17-one-3,5,6-triols (VII and VIII) can therefore also be applied here. If there actually is a *cis* linkage of rings A and B the labeling of these compounds as pregnane rather than allopregnane derivatives would be justified.***

*** When this paper was in press ELLIS AND PETROW, *J. Chem. Soc.*, **1939**, 1078, reported on the stereochemical configurations of the cholestane-3,5,6-triols. The stereochemical considerations of the present paper are not at variance with the conclusions of the English authors concerning the cholestane series.

When a chloroform solution of pregnane-3,6,20-trion-5-ol (XIII) was subjected to a stream of dry hydrochloric acid gas it was dehydrated to 4-pregnene-3,6,20-trione [6-oxoprogesterone] (XIV). The absorption curve (Figure 1) of this compound was kindly furnished by Dr. G. O. Langstroth of the Department of Physics of the Massachusetts Institute of Technology.

In preliminary tests† on two mice, each given 4 × 500 γ, there was a moderate oestrogenic reaction. In comparison, Korenchevsky and Hall[14] obtained no oestrogenic action upon the vagina with 500 γ of pure progesterone per day.

The substance was tested for progestational activity by the Corner-Allen technique. A total dose of 5 milligrams failed to produce any reaction, whereas a total dosage of 1 milligram of progesterone produces a strong response by the same method.

EXPERIMENTAL‡

Androstane-3,6,17-trion-5-ol (VI) from dehydroisoandrosterone (III).—A. By direct chromic acid oxidation of dehydroisoandrosterone (III).[14]—Two hundred milligrams of dehydroisoandrosterone (III) was dissolved in 6 cc. of glacial acetic acid; thereafter a solution of 280 mg. of chromium trioxide dissolved in a few drops of water was added; 3 cc. of glacial acetic acid was used for rinsing. The mixture was shaken for seven hours at room temperature (29°). Thereafter it was diluted with water and extracted several times with ample quantities of ether. After the washing of the combined ether phases with 2*N* sodium carbonate and water, followed by drying over anhydrous sodium sulfate, the ether was removed. The yellow, partly resinous and partly crystalline residue was extracted twice with benzene at room temperature and once on the water bath. After the removal of the solvent *in vacuo* a yellow, largely resinous, but somewhat crystalline residue was obtained. It was treated with some 95% alcohol at room temperature, whereby some white material remained undissolved. The white precipitate was washed several times by decantation with fresh alcohol. On concentrating the combined alcoholic extracts a white crystalline substance (8.1 mg.) was secured. All the white material was combined and recrystallized from 95% alcohol. It crystallized as flat prisms in rosette arrangement. A total yield of 4.8 mg. of this desired substance was obtained. The melting point was 248–249° which is in agreement with the statements of Butenandt and Riegel[15]. The latter give as optical rotation $[\alpha]_D^{22} + 54.6°$ (in acetone).

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† The author is grateful to Dr. Franklin Payne and Dr. Carl Bachman for conducting the oestrin and progestin assays respectively.

[14] KORENCHEVSKY AND HALL, *Nature*, **140**, 154 (1937).

‡ The dehydro-iso-androsterone and pregnenonol were kindly furnished by Dr. Erwin Schwenk of the Schering Corporation in Bloomfield, N. J.

All melting points were determined with the Fisher-Johns Melting Point apparatus of the Fisher Scientific Company. The readings are sufficiently near the true melting points so that no corrections have been made.

All micro-analyses were carried out by Dr. Ing. A. Schoeller, Berlin-Schmargendorf.

[15] See BUTENANDT AND RIEGEL, *Ber.*, **69**, 1167 (1936).

No attempt was made to isolate the main product of the chromic acid oxidation, 4-androstene-3,6,17-trione (V).

B. From dehydroisoandrosterone acetate (IV) by way of androstan-17-one-3(β),5,6-(trans)-triol (VII).

The acetate of dehydroisoandrosterone (IV) was obtained by treating 250 mg. of dehydroisoandrosterone (III) with 1 cc. of pyridine and 1 cc. of acetic anhydride overnight at room temperature. After the mixture has been poured into water the crude acetate was recrystallized from aqueous alcohol; yield, 239.6 mg.; melting point, 171–172°.

Androstan-17-one-3(β),5,6(trans)*-triol (VII)*[8].—To a solution of 200 mg. of dehydroisoandrosterone acetate (IV) in 1 cc. of glacial acetic acid was added 0.2 cc. of 30% hydrogen peroxide. The mixture was heated on the water bath for two hours. The major part of the acetic acid was removed *in vacuo* (45°). The residue was a light-colored resin which was saponified with 5 cc. of 5% methanolic potassium hydroxide for 7½ hours on the water bath. Thereafter water was added, and the methanol was removed *in vacuo*. To the aqueous residue was added sodium chloride; this mixture was extracted several times with ample quantities of hot chloroform. The combined chloroform extracts were brought to dryness *in vacuo*; they left a preponderantly white residue which was recrystallized from acetone, yielding colorless prisms. Melting point of the first crop (48.7 mg.): 295–298° with decomp. Later crops (18.0 mg.) of somewhat lower melting points could be secured.

Androstane-3,6,17-trion-5-ol (VI)[9].—Fifty milligrams of androstan-17-one-3(β),5,-6 (*trans*)-triol (VII) was dissolved in 4 cc. of glacial acetic acid on a water bath. After the solution had reached room temperature (29°) 37.5 mg. of chromium trioxide, dissolved in a mixture of a trace of water and 1.5 cc. of glacial acetic acid, was added. After standing about 22 hours at room temperature, 2 cc. of ethyl alcohol was added, and the mixture was then concentrated to a low volume *in vacuo* (45°). During concentration a precipitate of glistening crystals appeared. After the addition of water, the crystals were collected by filtration and washed with water; yield of crude crystalline material: 29.2 mg., melting point 238.5–242°. After recrystallizing from 95% alcohol 20.1 mg. of flat crystals in rosettes were obtained. The melting point was 249.5–250.5° (decomp.). The melting point of a mixture with the substance obtained by directly oxidizing dehydroisoandrosterone with chromium trioxide[15] was 249.5–251° (decomp.). From the mother liquors was secured 3.9 mg. of crystals with a melting point of 247–248.5°; $[\alpha]_D^{25°} + 62.2°$ (4.5 mg. in 2.0 cc. acetone). (The experimental error of this determination is rather large.)

Anal. Calc'd for $C_{19}H_{26}O_4$: C, 71.65; H, 8.23.
Found: C, 71.33, 71.30; H, 8.11, 8.03.

C. From dehydroisoandrosterone (III) by way of androstan-17-one-3(β),5,6(cis)*-triol (VIII).—Androstan-17-one-3(β),5,6*(cis)*-triol (VIII)*[11].—To a solution of 350 mg. of dehydroisoandrosterone (III) in 18 cc. of absolute ether was added a solution of 350 mg. of osmic acid in 35 cc. of absolute ether. After three days' standing at room temperature (28–30.5°) the ether was removed from this mixture *in vacuo*. To the black residue was added a solution of 2.5 g. of sodium sulfite in dilute alcohol (25 cc. 95% alcohol, 50 cc. water), and the mixture was refluxed on a water bath for 2½ hours. After filtration, the black precipitate was refluxed three times with 95% alcohol. The combined filtrates were brought to a low volume *in vacuo*, causing needles to settle out of the concentrated aqueous solution. The concentrate was saturated with sodium chloride and extracted four times with chloroform. The combined chloroform extracts were washed with a little water, dried with anhydrous sodium sulfate and brought to dryness. The residue consisted of 385 mg. of a resin which manifested a tendency to crystallize. It was dissolved in ethyl acetate by

refluxing with a comparatively large amount of solvent. Glistening crystals (prisms) of a melting point of 243–245.5° separated from the concentrated solution; yield: 133.5 mg. Other crops with slightly lower melting points could be secured from the mother liquors. $[\alpha]_D^{26°} + 79.5°$ (19.0 mg. in 2.0 cc. methanol).

Anal. Calc'd for $C_{19}H_{30}O_4$: C, 70.75; H, 9.38.

Found: C, 71.35; H, 9.40.

Androstane-3,6,17-trion-5-ol (VI).—One hundred milligrams of androstan-17-one-3(β),5,6(*cis*)-triol (VIII) was dissolved in 8 cc. of glacial acetic acid on the water bath. To this solution was added at room temperature (27.5°) a mixture of 75 mg. of chromium trioxide in a trace of water and 3 cc. of glacial acetic acid. After standing at room temperature for 18½ hours 4 cc. of ethyl alcohol was added, and the mixture was then concentrated *in vacuo* (45–50°) to a green gummy residue. On addition of water, a white precipitate appeared; after standing a few hours the product was separated by filtration; yield: 38.9 mg.; m.p. 235.5–239° (decomp.). It was recrystallized from 95% alcohol from which 22.1 mg. of long, flat crystals was obtained; the melting point was 249–250.5° (decomp.). The melting point of a mixture with the compound obtained by chromic acid oxidation of androstan-17-one-3(β),5,6(*trans*)-triol (VII) was 246.5–249°.

Anal. Calc'd for $C_{19}H_{26}O_4$: C, 71.65; H, 8.23.

Found: C, 72.17, 71.59; H, 8.49, 8.54.

Pregnane-3,6,20-trion-5-ol (XIII) from 5-pregnen-20-on-3-ol (IX).—A. By direct chromic acid oxidation of 5-pregnen-20-on-3-ol (IX).—To a solution of 396.2 mg. of pregnenonol (IX) in 15 cc. of glacial acetic acid was added a solution of 506 mg. of chromium trioxide in a trace of water; 3 cc. of glacial acetic acid was used for rinsing. The mixture was shaken at room temperature (27°) for about 5½ hours. After addition of 150 cc. of water it was extracted four times with ample quantities of ether. The combined ether solutions were washed with 2*N* sodium carbonate solution, and thereafter with water. After the sodium carbonate solution had been made acid to Congo red by the addition of dilute sulfuric acid, and extracted with ether, an acid residue was secured; it was a yellow resin, and was not investigated further. The neutral ether solution was dried with anhydrous sodium sulfate. On concentration of this ether solution a white crystalline precipitate appeared; the supernatant mother liquor was slightly yellow. The crystals were washed several times by decantation with fresh ether. The solvent was completely evaporated from the combined ether washings. The residue was a yellow resin which has thus far not yielded any further crystalline material. The white crystals weighed 61.2 mg. after drying; the melting point was 252–254°. The product was dissolved in about 30 cc. of hot 95% alcohol; this solution was concentrated to one-fourth to one-fifth of its original volume. On cooling, crystallization started at once, yielding rather flat prismatic crystals with various shapes, showing some rosette arrangement; yield, 38.7 mg.; melting point: 267–268° (melts to a dark brown liquid). Further crops with somewhat lower melting points were secured from the mother liquor.

Anal. Calc'd for $C_{21}H_{30}O_4$: C, 72.78; H, 8.73.

Found: C, 72.72, 72.78; H, 8.70, 8.77.

B. From 5-pregnen-20-on-3-ol acetate (X) by way of pregnan-20-one-3(β),5,6(trans)-*triol (XI).*—Seven hundred fifty milligrams of pregnenonol (IX) was dissolved in 3 cc. of pyridine on the water bath; to this solution was added 3 cc. of acetic anhydride. The mixture was kept at room temperature for about 16 hours and then was poured into water. The crystalline precipitate was collected by filtration after a few hours and recrystallized from 95% alcohol; yield, 797.3 mg.; melting point, 144.5–146.5°.

Pregnan-20-one-3(β),5,6(trans)-*triol (XI).*—To a solution of 400 mg. of pregnen-

onol acetate (X) in 2 cc. of glacial acetic acid was added 0.4 cc. of 30% hydrogen peroxide. This mixture was heated on a water bath for two hours; thereafter the major part of the acetic acid was removed *in vacuo* (50°). The residue was a light-yellow resin which was refluxed with 10 cc. of 5% methanolic potassium hydroxide for 6½ hours. Then two parts of water was added, and the methanol was removed *in vacuo* (45°). The remaining aqueous solution was saturated with sodium chloride and then extracted with chloroform three times at room temperature and three more times at a gentle water bath temperature. The combined chloroform phases were washed with a little water and then brought to dryness *in vacuo* (45°) yielding 350.4 mg. of a light-yellow very sticky resin. On treating the latter with a little acetone a mass of white crystals separated almost instantaneously. The crystals were filtered, washed with acetone and dried; yield: 101.7 mg. The melting point of this crude material was between 243.5 and 251°. A sample was recrystallized from acetone. It was necessary to dissolve it first in a rather large amount of solvent and to concentrate this solution to a small volume. The substance crystallized in rectangular platelets; the melting point was 256–258° (without decomp.).

Anal. Calc'd for $C_{21}H_{34}O_4$: C, 71.94; H, 9.78.
Found: C, 72.47, 72.23; H, 9.81, 9.72.

Pregnane-3,6,20-trion-5-ol (XIII).—Seventy milligrams of crude crystalline pregnan-20-one-3(β),5,6(*trans*)-triol (XI) was dissolved in 5 cc. of glacial acetic acid on a water bath. To this was added at room temperature 45 mg. of chromium trioxide dissolved in a little water and 1.5 cc. of glacial acetic acid; 1 cc. of glacial acetic acid was used for rinsing. The mixture was kept at room temperature overnight. The next morning a few glistening white crystals were visible in the green solution. The latter was concentrated to a low volume *in vacuo* (43°) after 2 cc. of alcohol had been added. On diluting the concentrate with water the quantity of white crystalline material was increased. It was filtered and thoroughly washed with water; yield of the dried material: 46.3 mg. The melting point of this crude substance was between 262 and 269°. This was dissolved in 25 cc. of 95% alcohol. After concentrating to about one-fourth of its volume crystals (platelets) began to separate; yield: 36.9 mg. The substance melted and turned dark-brown at 271°. The melting point of a mixture with the compound obtained by direct chromic acid oxidation of 4-pregnen-20-on-3-ol (IX) was 268.5–269.5°.

Anal. Calc'd for $C_{21}H_{30}O_4$: C, 72.78; H, 8.73.
Found: C, 72.50, 72.59; H, 8.51, 8.68.

C. From 5-pregnen-20-on-3-ol (IX) by way of pregnan-20-one-3(β),5,6(cis)*-triol (XII).—Pregnan-20-one-3(β),5,6*(cis)*-triol.*—To a suspension of 340 mg. of 5-pregnen-20-on-3-ol (IX) in 27 cc. of absolute ether was added a solution of 310 mg. of osmic acid in 31 cc. of absolute ether. The mixture was left at room temperature for four days. After the removal of the ether *in vacuo*, the black residue was refluxed for 3 hours with a solution of 2.2 g. of anhydrous sodium sulfite in 40 cc. of water and 25 cc. of 95% alcohol. After filtration, the black residue was boiled four times with alcohol. The combined filtrates were concentrated to a low volume *in vacuo*, producing a crystalline precipitate. After adding sodium chloride the concentrate was extracted four times with chloroform. After the usual manipulations the combined chloroform extracts left a crystalline white residue, weighing 341.4 mg. On being recrystallized from absolute or aqueous methanol, various fractions were obtained, which apparently consisted in large part of unchanged starting material which melts at 190°. There was an indication that traces of a higher-melting substance were present. The conclusion was drawn that the reaction had taken place only to a limited extent, as a result of the slight solubility of the starting material in ether.

The recovered material which obviously represented a mixture proved to be easily soluble in dioxane. Therefore 286 mg. of this substance was dissolved in 10 cc. of re-purified dioxane, and then 300 mg. of osmic acid was added. After three days standing the solvent was removed *in vacuo*. The black residue was treated with 2.2 g. of anhydrous sodium sulfite and the other reagents as described above. When the combined chloroform extracts were concentrated, an ample quantity of white crystals settled out. The chloroform was evaporated to dryness, yielding a white crystalline residue (277 mg.). It was dissolved in 40 cc. of hot ethyl acetate. When this solution was concentrated to about one-third of its volume on the water bath, the separation of needles began and greatly increased on standing at room temperature. The first crop weighed 170.3 mg.; the melting point was 231–232.5° (no decomp.; sintering at 229°). $[\alpha]_D^{26°}$ + 59.8° (18.4 mg. in 2.0 cc. methanol).

Anal. Calc'd for $C_{21}H_{34}O_4$: C, 71.94; H, 9.78.
Found: C, 72.09, 71.67; H, 9.77, 9.65.

Pregnane-3,6,20-trion-5-ol (XIII).—To a solution of 140 mg. of pregnan-20-on-3(β),5,6(*cis*)-triol (XII) in 10 cc. of glacial acetic acid was added a solution of 90 mg. of chromium trioxide in a trace of water and 3 cc. glacial acetic acid; 2 cc. of glacial acetic acid was used for rinsing. The mixture was left at room temperature (25°) overnight. After adding 4 cc. of alcohol the green solution was concentrated almost to dryness *in vacuo* (45°). Thereby a white precipitate separated, which greatly increased after the addition of water. It was filtered after about one hour and thoroughly washed with water; weight of the dried material, 68.2 mg. It was dissolved in 20 cc. of hot 95% alcohol; this solution was then concentrated until crystallization began, and was allowed to stand at room temperature. The first crop weighed 35.7 mg. and melted at 267–268.5° to a dark-brown fluid. The melting point of a mixture with the compound obtained by chromic acid oxidation of pregnan-20-one-3(β),5,6(*trans*)-triol (XI) was 269–269.5°.

Anal. Calc'd for $C_{21}H_{30}O_4$: C, 72.78; H, 8.73.
Found: C, 72.50, 72.36; H, 8.79, 8.61.

4-Pregnene-3,6,20-trione ["6-oxoprogesterone"] (XIV) by dehydration of pregnane-3,6,20-trion-5-ol (XIII).—Seventy milligrams of crude pregnane-3,6,20-trion-5-ol (XIII) (m.p. 265.5–266.5°) was suspended in 16 cc. of pure chloroform which had been dried over calcium chloride. A gentle stream of dry hydrogen chloride was passed through this suspension from almost three hours at 4–5° (ice-cooling). The suspended material went into solution within a few minutes; the solution soon turned yellow, and eventually orange. The orange solution was poured into ice-cooled *N* sodium carbonate solution, which caused the color to disappear. After shaking this mixture in a separatory funnel, the chloroform phase was washed with water and dried with sodium sulfate. The chloroform was distilled *in vacuo*; the residue was a yellow oil which crystallized completely after standing some time in a vacuum desiccator; weight: 73.0 mg. The residue was easily dissolved by 10 cc. of 95% alcohol. This solution was concentrated to a low volume; then a few drops of ether was added, and the mixture was allowed to stand in the ice-box overnight. This treatment resulted in the separation of stout lemon-yellow needles, which were washed with 95% alcohol; yield: 26.1 mg.; melting point, 185–188°. From the mother liquor was secured 8.5 mg. of melting point 181–184.5°.

Anal. Calc'd for $C_{21}H_{28}O_3$: C, 76.78; H, 8.60.
Found: C, 75.80, 75.74; H, 8.61, 8.51.

Whether or not the low carbon figure is due to the presence of some pregnane-3,6,20-trion-5-ol is uncertain. Repeated crystallizations did not raise the melting point above 188°.

Treatment of 5-pregnen-20-on-3-ol acetate (X) with osmic acid.—One hundred fifty milligrams of 5-pregnen-20-on-3-ol acetate (X) was dissolved in 8 cc. of absolute ether in which it was easily soluble. A solution of 120 mg. of osmic acid in 12 cc. of absolute ether was added, and the mixture was left at room temperature (28–31°) for 5 days. Then the mixture was worked up as described above. The white crystalline residue was saponified, thereby yielding 132 mg. of saponified material. After recrystallization from ethyl alcohol the melting point was not very sharp; it indicated, however, mainly unchanged 5-pregnen-20-on-3-ol (IX). The recovered material was acetylated with a mixture of acetic anhydride and pyridine at room temperature. The melting point of the acetate was somewhat lower than that of the acetate of 5-pregnen-20-on-3-ol (X).

SUMMARY

(1) Dehydroisoandrosterone (III) can be hydroxylated either to androstan-17-one-3(β),5,6(*trans*)-triol (VII) or androstan-17-one-3(β),5,6(*cis*)-triol (VIII). Both compounds treated with chromic acid yield the same androstane-3,6,20-trione-5-ol (VI).

(2) 5-Pregnen-20-on-3-ol (IX) was oxidized with chromic acid to pregnane-3,6,20-trion-5-ol (XIII). Furthermore, it (IX) can be hydroxylated either to pregnan-20-one-3(β),5,6(*trans*)-triol (XI) or pregnan-20-one-3(β),5,6(*cis*)-triol (XII). Both compounds (XI or XII) give with chromic acid the same pregnane-3,6,20-trion-5-ol (XIII). The latter can be dehydrated to 4-pregnene-3,6,20-trione (6-oxoprogesterone) (XIV).

(3) The stereochemical configurations of the above-mentioned substances are discussed.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ON THE RELATIONS OF "OXYGEN AND PEROXIDE EFFECT," AND OF HYPOCHLOROUS ACID ADDITION, TO THE STRUCTURES OF UNSATURATED ORGANIC COMPOUNDS

ARTHUR MICHAEL

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Related to the influence of solvents on the course of addition of hydrogen bromide to acetylenic acids[1] are recent experimental results showing that the presence of oxygen and peroxides effects abnormal additions[2] of hydrogen bromide to certain classes of unsaturated compounds.[3] It seems probable that this abnormal addition decreases with the increase in the difference between the energy degradations accompanying the formation of the theoretically possible isomers, *i.e.*, it follows the same rule that obtains in the influence of solvents.[1] Contrary to the effect of solvents, however, oxygen and peroxides may function catalytically and the presence of small amounts may greatly increase, therefore, addition velocity in the direction of the abnormal product. Extensive experimental data have accumulated on this subject,[4] but no theoretical relationship has been advanced to correlate the appearance and facility of the phenomena with the chemical structures of the unsaturated compounds.

Excellent experimental evidence for establishing the relationship to chemical structure is known.[4] For example, in certain solvents, unsaturated acids of the type $CH_2=CH(CH_2)_n\,COOH$, in which n represents numerals from one to eight, yield secondary bromides with hydrogen bromide, when oxygen and peroxide influence is rigorously excluded, but in their presence the corresponding primary bromides appear.[4b] On the

[1] MICHAEL, J. ORG. CHEM., **4**, 128 (1939).

[2] An addition is considered normal when the addition proceeds without intramolecular rearrangement [see *Ann.*, **385**, 243 (1911)] and the result conforms with the positive-negative addition rule, *i. e.*, to the formation of that product in which the relatively negative component of the addendum has united with the relatively positive atom of the unsaturated group and *vice versa* [MICHAEL, *Ber.*, **39**, 2139 (1906); *J. Am. Chem. Soc.*, **32**, 1005 (1910); *Am. Chem. J.*, **43**, 322 (1910)]. The terms positive and negative do not refer to electro-polar relations of atoms in a molecule, but to chemical relationships determined by the relative metallic and nonmetallic chemical character, which finds chemical expression in the properties of the respective atoms. The rule, however, is subject to the principle of partition.

[3] KHARASCH, MCNAB, AND MAYO, *J. Am. Chem. Soc.*, **55**, 2531 (1933).

[4] For literature, see (*a*) Kharasch, J. ORG. CHEM., **2**, 288 (1937); (*b*) SMITH, *Chem. & Industry*, **16**, 833 (1937).

other hand, no such effect is noticed with acrylic and crotonic acids.[5] The indifference of crotonic acid to "peroxide effect" has been connected[5] with the absence of terminal carbon unsaturation, but acrylic acid, which is likewise inert in this respect,[5] has a terminally unsaturated structure. The real reason is to be sought in the considerable difference in the positive-negative relations of the respective unsaturated carbons, which coincide with corresponding differences in the energy degradations accompanying the formation of the respective saturated α- and β-bromo acids. This relationship is manifested in the great difference in the K values of the latter acids, as compared with the relatively slight change between those in which the groups with halogens are farther removed than the α,β-positions from the carboxyl.*

Interesting is the behavior of 1-butene and isobutylene towards hydrogen bromide.[6] Thermal data show that the difference between the energy contents of isomeric primary and secondary alkyl halides is considerably less than that between the corresponding primary and tertiary derivatives. This energy relationship accounts for the resistance of isobutene to oxygen effect; 1-butene functions abnormally facilely with oxygen, but isobutylene requires the action of peroxide in considerable concentration. It is obvious that oxygen and peroxide function in these reactions in some way to alter the energy relationships of the unsaturated carbon atoms so as to prevent what is in their absence the attainment of the maximum degradation of energy. To be effective, the extent of the alteration must overcome the difference in the energy degradations proceeding with the formation of the possible isomeric addition products. Thus, oxygen is sufficient to overcome the comparatively small thermal difference between primary and secondary butyl bromide, whereas the more powerful ascaridole is necessary for the larger difference between that of isobutyl and tertiary butyl bromides.[7] Finally, no oxidant has been found effective enough to cancel

[5] KHARASCH *et al.*, J. ORG. CHEM., **2**, 289 (1937).

* If the difference in this energy relation between the α- and β-unsaturated carbons can be sufficiently reduced through structural changes, such α,β-unsaturated acids may be expected to undergo the abnormal addition through peroxide effect. The subject is under experimental investigation.

[6] KHARASCH AND HINCKLEY, *J. Am. Chem. Soc.*, **56**, 1212 (1934).

[7] KHARASCH AND POTTS [*ibid.*, **58**, 57 (1936)] found that isobutylene, in the presence of ascaridole, in different solvents, gave mixtures of the primary and tertiary bromide in variable proportions, but with the "antioxidant" diphenylamine, the latter derivative appeared exclusively in all solvents. They assume that there is no direct solvent influence on the course of the reaction and that it functions by modifying the extent of the peroxide effect. On the other hand, Smith and co-workers (4*b*, p. 835) have proved that the course of the addition of hydrogen bromide to the oxygen-sensitive Δ^{10}-undecenoic acid is susceptible to solvent effect, independent of the presence of oxygen. See the following paper for further experimental evidence on this subject.

the much larger differences between the α-bromopropionic and α-bromobutyric acids and the corresponding isomeric β-bromo acids.

These considerations are well exemplified in the following results. Kharasch, McNab, and McNab[8] found that hydrogen bromide and methylacetylene in air gave the normal addition product (I), but in the presence of ascaridole, the isomeric 1,2-dibromide (II) appeared; compounds formed through the primary addition products III and IV. In III, the decidedly more negative end of the unsaturated group, $-CBr=$

$CH_3CBr_2CH_3$	$CH_3CHBrCH_2Br$	$CH_3CBr{=}CH_2$	$CH_3CH{=}CHBr$
I	II	III	IV

CH_2, is directly joined to the relatively positive methyl and, therefore, in its formation there must be a considerably greater energy degradation than in that of IV. Accordingly, it requires a stronger oxidant influence than free oxygen, *viz.*, ascaridole, to overcome normal addition in favor of structure IV.[2] The difference in chemical behavior of 1- and 2-bromopropene (IV and III), with and without oxygen and peroxide effect, is decided.[4a] Under oxygen and under mild peroxide influence, III and hydrogen bromide yield 2,2-dibromopropane (I), but with more peroxide the abnormal 1,2-dibromide (II) is formed. Under peroxide conditions, derivative IV yields exclusively the 1,2-addition product (II); in its absence, a mixture of I and II appears as the addition product.[9] The group —CBr joined to an unsaturated carbon shows a decided affinity for the halogen of hydrogen bromide;[10] hence, only in III are there two groups, —CBr and CH_3—, exerting attractive forces orienting the bromine to the intermediate unsaturated carbon. In isopropylidene bromide (I), the negative nucleus (—CBr) is symmetrically distributed towards the two, relatively positive, methyl groups and its heat of formation must be considerably greater than that of the isomeric, unsymmetrically structured, propylene bromide (II). On the other hand, it was found[4a] that the normal addition to form propylene bromide (II) from 1-bromopropene (IV) was not effected by oxygen, or even by peroxide.*

[8] KHARASCH, MCNAB AND MCNAB, *ibid.*, **57**, 2463 (1935).

[9] REBOUL [*Ann.*, **155**, 30, 215 (1870)] obtained ethylene dibromide from vinyl bromide and hydrobromic acid saturated at 0°, but ethylidene dibromide after dilution with ½ volume of water. This reversal may have been due to an oxygen effect associated with the added water. Apparently, an oxygen effect has been noticed in the rearrangement velocity of iso- into *tert.*-butylbromide. MICHAEL AND COWORKERS [*ibid.*, **379**, 309 (1911); *J. Am. Chem. Soc.*, **38**, 671 (1916)] showed that the isoderivative absorbed a gas from air, and that the velocity of rearrangement increased decidedly with the surface of the liquid exposed to air.

[10] MICHAEL, *J. prakt. Chem.*, **60**, 291 (Rule V), 328–331 (1899); *J. Am. Chem. Soc.*, **32**, 1004 (1910).

* Hydrogen bromide and 1-chloropropene give mainly the 1,1-dihalide, while 1-bromopropene yields the 1,1- and 1,2-dibromide in a ratio of about 1:2.[4a] This

Interesting is the indifference of styrene to peroxide influence,[3] in opposition to the sensitivity of normal 1-alkenes to the less developed oxygen influence. Phenyl exerts upon a directly attached atom a far greater positive influence than ethyl and a negative influence upon the next following, indirectly attached, atom.[11] There should be, therefore, a much greater difference in the energy degradation accompanying the formation of the α- and β-bromides from phenylethene than in the corresponding products resulting from ethylethene. This accounts for the indifference of the aromatic compound to peroxide influence. However, under a still stronger oxidant influence, styrene may add partially abnormally.

After a discussion of the three theoretically possible interpretations of the modes of addition of hypochlorous acid to unsaturated compounds, it was stated that "the experimental data essential to explain this reaction are not known."[12] With the discovery of peroxide effect,[3] the most important factor in causing the abnormal behavior of hypochlorous acid became evident. Owing to the extreme weakness of the acid ($K = 6.7 \times 10^{-10}$), the electrolytic components, H— and —OCl, cannot possibly function as addenda; since the additions are carried out in dilute aqueous solution, only an extremely slow addition of water could possibly occur.[13] Further, the addition as H and OCl would lead to the formation of a hypochlorous ester and, undoubtedly, to an endothermal reaction. However, the investigation of Noyes and Wilson[14] made it probable that in aqueous solution hypochlorous acid also contains HO— and —Cl and the addition of these components would explain the formation of stable chlorohydrins in the addition reactions. From the positive-negative addition rule,[2] with the wide divergence in the polarity of HO— (positive) and Cl— (negative),[15] the addition products with propene and isobutylene should be, if normally formed, mainly $CH_3CHClCH_2OH$ and $(CH_3)_2CClCH_2OH$. Actually, the isomeric chlorohydrins, $CH_3CH(OH)CH_2Cl$[16] and $(CH_3)_2C(OH)CH_2Cl$[17] are formed almost exclusively. However, hypochlorous acid in aqueous solution is not only a very powerful oxidant, destroying unsaturated compounds by far-reaching oxidation even in moderately

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was attributed by Kharasch[5] to the difference in the directive influences of the halogens when opposed to methyl, which seems more like a restatement of facts than an explanation. More probably, it is due to the greater affinity of the Br or HBr for $-CCl$ than for $-CBr$. Thus, Cl_2 acts upon Br_2 to form 2ClBr.

[11] MICHAEL, *Ber.*, **39**, 2792 (1906); *J. Am. Chem. Soc.*, **32**, 997 (1910).

[12] MICHAEL, *J. prakt. Chem.*, [2], **60**, 468 (1899).

[13] MICHAEL AND BRUNEL, *Am. Chem. J.*, **48**, 267 (1912).

[14] NOYES AND WILSON, *J. Am. Chem. Soc.*, **44**, 1630 (1922).

[15] MICHAEL, *Ber.*, **39**, 2140 (1906). See footnote†, p. 524.

[16] MICHAEL, *J. prakt. Chem.*, **60**, 454 (1899).

[17] MICHAEL AND LEIGHTON, *Ber.*, **39**, 2159 (1906).

concentrated solution, but structurally it is an intramolecularly oxidized hydrogen chloride and may be compared chemically to a peroxide. With ethenic acids both classes of the saturated acids, or mixtures, are formed, but no relation to the structures of the unsaturated acids has yet been established. The quantitative results[18] in addition to the aliphatic unsaturated acids are collected in the accompanying table.

In the table, the homologous acids differ by unilateral replacement of a hydrogen, joined to an unsaturated carbon, by alkyl, which is, therefore, the dominating chemical factor changing the relative positive-negative relations of the respective unsaturated carbons. Replacement of the α-hydrogen in acrylic acid by comparatively positive methyl increases the relative positivity of the α-unsaturated carbon; directly through the influence of the positive alkyl and indirectly by decreasing the negativity of the carboxyl. Therefore, the positive-negative difference between the

TABLE

ADDITION OF HYPOCHLOROUS ACID TO ETHENIC ACIDS AND ESTERS

ACID	$K \times 10^{-5}$	% ABNORMAL PRODUCT
I $CH_2{=}CHCOOH$	5.6	Very little
II $CH_2{=}C(CH_3)COOH$		10% α-Cl, β-OH acid
III $CH_2{=}C(CH_3)COOC_2H_5$		30% α-Cl, β-OH ester
IV $CH_3CH{=}CHCOOH$ (fum.)	2.0	74% α-Cl, β-OH acid
V $CH_3CH{=}C(CH_3)COOH$ (fum.)	1.0	38% α-Cl, β-OH acid
VI $CH_3CH{=}C(CH_3)COOC_2H_5$		50% α-Cl, β-OH ester
VII n-$C_3H_7CH{=}CHCOOH$ (fum.)	1.9	100% α-Cl, β-OH acid
VIII $C_2H_5CH{=}CHCH_2COOH$ (fum.)	2.6	Mixtures of isomers
IX $CH_3CH{=}CHCH_2CH_2COOH$ (fum.)	1.7	Mixtures of isomers

unsaturated carbons in methacrylic acid must be less than that between those in acrylic acid. The K value of methacrylic acid (II) has not been determined, but it is probably about 3.5×10^{-5} and the small proportion of the abnormal α-chloro acid formed (10 per cent.) shows definitely that the abnormal addition with acrylic acid ($K = 5.6 \times 10^{-5}$)[19] must be very slight. A similar effect appears when the relative negativity of the carboxyl of methacrylic acid is decreased by esterification (III) and the

[18] BLOOMFIELD AND FARMER, *J. Chem. Soc.*, **1932**, 2062, 2072; BLOOMFIELD, FARMER, AND HOSE, *ibid.*, **1933**, 800; FARMER AND HOSE, *ibid.*, **1933**, 962.

[19] For a discussion of the relations of the values of K to the structures and stereostructures of organic acids, see *J. Am. Chem. Soc.*, **41**, 706–723 (1918). The advanced theoretical views not only coördinate acidity values with chemical structure, but explain quite a number of supposed anomalies, which have otherwise received no solution.

abnormal addition increased from 10 per cent. to 30 per cent. By replacement of the *trans* β-hydrogen of acrylic acid by methyl, the relative positivity of the β-unsaturated carbon is increased, while the relative negativity of the carboxyl falls off decidedly (K from 5.6 to 2×10^{-5}). This causes a much closer approach to equalization of the positive-negative relations of the unsaturated carbons than in methacrylic acid and the percentage of the abnormal chloro acid increases from 30 per cent. to 74 per cent. In the transition of crotonic to isocrotonic acid, the methyl shifts from the *trans* to the *cis* position, with a transposition of the *cis* β-hydrogen in the opposite direction and the K value[20] increases from 2 to, probably, *ca.* 5×10^{-5}; the negativity of the carboxyl is considerably augmented, while that of the β-unsaturated carbon is slightly decreased. These changes should result in a decided decrease in the proportion of the abnormal α-chloro addition product. A mixture of the two isomeric chlorohydroxy acids is formed[21] and, because the isocrotonic contained crotonic acid,[22] some α-chloro-β-hydroxybutyric acid, formed from crotonic acid also appeared. The K value of fumaroid β-propylacrylic acid (VII) is only about one-third that of acrylic acid and slightly less than that of crotonic acid, which, combined with the increased, direct, positive influence of propyl over that of methyl on the β-unsaturated carbon, brings the energies of the α- and β-unsaturated carbons nearer together than in those of crotonic acid. Accordingly, the amount of abnormal α-chloro acid increased from 74 per cent. to about 100 per cent. The data for a full analysis of acids VIII and IX are not known, but, as the carboxyl is not directly joined to unsaturated carbon, it is obvious that a mixture of the isomeric chlorohydroxy addition products should be formed.†

[20] For an explanation, see *J. Am. Chem. Soc.*, **40**, 708 (1918).

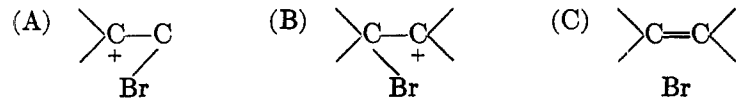
[21] MELLIKOFF AND PETRENKO-KRITSCHENKO, *Ann.*, **266**, 358 (1891).

[22] MICHAEL AND SCHULTHESS, *J. prakt. Chem.*, **46**, 251 (1892). The isocrotonic acid used before this paper contained about 50 per cent. of crotonic acid and the recorded K value should be changed accordingly. The statement in Beilstein, II, 413 (1920), in larger type, that before *1895* all preparations of isocrotonic acid consisted of mixtures of this acid with crotonic and tetrolic acids, misrepresents actuality, but it may be an erratum in the date. The above isocrotonic acid melted only 8° lower than that which WISLICENUS [*Chem. Zentr.*, **1897**, II, 260] prepared later by essentially the same method and was practically pure. The greater part of our chemical knowledge on isocrotonic acid dates from the 1892 paper and there is no valid reason to doubt its accuracy. See *Ber.*, **42**, 322, footnote 4 (1909); *J. prakt. Chem.*, **52**, 368 (1895).

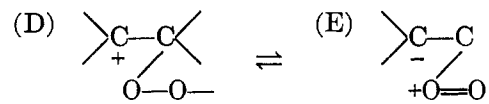
† The action of hypochlorous acid on angelic acid[21] proceeds with considerable bichlorination, decarboxylation, and polymerization of the formed chlorohydrins. The addition product that escaped these by-reactions is, therefore, not amenable to theoretical interpretation. In cinnamic acid the strong positive influence of the phenyl upon the β-unsaturated carbon is ranged against its indirect negative influence[11] and that of the directly attached carboxyl upon the α-unsaturated carbon.

Experimental data show that in abnormal hydrogen bromide additions the catalysts cause an increase in addition velocity; correspondingly, hypohalous acids add more rapidly and, also, under conditions under which the corresponding hydrohalic acids do not add at all. The introduction of an oxygen atom between the atoms of the latter compounds should proceed with a decrease in the chemical hindrance to the separation of the addendum components (HO— and —Hal.) and should, therefore, facilitate addition veolocity. Analogous to the procedures in other catalytic conversions,[23] *e.g.*, of maleic into fumaric acid, in those alkenes, and related derivatives, where the mode of addition is easily reversed, a small amount of oxygen, in the presence of sufficient hydrogen bromide, may serve as a catalyst. Thus, Urushibara and Takebayashi[24] found that one molecule of oxygen sufficed to induce the abnormal addition of hydrogen bromide to three thousand molecules of allyl bromide.

The abnormal addition of hydrogen bromide, through oxygen and peroxide effect, has been interpreted by Winstein and Lucas[25] from an electronic-resonance viewpoint. They assume the formation of intermediate, resonating, oxygen complexes, "strictly analogous" to the following resonating, "positive bromide complexes";



However, only oxygen complex D, corresponding to A, is used in explaining the abnormal addition of hydrogen bromide and it is considered necessary to assume that D resonates with "bonded form" E:



"The directive influence of oxygen in the abnormal additions of hydrogen bromide to the double bond, is due to the fact that in the complex the

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Since the relative values of the opposing factors are unknown, the course of the addition cannot be deduced theoretically. However, cinnamic acid yields only the abnormal α-chloro-β-hydroxy acid.

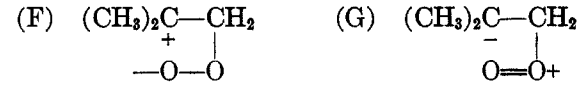
It is evident from the above discussion that the acceptance of the assumption that HO^- and Cl^+ represent the polar charges of hypochlorous acid would not explain the course of the additions of the unsaturated acids.

[23] See MICHAEL, *Am. Chem. J.*, **39**, 4 (1908).

[24] URUSHIBARA AND TAKEBAYASHI, *Bull. Chem. Soc. Japan*, **12**, 173 (1937). Interesting are the observations of these chemists [*ibid.*, **11**, 642, 754 (1936); **12**, 51 (1937)] that abnormal additions may be brought about by ferromagnetic metals.

[25] WINSTEIN AND LUCAS, *J. Am. Chem. Soc.*, **60**, 836 (1938).

contributions of the bonded forms D and E, in which oxygen occupies the position which the proton would normally take, are more important." The abnormal addition occurs through resonating form E, since the "proton can combine with the oxygen complex at the negative carbon of E and an exchange can take place between halide ion and oxygen."[25] According to this variety of resonance, the phenomenon may appear through the implication of a group of atoms, "loosely," or "moderately stably," coördinated at a carbon atom. Since the abnormal addition thus depends upon resonance between D and E, it is apparently independent of the chemical nature of the atoms, or groups of atoms, linked to the designated unsaturated carbons. However, the known reactions of corresponding unsaturated compounds prove conclusively that the course of addition is dependent on the chemical nature of the groups attached to the unsaturated carbons. From this point of view, the theoretical explanation of Winstein and Lucas is untenable. The following discussion is therefore based upon a specific alkene, *viz.*, isobutene:



In F and G, the oxygen is coördinated at the terminal, unsaturated carbon of isobutylene; in the resonance of F to G, the directly coördinated oxygen polarly becomes positive and the intermediate carbon negative, while the terminal oxygen is negative in F.

There are a number of debatable points connected with this electronic-resonance explanation. Why should negative oxygen coördinate in the addition mainly at the terminal carbon of isobutylene? This assumption is in opposition to everything known on addition of halogen hydrides to isobutene; the relatively negative component of the addendum always combines with the intermediate unsaturated carbon. It is also opposed to the chemical properties of carbon; *e.g.*, isobutylene and diisobutylene do not combine with oxygen, as far as is known, but the further accumulation of methyl groups in triisobutylene gives the unsaturated carbons of that alkene the capacity to unite with the oxygen of air at room temperature.[26] This leads to the question: what should be the outcome of the addition of hydrogen bromide to isobutylene from the electronic-resonance formulation? The electronic formulation of isobutylene is $(CH_3)_2C{:}\,CH_2$, which on approach of a dipolar addendum resonates in forms $(CH_3)_2\overset{+}{C}{:}\,CH_2$, $(CH_3)_2C{:}\,\overset{+}{C}H_2$, and $(CH_3)_2C{:}\,CH_2$, of which only the first two are considered in addition reactions. Accordingly, an equilibrium mixture of the primary and tertiary derivatives, in approximately equal proportion, should

[26] BUTLEROFF, *Ber.*, **12**, 1482 (1879).

be formed, whereas the tertiary derivative appears practically alone. It seems, therefore, that resonance does not explain one of the most fundamental reactions of isobutylene and has to fall back on the results of chemical experiment. It is obvious, that a chemical hypotheses is not viable if it cannot accurately predict, or agree with, the results obtained in simple reactions. It may be asked, also, why "bonded complex" E is "more important" than that corresponding to B, *i.e.*, $(CH_3)_2C(O_2)—\overset{+}{C}H_2$ (H), which is more favored from the chemical point of view. If the relatively negative Br of HBr can effect "an exchange" with the "moderately stable," coördinated oxygen grouping in E, should not the positive H of HBr be able to do so in H? In that case, without recourse to the chemically so improbable resonating forms D and E, the *abnormal, primary bromide* would be the direct addition product.‡ However, this far simpler, and chemically more probable interpretation of the abnormal addition, does not explain why it depends upon the chemical character of the groups of atoms attached to the unsaturated carbons and upon that of the oxidant. Accepting the existence of a "bonded complex" like G, it is still questionable whether it would react with hydrogen bromide to yield the primary bromide, as it conforms in its spatial and affinity relations to form first a hexagon-shaped polymolecule with hydrogen bromide. In this polymolecular structure, the bromine atom should be in contact with the intermediate carbon, as that atom is directly joined to the two methyl groups, and the hydrogen atom at the terminal, unsaturated oxygen atom. The reaction may proceed, therefore, by 1,4 addition[27] and result in the formation of the tertiary bromide:

$$(CH_3)_2\overset{+}{C}{=}CH_2 \quad \overset{HBr}{\longrightarrow} \quad (CH_3)_2CBrCH_2 \quad \rightarrow \quad (CH_3)_2CBrCH_3 \quad + \quad O_2^{\dagger\dagger}$$

$$\underset{-}{O{=}O} \qquad\qquad\qquad HO—O$$

The intermediate carbon in D is considered positive, but becomes "negative" in E when the terminal carbon is coördinated with oxygen. In every known addition of a dipolar addendum to an ethenic group, one of

‡ In the absence of oxygen, Winstein and Lucas (*loc. cit.*) assume that the proton of HBr "conjugates" to the same carbon as negative oxygen "coördinates" with in "bonded complexes" D and E.

[27] See MICHAEL AND WEINER [*J. Am. Chem. Soc.*, **57**, 160, figure III (1935)] for a graphic illustration of an analogous polymolecular grouping. According to WINSTEIN AND LUCAS [*ibid.*, **60**, 843 (1938)] the "complexes of different types appear to be moderately stable"; accordingly, there seems to be no reason why 1,4 addition may not take place.

†† Ethyl hydrogen peroxide is not a stable compound; it is decomposed by silver, yielding alcohol and oxygen, and explodes violently with hydrogen iodide. The primary peroxide, assumed in the above addition, would undoubtedly be decomposed by the hydrogen bromide present in the reaction mixture.

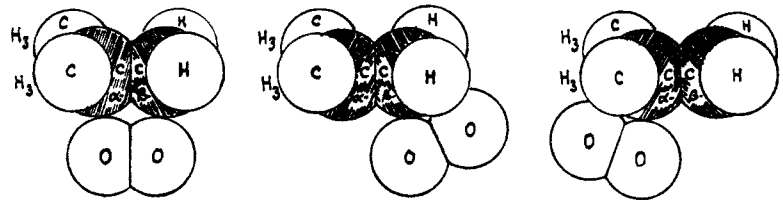
whose carbons is attached to a negative radical, the hydrogen invariably becomes attached to that carbon and the bromine to the other unsaturated carbon. From a factual chemical standpoint, it is, therefore, impossible that the intermediate, "positive" carbon of D could become "negative" in E through the influence of the negative oxygen at the terminal unsaturated carbon. The conclusion is important for Winstein and Lucas' interpretation of the abnormal addition, as it depends upon the reversal of this polar relationship. How is "an exchange" brought about between the "halide ion" (presumably the halogen ion of hydrogen bromide) and oxygen? According to Winstein and Lucas[25] "an ethylenic linkage forms compounds with oxygen moderately stable." If so, do the oxygen atoms exist in an energy state, as represented in E? Should there not be an additional amount of free chemical energy at the terminal oxygen, corresponding to that used between the oxygen designated as +O and the coördinated carbon? Finally, the chemical relations of oxygen and peroxide effect may vary, qualitatively and quantitatively, with the structure of the additive compound. It is subject to the position of double carbon linkage in organic acids and to certain organic solvents (see following paper). An explanation of the complicated relations, especially to chemical structure, which are not apparent in Winstein-Lucas electronic-resonance interpretation, would be of undoubted theoretical interest.

Conn, Kistiakowsky, and Smith[28] also assume the union of the peroxide "to one end of the double bond." "This is then blocked for the addition of one of the atoms in the hydrogen halide and the reaction is forced to take the unnatural course." The chemical nature of the peroxide addition complex is not explained; no reason is given why the peroxide should unite with a particular unsaturated carbon of the compound, nor is an explanation advanced why the oxygen-carbon unsaturated grouping is "blocked" towards the action of the hydrogen or the bromine of hydrogen bromide. The statements are so uncertain that they do not convey a definite conception of the reason for, or the mechanism of, the abnormal addition.

Designating the "vibratory or co-volume" of an atom as a sphere,[29] the primary phase of a chemical reaction, *i.e.*, polymolecular formation, may be represented by contact of these spheres and further reaction by segmentation, increasing with the conversion of the free chemical into bound chemical energy.[30] The "oxygen-peroxide effect" functions catalytically; in agreement, the first phase in the abnormal reaction may be conceived as a polymolecule of oxygen, or peroxide at its oxygens, and the unsaturated carbons of the substance. According to the principle of

[28] Conn, Kistiakowsky, and Smith, *J. Am. Chem. Soc.*, **60**, 2770 (1938).
[29] Traube, "*Raum der Atome*", p. 70 (1899).
[30] Michael, *J. Am. Chem. Soc.*, **40**, 705 (1918); **42**, 818 (1920).

partition,[2] the polymolecular formation with isobutylene with the oxygen molecule may proceed in three directions: (*1*), by bilateral contact between the oxygen and the unsaturated carbon atoms; (*2*), by unilateral union at the terminal unsaturated carbon (corresponding to the view of Winstein and Lucas); and (*3*), at the intermediate, relatively positive, unsaturated carbon. Projections of these polymolecular configurations are represented by:



I II III

The oxygens in I should not noticeably alter the affinity relations of the unsaturated carbons for the components of hydrogen bromide and, therefore, the course of the addition. In II, the oxygens accentuate the difference between the affinities of the unsaturated carbons for the components of the addendum; therefore, whether the union proceeds by 1,2 or 1,4 addition, the tertiary bromide should be formed. Polymolecule III is the single intermolecular structure that can lead to the abnormal addition, and only when the difference between the affinity relations of the unsaturated carbons of the compound for the components of hydrogen bromide is overcome by the added negative influence of the oxygens. If the latter influence is greater, then the α- may become *relatively* negative to the β-carbon and, in thus reversing the affinity relations, oxygen and peroxides may cause a corresponding reversal in the mode of addition.§ If the negative influence of the oxygen or peroxide is insufficient to alter noticeably the positive-negative relationship of the unsaturated carbons, no reversal effect is apparent, as is exemplified by the examples discussed above in the alkene and unsaturated acid series. However, by increasing the oxidant influence of the catalyst, *e.g.*, using hypohalous acids, abnormal

§ The ratio of polymolecules II to those of III must be very small; much lower than the ratio of propyl to isopropyl iodide (1:200–300), formed in the addition of hydrogen iodide to propene [*Ber.*, **39**, 2140 (1900)]. The unilateral union of oxygen to the doubly linked carbon is probably due to the slight negativity of oxygen and the increase in II of its affinity for the β-carbon, with the relative positivity of that atom. However, the union is associated with the presence of hydrogen bromide, which, probably, enters into the primarily formed polymolecule (see the following paper).

additions can be brought about that cannot be effected either by oxygen or by a peroxide.**

SUMMARY

The above theoretical interpretations rationally explain the structures of, and the quantitative relations between, the halohydrins formed from aliphatic α,β-unsaturated compounds and hypohalous acids; the accelerated velocity of these additions over those of the hydrogen halides; and formulate the direct connection between the abnormal additions and the chemical structures of the unsaturated compounds. They explain, also, how molecular oxygen and peroxides function catalytically in abnormal hydrogen bromide additions; connect changes in the mode of addition with relative reaction facility; and suggest a further experimental development of the phenomena (see the following paper). In the Winstein and Lucas interpretation,[25] there is no connection between the appearance of the abnormal addition and the magnitude of the oxidant effect or with the structures of the unsaturated organic compounds. It is based upon a series of speculations, which are wholly without experimental support and which are opposed not only to the fundamental laws on addition in organic reactions, but to the affinity relations between carbon and oxygen.

** See the following paper for a discussion of Kharasch's interpretation of the abnormal addition of hydrogen bromide.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

SOLVENT AND PEROXIDE EFFECT IN THE ADDITION OF HYDROGEN BROMIDE TO TRIMETHYLETHYLENE

ARTHUR MICHAEL AND NATHAN WEINER

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In an investigation of the addition of hydrogen bromide to trimethylethylene, Ipatieff and Dechanoff[1] found that tertiaryamyl bromide was formed in the presence of water, but in acetic acid solution the secondary bromide (10–15 per cent.) also appeared. With isopropylethylene and aqueous acid, the normal secondary bromide was formed almost exclusively, while in acetic acid the primary derivative was the main product. However, Michael and Zeidler[2] showed that the formation of the secondary bromide from trimethylethylene in acetic acid was due to the presence of a small amount of an undetermined impurity in the hydrocarbon and, after treatment with dilute sulfuric acid, the alkene yielded only the normal tertiary bromide. On the other hand, isopropylethylene and aqueous hydrogen bromide gave about equal amounts of the secondary and tertiary bromides, while in acetic acid solution a mixture of the tertiary (65.5 per cent.), secondary (28.5 per cent.), and primary (6 per cent.) bromides appeared. This radical change in the mode of addition was attributed to solvent effect.* Kharasch[3] believes that the abnormal addition of trimethylethylene is not due to a direct solvent influence, but to that of the solvent upon an unrecognized peroxide effect. Not in accord with this view is the fact that acetic acid, the solvent in which the abnormal addition is so marked, is, according to Kharasch,[3] an antioxidant and, therefore, should favor normal, not abnormal, addition. From observations on numerous unsaturated compounds, Kharasch[4] concluded that abnormal addition through peroxide influence occurs only in alkenes with terminal unsaturation. Accordingly, trimethylethylene should not exhibit additive abnormality and also should not be susceptible directly to solvent influence. On the other hand, from the theoretical viewpoint developed in the pre-

[1] IPATIEFF AND DECHANOFF, *Chem. Zentr.*, **1904**, II, 691.

[2] MICHAEL AND ZEIDLER, *Ann.*, **385**, 245 (1913).

* Further investigation has shown that this alkene is subject to the influence of other solvents, with intramolecular migration of the tertiary hydrogen, and also to that of ascaridole.

[3] KHARASCH, MCNAB, AND MAYO, *J. Am. Chem. Soc.*, **55**, 2531 (1933).

[4] KHARASCH, ENGELMAN, AND MAYO, J. ORG. CHEM., **2**, 288 (1937).

ceding paper, it may not only manifest a direct peroxide but also a direct solvent effect. Therefore, trimethylethylene was used as the first unsaturated compound in an investigation to test experimentally the theoretical views developed in the preceding paper.

Trimethylethylene, prepared by dehydration of tertiary amyl alcohol, was purified by repeated fractionation (see experimental part) and agreed in properties with the trimethylethylene used by Kistiakowsky and coworkers.[5] It gave no test for peroxide, and at −78° it absorbed dry hydrogen bromide to give a practically quantitative yield of tertiary amyl bromide; the reaction was conducted without exclusion of air. Therefore, the slight impurity, which remains in the hydrocarbon after ordinary preparation, and which can be removed by dilute sulfuric acid,[2] can also be eliminated by careful fractionation.

TABLE I

ADDITION OF HYDROGEN BROMIDE TO TRIMETHYLETHYLENE AT −78°, WITHOUT SOLVENT

EXPT.	MOLAR CONCENTRATION OF ASCARIDOLE	TIME (HRS.)	PER CENT. $(CH_3)_2CHCHBrCH_3$
1	0	2	None
2	0.002	2	77.5
3	0.008	2	86.2
4	0.008	2	83.1
5	0.016	2	92.5
6	0.016	2	91.2
7	0.016	2	91.9
8	0.02	2	92.2

When the addition of hydrogen bromide to trimethylethylene was carried out at −78° in the presence of ascaridole, the product was chiefly the secondary bromide. According to our results, the proportion of this abnormal product increased with the concentration of ascaridole. The results are given in Table I.

These results prove that the mode of addition of hydrogen bromide to trimethylethylene can be largely reversed by the peroxide, which agrees with the results obtained by Kharasch[4] with 1-alkenes, but they show that the peroxide effect in alkenes is not limited to derivatives with terminal unsaturation. We next examined the effect of solvents on the mode of addition. In pentane, carbon disulfide, and ethyl acetate at −78°, the product was exclusively the tertiary bromide. However, in pure ether at −78°, about 45 per cent of the secondary bromide was formed. This percentage remained unchanged whether the addition was carried out in

[5] KISTIAKOWSKY AND CO-WORKERS, *J. Am. Chem. Soc.*, **58**, 141 (1936).

the presence of air, in an atmosphere of nitrogen with all the substances previously purified in this gas, or according to the vacuum technique of Kharasch.[3] The ether, and the other solvents employed in this research, were purified to render them peroxide-free and gave absolutely no test with ferrous sulfate and ammonium thiocyante. The proportion of the (abnormal) secondary bromide, increased decidedly with rise of temperature from −78° to −20°, but was practically unchanged by further rise to 0°. As is shown below in Table II, in ether at −78° the presence of the antioxidant diphenylamine had no apparent effect on the amount of the secondary bromide formed, and caused only a relatively slight diminution

TABLE II

ADDITION OF HYDROGEN BROMIDE TO TRIMETHYLETHYLENE IN ABSOLUTE ETHER.

(Ten grams of trimethylethylene dissolved in 20 g. of ether.)

EXPT.	RATIO, $\frac{\text{MOLES ANTIOXIDANT}}{\text{MOLES TRIMETHYLETHYLENE}}$	TEMP., °C.	PER CENT. $(CH_3)_2CHCHBrCH_3$	REMARKS
12	0	−78	44.2	
13	0	−78	45.4	Vacuum[3]
14	0	−78	45.5	Nitrogen
15	0	−20	82.0	
16	0	−20	84.1	
17	0	0	79.5	
18	0	0	82.2	
19	0.004 $(C_6H_5)_2NH$	−78	46.5	
20	0.004 $(C_6H_5)_2NH$	−20	63.1	
21	0.004 $(C_6H_5)_2NH$	0	71.3	
22	0.006 Hydroquinone	−78	11.0	
23	0.006 Hydroquinone	−78	14.3	
24	0.006 Hydroquinone	−20	1.7	
25	0.006 Hydroquinone	0	1.8	

over that obtained in its absence at −20° (63 per cent.) and at 0° (71 per cent.). On the other hand, the antioxidant hydroquinone reduced the proportion of secondary bromide formed at −78° greatly (45 per cent. to 12 per cent.) and almost completely at −20° and 0°. The small amount of secondary bromide, which our analytical method showed at the higher temperatures, is, we believe, close to the limit of accuracy of the method. This difference in the effect of hydroquinone and diphenylamine is very similar to that described by Urushibara,[6] who found that the amount of abnormal addition of hydrogen bromide to allyl bromide induced by reduced nickel was lowered only slightly by the presence of diphenylamine,

[6] URUSHIBARA AND TAKEBAYASHI, *Bull. Chem. Soc. Japan*, **13**, 400, 404 (1938).

but to a considerable extent by hydroquinone and catechol.† It is evident from the above results that ether acts similarly to ascaridole in effecting an abnormal addition.

In acetic acid solution at 0°, a small proportion of the secondary bromide (11 per cent.) was formed, which increased at 25° to 16.8 per cent. As in ether, this percentage at 25° was reduced slightly by the presence of diphenylamine, and disappeared completely with that of hydroquinone. However, when the reaction was carried out at 25° in acetic acid containing ascaridole, in a concentration in which the pure hydrocarbon yielded about 75 per cent. of the secondary bromide at −78°, there was no increase in the proportion of this product over that formed in pure acetic acid.

Acetic acid, therefore, acts at 25° like the peroxide in small concentration upon the course of addition to trimethylethylene, but at that temperature it suppresses entirely the strongly developed property of ascaridole

TABLE III

ADDITION OF HYDROGEN BROMIDE TO TRIMETHYLETHYLENE (10 g.) IN GLACIAL ACETIC ACID (15 g.).

(Reactions completed in 1 hour.)

EXPT.	RATIO, $\frac{\text{MOLES CATALYST}}{\text{MOLES TRIMETHYLETHYLENE}}$	TEMP., °C.	PER CENT. $(CH_3)_2$-$CHCHBrCH_3$
27	0	0	11.0
28	0	25	16.8
29	0.008 Ascaridole	25	16.1
30	0.004 Diphenylamine	25	9.5
31	0.006 Hydroquinone	25	0

to cause abnormal addition. In acetone at 0°, the product was only the tertiary bromide, whether formed in the solvent alone or in the presence of ascaridole (Table IV). In absolute methanol, a very small amount of the secondary bromide was formed at −78°, which from −20° to 20° gave way to exclusive formation of the tertiary bromide. At −78°, the addition of ascaridole gave considerable secondary bromide (66 per cent.), but the percentage decreased with rise in temperature (24 per cent. at −20°, 4 per cent. at 0°), and at 20° not more than two per cent., if any, appeared. Reactions in ethanol gave almost parallel results, except that the solvent led, apparently, to the formation of only a small amount of the secondary bromide (ca. 2.5–5 per cent.) over the temperature range investigated. The results are given in Table IV.

† The apparently anomalous behavior of diphenylamine may be connected with the primary formation of an inert hydrobromide, whose stability depends upon the temperature and nature of the solvent.

Since both the effect of the peroxide and that of solvents made trimethylethylene an example of addition reversibility with hydrogen bromide, it was of interest to determine whether this property extended to the other hydrogen halides. However, under conditions most favorable to addition reversal with the bromide, only the tertiary amyl chloride and iodide were obtained.

A comparison of the experimental results obtained with trimethylethylene with those of Kharasch with 1-alkenes, as far as is permissible

TABLE IV

ADDITION OF HYDROGEN BROMIDE TO TRIMETHYLETHYLENE (10 g.) IN ACETONE (15 g.), ABSOLUTE METHANOL (10 g.), AND ABSOLUTE ETHANOL (12 g.).

(All additions completed at the end of 12 hours.)

EXPT.	SOLVENT	RATIO, MOLES ASCARIDOLE / MOLES TRIMETHYLETHYLENE	TEMP., °C.	PER CENT. $(CH_3)_2CHCHBrCH_3$
33	Acetone	0	0	0
34	Acetone	0.008	0	0
35	Methanol	0	−78	3.3
36	Methanol	0.008	−78	66.0
37	Methanol	0	−20	0
38	Methanol	0.008	−20	25.2
39	Methanol	0.008	−20	23.2
40	Methanol	0	0	0
41	Methanol	0.008	0	4.0
42	Methanol	0	20	0
43	Methanol	0.008	20	1.8
44	Ethanol	0	−78	6.0
45	Ethanol	0	−78	3.9
46	Ethanol	0.008	−78	53.5
47	Ethanol	0	−20	2.7
48	Ethanol	0.008	−20	24.7
49	Ethanol	0.008	0	17.4
50	Ethanol	0	20	2.9
51	Ethanol	0.008	20	2.1

from the partially different experimental conditions, is of theoretical interest. Pure trimethylethylene, at −78°, gave only the tertiary derivative; with addition of ascaridole, in 0.002 molar concentration, it gave 77 per cent. of the abnormal secondary bromide, which increased with the concentration of the peroxide and at 0.02 attained 92 per cent. This is the same general relationship exhibited by 1-alkenes at higher temperatures. The effect of solvents, with and without peroxide and antioxidant influence, upon 1-alkenes was less thoroughly examined by Kharasch, who

believed the sometimes apparent rôle of a solvent in his experiments is due to its influence upon the peroxide effect.[7] The above results, however, show that a specific solvent effect is well developed in hydrogen bromide-trimethylethylene additions. At −78°, in carbon disulfide, ethyl acetate, and pentane no formation of secondary bromide could be detected and the same negative result was obtained in acetone solution at 0°. On the other hand, even at −78°, ether functioned decidedly, and in the same direction as the peroxide, leading to the formation of about 45 per cent. of the secondary bromide (Table II). At that low temperature, ether is also able to overcome the antioxidant influence of diphenylamine and even that of hydroquinone to an appreciable extent, since the latter mixture gave only about 12 per cent. of the secondary bromide. The influence of tempera-

TABLE V[a]

ADDITION OF HYDROGEN CHLORIDE AND HYDROGEN IODIDE TO TRIMETHYLETHYLENE

EXPT.	ACID[b]	SOLVENT OR CATALYST	TEMP., °C.	TIME	n_D^{20}
52	HCl	0.02 Ascaridole	−78 to 25	48 hrs.	1.4058
53	HCl	12 g. Ether	−20	6 days	1.4056
54	HCl	0.02 Ascaridole-HBr[c]	−78 to 25	48 hrs.	1.4058
55	HI	None	−20	1 hr.	1.5002
56	HI	0.02 Ascaridole	−20	18 hrs.	1.5000
57	HI	25 g. Ether	−20	18 hrs.	1.5002
58	HI	25 g. Ether	−78	18 hrs.	1.5000

[a] All the products were identified as consisting completely of the tertiary halide (see experimental part).

[b] Ten grams of trimethylethylene used in experiments with hydrogen chloride, and 5 g. in experiments with hydrogen iodide.

[c] Ascaridole, in pentane solution treated with hydrogen bromide at −20°, solvent removed at reduced pressure, and residue dissolved in trimethylethylene.

ture upon the solvent effect was as marked; at −20° and 0°, the formation of the secondary bromide increased to about 82 per cent., which, on addition of hydroquinone, was reduced to practically *nil.* Very peculiar are the results obtained with glacial acetic acid as solvent, which, according to Kharasch's results,[3] acts as an antioxidant. However, in the trimethylethylene additions it functions mildly oxidant; the effect at 25° is not augmented by the addition of 0.008 mole of ascaridole, but half that concentration of hydroquinone caused it to disappear entirely. The same relation between solvent and peroxide effect appeared in acetone solution; no secondary bromide was formed *without or with ascaridole.* Thus, the combined action of solvent and peroxide, or antioxidant, gave results

[7] KHARASCH AND POTTS, *J. Am. Chem. Soc.*, **58**, 57 (1936).

unexpected from those obtained with 1-alkenes. The interesting results in methanol and ethanol mentioned above exemplify this strongly. In these solvents, the peroxide influence of ascaridole was effective at −78°, but decreased *with rise in temperature* very rapidly, and at 20° under otherwise unchanged conditions, it disappeared almost completely.

It is apparent that the influence of certain solvents upon the course of the addition of hydrogen bromide to trimethylethylene is definite and cannot be explained by assuming undetectable traces of an oxidant.[3] It is obvious that the mechanism involved in peroxide effect in this reaction is more intricate than that found by Kharasch in the 1-alkene additions, but it is not impossible that these too may yield, under experimental conditions similar to those of trimethylethylene, more comparable results. Not only solvents, but certain reduced metals,[8] cause the peroxide effect and it is therefore necessary to base the interpretation of these reactions upon a mechanism that satisfactorily accounts for all the different relations associated with this abnormal addition.

Kharasch's postulation[9] of the primary formation of bromine atoms from peroxide and hydrogen bromide is conceivable, although, actually, there is no experimental evidence of the liberation of bromine by the interaction of these compounds under the conditions of the abnormal addition. Further, the appearance of addition reversals with the use of ether, and acetic acid, seems incompatible with his viewpoint and, therefore, this interpretation of peroxide effect seems untenable. Other assumptions on the assumed course of the reaction are difficult to understand. Why, from this viewpoint, should the liberated bromine unite solely with only one of the two unsaturated carbon atoms of the alkene and what precedents exists for the assumption that free radicals should decompose hydrogen bromide with the formation of the abnormal bromo derivative and liberation of bromine atoms? These assumptions are without factual chemical precedents or experimental basis and are, therefore, arbitrary.

The statement[10] that hydrogen chloride does not show the abnormal addition because the corresponding halogen atom is not set free by the peroxide is not convincing. As stated above, there is no evidence that bromine is thus liberated from hydrogen bromide. Except in forming tertiary alkyl chlorides from correspondingly structured alkenes, hydrogen chloride does not add to alkenes under the above experimental conditions. For this reason, the appearance of a secondary chloride and the corresponding addition reversal with this addendum is not possible. The in-

[8] URUSHIBARA AND TAKEBAYASHI, *Bull. Chem. Soc. Japan*, **11**, 642, 754 (1936); **12**, 51, 173 (1937); *et. seq.*

[9] KHARASCH, J. ORG. CHEM., **2**, 299 (1937).

[10] KHARASCH, MAY, AND MAYO, *Ibid.*, **3**, 183 (1938).

effectiveness of peroxide in producing reversals with hydrogen iodide was attributed to the reduction of the peroxide by hydrogen iodide, but this reduction should likewise produce iodine atoms which should function similarly to bromine atoms in initiating an addition chain leading to addition reversal. Finally, concentrated sulfuric acid may be facilely subject to peroxidation, under the conditions of an addition reversal through peroxide influence, and may thus destroy the essential catalytic effect.‡

In the preceding paper, abnormal addition to unsaturated compounds through oxygen and peroxide effect is interpreted by the primary formation of double molecules (polymolecules) with definite intermolecular structures. It is probably due to the relatively slight negativity of oxygen that a polymolecule is formed in which the oxygen atoms are mainly attached to the relatively positive of the two unsaturated carbon atoms of the alkene. When the difference in the energy degradations accompanying the formation of the possible, isomeric addition products is large, practically only the bromide associated with the maximum energy degradation should appear as reaction product, but the nearer together are the energy degradation factors in the possible addition products, the closer together, quantitatively, should be the relative amounts of the isomers. Solvent effect is usually small in comparison to peroxide influence, and the effect of solvents upon the course of an addition should be manifest only when there is not a large difference between the degradations of energy occurring in the formation of the isomers.

With trimethylethylene the effective solvents as yet examined contain oxygen and an interpretation of solvent influence may be advanced analogous to that developed for peroxide effect. The usually small, *per se*, influence of solvents is probably increased somewhat by mass action; further, the additions proceed in the presence of hydrogen bromide, and the effective solvents not only combine with it to form isolable double compounds, *i.e.*, polymolecules, but do so far more readily than a pair of linked unsaturated carbon atoms. It is probable, therefore, that the primary phase in solvent effect is the formation of polymolecules of the solvent

‡ The literature records few scientific studies on the action of concentrated sulfuric acid on alkenes, other than ethylene. The only observation on propene is by Berthelot [*Ann. chim.*, [7], **4**, 104 (1895)], who found that it was absorbed by sulfuric acid with formation of diisopropyl sulfate. As this experiment was performed with exclusion of air, it lends no support to Kharasch's statement that the addition of sulfuric acid is not sensitive to peroxide effect. Under the same conditions, isobutylene and commercial isoamylene gave oils, which were hydrolyzed to give the acid and the polymerized alkenes. Since the latter hydrocarbons require peroxide in considerable concentration to reverse the addition with hydrogen bromide, the deduction concerning the inertness of sulfuric acid to peroxide influence lacks experimental support.

and hydrogen bromide,†† followed largely by its intermolecular union with the relatively more positive of the unsaturated atoms. When the positive-negative relationship of the unsaturated carbons is thereby reversed, the appearance of abnormal addition should then follow; either (*1*) by a direct migration of Br of the HBr-solvent-alkene polymolecule to the positive carbon and the hydrogen to the relatively negative carbon; or (*2*) by direct addition of hydrogen bromide to the polymolecule, with dissociation of the formed saturated complex into an abnormal, saturated bromide and the double molecule of hydrogen bromide and solvent.

This hypothesis explains the results obtained with ether as solvent; the ether-HBr polymolecule is unusually stable for this class of substance. Accordingly, the proportion of the secondary bromide is considerable at −78°, increases decidedly at −20°, and, perhaps, falls off very slightly at 0°. On the other hand, the polymolecules of methanol and ethanol with hydrogen bromide show markedly lower thermal stability and, in keeping with this property, the formation of the secondary bromide is higher at the lower temperatures. That the capacity of the trimolecular solvent-HBr-alkene polymolecule for the abnormal additions is dependent on the above chemical properties of the solvent is plainly evident from the quantitative results obtained with the different solvents.

Of theoretical interest are the experimental data on the effect of ascaridole on the reactions in the alcoholic solutions. Without solvent, the peroxide exercized a strong abnormal effect at −78°, which was completely neutralized in acetic acid at 25°, but still showed a decided effect in the alcoholic solutions at −78° (increase of 63 per cent. and 49 per cent. respectively). In the same concentrations at −20°, there occurred a decrease (41 per cent. and 29 per cent. respectively) and again at 0° and at 20°, when only quite small percentages of the abnormal bromide appeared. This anomalous, reversed relation of reaction velocity to temperature is probably connected with a disturbance of the stability of the trimolecular polymolecule with elevation of temperature.

It does not seem possible to explain the complicated phenomena associated with the formation of secondary isopentyl bromide from trimethylethylene, without the assumption of intermediate, more or less stable, polymolecular derivatives. However, a wider experimental investigation of the phenomena from the advanced theoretical views is essential before they can be considered definitely proven.

EXPERIMENTAL

Materials.—Trimethylethylene was prepared by dehydration of fractionated tertiary amyl alcohol, b. p. 102.5°/760 mm., with 10% hydrochloric acid. The

†† Such polymolecules must exert a far greater negative influence than that of the solvents alone.

product was dried over calcium chloride and distilled through a 12-in. Widmer column, taking the fraction boiling at 37.5–39°. This was dried over sodium wire and distilled through a 150-cm. column, packed with glass helices, and the fraction boiling at 38.8°/789 mm., n_D^{20} 1.3869, corresponding to the pure material of Kistiakowsky,[5] was used in the investigation. The trimethylethylene was stored over sodium wire until ready for use.

Ether was purified by drying over sodium wire and was stored over butylmagnesium bromide, from which it was distilled just before use. Glacial acetic acid was refluxed over potassium permanganate from which it was then distilled. Mallinckrodt "Reagent Grade" acetone was purified by this same procedure. Mallinckrodt "Reagent Grade" methanol was distilled from magnesium methoxide. Ethanol was Rossville "Gold Seal Absolute," which gave no peroxide test.

Hydrogen bromide was generated from hydrogen and bromine by the method of Ruhoff and Reid.[11] The gas was dried by passing over anhydrous calcium sulfate (Drierite).

Hydrogen chloride was generated by dehydration of concentrated hydrochloric acid with concentrated sulfuric acid, and dried with Drierite.

Hydrogen iodide was formed by the action of iodine on boiling tetralin. The gas was passed through a tube of glass pearls at −20°, a meter of reduced copper gauze and a U-tube, the bend of which was almost sealed with fresh mercury. This effectively removed all traces of iodine from the gas, which was then dried over Drierite.

Apparatus and technique.—The addition reactions were carried out in an absorption vessel consisting of a tube of about 100-cc. capacity, with a sealed-in tube reaching about half-way into the vessel. This could be closed by a stopcock, and was attached to the hydrogen bromide generator by a standard taper joint. During the absorption of hydrogen bromide, the exit tube was protected by a calcium chloride tube, which was connected by a standard taper joint, and could be replaced by a glass stopper.

All the experiments were carried out uniformly. Ten grams of trimethylethylene was distilled from sodium through a Widmer column into the absorption vessel, which in the ascaridole experiments already contained the required amount of the catalyst. In the solvent and solvent-antioxidant experiments, the antioxidant was added first and the solvent added after the trimethylethylene had been distilled into the tube. Ether was added by direct distillation into the tube, and other solvents through a pipet.

In experiment 14, the ether and the trimethylethylene were refluxed in a current of nitrogen and distilled in a current of the gas into the nitrogen-swept absorption tube. The tube was brought to the desired temperature and a fairly rapid stream of hydrogen bromide, chloride, or iodide was conducted over the surface until the weight increased by at least 15, 7, or 10 g. respectively. Only 5 g. of trimethylethylene was used in each experiment with hydrogen iodide. The mixtures stood at the reaction temperature for the specified time (Tables I–V) and were worked up by one of the following methods.

The products in the solvent-free experiments were separated from ascaridole by distillation *in vacuo* (8–15 mm.) at room temperature, from the reaction bulb to a similar bulb cooled at −78° and connected through the ground joint. The distillate was protected from the water vapor of the water pump by a calcium chloride tube. It was allowed to warm *in vacuo* to room temperature and dried, successively, over

[11] RUHOFF AND REID, *Organic Syntheses*, **15**, 24 (1935).

anhydrous potassium carbonate and phosphorus pentoxide. The reaction mixtures in solvents not miscible with water were distilled in an 18-cm., partial-reflux column, packed with glass helices, until the residue was free of solvent. The residual bromide was distilled *in vacuo* and dried in the manner described above. The reaction mixtures from acetic acid, acetone, methanol, and ethanol were washed rapidly three times with 50 cc. of ice water, and then dried over potassium carbonate and phosphorus pentoxide.

Analytical method.—It was thought possible that the composition of the hydrogen bromide reaction products could be determined by the refractive index method. Pure tertiary amyl bromide, prepared in experiment 1, was distilled through the 18-cm. packed column. It passed over entirely at 107.4°/760 mm. and had $n_D^{20} = 1.4430$. Secondary isopentyl bromide was prepared by the method of Michael and Zeidler[2] from isopropylethylene and, after drying over phosphorus pentoxide, boiled at 115.3°/760 mm.; n_D^{20} 1.4454. Since the difference in the two values is small, and the limit of accuracy of this method is ±10%, it was replaced by a modification of the method of Michael and Zeidler[2] for the total bromide estimation. The tertiary bromide was determined by shaking a weighed sample (0.1 g.–0.2 g.) with 15 cc. of distilled water for forty-five minutes at room temperature and titration of the liberated hydrobromic acid by the Volhard method. The aqueous silver nitrate for the determination of the combined secondary and tertiary bromides[2] was replaced by alcoholic 0.1 *N* silver nitrate. A standard solution of silver nitrate was made by dissolving 16.989 g. of silver nitrate in 100 cc. of water and diluting to one liter with absolute ethanol. It was found that the bromides reacted completely with an excess of this solution in forty-five minutes. The weighed sample (0.1–0.2 g.) was treated with exactly 20 cc. of 0.1 *N* alcoholic silver nitrate and allowed to stand at room temperature for forty-five minutes; 15 cc. of water and 3 cc. of ferric alum indicator were added and the excess of silver nitrate was determined with ammonium thiocyanate. In all the experiments, excepting when acetone was used, the analyses showed between 98.5% and 100.5% of the combined bromides. The products from acetone as solvent gave 92.5% and 90.8% respectively, of the tertiary bromide and exactly the same percentages of total bromides. The low results were due to the presence of an unremoved, small amount of mesityl oxide, formed by the action of hydrogen bromide on acetone and identified by its pronounced odor.

Tertiary amyl chloride was identified by its boiling point, 85.7°/760 mm., and refractive index, n_D^{20} 1.4058,[12] (compare $(CH_3)_2CHCHClCH_3$, b. p. 91.9°/736 mm., n_D^{20} 1.4095).

Tertiary amyl iodide was estimated by the complete liberation of the iodine as hydrogen iodide, shaking a weighed sample with 15 cc. of distilled water for forty-five minutes.[2]

SUMMARY

1. Ascaridole causes the formation of the abnormal secondary isopentyl bromide from trimethylethylene and hydrogen bromide. The extent of this effect increases with the concentration of ascaridole. Contrary to Kharasch, therefore, the abnormal addition is not limited to 1-alkenes.

2. In carbon disulfide, pentane, and acetic ester at −78°, hydrogen bromide, and trimethylethylene give the (normal) tertiary amyl bromide.

[12] WHITMORE AND JOHNSTON, *J. Am. Chem. Soc.*, **60**, 2265 (1938).

3. In ether solution at $-78°$, trimethylethylene and hydrogen bromide yield the abnormal bromide in a considerable proportion, which increases with rise in temperature. It is reduced only slightly by the presence of "antioxidant" diphenylamine, but to a large extent by hydroquinone.

4. Under the above conditions, trimethylethylene and hydrogen chloride and iodide yield only the tertiary amyl halides.

5. Acetic acid induces the formation of a small proportion of the (abnormal) secondary bromide. The amount, not affected by the presence of ascaridole, is reduced slightly by diphenylamine and completely by hydroquinone.

6. In acetone solution, the addition yields only the tertiary bromide, as it does, also, in the presence of ascaridole.

7. Methanol and ethanol effect a small percentage of the abnormal addition at $-78°$, which decreases with rise in temperature. In these solvents, ascaridole causes a large proportion of the abnormal addition at $-78°$, but its effect falls off with rise in temperature and at $20°$ it has no measurable influence on the normal course of the reaction.

8. The chemical mechanism for the peroxide effect, advanced by Kharasch, is not applicable to explain the above results of certain solvents in causing the abnormal addition, or to interpret the specific combined effect of solvent and peroxide. This interpretation has been discussed.

9. It has been shown that in the abnormal addition to trimethylethylene, the relations between solvent effect and peroxide effect vary decidedly when used separately and together. The abnormal effect of solvents on the addition of hydrogen bromide to trimethylethylene is specific, depending upon their chemical character. In certain solvents, ascaridole exercises a marked effect upon the course of the addition, while in other solvents it remains inert. The influence of diphenylamine as "antioxidant" depends upon the nature of the solvent and may be practically ineffective in reducing the abnormal addition, which is usually suppressed by hydroquinone; in some solvents, however, this effect is only partial and dependent on the temperature. These relations differ to a considerable extent from those observed in the corresponding reactions with 1-alkenes.

10. An explanation of the abnormal addition of hydrogen bromide to trimethylethylene by solvent influence is advanced, based upon the primary formation of double molecules of hydrogen bromide and solvent. These then unite, in accordance with the partition principle, with the relatively more positive unsaturated carbon of the alkene, and reversal occurs when the formed unsaturated carbon-solvent-HBr grouping functions as relatively negative to the terminal, formerly relatively negative, unsaturated carbon. A corresponding chemical change is believed to take place in the addition reversal by peroxide effect.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE SYNTHESIS OF 2-METHYLPHENANTHRENE FROM *l*-MENTHONE

RUBY MURRAY ORCUTT AND MARSTON TAYLOR BOGERT

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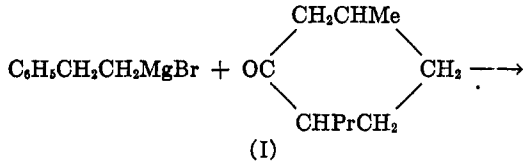
Previous work in this[1,2] and other[3] laboratories has indicated that when methyl-1-phenethyl-1-cyclohexanols are cyclodehydrated, a methyl group in position 3 on the cyclohexane nucleus causes the cyclization to occur on carbon number 6 of this same nucleus. The experiments reported in this paper show that this is the case even when carbon number 6 carries also an isopropyl group.

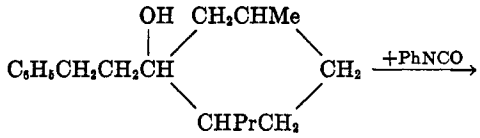
The initial material for this research was *levo*-menthone, and the various products obtained are depicted on the following flow sheet.

FLOW SHEET

(Pr = isopropyl)



(I)



(II)

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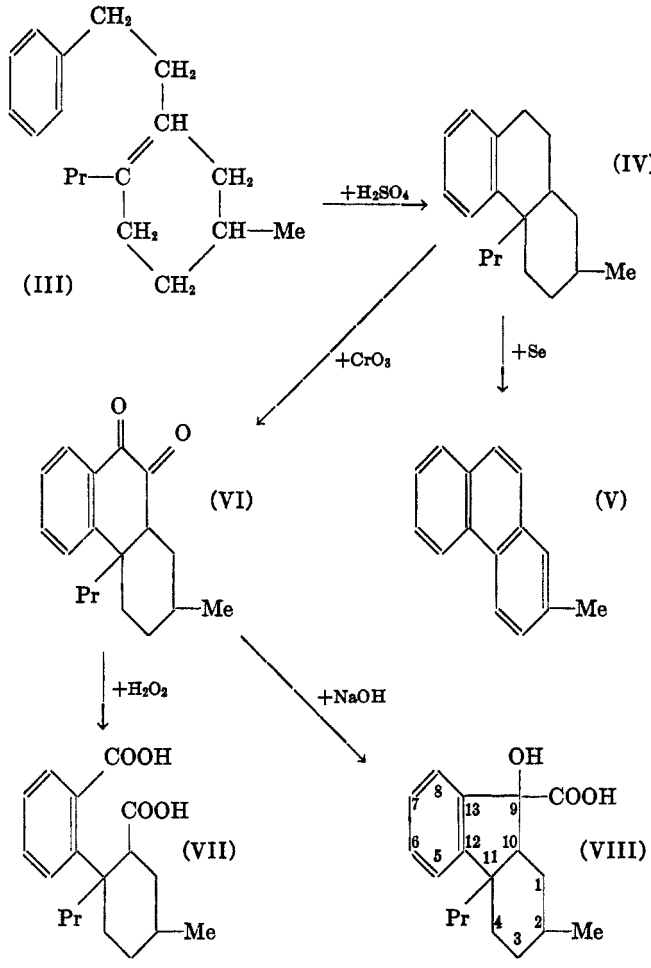
[1] PERLMAN, DAVIDSON, AND BOGERT, J. ORG. CHEM., **1**, 300 (1936).

[2] PERLMAN AND BOGERT, *J. Am. Chem. Soc.*, **59**, 2534 (1937).

[3] KON, *J. Chem. Soc.*, 1081 (1933).



EXPERIMENTAL

1-Phenethyl-3-methyl-6-isopropylcyclohexanol (*II*).—Phenethylmagnesium bromide was prepared in an atmosphere of nitrogen from 23.4 g. of phenethyl bromide and 3.5 g. of magnesium turnings, in 75 cc. of dry ether. These amounts are approximately 25% in excess of those theoretically required for the amount of menthone used.

To the well-cooled solution of this magnesium compound, there was added 15.4 g. of *l*-menthone in 20 cc. of dry ether and, after stirring of the cooled mixture for two hours, it was left overnight at room temperature. It was then decomposed carefully with acidulated ice water, and extracted with ether; the solvent was removed, and the residual liquid was distilled at 2 mm. pressure. The fraction boiling at 150–165° was fractionated repeatedly until a cut was obtained, b.p. 167–169° at 2 mm.,

as a viscous fragrant colorless oil, which refused to congeal on cooling or on long standing, and could not be crystallized from any of the solvents tried; yield, 50%.

Anal. Calc'd for $C_{18}H_{28}O$: C, 83.0; H, 10.9.
Found: C, 83.3; H, 11.0.

1-Phenethyl-2-isopropyl-5-methylcyclohexene (III).—When a mixture of the above cyclohexanol (II) and phenyl isocyanate was allowed to stand in a flask protected from ingress of moisture, crystals of carbanilide slowly separated. The residual liquid was removed with petroleum ether, the solution washed with water and left overnight in contact with water, to destroy any unchanged phenyl isocyanate. It was then filtered; the filtrate was dried, concentrated, and finally distilled over sodium. There was thus obtained a clear, colorless oil of spicy odor, b.p. 145° at 4 mm.; yield, 2.7 g. from 3 g. of the cyclohexanol.

Anal. Calc'd for $C_{18}H_{26}$: C, 89.2; H, 10.8.
Found: C, 89.4; H, 10.8.

The compound was highly unsaturated toward cold solutions of bromine in carbon tetrachloride or of potassium permanganate in acetone. It was not cyclized when its solution in petroleum ether was shaken thrice in the cold with 90% sulfuric acid.

2-Methyl-12-isopropyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (IV).—When concentrated sulfuric acid was used in place of the 90% acid, the rearrangement of III was achieved, and the phenanthrene (IV) was obtained. Purified by distillation over sodium, it appeared as a clear, colorless oil, of terpenoid odor, b.p. 123–127° at 2 mm.; yield, nearly that calculated. With cold solutions of bromine in carbon tetrachloride, or potassium permanganate in acetone, it gave no evidence of the presence of any cyclohexene.

Anal. Calc'd for $C_{18}H_{26}$: C, 89.2; H, 10.8.
Found: C, 89.3; H, 10.9.

2-Methylphenanthrene (V).—To 7 g. of the above octahydro derivative (IV), there was added, in three successive portions, 15 g. of selenium, while the mixture was heated at 345–365° for a total of 50 hours. The dark, viscous product was extracted with ethanol, the extract was boiled with Norite, to remove fluorescent impurities, was filtered, and the filtrate was concentrated. On standing, a dark oil separated which, on distillation at 3 mm. pressure, yielded 2 fractions, one (3 g.) b.p. 135–155°; and the other b.p. 155–160°. From the higher-boiling fraction there was recovered a solid, which yielded 2 g. of colorless crystals, m.p. 56°, when crystallized from ethanol. This m.p. agrees with that recorded for 2-methylphenanthrene by Haworth[4], Sengupta[5], and Perlman and Bogert[6].

The lower-boiling fraction (135–155°) was subjected to a further heating with selenium and gave a dark, semi-solid product which was extracted with ethanol; the extract was decolorized with Norite, concentrated, and treated with picric acid. A golden-yellow picrate separated, m.p. 117–118° (corr.), apparently identical with the 2-methylphenanthrene *picrate* already described in the literature[4,5,6], and in an amount corresponding to 0.8 g. of the hydrocarbon (V). The total yield of the latter was therefore 2.8 g., or 60%.

Anal. Calc'd for $C_{21}H_{15}N_3O_7$: N, 10.0. Found: N, 9.7.

The picrate was prepared also from the hydrocarbon, m.p. 56°, obtained from the first fraction. This picrate melted at 117.5–118.5° (corr.). Mixed with the picrate prepared from the second fraction, the m.p. was 117–118.5° (corr.).

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[4] HAWORTH, *J. Chem. Soc.*, **1932**, 1133.
[5] SENGUPTA, *J. prakt. Chem.*, [2] **152**, 9 (1939).
[6] PERLMAN AND BOGERT, *J. Am. Chem. Soc.*, **59**, 2535 (1937).

2-Methyl-12-isopropyl-1,2,3,4,11,12-hexahydrophenanthraquinone (VI).—A boiling solution of 2 g. of the octahydrophenanthrene (IV) in 20 cc. of glacial acetic acid was treated with a hot solution of 10 g. of chromium trioxide in 10 cc. of glacial acetic acid and 10 cc. of water, added in 5 successive portions. The reaction was vigorous at first, but decreased toward the end of the addition of the chromic acid solution. After refluxing of the mixture for 10 minutes, most of the acid was distilled; the residue was diluted with 100 cc. of water and boiled. As the liquid cooled, oily crystals separated. The mixture was extracted repeatedly with ether, the extracts were washed thoroughly with cold *N* sodium hydroxide, and dried, and the ether was distilled. The residue, crystallized from dilute ethanol, yielded in various experiments from 0.5 to 1.2 g. of sulfur-yellow needles, m.p. 151° (corr.), of the quinone (VI).

Anal. Calc'd for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2.
Found: C, 79.8; H, 8.5.

The color of the quinone was immediately discharged by the addition of sodium hydrosulfite. Addition of a drop of Superoxol to the colorless solution immediately regenerated the color, and, on standing, the quinone crystallized out. In cold concentrated sulfuric acid, it dissolved to a deep amber solution.

Quinoxaline.—Pale-yellow needles, from dilute ethanol, m.p. 121° (corr.).

Anal. Calc'd for $C_{24}H_{26}N_2$: N, 8.2. Found: N, 8.4.

2-Methyl-9-hydroxy-11-isopropyl-1,2,3,4,10,11-hexahydrofluorene-9-carboxylic acid (VIII).—The pure quinone (VI), when shaken with cold sodium hydroxide solution, yielded an alkaline solution, acidification of which precipitated the fluorene acid (VIII). This same acid was recovered from the alkaline washings of the ether extract of the quinone, by concentration and acidification.

In one experiment for the preparation of the quinone, the ether extract containing the crude reaction product was not treated with alkali, but was washed twice with water, and dried over calcium chloride, and the ether was removed. On crystallization of the residue from dilute methanol, yellow crystals of the quinone separated first (m.p. 150–151°), and from the mother-liquor there were obtained colorless crystals, m.p. 210–222° (corr.), of the fluorenecarboxylic acid (VIII), thus indicating that this quinone may undergo rearrangement even in the absence of alkali.

When the acid was purified by crystallization from ethyl alcohol, it appeared in fine white needles when it separated rapidly, or in large transparent glassy prisms or plates when formed slowly. When heated, the acid melted at 210–222° (corr.), with evolution of water and the formation of a viscous mass. On re-heating of this mass, it began to liquefy slowly at about 200°, giving a clear melt finally at about 222° (corr.). Heated rapidly in a sealed capillary, the m.p. was 215–222° (corr.). The viscous product was insoluble in cold alkali, and could not be obtained in good crystals. The yields of crystalline acid, from 2 g. of the hydrocarbon, varied from 0.5 g. to 1 g.

Of the following analyses of the acid (VIII), (*a*) represents the product of the direct action of alkali upon the quinone, and (*b*) the fluorene acid separated as a by-product in the preparation of the quinone.

Anal. Calc'd for $C_{18}H_{24}O_3$: C, 75.0; H, 8.4.
Found: C, (*a*) 74.5, (*b*) 74.9; H, (*a*) 8.5, (*b*) 8.5.

1-Isopropyl-4-methyl-1,2,3,4,5,6-hexahydrobiphenyl-2,2'-dicarboxylic acid (VII).—A solution of 1 g. of the pure quinone (VI) in 20 cc. of glacial acetic acid and 10 cc.

of Superoxol was refluxed until decolorized (8 hours)[7]. The acetic acid was distilled, the residue was dissolved in *N* sodium hydroxide solution, and filtered from a very small quantity of oily material, and the filtrate was acidified. The somewhat oily precipitate was taken up in ether, the filtered ether extract was dried, and the solvent was removed. The residue (about 1 g.), crystallized from dilute acetic acid, and then twice from dilute ethanol, was obtained in snow-white flocculent or microscopic crystals, m.p. 194–198° (corr.), with formation of a yellow anhydride.

Anal. Calc'd for $C_{18}H_{24}O_4$: C, 71.0; H, 8.0.
Found: C, 71.2; H, 8.4.

The m.p. and analysis indicate that the product was still slightly impure, but the quantity of material available was insufficient for further purification.

SUMMARY

1. *levo*-Menthone has been condensed with phenethyl bromide, by the Grignard reaction, to the 1-phenethyl-3-methyl-6-isopropylcyclohexanol.

2. By the action of phenyl isocyanate upon this cyclohexanol, the corresponding cyclohexene has been obtained; and from the latter and concentrated sulfuric acid, the 2-methyl-12-isopropyloctahydrophenanthrene, fusion of which with selenium yielded 2-methylphenanthrene.

3. The methylisopropyloctahydrophenanthrene has been oxidized to the corresponding quinone, which latter gave the analogous hydroxyfluorenecarboxylic acid by the benzilic acid rearrangement, and the corresponding biphenic acid by oxidation.

[7] *Cf.* HOLLEMAN, *Rec. trav. chim.*, **23**, 169 (1904).

[CONTRIBUTION FROM THE SCHOOL OF CHEMICAL TECHNOLOGY OF THE NORTH DAKOTA AGRICULTURAL COLLEGE]

THE SEPARATION OF THE ISOMERIC DINITRO-1,4-DIBROMOBENZENES AND THEIR REACTIONS WITH *p*-PHENYLENEDIAMINE*

C. J. SUNDE, GESTUR JOHNSON, AND C. F. KADE

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1,4-Dibromobenzene, when treated with fuming nitric acid and concentrated sulfuric acid, gives a mixture of isomeric dinitro-1,4-dibromobenzenes. Austen[1] isolated two of these isomers and showed that the structure of the one melting at 120° is 1,4-dibromo-2,6-dinitrobenzene, but later reported a melting point of 99–100° for this compound[2].

Calhane and Wheeler[3] determined the structure of Austen's second isomer (m.p. 159°) to be 1,4-dibromo-2,3-dinitrobenzene. Later, Jackson and Calhane[4] isolated the third isomer (m.p. 127°) and proved that it has the structure: 1,4-dibromo-2,5-dinitrobenzene.

Heller and Meyer[5], using Austen's method, were unable to isolate 1,4-dibromo-2,6-dinitrobenzene, or even to obtain evidence of its existence in the reaction mixture obtained on nitrating *p*-dibromobenzene.

In the present study it was found very difficult, using Austen's procedure, to obtain 1,4-dibromo-2,6-dinitrobenzene in sufficient quantity to study its reaction with *p*-phenylenediamine. As a result the method of separation has been simplified and improved so as to increase the yield of 1,4-dibromo-2,6-dinitrobenzene from a "small amount" to a yield of 7.1 per cent., and to double the yield of 1,4-dibromo-2,5-dinitrobenzene. Dioxan proved to be a good solvent for obtaining the 2,5-dinitro compound. No 1,4-dibromo-2,6-dinitrobenzene having a melting point of 99–100° could be obtained. There was no change after a melting point of 119–120° was reached on crystallizing from carbon disulfide, acetic acid, or alcohol. To check further the purity of the 119–120° melting material a small amount was treated with an equal weight of potassium nitrite in dilute alcohol according to the procedure of Austen[2]

* This paper is taken in part from theses submitted in partial fulfilment of the M.S. degree by Gestur Johnson and C. F. Kade.

[1] AUSTEN, *Ber.*, **8**, 1182–1184 (1875); *ibid.*, **9**, 621–623, 918–921 (1876).

[2] AUSTEN, *Am. J. Sci.* (Silliman's), [3] **16**, 46 (1878).

[3] CALHANE AND WHEELER, *Am. Chem. J.*, **22**, 449–458 (1899).

[4] JACKSON AND CALHANE, *ibid.*, **28**, 451–474 (1902).

[5] HELLER AND MEYER, *J. prakt. Chem.*, [2], **72**, 197–200 (1905).

with the result that a 98 per cent. yield of 4-bromo-2,6-dinitrophenol was obtained.

REACTIONS WITH *p*-PHENYLENEDIAMINE

1,4-Dibromo-2,3-dinitrobenzene does not react with *p*-phenylenediamine when an alcoholic solution containing sodium acetate is refluxed according to the method of Nietzki and Ernst[6]. When refluxed with an equivalent quantity of *p*-phenylenediamine in alcohol solution in the presence of copper bronze, potassium iodide and potassium carbonate, according to the method of Irma Goldberg[7] 1,4-dibromo-2,3-dinitrobenzene reacts to give 3,6-dibromo-2-nitroanisole. The same product is obtained by omitting the *p*-phenylenediamine in the above reaction mixture. 3,6-Dibromo-2-nitroanisole was also prepared according to the method of Jackson and Calhane[4] for the preparation of the phenetole. However, when 1,4-dibromo-2,3-dinitrobenzene is treated with an excess of *p*-phenylenediamine in alcohol solution according to the procedure of Goldberg, 3,6-dibromo-2-nitro-4′-aminodiphenylamine is formed. Here also the bromine does not react, but a nitro group is replaced.

1,4-Dibromo-2,5-dinitrobenzene reacts with an equivalent quantity of *p*-phenylenediamine in alcohol solution containing sodium acetate to give 4-bromo-2,5-dinitro-4′-aminodiphenylamine, with the loss of a molecule of hydrogen bromide. It was found impossible, however, to replace the second bromine atom. 4-Bromo-2,5-dinitro-4′-aminodiphenylamine reacts with excess *p*-phenylenediamine in alcohol solution containing copper bronze, potassium iodide, and potassium carbonate to give the Bandrowski base. This is analogous to Crippa's[8] method of preparing the Bandrowski base by the oxidation of *p*-phenylenediamine with nitrobenzene.

An alcohol solution of the acetyl derivative of 4-bromo-2,5-dinitro-4′-aminodiphenylamine with excess *p*-phenylenediamine refluxed for seven hours gives a red crystalline substance that is not readily purified. A condensation reaction takes place, but a nitro group, and not the bromine atom, is replaced. No attempt has as yet been made to determine which nitro group is replaced.

1,4-Dibromo-2,6-dinitrobenzene reacts very readily with *p*-phenylenediamine. In alcohol solution with excess *p*-phenylenediamine and sodium acetate a greenish-black crystalline compound, 4-bromo-2,6-dinitro-4′-aminodiphenylamine melting at 193–194°, is obtained in a quantitative yield. If, however, two moles of 1,4-dibromo-2,6-dinitrobenzene and

[6] NIETZKI AND ERNST, *Ber.*, **23**, 1852–1856 (1890).
[7] GOLDBERG, *ibid.*, **40**, 4541–4546 (1907).
[8] CRIPPA, BELLANI, AND MARUBINI, *Gazz. chim. ital.*, **60**, 644 (1930).

one mole of *p*-phenylenediamine are condensed a dark-red product melting at 276–277° after one crystallization from glacial acetic acid is obtained. The same *N,N'*-bis-(2,6-dinitro-4-bromophenyl)-*p*-phenylenediamine is obtained by condensing 4-bromo-2,6-dinitro-4'-aminodiphenylamine with 1,4-dibromo-2,6-dinitrobenzene.

In the formation of both of the above condensation products the bromine atom flanked by nitro groups in both ortho positions is replaced. The other bromine atom does not react. Neither does it react when 4-bromo-2,6-dinitro-4'-aminodiphenylamine is acetylated and the acetyl derivative is treated with *p*-phenylenediamine in alcohol solution according to the method of Nietzki and Ernst[6] or that of Goldberg[7]. In both cases unchanged starting material was recovered.

The *N,N'*-bis-(2,6-dinitro-4-bromophenyl)-*p*-phenylenediamine, prepared by the condensation of 1,4-dibromo-2,6-dinitrobenzene is identical with the *N,N'*-bis-(2,6-dinitro-4-bromophenyl)-*p*-phenylenediamine prepared from 1-chloro-4-bromo-2,6-dinitrobenzene and *p*-phenylenediamine according to the method of Joshi and Sane[9], as shown by melting points and mixture melting points. Joshi and Sane reported a melting point for their product of over 300°. In the present study a melting point of 276–277° was obtained after one crystallization from glacial acetic acid, and this melting point did not change after four more crystallizations alternately from nitrobenzene and glacial acetic acid.

EXPERIMENTAL

Nitration of p-*dibromobenzene and separation of 1,4-dibromo-2,3-dinitrobenzene.*—Two hundred grams of *p*-dibromobenzene (Eastman Kodak Co.) was nitrated according to the directions of Jackson and Calhane.[4] The reaction product was poured on cracked ice, and after a few minutes the oil solidified. It was allowed to stand overnight, filtered, washed thoroughly with water, and dried. A yield of approximately 250 g. was obtained. The product was dissolved in 425 ml. of hot glacial acetic acid and allowed to stand in a cool place overnight. The crystals which formed were removed by filtration, and the filtrate was concentrated by removing about 100 ml. of acid by vacuum distillation. The solution was again allowed to stand overnight, when a second crop of crystals was obtained. Another 100 ml. of acid was removed by distillation under reduced pressure, and after standing overnight a third crop of crystals was obtained. The three crops of crystalline material were combined giving a total yield of 35 g. of product melting at 98–145°. After two crystallizations from glacial acetic acid the substance melted at 159–160° (Austen, 159°). It was necessary to remove at least 35 g. of crude 1,4-dibromo-2,3-dinitrobenzene at this point in order to prevent its appearance after most of the 1,4-dibromo-2,5-dinitrobenzene had been removed.

Separation of 1,4-dibromo-2,5-dinitrobenzene.—To the filtrate from the third crop of 1,4-dibromo-2,3-dinitrobenzene 800 ml. of water was added. A yellow oil, which

[9] JOSHI AND SANE, *J. Ind. Chem. Soc.*, **10**, 459–463 (1933).

solidified on cooling, separated. This was filtered, washed repeatedly with water, and dried. The solid was broken into small pieces and washed thoroughly with water by decantation. The dried material, 200–215 g., was dissolved in 500 ml. hot dioxan. After standing overnight the crystals which had formed were removed by filtration, and the filtrate was concentrated by removing 160 ml. dioxan by distillation under reduced pressure. A second crop of crystals was obtained, and another 150 ml. of dioxan was removed by vacuum distillation. On standing, a third crop of crystals formed, and was combined with the two previous crops. The total yield of crude 1,4-dibromo-2,5-dinitrobenzene (m.p. 68–104°) averaged 66 g. After two crystallizations from hot alcohol 30–35 g. of material, m.p. 126–127°, was obtained. (Jackson and Calhane, 127°).

Separation of 1,4-dibromo-2,6-dinitrobenzene.—The dioxan filtrate after removal of the third crop of 1,4-dibromo-2,5-dinitrobenzene was concentrated by the removal of about 100 ml. of solvent under reduced pressure. On standing a precipitate was obtained, giving 30 g. of material, m.p. 70–80°. After five crystallizations from alcohol 16 g. of material melting at 119–120° was obtained. The filtrate was brought to a syrupy consistency under reduced pressure and transferred to a beaker from which the residual dioxan was evaporated by heating on a steam plate for a few days. The oily liquid solidified on cooling. The solid was dissolved in 90–125 ml. of carbon disulfide, from which on cooling 10–15 g. of material, melting at 93–114°, was obtained. This gave, after two crystallizations, 5.5–8 g. of product, m.p. 119–120°. There was no change in the melting point on further crystallizations from either glacial acetic acid, alcohol, or carbon disulfide.

Conversion of 1,4-dibromo-2,6-dinitrobenzene to the phenol.—A mixture of 0.5 g. of material (m.p. 119–120°), 8 ml. of alcohol, 0.5 g. of potassium nitrite and 4 ml. of water was heated on a steam bath until all solid material was in solution. On cooling, a mass of red crystals formed. After standing overnight, 12*N* hydrochloric was added until the mixture was acid. On heating and shaking, the red crystals dissolved, giving a yellow solution. This was cooled in an ice-salt mixture, giving a yellow crystalline substance. A yield of 0.395 g. (98% of the theoretical) was obtained, m.p. 73–74°. After one crystallization from alcohol or water, m.p. 74–75°. (Austen, 71°; Fromm and Ebert, 78°). This phenol is identical with the phenol obtained by brominating (Eastman Kodak Co.) 2,6-dinitrophenol according to the method of Fromm and Ebert,[10] as shown by m.p. and mixture m.p.

Reactions of the Dinitro-1,4-Dibromobenzenes with p-*Phenylenediamine*

A. Reactions of 1,4-dibromo-2,3-dinitrobenzene. (*a*) *Preparation of 3,6-dibromo-2-nitroanisole.*—An equimolar mixture of 1,4-dibromo-2,3-dinitrobenzene (1 g.) and *p*-phenylenediamine (0.330 g.) was refluxed for two hours with 0.44 g. of potassium carbonate, 0.10 g. of potassium iodide and 0.05 g. of copper bronze in 40 ml. of methyl alcohol. The mixture was filtered while hot and 100 ml. of water added to the filtrate. The product was crystallized three times from methyl alcohol with the aid of a little Norite. A colorless, crystalline substance melting at 82.5–83° was obtained. The yield was 5% of the theoretical. The same product was obtained without the presence of *p*-phenylenediamine in the above reaction as shown by a mixture melting point. 3,6-Dibromo-2-nitroanisole (m.p. 82.5–83°, mixture m.p. with material from the above reaction 82.5–83°) was also prepared by the action of sodium methoxide on 1,4-dibromo-2,3-dinitrobenzene in benzene solution according

[10] FROMM AND EBERT, *J. prakt. Chem.*, **108**, 75–87 (1924).

to the method of Jackson and Calhane[4] for the preparation of the corresponding phenetole.

Anal. Calc'd for $C_7H_5Br_2NO_3$: N, 4.50; Br, 51.44; mol. wt., 311.
Found: N, 4.56; Br, 51.46; mol. wt. (Rast camphor method), 306.

(*b*) *Preparation of 3,6-dibromo-2-nitro-4'-aminodiphenylamine.*—A mixture of 1 g. of 1,4-dibromo-2,3-dinitrobenzene, 3 g. (excess) of *p*-phenylenediamine, 0.44 g. of anhydrous potassium carbonate, 0.10 g. of potassium iodide and 0.05 g. of copper bronze was refluxed for five or six minutes. The reaction mixture was filtered hot and to the filtrate was added 100 ml. of water. A chocolate-brown product precipitated, and was purified by crystallization from methyl alcohol with the aid of Norite. After one crystallization it melted at 146–147°. There was no change in m.p. on further crystallizations.

Anal. Calc'd for $C_{12}H_9Br_2N_3O_2$: C, 37.20; H, 2.34; mol. wt., 387.
Found: C, 37.04; H, 2.19; mol. wt. (Rast camphor method), 365.

B. Reactions of 1,4-dibromo-2,5-dinitrobenzene. (*a*) *Preparation of 4-bromo-2,5-dinitro-4'-aminodiphenylamine.*—To 1 g. of the dibromodinitrobenzene and 0.330 g. of *p*-phenylenediamine dissolved in 40 ml. of alcohol was added 0.1 g. of sodium acetate, and the mixture was refluxed for one hour on a steam bath. The colorless reaction mixture soon developed a characteristic dark red color which gradually deepened. The reaction mixture on addition of water and cooling gave a dark-brown crystalline product. The residue, after filtration, was dissolved in hot alcohol, a little Norite was added, and after a few minutes the suspension was filtered. A few ml. of water was added to the filtrate, and on standing a small amount of an amorphous dark-brown solid precipitated. This was removed by filtration, and more water was added to the filtrate. Crystals formed immediately and more water was added to complete the precipitation. Three-tenths of a gram of a dark-blue crystalline substance melting at 167–170° was obtained after one crystallization from dilute alcohol. After being recrystallized twice from dilute alcohol, once from chloroform, and finally from 95% alcohol it melted at 180–181°. There was no change in m.p. on further crystallizations. The substance is sparingly soluble in alcohol, soluble in chloroform but insoluble in petroleum ether (b.p. 30–60°).

Anal. Calc'd for $C_{12}H_9BrN_4O_4$: C, 40.79; H, 2.57.
Found: C, 40.99; H, 3.02.

The acetyl derivative, a dark-red substance, prepared in the usual manner, was crystallized once from dilute alcohol, and once from 95% alcohol, m.p. 227–228°.

Anal. Calc'd for $C_{14}H_{11}BrN_4O_5$: C, 42.53; H, 2.80.
Found: C, 42.31; H, 2.73.

(*b*) *1. Attempted condensation of 4-bromo-2,5-dinitro-4'-aminodiphenylamine with* p-*phenylenediamine.*—Five-tenths of a gram of the substituted diphenylamine and 2 g. (excess) of *p*-phenylenediamine were dissolved in 40 ml. of alcohol. One-tenth of a gram of copper bronze, 0.2 g. of potassium iodide and 0.2 g. of anhydrous potassium carbonate were added, and the mixture was refluxed for eighteen hours on a steam bath. The hot reaction mixture was filtered, and, on cooling, a dark-red precipitate formed, (m.p. 235–237°). The crude reaction product was acetylated by heating with excess acetic anhydride on a steam bath for two hours. On pouring into excess water a red solid was obtained. Crystallized twice from acetic acid, and once from nitrobenzene, the compound had the m.p. 293–294°. Mixture m.p. with a known specimen of the tetraacetyl derivative of the Bandrowski base 293–294°.

2. Condensation of 4-bromo-2,5-dinitro-4'-acetaminodiphenylamine with p-*phenylenediamine.*—Three-tenths of a gram of the acetyl derivative of the bromo-substituted diphenylamine and 3 g. (excess) of *p*-phenylenediamine were dissolved in

50 ml. of alcohol, and refluxed for seven hours. Three-tenths of a gram of crude reaction product, a dark red crystalline substance, was obtained. This melts at 245–246°, and no change in m.p. was obtained on crystallization from alcohol. The Beilstein test for halogen on this substance was positive. The filtrate from the original reaction mixture gave a negative test for halogen with silver nitrate and a positive test for nitrous acid with starch iodide paper.

Anal. Calc'd for $C_{20}H_{18}BrN_5O_8$: C, 52.60; H, 3.95; N, 15.3.
Found: C, 52.27; H, 4.47; N, 15.11.

C. Reactions of 1,4-dibromo-2,6-dinitrobenzene with p-*phenylenediamine.* (*a*) *Preparation of 4-bromo-2,6-dinitro-4′-aminodiphenylamine.*—One gram of 1,4-dibromo-2,6-dinitrobenzene, 0.60 g. (excess) of *p*-phenylenediamine and 0.3 g. of sodium acetate were added to 40 ml. of alcohol. The solution turned dark-red immediately. After refluxing for fifteen minutes, water was added to complete precipitation. A yield of 1.060 g. (98% of the theoretical) of a dark-green crystalline substance, m.p. 192–194°, was obtained. Crystallized once from alcohol, m.p. 193–194°.

Anal. Calc'd for $C_{12}H_9BrN_4O_4$: C, 40.79; H, 2.57; mol. wt., 353.
Found: C, 40.70; H, 2.63; mol. wt. (Rast camphor method), 364.

The acetyl derivative was prepared in the usual manner. Melting point of the crude material, a red crystalline substance, 270–271°. Crystallized once from glacial acetic acid and once from nitrobenzene, m.p. 271–272°.

Anal. Calc'd for $C_{14}H_{11}BrN_4O_5$: C, 42.58; H, 2.78.
Found: C, 42.56; H, 2.90.

The acetyl derivative, when treated with *p*-phenylenediamine in alcohol solution, does not react. A mixture of 2,6-dinitro-4-bromo-4′-acetaminodiphenylamine and *p*-phenylenediamine in alcohol was refluxed for eight hours. On cooling, a quantitative yield of unchanged starting material was recovered. In a second trial the reaction was attempted in the presence of potassium carbonate, potassium iodide, and copper bronze in alcohol as the solvent, but here also unchanged starting material was recovered.

(*b*) *Preparation of* N,N′-*bis*-(*2,6-dinitro-4-bromophenyl*)-p-*phenylenediamine.* (*1*) *From two moles of 1,4-dibromo-2,6-dinitrobenzene and one mole of* p-*phenylenediamine.*—One gram of 1,4-dibromo-2,6-dinitrobenzene, 0.150 g. of *p*-phenylenediamine and 1 g. of sodium acetate were placed in 40 ml. of alcohol. A dark mahogany color developed immediately. After refluxing for one hour, water was added to complete the precipitation of the dark-red substance. Eight-tenths of a gram of material m.p. 274–277° was obtained. After crystallization from glacial acetic acid, nitrobenzene, and again from glacial acetic acid, m.p. 276–277°. There was no change in m.p. on further crystallizations.

Anal. Calc'd for $C_{18}H_{10}Br_2N_6O_8$: C, 36.12; H, 1.69; Br, 26.73; mol. wt., 598.
Found: C, 36.19; H, 1.75; Br, 26.70; mol. wt. (Rast camphor method), 621.

(*2*) *Preparation from 4-bromo-2,6-dinitro-4′-aminodiphenylamine and 1,4-dibromo-2,6-dinitrobenzene.*—A mixture of 0.2 g. of 4-bromo-2,6-dinitro-4′-aminodiphenylamine, 0.4 g. of 1,4-dibromo-2,6-dinitrobenzene and 0.2 g. of sodium acetate in 25 ml. of alcohol was refluxed for two hours giving 0.22 g. of material, m.p. 273–276°. After one crystallization from glacial acetic acid, m.p. 276–277°. Mixture m.p. with material from the previous preparation 276–277°.

Preparations Using 1-Chloro-4-Bromo-2,6-Dinitrobenzene

A. Preparation of 4-bromo-2,6-dinitro-4′-aminodiphenylamine.—One gram of 1-chloro-4-bromo-2,6-dinitrobenzene (prepared according to the method of Joshi

and Sane[9]), 0.68 g. (excess) of *p*-phenylenediamine, and 0.5 g. of sodium acetate were refluxed in 30 ml. of alcohol for fifteen minutes. On cooling and addition of water, 1 g. of a dark-green crystalline product, m.p. 192–194°, was obtained. Crystallized once from alcohol m.p. 193–194°. Mixture m.p. with 4-bromo-2,6-dinitro-4′-aminodiphenylamine, made from 1,4-dibromo-2,6-dinitrobenzene, 193–194°. Acetyl derivative, m.p. 271–272°. Mixture m.p. with acetyl derivative of 4-bromo-2,6-dinitro-4′-aminodiphenylamine, made from the dibromo compound, 271–272°.

B. Preparation of N,N′-*bis*-(*2,6-dinitro-4-bromophenyl*)-p-*phenylenediamine from the chloro compound.*—(*a*) Two-tenths of a gram of the above 4-bromo-2,6-dinitro-4′-aminodiphenylamine, 0.4 g. of 1-chloro-4-bromo-2,6-dinitrobenzene, and 0.2 g. of sodium acetate in 25 ml. of alcohol were refluxed for two hours. On addition of water and cooling a quantitative yield of product was obtained. Crystallized once from glacial acetic acid, m.p. 276–277°. Mixture m.p. with material made, starting with the dibromo compound, 276–277°.

(*b*) Five-tenths of a gram (0.00176 mole) of 1-chloro-4-bromo-2,6-dinitrobenzene, 0.095 g. (0.00088 mole) of *p*-phenylenediamine and 0.3 g. of sodium acetate in 25 ml. of alcohol were refluxed for forty-five minutes. On addition of water and cooling, 0.48 g. of product (91% of the theoretical), m.p. 268–271° was obtained. Crystallized from glacial acetic acid, nitrobenzene, and again from glacial acetic acid, m.p. 276–277°. No change in m.p. on further crystallizations. Mixture m.p. with material made from the dibromo compound, 276–277°.

SUMMARY

1. A simplified and improved method for the separation of the three isomeric dinitro-1,4-dibromobenzenes, produced on nitrating *p*-dibromobenzene, has been described.

2. The reactions of the dinitro-1,4-dibromobenzenes with *p*-phenylenediamine have been studied.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

THE ACTION OF NITROUS ACID ON CERTAIN HALOGENATED SUBSTITUTION PRODUCTS OF 2,5-, 3,4- AND 3,5-DIMETHYLPHENOLS

L. CHAS. RAIFORD AND DONALD W. KAISER

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Zincke and collaborators[1] proved that when a brominated phenol or cresol is treated with nitrous acid, bromine or a hydrogen atom in a favorable position as respects hydroxyl may be replaced by the nitro group. Raiford and others[2] have shown that when both ortho and para positions are occupied by bromine isomeric *o*- and *p*-mononitrohalogenated derivatives may be formed by this treatment in a single experiment. Chlorine is not replaceable by the nitro group under these conditions. Later Raiford and Scott[3] found that *sym*-tribromo-*m*-xylenol gives a mixture of 2,6-dibromo-4-nitro-*m*-xylenol and 2,6-dibromo-*m*-xyloquinone. In view of the fact that bromine was replaced from position 4 only, it was desired to obtain for comparison the isomeric 2-nitro-4,6-dibromo-*m*-xylenol, and also to examine the behavior of the tribromo substitution products of other xylenols.

Nitration of 2,5-dimethyl-3,4,6-tribromophenol[4] with nitrous acid gave a mononitrodibromo compound in which halogen was replaced from position 4 (OH=1). Treatment of this product with fuming nitric acid eliminated the nitro group and gave 3,6-dibromo-*p*-xyloquinone. Further proof that the compound in question was a 4-nitrophenol was obtained by study of the acetyl-benzoyl derivatives of its reduction product. Introduction of the required acyl radicals in both possible orders led to isomeric mixed diacyl derivatives. The relationships are indicated in Figure 1.

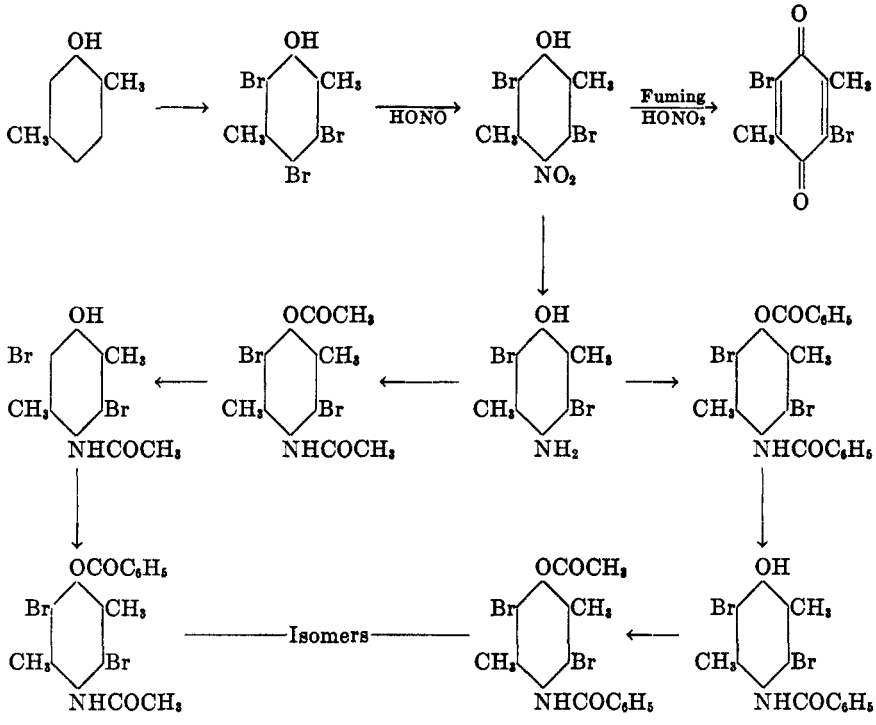
2,5,6-Tribromo-3,4-dimethylphenol[4] was next tested. Treatment of this with nitrous acid as directed by Zincke gave an *o*-nitrodibromo compound. The relative positions of the hydroxyl and nitro radicals were determined by a study of the reduction product. The aminophenol obtained here gave but one mixed acetyl-benzoyl derivative, regardless of

[1] ZINCKE, *J. prakt. Chem.*, [2], **61**, 561 (1900); DAHMER, *Ann.*, **333**, 353 (1904).
[2] RAIFORD AND MILLER, *J. Am. Chem. Soc.*, **55**, 2131 (1933).
[3] RAIFORD AND SCOTT, J. ORG. CHEM., **2**, 221 (1937).
[4] JACOBSEN, *Ber.*, **11**, 27 (1878).

the order of introduction of the acyl groups, and in this product the heavier of these radicals was found attached to nitrogen.[5]

Although the facts cited above showed that an ortho aminophenol was involved, it was still a question whether the amino group occupied position 2 or 6. An attempt to decide between these positions was made by trying to brominate 3,4-dimethyl-6-nitrophenol. To obtain this material the required xylenol was nitrated in accordance with Diepolder's directions.[6] By fractional crystallization of the product from alcohol the mon-

FIGURE 1



onitro compound was isolated in small yellow plates that had the melting point recorded in the literature. This product was brominated, but only

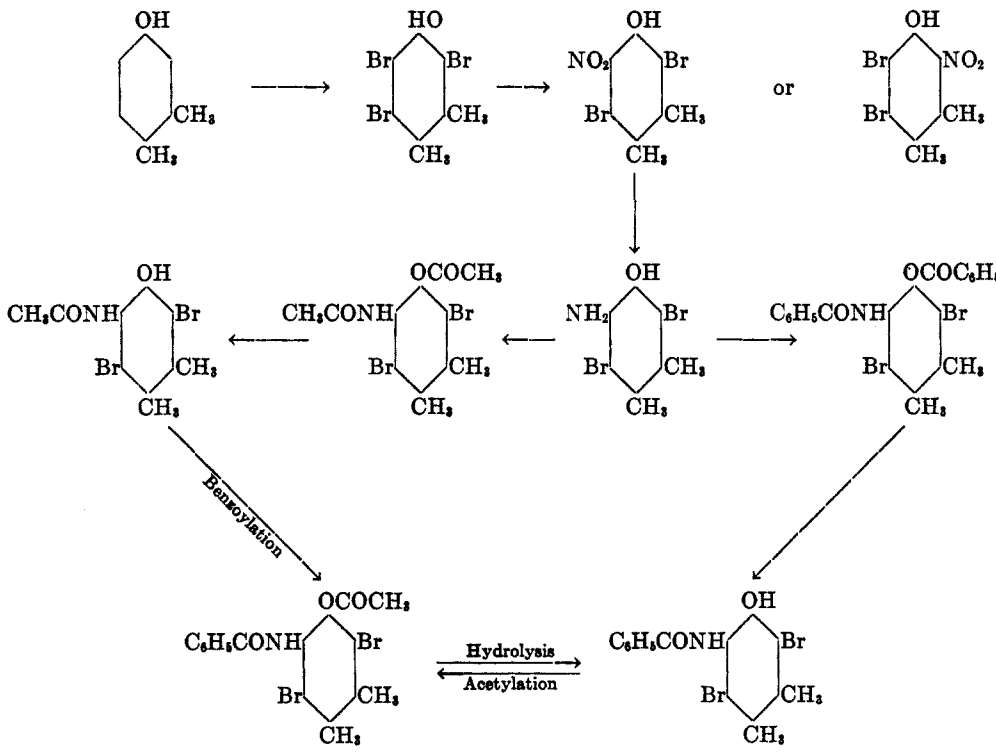
[5] This behavior has previously been shown by RAIFORD AND OTHERS [*J. Am. Chem. Soc.*, **48**, 483 (1926)] to be characteristic of *o*-aminophenol derivatives.

[6] By nitration of 3,4-dimethylphenol DIEPOLDER [*Ber.*, **42**, 2916 (1909)] obtained the 6-nitro compound, m.p., 87°, and the 2,6-dinitro derivative, m.p., 127°. No directions for separation and purification of these products were given except the statement that the mononitro compound was isolated by crystallization from alcohol, and that both products are volatile with steam, but at different rates.

one halogen atom could be introduced. Treatment of the reduction product with bromine did not permit further halogenation. Nevertheless, in the nitrodibromo compound in question the nitro group will be recorded as occupying position 6, since that is the most likely place in terms of the orientation rules. The relationships of these derivatives are indicated in Figure 2.

It was indicated above that when *sym*-tribromo-*m*-xylenol was nitrated the 4-nitro compound only was produced. On this account it was of in-

FIGURE 2

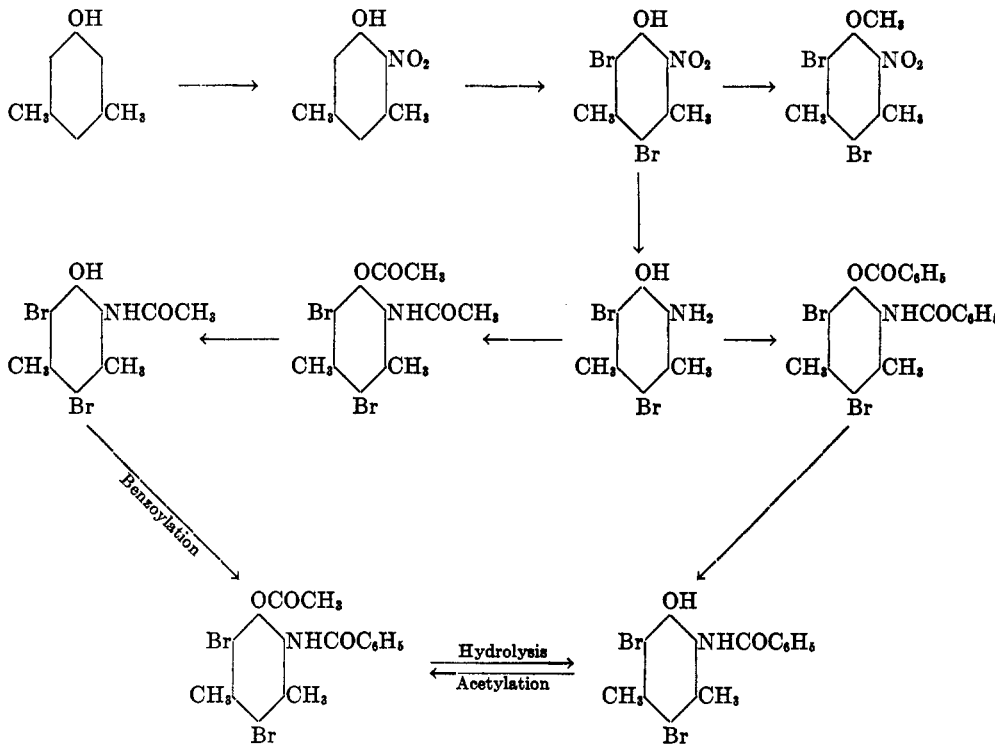


terest to obtain for comparison the isomeric 2-nitro derivative. To do this an indirect method was used. 2-Nitro-3,5-dimethylphenol[7] was brominated as described in the experimental part hereafter. The product was characterized by a study of its methyl ether, and particularly by the behavior of its reduction product. This aminophenol gave but one acetylbenzoyl derivative, although the acyls were introduced in both possible

[7] This was prepared by directions recorded by AUWERS AND BORSCHE [*Ber.*, **48**, 1714 (1915)].

orders, which characterized it as an ortho compound. Figure 3 shows the relations of the compounds involved. In previous work in this field Raiford and Miller[8] found that in the compounds they studied the chlorine atom could not be replaced by the nitro group when the Zincke method is used. In view, however, of the observations of Raiford[9] on the behavior of 2,4,6-trichloro-*m*-cresol, and of Raiford and Scott[3] in their study of 2,4,6-tribromo-*sym*-*m*-xylenol, in the latter of which nitration gave rise to a nitro compound and a quinone, the corresponding trichloro-*m*-xylenol

FIGURE 3



was examined. With this fuming nitric acid gave a quinone but no nitro compound. When formed through the action of nitrous acid the quinone immediately combined with two molecular proportions of the unchanged phenol and was isolated as a molecular compound.[10] Attempts to convert

[8] RAIFORD AND MILLER, *J. Am. Chem. Soc.*, **55**, 2125 (1933).

[9] RAIFORD, *Am. Chem. J.*, **46**, 425 (1911).

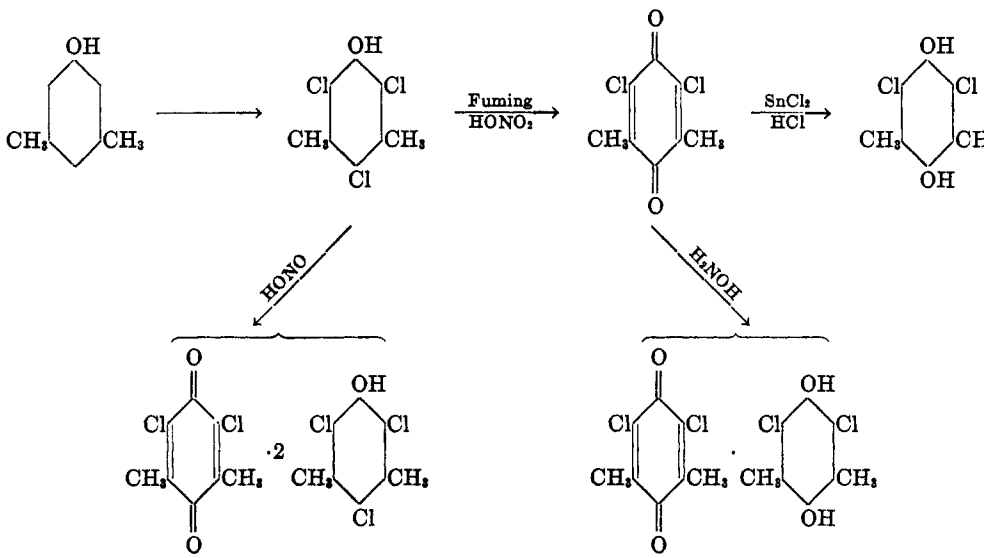
[10] MEYER [*Ber.*, **42**, 1149 (1909)] AND WOOLLETT AND OTHERS [*J. Am. Chem. Soc.*, **59**, 862 (1937)] have referred to such products as phenoquinones.

the quinone into a monoxime by treatment with hydroxylamine gave the corresponding quinhydrone. When a mixture of stannous chloride and hydrochloric acid was used as a reducing agent, the hydroquinone was obtained. The relations involved in this case are shown in Figure 4.

EXPERIMENTAL

2,5-Dimethyl-3,6-dibromo-4-nitrophenol.—Two hundred and fifty grams of 2,5-dimethyl-3,4,6-tribromophenol[11] was dissolved as far as possible in a mixture of 3 liters of acetic acid and 200 cc. of dioxane*, cooled to 7–10°, 12 g. of sodium nitrite was added with stirring during a period of two hours, the mixture was allowed to stand overnight and was then poured with rapid stirring into about 18 liters of water to precipitate the product. A yield of 81% was obtained. Crystallization from

FIGURE 4



ligroïn (b.p. 60–70°) containing about 10% of benzene gave large yellow needles that melted at 152–153° with decomposition[12].

Anal. Calc'd for $C_8H_7Br_2NO_3$: Br, 49.23. Found: Br, 48.99.

2,5-Dimethyl-3,6-dibromo-4-nitrophenyl methyl ether.—This was prepared for

[11] This was obtained in quantitative yield by bromination of 2,5-dimethylphenol as directed by AUWERS AND ERCKLENTZ [*Ann.*, **302**, 114 (1898)].

* Dioxane increased the solubility of the halogenated xylenol and lowered the freezing point of acetic acid. When a Zincke nitration is conducted at 14° much of the acetic acid may solidify.

[12] ZINCKE AND BREITWIESER [*Ber.*, **44**, 182 (1911)] reported 154° for this product which they obtained from the corresponding chinitrol, and which they said was colorless. They reported no yield.

further identification of the above nitro compound. Ten g. of the latter was dissolved in 75 cc. of methanol containing 2 g. of potassium hydroxide, 3 g. of dimethyl sulfate was slowly added, the mixture was refluxed for two hours, and then poured into a large volume of ice water containing caustic potash. The colorless precipitate was obtained in 58% yield, and crystallization of it from methanol gave slender needles that melted at 85–86°.

Anal. Calc'd for $C_9H_9Br_2NO_3$: Br, 47.17. Found: Br, 47.01.

2,5-Dimethyl-3,6-dibromo-4-nitrophenyl acetate.—Five grams of the required nitro compound was warmed with 1 g. of anhydrous sodium acetate and 5 cc. of acetic anhydride, the cooled mass was extracted with water, and the residue was crystallized from dilute acetic acid. Small needles that melted at 114–115° were obtained†.

Anal. Calc'd for $C_{10}H_9Br_2NO_4$: Br, 43.59. Found: Br, 43.42.

*3,6-Dibromo-*p*-xyloquinone.*—Ten grams of the above-described nitrophenol was sprinkled into 50 cc. of fuming nitric acid that had previously been cooled to 0°, the mixture was allowed to come to room temperature, the red solution obtained was heated on a steam bath for five minutes after red fumes began to appear, and the liquid poured into ice water. The solid obtained was crystallized from carbon tetrachloride from which it separated in small yellow scales that melted at 185–186°. The yield of purified material was 58%[13].

Anal. Calc'd for $C_8H_6Br_2O_2$: Br, 54.42. Found: Br, 54.45.

Hydrochloride of 2,5-dimethyl-3,6-dibromo-4-aminophenol.—Fifty grams of the required nitro compound was reduced with stannous chloride and hydrochloric acid as directed by Raiford and Colbert[14] and the colorless amorphous product was washed with hydrochloric acid and then with ether. The yield was 72%. The compound decomposed at about 225°.

Anal. Calc'd for $C_8H_{10}Br_2ClNO$: Hal., 58.92. Found: Hal., 59.10.

2,5-Dimethyl-3,6-dibromo-4-aminophenol.—A portion of the required hydrochloride was suspended in water, treated with ammonium carbonate solution, and the residue was crystallized from methanol. The pale-brown plates obtained melted with decomposition at 187–188°. Zincke and Breitwieser (*loc. cit.*) reported 186–188°, but recorded no analyses.

Anal. Calc'd for $C_8H_9Br_2NO$: Br, 54.23. Found: Br, 54.12.

The above aminophenol was further characterized by a study of its acetyl-benzoyl derivatives, for which analytical data and other properties are given in Table I.

Nitration of 3,4-dimethylphenol.—To a solution of 10 g. of the phenol in 100 cc. of glacial acetic acid in a suitable flask cooled in tap water, there was added, as rapidly as possible, a mixture of 15 cc. of concentrated nitric acid and 50 cc. of acetic acid. The solution turned red instantly, and after one minute was poured slowly into five volumes of ice water that was being stirred rapidly. The yellow oil that separated became solid in about half an hour. By fractional crystallization from alcohol the mononitro compound was obtained in 19% yield of small yellow plates that melted at 86–87°[15]; while only 8% of the dinitro product was secured. This melted at 126–

† ZINCKE AND BREITWIESER (*loc. cit.*) reported 116° but did not analyze their product.

[13] This product should be identical with that of m.p. 184°, obtained by CARSTANJEN [*J. prakt. Chem.*, [2], **23**, 434 (1881)] by bromination of *p*-xyloquinone. AUWERS AND RAPP [*Ann.*, **302**, 166 (1898)] found 185–186°. Neither worker recorded a yield.

[14] RAIFORD AND COLBERT, *J. Am. Chem. Soc.*, **47**, 1457 (1925).

[15] DIEPOLDER, reference 6, found 87°.

TABLE I

ACYL DERIVATIVES OF 2,5-DIMETHYL-3,6-DIBROMO-4-AMINOPHENOL

POSITION OF ACYL	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
N-Acetyl-*O*-acetyl	77	Alcohol	Colorless plates	237–238	$C_{12}H_{13}Br_2NO_3$	42.21	42.06
Acetylaminophenol	89	Alcohol	Colorless plates	230–231 (decomp.)	$C_{10}H_{11}Br_2NO_2$	47.47	47.43
N-Benzoyl-*O*-benzoyl	86	Alcohol	Small plates	275 (above)	$C_{22}H_{17}Br_2NO_3$	31.80	31.74
Benzoylaminophenol	92	Alcohol	Colorless plates	221–222	$C_{15}H_{13}Br_2NO_2$	40.10	39.88
N-Benzoyl-*O*-acetyl	73	Alcohol	Colorless needles	244–[a]245	$C_{17}H_{15}Br_2NO_3$	36.28	36.17
N-Acetyl-*O*-benzoyl	72	Alcohol	Small needles	250–[a]251	$C_{17}H_{15}Br_2NO_3$	36.28	36.11

[a] A mixture of these liquefied below 226°.

127°, as recorded by Nölting and Pick[16]. By steam-distillation of the crude nitration product, and crystallization of the volatile material from ligroïn (60–70°), the mononitro compound was obtained in 38% yield.

Bromination of 3,4-dimethyl-6-nitrophenol.—Ten grams of the nitro compound was dissolved in 40 cc. of acetic acid, 0.5 g. of iron powder was added, and the mixture was heated on the steam bath while a solution of 21 g. of bromine in 10 cc. of acetic acid was slowly added from a tap funnel. The liquid was heated for three hours and then poured into ice water containing sodium bisulfite. Crystallization of the product from methanol and then from ligroïn (60–70°) gave slender yellow needles that melted at 74–75°. The yield was 82%.

In a second experiment 2 g. of the nitro compound dissolved in 10 cc. of carbon disulfide was treated with 3 cc. of bromine containing about 1% of aluminum bromide, the mixture was allowed to stand overnight, the solvent was distilled off, the dark oil was dissolved in caustic alkali solution, boiled with charcoal, the mixture was filtered and the filtrate was mixed with concentrated hydrochloric acid. Crystallization of the precipitate as explained above gave yellow needles that melted at 74–75°. The yield was 73%.

In a third experiment the phenol was subjected to the action of bromine without solvent, but the product was identical with those mentioned above. Analysis indicated a monobromo compound.

Anal. Calc'd for $C_8H_8BrNO_3$: Br, 32.52. Found: Br, 32.60.

Hydrochloride of 2-bromo-3,4-dimethyl-6-aminophenol.—Forty grams of the required nitro compound was reduced with a mixture of stannous chloride and hydrochloric acid, as previously explained. A yield of 74% was obtained. The product decomposed at about 260°.

Anal. Calc'd for $C_8H_{11}BrClNO$: Hal., 45.74. Found: Hal., 45.88.

2-Bromo-3,4-dimethyl-6-aminophenol.—This was obtained by treatment of an aqueous suspension of the required hydrochloride with ammonium carbonate solution until effervescence ceased. Crystallization of the residue from methyl alcohol gave pale pink plates that melted at 103–104°.

Anal. Calc'd for $C_8H_{10}BrNO$: Br, 37.03. Found: Br, 37.17.

2-Bromo-3,4-dimethyl-6-acetylaminophenyl acetate.—A mixture of 20 g. of the above aminohydrochloride, 8 g. of fused anhydrous sodium acetate and 25 g. of acetic anhydride was heated on a steam bath for one hour, the cooled mixture was extracted with water, and the residue was crystallized from alcohol. The material separated in masses of colorless fluffy needles that resembled cotton and melted at 199–200°. The yield was 88%.

Anal. Calc'd for $C_{12}H_{14}BrNO_3$: Br, 26.66. Found: Br, 26.72.

Attempts to introduce a second atom of bromine into this compound were unsuccessful.

2,5,6-Tribromo-3,4-dimethylphenol.—Jacobsen recorded a melting point of 169°, Auwers and Rapp found 171°, while Crossly and Renouf[17] reported 172–173° for a product which probably had the composition and structure indicated above. Auwers and Rapp alone indicated a method of preparation while neither of them gave analytical data for the product. In the present work 75 cc. of bromine (an excess) was allowed to drop slowly on 50 g. of Eastman's purest 3,4-dimethylphenol

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[16] Nölting and Pick, *Ber.*, **21**, 3158 (1888).

[17] Jacobsen, *Br.*, **11**, 28 (1878); Auwers and Rapp, *Ann.*, **302**, 160 (1898); Crossly and Renouf, *J. Chem. Soc.*, **105**, 177 (1914).

contained in a dry 250 cc. flask with an outlet tube to convey hydrogen bromide to a suitable trap. The mixture, which became liquid as the reaction progressed, but which solidified after all bromine had been added, was allowed to remain overnight, and was then treated with a concentrated solution of sodium acid sulfite. The solid was removed from the flask, and triturated with more sulfite solution; the mixture was filtered, and the residue was washed several times. A quantitative yield of colorless solid was obtained. Crystallization from alcohol gave lustrous needles that melted at 173–174°.

Anal. Calc'd for $C_8H_7Br_3O$: Br, 66.85. Found: Br, 66.90.

Nitration of 2,5,6-tribromo-3,4-dimethylphenol.—Fifty grams of the above-described crude tribromo compound was suspended in 400 cc. of acetic acid; the mixture was stirred continuously, while 20 g. of solid sodium nitrite was added during a period of about three hours. The starting material that caked on the walls of the beaker was dislodged frequently, and the lumps were broken up with a heavy glass rod. The mixture was allowed to stand overnight and was then poured slowly into 5 volumes of ice water that was being stirred rapidly. The product that separated gave, after two crystallizations from methanol, slender yellow needles that melted at 168–169° with apparent decomposition. By working up the filtrates a yield of 61% of purified material was obtained.

Anal. Calc'd for $C_8H_7Br_2NO_3$: Br, 49.23. Found: Br, 49.23.

2,5-Dibromo-3,4-dimethyl-6-nitrophenyl methyl ether.—Six grams of the above-described nitro compound was dissolved in 50 cc. of methanol containing 1.2 g. of potassium hydroxide, the deep-red solution was gently refluxed while 2 g. of dimethyl sulfate was slowly added through the condenser, the mixture was heated for two hours and then was poured into ten volumes of ice water containing some alkali. Crystallization of the precipitate from methanol gave small, nearly colorless needles that melted at 100–101°. A yield of 67% was obtained.

Anal. Calc'd for $C_9H_9Br_2NO_3$: Br, 47.19. Found: Br, 46.98.

Hydrochloride of 2,5-dibromo-3,4-dimethyl-6-aminophenol.—Forty grams of the above nitrophenol was reduced with stannous chloride as previously explained. The small colorless plates that separated were collected, washed with concentrated acid and with methanol. The yield was 87%. The product decomposed about 230° without melting.

Anal. Calc'd for $C_8H_{10}Br_2ClNO$: Hal., 58.92. Found: Hal., 59.02.

2,5-Dibromo-3,4-dimethyl-6-aminophenol.—A water suspension of the above-described amino hydrochloride was treated with ammonium carbonate solution until effervescence ceased, and the residue was collected. Crystallization from methanol gave nearly colorless slender needles that decomposed at 130–131°.

Anal. Calc'd for $C_8H_9Br_2NO$: Br, 54.23. Found: Br, 54.04.

This base was further characterized by the study of its acyl derivatives. Only one acetyl-benzoyl derivative could be obtained. Analytical data and other properties for this and related compounds are given in Table II.

2-Nitro-3,5-dimethyl-4,6-dibromophenol.—To a solution of 20 g. of the required nitrodimethyl phenol[18] in 100 cc. of acetic acid held at the temperature of the steam bath, there was slowly added 13 cc. of bromine diluted with 20 cc. of acid, and the

[18] This product was obtained by nitration of the corresponding phenol as directed by AUWERS AND BORSCHE [*Ber.*, **48**, 1914 (1915)]. Along with it some of the isomeric 4-nitro compound was formed. The yield of the first was 16% and that of the second about 3.5%.

TABLE II

ACYL DERIVATIVES OF 2,5-DIBROMO-3,4-DIMETHYL-6-AMINOPHENOL

POSITION OF ACYL	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
N-Acetyl-*O*-acetyl	82	Alcohol	Colorless, silky needles	217–218	$C_{12}H_{13}Br_2NO_3$	42.21	42.09
Acetylaminophenol	90	Alcohol	Very small needles	181–182	$C_{10}H_{11}Br_2NO_2$	47.47	47.30
N-Benzoyl-*O*-benzoyl	85	Alcohol	Colorless needles	207–208	$C_{22}H_{17}Br_2NO_3$	31.80	31.64
Benzoylaminophenol	90	Alcohol	Colorless, glossy needles	227–228	$C_{15}H_{13}Br_2NO_2$	40.10	39.90
N-Benzoyl-*O*-acetyl	62	Alcohol	Chalky needles	209–210	$C_{17}H_{15}Br_2NO_3$	36.28	36.35

mixture was allowed to stand overnight. The solid that separated was collected, and washed with small portions of dilute methyl alcohol; the filtrate was poured into 5 volumes of water, and a small portion of solid was recovered. This was mixed with the original solid. A yield of 90% was obtained. Crystallization of the product from alcohol gave pale yellow needles that decomposed at 160–161°. A mixture of this product and the isomeric 4-nitro compound, m.p., 172–173°[19], decomposed at about 148°.

Anal. Calc'd for $C_8H_7Br_2NO_3$: Br, 49.23. Found: Br, 49.02.

2-Nitro-3,5-dimethyl-4,6-dibromophenyl methyl ether.—Thirty-two grams of the required nitro compound was dissolved in 125 cc. of methanol and a solution of 6 g. of potassium hydroxide in 35 cc. of the same solvent was added. The deep-red solution was heated for two hours under reflux on a steam bath, and the mixture was poured into a large volume of ice-water containing caustic alkali. The nearly colorless solid that precipitated was crystallized from methanol, from which it separated in colorless, silky needles that melted at 99–100°. The yield of purified material was 69%.

Anal. Calc'd for $C_9H_9Br_2NO_3$: Br, 47.19. Found: Br, 47.02.

Hydrochloride of 2-amino-3,5-dimethyl-4,6-dibromophenol.—Forty grams of the required nitro compound was dissolved in 250 cc. of alcohol and was reduced with a mixture of stannous chloride and hydrochloric acid as explained above. The solid that separated was collected, and washed with acid. A yield of 89% was obtained. The compound decomposed at about 241°.

Anal. Calc'd for $C_8H_{10}Br_2ClNO$: Hal., 58.97. Found: Hal., 58.99.

2-Amino-3,5-dimethyl-4,6-dibromophenol.—A portion of the salt indicated above was made into a thin paste with water, a slight excess of ammonium carbonate was added, and the mixture filtered. Crystallization of the residue from methanol gave small ivory needles that melted at 141–142°.

Anal. Calc'd for $C_8H_9Br_2NO$: Br, 54.23. Found: Br, 54.34.

This aminophenol was acylated by means of standard methods, but only one acetyl-benzoyl derivative was obtained. Analytical data and other properties of these compounds are given in Table III.

2,4,6-Trichloro-3,5-dimethylphenol.—This compound was first obtained by Katscher and Lehr[20] by the action of a mixture of chlorosulfonic acid, concentrated hydrochloric acid and hydrogen peroxide on 3,5-dimethylphenol. It was here prepared by direct action of chlorine on the phenol. One hundred twenty-two grams of 3,5-dimethylphenol was dissolved in 1500 cc. of carbon tetrachloride in a two-liter flask bearing a two-hole rubber stopper. Through one hole a delivery tube for chlorine extended to the bottom of the flask. The other was connected by a wide tube to the lower end of a condenser set at an angle of about 45°. The upper end of the condenser was connected to a series of three wash bottles containing caustic alkali solution. The solution of phenol was first heated, chlorine was bubbled through briskly, and the heat of reaction kept the mixture hot until the experiment was over. Considerable carbon tetrachloride distilled over into the alkali solution, and the reaction was regarded as complete when the space above the liquid in the reaction flask became greenish and the carbon tetrachloride that distilled over was yellowish-green. By standing overnight the mixture deposited colorless silky needles that melted at 177–178° which was not changed by recrystallization. Con-

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[19] RAIFORD, J. ORG. CHEM., **2**, 214 (1937).

[20] KATSCHER AND LEHR, *Monatsh.*, **64**, 239 (1934).

TABLE III

ACYL DERIVATIVES OF 2-AMINO-3,5-DIMETHYL-4,6-DIBROMOPHENOL

POSITION OF ACYL	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
N-Acetyl-*O*-Acetyl	78	Alcohol	Colorless needles	244–245 (decomp.)	$C_{12}H_{13}Br_2NO_3$	42.21	42.27
Acetylaminophenol	91	Alcohol	Slender needles	190–191	$C_{10}H_{11}Br_2NO_2$	47.47	47.59
N-Benzoyl-*O*-Benzoyl	87	Alcohol	Small colorless needles	178–179	$C_{22}H_{17}Br_2NO_3$	31.80	31.60
Benzoylaminophenol	93	Alcohol	Fine colorless needles	224–225 (decomp.)	$C_{15}H_{13}Br_2NO_2$	40.10	40.24
N-Benzoyl-*O*-Acetyl	64	Alcohol	Microscopic chalky masses	175–176	$C_{17}H_{15}Br_2NO_3$	36.28	36.11

centration of the mother liquor increased the yield to 87%. The previous authors reported no yield.

2,6-Dichloro-m-*xyloquinone* was obtained in 64% yield of large golden plates that melted at 177–178° by oxidation of the trichlorophenol with fuming nitric acid as directed by Kohn and Rabinowitsch in similar cases[21]. The physical properties of the compound agreed with those recorded by Claus and Runschke[22] who first prepared it, but in a different way.

2,6-Dichloro-m-*xyloquinhydrone.*—Ten grams of the above finely powdered, quinone was suspended in 180 cc. of alcohol and to this there was added 3.4 g. of hydroxylamine hydrochloride 3 g. of potassium hydroxide in 10 cc. of water, and the mixture heated on a steam bath for two hours. The mixture became dark-colored, evolved much gas, and was cooled and poured into dilute sulfuric acid. The dark-purple solid that separated was purified by crystallization from alcohol and was obtained in nearly black metallic-looking plates resembling iodine, which melted at 177–178°. A test for nitrogen was negative. A mixture of this product and the quinone used as starting material melted with pronounced depression. The yield of purified material was 67%.

Anal. Calc'd for $C_{16}H_{14}Cl_4O_4$: Cl, 34.46. Found: Cl, 34.22.

2,6-Dichloro-m-*xylohydroquinone.*—Claus and Runschke[22] obtained a product which they state had this composition, but they gave no details concerning its preparation and furnished no analytical data for it. It was obtained in this work by treatment of the quinone with two molecular proportions of hydroxylamine. A much more satisfactory method was reduction with stannous chloride, by which it was obtained in 86% yield. Crystallization from alcohol gave yellow needles that melted at 225–226°.

Anal. Calc'd for $C_8H_8Cl_2O_2$: Cl, 34.29. Found: Cl, 34.25.

Molecular compound obtained by the action of nitrous acid on trichloro-sym-m-*xylenol* (*phenoquinone*).—One hundred grams of 2,4,6-trichloro-3,5-dimethylphenol was dissolved in 1800 cc. of glacial acetic acid at room temperature, and 50 g. of solid sodium nitrite was added, in small portions, during an hour, and the mixture allowed to stand overnight. Sodium acetate that had separated was removed by filtration, and the ruby-colored filtrate was poured with stirring into six volumes of water, and the whole allowed to stand twelve hours. The orange-colored solid was collected and dried in a desiccator for three days. Crystallization from carbon tetrachloride gave crimson cubes that represented one mole of quinone and two moles of phenol. The yield was 48%. It was also obtained by mixing solutions of the quinone and the phenol in the proper proportions.

When a crystal was crushed to obtain material for melting-point determination an orange powder was obtained. At 118–119° the powder became yellow but did not melt. Between 133° and 164° it melted solwly to a yellow liquid. On cooling it became orange again.

Anal. Calc'd for $C_{24}H_{20}Cl_8O_4$: Cl, 43.29. Found: Cl, 43.41.

SUMMARY

The action of nitrous acid on certain halogen substitution products of the 2,5-, 3,4- and 3,5-dimethylphenols have been studied, and the following observations have been made.

[21] KOHN AND RABINOWITSCH, *Monatsh.*, **48**, 360 (1927).

[22] CLAUS AND RUNSCHKE, *J. prakt. Chem.*, [2], **42**, 124 (1890).

1. Nitrous acid reacts with 2,5-dimethyl-3,4,6-tribromophenol to replace bromine from position 4 (OH=1) by the nitro radical. Treatment of the resulting nitro compound with fuming nitric acid gives 3,6-dibromo-*p*-xyloquinone.

2. When the tribromo derivative of 3,4-dimethylphenol was tested the halogen from position 6 was substituted by the nitro group.

3. Nitrous acid acts on 2,4,6-trichloro-3,5-dimethylphenol to convert a portion of it into 2,6-dichloro-*m*-xyloquinone which combines at once with two molecular proportions of the unchanged phenol. When fuming nitric acid is used pure dichloroquinone is obtained. Treatment of the latter with one molecular proportion of hydroxylamine gives the related quinhydrone.

4. Further evidence has been obtained to support the views previously recorded, *viz.*, that, in general, only one acetyl-benzoyl derivative can be prepared from an *o*-aminophenol regardless of the order of introduction of the acyl radicals.

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

ALLENES. I. THE PREPARATION OF 1-PHENYL-1,2-BUTADIENE

FRED ACREE, JR., AND F. B. LAFORGE

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Pyrethrolone, the alcoholic component of the two insecticidal esters of pyrethrum flowers, pyrethrins I and II, contains an unsaturated five-membered substituent which catalytic hydrogenation with absorption of two moles of hydrogen converts into the *n*-amyl group. According to Staudinger and Ruzicka,[1] who first investigated pyrethrolone, the compound itself has an open side-chain containing the cumulated system of double bonds. The evidence for this conclusion has always been considered inadequate, and even Ruzicka[2] later indicated a preference for a conjugated system.

Recently LaForge and Haller[3] investigated the nature of the pyrethrolone side-chain, but were unable to reach a definite solution, although their results seemed to exclude the presence of the conjugated system. Their most striking observation had to do with the behavior of pyrethrolone (and pyrethrone, in which only the hydroxyl group of pyrethrolone had been replaced by hydrogen) toward bromine. The reaction with one mole of bromine in ethanol solution appeared to be one of substitution instead of addition, as previously supposed, and furnished a monobromo derivative with liberation of free hydrobromic acid. When the product was reduced with zinc, the original pyrethrolone (or pyrethrone) was regenerated.

Such a reaction was not in agreement with the known behavior of either the cumulated or the conjugated system. It seemed, therefore, that further investigation of the action of halogens on allenes, especially substituted methylallenes (*i.e.* 1,2-butadienes), might by analogy throw some light on the nature of the side chain of pyrethrolone. The substituted 1,2-butadienes have been considered, because evidence points to the presence of a terminal methyl group in the pyrethrolone side-chain.

This article describes the preparation of 1-phenyl-1,2-butadiene, $C_6H_5CH{=}C{=}CHCH_3$ (I), a compound not previously reported in the

[1] STAUDINGER AND RUZICKA, *Helv. Chim. Acta*, **7**, 212 (1924).
[2] RUZICKA AND PFEIFFER, *ibid.*, **16**, 1208 (1933).
[3] LAFORGE AND HALLER, J. ORG. CHEM., **2**, 546 (1938).

literature, by two procedures. The first procedure involves the following series of reactions: α-chlorocrotonic aldehyde furnishes 1-phenyl-1-hydroxy-2-chloro-2-butene, $C_6H_5CHOHCCl{=}CHCH_3$ (II), by the Grignard reaction with bromobenzene. Substitution of the hydroxyl group with chlorine gives 1-phenyldichlorobutene (III), in which the double bond may be in either the 1,2 position ($C_6H_5CH{=}CClCHClCH_3$) or the 2,3 position ($C_6H_5CHClCCl{=}CHCH_3$), or the product may be a mixture of the two, depending upon whether or not the allylic rearrangement has taken place. This is immaterial, however, since dehalogenation of either dichloro compound would furnish I.

The second and more convenient method of preparing the compound is by way of the following steps: 1-phenyl-2,2,3-trichloro-1-butanol, $C_6H_5CHOHCCl_2CHClCH_3$ (IV), obtained by the Grignard reaction of 2,2,3-trichlorobutanal with bromobenzene, is chlorinated to furnish 1-phenyl-1,2,2,3-tetrachlorobutane, $C_6H_5CHClCCl_2CHClCH_3$ (V), which on treatment in ethanol solution with zinc furnishes I.

Prepared by either method the hydrocarbon is a colorless, very mobile liquid. In contact with the air it soon turns yellow, and on longer standing it becomes a viscous mass. The changes are probably due to both oxidation and polymerization. The compound is especially sensitive to mineral acids, which cause rapid polymerization or decomposition. Because of its instability, which may be due to the presence of the styrene functional group, it should be prepared fresh before employment for reactions, and it should be distilled and kept under carbon dioxide or some other inert gas.

1-Phenyl-1,2-butadiene does not react with maleic anhydride or with α-naphthoquinone. On catalytic hydrogenation it absorbs two moles of hydrogen to form *n*-butylbenzene. It is oxidized by potassium permanganate to benzoic and acetic acids.

The behavior of 1-phenyl-1,2-butadiene and some other allenes toward halogens will be described in subsequent articles of this series.

EXPERIMENTAL

1-Phenyl-1-hydroxy-2-chloro-2-butene (II).—The Grignard reagent was prepared from 6 grams of magnesium and 37 grams of bromobenzene in 200 cc. of dry ether. A solution of 23 grams of α-chlorocrotonic aldehyde[4] in 200 cc. of the same solvent was slowly run into the solution of the reagent, constantly stirred, and cooled in an ice-salt mixture. After the reaction product had been kept overnight in the cold, it was decomposed by adding it, with mechanical agitation, to a solution of 25 grams of ammonium chloride in 300 cc. of water containing ice. A small quantity of acetic acid was added to clear the emulsion, and the reaction product was extracted with ether. The ethereal solution, after being washed with water and dilute sodium

[4] MOUREU, MURAT AND TAMPIER, *Bull. soc. Chim.*, [4], **29**, 32 (1921).

bicarbonate, was dried, and the solvent was removed. The product distilled at 122–124° (0.5–1.0 mm.); n_D^{20} 1.5545; n_D^{30} 1.5502. The yield was 21.8 grams. It crystallized on cooling, and was recrystallized from petroleum ether, from which it separated in long needles, m.p. 50–51°.

Anal. Calc'd for $C_{10}H_{11}ClO$: C, 65.75; H, 6.04.
Found: C, 65.02, 65.93; H, 6.01, 6.32.

The same compound was obtained by dehalogenation of 1-phenyl-2,2,3-trichloro-1-butanol (IV) as follows: Ten grams of IV in 25 cc. of ethanol was dropped into a stirred suspension of 10 grams of zinc dust in 25 cc. of ethanol that had been heated to the boiling point. The reaction proceeded with heat evolution sufficient to boil the solvent. After all the solution had been added, the reaction mixture was refluxed for 30 minutes, cooled, and the zinc removed by filtration. The ethanol solution was diluted with several volumes of water, and the reaction product was extracted with ether. After repeated washings with water the ethereal solution was dried, and the solvent was removed. The residue crystallized on seeding with crystals prepared by the preceding method. The yield was 7.2 grams. It was recrystallized from petroleum ether with very little loss and melted at 49°.

1-Phenyldichlorobutene (III), $C_6H_5CH{=}CClCHClCH_3$ or $C_6H_5CHClCCl{=}CHCH_3$.—Four grams of II was dissolved in 30 cc. of benzene, and 1 gram of dry hydrochloric acid (20% in excess of the theoretical equivalent) was slowly passed into the cooled solution, the amount of hydrochloric acid being determined by the gain in weight. The solution became turbid with the separation of water. The excess acid was removed by washing with water and bicarbonate solution, and the solvent was removed under reduced pressure. The residue was distilled and yielded 3.5 grams (80% of theoretical) of distillate boiling at 100° (0.7 mm.); n_D^{20} 1.5712; n_D^{30} 1.5666. In another experiment 20 grams of II yielded 19 grams of dichloro compound.

Anal. Calc'd for $C_{10}H_{10}Cl_2$: C, 59.70; H, 4.97; Cl, 35.28.
Found: C, 60.61, 60.93; H, 5.29, 5.28; Cl, 34.62, 34.72.

The chlorination of 1-phenyl-1-hydroxy-2-chloro-2-butene (II) was also carried out by means of thionyl chloride. In this case, as was subsequently shown, the product was essentially 1-phenyl-2,3-dichloro-1-butene. One and five-tenths grams of purified thionyl chloride was added to 2.6 grams of II. The reaction started at once with liquefaction of the mass and evolution of hydrochloric acid. After being warmed for a few minutes, the reaction mixture was poured onto cracked ice and water, and the product was extracted with ether. The ethereal solution was washed with water and sodium carbonate solution and dried. After removal of the solvent the residue was distilled and boiled at 82–87° (0.5–1.0 mm.); n_D^{28} 1.5727.

Anal. Calc'd for $C_{10}H_{10}Cl_2$: Cl, 35.26. Found: Cl, 35.41, 35.66.

1-Phenyl-1,2-butadiene (I) (first method).—The dehalogenation of 1-phenyldichlorobutene (III) was carried out a number of times with variations in the experimental conditions. The following procedure gave satisfactory results, but the reaction with zinc dust as applied in the dehalogenation of 1-phenyl-2,2,3-trichloro-1-butanol (IV) would have been more convenient.

A solution of 12 grams of the phenyldichlorobutene in 100 cc. of ethanol was placed in a flask provided with a condenser and equipped for mechanical stirring. The solution was warmed, and 12 grams of zinc dust was added in small portions. After the reaction had started, it proceeded with evolution of heat, sometimes making cooling necessary. Finally the reaction mixture was refluxed for several minutes. After removal of the excess zinc by filtration, part of the ethanol was removed under reduced pressure, and the solution was strongly diluted with water and ex-

tracted with ether. The ethanol was washed from the ethereal solution, which was then dried with sodium sulfate.

The residue obtained on removal of the solvent was distilled from a flask provided with a 15-cm. reflux column, and yielded 4.5 grams of colorless distillate which boiled at 44–47°, (0.5–1.0 mm.); n_D^{20} 1.5754, $n_F^{20}-n_C^{20}$ 0.025; n_D^{30} 1.5698; $d_4^{25.5}$ 0.9240 M.R. calc'd for $C_{10}H_{10}$: 43.84; found: 46.33. (The refractive index for 1-phenyl 1,3-butadiene is reported as n_D^{19} 1.6140).

Anal. Calc'd for $C_{10}H_{10}$: C, 92.31; H, 7.69.
Found: C, 92.65, 91.87, 91.30: H, 8.11, 7.87, 7.90.

The compound turns yellow in a short time in contact with the air, and slowly changes to a thick liquid; it is therefore necessary to keep it under some inert gas and to prepare it fresh for subsequent reactions. Owing to its tendency to oxidize and polymerize, and also because of its volatility, it is difficult to obtain sharp analytical results.

Hydrogenation of 1-phenyl-1,2-butadiene to n-*butylbenzene.*—One gram of I was hydrogenated with platinum oxide catalyst in ethanol solution. In 10 minutes 375 cc. of hydrogen was absorbed, and in the next 10 minutes 25 cc. The theoretical quantity of hydrogen for 2 moles is 343 cc. The hydrogenated product was isolated by dilution of the filtered solution with water and extraction with ether. The residue on distillation yielded 0.6 gram of product boiling at 183° (760 mm.); n_D^{18} 1.4907. [n_D^{18} 1.4940 is reported for *n*-butylbenzene, which boils at 179° (760 mm.).]

Behavior of 1-phenyl-1,2-butadiene toward maleic anhydride and α-naphthoquinone.—The Diels-Alder reaction was attempted in order to show that the hydrocarbon prepared as above described was not 1-phenyl-1,3-butadiene or a mixture containing this. Four-tenths of a gram of I was warmed for 30 minutes on the steam bath with 0.15 gram of pure maleic anhydride. The anhydride quickly dissolved, but no crystallization occurred. The reaction product became viscous and gummy due to polymerization, and nothing crystalline could be isolated. The result of the reaction in no way resembled that observed when 1-phenyl-1,3-butadiene was subjected to the same treatment.

Five-tenths of a gram of 1-phenyl-1,2-butadiene and the same quantity of α-naphthoquinone when heated together changed to a reddish-brown mass of gummy consistency. It was dissolved in a little methanol and seeded with 1-phenylanthraquinone, but no crystallization could be induced. Again it did not show the characteristic behavior of 1-phenyl-1,3-butadiene.

1-Phenyl-2,2,3-trichloro-1-butanol (IV).—Since butyl chloral hydrate is available commercially and is easily dehydrated to 2,2,3-trichlorobutanal, 1-phenyl-1,2-butadiene was prepared by the following procedure:

The preparation of the carbinol from 2,2,3-trichlorobutanal and bromobenzene by the Grignard reaction has been described by Helferich and Besler[5]. Following essentially the recorded procedure, 85 grams of product was obtained from 82 grams of aldehyde, 118 grams of bromobenzene, and 18 grams of magnesium. It boiled at 140–145° (0.5 mm.); $n_D^{25.7}$ 1.5627. The compound, which solidified on cooling, was melted and dissolved in warm petroleum ether, from which nearly all of it crystallized. The crystalline product melted at 53°. Helferich and Besler record that the compound distils at 172–173° (13 mm.), and that it melts at 53°.

1-Phenyl-1,2,2,3-tetrachlorobutane (V).—By treatment with phosphorus pentachloride, 1-phenyl-2,2,3-trichloro-1-butanol (IV) is quantitatively converted into

[5] HELFERICH AND BESLER, *Ber.*, **57**, 1276 (1924).

1-phenyl-1,2,2,3-tetrachlorobutane. The proportions employed in a typical experiment were 20 grams of the carbinol and the same quantity of powdered phosphorus pentachloride. When the two components were mixed, the reaction set in at once with evolution of hydrochloric acid and liquefaction of the mass. The cooled reaction mixture was warmed a few minutes, ice was added, and the product was extracted with ether. After being washed with water, and finally with bicarbonate solution, the ethereal solution was dried, and the solvent was removed. The product distilled at 110–125° (0.5–1.0 mm.); n_D^{20} 1.5618. The yield was 18 grams. It solidified on standing and melted at 54–55° when recrystallized from ethanol. In another experiment 50 grams of IV yielded 48 grams of V boiling at 122–125° (0.5–1.0 mm.); n_D^{20} 1.5625. It will be noted that the refractive index is almost the same as that of 1-phenyl-2,2,3-trichloro-1-butanol (IV).

Anal. Calc'd for $C_{10}H_{10}Cl_4$: Cl, 52.20. Found: Cl, 51.67, 52.68, 52.38.

1-Phenyl-1,2-butadiene (*I*) (*second method*).—The reaction of 1-phenyl-1,2,2,3-tetrachlorobutane with zinc dust proceeds with unusual, even explosive, violence when the reactants are heated in ethanol. The reaction takes place moderately, however, under the following conditions.

Ten grams of V was dissolved in 25 cc. of warm ethanol, and the solution dropped into a stirred suspension of 20 grams of zinc dust in 25 cc. of boiling ethanol. (The zinc dust had been treated with a large volume of very dilute aqueous hydrochloric acid to remove zinc oxide, and then washed free of acid with water and finally with ethanol.) The reaction flask was provided with a reflux condenser and a dropping funnel. After the zinc-dust suspension had been heated to the boiling point of the solvent, the solution of V was introduced at a rate necessary to cause uniform ebullition without additional application of heat. The reaction was completed by boiling for about 15 minutes; the solution was then cooled and filtered from the excess zinc. Several volumes of water were added to the filtrate, which was then extracted with ether. A white precipitate, which probably consisted of zinc compounds, appeared in the aqueous solution, but vanished upon extraction with ether. The ethereal solution was repeatedly washed with water, and finally with sodium carbonate solution, dried with sodium sulfate, and the ether was removed by evaporation on the steam bath. The residue was distilled in an atmosphere of carbon dioxide, from a flask with a 15-cm. reflux column. The yield was 3.7 grams, boiling at 76–77°, (10 mm.); n_D^{24} 1.5716.

Anal. Calc'd for $C_{10}H_{10}$: C, 92.31; H, 7.69.
Found: C, 91.14; H, 7.88.

Oxidation of 1-phenyl-1,2-butadiene (*I*).—One and six-tenths grams of I was suspended in 150 cc. of water and oxidized by the gradual addition of powdered potassium permanganate while the suspension was agitated mechanically and cooled with an ice bath. The process required about 24 hours, and 7.6 grams of permanganate was added, leaving an excess in solution.

The manganese dioxide was removed by filtration, and the excess permanganate was removed by addition of a little oxalic acid to the boiling solution. After filtration the solution was neutralized and concentrated to about 10 cc. On acidification with dilute sulfuric acid the voluminous precipitate was removed by filtration and washed with water. The yield was 1 gram. It was melted at 121–122° and was identified as benzoic acid by the mixture melting point. The filtrate was distilled with steam. The distillate was neutralized with sodium hydroxide, and after complete evaporation and dehydration there remained a residue weighing 0.7 gram. It was essentially sodium acetate, for when 0.4 gram was treated with *p*-toluidine

and concentrated hydrochloric acid according to Mulliken's method[6] it yielded 0.2 gram of *N*-acetyl-*p*-toluidine, which after recrystallization from benzene melted at 146–147° and was identified as such by the mixture melting point with authentic material.

One and three-tenths grams of I was oxidized with 6.3 grams of potassium permanganate in 130 cc. of acetone previously treated with permanganate. The acetone solution combined with the aqueous extract of the manganese dioxide was evaporated and the residue dissolved in a few cubic centimeters of water and acidified. The benzoic acid was removed by filtration and identified by its melting point. The filtrate was steam-distilled, and the distillate was neutralized with potassium hydroxide, concentrated to a small volume, and treated with silver nitrate solution. The silver salt was recrystallized with some loss from water and was still not pure.

Anal. Calc'd for $C_2H_3O_2Ag$: Ag, 64.6.

Found: Ag, 60.0.

The silver salt was treated with hydrochloric acid, the silver chloride removed by filtration, and the filtrate neutralized and concentrated to dryness. The residue on treatment with *p*-toluidine yielded the acetyl derivative, which after recrystallization melted at 146–147° and was identified by the mixture point, 146–147°, with acetyl-*p*-toluidide. When mixed with propionyl-*p*-toluidide, the melting point was 115–118°.

SUMMARY

The preparation of 1-phenyl-1,2-butadiene by two procedures is described. This hydrocarbon is only moderately stable in contact with the air, and it is easily polymerized by acids. It does not react with maleic anhydride or with α-naphthoquinone. Its structure is proved by its oxidation to benzoic and acetic acids and by its reduction to *n*-butylbenzene.

[6] MULLIKEN, "Identification of Pure Organic Compounds," 1st ed., John Wiley and Sons, Inc., New York City, **1904**, Vol. 1, p. 80.

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

THE ACTION OF ALKYLMAGNESIUM HALIDES ON COUMARIN AND RELATED COMPOUNDS. SYNTHESIS OF 2,2-DIALKYL-1,2-BENZOPYRANS

R. L. SHRINER AND A. G. SHARP

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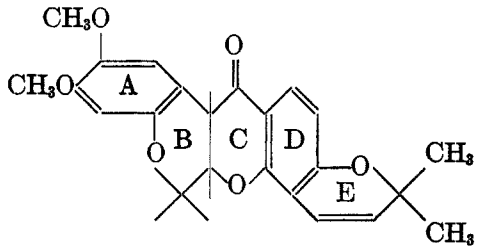
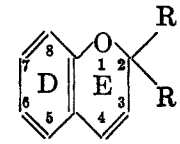
Insecticides such as deguelin (I),[1] tephrosin, and toxicarol are characterized by the presence of a dihydrobenzopyran ring system (AB) and a dimethylbenzopyran system (DE) as illustrated by formula I. The present study was undertaken to determine whether portions of this mole-



I



II

cule would possess insecticidal activity, and describes the preparation of a series of 2,2-dialkyl-1,2-benzopyrans (II).

The method used for the synthesis of these compounds is that of Houben,[2] who prepared the first two members of the series by treating coumarin with an excess of the alkylmagnesium halide. Using this same method the series of 2,2-dialkyl-1,2-benzopyrans (II), in which the alkyl group ranged from methyl to *n*-heptyl, was prepared. It was found that the yields increased as the size of the alkyl groups increased, ranging from 59 per cent. for the dimethyl derivative to 91 per cent. for the di-*n*-heptyl.*

No proof of the structure of these compounds was given by Houben. Since the Grignard reagent may react with the conjugated system in coumarin to yield products formed by either 1,2 or 1,4 addition,[3] it was, therefore, necessary to establish the structure of the products of this reaction. The physical properties of the compounds were found to be

[1] CLARK, *J. Am. Chem. Soc.*, **54**, 3000 (1932).

[2] HOUBEN, *Ber.*, **37**, 489 (1904).

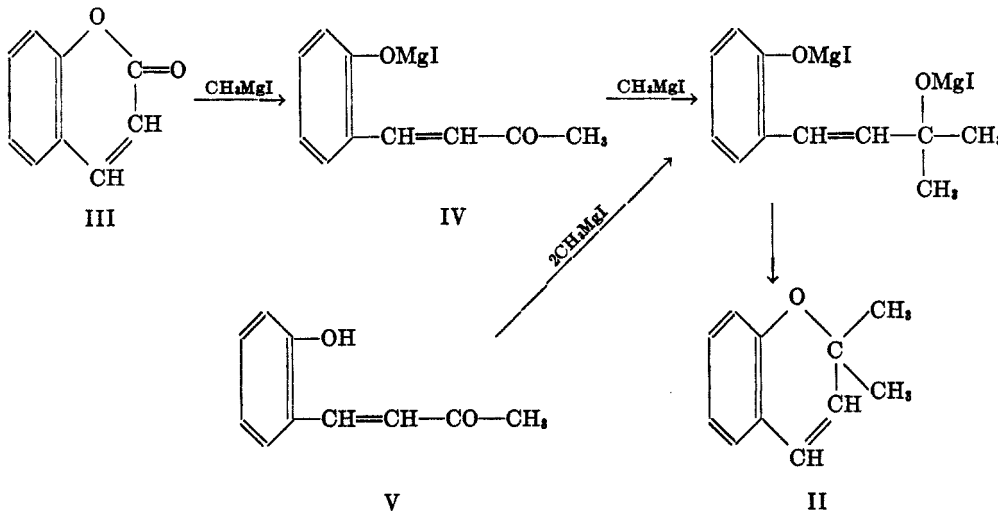
* The insecticidal activity of these compounds will be reported separately.

[3] HEILBRON AND HILL, *J. Chem. Soc.*, **1927**, 2005.

gradational throughout the series, and all the molecular refractivities indicated that the double bond of the pyran ring was conjugated with the benzene ring (see Table I). The formation of salicylaldehyde by ozonolysis also shows that the double bond was in the 3,4 position, and hence the two alkyl groups in the 2,2 position. Catalytic reduction produced 2,2-dimethylchroman, whose physical properties agreed with those observed by Claisen.[4]

The mechanism advanced for this reaction by Houben[2] postulated that the lactone ring of coumarin (III) was first broken by the Grignard reagent to give IV. Addition of the reagent to the carbonyl group was followed by ring closure. If this is the correct mechanism, addition of methylmagnesium iodide either to coumarin or to *o*-hydroxybenzalacetone should give the same product, as is shown by the reactions in Series A.

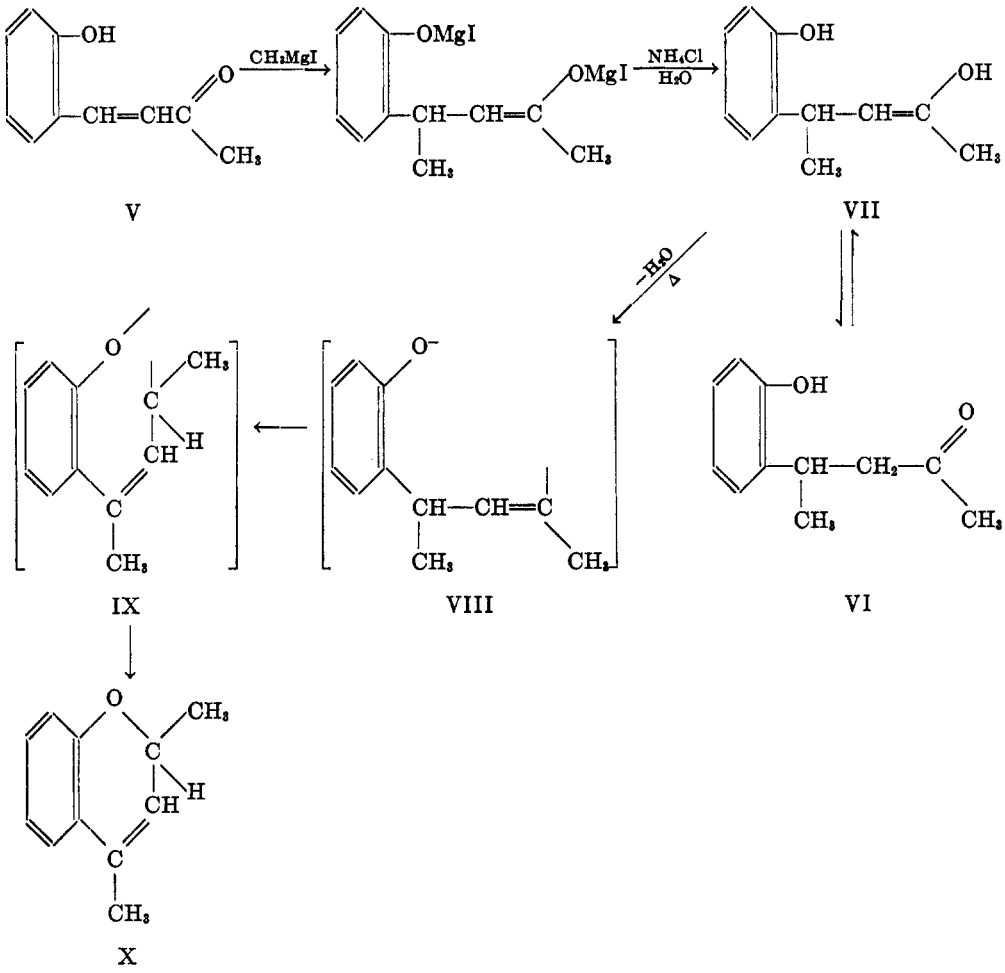
SERIES A



In order to test this concept, *o*-hydroxybenzalacetone (V) was treated with methylmagnesium iodide. Decomposition of the reaction mixture yielded 4-(*o*-hydroxyphenyl)-2-pentanone (VI) (reactions in Series B), which was characterized as the semicarbazone. When this ketone was heated to its melting point, loss of water occurred, and ring closure took place, forming 2,4-dimethyl-1,2-benzopyran (X). The structure of X was shown by the fact that ozonolysis produced *o*-hydroxyacetophenone.

[4] CLAISEN, *Ber.*, **54**, 200 (1921).

SERIES B



The pyran (X) may be formed by hydrolysis of the Grignard adduct to VII, dehydration to VIII, which shifts to its resonance isomer IX, and the latter forms the pyran (X) with the double bond conjugated with the ring. It is evident that coumarin and *o*-hydroxybenzalacetone react with the alkylmagnesium halides in different fashions, and that the mechanism for the reaction suggested by Houben (Series A) is not correct.

Since coumarin is the lactone of *cis*-*o*-hydroxycinnamic acid, it was of interest to study the behavior of *trans*-*o*-hydroxycinnamic with methylmagnesium iodide. It was found that this reaction produced *o*-hydroxybenzalacetone, which was identical with the compound obtained by the

condensation of salicylaldehyde with acetone. The *o*-hydroxybenzalacetone used in the above experiments was therefore the *trans* form. The *cis* form of this ketone has not been prepared. It is evident that stereochemical considerations play a part in determining the mode of action of the Grignard reagent on conjugated systems.

Löwenbein[5] suggested that the addition of the Grignard reagent to coumarin takes place with no rupture of the lactone ring. Heilbron and Hill[4] proposed the mechanism that addition to the carbonyl took place, followed by rupture of the lactone ring. A coumarin with no substituent in the 4 position would then undergo 1,4 addition. That this is not the case with *n*-alkylmagnesium halides is evident from the fact that addition of coumarin to an excess of these aliphatic Grignard reagents gave no 1,4 addition product.

Benzopyrrylium derivatives have been synthesized from coumarin by Decker and Fellenberg.[6] The Grignard reagent was added to the coumarin in molar amounts. This gave a yellowish precipitate, which was converted to the pyrrylium salt by hydrolysis with concentrated acid.

That an oxonium type[7] of intermediate is present in the synthesis of 2,2-dialkyl-1,2-benzopyrans was indicated by the formation of a very transitory yellowish precipitate when coumarin was added to an excess of the Grignard reagent. Also, addition of the Grignard reagent to coumarin in molar quantities gave a yellowish pasty precipitate. Hydrolysis of this product by dilute ammonium chloride solution *regenerated coumarin.* Hence, the initial reaction between coumarin and alkylmagnesium chloride probably involves the formation of a coördination compound involving the carbonyl group and the magnesium (XI in Series C). An α, γ shift[8,9] of the alkyl group in XI would lead to XII, which upon treatment with strong mineral acids would produce the pyrrylium salts (XIII) found by Decker and Fellenberg.[6] Further action of the second mole of the Grignard reagent would produce the 2,2-dialkyl-1,2-benzopyran by double decomposition. This mechanism, which does not involve the opening of the lactone ring and which is similar to that suggested by Johnson[9] for the normal reaction of the Grignard reagent with a ketone, satisfactorily explains the experimental observations.

Since deguelin and similar compounds cause paralysis of the respiratory system of fish, some preliminary tests were carried out on these 2,2-

[5] LÖWENBEIN, *ibid.*, **57**, 1517 (1924).

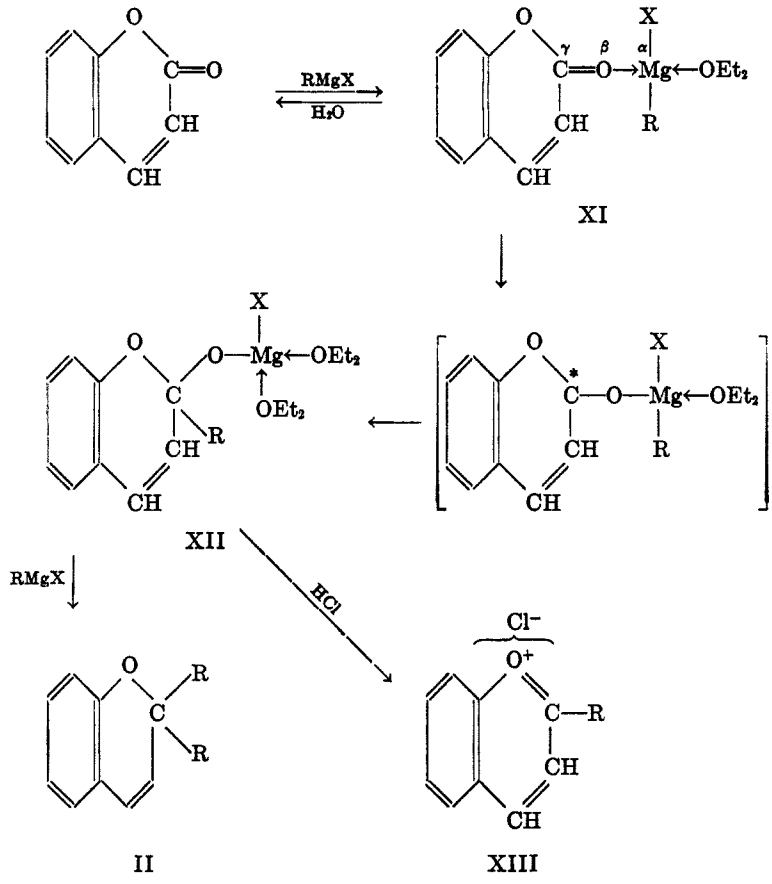
[6] DECKER AND VON FELLENBERG, *Ann.*, **356**, 281 (1907).

[7] GILMAN, "Organic Chemistry," John Wiley and Sons, New York, **1938**, Vol. I, p. 420.

[8] GILMAN, *ibid.*, Vol. II, p. 1649.

[9] JOHNSON, *J. Am. Chem. Soc.*, **55**, 3029 (1933).

SERIES C



dialkyl-1,2-benzopyrans. A saturated aqueous solution of the 2,2-dimethyl derivative caused paralysis of a goldfish in three minutes, whereas the 2,4-dimethyl derivative required fifteen minutes to produce the same effect. The 2,2-diethyl-1,2-benzopyran had only a very slight effect, and the higher members of the series none. It is of interest that the 2,2-dimethyl-1,2-benzopyran containing only two of the five rings in deguelin did cause paralysis of the respiratory tract.

EXPERIMENTAL

2,2-Dialkyl-1,2-benzopyrans. General procedure.—Into a three-necked 500-cc. flask equipped with a reflux condenser, mercury-sealed stirrer, and a dropping funnel, were placed 0.41 mole of magnesium turnings and 75–100 cc. of anhydrous ether. The alkyl halide (0.4 mole), dissolved in 75 cc. of dry ether, was then added dropwise

over a period of three to five hours and stirred for an additional three hours. In 200 cc. of dry ether was dissolved 0.125 mole of coumarin, and this solution added dropwise to the Grignard reagent over a period of two to four hours. The mixture was decomposed by approximately 200 cc. of 22% ammonium chloride solution to which 2–5 cc. of concentrated hydrochloric acid had been added. The ether layer was separated, and the aqueous solution was extracted once with 50 cc. of ether. The combined ether extracts were dried with calcium chloride, and the ether was

TABLE I

PROPERTIES OF 2,2-DIALKYL-1,2-BENZOPYRANS (II)

ALKYL GROUP	YIELD, %	B.P.	$d_{4^\circ}^{20^\circ}$	$n_D^{20^\circ}$	M_D*	
					Calc'd	Found
Methyl[2]	59.0	79–80°/2.5 mm.	1.0163	1.5490	49.8	50.1
Ethyl[2]	64.0	99–100/2.8 mm.	1.0049	1.5428	59.0	59.0
n-Propyl	68.0	118–120/2.8 mm.	0.9773	1.5320	68.3	68.6
n-Butyl	70.0	138–140/2.8 mm.	.9656	1.5257	77.5	77.5
n-Amyl	77.3	156–158/3 mm.	.9487	1.5184	86.8	87.2
n-Hexyl	83.0	174–176/3 mm.	.9351	1.5136	96.0	96.5
n-Heptyl	91.5	192–193/3 mm.	.9233	1.5095	105.2	105.2

* Note: The values used to calculate M_D were C = 2.42; H = 1.10; O (from chromone) = 1.83; carbon double bond = 1.75; conjugation (from *cis*-isoeugenol) = 1.15.

TABLE II

ANALYSES OF 2,2-DIALKYL-1,2-BENZOPYRANS

ALKYL GROUP	MOL. FORMULA	ANALYSIS, %			
		Calc'd		Found	
		C	H	C	H
n-Propyl	$C_{15}H_{20}O$	83.34	9.25	83.23	9.36
n-Butyl	$C_{17}H_{24}O$	83.61	9.83	83.79	9.60
n-Amyl	$C_{19}H_{28}O$	83.83	10.28	83.87	10.21
n-Hexyl	$C_{21}H_{32}O$	84.01	10.66	83.76	10.50
n-Heptyl	$C_{23}H_{36}O$	84.15	10.96	83.80	10.98

distilled. The residual liquid was distilled in a vacuum. The physical properties and analyses of the compounds are summarized in Tables I and II.

Chemical properties.—A clear solution of 2,2-dimethyl-1,2-benzopyran turned to a reddish color on standing, reduced potassium permanganate, and decolorized bromine. Boiling for ten hours in alcoholic alkali, according to the method used by Heyes and Robertson[10] to degrade deguelin to acetone, did not affect the compound. Cold concentrated sulfuric acid with these benzopyrans gave a deep-red color, which decreased in intensity with the higher members of the series. The cold

[10] HEYES AND ROBERTSON, *J. Chem. Soc.*, **1935**, 681.

sulfuric acid gave a polymeric product, which, in the case of the dimethylbenzopyran, possessed a molecular weight of 650–800.

The addition of ferric chloride to an ether or glacial acetic acid solution of the dimethylbenzopyran that had been saturated with dry hydrogen chloride, gave apparently a polymeric product.

Boiling acetic acid, according to the method of Löwenbein[5], caused no isomerization of 2,2-dimethyl-1,2-benzopyran.

2,2-Dimethylchroman.—Twelve grams (0.075 mole) of 2,2-dimethyl-1,2-benzopyran was dissolved in 100 cc. of alcohol and reduced by hydrogen with 0.1 gram of platinum oxide catalyst.[11] After nine hours, the calculated amount of hydrogen was absorbed. The alcoholic solution was filtered, and the platinum oxide was washed with more alcohol. The alcohol was evaporated on the steam bath and the residue was distilled. The yield was 11 grams (92%) of the chroman; b.p., 67.5–68° (2 mm.), n_D^{20}, 1.5264; d_4^{20}, 1.0237. The molecular refractivity: calc'd, 49.10; found, 48.64.

The compound has a spicy odor. This compound had been obtained from isoprene and phenol and also synthesized from ethyl *o*-hydroxycinnamate by Claisen.[4]

Ozonization of 2,2-Dimethyl-1,2-benzopyran.—Five grams of 2,2-dimethyl-1,2-benzopyran in 30 cc. of carbon tetrachloride was ozonized and the product was decomposed with 50 cc. of water, 1 g. of zinc dust, and 1 cc. of acetic acid, in the presence of 0.2 g. of hydroquinone. Treatment of the carbon tetrachloride layer with 2,4-dinitrophenylhydrazine yielded the 2,4-dinitrophenylhydrazone of salicylaldehyde. This melted at 250.5–251° after recrystallization from ethanol. This agrees with the value reported by Campbell.[12] The aqueous layer, after filtration, was treated with semicarbazide hydrochloride and sodium acetate. The crude semicarbazone which separated (m.p. 228–230°) was fractionally crystallized from 50% ethanol. The only pure compound isolated was the semicarbazone of salicylaldehyde, m.p. 231–233°. No indication of the presence of the semicarbazone of α-methylacrolein, one of the possible products of ozonolysis, was obtained. In another ozonolysis the carbon tetrachloride solution was distilled, and the distillate was tested for α-methylacrolein, which has the boiling point 73.5°, very close to that of carbon tetrachloride. However, none could be found. The oil left after distillation was allowed to stand in the air for two days, and was oxidized to salicylic acid, m.p. 158°. No ozonolysis products other than salicylaldehyde could be isolated. Fischer[13] has reported that ozone splits ethers into a complex mixture of products.

4-(o-Hydroxyphenyl)pentan-2-one.—Seven and one-half grams (0.046 mole) of *o*-hydroxybenzalacetone, prepared according to the procedure of Harries,[14] was dissolved in 400 cc. of dry ether and added during one hour to exactly 0.1 mole of methylmagnesium iodide. A yellow precipitate was formed, which did not dissolve on further stirring for twelve hours. The mixture was decomposed by 150 cc. of 20% ammonium chloride solution, and the ether layer was separated. The aqueous layer was extracted once with ether, and the combined ether extracts were dried with calcium chloride. The ether was carefully evaporated by an air stream, giving 1.5 g. of a solid which was recrystallized from petroleum ether (b.p. 80–120°). This compound melted at 127–129° with dehydration.

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[11] GILMAN, *Organic Syntheses*, John Wiley and Sons, New York, Col. Vol. I, p. 452.

[12] CAMPBELL, *Analyst*, **61**, 391 (1936).

[13] FISCHER, *Ann.*, **476**, 233 (1929).

[14] HARRIES, *Ber.*, **24**, 3180 (1891).

Anal. Calc'd for $C_{11}H_{14}O_2$: C, 74.17; H, 7.86.
Found: C, 74.20; H, 8.01.

Semicarbazone of 4-(o-hydroxyphenyl)pentan-2-one.—An alcohol solution of the above compound was added to an aqueous solution of sodium acetate and semicarbazide hydrochloride. After the solution had stood for two days at room temperature, the semicarbazone was extracted by ether and crystallized from alcohol; m.p., 155–155.5°.

Anal. Calc'd for $C_{12}H_{17}N_3O_2$: N, 17.86. Found: N, 17.91.

2,4-Dimethyl-1,2-benzopyran.—When 4-(*o*-hydroxyphenyl)pentan-2-one was heated at its melting point for ten minutes, there was obtained a liquid which distilled at 79–80° (3 mm.). Its density was 1.0196_4^{20} and refractive index, n_D^{20}, 1.5428. The molecular refractivity: calc'd, 49.81; found, 49.44.

Anal. Calc'd for $C_{11}H_{12}O$: C, 82.51; H, 7.48.
Found: C, 82.29; H, 7.67.

The hydroxy ketone and benzopyran gave an orange color in concentrated sulfuric acid. The odor of the above benzopyran differed slightly from that of the 2,2-dimethyl-1,2-benzopyran.

Ozonization of 2,4-dimethyl-1,2-benzopyran.—Ozonization of 2 cc. of 2,4-dimethyl-1,2-benzopyran in carbon tetrachloride, followed by decomposition of the ozonide by water and zinc dust, separation of the carbon tetrachloride layer, and evaporation of the carbon tetrachloride, gave an oil having a boiling-point range of 215–220° and giving a bluish-purple color with ferric chloride. Its semicarbazone was prepared, and after crystallization from ligroïn, was found to melt at 205–207°, which agreed with the value reported by Pauly and Lockemann[15] for the semicarbazone of *o*-hydroxyacetophenone.

Action of methylmagnesium iodide on trans-*o-hydroxycinnamic acid.*—Ten grams (0.06 mole) of *trans-o*-hydroxycinnamic acid prepared according to the method of Dodge[16] was dissolved in a liter of dry ether and added dropwise over a period of two hours to 0.36 mole of methylmagnesium iodide in 250 cc. of ether. The mixture was stirred for three hours, and decomposed by 350 cc. of 20% ammonium chloride solution. The aqueous layer was separated and extracted once with 50 cc. of ether. The combined ether solution was concentrated to 50 cc., and the remainder of the ether was removed by an air stream. The solid which formed was filtered, washed, and recrystallized from petroleum ether. There was obtained 1.5 g. (15%) of *o*-hydroxybenzalacetone melting at 136–138°. A mixed melting point with *o*-hydroxybenzalacetone prepared from salicylaldehyde and acetone showed no depression.

SUMMARY

A series of 2,2-dialkyl-1,2-benzopyrans has been prepared by the action of alkylmagnesium halides on coumarin. The structure of these compounds has been demonstrated by means of their physical constants, ozonolysis to salicylaldehyde, and hydrogenation to 2,2-dimethylchroman.

The mechanism by which these 2,2-dialkyl-1,2-benzopyrans are produced probably involves the formation of an intermediate coördination compound, in which the alkyl group undergoes an α, γ shift. Subsequent reaction with a second mole of the Grignard reagent produces the dialkylbenzopyran. The evidence supporting this mechanism is given.

[15] PAULY AND LOCKEMANN, *ibid.*, **48**, 28 (1915).
[16] DODGE, *J. Am. Chem. Soc.*, **38**, 446 (1916).

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE SYNTHESIS OF 9,10-DIALKYLANTHRACENES

W. E. BACHMANN AND J. M. CHEMERDA

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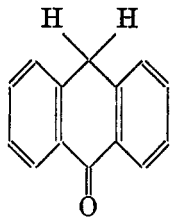
9,10-Dimethylanthracene has been prepared by the reaction of 9-methylanthrone (II) with methylmagnesium iodide[1]. The 9-methylanthrone was obtained by hydrolysis of the methyl ether of 9-methylanthranol which was formed when anthrone (I) was methylated with methyl iodide in strong potassium hydroxide solution[2]. We found it is



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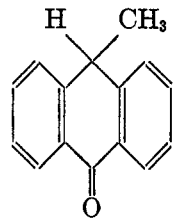
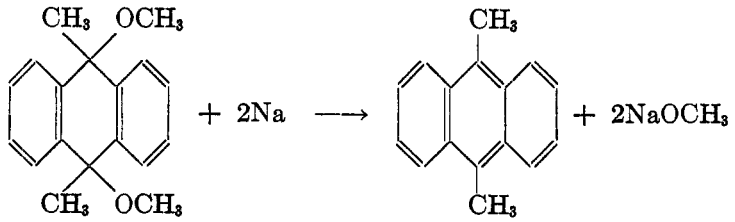


II

difficult to obtain 9-methylanthrone by this method, and employed the action of methyl iodide on the sodium compound formed by reaction of anthrone with sodium ethylate. By treating the product with methylmagnesium iodide, low (15–20 per cent.) but reproducible yields of 9,10-dimethylanthracene were obtained. The method was also applicable to the preparation of 9,10-dibenzylanthracene.

A much more satisfactory procedure for preparing 9,10-dimethylanthracene and other 9,10-dialkylanthracenes consisted in the extension of the method which was described recently for preparing 9,10-dimethyl-1,2-benzanthracene and related hydrocarbons[3]. In this method 9,10-dimethyl-9,10-dimethoxy-9,10-dihydroanthracene was allowed to react with exactly two equivalents of sodium in a mixture of ether and benzene.



[1] BARNETT AND MATTHEWS, *Ber.*, **59**, 767, 1437 (1926).
[2] MEYER AND SCHLÖSSER, *Ann.*, **420**, 126 (1920).
[3] BACHMANN AND CHEMERDA, *J. Am. Chem. Soc.*, **60**, 1023 (1938).

By this reaction a nearly quantitative yield of 9,10-dimethylanthracene was obtained. Similarly 9,10-diethylanthracene was prepared in nearly quantitative yield.

If more than two equivalents of sodium are employed in the reaction, the hydrocarbon which is formed reacts with the sodium to give a deeply-colored 9,10-disodio addition product. With exactly two equivalents of the metal, only the diol dimethyl ether enters into the reaction. In only one instance was there evidence of reaction of the hydrocarbon with sodium before all of the diol dimethyl ether had been converted to the hydrocarbon. In the preparation of 2,9,10-trimethylanthracene some of the disodio addition product was formed and only an 85 per cent. yield of the hydrocarbon was obtained. It is of interest that Schlenk and Bergmann[4] were of the opinion that 9,10-diphenylanthracene was an intermediate in the conversion of 9,10-diphenyl-9,10-dimethoxy-9,10-dihydroanthracene to 9,10-diphenyl-9,10-disodio-9,10-dihydroanthracene by reaction of the diol dimethyl ether with excess of sodium.

EXPERIMENTAL

Preparation of 9,10-dimethylanthracene from anthrone.—To 20 g. of anthrone, partially dissolved in 120 cc. of absolute alcohol, was added 2.4 g. of sodium. Ten cubic centimeters of methyl iodide was added to the dark-brown solution, and the mixture was refluxed overnight. Water and acetic acid were added to the solution, and the oil which precipitated was extracted with benzene. Evaporation of the benzene gave an oil with some unreacted anthrone which was separated by filtration. Attempts to crystallize the oil failed.

A dried solution of the crude methylanthrone in toluene was added to an ice-cold solution of methylmagnesium iodide prepared from 18.5 cc. of methyl iodide and 75 cc. of ether. After standing at room temperature overnight, the solution was hydrolyzed, and the solvent was evaporated. A solution of the residue in benzene, when seeded with 9,10-dimethylanthracene, deposited 4.3 g. of the hydrocarbon; m.p. 171–179°. After treatment of a benzene solution of the product with sodium hydrosulfite-sodium hydroxide solution 3.4 g. of 9,10-dimethylanthracene was obtained as yellow needles; m.p. 180.5–181°.

Preparation of 9,10-dibenzylanthracene from anthrone.—To 10 g. of anthrone in 50 cc. of absolute alcohol was added 1.2 g. of sodium. When 6.2 cc. of benzyl chloride was added, a vigorous reaction took place, accompanied by the precipitation of sodium chloride. The solution was refluxed for five hours, and then 200 cc. of water was added. Extraction of the precipitated oil with benzene gave 14.5 g. of a dark-colored oil.

Seven grams of the above oil was added to an ice-cold solution of benzylmagnesium chloride prepared from 12 cc. of benzyl chloride and 50 cc. of ether. A brown addition product was formed, but disappeared in two hours at room temperature to give a light-green fluorescent solution. After the mixture had been worked up in the usual fashion and steam-distilled to remove dibenzyl, the crude product recrystallized from acetic acid gave 2.6 g. (17%) of 9,10-dibenzylanthracene; m.p. 243–245°.

[4] SCHLENK AND BERGMANN, *Ann.*, **463**, 134 (1928).

Barnett and Cook[5] prepared 9,10-dibenzylanthracene from 9,9,10-tribenzyl-9,10-dihydroanthranol; they reported 245° for the melting point.

9,10-Dimethyl-9,10-dihydroxy-9,10-dihydroanthracene.—The general procedure for the reactions of anthraquinone with Grignard reagents is described in the case of the methyl diol. Attempts to carry out the reaction by adding solid anthraquinone to the Grignard reagent provided only small amounts of the diol with much unchanged quinone. Apparently the insoluble addition product which is formed in the reaction coats the undissolved quinone. By working with solutions of anthraquinone this difficulty can be avoided, but large volumes of solvent are required to dissolve the anthraquinone. We found it more convenient to extract the quinone into the Grignard reagent using a Soxhlet extractor or some suitable modification.

The Grignard reagent was prepared from 10 cc. of methyl iodide in 100 cc. of ether. A Soxhlet thimble was slit vertically, and a piece of cellophane was pasted in to allow observation of the progress of the extraction. In the thimble was placed 10.4 g. of anthraquinone, the extractor was attached to the flask, and the mixture was refluxed over a water bath. The almost colorless dilute solution of anthraquinone reacted immediately with the Grignard reagent with precipitation of a yellow complex. After two and one-half days, 0.5 g. of the quinone remained in the thimble. The ether suspension was hydrolyzed, the ether was evaporated, and the insoluble diol was removed by filtration. When dry it was dissolved in hot methanol, and an additional 0.5 g. of anthraquinone was separated by filtration. The hot methanol solution was treated with sodium hydroxide-sodium hydrosulfite solution and much water. The diol (8.5 g.) was filtered off and washed with much water. Recrystallization from methanol gave colorless needles of the diol containing solvent of crystallization which was easily driven off when heated; m.p. 185–195°. Guyot and Staehling[6] reported 181°.

A more rapid extraction resulted when a thimble containing the quinone was suspended from copper wires into the reaction flask directly below the reflux condenser. Using ether as a solvent, thirty hours was required to extract 19.6 of anthraquinone from a charge of 20.8 g. When ether-benzene (2:3) was used as a solvent and the mixture refluxed upon a steam bath, only six hours was required to extract 20.1 g. from 20.8 g. The last portion of quinone was always extracted more slowly. The yield of diol did not vary markedly with the method of extraction.

9,10-Dimethyl-9,10-dimethoxy-9,10-dihydroanthracene.—Five grams of the diol was dissolved in a solution of 25 cc. of benzene and 25 cc. of methanol containing 5 drops of sulfuric acid. A clear solution was obtained immediately. After standing at room temperature for half an hour, much water was added, and the benzene solution was treated with dilute ammonium hydroxide to remove traces of sulfuric acid which are harmful. Concentration of the benzene solution followed by addition of methanol gave 5.36 g. (96%) of the diol dimethyl ether. Guyot and Staehling[6], who used hydrogen chloride in place of sulfuric acid, reported a melting point of 197°.

9,10-Dimethylanthracene from the diol dimethyl ether.—A mixture of 5.36 g. of the diol dimethyl ether and 0.82 g. of powdered sodium was shaken in 30 cc. of ether and 30 cc. of benzene with about a half-dozen sharp glass particles for four days. The resulting mush was filtered; the residue was washed with water, and dried, giving 2.54 g. of 9,10-dimethylanthracene; m.p. 180–181°. Treatment of the ether-benzene filtrate with hydrochloric acid, and recrystallization of the residue after evaporation

[5] BARNETT AND COOK, *J. Chem. Soc.*, **1928**, 566.

[6] GUYOT AND STAEHLING, *Bull. soc. chim.*, [3], **33**, 1144 (1905).

from alcohol-acetone gave an additional 1.25 g. (m.p. 179–181°) of hydrocarbon making a total yield of 92%.

9,10 - Diethyl - 9,10 - dihydroxy - 9,10 - dihydroanthracene.—9,10 - Diethyl - 9,10 - dihydroxy-9,10-dihydroanthracene was prepared from 10.4 g. of anthraquinone, using the modified extractor, and ether as a solvent. Considerable gas was evolved during the reaction, and ether must be added from time to time to replace that lost by evaporation. When purified in the manner described, 4.7 g. of a light-brown product was obtained; m.p. 147–153° with darkening. In another experiment starting with 20.8 g. of quinone, the ether was removed in a current of air at room temperature, and the crude diol dissolved in benzene was extracted with hot sodium hydroxide-sodium hydrosulfite solution. The dried benzene solution, when concentrated carefully, deposited 6.45 g. of colorless 9,10-diethyl-9,10-dihydroxy-9,10-dihydroanthracene; m.p. 169–171° with previous sintering (Clarke and Carleton[7], m.p. 175°).

9,10-Diethyl-9,10-dimethoxy-9,10-dihydroanthracene.—A solution of 3.65 g. of the diol in 17 cc. of methanol was treated with 0.17 cc. of sulfuric acid in 7 cc. of methanol. The precipitated diol dimethyl ether was collected, dissolved in benzene and purified as described above; yield 3.29 g., m.p. 176–178° with previous softening. After one recrystallization from benzene-methanol and one recrystallization from ethyl acetate, it melted constantly at 179–180.5°; yield 1.6 g. Clarke and Carleton[7] reported a melting point of 178°.

9,10-Diethylanthracene.—To 0.255 g. of powdered sodium in 25 cc. of ether and 25 cc. of benzene was added 1.64 g. of the diol dimethyl ether (m.p. 179–180.5°). After two days' shaking, the reaction mixture (slightly green in color) was worked up in the manner described, and a total yield of 1.23 g. (95%) of 9,10-diethylanthracene was isolated; m.p. 144–147°. Sublimation of a portion of the product followed by recrystallizations from alcohol-acetone and acetic acid gave colorless diamond-like prisms; m.p. 146–147°. Hugel and Lerer[8] who prepared 9,10-diethylanthracene by dehydrogenation of the dihydro derivative obtained by the treatment of 9,10-disodio-9,10-dihydroanthracene, with ethyl bromide reported a melting point of 145.5°.

9,10-Diethylanthracene dissolved in a hot absolute alcoholic solution of picric acid deposited black needles of a picrate when cooled; m.p. 128–129°. It is somewhat unstable, and cannot be recrystallized without decomposition.

2,9,10-Trimethyl-9,10-dihydroxy-9,10-dihydroanthracene.—This diol could be prepared either by the addition of solid *beta*-methylanthraquinone to an ice-cold solution of the Grignard reagent in ether-benzene and allowing the mixture to stand at room temperature overnight, or by extraction with ether, using the modified extractor (11g. required three hours). Although a yellow addition product was formed, the quinone dissolved before the addition product crystallized. After hydrolysis with ice-cold ammonium chloride solution, it is best to dissolve the diol in benzene, extract any unchanged quinone as described above for the ethyl diol, and allow the benzene solution to evaporate spontaneously.

Much crystalline material was obtained together with a red oil; the oily portion concentrates in the upper portion of the evaporating dish and these portions are separated mechanically, triturated separately with ligroin containing a small amount of acetone and filtered; yield (from 11 g. of quinone by either method) 8–9 g.; m.p.

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[7] CLARKE AND CARLETON, *J. Am. Chem. Soc.*, **33**, 1966 (1911).

[8] HUGEL AND LERER, *Bull. soc. chim.*, **53**, 1497 (1933).

112–130°. This diol retains solvent of crystallization quite tenaciously and was analyzed as the dimethyl ether.

2,9,10-Trimethyl-9,10-dimethoxy-9,10-dihydroanthracene.—Five grams of the diol was dissolved in 20 cc. of methanol and treated with 5 cc. of methanol containing 0.25 cc. of sulfuric acid. The diol dimethyl ether crystallized, and after purification in a manner already described, 4.35 g. of 2,9,10-trimethyl-9,10-dimethoxy-9,10-dihydroanthracene was obtained; m.p. 181–182.5°. Recrystallization from methanol containing a little benzene gave colorless tablets of the diol dimethyl ether; m.p. 181.5–182.5°.

Anal. Calc'd for $C_{19}H_{22}O_2$: C, 80.8; H, 7.9.
Found: C, 80.5; H, 7.8.

2,9,10-Trimethylanthracene.—One and one-half grams of pure diol dimethyl ether and 0.245 g. of powdered sodium in 25 cc. of ether and 25 cc. of benzene were shaken for two days. After a day a light pea-green solution which contained much sodium was obtained. After two days the solution was dark-green. Decolorized with methanol and worked up in the usual fashion, the reaction mixture gave 1.0 g. (85%) of 2,9,10-trimethylanthracene as yellow needles from alcohol-acetone. Evidently this hydrocarbon can exist in two polymorphic modifications. A portion of the hydrocarbon, when sublimed and allowed to crystallize slowly from alcohol, had a melting point of 100–101°. When crystallized rapidly it melted at 95–96°. Often a mixture is obtained which melts at an intermediate temperature. When remelted several times, the higher-melting form changes over gradually to the lower-melting form. A sample for analysis purified through the picrate melted at 96–101°. After two weeks it melted at 99–101°.

Anal. Calc'd for $C_{17}H_{16}$: C, 92.7; H, 7.3.
Found: C, 92.2; H, 7.5.

A solution of the hydrocarbon and picric acid in hot absolute alcohol containing a little benzene deposited jet black needles of a monopicrate when cooled. After recrystallization from benzene the *picrate* melted at 162–162.5°.

Anal. Calc'd for $C_{17}H_{16}\cdot C_6H_3N_3O_7$: N, 9.4. Found: N, 9.3.

SUMMARY

A method has been devised for preparing 9,10-dimethylanthracene, 9,10-diethylanthracene and 2,9,10-trimethylanthracene in excellent yields.

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

HYDROLYSIS OF SUBSTITUTED BENZENESULFONANILIDES. IV. SOLUBILITY OF SULFONANILIDES IN WATER AND HYDROCHLORIC ACID

R. L. SHRINER, J. D. OPPENLANDER, AND R. S. SCHREIBER

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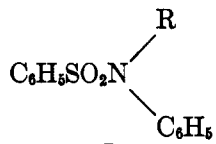
A previous study[1] of the acid hydrolysis of sulfonanilides has shown that an *N*-alkylbenzenesulfonanilide (I) hydrolyzed in about one-third the time required for the hydrolysis of an unsubstituted benzenesulfonanilide (II).



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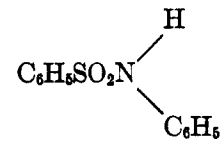


II

In searching for an explanation of these results, it was thought that solubility might play an important part. Hence, the present investigation had for its purpose the preparation, and determination of the solubility in water and in constant-boiling hydrochloric acid, of benzene- and *p*-toluenesulfonanilides and their *N*-alkyl derivatives.

EXPERIMENTAL

Preparation of compounds.—The sulfonanilides were all prepared by treating one equivalent of the freshly-distilled amine with one equivalent of benzene- or *p*-toluenesulfonyl chloride in the presence of an excess of dilute sodium hydroxide solution. They were purified by four recrystallizations from 95% alcohol and preserved in a vacuum desiccator over phosphorus pentoxide. The low-melting amides were distilled *in vacuo*. In order to check on the purity of some of the *N*-alkyl sulfonanilides, samples were prepared by alkylation[2] of benzenesulfonanilide and *p*-toluenesulfonanilide. All of these compounds except one have been previously described.

Benzenesulfonanilide,[3] m.p. 111°; *N*-methylbenzene sulfonanilide,[3] m.p. 79°; *N*-ethylbenzenesulfonanilide, b.p. 187–189° (3 mm.). This compound has been reported as an oil by three different workers.[4,5,6] A sample of it was prepared by

[1] SCHREIBER AND SHRINER, *J. Am. Chem. Soc.*, **56**, 1618 (1934).
[2] YOUNG, *ibid.*, **56**, 2167 (1934); GILLESPIE, *ibid.* **56**, 2740 (1934).
[3] OTTO, *J. prakt. Chem.*, [2], **47**, 367 (1893).
[4] VOSS AND BLANKE, *Ann.*, **485**, 258 (1931).
[5] GINZBERG, *Ber.*, **36**, 2706 (1903).
[6] HICKINBOTTOM, *J. Chem. Soc.*, **1933**, 1072.

alkylation of benzenesulfonanilide with ethyl bromide. It was also an oil. After standing several months this oil finally crystallized. It melted at 37–38°; *N*-(*n*-propyl)benzenesulfonanilide,[3] m.p. 54.2°; *N*-(*n*-butyl)benzenesulfonanilide, b.p. 182–184° (1 mm.) m.p. 33°. This has not been described previously.

Anal. Calc'd. for $C_{16}H_{19}NO_2S$: S, 11.09. Found: S, 11.13.

p-Toluenesulfonanilide,[3] m.p. 102°; *N*-methyl-*p*-toluenesulfonanilide,[3] m.p. 94.2°; *N*-ethyl-*p*-toluenesulfonanilide, m.p. 86.9°; *N*-(*n*-propyl)-*p*-toluenesulfonanilide,[3] m.p. 56°; *N*-(*n*-butyl)-*p*-toluenesulfonanilide,[6] m.p. 53.6°.

Solubility determinations.—These were carried out at 100°. A light lubricating oil was used in the bath, whose temperature was kept constant within ±0.1°. The solubilities were determined in a 500-cc., three-necked flask fitted with a reflux condenser, mercury-sealed stirrer, and thermometer. It was found that a bath temperature of 102° gave a temperature inside the flask of 100 ± 0.1°.

TABLE

SOLUBILITY OF *N*-ALKYL BENZENE- AND *p*-TOLUENESULFONANILIDES AT 100°

COMPOUND (LIQUID STATE)	SOLUBILITY, G./100 G. SOLUTION		RATIO $\frac{S_{HCl}}{S_{H_2O}}$
	Water	Constant-Boiling Hydrochloric Acid	
$C_6H_5SO_2NHC_6H_5$	0.2204	0.2841	1.3
$C_6H_5SO_2N(CH_3)C_6H_5$	.0506	.1243	2.5
$C_6H_5SO_2N(C_2H_5)C_6H_5$	.0115	.0963	8.3
$C_6H_5SO_2N(C_3H_7(n))C_6H_5$	.0062	.0681	10.9
$C_6H_5SO_2N(C_4H_9(n))C_6H_5$	.0032	.0254	7.9
.....	.....	.....	.....
$C_7H_7SO_2NHC_6H_5$	.1361	.1439	1.1
$C_7H_7SO_2N(CH_3)C_6H_5$	.0234	.0875	4.1
$C_7H_7SO_2N(C_2H_5)C_6H_5$	.0094	.0823	8.6
$C_7H_7SO_2N(C_3H_7(n))C_6H_5$	.0056	.0429	7.3
$C_7H_7SO_2N(C_4H_9(n))C_6H_5$	.0027	.0152	5.8

Two and one-half grams of the anilide and 250 cc. of solvent were placed in the flask and stirred for one hour. In the case of the anilides of melting point above 100°, the temperature of the outside bath was raised to 110° at the start. This insured the presence of the anilide as a liquid. All of the data were collected with reference to the solubility of the compounds in the *liquid state*. The temperature of the bath was then lowered so that the inside temperature was 100°. At the end of one hour the stirrer in the flask was stopped and a filter-tube was inserted in place of the thermometer. The end of the filter-tube was filled with glass wool and was placed about three centimeters from the bottom of the flask. A condenser was placed around the tube at the point where it left the flask and continued to within three centimeters of the end placed in the receiving flask. Steam was passed through this condenser. The mixture was allowed to settle for fifteen minutes, and then air pressure was applied through the reflux condenser. The solution was forced out the filter-tube into a weighed receiving flask. The first few cubic centimeters of the solution which passed through was discarded. This insured a hot filter-tube, and the steam jacket kept the filtered solution at a temperature of 100° until it

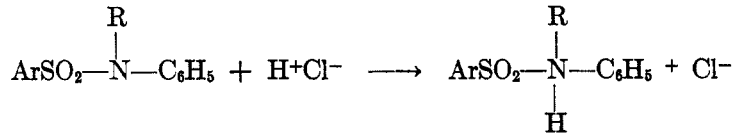
reached the receiving flask. Care was taken to watch the solution in the filter tube. If any signs of cloudiness appeared, the run was discarded. About 50 cc. of the solution was filtered into the weighed receiving flask. After it had cooled it was carefully weighed, and then evaporated almost to dryness on an electric hot plate, and dried completely in an oven at 110° for one hour. The dried residue was accurately weighed, and the solubility of the anilide was calculated on the basis of 100 g. of solution.

The data are shown in the accompanying table. The values given represent the average of at least two and sometimes four determinations. The solubilities represent the solubility of these compounds in the *liquid* state at 100°. Although the hydrolyses previously reported were carried out by refluxing the compounds with constant-boiling hydrochloric acid, it was experimentally impossible to get solubility determinations in the boiling solution. Hence, the temperature of 100° was chosen as a convenient one, since it also permitted determinations of the solubility in water for comparison.

DISCUSSION

The tabulated data show that the solubility of the sulfonanilides decreased when the hydrogen atom on the nitrogen was replaced by an alkyl group and that as the size of the latter increased the solubility decreased. The solubilities, therefore, follow the general rule that increased molecular weight causes a decrease in solubility. It is to be emphasized that the compounds were in the liquid state, and that the solubility determinations were carried out at 100°. These experimental conditions minimize any factors of association due to hydrogen-bond formation, which exerts a profound influence on the solubilities of solids.

The most interesting result of this study is the fact that each of these sulfonanilides exhibited a greater solubility in hydrochloric acid than in water. As the size of the alkyl group increased, the ratio of S_{HCl} to S_{H_2O} increased to a maximum and then decreased. Although arylsulfonanilides are usually classed as weakly acidic substances, and the *N*-alkylarylsulfonanilides as neutral compounds, the fact that the above ratio is always greater than 1.0 suggests that even in these sulfonamides the nitrogen atom retains to a slight extent its proton-accepting power, and that a slight amount of salt formation takes place.



Such an assumption would explain the increase in solubility in hydrochloric acid. The increase and then decrease in the ratio of S_{HCl} to S_{H_2O} probably represents a combination of the effects of the alkyl group on the nitrogen atom plus the general effect of molecular weight on the solubilities in the two solvents.

The larger values for the ratio of S_{HCl} to S_{H_2O} for the *N*-alkyl arylsulfonanilides may thus be one of the factors which cause them to be hydrolyzed more rapidly.[1]

SUMMARY

A study of the solubilities of benzenesulfonanilide, *p*-toluenesulfonanilide and their *N*-alkyl derivatives in water and constant-boiling hydrochloric acid has shown that: (*1*) the solubility of each series in either solvent decreases as the size of the alkyl group increases, and (*2*) the ratio of the solubility in hydrochloric acid to that in water is not only greater than 1.0 but rises to a maximum value and then decreases. The increase in solubility of the *N*-alkyl arylsulfonanilides in hydrochloric acid may be one of the reasons why they are hydrolyzed by acids more rapidly than unsubstituted arylsulfonanilides.