Notes

A department for short papers of immediate interest.

Method for the Cleavage of Osmate Esters

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Osmate esters obtained in the oxidation of alkenes with osmium tetroxide have been cleaved with reagents such as strong aqueous base and mannitol,[1] refluxing aqueous alcoholic sodium sulfite[2] or bisulfite,[3] and hydrogen sulfide.[4] This communication describes a method for the smooth transformation of osmate esters to *cis*-glycols under mild conditions which avoid the often troublesome separation of product from osmium or its inorganic derivatives.

In this modified technique an osmate ester which is prepared in pyridine is stirred at room temperature for 5 to 30 minutes with a solution of sodium bisulfite and aqueous pyridine. The clear orange solution which results contains the *cis*-glycol and a soluble osmium salt. Extraction of the aqueous pyridine solution with chloroform yields a colorless chloroform and pyridine solution which contains only the *cis*-glycol. By this method 3β-hydroxyandrost - 5 - en - 17 - one, 17 - vinyltestosterone, and ouabagenin tetraacetate have been oxidized to glycols in crude yields of 86, 72, and 81%, respectively.

EXPERIMENTAL

General procedure. A 3.9-mmol. sample of the alkene to be oxidized was dissolved in 15 ml. of pyridine and stirred with 1.0 g. (3.94 mmol.) of osmium tetroxide for an appropriate time. To this mixture was added with stirring a solution of 1.8 g. of sodium bisulfite, 30 ml. of water, and 20 ml. of pyridine. The ratio of sodium bisulfite, and water, and pyridine in the final mixture should be about 2:30:35. When a clear orange solution was obtained (5 to 30 min.), it was extracted thoroughly with chloroform. The chloroform extract was dried over potassium carbonate or sodium sulfate and evaporated to dryness *in vacuo* to yield the product.

3β,5α,6α-Trihydroxyandrostan-17-one.[5] A solution of 1.14 g. (3.9 mmol.) of 3β-hydroxyandrost-5-en-17-one, 1.0 g. (3.94 mmol.) of osmium tetroxide and 15 ml. of pyridine was stirred for 2 hr. The mixture was then stirred for 5 min. with a solution of 1.8 g. of sodium bisulfite, 30 ml. of water, and 20 ml. of pyridine. The orange solution which was obtained was extracted with one 150-ml. and two 50-ml. portions of chloroform. The combined organic extract was dried over potassium carbonate and evaporated to dryness *in vacuo*. The crude crystalline product was triturated with ethyl acetate, collected by filtration, and dried. It weighed 1.05 g. (86%) and melted at 240–243°.

17,20ε,21ε-Trihydroxy-17α-pregn-4-en-3-one.[6] A solution of 3 g. (9.65 mmol.) of 17-vinyltestosterone, 3.0 g. (11.8 mmol.) of osmium tetroxide and 60 ml. of pyridine was stirred in the dark for 20 hr. To the mixture was added with stirring a solution of 5.6 g. of sodium bisulfite, 90 ml. of water, and 45 ml. of pyridine. The solution was then extracted thoroughly with chloroform. The chloroform extract was washed with water, dilute hydrochloric acid, water, and aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from methanol yielded 2.5 g. (72%) of product which melted at 186–193°.

1β,3β,5β,11α,14,19,20ε,22ε-Octahydroxycardanolide-1,3,11,-19-tetraacetate. A solution of 2.2 g. (3.25 mmol.) of ouabagenin-1,3,11,19-tetraacetate,[7] 1.0 g. (3.94 mmol.) of osmium tetroxide and 20 ml. of pyridine was stirred for 1 day. The mixture was then stirred for 30 min. with a solution of 1.8 g. of sodium bisulfite, 30 ml. of water, and 15 ml. of pyridine. The solution was extracted thoroughly with chloroform. The chloroform extract was washed with water, dilute hydrochloric acid, water, and aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from ethyl acetate yielded a crude product which melted at 285–290° and weighed 1.7 g. (81%). An analytical sample prepared by crystallization of the crude product from methanol melted at about 318°.

Anal. Calcd. for $C_{31}H_{44}O_{14}$: C, 58.11; H, 6.92. Found: C, 57.86; H, 7.07.

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(1) R. Criegee, B. Marchand, H. Wannowius, *Ann.*, **550**, 99 (1941).
(2) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1454 (1948).
(3) H. Wieland and H. Behringer, *Ann.*, **549**, 209 (1941).
(4) D. H. Barton and D. Elad, *J. Chem. Soc.*, 2090 (1956).
(5) M. I. Ushakow and A. I. Lutenburg, *Nature*, **140**, 466 (1937).
(6) C. Ruzicka and P. Muller, *Helv. Chim. Acta.*, **22**, 755 (1939).
(7) C. Mannich and G. Siewert, *Ber.*, **75**, 737 (1942).

Aliphatic Nitriles from Alkyl Chlorides

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The preparation of nitriles by the reaction of primary alkyl halides with alkali metal cyanides is an old and well known procedure. However, alkyl chlorides, except for benzyl- or allyl-type compounds, have not been used very frequently because of excessive reaction times required with the aqueous alcohol solvent usually used for this type reaction.[1] Other solvent systems, such as ethylene glycol monomethyl ether[2] or polyethylene glycol,[3]

(1) D. T. Mowry, *Chem. Revs.*, **42**, 189 (1948).
(2) O. W. Cass, *Chem. Eng. News*, **32**, 2197 (1954).
(3) A. Brändstrom, *Acta Chem. Scand.*, **10**, 1197 (1956).

TABLE I

REACTION OF ALKYL CHLORIDES WITH SODIUM CYANIDE IN DMSO

	Reaction Time, Min.	Product	Yield, %	B.P., Mm.	n_D^{25}
1,2-Dichloroethane	20	Succinonitrile	56	114 (3.4)	—
1,3-Dichloropropane	30	Glutaronitrile	67	101–102 (1.5)	1.4339
1,4-Dichlorobutane	30	Adiponitrile	88	115 (0.7)	1.4369
1,5-Dichloropentane	30	Pimelonitrile	75	149 (1.0)	1.4398
1-Chlorobutane	20	Valeronitrile	93	139	1.3949
1-Chloropentane	20	Capronitrile	97	80 (48)	1.4050
1-Chlorohexane	20	Heptanenitrile	91	96–97 (50)	1.4125
1-Chlorodecane	20	Hendecanenitrile	94	87–88 (1.2)	1.4314
2-Chlorobutane	180	2-Cyanobutane	69	125–126	1.3873
2-Chlorooctane	60	2-Cyanooctane	70	88 (12)	1.4179

have recently been disclosed which permitted the use of primary chlorides in the preparation of nitriles in reasonable reaction times, but no mention has been made of the use of secondary chlorides.

It has now been found that both primary and secondary alkyl chlorides react with sodium cyanide in dimethyl sulfoxide solvent to give high yields of the corresponding nitrile in shorter reaction times than have been obtained with bromides or iodides in aqueous alcohol solvent. Both mono- and di-primary alkyl chlorides react in thirty minutes or less while secondary chlorides require one to 3 hours depending on the boiling point of the chloride. The yield of secondary nitrile by this method far exceeds the 25–30% yield generally given for the displacement of secondary halides by cyanide.[1] Table I shows the reaction times and the yields of nitriles from a number of representative chlorides.

EXPERIMENTAL

Starting materials. Dimethyl sulfoxide, obtained from the Stepan Chemical Co., was dried over calcium hydride before use. Reagent grade sodium cyanide was dried at 110° overnight and stored in a tightly stoppered bottle. Failure to dry the sodium cyanide sometimes caused the reaction mixtures to become very dark in color. The alkyl halides were all Eastman Kodak Co. White Label grade and were used as received.

Procedure for primary chlorides. Dry sodium cyanide (30 g.) was added to 150 ml. of dimethyl sulfoxide in a flask fitted with a stirrer, reflux condenser, dropping funnel, and thermometer. The thick slurry was heated on a steam bath to 90° and the steam bath was then removed. The halide (0.5 mol. of monochloride or 0.25 mol. of dichloride) was slowly added to the stirred mixture causing the temperature to increase immediately. The rate of addition was such that the temperature of the reaction did not go above about 160°. After all the halide was added (about 10 min.) the mixture was stirred for 10 min. more, or until the temperature dropped below 50°. In the preparation of mononitriles, the reaction mixture was then poured into water and the product extracted with chloroform or ethyl ether. The extract was washed several times with saturated sodium chloride solution, dried over calcium chloride, and the product distilled.

With the dinitriles a slightly different procedure was used due to their water solubility. After the reaction had cooled, 150 ml. of chloroform was added to the flask and this mixture was then poured into saturated salt solution. Enough water was added to dissolve precipitated salt and the chloroform layer was separated. The aqueous layer was extracted once with chloroform. The combined extracts were then washed twice with salt solution, dried, and distilled.

Secondary chlorides. With a low-boiling chloride such as 2-chlorobutane, a stirred slurry of 30 gm. of sodium cyanide in 150 ml. of dimethyl sulfoxide was heated to 90° with a heating mantle and 0.5 mol. of the chloride was slowly added over a period of 30 min. The temperature of the refluxing reaction mixture slowly increased as nitrile was formed. Refluxing continued as the temperature slowly rose to 150° after 3 hr. reaction time. The flask was then cooled and the reaction mixture worked up in the same way as for the primary nitriles. With 2-chlorooctane, the sodium cyanide–dimethyl sulfoxide slurry was heated to 130° and 0.5 mol. of the chloride added. The reaction mixture was maintained at 135–145° for 1 hr., then cooled, and the product isolated.

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Reactions of Ethyl Isobutenyl Ether

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The ready availability of ethyl isobutenyl ether[1] prompted our investigation of some of its reactions.

The acid-catalyzed addition of ethyl orthoformate[2] to ethyl isobutenyl ether gave dimethylmalonaldehyde tetraethyl acetal in good yield. Although the dimethylmalonaldehyde bis(2,4-dinitrophenylhydrazone) could be obtained in the usual manner from the acetal, repeated attempts to obtain the free aldehyde by hydrolysis failed; either the acetal was recovered or the hydrolytic cleavage products of the aldehyde, formic acid, and isobutyraldehyde were obtained.

The acid-catalyzed addition of diethyl acetals to ethyl isobutenyl ether occurred smoothly,

(1) (a) M. G. Voronkov, *J. Gen. Chem. U.S.S.R.*, (Eng. Transl.), **20**, 2060 (1950). (b) J. L. E. Erickson and M. Z. Woskow, *J. Org. Chem.*, **23**, 670 (1958).

(2) F. G. Young, U. S. Patent **2,556,312** (1949).

giving 1,1,3-triethoxy-2,2-dimethylalkanes in good yields. Because of the greater stability of ethyl isobutenyl ether, a much smaller excess of the acetal is required for optimum yields than when the vinyl ethers are used.[3] The 1,1,3-triethoxy-2,2-dimethylalkanes were easily hydrolyzed to the corresponding 3-ethoxy-2,2-dimethylalkanals which, in turn, were easily reduced to the 3-ethoxy-2,2-dimethyl-1-alkanols.

Ethyl isobutenyl ether underwent the Diels-Alder reaction with acrolein to give 2-ethoxy-3,4-dihydro-3,3-dimethyl-2H-pyran.[4]

Hydroformylation of ethyl isobutenyl ether gave two isomeric aldehydes. The major product was the expected 2-ethoxy-3-methylbutyraldehyde. The minor product was 4-ethoxy-3-methylbutyraldehyde, which must have arisen from a rearrangement of the double bond of the isobutenyl group.

EXPERIMENTAL

Ethyl isobutenyl ether. The method used was essentially that of Voronkov,[1a] except that phosphoric acid was used as the catalyst.[5] Distillation of isobutyraldehyde diethyl acetal (441 g., 3 mol.) from 0.2 g. of 85% phosphoric acid through a 1-ft. Vigreux column at a rate that maintained a head temperature of 72–84° (flask temperature 113–150°) gave 408.5 g. of distillate. The distillate was washed once with a 500-ml. portion and twice with 250-ml. portions of 0.5% aqueous potassium carbonate solution to remove the ethyl alcohol. The remaining organic phase was dried over potassium carbonate and distilled to give 252 g. (84%) of ethyl isobutenyl ether, b.p. 91–92°, n_D^{20} 1.4081 (lit.[1a] b.p. 94°, n_D^{20} 1.4053; lit.[1b] b.p. 92–94°, n_D^{25} 1.4060).

Dimethylmalonaldehyde tetraethyl acetal. Ethyl isobutenyl ether (150 g., 1.5 mol.) was added over a 1-hr. period to ethyl orthoformate (296 g., 2 mol.) containing 5 ml. of boron trifluoride etherate. The temperature was maintained at 20–25° by cooling. The mixture was stirred for an additional 1.5 hr. and the catalyst was then neutralized by addition of excess potassium carbonate solution. The organic phase was separated and distilled to give, after removal of unreacted starting materials, 268 g. (72%) of dimethylmalonaldehyde tetraethyl acetal, b.p. 52°/2 mm., n_D^{20} 1.4192, and 20 g. of residue.

Anal. Calcd. for $C_{13}H_{28}O_4$: C, 62.9; H, 11.4. Found: C, 62.9; H, 11.5.

The acetal gave the very insoluble bis(2,4-dinitrophenylhydrazone), which was recrystallized from acetone; m.p. 260–261°.

Anal. Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.4; H, 3.5. Found: C, 44.3; H, 3.7.

Products from addition of isobutyraldehyde diethyl acetal to ethyl isobutenyl ether. A. Ethyl isobutenyl ether (140 g., 1.4 mol.) was added over a 2.5-hr. period to isobutyraldehyde diethyl acetal (307 g., 2.1 mol.) containing 1.5 ml. of boron trifluoride etherate at 35–40°. Stirring was continued for 1 hr., and the catalyst was then neutralized by addition of excess potassium carbonate solution. The organic phase was separated and distilled to give, after removal of unused starting materials, 218 g. (63.5%) of 1,1,3-triethoxy-2,2,4-trimethylpentane, b.p. 53–54°/0.5–1 mm., n_D^{20} 1.4259.

Anal. Calcd. for $C_{14}H_{30}O_3$: C, 68.3; H, 12.3. Found: C, 68.1; H, 12.0.

B. A solution of 24 ml. of concentrated sulfuric acid in 1 l. of water was stirred for 16 hr. with 1,1,3-triethoxy-2,2,4-trimethylpentane (360 g., 1.46 mol.) at room temperature. The organic phase was taken up in ether and distilled to give 232.5 g. (92.5%) of 3-ethoxy-2,2,4-trimethylvaleraldehyde, b.p. 66–67°/7.5 mm., n_D^{20} 1.4262.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.7; H, 11.7. Found: C, 69.4; H, 11.7.

The 2,4-dinitrophenylhydrazone melted at 102–103°.

Anal. Calcd. for $C_{16}H_{24}N_4O_5$: C, 54.5; H, 6.9. Found: C, 54.4; H, 6.9.

C. Hydrogenation of the 3-ethoxy-2,2,4-trimethylvaleraldehyde over Raney nickel at 125° and 100 atm. gave 3-ethoxy-2,2,4-trimethyl-1-pentanol, b.p. 47–48°/0.5 mm., n_D^{20} 1.4370, in 92% yield.

Anal. Calcd. for $C_{10}H_{22}O_2$: C, 68.9; H, 12.7. Found: C, 69.1; H, 12.6.

Products from addition of acetaldehyde diethyl acetal to ethyl isobutenyl ether. A. In a manner similar to that described above, acetaldehyde diethyl acetal and ethyl isobutenyl ether gave 1,1,3-triethoxy-2,2-dimethylbutane, b.p. 77°/7 mm., n_D^{20} 1.4182, in 76% yield.

Anal. Calcd. for $C_{12}H_{26}O_3$: C, 66.0; H, 12.0. Found: C, 65.8; H, 11.9.

B. 3-Ethoxy-2,2-dimethylbutyraldehyde, b.p. 62–64°/23 mm., n_D^{20} 1.4133, was obtained in 87% yield.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.6; H, 11.2. Found: C, 66.5; H, 11.2.

The 2,4-dinitrophenylhydrazone melted at 116–118°.

Anal. Calcd. for $C_{14}H_{20}N_4O_5$: C, 51.8; H, 6.2. Found: C, 51.6; H, 6.3.

C. 3-Ethoxy-2,2-dimethyl-1-butanol, b.p. 128–130°/160 mm., n_D^{20} 1.4262, was obtained in 90% yield.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.7; H, 12.4. Found: C, 65.9; H, 12.5.

Products from addition of benzaldehyde diethyl acetal to ethyl isobutenyl ether. A. 1,1,3-Triethoxy-2,2-dimethyl-3-phenylpropane, b.p. 89–91°/0.5 mm., n_D^{20} 1.4770, was obtained in 77% yield using a 1:1 ratio of acetal to ether.

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.8; H, 10.1. Found: C, 72.9; H, 10.0.

B. 3-Ethoxy-2,2-dimethylhydrocinnamaldehyde, b.p. 64°/0.5 mm., n_D^{20} 1.4950, was obtained in 92% yield.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.7; H, 8.8. Found: C, 75.6; H, 8.8.

The 2,4-dinitrophenylhydrazone melted at 134°.

Anal. Calcd. for $C_{19}H_{22}N_4O_5$: C, 59.1; H, 5.7. Found: C, 59.3; H, 5.9.

C. 3-Ethoxy-2,2-dimethyl-3-phenyl-1-propanol, b.p. 88°/1.3–1.4 mm., n_D^{20} 1.5022, was obtained in 89% yield.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 75.0; H, 9.7. Found: C, 75.5; H, 9.8.

2-Ethoxy-3,4-dihydro-3,3-dimethyl-2H-pyran. A mixture of ethyl isobutenyl ether (252 g., 2.52 mol.) and acrolein (168 g., 3 mol.) containing 0.2 g. of hydroquinone was heated for 3 hr. at 180° in an autoclave. Distillation of the reaction mixture gave, after removal of unreacted starting materials and a small amount of acrolein dimer, 212 g. (54%) of 2-ethoxy-3,4-dihydro-3,3-dimethyl-2H-pyran, b.p. 158°, n_D^{20} 1.4344.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.2; H, 10.3. Found: C, 69.3; H, 10.2.

The dihydropyran gave, by the usual procedure, the bis-(2,4-dinitrophenylhydrazone) of 2,2-dimethylglutaraldehyde, m.p. 237–239°.

Anal. Calcd. for $C_{19}H_{20}N_8O_8$: C, 46.7; H, 4.1. Found: C, 46.6; H, 4.1.

Hydroformylation of ethyl isobutenyl ether. A mixture of ethyl isobutenyl ether (136 g., 1.36 mol.) in 500 ml. of benzene and 10 g. of cobalt carbonyl was placed in an autoclave. Hydrogen was admitted to the autoclave to a pressure of 30 atm., and then hydrogen–carbon monoxide was admitted to a pressure of 100 atm. The temperature was raised to 130° and held for 1 hr. The reaction mixture was

(3) R. I. Hoaglin and R. Hirsch, *J. Am. Chem. Soc.*, **71**, 3468 (1949); U. S. Patent **2,564,760** (1957).

(4) R. I. Longley, Jr., and W. S. Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950).

(5) A. Duhamel, *Bull. soc. chim. France*, 156 (1956).

then steam-distilled. The organic phase was separated and then fractionated. Two well defined fractions were obtained. The first fraction (46 g., 27%), b.p. 137–138°, n_D^{20} 1.4029, was 2-ethoxy-3-methylbutyraldehyde.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.8; H, 10.9.

The 2,4-dinitrophenylhydrazone melted at 125–126°.

Anal. Calcd. for $C_{13}H_{18}N_4O_5$: C, 50.3; H, 5.8. Found: C, 50.1; H, 5.8.

The second fraction (21 g., 12%), b.p. 160–162°, n_D^{20} 1.4132, was 4-ethoxy-3-methylbutyraldehyde.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.9; H, 10.9.

The 2,4-dinitrophenylhydrazone, m.p. 48–50°, was very soluble and therefore difficult to purify.

Anal. Calcd. for $C_{13}H_{18}N_4O_5$: C, 50.3; H, 5.8. Found: C, 49.7; H, 6.1.

The structures of the two aldehydes were assigned on the basis of their nuclear magnetic resonance spectra. These spectra were in full agreement with the assigned structures and preclude the other possible isomer, ethoxypivalaldehyde.

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Studies of Configuration. VI. *cis*- and *trans*-4-Methoxycyclohexanol[1,2]

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The isomeric mixture of the 4-methoxycyclohexanols is well known, having been prepared frequently by hydrogenation of hydroquinone monomethyl ether.[3] However, there are only three reports concerning individual isomers. In 1941, Ruggli, Leupin, and Businger[4] reported that 4-methoxycyclohexyl tosylate could be separated into a solid, m.p. 87°, and a liquid. They suggested the *trans*-configuration for the solid 4-methoxycyclohexaneacetic acid prepared by treatment of the tosylate with sodio diethylmalonate, but made no assignment to the 4-methoxycyclohexyl tosylate.

Almost simultaneously with our preliminary report on the solvolysis of the *cis*- and *trans*-4-methoxycyclohexyl tosylates, Henbest and Nichols[5] reported the 3,5-dinitrobenzoate of the *trans*-isomer.

We have reported the separation of the isomers through the acid phthalates and a preliminary correlation of the configuration with the known 1,4-dihydroxycyclohexane by partial methylation. In view of the very interesting behavior of the two isomers, it seemed essential to present a definitive proof of configuration. Such is the purpose of the present report.

The known *cis*-4-hydroxycyclohexanecarboxylic acid[6] (I) was converted by methylation with methyl iodide and silver oxide following the procedure used by Noyce and Denney[7] to methyl *cis*-4-methoxycyclohexanecarboxylate (II). Ample evidence is available to show that this reaction proceeds without jeopardizing the stereochemical integrity of the system. The ester II was hydrolyzed to *cis*-4-methoxycyclohexanecarboxylic acid (III), m.p. 54.5–55.7°. This material was shown to be identical, by mixed melting point and comparison of infrared spectra, with the isomer of 4-methoxycyclohexanecarboxylic acid assigned the *cis*-configuration by Noyce and Weingarten.[8] Thus, confirmation of the previous assignment on the basis of rearrangement behavior is obtained.

Treatment of *cis*-4-methoxycyclohexanecarboxylic acid with methyllithium afforded the ketone *cis*-4-methoxy-1-acetylcyclohexane (IV). This reaction has been shown by Dauben and Hoerger[9] to proceed without any inversion or epimerization adjacent to the carbonyl group. Treatment of the ketone with perbenzoic acid afforded *cis*-4-methoxycyclohexylacetate (V), a reaction shown to proceed with retention of configuration by Turner.[10] Hydrolysis of the acetate afforded *cis*-4-methoxycyclohexanol (VI), which was characterized by infrared spectra and preparation of derivatives. Each of the steps proceeded in satisfactory yield.

The second method which was used was the partial methylation of the known *trans*-1,4-dihydroxycyclohexane.[11] Unfortunately, the yield of the monomethyl ether was low (10%) and the more definitive sequence above was carried through.

The chemical transformations are summarized in Chart I, and the properties of derivatives of *cis*- and *trans*-4-methoxycyclohexanol are given in Table I.

(1) A portion of this work has been published in preliminary form [D. S. Noyce and B. R. Thomas, *J. Am. Chem. Soc.*, **79**, 755 (1957)].

(2) Supported in part by the National Science Foundation (G-2387).

(3) For recent examples, see F. Hunziker, F. X. Mullner, and H. Schaltegger, *Helv. Chim. Acta*, **38**, 1943 (1955); D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Am. Chem. Soc.*, **76**, 4446 (1954).

(4) P. Ruggli, O. Leupin, and A. Businger, *Helv. Chim. Acta*, **24**, 339 (1941).

(5) H. B. Henbest and B. Nichols, *Proc. Chem. Soc.*, 61 (1957); *J. Chem. Soc.*, 227 (1959).

(6) N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1379 (1950).

(7) D. S. Noyce and D. B. Denney, *J. Am. Chem. Soc.*, **76**, 768 (1954).

(8) D. S. Noyce and H. I. Weingarten, *J. Am. Chem. Soc.*, **79**, 3093 (1957).

(9) W. G. Dauben and E. Hoerger, *J. Am. Chem. Soc.*, **73**, 1504 (1951).

(10) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 878 (1950).

(11) W. Nudenberg and L. W. Butz, *J. Am. Chem. Soc.*, **66**, 307 (1944).

Chart I

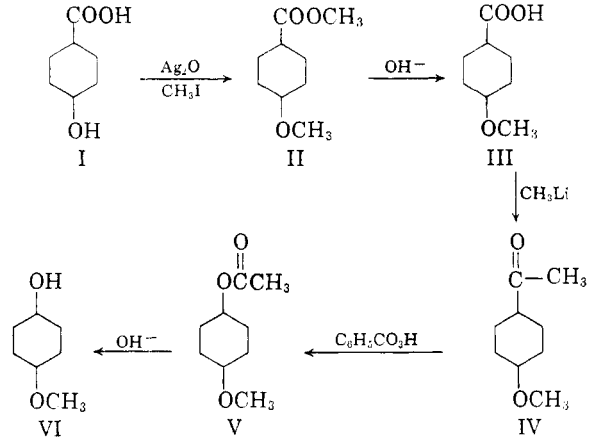

TABLE I

MELTING POINTS OF 4-METHOXYCYCLOHEXANOL DERIVATIVES

	M.P., °C.	
	cis-	*trans-*
3,5-Dinitrobenzoate	116.2–116.5	125.5–126.5
p-Toluene sulfonate	87.8–88.2	66.4–67.2
Acid phthalate	61–65	148.6–149.0

It is to be noted that the tosylate of the *cis*-isomer is the higher melting of the pair.

Another very interesting observation made during the course of this work is that the lithium aluminum hydroxide reduction of 4-methoxycyclohexanone affords 70% of the *cis*-isomer. Further study is in progress in this area.

EXPERIMENTAL[12]

cis-4-Hydroxycyclohexanecarboxylic acid (I). *p*-Hydroxybenzoic acid in acetic acid was hydrogenated over 5% rhodium-on-alumina at an initial hydrogen pressure of 45 p.s.i. After removal of the catalyst by filtration, the remaining solution was distilled at atmospheric pressure to afford a main fraction b.p. 235–245°. This fraction was redistilled to afford the lactone of *cis*-4-hydroxycyclohexanecarboxylic acid, b.p. 120–123° (11 mm.). Crystallization from benzene-pentane afforded the pure lactone, m.p. 127.2–128.0° (lit.[6] 126–128°).

The lactone was dissolved in a minimum amount of water and heated on a steam bath. The *cis*-4-hydroxycyclohexanecarboxylic acid (I) obtained by continuous ether extraction was crystallized from acetonitrile, m.p. 150.1–151.2° (lit.[6] 152°).

Methyl cis-4-methoxycyclohexanecarboxylate (II) was prepared by the procedure of Noyce and Fessenden[13] from 4.0 g. of *cis*-4-hydroxycyclohexanecarboxylic acid, 50 g. of freshly prepared silver oxide (anhydrous), and 150 ml. of methyl iodide. The crude ester was fractionally distilled at reduced pressure to afford 2.8 g. (58%) of methyl *cis*-4-methoxycyclohexanecarboxylate, II, b.p. 99–99.5° (10.5 mm.), n_D^{22} 1.4503.

cis-4-Methoxycyclohexanecarboxylic acid (III). The ester (2.35 g.) was heated under reflux with 15 ml. of water and 50 ml. of aqueous 1*N* sodium hydroxide for 3 hr. The acidified solution was continuously extracted with ether. The dried ether extracts were concentrated, and the residue crystallized from pentane (charcoal). The *cis*-4-methoxycyclohexanecarboxylic acid obtained had a m.p. 54.5–55.7° and weighed 1.33 g. (62%). When mixed with a sample of *cis*-4-methoxycyclohexanecarboxylic acid, m.p. 54.8–55.8°, prepared by Noyce and Weingarten,[8] the m.p. was 54.5–55.7°.

cis-4-Methoxy-1-acetylcyclohexane (IV). To a solution of 9.5 g. of *cis*-4-methoxycyclohexanecarboxylic acid in anhydrous ether was added dropwise 300 ml. of a freshly prepared 0.52 molar methyllithium solution in anhydrous ether.[14] After addition was complete, the cloudy solution was stirred for an additional 20 min., and then poured onto 100 g. of ice. The crude ketone was distilled to afford 6.4 g. (69%) of *cis*-4-methoxy-1-acetylcyclohexane, b.p. 99–102° (12 mm.), n_D^{27} 1.4576.

The dinitrophenylhydrazone was prepared in aqueous ethanol and crystallized from 50% ethanol, m.p. 104.2–105.4°.

Anal. Calcd. for $C_{15}H_{20}O_5N_4$: C, 53.56; H, 5.98; N, 16.73. Found: C, 53.7; H, 5.95; N, 16.70.

Conversion of cis-4-methoxy-1-acetylcyclohexane to cis-4-methoxycyclohexyl acetate (V). *cis*-4-Methoxy-1-acetylcyclohexane, 5.3 g., was treated with a 50% excess of freshly prepared perbenzoic acid in chloroform,[15] and allowed to stand at room temperature for 14 days. The solution was diluted with ether, washed with dilute sodium hydroxide and water, and dried over magnesium sulfate. Fractionation afforded *cis*-4-methoxycyclohexyl acetate (V), b.p. 98–100° (12.5 mm.) n_D^{28} 1.4438. The yield was 3.0 g. (52%).

cis-4-Methoxycyclohexanol (VI). Hydrolysis of V, 3.0 g., with 1*N* sodium hydroxide was followed by continuous extraction with ether. Fractionation of the dried ether extract afforded 1.3 g. (57%) of *cis*-4-methoxycyclohexanol, b.p. 98–99° (11 mm.) n_D^{27} 1.4641.

cis-4-Methoxycyclohexyl 3,5-dinitrobenzoate was prepared in the usual manner and crystallized from hexane, m.p. 115.6–116.2°.

Separation of isomers of 4-methoxycyclohexanol. 4-Methoxycyclohexyl hydrogen phthalate was fractionally crystallized from benzene. Three crystallizations afforded the *trans*-4-methoxycyclohexyl hydrogen phthalate, m.p. 148.6–149.0°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.71; H, 6.49.

From the mother liquors a low melting form, m.p. 61–65°, was obtained, which subsequent investigation showed to be primarily *cis*-4-methoxycyclohexyl hydrogen phthalate.

Anal. Found: C, 64.66; H, 6.45.

The *p-toluenesulfonates* were prepared in the usual manner, m.p. *cis*-, 87.8–88.2°; *trans*-, 66.4–67.2°. The *p*-toluenesulfonates may also be separated by fractional crystallization of the mixed isomers from petroleum ether.

Anal. Calcd. for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09; S, 11.27. Found (*cis*-): C, 59.25; H, 7.18; S, 11.16. Found (*trans*-): C, 59.03; H, 7.13; S, 11.18.

The 3,5-dinitrobenzoates were prepared in the usual manner from the regenerated alcohol. *cis-4-Methoxycyclohexyl 3,5-dinitrobenzoate* was crystallized from hexane, m.p. 116.2–116.5°. *trans-4-Methoxycyclohexol 3,5-dinitrobenzoate* was crystallized from methanol, m.p. 125.5–126.5°.

Anal. Calcd. for $C_{14}H_{16}O_7N_2$: C, 51.85; H, 4.95; N, 8.64. Found (*cis*-): C, 52.03; H, 4.73; N, 8.65. Found (*trans*-): C, 51.61; H, 4.93; N, 8.79.

trans-4-Methoxycyclohexanol from trans-1,4-cyclohexanediol. Treatment of 5 g. of *trans*-1,4-cyclohexanediol with an eightfold excess of methyl iodide and silver oxide using methanol as a solvent afforded 0.6 g. (10%) of *trans*-4-

(12) Melting points are corrected; boiling points are uncorrected. Analyses are by the Microanalytical Laboratory of the University of California.

(13) D. S. Noyce and J. S. Fessenden, *J. Org. Chem.*, **24**, 715 (1959).

(14) D. A. Van Dorp and J. A. Arens, *Rec. trav. chim.*, **65**, 338 (1946).

(15) G. Braun, *Org. Syntheses*, **Coll. Vol. I**, 431 (1941).

methoxycyclohexanol (VII), b.p. 90–95° (10 mm.) n_D^{25} 1.4650.

The distillation residue afforded 2 g. of recovered *trans*-1,4-cyclohexanediol on crystallization from acetone, m.p. 141–142°.

The *p*-toluene sulfonate and 3,5-dinitrobenzoate of VII were prepared, m.p. 65–66° and 126–127°, respectively.

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Conformational Analysis. VII. The Dipole Moment of 2-Bromocyclooctanone[1,2]

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Recently a conformational analysis of the 2-bromocyclooctanone molecule (I) was reported.[3] This molecule was predicted to exist as a mixture of the five conformational species III–VI[4] depicted in Fig. 1. (There are two species having the gross geometry of III which differ in dihedral angle.) The percentage compositions of the equilibrium mixtures of III–VI (see Table I) in the solvents *n*-heptane benzene, and dioxane were calculated from theoretical considerations and these values predicted rather small changes in the position of the conformational equilibrium with respect to the effective dielectric constant of the medium. A small influence of solvent upon the equilibrium composition was detected by experimental measurements of the absorption intensities of the infrared and ultraviolet carbonyl absorption maxima of I in various media and these spectral data were qualitatively consistent with the theoretical predictions. The exact extent of the agreement between theory and experiment was somewhat obscured, however, by the fact that at present there is no theory available which could be used to quantitatively predict the results of the spectral measurements. On the other hand, the determination of the dipole moment of I in benzene solution did provide an accurate physical measurement which could be directly compared to a calculated value. The experimental value of 3.36 D was in excellent agreement with the predicted dipole moment of 3.28 D for the compound in this solvent.

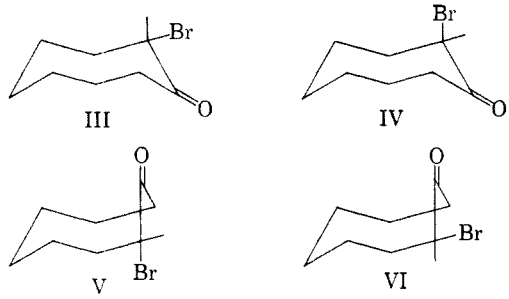

Figure 1

TABLE I

CALCULATED PERCENTAGE CONFORMATIONAL ISOMER COMPOSITION OF 2-BROMOCYCLOOCTANONE

Conformational Isomer	Dihedral Angle	Solvent (D_{effec}) *n*-Heptane (4.83)	Benzene (6.44)	Dioxane (10.3)
IIIa	40°	16	19	22
IIIb	63°	26	27	28
IV	166°	2	1	1
V	132°	47	41	34
VI	12°	9	12	15

The present study was undertaken to extend the dipole moment data for 2-bromocyclooctanone to the solvents *n*-heptane and dioxane and thus to provide a more extensive experimental test of the theoretical analysis. The dipole moments of I were obtained from dielectric constant measurements and had the values 3.29 D and 3.42 D in the solvents *n*-heptane and dioxane, respectively. These values, along with the experimental dipole moment of I in benzene solution and the dipole moments calculated from the estimated compositions for each solvent of Table I, are listed in Table II.

TABLE II

DIPOLE MOMENT OF 2-BROMOCYCLOOCTANONE AT 25°

Solvent	μ Calcd.	μ Observed
n-Heptane	3.13	3.29
Benzene	3.28	3.36
Dioxane	3.41	3.42

The qualitative prediction that only small changes in the conformational composition of the equilibrium mixture of IIIa–VI would result from the changing effective dielectric constant is substantiated by the small differences observed between the magnitudes of the dipole moment in each solvent. The deviations between the calculated and observed moments as the solvent is varied appear to be systematic, but are certainly as small as could be hoped for. The variation of the dipole moment of 2-bromocyclooctanone with solvent is to be compared with the similar corresponding changes in the moment of 2-bromocyclohexanone.[5]

(1) Sponsored by the Office of Ordnance Research, U. S. Army.

(2) Paper VI, *J. Org. Chem.*, **25**, in press (1959).

(3) J. Allinger and N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5736 (1959).

(4) For reference, the numbers assigned to these isomers in Paper V (ref. 3) have been retained herein.

(5) The dipole moments of 2-bromocyclohexanone in *n*-heptane, benzene, and dioxane, respectively, are 3.37, 3.50, and 3.64 D. [W. D. Kumler and A. C. Huitric, *J. Am. Chem. Soc.*, **78**, 3369 (1956)].

EXPERIMENTAL

The *n*-heptane solvent was freed from olefinic contaminant by passage through a silica gel chromatographic column and then dried by distillation from sodium metal. The dioxane solvent was purified according to the method of Fieser.[6]

Dipole moment study. The dipole moment of 2-bromocyclooctanone in *n*-heptane and dioxane solution was determined at 25°. The data were treated by the method of Halverstadt and Kumler,[7] and the actual calculations were performed by applying automatic computing methods with an IBM 650 computer as described earlier.[8]

The molar refractivity was calculated from standard values of atomic refractivities[9] and had the value 44.720 cc. Atomic polarization was neglected. The data are summarized in Table III.

TABLE III

DIPOLE MOMENT DATA FOR 2-BROMOCYCLOOCTANONE AT 25°

N_2	d_{12}	ϵ_{12}
Dioxane Solvent		
0.0071283	1.031228	2.3191
0.0041682	1.029428	2.2697
0.0027629	1.028583	2.2465
0.0016669	1.027949	2.2283
0.0008651	1.027463	2.2143
0.0000000	1.026897	2.2013
α = 16.5874	β = 0.6039	ϵ_1 = 2.2007
d_1 = 1.026921	$P_{2\infty}$ = 284.60	μ = 3.426D
n-Heptane Solvent		
0.0079180	0.683125	1.9706
0.0059871	0.681701	1.9547
0.0041774	0.680434	1.9409
0.0024350	0.679182	1.9261
0.0012521	0.678316	1.9174
0.0000000	0.677423	1.9069
α = 8.0093	β = 0.7188	ϵ_1 = 1.9070
d_1 = 0.677422	$P_{2\infty}$ = 266.67	μ = 3.295D

Acknowledgment. The authors are indebted to Dr. Max Rogers, Michigan State University, for kindly allowing them to use his apparatus for the dipole moment measurements described in this paper.

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(6) L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath and Co., New York, 1941, p. 368.

(7) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

(8) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

(9) J. A. Leermakers and A. Weissberger, *Organic Chemistry*, Vol. II, H. Gilman, ed., J. Wiley and Sons, Inc., New York, 1947, p. 1751.

N-Bromocaprolactam

B. TAUB AND J. B. HINO

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In the course of investigating the halogenation of caprolactam we had occasion to prepare the heretofore unknown *N*-bromocaprolactam. We have found that *N*-bromocaprolactam is useful as a brominating agent in much the same manner as *N*-bromosuccinimide,[1] *N*-bromophthalimide[2] and *N*-bromo-5,5-dimethylhydantoin.[3] We have also found that the new *N*-bromo derivative functions in many instances as an oxidizing agent in the same manner as *N*-bromoacetamide.[4] Whereas the known *N*-bromo-derivatives usually require a peroxide catalyst and/or actinic light to initiate bromination, *N*-bromocaprolactam can be employed without the aid of a catalyst.

The *N*-bromocaprolactam can be prepared following the procedure of Oliveto[5] for the synthesis of *N*-bromoacetamide. However, the product obtained by this method is usually difficult to crystallize, and in most cases can be purified only after several recrystallizations from water. We have found that a relatively pure *N*-bromocaprolactam can be obtained by a modified procedure, which involves adding liquid bromine to an aqueous solution of caprolactam followed by the addition of 50% aqueous potassium or sodium hydroxide until the bromine color is discharged, and treating the resultant solution with common salt to precipitate the *N*-bromocaprolactam, which after several ice water washes, melts at 64–66°.

EXPERIMENTAL

N-Bromocaprolactam. Into a flask equipped with an agitator, thermometer, and dropping funnel was placed a mixture of 271.2 g. (2.4 mol.) of caprolactam and 90 ml. of water. The reaction mixture was cooled to about 0° by an ice-salt bath, following which 320 g. (2.0 mol.) of liquid bromine was added dropwise over a 30-min. period. After the addition was complete, 270 ml. of a 50% aqueous potassium hydroxide solution (previously cooled to 10°) was added dropwise maintaining the temperature of the reaction mixture below 10° throughout the addition. The resultant yellow solution was stirred at ice temperatures for an additional 2 hr., following which 80 g. of sodium chloride was added, effecting precipitation of the *N*-bromocaprolactam. The product was filtered, washed thoroughly with ice water, and dried at room temperature *in vacuo*. There was obtained 288 g. (75%) of *N*-bromocaprolactam; m.p. 64–66°.

Anal. Calcd. for $C_6H_{10}NOBr$: Br, 41.6; N, 7.3. Found: Br, 41.2; N, 7.0.

4-Bromoacetanilide. Into a flask equipped with an agitator and reflux condenser was placed a solution of 13.5 g. (0.1 mol.) of acetanilide in 100 ml. of chloroform. Then while stirring, 19.2 g. (0.1 mol.) of *N*-bromocaprolactam was added all at once. After a short induction period (*ca.* 15 min.), the reaction mixture began to reflux, after which the solution was stirred at room temperature for 2 hr. The solid residue obtained after evaporating the solvent was washed with cold water to remove the caprolactam formed during

(1) K. Ziegler, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 120 (1942).

(2) A. Wohl and K. Jaschinowski, *Ber.*, **54**, 476 (1921).

(3) J. F. Salellas and O. O. Orazi, *Anales asoc. quim. argentina*, **39**, 175–183 (1951).

(4) A. Wohl, *Ber.*, **52**, 51 (1919).

(5) E. P. Oliveto and C. Gerold, *Org. Syntheses*, **31**, 17 (1951).

the reaction. There was obtained 18 g. (84%) of 4-bromoacetanilide; m.p. 165°; lit.[6a] 167°.

5-Bromoisatin. A suspension of 16.2 g. (0.11 mol.) of isatin in 100 ml. of carbon tetrachloride was treated with 21.2 g. (0.11 mol.) of *N*-bromocaprolactam. The reaction mixture was heated to reflux to initiate bromination, following which it was stirred at room temperature overnight. The insoluble product was filtered, washed with carbon tetrachloride to insure the removal of residual caprolactam, and finally dried. There was obtained 19 g. (77%) of 5-bromoisatin; m.p. 254–256°; lit.[7] m.p. 255–256°.

Cyclohexanone. Into a flask equipped with a stirrer and reflux condenser were placed 5 g. (0.05 mol.) cyclohexanol, 75 ml. benzene, and 10 ml. pyridine. While agitating, 9.6 g. (0.05 mol.) of *N*-bromocaprolactam was added all at once. After a short induction period (*ca.* 15 min.), an exothermic reaction occurred, causing the benzene to reflux. The mixture was then allowed to stir without further application of heat for 18 hr. The solid pyridine hydrobromide was filtered. The filtrate was washed with a dilute aqueous solution of sodium hydrosulfite to decompose any unreacted *N*-bromocaprolactam, following which the organic layer was washed successively with two 50-ml. portions of 2*N* sulfuric acid, two 50-ml. portions of distilled water, and finally dried over anhydrous sodium sulfate. After removing the benzene by distillation, there was obtained 4 g. (82%) of cyclohexanone. The ketone was identified by converting it to its 2,4-dinitrophenylhydrazone; m.p. 159°; lit.[6b] 162°.

Benzophenone. To a solution of 9.2 g. (0.05 mol.) of benzhydrol in 75 ml. of benzene was added 10 ml. of pyridine, following which 9.6 g. (0.05 mol.) of *N*-bromocaprolactam was added all at once. The solution was refluxed for 1 hr. to initiate the reaction, following which the mixture was stirred at room temperature for 18 hr.

The product was isolated as in the previous experiment. There was obtained 8 g. (88%) of benzophenone; 2,4-dinitrophenylhydrazone; m.p. 239–240°; lit.[6c] 239°.

Acknowledgment. The authors are indebted to Mr. M. D. Edelman for his helpful suggestions during the course of this investigation.

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(6) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, J. Wiley and Sons, Inc., New York, 1948, (a) p. 232, (b) p. 262, (c) p. 264.

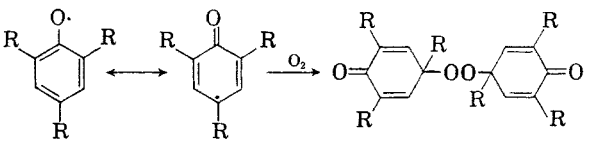
(7) Ng. Ph. Buu-Hoï, *Rec. trav. chim.*, **73**, 197–202 (1954).

Oxidation of Hindered Phenols. Preparation of Bis(1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one) Peroxide

HARRY S. BLANCHARD

Received August 31, 1959

Cook and Woodworth[1] have reported the quantitative preparation of the stable 2,4,6-tri-butylphenoxy radical (I) by oxidation of 2,4,6-tri-*t*-butylphenol (II) with alkaline ferricyanide. Moreover, they found that I could be converted to bis-(1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one) peroxide (III) if the oxidation of II were carried out in the presence of air or oxygen. In this manner they were able to prepare III in a crude yield of 81% utilizing a reaction time of a few hours. We have found that III can be prepared quickly in a state of high purity and in essentially quantitative yield by oxidizing II with silver oxide in the presence of oxygen. Interestingly enough, although the yield of III is nearly quantitative, the solutions never absorb the theoretical amount of oxygen. Thus, in a typical experiment, when 0.01 mol. of II was oxidized in 100 ml. of benzene with 0.022 mole of silver oxide, 0.0035 mol. of oxygen was absorbed. This corresponds to only 70% of the theoretical quantity of oxygen, although 0.0049 mol. (98%) of III was isolated. This finding suggests that some of the oxygen which ultimately ends up in the peroxide must come directly from the silver oxide.



I R = *t*-butyl III

Silver oxide is known to undergo a rather facile thermal decomposition to silver metal and oxygen although the reaction is very slow below 160°.[2] However, as the decomposition is catalyzed by light as well as by silver metal itself, it is perhaps not unreasonable that some of the oxygen does come from the oxide. Moreover, as silver metal is a catalyst for the decomposition, it may not be unreasonable to suggest that I can also function as a catalyst for this decomposition. In this connection, Witsiepe[3] has recently investigated the use of silver oxide in preparing stable phenoxy radicals, including I. He found that II could be converted quantitatively to I only when freshly prepared silver oxide was employed under rather special conditions. Most of the present work was carried out utilizing a sample of commercial silver oxide. However, the same results were also obtained when we employed a sample of silver oxide freshly prepared according to Witsiepe's directions. In view of these results we would suggest that silver oxide is a poor choice as a reagent when the object is to prepare I itself. Along these same lines Müller and co-workers[4] found that when II was oxidized with lead dioxide, the yield of I was not quantitative, apparently because of reaction of I with the lead dioxide. In view of the present results it would seem likely that here too there is a direct reaction

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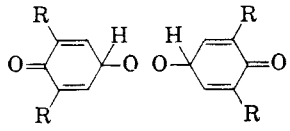
(2) H. Remy, "Treatise on Inorganic Chemistry," Elsevier Publishing Co., New York, 1956, p. 398.

(3) W. K. Witsiepe, *The Effect of t-Butyl Groups and Phenyl Groups on the Dissociation of Phenoxy Radicals*, University Microfilms, Publication No. 20,540, Ann Arbor, Michigan, 1956, pp. 61–65.

(4) E. Müller, K. Ley, and W. Keidaisch, *Ber.*, **87**, 1605 (1954).

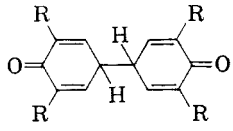
between I and lead dioxide probably resulting in III.

As we were also interested in obtaining bis(1-hydro-3,5-di-*t*-butyl-2,5-cyclohexadiene-4-one) peroxide (IV), we briefly examined the oxidation of 2,6-di-*t*-butylphenol (V) with silver oxide and also with alkaline potassium ferricyanide. Recently



IV R = *tert*-butyl

Kharash and Joshi[5] oxidized V with alkaline ferricyanide in the absence of air and isolated 3,5,3′,5′-tetra-*t*-butyl-1,1′-dihydro-2,5,2′,5′-biscyclohexadiene-4,4′-dione (VI), along with the known of 2,6,-2′,6′-tetra-*t*-butyldiphenoquinone. This interesting keto tautomer was reported by Kharasch and



VI R = *t*-butyl

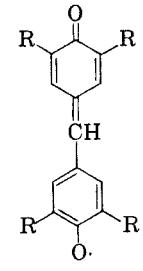
Joshi to be stable in non-polar solvents, but to tautomerize immediately to the bisphenol in hydroxylic solvents such as alcohols.

We found that V is oxidized by silver oxide to essentially the same mixture as reported by Kharasch and Joshi. Moreover, this same mixture results even when the oxidation is run in the presence of oxygen. We could find no evidence for a reaction between the phenoxy radical intermediates and oxygen. Further, we were somewhat surprised by the fact that VI itself did not react directly with oxygen yielding the corresponding diphenoquinone, particularly in the presence of the silver oxide.

As VI rearranges to the corresponding bisphenol in polar solvents, it seemed of interest to examine the oxidation in methanol and ethanol. Here we found, as expected, that a good yield of the tetra-*t*-butyldiphenoquinone resulted, apparently via the rearrangement of VI to the bisphenol and further oxidation of this to the diphenoquinone.

Because we were unable to prepare IV via the silver oxide route, it seemed of interest to oxidize V under Kharasch's and Joshi's conditions, except in the presence of oxygen. To this end we oxidized V with alkaline potassium ferricyanide in the presence of oxygen. However, as in the silver oxide oxidations oxygen had no effect on this reaction, and the same mixture of VI and the tetra-*t*-butyldiphenoquinone was obtained in the presence as well as in the absence of oxygen.

Recently, Müller and co-workers[6] presented convincing evidence that the oxidative coupling of V proceeds via the corresponding phenoxy radical. In view of this it seems somewhat surprising that oxygen is such an inefficient scavenger for these radicals. By way of comparison, carbon radicals are scavenged very effectively by oxygen even in the presence of efficient phenolic type inhibitors.[7] It should be pointed out that certain phenoxy radicals such as VII have been shown to be unreactive toward oxygen.[8] However, such phenoxy radicals as VII possess unique resonance stabiliza-



VII R = *t*-butyl

tion, a characteristic difficult to ascribe to the phenoxy radical resulting from oxidation of V. Rather, one must conclude either that the intermediate 2,6-di-*t*-butylphenoxy radicals prefer to undergo a coupling reaction or that V itself is a very efficient scavenger for the corresponding 2,6-di-*t*-butylphenoxy radical, resulting in the observed products.

EXPERIMENTAL

Materials. 2,4,6-Tri-*t*-butylphenol (II) was prepared by the procedure of Stillson, Sawyer, and Hunt.[9] It was purified by recrystallization from ethanol, m.p. 131–132° (lit.[6] m.p. 130–131°. 2,6-Di-*t*-butylphenol (V) (Eastman Kodak) was purified by several recrystallizations from *n*-hexene, m.p. 36–37°. Silver oxide (Eastman Kodak) was used without further purification. The freshly prepared silver oxide was made according to the directions of Witsiepe.[3]

Bis(1,3,5-tri-t-butyl-2,5-cyclohexadiene-4-one) peroxide (II). In a typical experiment 2.62 g. (0.01 mol.) of 2,4,6-tri-*t*-butylphenol in 100 ml. of benzene containing 5 g. (0.022 mol.) of commercial silver oxide was agitated at room temperature with oxygen. Adequate mixing was obtained by the use of a Fisher "Vibro-Mixer." After 0.5–1 hr., the solids were removed by filtration and the benzene evaporated at room temperature. In this manner 2.7 g. (98%) of a very pale green solid was isolated, m.p. 148–149° (lit.[1] m.p. 148–149°). Recrystallization from ethanol had no effect on the melting point. Several experiments were run in which the oxygen absorption was followed by means of a gas burette. In every instance including the use of freshly prepared silver oxide, only 60–70% of the theoretical quantity of oxygen was absorbed while the yield of III varied between 90–100%.

3,5,3′,5′-Tetra-t-butyl-1,1′-dihydro-2,5,2′,5′-bis-cyclohexadiene-4-one (VI). a. *Silver oxide in benzene.* In a typical experiment 4.12 g. (0.02 mol.) of 2,6-di-*t*-butylphenol in 300

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ml. benzene was stirred for 2 hr. with 9.3 g. (0.04 mol.) of commercial silver oxide. The solids were removed by filtration and the red colored filtrate evaporated in a rotary film evaporator at 15–20 mm. The dark residue was transferred with the aid of petroleum ether to a filter funnel and the solids washed with petroleum ether leaving very light lemon colored crystals, 2.8 g., m.p. 151–152° (lit.[5] m.p. 151–152°) mixed m.p. 151–152°. The filtrate was evaporated leaving 1 g. of a dark brown solid, m.p. 243°, which was identified by infrared comparison as 2,6,2′,6′-tetra-*t*-butyldiphenoquinone. This same mixture resulted when the reaction was carried out in the presence of oxygen.

b. *Alkaline ferricyanide in benzene.* The experiment reported by Kharasch and Joshi[5] was repeated in both a nitrogen atmosphere as well as in an oxygen atmosphere. In the case of the experiments with oxygen, mixing was accomplished with a Fisher "Vibro-Mixer." The reactions were worked up as described by Kharasch and Joshi and in each instance the same mixture of VI and the tetra-*t*-butyldiphenoquinone was obtained regardless of the presence or absence of oxygen. Thus oxygen appears to have no effect on this reaction.

2,6,2′,6′-Tetra-t-butyldiphenoquinone. In a typical experiment 2.06 g. (0.01 mol.) of 2,6-di-*t*-butylphenol in 200 ml. of methanol or ethanol was stirred with 4.7 g. (0.02 mol.) of silver oxide for 1 hr. The solids were removed by filtration and washed with hot benzene, the benzene being combined with the filtrate. The filtrate was then concentrated to approximately one quarter of its original volume and the red solids (2.0 g., 97%) which had separated were collected by filtration, m.p. 246° (lit.[5] for the diphenoquinone, 245°). The material was further identified by infrared comparison with an authentic sample.

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Improved Synthesis of Salts and Esters of Nitroacetic Acid

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The esters of nitroacetic acid are usually prepared from nitromethane by means of a two-step synthesis. The dipotassium salt of nitroacetic acid is made *via* the self-condensation of two molecules of nitromethane in the presence of strong, aqueous alkali[2] and the salt is then esterified directly by acidification in the presence of the appropriate alcohol.[3] The best yields reported by previous investigators were about 57% of relatively pure salt for the first step and 60% for the esterification, or an over-all yield of nitroacetate ester of 34%, based on nitromethane.[3]

In an effort to improve these yields, a study of both the salt formation and the esterification procedures was undertaken in this laboratory. The first step contains an inherent disadvantage in that the salts of nitroacetic acid are unstable in aqueous base solution, decomposing to give the alkali metal salt of nitromethane and the corresponding alkali carbonate.[4,5] Consequently, there

$$KO_2N{=}CHCOOK + KOH \longrightarrow K^+CH_2NO_2^- + K_2CO_3$$

is an upper limit to the yield of dipotassium nitroacetate which can be obtained by the self-condensation of nitromethane in aqueous potassium hydroxide. It appeared that if the amount of water in the reaction system could be minimized, the decomposition of the nitroacetate salt could be lessened and higher yields obtained.

The ultraviolet absorption spectra of nitroacetate ion and its precursors, nitromethane and methazonate ion, have been determined under a variety of conditions[5] and the effect of *p*H on the position and intensity of the methazonate absorption band has been investigated.[6] An analytical method based on the ultraviolet absorption spectra of the various entities was developed for the determination of nitroacetate in mixtures. This method is described further in the Experimental section.

Application of the optical analytical method to the study of the reaction of nitromethane with potassium hydroxide in various alcohols showed that when the condensation is carried out in *n*-butanol, yields of dipotassium nitroacetate of from 80–90% can be obtained. Results found using various solvents are listed in Table I.

TABLE I

Effect of Solvent on the Reaction of Nitromethane with Potassium Hydroxide

Mole Ratio of KOH/CH_3NO_2, 4/1

Solvent	Max. Reaction Temp.	Reflux Time, Hr.	Yield, % Nitroacetate (±2%)	Yield, % Methazonate
50% aq. KOH	118	25 min.	51	0
CH_3OH	73	38.3	0	17[a]
C_2H_5OH	95	23.25	0	81
C_4H_9OH[b]	118	20	84	3
n-Hexanol	142	20	83	0

[a] Recovered some material which had a λ_{max} of 288 mμ in 1*N* KOH. [b] When potassium butoxide was substituted for potassium hydroxide, no dipotassium nitroacetate was formed, but high yields (90–100%) of potassium methazonate were recovered.

Further studies of the reaction in butanolic potassium hydroxide gave the results shown in Table II.

The crude solids obtained from the reaction mixtures are always contaminated with varying amounts of alkali, alcohol, and unconverted potassium methazonate. However, they may be recrystal-

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(2) W. Steinkopf, *Ber.*, **42**, 3925 (1909).

(3) H. Feuer, H. B. Hass, and K. S. Warren, *J. Am. Chem. Soc.*, **71**, 3078 (1949).

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TABLE II

EFFECT OF REFLUX TIME ON REACTION OF NITROMETHANE AND POTASSIUM HYDROXIDE IN BUTANOL

Mole Ratio KOH/CH_3NO_2, 4/1

Reflux Time, Hr.	Yield, % Nitroacetate (±2%)	Yield, % Methazonate
6	63	33
9.5	71	31
12.4	80	5
15	84[a,b]	5
17	83[c]	4
20	84	3
33.25	77	0

[a] Average of three experiments. [b] For six experiments with discontinuous heating at reflux for 15 hr. (mixture allowed to stand at room temperature overnight; heating resumed next morning), the average yield of nitroacetate was 90%. [c] Average of two experiments.

lized from hot aqueous alkali to give average overall yields of relatively pure dipotassium nitroacetate of 71–77% based on nitromethane.

Preparation of methyl nitroacetate. The previously recommended procedure for the conversion of dipotassium nitroacetate to methyl nitroacetate requires reaction with concentrated sulfuric acid at from −50 to −60° for 24 hours, followed by standing at room temperature for 144 hours before isolation of the product, in order to obtain 60% yields of ester.[3] It has now been found that yields of 60–66% methyl nitroacetate can be obtained if the acidification is carried out at from −5 to −10° for 17 hours and the reaction mixture is allowed to stand at room temperature for 2 hours prior to workup. In agreement with Feuer *et al.*,[3] it was found that the omission of anhydrous sodium sulfate or use of less than 2 moles of sulfuric acid per mole of dipotassium nitroacetate gave much lower yields of ester.

In addition, the procedure used by Feuer *et al.*[3] for the isolation of methyl nitroacetate was modified. We obtained considerably better yields of the ester by extracting the excess sulfuric acid with water before distillation rather than by neutralization of the acid with aqueous sodium carbonate. This averts losses of the ester to the aqueous layer as the salt (K_a of ethyl nitroacetate is 1.4×10^{-6}).[7]

EXPERIMENTAL[8]

Spectral analysis.[9] Reference samples of dipotassium nitroacetate, methazonic acid, and nitroacetonitrile were prepared, and their absorption maxima and specific extinction coefficients were determined in water and 1*N* potassium hydroxide. The results are given in Table III. On standing in 1*N* potassium hydroxide for two weeks, the absorption maximum of nitroacetonitrile shifted from 288 mμ to 278 mμ, indicating gradual conversion to dipotassium nitroacetate. In water, no shift in the absorption maximum was observed after two weeks' standing, but the specific extinction coefficient decreased markedly. It is to be noted that the λ_{max} of methazonic acid in potassium hydroxide solution shifts from 298 mμ at a *p*H of 10 to 310 mμ in 1*N* potassium hydroxide.[10]

TABLE III

ULTRAVIOLET ABSORPTION OF DIPOTASSIUM NITROACETATE AND ITS PRECURSORS

Compound	Solvent	λ_{max}, mμ	$k = \frac{D^a}{c}$
Dipotassium nitroacetate	Water	None[b]	—
	1*N* KOH	276	60.6
Methazonic acid	Water	298	80.0
	Dil. KOH (*p*H 10)	298	115.3
	1*N* KOH	310	197.3
	1*N* KOH	276[c]	45.0
Nitroacetonitrile (initial)	Water	288	140
	1*N* KOH	288	132
(After standing 2 weeks)	Water	288	87
	1*N* KOH	278	112

[a] Specific extinction coefficient; $D = kcl$ where l is in cm., c in g./l. [b] λ_{max} at 276 fades within seconds. [c] This value is not λ_{max} but the absorption of methazonate at this λ.

The values of the specific extinction coefficients are somewhat uncertain since they depend on the purity of the samples used for calibration.

The crude reaction products were analyzed by determining the concentration of potassium methazonate at 298 mμ in aqueous solutions having a *p*H of 10.0, followed by correcting the absorbance of the sample in 1*N* potassium hydroxide at 276 mμ for the absorbance of the methazonate and subsequent calculation of the dipotassium nitroacetate concentrations. No evidence for the presence of nitroacetonitrile was observed. Preparation of synthetic mixtures of methazonate, nitroacetonitrile, and nitroacetate and subsequent analysis indicated that the accuracy of the method was 2% for nitroacetate when the amount of methazonate present was less than 10% of the total material.

Apparatus and method. Spectral measurements were made using a Beckman Model DK recording spectrophotometer.

(7) H. Ley and A. Hantzsch, *Ber.*, **39**, 3149 (1906).

(8) All melting and boiling points are reported uncorrected.

(9) We are indebted to Mr. C. T. Desmond of these laboratories for the development of the ultraviolet spectral method.

(10) Other investigators[6] have noted that methazonate salts exhibited only one very pronounced ultraviolet absorption peak with λ_{max} at 298 mμ, and that absorption of methazonate ion at 298 mμ obeys Beer's law only at a *p*H of 10.5 or higher. At *p*H 11 to 11.5, they found a value of ε for ammonium methazonate in sodium hydroxide of 17,840. They made no mention of a λ_{max} shift at higher *p*H values. In this laboratory, the ε value for methazonic acid in 1*N* potassium hydroxide at λ_{max} = 310 mμ was 28,086; at λ_{max} = 298, *p*H = 10, ε was 16,407. Recent evidence has shown that methazonic acid forms a disodium salt.[11] λ_{max} at 298 is undoubtedly due to the monopotassium salt (I), while that observed at 310 mμ may be due to the dipotassium salt (II).

$O_2NCH_2CH{=}NOK$ (I) $\qquad$ $K{-}ON{=}CH{-}CH{=}NO_2K$ (II)

(11) D. J. Morgan, *J. Org. Chem.*, **23**, 1069 (1958).

The *p*H values were measured with a Leeds-Northrup *p*H meter having a Leeds-Northrup Standard 1199-30 calomel reference electrode and a Leeds-Northrup Standard 1199-31 glass electrode. Measurements were referred to standards prepared from Coleman Buffer tablets.

The dilutions used were approximately 1×10^{-2} g./l. They were allowed to stand for 1 hour after preparation before the absorbance was measured to allow for complete hydrolysis of dipotassium nitroacetate in the aqueous solutions of *p*H 10. The glassware used for the sample dilutions was caustic-free.

Methazonic acid. This compound was prepared by a modification of the method of Reid and Köhler.[12] In the reaction flask were placed 40 g. (1 mole) of sodium hydroxide and 80 ml. of water. After the resulting solution had cooled to 48°, 40 g. (0.653 mole) of distilled nitromethane was added, with vigorous stirring, at a rate designed to keep the reaction temperature between 45 and 50°. The addition took 1.5 hour.

The deep amber-colored solution was then cooled to 0° and acidified by the dropwise addition of 85 ml. of concentrated hydrochloric acid. The reaction temperature was maintained at 0 to +5° throughout this addition, which took 44 min. Upon reaching an acid *p*H value, the solution changed color from amber to bright yellow, and a solid precipitated. This solid was collected by immediate filtration, pressed on a clay plate, and taken up in 200 ml. of ethyl ether. The ether solution was dried over anhydrous calcium chloride overnight, filtered, and evaporated to dryness *in vacuo* without heating. The resulting bright orange solid weighed 17.0 g., representing a 50% yield of crude methazonic acid. A portion of the solid was recrystallized from hot chloroform to give yellow needles; m.p. 70–72°.[13,14]

Anal. Calcd. for $C_2H_4O_3N_2$: N.E. 104.07. Found: N.E. 105.3.

The material is very unstable. It decomposes to a red resin within 3 days even when stored below 0°.

Nitroacetonitrile. This material was made by the procedure of Ried and Köhler,[12] using 14.7 g. (0.141 mole) of recrystallized methazonic acid, 17.1 g. (0.145 mole) of freshly distilled thionyl chloride (b.p. 75°/atm.) and 80 ml. of absolute ethyl ether. There was obtained 3.7 g. (31% yield) of pale yellow nitroacetonitrile. This liquid, which could have contained some methazonic acid as an impurity, was used as a standard for the determination of nitroacetonitrile in crude nitroacetate samples.

Dipotassium nitroacetate. The analytical standard was prepared by the method of Feuer, Hass, and Warren.[3] A yield of 47.5% of fairly high purity material was obtained in two crops. A sample was recrystallized from the minimum amount of hot 50% aqueous potassium hydroxide, washed with methanol, and dried *in vacuo* at 100°.

Anal. Calcd. for $C_2HNO_4K_2$: K, 43.15; N, 7.73. Found: K, 42.8; N, 7.29.

Reactions in alcoholic potassium hydroxide. The studies of the effect of various conditions on the reaction of nitromethane with potassium hydroxide were carried out using similar procedures. Generally, the reactions were carried out in 1-, 2-, or 5-l. flasks fitted with air-driven, high speed stirrers. The reaction flasks were also fitted with reflux condensers, dropping funnels, and thermowells.

Potassium butoxide was prepared by adding freshly cut slivers of potassium to an excess of distilled *n*-butanol with vigorous stirring under a nitrogen purge. The resulting solutions were heated at 96° for 2 hours to insure complete reaction, and the reaction with nitromethane was carried out in the same system.

A representative reaction procedure is described below. Results of the various studies are given in the tables.

In a 2-l. creased flask was placed 705 g. of a 15.9% solution of potassium hydroxide in *n*-butanol. Nitromethane (31 g., 0.5 mole) was added dropwise with vigorous stirring over a 25-minute period. The temperature rose from 30 to 49° during the addition. The mixture was then warmed to reflux in a 58-minute period and heated at reflux (117 to 120°) for 15 hours.

The reaction mixture was cooled, and the pale yellow solid product was removed by filtration (sintered glass filter) washed with methanol, crushed, and dried in a vacuum desiccator for 8 hr. The material was powdered and dried in a vacuum oven at 60°/1 mm. for 7.5 hr. The dried material (66.3 g.) was off-white, and contained 62% (by ultraviolet analysis; 41.1 g., 0.226 mole) of dipotassium nitroacetate and 1% (0.66 g., 0.006 mole) of potassium methazonate, corresponding to yields of 91% and 2%, respectively, based on nitromethane.

Recrystallization of crude dipotassium nitroacetate. There was dissolved 472 g. of crude reaction product, which contained 319 g. of dipotassium nitroacetate, in hot 50% aqueous potassium hydroxide. The mixture was cooled in an ice bath to yield two crops of silky white needles. The solid was collected by filtration, washed with methanol, and dried in the vacuum oven at 90°/1 mm. for 5 hours. The crops weighed 230 g. and 41 g., respectively, and had purities of 100% and 98% as dipotassium nitroacetate. This represented a recovery of 85%.

Methyl nitroacetate. To 90.5 g. (0.5 mole) of 100% pure dipotassium nitroacetate in a jacketed kettle there were added 600 ml. (471 g., 14.69 moles) of methanol and 15 g. (0.11 mole) of anhydrous sodium sulfate. The flask contents were cooled to −11° by circulating brine through the outer jacket while stirring the cream-colored slurry. One hundred g. of 98% sulfuric acid was added dropwise to the stirred mixture over a period of 2.1 hours. The resulting white slurry was stirred at −5 to −11° for 17 hours, then for 2.3 hours at room temperature. The precipitated white solid was filtered, washed with methanol, and discarded. The excess methanol was stripped at room temperature from the amber-colored filtrate at reduced pressure. The oily residue was shaken with 150 ml. of methylene chloride and 100 ml. of water. The resulting layers (a light yellow, organic layer, and a deep amber water layer) were separated and the organic layer was washed with 100 ml. of water. The aqueous washings were combined, extracted with 50 ml. of ether, and discarded. The combined organic layers were dried over anhydrous sodium sulfate and the solvent was distilled through a 30 × 180 mm., glass ring-packed column at atmospheric pressure. Vacuum distillation of the residue from a smaller flask *via* the same column (heated) gave 39.3 g. (0.33 mole, 66% yield) of methyl nitroacetate, boiling at 46–47°/0.8 mm.; n_D^{20} 1.4260 (lit.[3] gives b.p. 93–94°/15 mm., n_D^{20} 1.4245).

Anal. Calcd. for $C_3H_5O_4N$: N, 11.77; neut. equiv. 119. Found: N, 11.98; neut. equiv. 119.

Acknowledgments. We are indebted to Mr. J. E. Free for the determination of the spectral data and to Mr. J. S. Bodenschatz for the elemental analyses. The assistance of Mr. R. G. Lowther with the experimental work is gratefully acknowledged.

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Preparation of *o*-Dibenzoylbenzene and *o*-Dibenzylbenzene

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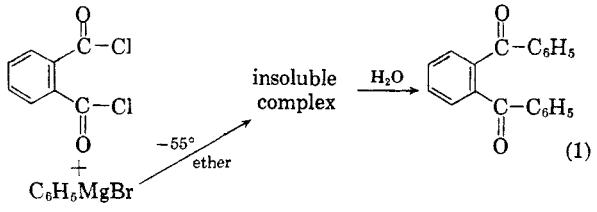
o-Disubstituted benzene derivatives are frequently difficult to prepare, and often cannot be synthesized by conventional methods. No convenient methods have been reported for the preparation of the useful compounds, *o*-dibenzoylbenzene and *o*-dibenzylbenzene. Since it was desired to obtain substantial quantities of these compounds, a number of methods for their preparation were investigated. The most satisfactory methods found are reported here.

Although the yield is poor (32%) in the method given for the preparation of *o*-dibenzoylbenzene, the procedure involves a simple reaction using cheap, commercially available starting materials. The reaction was carried out by adding phenylmagnesium bromide to a solution of phthaloyl chloride in ether at −55° (Equation 1). The product forms an ether insoluble complex with magnesium bromide. The side products are largely removed

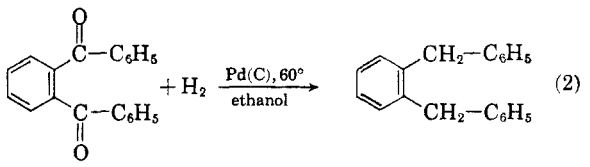


(1)

by decanting the ether solution from the complex. Addition of water liberates the *o*-dibenzoylbenzene from the complex.

The preparation of *o*-dibenzoylbenzene from phthaloyl chloride and phenylmagnesium bromide (unreported yield) has been carried out previously,[1] but the preparation could not be repeated satisfactorily. Cason and Reist[2] have shown that succinyl dichloride gives reactions with ethylmagnesium bromide characteristic of the unsymmetrical form at room temperature and the symmetrical form at low temperature. It had been hoped that *o*-dibenzoylbenzene could be prepared by the reaction of diphenylcadmium with phthaloyl chloride,[3] but the principal product of the reaction was diphenylphthalide.

It was found that *o*-dibenzylbenzene can be conveniently prepared by reducing *o*-dibenzoylbenzene with hydrogen in the presence of palladium on charcoal (Equation 2). *o*-Dibenzylbenzene has usually been obtained previously from the complex



(2)

mixture resulting from the reaction of benzyl chloride and diphenylmethane in the presence of aluminum chloride.[4]

EXPERIMENTAL

o-Dibenzoylbenzene. A solution containing 1.11 mol. phenylmagnesium bromide and 1000 ml. ether was prepared in the usual manner. This solution (without cooling) was added over a period of 15 min. to a stirred mixture of 107.6 g. (0.53 mol.) phthaloyl chloride (Eastman Organic Chemical Co., practical grade) and 1000 ml. anhydrous ether, which was cooled in a Dry Ice–trichloroethylene bath. The temperature in the reaction vessel was about −55°. During the addition, a solid separated from the solution. (A powerful stirred was found necessary to keep the mixture agitated.) After the addition was complete, the low temperature bath was removed and the mixture was allowed to warm to room temperature while being stirred.

The ether solution was decanted from the solid, 2000 ml. technical ether was added to the complex, and then the solid complex was decomposed by adding 1000 ml. water containing 5 ml. acetic acid. The ether solution was separated, and then washed with 500-ml. portions of water, 5% sodium bicarbonate solution, and water. Ether was added as necessary to keep the product in solution. After drying the solution with magnesium sulfate, the bulk of the ether was removed. *o*-Dibenzoylbenzene separated in almost pure form, in a yield of 45.7 g. (32%), m.p. 146–147°. The crystals contained a very small amount of highly colored material which was difficult to remove. This product was found to be suitable for most purposes. Recrystallization from ethanol was found to be convenient, but the product was yellow with m.p. 147.6–148.5°. Pure *o*-dibenzoylbenzene, m.p. 147.6–148.8° (lit.,[5] m.p. 148°), was obtained by clarifying and recrystallizing the compound in heptane-acetone.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.92; H, 4.89. Found: C, 84.08; H, 5.07.

o-Dibenzylbenzene. A mixture of 23 g. (0.081 mol.) *o*-dibenzoylbenzene (m.p. 146–147°), 4 g. palladium (5%) on charcoal and 200 ml. absolute ethanol was placed in a Parr low-pressure hydrogenation unit. After heating the reaction vessel to 60°, the hydrogenation was started using an initial pressure of 44 p.s.i. In 10 hr., the calculated amount of hydrogen was taken up, and the hydrogenation was stopped. Since the hydrogen uptake continued slowly beyond the calculated amount, the yield was diminished if the reaction was allowed to continue.

The reaction mixture was heated to boiling and then filtered while hot. After allowing the mixture to cool to room temperature, the solution was placed in a refrigerator at 6°. The crystals were collected, and recrystallized from absolute ethanol to give 13.9 g. (0.054 mol.) *o*-dibenzylbenzene (66%) as white needles with m.p. 78.7–79.4° (lit.,[3] m.p. 78°).

Anal. Calcd. for $C_{20}H_{18}$: C, 92.98; H, 7.07. Found: C, 92.73; H, 6.86.

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Convenient Synthesis of Vinylcyclohexane-α-*d*

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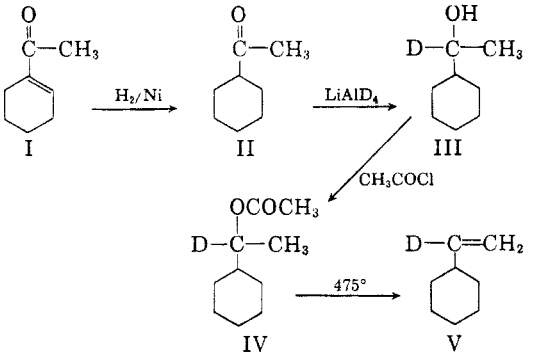
A recent note[3] on the preparation of methyl cyclohexyl ketone has prompted us to report some results we have obtained in the course of preparing the monomer vinylcyclohexane-α-*d* (V).

A convenient laboratory preparation of the deuterated vinylcyclohexane (V) utilized ketone (II) as the starting material.[4] Vinylcyclohexane has previously been reported by Van Derby and Kooyman, prepared by preparation of methyl cyclohexylcarbinol by reaction of cyclohexylmagnesium bromide and acetaldehyde, followed by acetylation and pyrolysis. The ketone (II) had also been prepared by oxidation of 1-cyclohexylethanol[5,6] and more recently by the catalytic reduction of methyl cyclohexen-3-yl ketone.[2]

The ketone (II) was readily accessible from the reduction of methyl cyclohexen-1-yl ketone[5,7] (I). Reduction was carried out in an 86% yield by



hydrogenation at room temperature with Raney Nickel W-2[8] as the catalyst. Reduction with lithium aluminum deuteride gave the deuterated alcohol (III) in 91.5% yield which was smoothly acetylated to the deutero acetate (IV) in a 95.3% yield. Pyrolysis of the acetate (IV) gave the desired deuterated monomer (V) after careful fractionation (71%). Fractionations were followed by vapor phase chromatography to insure purity of the monomer. Vinylcyclohexane[4] (V. D = H) was prepared in analogous fashion using lithium aluminum hydride for the reduction of the ketone (II).

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(8) R. Mozingo, *Org. Syntheses*, **Coll. Vol. III**, 181 (1955).

EXPERIMENTAL

Methyl cyclohexyl ketone (II). A mixture of methyl cyclohexen-1-yl ketone,[6] 17.5 g. (0.138 mol.), 75 ml. of methanol and 1 g. of W-2 Raney Nickel catalyst[7] in a rocking autoclave pressurized to 500 lbs./in.[2] was shaken at room temperature for 20–30 min. after which no further hydrogen was absorbed. The catalyst and methanol were removed and distillation of the residual oil furnished 15.2 g. (86%), b.p. 66° (12 mm.), n_D^{26} 1.4491, of methyl cyclohexyl ketone (reported[6] b.p. 182.5–184.5° (676 mm.), $n_D^{25.9}$ 1.44955).

1-Cyclohexylethanol-1-d (III). To a solution of 3.3 g. (6.078 mol.) of lithium aluminum deuteride[9] in 300 ml. of absolute ethyl ether was added dropwise 37.9 g. (0.3 mol.) of II in 100 ml. of absolute ethyl ether. Upon completion of the addition, the mixture was refluxed for 1 hr. and then decomposed with water. The ether was removed and the residual oil was distilled yielding 35.5 g. of carbinol (91.5%), b.p. 65° (3.9 mm.), n_D^{25} 1.4632.

Anal. Calcd. for $C_8H_{15}DO$: C, 74.35; H + D, 13.26. Found: C, 74.31; H + D, 13.23, 0.891 deuterium atom/mol.[10]

1-Cyclohexylethyl-1-d acetate (IV). 1-Cyclohexylethanol-1-*d*, 33.0 g. (0.26 mol.), (III), was added dropwise to 30 g. of acetyl chloride at a rate to maintain reflux and the mixture was refluxed for 2 additional hr. Excess acetyl chloride was removed and the residual oil was distilled to yield 41.6 g. (95.3%), b.p. 67° (4.3 mm.), n_D^{25} 1.4445, of acetate.

Anal. Calcd. for $C_{10}H_{17}DO_2$: C, 70.13; H + D, 11.18. Found: C, 70.29; H + D, 11.28; 0.942 deuterium atom/mol.[9]

Vinylcyclohexane-α-d (V). 1-Cyclohexylethyl-1-*d* acetate, 34.5 g. (0.20 mol.), (IV), was pyrolyzed[11] by dropping the liquid at a rate of 8–12 drops per min. through a 12″ tube packed with Pyrex glass Raschig rings at 475° under a nitrogen atmosphere. The pyrolyzate was washed with aqueous sodium bicarbonate and water and dried over anhydrous sodium sulfate. Distillation in a seventy-five plate concentric tube column yielded 17.8 g. (80%), boiling at 127–129°, n_D^{25} 1.4459, of crude olefin. Careful distillation yielded 12.7 g. (71%), boiling at 127.5–128°, n_D^{25} 1.4441, of vinylcyclohexane-α-*d*. The product was pure as determined by vapor phase chromatography. It absorbed strongly at 11.0 μ in the infrared which indicated that it was a terminal olefin.

Anal. Calcd. for $C_8H_{13}D$: C, 86.40; H + D, 13.60. Found: C, 86.13; H + D, 13.62; 0.889 deuterium atom/mol.[10]

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(9) Purchased from Metal Hydrides, Inc., Beverly, Mass.

(10) Deuterium analyses were performed by Professor D. B. Denney of Rutgers, the State University of New Jersey, by means of a mass spectrograph.

(11) C. G. Overberger and D. Tanner, *J. Am. Chem. Soc.*, **77**, 369 (1955).

Preparation and Properties of 1-Phenyl-4-methyl-2-penten-1-one

Kurt Kulka, Robert J. Eiserle, James A. Rogers, Jr., and Fred W. Richter

Received March 23, 1959

The recent availability of isobutyraldehyde in commercial quantities through the oxo process[1]

(1) H. J. Hagemeyer and G. C. DeCroes, *The Chemistry of Isobutyraldehyde and its Derivatives*, Tennessee Eastman Co., Kingsport, Tenn., 3 (1953).

prompted us to prepare a sample of isobutylideneacetophenone for investigation of its organoleptic properties. The reaction of isobutyraldehyde with acetophenone under alkaline conditions yielded a small amount of unreacted acetophenone, a liquid boiling at 130° at 8 mm. and, as the main product, a solid. The latter, white, odorless crystals, melted at 144.5–145° after repeated recrystallizations from a methanol-benzene mixture.

The liquid was not the aldol since water was not produced upon heating in the presence of iodine or oxalic acid, but the starting material was recovered. A carbon-hydrogen ratio determination of the liquid and the solid compounds gave identical results. Consequently, we investigated the possibility that the solid and the liquid reaction products were geometrical isomers, or that the double bond in the side chain of either compound was out of conjugation with the carbonyl group.

The structure of the liquid isomer was proven by its reduction products which were previously reported in the literature. Thus catalytic hydrogenation with Raney nickel in methanol solution at 50 p.s.i. yielded 1-phenyl-4-methyl-pentan-1-one and 1-phenyl-4-methylpentan-1-ol. By potassium borohydride reduction and also by Meerwein, Ponndorf-Verley reduction the unsaturated alcohol 1-phenyl-4-methyl-2-penten-1-ol was obtained. This alcohol was reduced by catalytic hydrogenation with Raney nickel in methanol solution at 50 p.s.i. to 1-phenyl-4-methylpentane. As these compounds were previously obtained by more complicated synthesis such as Grignard reactions, the above reductions are novel and simple ways for their preparation.

Attempted reduction of the solid compound at 50 p.s.i. in various solvent systems, with various catalysts including Raney nickel, Adams platinum oxide and palladium on charcoal were unsuccessful. Bromination in carbon tetrachloride and in hexane solution did not proceed satisfactorily. Hydrogen bromide was given off and resins were formed. The absence of a double bond in the solid compound became obvious and suggested the possibility that it was a dimer having the uncommon cyclobutane structure similar to that in truxillic acid which is formed by the dimerization of cinnamic acid. Molecular weight determinations of the liquid as well as the solid reaction products by a modified Rast method gave evidence that the liquid was the monomer and the solid a dimer of 1-phenyl-4-methyl-2-penten-1-one.

Prior to this paper, the crystalline dimer was erroneously defined as the monomer by Thoms and Kahre[2]; the actual monomer was not reported.

It was of interest to prepare these compounds by other syntheses. Isobutyraldehyde was treated with malonic acid in pyridine solution using piperidine as the catalyst to obtain 4-methyl-2-pentenoic acid which was converted to its acid chloride. The acid chloride was treated with benzene in a Friedel-Crafts synthesis to give mainly the liquid monomer and a small amount of the solid dimer. Knoevenagel reaction of benzoylacetic acid with isobutyraldehyde in pyridine solution, using piperidine as the catalyst, gave only the liquid monomer after decarboxylation.

Depolymerization of the dimer to the monomer was accomplished by vacuum distillation in the presence of a catalytic amount of sodium acetate. Dimerization of the liquid monomer was carried out under identical conditions as in the previously described condensation, *i.e.*, in methanol solution using potassium hydroxide as the catalyst. It was further observed that the liquid on standing in a stoppered brown bottle over a prolonged period of time was partly dimerized.

The degree of reactivity of these two compounds is best demonstrated by the fact that it took 480 hr. for the solid and only 24 hr. for the liquid to react completely with hydroxylamine hydrochloride at room temperature. Molecular weight determinations of these two oximes by a modified Rast method showed the first to be the oxime of a dimer and the latter to be the oxime of the monomer.

The next higher member of this series of branched-chain, unsaturated ketones (1-phenyl-5-methyl-2-hexen-1-one) was obtained from the reaction of acetophenone with isovaleraldehyde under identical (alkaline) conditions. In this reaction only the liquid monomer was formed.

Infrared curves of 1-phenyl-4-methyl-2-penten-1-one (monomer and dimer) were run on a Perkin-Elmer Model 21 spectrophotometer with sodium chloride prism. The liquid ketone gave the normal spectrum for a conjugated unsaturated actophenone except for a splitting of the monosubstituted phenyl peak in the 750 cm.$^{-1}$ range. The recrystallized solid ketone melted film run on a hot stage cell showed aromatic carbon-carbon double bond and carbonyl stretching bands and monosubstituted phenyl ring peaks. It lacked aliphatic carbon-carbon double bond stretching peaks, indicating saturation of the *trans* double bond. A medium intensity peak at 880 cm.$^{-1}$ can be assigned to the cyclobutane ring which according to Reid and Sack[3] is the expected range for 1,2,3,4-tetrasubstituted cyclobutane compounds.

Thus the spectrum and previously reported experimental findings indicate the structure of our solid to be either of the two structures following:

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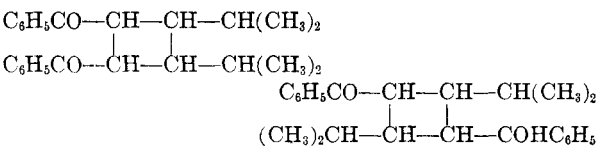
(2) H. Thoms and H. Kahre, *Arch. Pharm.*, **263**, 251 (1925).

(3) E. B. Reid and M. Sack, *J. Am. Chem. Soc.*, **73**, 1985 (1951).



EXPERIMENTAL

All boiling points and melting points are uncorrected.

Dimer of 1-phenyl-4-methyl-2-penten-1-one (I). During 1.5 hr. at a temperature of 50°, 72.1 g. isobutyraldehyde was added to a well agitated solution of 120.7 g. acetophenone, 17 g. potassium hydroxide (reagent grade), 125 ml. methanol, and 125 ml. water. On continuing agitation at 48–50° a white solid formed. After 3.5 hr. the reaction mass was cooled to room temperature neutralized with acetic acid, and filtered on a Buchner funnel. The separated solid was washed with 100 ml. methanol and dried; it weighed 107 g. (61% yield). After 3 recrystallizations from a mixture of 70% methanol and 30% benzene, it gave a constant melting point of 144.5–145°, the dimer of 1-phenyl-4-methyl-2-penten-1-one (I). The liquid organic filtrate combined with the above methanol was fractionated through a 40-cm. Vigreux column yielding 10.5 g. unreacted acetophenone and 38 g. of a liquid boiling 133–134° at 8 mm. n_D^{20}: 1.5385, which on redistillation boiled at 130° at 8 mm. n_D^{20}: 1.5385. This liquid was identified as the *monomer of 1-phenyl-4-methyl-2-penten-1-one* (II). The distillation residue (12.2 g.) after recrystallization from a methanol-benzene mixture was found to be identical with I having a melting point of: 144.5–145°.

Anal. Calcd. for I: $C_{24}H_{18}O_2$: C, 82.2; H, 8.1. Found: C, 81.6; H, 7.8.

Anal. Calcd. for II: $C_{12}H_{14}O$: C, 82.2; H, 8.1. Found: C, 83; H, 7.86.

Molecular weight determination of I. The modified Rast procedure described by Becker[4] for the semimicro molecular weight determination was applied in principle. When the solution of the organic compound in camphor, prepared as advised by Becker, was used, erroneous and nonreproducible results were obtained, probably due to partial depolymerization of the dimer. The compound to be analyzed was, therefore, thoroughly mixed with the camphor. As five consecutive experiments gave almost identical results, we consider this abbreviation of the procedure to give sufficiently accurate results. Calculated molecular weight: 348, Found: 344 (average).

Determination of the carbonyl content of I *and* II *using hydroxylamine hydrochloride.* The method described by Guenther[5] was employed: Thus 0.5421 g. of I was treated at room temperature with 35 ml. of 0.5*N* hydroxylamine hydrochloride solution, and the liberated hydrochloric acid titrated with 0.5*N* sodium hydroxide solution. The following ketone contents were obtained: After 24 hr.: 32.3%; after 384 hr.: 93.3% and after 480 hr.: 99.9%. In the same way 0.5384 g. of II was treated as I, but gave after 24 hr. a ketone content of 98.2%.

Dioxime of I. The dioxime was prepared according to a procedure described by Vavon and Anziani:[6] Thus 8.9 g. of I, 10 g. hydroxylamine hydrochloride, 70 g. ethanol, 30 g. water, and 3.6 g. sodium hydroxide (reagent grade) were refluxed for 24 hr. The solution was poured into 100 ml. water, the precipitated crystals collected on a Buchner funnel, and recrystallized 4 times from 80% ethanol to a constant m.p. of 184–185°.

Anal. Calcd. for $C_{24}H_{30}N_2O_2$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.13; H, 8.06; N, 7.39.

Oxime of II. The above procedure was followed with the exception that the solution was permitted to stand at room temperature (25–30°) for 24 hr. The oxime, recrystallized 4 times from 80% ethanol, had an m.p. of 57°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.12; H, 8.02; N, 7.41.

Depolymerization of I *to* II. A mixture of 50 g. of I and 1.5 g. anhydrous sodium acetate (reagent grade) was heated in a vacuum of 8 mm. At 185° the mixture became completely liquid, and the depolymerization was considered complete. On distillation without a column, 41 g. were collected, boiling from 130–135° at 8 mm. n_D^{20}: 1.5392. On redistillation through a 40-cm. Vigreux column, the ketone (II) boiled at 130° at 8 mm.; n_D^{20}: 1.5385.

Dimerization of II *to* I. At a temperature of 50°, 70 g. of I was agitated for 45 min. with a solution of 6 g. potassium hydroxide in 70 g. methanol and 70 g. water. The solid was collected on a Buchner funnel and recrystallized twice from methanol. The resulting white crystals had an m.p. of 143–144°. A mixed melting point with the original ketone (I) showed no depression.

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(4) E. I. Becker, *Chemist Analyst*, **40**, 80 (1951).

(5) E. Guenther, *The Essential Oils*, Vol. I, D. Van Nostrand Co., N. Y., 1948, p. 286.

(6) G. Vavon and P. Anziani, *Bull. soc. chim.*, **5**, 2026 (1937).

Synthesis of 2-Phenyltriphenylene and 2,6,10-Trimethyltriphenylene

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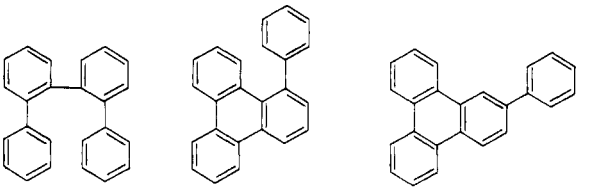
Hansch and Geiger[1] recently prepared a phenyltriphenylene by cyclodehydrogenation of 2,2′-diphenylbiphenyl (I). Although 1-phenyltriphenylene (II) might be expected from this reaction, the authors considered rearrangement to the 2-isomer (III) very likely. In the course of related work in



I II III

this laboratory, 2-phenyltriphenylene was prepared by an unequivocal method, an adaptation of the Rapson synthesis as improved by Barker, Emmerson, and Periam.[2] The sample was compared with one kindly supplied by Dr. Corwin Hansch and the physical properties including infrared spectra were found to be identical. The melting point of a mixture sample was not depressed. It may therefore be concluded that the phenyl group does migrate under the cyclodehydrogenation conditions employed in ref. 1.

(1) C. Hansch and C. F. Geiger, *J. Org. Chem.*, **23**, 477 (1958).

(2) C. C. Barker, R. G. Emmerson and J. D. Periam, *J. Chem. Soc.*, 1077 (1958).

The ultraviolet spectrum of 2-phenyltriphenylene does not exhibit as much fine structure as that of triphenylene or its alkyl derivatives.[2-4]

In the course of our study a sample of 2,6,10-trimethyltriphenylene was prepared by dehydrogenation of the product obtained by self-condensation of 4-methylcyclohexanone under conditions employed in the Mannich triphenylene synthesis.[5] Although the spectrum of this compound was reported recently,[2] no details of its preparation were given. The procedure employed by us is therefore included here.

EXPERIMENTAL

2-(1'-Cyclohexenyl)-1-p-biphenylylcyclohexanol. To a solution of 0.80 moles of *n*-butyllithium[6] was added in 5 to 10 g. portions 167 g. of 4-bromobiphenyl while the temperature was held below 0°. The mixture was then warmed to 5° and stirred for 30 min. (until all the 4-bromobiphenyl had dissolved). A solution of 133 g. of 2-(1'-cyclohexenyl)-cyclohexanone in 200 ml. of ether was added while the temperature was held just below 5° with external cooling. The mixture was allowed to warm to room temperature and stand overnight. The ethereal solution was treated with 1*N* hydrochloric acid, separated, and dried over anhydrous sodium sulfate. Ether and volatile material was removed by distillation, eventually on a steam bath at water pump pressure. The residual crude oil (170 g.) was used directly in the next step.

2-(1',2'-Epoxycyclohexyl)-1-p-biphenylylcyclohexanol. To a solution of 160 g. of the crude oil above in 400 ml. of ether cooled to −40° was slowly added 1.25 l. of the ether solution of perphthalic acid.[7] After 3 hr. at −40° the mixture was allowed to warm to +5° and was kept at that temperature for 16 hr. The resulting precipitate was separated; it contained only a small amount of desired product which remained after extraction with aqueous sodium bicarbonate. The ethereal solution was dried and the ether was evaporated. The oily residue was extracted with 250 ml. of ethanol at 5° and the residue was collected and washed with more cold ethanol. Yield: 82 g.; 35% based on 4-bromobiphenyl; m.p. 147–148°.

Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 81.46; H, 8.17.

2-Phenyltriphenylene. A solution of 70 g. of the epoxide in 400 ml. of acetic acid and 350 ml. of 48% hydrobromic acid was refluxed for 20 hr. The reaction mixture was poured into 3 l. of water, the product was extracted with benzene, and the benzene solution was washed with aqueous sodium bicarbonate and dried over sodium sulfate. The crude oil (5,6,7,8,9,10,11,12-octahydro-2-phenyltriphenylene) obtained after evaporation of the benzene was mixed with 15 g. of 5% palladium on charcoal and dehydrogenated at 300° for 6 hr. under nitrogen. The cooled product was extracted with 250 ml. of benzene. The benzene was evaporated and the residue slowly crystallized. Oily products were extracted with 200 ml. of petroleum ether (63–69°). Yield: 6.0 g.; m.p. 180–185°. The sample was further purified by chromatography in benzene on alumina and by recrystallization from 3:1 ethanol-benzene. M.p. 182–185° (lit.[1] 183–184°), small needles.

Anal. Calcd. for $C_{24}H_{16}$: C, 94.70; H, 5.30. Found: C, 94.82; H, 5.14. Ultraviolet maxima in 95% ethanol: 261.5 mμ (log ε, 4.91); 268.5 mμ (log ε, 4.96); 301 mμ (inflection, log ε, 4.37).

2,6,10-Trimethyltriphenylene. A mixture of 450 g. of 4-methylcyclohexanone with 1.4 l. of methanol containing 246 g. of concentrated sulfuric acid was refluxed for 12 hr. After dilution with 2.5 l. of methanol, crystals of 1,2,3,4,5,-6,7,8,9,10,11,12-dodecahydro-2,6,10-trimethyltriphenylene separated. These were collected and washed with acetone. Yield: 20 g.; 5%; m.p., 194–196° (lit.[3] 195°).

The dodecahydro compound was dehydrogenated like the 2-phenyl analog and the product was recrystallized from ethanol. Yield: 90%; m.p. 188–189° (lit.[3] 190°).

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(3) R. C. Hinton, F. G. Mann, and I. T. Millar, *J. Chem. Soc.*, 4704 (1958).

(4) Analogous effects are recorded in R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, New York, 1951, p. 19.

(5) C. Mannich, *Ber.*, **40**, 153 (1907).

(6) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(7) H. Bohme, *Org. Syntheses*, **Coll. Vol. III**, 619 (1955).

A Fifth Route to 1,2,3-Triphenylazulene[1a]

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1,2,3-Triphenylazulene was synthesized by Assony and Kharasch,[1b] in one step, in 25% yield, by the reaction of diphenylacetylene with 2,4-dinitrobenzenesulfenylchloride, and also in very low over-all yield by a nine-step synthesis from cycloheptanone. Battiste and Breslow[2] have recently synthesized the azulene by dehydration of a diphenylcyclopropenecarboxylic acid derivative, and Büchi[3] reports its formation by irradiation of solutions of diphenylacetylene.

This note reports the synthesis of this unique hydrocarbon by a fifth route, based on the azulene synthesis which was briefly communicated by Ziegler and Hafner[4,5] and by Hafner and Kaiser.[6]

The essential steps in the synthesis, which involves reaction of 1,2,3-triphenylcyclopentadiene with *N*-methylpyridinium iodide, have been formulated by Ziegler and Hafner[4,5] and Hafner and Kaiser[6] for other cases.

(1) (a) This work was carried out as an assigned project, suggested by Mr. Earl M. Evleth, in the organic synthesis course conducted by Professor Norman Kharasch in the fall of 1958. The interest and assistance of Mr. Evleth and Dr. Kharasch are gratefully acknowledged. (b) S. J. Assony, and N. Kharasch, *J. Am. Chem. Soc.*, **80**, 5978 (1958).

(2) M. Battiste and R. Breslow, Division of Organic Chemistry, American Chemical Society, Abstracts of papers presented at the Boston meeting, April 5, 1959.

(3) G. Büchi and E. W. Robb, personal communication to N. Kharasch, April (1959); *Chimia*, **12**, 282 (1958).

(4) H. Hafner, *Angew Chem.*, **70**, 419 (1958).

(5) K. Hafner, *Angew Chem.*, **67**, 301 (1950).

(6) K. Hafner and H. Kaiser, *Ann.*, **618**, 140 (1958).

The triphenylazulene was obtained in 20% overall yield and was shown to be identical with the product of Assony and Kharasch by its melting point, mixture melting point, and infrared spectrum.

EXPERIMENTAL

1,2,3-Triphenylcyclopentadiene (III) was prepared in 55% yield from 1,2,3-triphenylcyclopentadiol, by the method of Paulson.[7]

1,2,3-Triphenylazulene. To 1,2,3-triphenylcyclopentadiene (2 g., 0.007 mol.) was added 20 ml. diphenyl ether and sodium methoxide (0.3 g., 0.007 mol.). The mixture was heated to 70° under nitrogen. Generation of the triphenylcyclopentadienyl anion was indicated by the intense red color of the reaction mixture. Pyridium methiodide (2.0 g., 0.01 mol.) was added to the solution, causing a distinct darkening of the reaction mixture. The solution was refluxed 1 hr., when evolution of methylamine was noted. The reaction mixture was chromatographed on a column of alumina (20 × 2.5 cm.) using low boiling mixed alkanes as solvent and eluting with a 50%, by volume, mixture of benzene and mixed alkanes. A blue band developed, which, after elution and aspiration of the eluate to dryness, yielded a blue solid (0.5 g., 20%). Recrystallization from nitromethane gave the characteristic blue compound melting at 215.5°.

A mixture-melting point of the product and that prepared *via* the sulfenyl chloride–diphenylacetylene route showed no depression and the infrared spectra of the two samples, run consecutively, also exhibited no observable differences.

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(7) P. L. Paulson, *J. Am. Chem. Soc.*, **76**, 2187 (1957).

A New Route to 2,5-Dimethoxyphenylacetic Acid

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The mechanism of the amination of various halobenzenes in the presence of sodium amide and liquid ammonia has been elucidated by Roberts and co-workers.[1] Such aminations of halobenzenes which are nonactivated for nucleophilic substitution appear to involve a "benzyne" intermediate. With an explanation of the course of these reactions came a renewed interest in the further characterization of similar reactions and in the synthetic possibilities of such reactions. Thus Bunnett and Brotherton prepared a number of dialkylanilines by the reaction of bromobenzene with sodium amide and dialkylamines[2] and studied some reactions of "benzyne" and "α-naphthalyne";[3] Hrutfiord and Bunnett recognized the utility of such reactions in the synthesis of heterocyclic and homocyclic compounds.[4] Scardiglia and Roberts have extended earlier studies from their laboratory to include reactions of nonactivated aryl halides with various nucleophilic agents induced by alkali amides in liquid ammonia.[5] Additionally extensive characterization of similar reactions has been carried out by Huisgen and co-workers.[6] Recently Leake and Levine have reported the phenylation of ketones by reaction with phenyl halides and alkali amides.[7]

It seemed that an improved synthesis of 2,5-dimethoxyphenylacetic acid might be achieved by reactions presumably involving a "benzyne" intermediate. 2,5-Dimethoxyphenylacetic acid may be readily converted to homogentisic acid (2,5-dihydroxyphenylacetic acid), a compound of considerable biochemical interest. Studies of the nature and mode of formation of homogentisic acid in animals have provided many of the fundamental data on the intermediary metabolism of tyrosine and phenylalanine. A strong indication that homogentisic acid is an intermediate in the oxidative degradation of phenylalanine and tyrosine was first obtained from isotopic experiments.[8-11]

An improved synthesis of homogentisic acid was desirable. In the best published synthesis of this compound the synthesis of the intermediate 2,5-dimethoxyphenylacetic acid presents serious limitations to the synthesis of homogentisic acid itself since the over-all yield of the intermediate is 30–40% and reactions and work-up procedures are lengthy.[12] It seemed of considerable interest to attempt the synthesis of this intermediate using 2,5-dimethoxybromobenzene with appropriate nucleophiles under conditions where formation of a "benzyne" intermediate might be expected, *i.e.*, in the presence of a metal amide and liquid ammonia. Attempts to use diethyl malonate as a potential nucleophile with potassium amide and liquid ammonia were unsuccessful. However the

(1) J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith, and C. W. Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953); J. D. Roberts, D. A. Semenow, H. E. Simmons, and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

(2) J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **22**, 832 (1957).

(3) J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **23**, 904 (1958).

(4) B. F. Hrutfiord and J. F. Bunnett, *J. Am. Chem. Soc.*, **80**, 2021 (1958).

(5) F. Scardiglia and J. D. Roberts, *Tetrahedron*, **3**, 197 (1958).

(6) H. Konig and R. Huisgen, *Chem. Ber.*, **92**, 429 (1959); see also earlier publications in this series.

(7) W. W. Leake and R. Levine, *J. Am. Chem. Soc.*, **81**, 1169 (1959).

(8) S. Weinhouse and R. H. Millington, *J. Biol. Chem.*, **175**, 995 (1948); S. Weinhouse and R. H. Millington, *J. Biol. Chem.*, **181**, 645 (1949).

(9) B. Schepartz and S. Gurin, *J. Biol. Chem.*, **180**, 663 (1949).

(10) A. B. Lerner, *J. Biol. Chem.*, **181**, 281 (1949).

(11) R. G. Ravdin and D. I. Crandall, *J. Biol. Chem.*, **189**, 137 (1951).

(12) H. Wolkowitz and M. S. Dunn, *Biochemical Preparations*, Vol. **4**, W. W. Westerfeld, ed., J. Wiley and Sons, Inc., New York, 1955, p. 6.

isolation of 2,5-dimethoxyaniline in 12% yield indicated that a "benzyne" intermediate had indeed formed. To minimize the competing reaction, sodium amide in liquid ammonia[13] was used in subsequent experiments in slight molar excess to the bromo compound plus nucleophile.

An attempt to use ethyl acetate as a potential nucleophile was also unsuccessful. Examination of Fisher-Hirschfelder-Taylor models suggested that the formation of the products expected from reaction with diethyl malonate or ethyl acetate would be unlikely for steric reasons.

α-Sodio sodium acetate[14] was also tried as a nucleophile at the boiling points of the inert solvents *p*-xylene and tetrahydrofuran as well as at room temperature with 2,5-dimethoxybromobenzene itself as a suspending medium. The α-sodio sodium acetate appeared to be partially soluble in each of these reaction media but in no case could the product of interest be isolated.

When acetonitrile was tested as a potential nucleophile, the reaction mixture after work-up yielded 2,5-dimethoxyphenylacetic acid. While synthesis of this compound *via* the nitrile results in yields of approximately 10%, the reaction takes little time and work-up procedures are short. Thus the synthesis appears to hold promise for the synthesis of homogentisic acid labeled in the side chain for metabolic studies. In addition the reactions constitute a novel route to 2,5-dimethoxyphenylacetic acid.

EXPERIMENTAL

Materials. 2,5-Dimethoxybromobenzene (I) was prepared in approximately 60% yield by the methylation of bromohydroquinone employing conventional reaction conditions with dimethyl sulfate and sodium hydroxide. The product was obtained as a colorless oil which was identified by boiling point, analysis for C, H, and Br, and infrared analysis.[15]

Attempted reaction of I with diethyl malonate. Isolation of 2,5-dimethoxyaniline (II). To approximately 300 ml. of liquid ammonia (−77°) and 0.28 g. of ferric nitrate·9 H_2O, approximately 2 g. of potassium was added and the mixture stirred for 15 min. to form the catalyst (metallic iron) for the preparation of potassium amide. Additional potassium (43.4 g., 1.14 mol.) was then added with stirring. After evolution of hydrogen was complete, 19.2 g. of diethyl malonate (0.12 mol.) was added dropwise with stirring, followed by 21.7 g. of 2,5-dimethoxybromobenzene (0.1 mol.) and the temperature of the reaction mixture raised to approximately −30° for 1 hr. Enough 10% ammonium chloride was then carefully added to convert amide ion to ammonia and the ammonia was then distilled out of the reaction mixture at reduced pressure. The reaction mixture was extracted with diethyl ether, and the ether removed by distillation to leave a dark brown oil. The oil was fractionated by distillation under reduced pressure and partial characterization of minor fractions gave no indication that diethyl(2,5-dimethoxyphenyl)malonate had been formed. The major fraction which distilled at about 1 mm. from 80–90° and crystallized in the condenser was collected. This solid was further purified by sublimation to yield 1.8 g. (12%) of white, crystalline II, which melted at 74–76° (literature m.p. 80°[16]) and behaved as a typical amine.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.59; H, 7.23; N, 9.27.

The infrared spectrum supported the structure of the product.

Reaction of I with acetonitrile. Preparation of 2,5-dimethoxyphenylacetic acid (III). Reaction conditions were similar to those described above except that to one flask (−30°) containing 150 ml. of ammonia and 3.84 g. of sodium (0.17 mol.), 6.93 g. of acetonitrile (0.17 mol.) was added followed by the addition of 17.8 g. of 2,5-dimethoxybromobenzene (0.083 mol.). The contents of a second flask (−30°) containing initially 250 ml. of ammonia, 3.84 g. of sodium (0.17 mol.), and a catalytic amount of ferric nitrate·9 H_2O were then slowly flushed into the first flask. After complete transfer, which took approximately 30 min., the reaction mixture was covered with anhydrous diethyl ether and ammonium chloride added to liberate ammonia. To the reaction mixture more diethyl ether was added, and the ether was then removed from the ether extract by distillation, leaving a brown oil. This oil was then submitted to hydrolysis in twice its volume of concentrated hydrochloric acid for 4 hr. During hydrolysis a viscous oil separated, and after hydrolysis this oil was dissolved in 10% sodium carbonate. Acidification of the bicarbonate solution to *p*H 2 yielded a tan crystalline compound which was isolated in 15% yield (2.38 g). Purification of the tan product by sublimation and recrystallization resulted in 50–70% recovery of the tan product as a white, crystalline compound (III). III melted at 121.0–121.5° (literature m.p., 122–123°[12]) and the infrared spectrum supported the proposed structure.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.19; H, 6.13.

Acknowledgment. The authors wish to thank Professor J. F. Bunnett for acquainting them with the synthetic possibilities of reactions presumably involving a "benzyne" intermediate.

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(13) Sodium amide is less soluble in ammonia at −30° than is potassium amide.

(14) We wish to thank Ethyl Corp., New York, for a generous gift of this compound.

(15) Elemental analyses were performed by Weiler and Strauss, Microanalytical Laboratory; infrared analyses were made by the Division of Industrial Research, Washington State University.

(16) A. Blackhall and R. H. Thomson, *J. Chem. Soc.*, 3916 (1954).

Epoxidation of Cinnamaldehyde by Alkaline *tert*-Butyl Hydroperoxide

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An attempt was made to form an epoxide of cinnamaldehyde with alkaline hydrogen peroxide using the technique recently described for the epoxidation of acrolein and α-methylacrolein.[1] As the

(1) G. B. Payne, *J. Am. Chem. Soc.*, **81**, 4901 (1959); E. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921) obtained only acidic product from the attempted alkaline epoxidation of cinnamaldehyde.

major product appeared to be an organic peroxide rather than the desired epoxy aldehyde, the reaction was carried out with *tert*-butyl hydroperoxide as oxidant rather than hydrogen peroxide.

$$C_6H_5CH{=}CH{-}CHO + t\text{-}C_4H_9OOH \xrightarrow[p\text{H } 8.5]{OH^-} C_6H_5\underset{\diagdown\,O\,\diagup}{CH{-}CH}{-}CHO + t\text{-}C_4H_9OH$$

I

Cinnamaldehyde and *tert*-butyl hydroperoxide were allowed to react in *methanol* solution at 35–40° for five to six hours while dilute sodium hydroxide was added continuously to neutralize acidic by-product and maintain a *p*H of about 8.5. β-Phenylglycidaldehyde (I) was readily obtained in 73% yield by Claisen-distillation of the crude product.

While this epoxidation of cinnamaldehyde by means of alkaline *tert*-butyl hydroperoxide appears to be the first such reaction with an α,β-unsaturated aldehyde, the corresponding reaction with α,β-unsaturated ketones has recently been described.[2] In that work, *benzene* was the solvent and no attempt was made to operate with controlled *p*H. When such a procedure was used with cinnamaldehyde, the crude product was mainly an organic peroxide (possibly *via* Michael addition); it was not further investigated.

EXPERIMENTAL

Epoxidation of cinnamaldehyde. To a 1-l., 5-neck, round bottom flask equipped with mechanical stirrer, dropping funnels, thermometer, and standard electrodes connected to a Beckman *p*H meter, were added 400 ml. of methanol and 71.2 g. (0.60 mol.) of *tert*-butyl hydroperoxide (Lucidol, 75.9% by iodometric titration). The meter *p*H was adjusted to 10.5 ± 0.2 (true *p*H of about 8.5 by indicator paper) by the addition of *N* sodium hydroxide and maintained there as 66 g. (0.50 mol.) of freshly distilled cinnamaldehyde was added at 35–40° over 1 hr. After another 4.5 hr., iodometric titration indicated that 0.48 mol. of hydroperoxide had been consumed and the reaction had essentially stopped; 20 ml. of alkali (4 mol. %) was utilized in maintaining the desired *p*H.

After dilution with 1.5 l. of water and extraction by three 200-ml. portions of chloroform, the combined extracts were washed, dried, concentrated to low volume under vacuum and finally Claisen-distilled. There was thus obtained 54 g. (73% yield) of β-phenylglycidaldehyde, b.p. 66–68° (0.2 mm.), n_D^{20} 1.5447. The infrared spectrum showed aldehyde carbonyl absorption at 5.76 μ and epoxide absorption at 8.14 and 11.50 μ.

Anal. Calcd. for $C_9H_8O_2$: C, 73.0; H, 5.4; carbonyl value, 0.68 equiv./100 g.; oxirane oxygen, 10.8. Found: C, 72.9; H, 5.7; carbonyl value, 0.69 equiv./100 g.; oxirane oxygen, 6.7.[3]

The *2,4-dinitrophenylhydrazone* was prepared from 3.0 g. of epoxy aldehyde by adding the latter to a hot solution of 4.0 g. of 2,4-dinitrophenylhydrazine and 2 ml. of acetic acid in 300 ml. of ethanol. After boiling for 1 min., the solution was cooled quickly to 60° and filtered. After standing overnight at room temperature, the derivative was recovered by filtration and washed well with ethanol. The weight of material melting at 138–139° was 3.3 g.

Anal. Calcd. for $C_{15}H_{12}N_4O_5$: N, 17.0. Found: N, 16.9.

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(2) N. C. Yang and R. A. Finnegan, *J. Am. Chem. Soc.*, **80**, 5845 (1958).

(3) Hydrochloric acid in dioxane; see J. L. Jungnickel, E. D. Peters, A. Polgar, and F. T. Weiss, "Organic Analysis, Vol. 1," Interscience Publishers, Inc., New York, 1953, p. 135; in a blank experiment, styrene oxide itself gave an oxirane oxygen value of only 88% of theory.

Diels-Alder Diene Synthesis With 1,1,1-Trichloro-3-nitropropene[1]

HOWARD BURKETT AND WILLIAM WRIGHT

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Although many examples of the Diels-Alder reaction for aromatic substituted nitroolefins, such as β-nitrostyrene and substituted β-nitrostyrenes, have been published,[2] few have been reported for non-aromatic nitroolefins. Nitroethene,[3,4] 1-nitro-1-propene,[3] 1-nitro-1-pentene,[3] 1-nitro-1-heptene,[5] 1-nitro-1-octene,[5] 2-nitropropene,[6,7] 2-nitro-1-butene[6] and 2-nitro-2-butene[7] react with cyclopentadiene to yield the normal Diels-Alder adduct in 33 to 72% yield. Both aromatic and non-aromatic nitroolefins react with anthracene[8] in yields up to 62%. Substituents on the nitroolefins reduce the yield[8] or appear to cause the reaction to proceed with greater difficulty.[5]

The present study was undertaken to learn the effect of the sterically bulky, electron attracting trichloromethyl group in 1,1,1-trichloro-3-nitropropene[9] (I) upon the Diels-Alder reaction. The dienes used were butadiene-1,3 (IIa), isoprene (IIb), pentadiene-1,3 (IIc), 2,3-dimethylbutadiene-1,3 (IId), cyclopentadiene (IIe), 2-chlorobutadiene-1,3,furan and 2,5-dimethylfuran. The latter two compounds were chosen because they react with less facility or fail to react in the Diels-Alder re-

(1) Supported in part by a grant from Research Corporation to whom the authors are grateful. Taken in part from the Masters thesis of W. W.

(2) For example: W. C. Wildman, R. B. Wildman, W. T. Norton, and J. B. Fine, *J. Am. Chem. Soc.*, **75**, 1912 (1953).

(3) K. Alder, H. Rickert, and E. Windemuth, *Ber.*, **71**, 2451 (1938).

(4) W. C. Wildman and C. H. Hemminger, *J. Org. Chem.*, **17**, 1641 (1952); J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954).

(5) W. E. Noland, R. E. Counsell, and M. H. Fisher, *J. Org. Chem.*, **21**, 911 (1956).

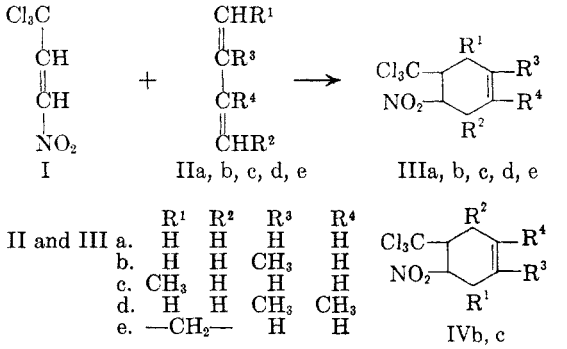
(6) D. V. Nightingale, M. Maienthal, and J. A. Gallagher, *J. Am. Chem. Soc.*, **75**, 4852 (1953).

(7) W. E. Noland and R. E. Bambury, *J. Am. Chem. Soc.*, **77**, 6386 (1955).

(8) W. E. Noland, H. I. Freeman, and M. S. Baker, *J. Am. Chem. Soc.*, **78**, 188 (1956).

(9) F. Brower and H. Burkett, *J. Am. Chem. Soc.*, **75**, 1082 (1953).

action. For example, both are reported not to react with β-nitrostyrene.[10]



The dienes listed, except the two furans and 2-chlorobutadiene-1,3, reacted with I to yield adducts in 65 to 88% yield. Attempts with the furans included standing at room temperature for thirty days without solvent, refluxing without solvent and refluxing in acetic acid. In each case both the furan and I were recovered and there was no residue. In all of the attempts with the 2-chlorobutadiene, I was completely or nearly completely recovered. The remainder of the reaction mixture was a non-distillable, resinous material. This reaction was tried, without solvent, in xylene and in acetic acid; with temperatures between room temperature and that of refluxing xylene; and with reaction times from four hours to nineteen days. In most of the attempts hydroquinone was added to inhibit polymerization.

Although no experiments were performed to prove the position of the double bond in the products, the infrared spectrum for each product was consistent with that expected for the normal Diels-Alder product.[11]

Two position isomers are possible for the products from both IIb and IIc. Treatment of the adduct from IIb with palladium on charcoal produced 4-methyl-2-nitrobenzoic acid. Heating the same material with concentrated sulfuric acid produced *m*-toluic acid. Evidently, the product contained both isomers, IIIb and IVb. No attempt was made to separate them. Although the presence of isomeric compounds in the product from IIc was not investigated, it probably contained both IIIc and IVc.

Whereas the reaction with IIe was exothermic and essentially complete at 35–50° within a few hours, that using IIa was quite slow. Table I indicates the percent yield isolated from reactions carried out at room temperature for different lengths of time. Maximum yields were obtained only when the reaction time was over two weeks. As the reaction was not exothermic for any of the other compounds, each was allowed to react at room temperature for at least two weeks before distilling.

TABLE I

PERCENT YIELD VS. REACTION TIME FOR BUTADIENE

Time (days)	Yield, %
0.25	1.7
0.5	3.5
1	7.8
3	19.5
6	37
8	50
11	65
15	78

EXPERIMENTAL

Dienes. 2-Chlorobutadiene-1,3 was distilled from a chloroprene-xylene mixture obtained from E. I. du Pont de Nemours.[12] The 1,3-butadiene (special purity grade), isoprene (polymerization grade), and pentadiene-1,3 were supplied by the Phillips Petroleum Company.[12] The 2,3-dimethylbutadiene-1,3 was supplied by the Borden Company.[12] Cyclopentadiene was obtained by the thermal depolymerization of dicyclopentadiene from the Enjay Company.[12]

2-Nitro-1,2,3,6-tetrahydrobenzotrichloride (IIIa). For each run 32.5 g. (0.6 mol.) of 1,3-butadiene and 80 g. (0.45 mol.) of I were sealed in a heavy-walled bottle. After the length of time given in Table I each mixture was distilled under reduced pressure. The yield of product was taken to be that distilling at *ca.* 109–112°/1 mm. The crude product from a run allowed to stand for 18 days was carefully fractionated, yielding 71 g. (67%) of a very pale yellow oil, b.p. 110–111°/1 mm., d_{20}^{20} 1.4801, n_D^{20} 1.5317.

Anal. Calcd. for $C_7H_8Cl_3NO_2$: N, 5.73; Cl, 43.52. Found: N, 5.74; Cl, 43.70.

4-Methyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride (IIIb) *and 5-methyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride* (IVb). A solution of 15 g. (0.22 mol.) of isoprene (IIb) and 39 g. (0.22 mol.) of I was placed in a stoppered flask. After 25 days the mixture was fractionated, yielding 48 g. (84.5%) of pale yellow oil, b.p. 117–118°/1 mm., d_{20}^{20} 1.4119, n_D^{20} 1.5271.

Anal. Calcd. for $C_8H_{10}Cl_3NO_2$: N, 5.42; Cl, 41.14. Found: N, 5.49; Cl, 41.23.

Evidence for IIIb in the product from isoprene. A mixture of 20 g. of the product from isoprene and 5 g. of 10% palladium on charcoal was heated in a flask at 190° until no more gas was evolved. The cooled residue was pulverized and extracted with three 40-ml. portions of ether. Evaporation of the ether left a brown sticky residue. Distillation gave 2.0 g. of a liquid, which solidified. Sublimation afforded a pale yellow product, m.p. 161–163°. The reported[13] melting point for 4-methyl-2-nitrobenzoic acid is 161°. The product was converted,[14] via the acid chloride, m.p. 158–160°, to the amide, m.p. 150–152°. The reported[13] melting points are 157° and 153°, respectively.

Evidence for IVb in the product from isoprene. The product (14 g.) was dissolved with cooling in 50 ml. of concentrated sulfuric acid. After standing at room temperature for 4 hr. and heating on the steam bath for 5 hr., the mixture was cooled and poured onto 125 g. of ice. After filtering, the

(10) C. F. H. Allen and A. Bell, *J. Am. Chem. Soc.*, **61**, 521 (1939).

(11) The authors are indebted to Dr. Harold Boaz of Eli Lilly and Company for help in interpreting the spectra.

(12) The authors are grateful to these companies for complementary samples.

(13) C. Joachim, *Ann.*, **266**, 210 (1891).

(14) S. M. McElvain, "The Characterization of Organic Compounds," The MacMillan Company, New York, N. Y., 1945, p. 193.

resulting solid was extracted with 225 ml. of boiling water in six portions. Chilling in ice and filtering left a brown crystalline solid. This was extracted with boiling 90–100° ligroin, decanting from the insoluble dark oil. Cooling and filtering yielded 0.8 g. of white crystals, m.p. 110.5–111.5°. The reported melting point for *m*-toluic acid is 111–112°. This product was converted,[14] *via* the acid chloride, to the amide, m.p. 93–94° (lit.[14] 94°).

3-Methyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride (IIIc) *and/or 6-methyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride* (IVc). A mixture of 15 g. (0.22 mol.) of pentadiene-1,3 and 39 g. (0.22 mol.) of I was allowed to stand in a stoppered flask for 14 days. Fractionation afforded 26 g. (65%) of pale yellow liquid, b.p. 110–111.5°/1 mm., d_{20}^{20} 1.3626, n_D^{20} 1.5232.

Anal. Calcd. for $C_8H_{10}Cl_3NO_2$: N, 5.42; Cl, 41.14. Found: N, 5.32; Cl, 41.34.

4,5-Dimethyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride (IIId). A mixture of 18 g. (0.22 mol.) of 2,3-dimethylbutadiene-1,3 and 39 g. (0.22 mol.) of I was allowed to stand in a stoppered flask at room temperature for 14 days. Fractionation gave 41 g. (69%) of pale yellow liquid, b.p. 118–119°/1 mm., d_{20}^{20} 1.4225, n_D^{20} 1.5253.

Anal. Calcd. for $C_9H_{12}Cl_3NO_2$: N, 5.14; Cl, 39.05. Found: N, 5.17; Cl, 39.21.

3,6-Endomethylene-2-nitro-1,2,3,6-tetrahydrobenzotrichloride (IIIe). To 78 g. (0.44 mol.) of cold I was added 31 g. (0.44 mol.) of cold freshly-prepared cyclopentadiene in 3-ml. portions with swirling and cooling in an ice bath so that the temperature was maintained at 35–50°. When the mixture was no longer exothermic, the container was stoppered and allowed to stand at room temperature. Fractionation yielded 98 g. (87.5%) of pale yellow liquid, b.p. 113.5–115°/1 mm., d_{20}^{20} 1.4831, n_D^{20} 1.5334.

Anal. Calcd. for $C_8H_8Cl_3NO_2$: N, 5.50; Cl, 41.45. Found: N, 5.40; Cl, 41.04.

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Reactions of Allene. I. Diels-Alder Adducts

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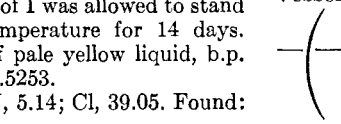
The Diels-Alder reaction between simple olefins and dienes is known[1] The same reaction between dienes and activated double bonds has received much attention.[2] However, the Diels-Alder reaction between dienes and compounds possessing cumulated double bonds has received very limited study.[3]

In this laboratory the Diels-Alder reactions between allene, which contains cumulated double bonds, and several conjugated dienes were studied. These Diels-Alder adducts were sought as intermediates for other studies now in progress in this laboratory. We wish to report at this time some results on cyclopentadiene and hexachlorocyclopentadiene.

Cyclopentadiene reacted with allene yielding four isolable products (II and III were not previously known): 5-methylenebicyclo[2.2.1]-2-heptene (I);[4] 1,2,3,4,4a,5,8,8a-octahydro-2-methylene-1,4,5,8 - dimethanonaphthalene (II); 1,2,3,4,4a,5,-5a,6,9,9a,10,10a-dodecahydro-2-methylene-1,4,5,-10,6,9-trimethanoanthracene (III); and a polymer (IV). The structures of the cuts corresponding to compounds II and III have not been proved but are probably as named. The characterization of IV has not been made, but collected data does not refute Lebedev and Merezhkovskii's[5] presumption that the polymerization of allene in metallic vessels yields a polymer of the structure



. Average molecular weight coupled with percent unsaturation would indicate that the average value of n is 11.5 in the particular sample of polymer reported here. Three different elemental analyses gave total carbon and hydrogen of about 95–97%. Mass spectroscopy analyses showed water present in the polymer. The infrared absorption at 11.45 μ is indicative of terminal unsaturation at the polymer chain end. While higher adducts such as four or five diene molecules to one of allene may have been formed in this reaction, they were in such low concentration that they were not isolated by distillation of the reaction mixture.

Hexachlorocyclopentadiene (V) reacted with allene yielding only one isolable product which was previously unknown: 1,2,3,4,7,7-hexachloro-5-methylenebicyclo [2.2.1]-2-heptene (VI). As would be expected, V reacted with allene at a lower temperature than cyclopentadiene and the yield of VI was higher than for I. No higher molecular weight adducts or polymer was isolated or indicated.

EXPERIMENTAL[6]

Allene. Fractional distillation of Dow methylacetylene–propadiene mixture (30% allene and 70% methylacetylene) at atmospheric pressure through a 60-inch glass, helices packed column yielded allene, b.p. −34.8° to −33.9°, having 98+% purity which was stored in steel cylinders until used.

Cyclopentadiene was prepared as 99+% pure material, b.p. 41–43°, by pyrolysis of Enjay dicyclopentadiene. The

(1) L. M. Joshel and L. W. Butz, *J. Am. Chem. Soc.*, **63**, 3350 (1941).

(2) H. L. Holmes, "Organic Reactions," John Wiley and Sons, Inc., New York, 1948, Vol. IV, 60.

(3) von O. Diels and W. Friedrichsen, *Ann.*, **513**, 145 (1934); O. Wickterle and J. Rocek, *Chem. Listy*, **47**, 1768 (1953); *Coll. Czechoslov. Chem. Comm.*, **19**, 282 (1954).

(4) This compound was made by dehydrobromination of the Diels-Alder adduct between allyl bromide and cyclopentadiene and was presented by P. von R. Schleyer and R. E. O'Connor before the Division Organic Chemistry, American Chemical Society, Chicago, Ill., September, 1958, Paper No. 66.

(5) S. V. Lebedev and B. K. Merezhkovskii, *J. Russ. Phys. Chem. Soc.*, **45**, 1249.

(6) Boiling points are uncorrected. Elemental analyses were carried out by Galbraith Laboratory, Knoxville, Tennessee. Yields are calculated on charged reactant as noted.

material was stored at −20° for periods not longer than one month before use.

Hexachlorocyclopentadiene was received as a sample from Hooker Electrochemical Company (C-56) and was used as such.

5-Methylenebicyclo[2.2.1]-2-heptene (I). A 2960 ml. stainless steel autoclave was cooled to −78° while purging with dry nitrogen and was then charged with 330 g. (5.0 mol.) cyclopentadiene and 200 g. (5.0 mol.) allene (determined by passage through a calibrated flow meter). The autoclave was capped, placed in a rocker, and heated to 200° over a 1.25-hr. period. At 200° the autogeneous pressure reached 620 p.s.i. and began dropping. During the next 5 hr. the temperature was maintained between 200 and 230° with a subsequent drop in pressure to 280 p.s.i. (210°). When the autoclave had cooled to room temperature, it was vented (while warming) through a trap at −78° to collect 55.4 g. of unreacted allene. The straw yellow liquid (479.2 g.) in the autoclave was distilled rapidly through a 3-inch tube containing a side arm at a total take off yielding 200.9 g. liquid, b.p. 26–100°/160 mm. This crude product was redistilled through a 10-inch glass spiral column at atmospheric pressure yielding 186 g. (48.6% yield based on allene) I, b.p. 115–120°, n_D^{25} 1.4834–1.4840. A heart cut, b.p. 73.0°/172 mm., n_D^{25} 1.4838, n_D^{20} 1.4860, d_4^{20} 0.889, from the redistillation of combined I from several runs was used for analyses. The infrared spectrum showed principal bands at 5.72, 6.03, 6.38, 11.44, 13.8, and 14.6 μ. Mass spectroscopy analyses support the structure of I.

Anal. Calcd. for C_8H_{10}: C, 90.6; H, 9.4. Found: C, 90.5; H, 9.5.

Mol. refr. calcd.: 33.8. Found 34.1. Mol. wt. calcd.: 106.2. Found (ebulioscopic): 114.

A sample of I, b.p. 73.0/160 mm., absorbed 4 equivalents of hydrogen in 4 hr. at 175–185° and 1500 p.s.i. over Harshaw 0104 Ni/Kieselguhr catalyst. Distillation gave a 95% yield of 2-methylbicyclo[2.2.1]heptane,[7] b.p. 124.5–125.0°, n_D^{25} 1.4516, n_D^{20} 1.4541.

1,2,3,4,4a,5,8,8a-Octahydro-2-methylene-1,4,5,8-dimethanonaphthalene (II). The residues from the rapid distillation and from the redistillation above were combined and distilled through a 10-inch glass spiral column yielding 74.8 g. (12.1% yield based on allene) II, b.p. 92–98°/7.0 mm., n_D^{25} 1.5312–1.5330, d_4^{20} 1.020. A heart cut, b.p. 92.0°/6 mm., n_D^{25} 1.5319, n_D^{20} 1.5338, d_4^{20} 1.012, from redistillation of combined II from several runs was used for analyses. The infrared spectrum showed principal bands at 5.72, 6.03, 6.38, 11.44, 13.2, and 13.6 μ.

Anal. Calcd. for $C_{13}H_{16}$: C, 90.6; H, 9.3. Found: C, 90.10; H, 9.88.

Mol. refr. calcd.: 52.5. Found: 52.8. Mol. wt. calcd.: 172. Found: 170.

1,2,3,4,4a,5,5a,6,9,9a,10,10a-Dodecahydro-2-methylene-1,4,5,10,6,9-trimethanoanthracene (III). Continued distillation of the above residues at reduced pressure yielded 10.9 g. (9.3% yield based on allene) III, b.p. 71–76°/0.07 mm., n_D^{25} 1.5444. A heart cut, b.p. 74.5°/0.07 mm., n_D^{25} 1.5442, n_D^{20} 1.5463, d_4^{20} 1.048, was used for analyses. The infrared spectrum of III showed principal bands at 5.72, 6.03, 6.38, 11.44, 13.29, and 13.4 μ.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.71; H, 9.33. Found: C, 90.0; H, 8.6. Mol. ref. calcd.: 71.6. Found: 71.9. Mol. wt. calcd.: 238.0. Found: 218.

Polymer. The 31.5 g. of residue from the above distillation cooled to a hard glass which was dissolved in 100 ml. boiling benzene. The cooled solution was slowly poured into 3 l. of methanol and the resulting brown precipitate was filtered, mixed with 300 ml. methanol, beaten 1 min. in a Waring blendor, filtered, and air dried 3 days yielding 30 g. (15.0% yield based on allene) of cream colored powder. This polymer softened at 81° and melted at 162–165°.

Anal. Calcd. for $(C_6H_8)_n$: C, 90.0; H, 10.0. Found: C, 86.5; H, 9.2. Mol. wt. calcd. for n = 11.5: 920. Found: 903 ± 1%. % Unsatn. calcd. for $(C_6H_8)_{11.5}$: 30. Found (Bromination): 29.

The infrared spectrum of a Nujol mull of this polymer has bands at 6.04, 11.45, and 12.57 μ.

1,2,3,4,7,7-Hexachloro-5-methylenebicyclo[2.2.1]-2-heptene (VI). A 2960 ml. stainless steel autoclave was charged as above with 1173.8 g. (4.3 mol.) hexachlorocyclopentadiene (V) and 208.7 g. (5.2 mol.) allene. After capping and placing in a rocker, the autoclave was heated to 150° while rocking. At 150° the autogeneous pressure reached 245 p.s.i. and remained constant during the next 6 min. while the temperature continued to rise to 176° without external heating. The heat of reaction produced a maximum rise in temperature to 200° while the pressure dropped to 190 p.s.i. over the next 23 min. The temperature then began dropping. Over a 2.25-hr. period the temperature had risen from 150° to a maximum 200° and dropped to 170° while the pressure dropped from 245 p.s.i. to a constant 150 p.s.i. After the autoclave had cooled to room temperature it was vented through a trap (−78°) yielding 7.8 g. allene. Gaseous hydrogen chloride was also liberated during venting. The black liquid (1347.1 g.) remaining in the autoclave was subjected to reduced pressure for 1 hr. to remove absorbed hydrogen chloride. Rapid distillation of the residual liquid through a 4-inch Vigreaux column yielded 1098.7 g. yellow liquid, b.p. 74 (0.5 mm.) −80° (0.08 mm.), and 185 g. black charred residue. Redistillation of the 1098.7 g. of distillate through a 24-inch glass helices packed column yielded 1021.9 g. (76% yield based on hexachlorocyclopentadiene charged) VI, b.p. 72° (0.08 mm.) −85° (0.25 mm.), n_D^{25} 1.5590. A heart cut, b.p. 90°/0.3 mm., n_D^{25} 1.5592, n_D^{20} 1.5611, d_4^{20} 1.605, was used for analyses. Infrared spectrum showed principal bands at 6.02, 6.23, 10.95, 13.5, 13.8, and 15.38 μ.

Anal. Calcd. for $C_7H_4Cl_6$: C, 30.73; H, 1.29; Cl, 68.0. Found: C, 30.44; H, 1.66; Cl, 67.97. Mol. refr. calcd.: 63.0. Found: 63.0. Mol. wt. calcd.: 312.9. Found: 326.

Acknowledgment. We wish to acknowledge the able assistance of Mr. W. D. Beck in carrying out several of the autoclave reactions and Mr. D. H. Wolfe for his help in hydrogenating one of the products.

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(7) These properties agree with the values, b.p. 126.9–127.3° and n_D^{20} 1.4540, reported by G. Calingaert, H. Soross, and H. Shapiro, *Ind. Eng. Chem.*, **36**, 1055 (1944).

The Chemistry of β-Bromopropionyl Isocyanate. II. Use in Identification of Alcohols[1]

HARRY W. JOHNSON, JR., HENRY A. KREYSSLER, AND HOWARD L. NEEDLES

Received August 24, 1959

The reaction of β-bromopropionyl isocyanate (I) with alcohols has been examined to determine the utility of I in making solid urethanes for the

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identification of alcohols. It has been found useful for this purpose.

Solid β-bromopropionylcarbamates ($BrCH_2CH_2CONHCO_2R$) were obtained from the reaction of compound I with most common alcohols: *e.g.*, methyl, *i*-propyl, *t*-butyl, propargyl, and allyl alcohols; benzohydrol and triphenylcarbinol; and several glycols. Long chain alcohols (cetyl and stearyl) and cholesterol formed solid urethanes without difficulty; the β-bromopropionylcarbamates appear to be among the most easily obtained derivatives of the long chain alcohols. The most important difficulty with compound I was the tendency of some secondary alcohols to form oils (in Table I, those alcohols which formed oils instead of solid urethanes are noted). Glycerol did not appear to react with compound I, apparently because of immiscibility with the chloroform solvent.

Compound I offers two advantages over the more conventional aryl isocyanates. First, it may be prepared as needed from the stable, easily stored *N*-bromosuccinimide.[2] Compound I is not isolated from the rearrangement; the alcohol is added to the solution in which the rearrangement was conducted. Secondly, the reaction product of compound I with water is β-bromopropionamide,[2,3] which can be removed in most instances by crystallization.[4] Thus terpin hydrate and pinacol hydrate gave normal diurethanes without removel of the water of hydration. 95% Ethanol also gave a satisfactory derivative. With the more soluble derivatives, particularly those of secondary alcohols, better results were obtained with dry alcohols. Compound I is more reactive than the aryl isocyanates, and forms carbamates with even the longer chain alcohols very rapidly. A study of quantitative differences in reactivity will be undertaken shortly.

The usual range of melting points is encountered with the β-bromopropionylcarbamates. Some have melting points too near to be of value in differentiation; the long chain urethanes are particularly poor in this respect.[5]

Reasonable care should be exercised in the use of compound I. Although it did not appear to be more toxic than phenyl or α-naphthyl isocyanates, 10% solutions of compound I in chloroform did produce rashes when allowed to come into contact with skin. No investigation of the toxicity of compound I or its derivatives was undertaken.

TABLE I. TABLE OF DERIVATIVES

Alcohol[a]	M.P. of β-Bromo-[b] propionylcarbamate, °C.	Nitrogen, %[c] Calcd.	Found
Methyl	137–139	[d]	
Ethyl	111–113	6.25	6.49[e]
n-Propyl	95–97	5.89	6.37
iso-Propyl	103–104	5.89	5.92
n-Butyl	90–92[f]	5.57	5.38[e]
iso-Butyl	80–82	5.57	5.61[e]
sec-Butyl	Oil		
tert-Butyl	97–99	5.57	5.18[e]
n-Amyl	81–83[f]	5.27	5.18[e]
2-Pentanol	85–87	5.27	4.96[e]
3-Pentanol	Oil		
iso-Amyl	87–88	5.27	5.03[e]
tert-Amyl	101–103	5.27	5.44[e]
n-Hexyl	72–74	5.01	4.60
n-Heptyl	75–77	4.77	4.37[e]
2-Octanol	Oil		
n-Decyl	86–88	4.17	4.46
n-Dodecyl	87–89	3.85	3.95
n-Tetradecyl	92–93	3.57	3.23
Cetyl	92–94[f]	3.34	3.53
Stearyl	97–98	3.12	2.76
Allyl	99–100	5.94	5.77
Propargyl	117–118	5.99	6.36
Cyclohexyl	82–84	5.04	5.44
Benzyl	125–127	4.91	5.24
p-Methoxybenzyl	113–115	4.44	4.24[e]
α-Phenylethyl	Oil		
β-Phenylethyl	86–88	4.67	4.71
γ-Phenylpropyl	76–77	4.47	4.33
β-Chloroethyl	125–127	5.45	5.49
β-Hydroxypropionitrile	152–154	11.37	11.62
Cinnamyl	132–133	4.49	4.19[e]
Cholesterol	238–240 (sl. dec.)[g]	2.49	2.76[e]
Terpin hydrate	162–163[g]	5.14	4.78
Furfuryl[h]	123–127 (dec.)		
Tetrahydrofurfuryl	96–98	5.08	4.68
2-Ethoxyethyl	90–92[f]	5.23	4.88[e]
Ethylene glycol	162–163	6.72	6.65
Diethylene glycol	162–164[g]	6.07	5.77
Isoborneol	122–124	4.19	3.82[e]
Benzohydrol	137–139	3.89	3.85
Triphenyl carbinol	82–84	2.94	3.20
Diacetone alcohol	109–110[f]	4.86	4.99[e]
Pinacol hydrate	200–201	5.98	5.62
meso-2,3-Butanediol	128–130	6.28	6.31[e]
1,1,1-Trichloro-2-2-methyl-2-propanol	137–138	3.94	4.29
1-Methoxy-2-propanol	102–104	5.23	5.33
2-Methoxyethanol	95–97	5.52	5.58
3-Hydroxy-2-butanone	105–107	5.26	5.49[e]
Geraniol	65–67	4.22	3.90[e]
Benzoin	135–137	3.59	3.25
2,2-Dimethylpropanediol	170–172	6.09	5.72[e]

[a] Alcohols were obtained from commercial sources and were used as obtained. [b] Melting points were measured on a Fischer-Johns block and were not corrected. [c] Dumas nitrogen by C. F. Geiger, 312 Yale St., Ontario, Calif. [d] Calcd. for $C_5H_8O_3NBr$: C, 28.60; H, 3.84; N, 6.67; Br, 38.05. Found: C, 28.7; H, 3.8; N, 6.5; Br, 38.0. Analyses by Analytical Laboratories, The Dow Chemical Co., Midland, Mich. [e] Determined by authors using Kjeldahl method. [f] Crystallized from benzene. [g] Crystallized from tetrahydrofuran. [h] Decomposed on standing at room temperature. No analysis performed.

(2) H. W. Johnson, Jr., and D. E. Bublitz, *J. Am. Chem. Soc.*, **80**, 3150 (1958).

(3) J. C. Martin and P. D. Bartlett, *J. Am. Chem. Soc.*, **79**, 2533 (1957).

(4) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Identification of Organic Compounds*, 4th ed., John Wiley & Sons, New York, N. Y., 1956, p. 207.

(5) See the melting points of the phenylurethanes and α-naphthylurethanes of lauryl, myristyl, and cetyl alcohols in ref. 4, p. 282, for other examples of similar behavior in this series.

EXPERIMENTAL

β-Bromopropionyl isocyanate. The rearrangement of *N*-bromosuccinimide was carried out as indicated previously.[2] The *N*-bromosuccinimide should be crushed to break up lumps of material for maximum rate. We have carried out the rearrangement on scales which ranged from 0.2 to 50 g. *N*-bromosuccinimide without difficulty.

Reaction of compound I *with alcohols.* In preparative scale reactions a solution of chloroform containing 5 g. of rearranged *N*-bromosuccinimide was allowed to react with 0.7 mol. equivalent of the alcohol. The solution was cooled in an ice bath. If a precipitate appeared, the solution was filtered, and the precipitate was recrystallized from methanol. If the derivative did not precipitate, the solution was evaporated on a steam bath using an air jet. The residue was induced to crystallize with Dry Ice, and the material was recrystallized.

On a smaller scale, 0.5 g. *N*-bromosuccinimide was rearranged in 5 ml. chloroform (dried over calcium chloride), *ca.* 0.5 ml. allyl chloride, and a trace of benzoyl peroxide. The solution was refluxed 30 min. beyond the time required for the *N*-bromosuccinimide to dissolve, and cooled to room temperature. Then 0.2–0.4 ml. of the alcohol was added, and the solution was cooled or evaporated as required. A slight excess of the isocyanate appears desirable to give the most easily crystallized urethanes. With secondary alcohols less trouble was encountered with oils if the reaction mixture were worked up reasonably quickly (less than 2 hr.) rather than allowing the mixture to stand overnight.

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A New Base-Catalyzed Aromatization Reaction[1]

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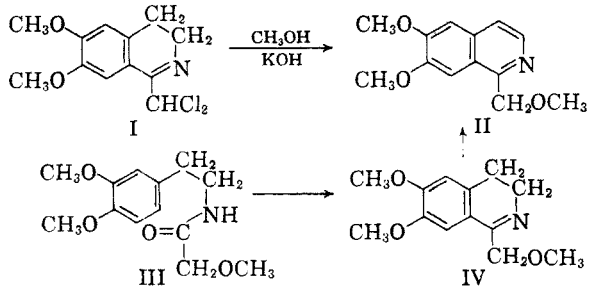
Received August 18, 1959

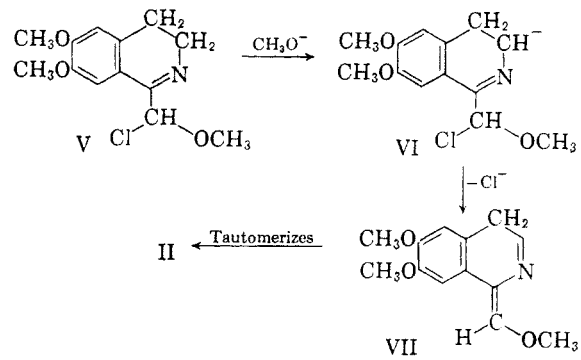
We have had occasion to study the effect of 5% methanolic potassium hydroxide solution on 1-dichloromethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline (I). The crystalline product, obtained in excellent yield, was shown to be halogen-free, and the infrared absorption spectrum was without significant absorption in the 5.83–5.90 region (aromatic aldehyde). The composition of the new compound did not correspond with that of a simple



acetal, but gave best agreement with the empirical formula $C_{13}H_{15}NO_3$.

Of the compounds which could have the observed composition the previously unknown 1-methoxymethyl-6,7-dimethoxyisoquinoline (II) appeared most likely, and an unequivocal synthesis was undertaken *via* the Bischler-Napieralski cyclization of *N*-homoveratrylmethoxyacetamide (III). Dehydrogenation of the cyclization product (IV) yielded 1 - methoxymethyl - 6,7 - dimethoxyisoquinoline identical in every respect with the product obtained by the action of methanolic potassium hydroxide on 1-dichloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (I).

Since this type of aromatization reaction does not appear to have been reported before, speculation concerning a possible mechanism is in order. A logical sequence of events would involve a simple



nucleophilic displacement of chlorine by methoxide ion to yield V. This would be followed by the abstraction of a proton to yield some of the anion (VI). The loss of a chloride ion from anion VI would, through the sequential shift of electrons lead to structure VII, which would be expected to tautomerize to 1-methoxymethyl-6,7-dimethoxyisoquinoline (II).

The new aromatization reaction occurs in 80–94% yield and is thus of preparative as well as theoretical interest.

EXPERIMENTAL[2]

1-Dichloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (I). A mixture containing 12 g. of *N*-homoveratryl-1,1-dichloroacetamide,[3] 100 ml. of dry toluene and 30 ml. of phosphorus oxychloride was refluxed for about 2 hr. when the majority of the solvent was removed under vacuum and the residue carefully decomposed with water and dilute hydrochloride acid. After the acidic solution had been extracted with ether to remove any neutral material, the aqueous solution was made basic and the dihydroquinoline derivative extracted with ether or benzene. The product afforded 7.0 g. (64%) of colorless plates from ligroin, m.p. 90–90.5°. A dilute hydrochloric acid solution of the product was not fluorescent.

Anal. Calcd. for $C_{12}H_{13}Cl_2NO_2$: N, 5.13; Cl, 25.65. Found: N, 5.22; Cl, 25.80.

(1) This research was supported by a research grant (H-2170) from The National Heart Institute of The National Institutes of Health.

(2) Except as noted all melting points were determined on the Fisher-Johns block and are uncorrected. The analyses were carried out by Drs. Weiler and Strauss, Oxford, England.

(3) A. P. Phillips, *J. Am. Chem. Soc.*, **74**, 6125 (1952).

1-Methoxymethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IV). A mixture containing 15 g. of *N*-homoveratrylmethoxyacetamide[4] (III), 150 ml. of dry toluene and 30 ml. of phosphorus oxychloride was refluxed and worked up as in the preparation of I. The product, 6 g. (43%), was isolated by distillation, b.p. 150–160° (0.7 mm.). The analytical sample boiled at 149° (0.7 mm.).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.30; H, 7.24; N, 5.96. Found: C, 65.96; H, 7.29; N, 5.97.

1-Methoxymethyl-6,7-dimethoxyisoquinoline (II). (a) *By action of methanolic potassium hydroxide on* I. A 1-g. sample of the dichloromethylisoquinoline (I) was refluxed with 10 ml. of 5% methanolic potassium hydroxide solution for 1 hr. (steam bath). The dichloro compound (I) dissolved, and precipitation of potassium chloride was soon observed. At the end of the hour the weight of the inorganic salt corresponded closely with that expected if 2 mol. equivalents of potassium chloride had formed. The filtrate was diluted with water and extracted repeatedly with benzene. The solution was treated with Norit, dried, concentrated and diluted with petroleum ether. The product which separated in 80–94% yield melted at 110–120°, and showed a negative test for halide. Recrystallized from ligroin it melted at 122.5–123.5°. A solution of the product in dilute hydrochloric acid gave a bright yellow fluorescence.

(b) *By dehydrogenation of 1-methoxymethyl-6,7-dimethoxy-3,4-dihydroisoquinoline* (IV). Dehydrogenation of the dihydroisoquinoline IV with 10% palladium charcoal catalyst was effected by heating at 160–175°. The product, b.p. 160–165° (1 mm.), obtained in 60% yield, solidified and on crystallization from ligroin, had m.p. 122–123°. This material did not depress the melting point of the product obtained by Procedure (a).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.44; N, 6.02. Found: C, 67.30; H, 6.52; N, 6.39.

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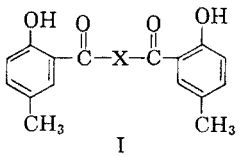
(4) This material, m.p. 40–43°, was prepared by the reaction of methoxyacetyl chloride [R. Leimu, *Ber.*, **70**, 1040 (1937)] with homoveratrylamine.

Study of the Double Fries Rearrangement. II. Rearrangement of Diesters of 4,4′-Biphenol

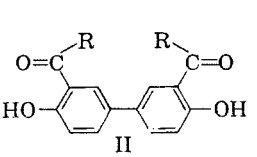
RESAN PAKKAL,[1] FORREST D. THOMAS, II, AND W. CONARD FERNELIUS

Received August 3, 1959

The preparation of a series of bis(*o*-hydroxyketones) of type I where X represents $(CH_2)n$ or *m*- or *p*-phenylene has been reported.[2]



I



II

(1) Appointment supported by the International Cooperation Administration under the Visiting Research Scientists Program administered by the National Academy of Sciences of the United States of America.

(2) F. D. Thomas II, M. Shamma, and W. Conard Fernelius, *J. Am. Chem. Soc.*, **80**, 5864 (1958).

A similar series of type II where the bis-functional starting material was a biphenol rather than a dicarboxylic acid was also desired. Although there has been a moderate amount of work on the Fries rearrangement of esters of polyhydroxybenzenes,[3] only two studies report the rearrangement of diesters of 4,4′-biphenol[4] to give 3,3′-diacetyl-4,4′-biphenol[4a,b] and 3,3′-dipropanoyl-4,4′-biphenol,[4a] whereas attempts to prepare 3,3′-dilauroyl-4,4′-biphenol were unsuccessful.[4b]

In the present study a number of esters of 4,4′-biphenol was prepared by treating the phenol with a series of acid halides in chlorobenzene solution. Each of these esters, when subjected to the Fries rearrangement under conditions previously described,[2] gave the corresponding 3,3′-diacyl-4,4′-biphenols in yields ranging from 19 to 92%.

Infrared spectra. The infrared spectra of the bis(*o*-hydroxyketones) show no absorption in the region of 2.77–2.79 μ (3610–3584 cm.$^{-1}$) characteristic of the free phenolic hydroxyl group, but they do exhibit one rather sharp absorption band in the region of 3.32–3.46 μ (3012–2890 cm.$^{-1}$). This corresponds to the broad absorption bands extending from 2.8–3.6 μ (3571–2778 cm.$^{-1}$) reported by Martin[5] for salicylaldehyde and *o*-hydroxyacetophenone which were attributed to the absorption of the hydroxyl group hydrogen bonded to the carbonyl group and, in part, to the carbon-hydrogen stretching frequency. Gordy[6] noted that the characteristic carbonyl group absorption of acetophenone at 5.96 μ (1678 cm.$^{-1}$) was shifted, in the case of *o*-hydroxyacetophenone, to 6.17 μ (1621 cm.$^{-1}$), due probably, to hydrogen bonding with the *o*-hydroxyl group. In a similar manner, each of the bis(*o*-hydroxyketones) exhibited one sharp absorption peak in the 6.10–6.14 μ (1639–1629 cm.$^{-1}$) region which could also be attributed to the absorption of the carbonyl group hydrogen-bonded to the *o*-hydroxyl group.

EXPERIMENTAL[7]

A. *4,4′-Biphenol esters.* All of the esters of 4,4′-biphenol were prepared from the same molar proportions and in the same general way as described for 4,4′-biphenol diacetate. Pertinent information is assembled in Table I.

4,4′-Biphenol diacetate. A solution of acetyl chloride (8.6 g., 0.11 mol.) in 25 ml. of dry chlorobenzene was added dropwise to a solution of 4,4′-biphenol (9.3 g., 0.05 mol.) and 25

(3) A. H. Blatt, *Organic Reactions*, Vol. I, Chap. 11, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 342–369. See Table E., pp. 364–366.

(4) (a) R. W. Stoughton, R. Baltzly, and A. Bass, *J. Am. Chem. Soc.*, **56**, 2007 (1934). (b) N. Boon-Long, *J. Pharm. Assoc. Siam*, **1**, No. 4, 5 (1948). [*Chem. Abstr.*, **43**, 5017h (1949)].

(5) A. E. Martin, *Nature*, **166**, 474 (1950).

(6) W. Gordy, *J. Chem. Phys.*, **8**, 516 (1940).

(7) All melting points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The 4,4′-biphenol was a gift of the Dow Chemical Company.

TABLE I

4,4′-BIPHENOL ESTERS

Diester, 4,4′-biphenol	Yield, %	M.P.	Recrystn. Solvents	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Diacetate	61.8	161–162.5[a]	Benzene	71.10	70.97	5.22	5.37
Dipropanoate	77	148–149	Ethanol	72.47	72.57	6.08	5.95
Dibutanoate	62.5	123–123.5	Ethanol	73.60	73.73	6.79	6.70
Dipentanoate	21	118–119	Ethanol	74.55	74.37	7.34	7.35
Dihexanoate	73	116–117	Ethanol	75.37	75 37	7.90	8.13
Diheptanoate	21.8	118–118.5	Ethanol	76.06	75.83	8.35	8.48
Dioctanoate	63	121.5–123	Ethanol	76.67	76.52	8.74	8.54
Dinonanoate	65	120–121.5	Ethanol	77.21	77.07	9.07	9.03
Didodecanoate	70	122.5–124[b]	1:1 Dioxane-ethanol	78.50	78.33	9.88	9.84
Dibenzoate	77	251–252[c]	Dioxane	79.17	79.09	4.60	4.65

[a] Reported m.p. 159–160[4b]; 159–160[8a]; 160–161[8b]; 160.5–161.5[8c]; 163–164[8d]. [b] Reported m.p. 119.5–120.5.[4b]. [c] Reported m.p. 240–241[4b]; 250.5–251.5[8d]; 241[9a]; 257[9b].

TABLE II

3,3′-DIACYL-4,4′-BIPHENOLS

3,3′-Diacyl-4,4′-biphenols	Yield, %	M.P.	Recrystn. Solvents	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Infrared Bands, μ 3.32–3.46	Infrared Bands, μ 6.10–6.14
3,3′-Diacetyl	19.2	215–216[b]	1:1 Ethanol-dioxane	71.10	71.07	5.22	5.36	3.35	6.10
3,3′-Dipropanoyl	58	143–144[c]	Ethanol	72.47	72.54	6.08	6.00	3.37	6.10
3,3′-Dibutanoyl	89	125–126	1:1 Ethanol-dioxane	73.60	73.72	6.79	6.72	3.33	6.10
3,3′-Dipentanoyl	92.2	70–80.5	Ethanol	74.55	74.60	7.39	7.45	3.32	6.10
3,3′-Dihexanoyl	53.3	92.5–93.5	Ethanol	75.37	75.33	7.90	7.78	3.44	6.11
3,3′-Diheptanoyl	52.4	93–94	Ethanol	76.06	75.88	8.35	8.27	3.45	6.12
3,3′-Dioctanoyl	88	88.5–90	Ethanol	76.67	76.74	8.74	8.65	3.45	6.11
3,3′-Dinonanoyl	72	72–73	Ethanol	77.21	77.13	9.07	8.99	3.46	6.12
3,3′-Didodecanoyl	85	87–88	2:1 Ethanol-dioxane	78.50	78.46	9.88	9.64	3.45	6.12
3,3′-Dibenzoyl	30[a]	184–185	1:1 Ethanol-dioxane	79.17	79.28	4.60	4.62	3.35	6.14

[a] Reaction mixture heated for 3 days. [b] Reported m.p. 219–219.5[4a]; 219–220.[4b] [c] Reported m.p. 140–141.[4a]

ml. of dry chlorobenzene in a 200-ml. round bottom flask fitted with a thermometer and reflux condenser attached to a Gilman trap filled with sulfuric acid. The exit of the Gilman trap led to a water trough which served to absorb the hydrogen chloride evolved during the reaction. The flask was heated to 80° by means of a heating mantle during which time the vigorous evolution of hydrogen chloride was observed. The solution was heated at 80° overnight and then cooled. The light brown crystalline material which formed was recrystallized from benzene to give 8.35 g. (61.8%) of a white crystalline material, m.p. 161–162.5°.

B. *3,3′-Diacyl-4,4′-biphenols.* All runs were made with the same molar proportions and in the same general manner as described for 3,3′-diacetyl-4,4′-biphenol. The apparatus was the same as just described for the preparation of 4,4′-biphenol diacetate. Pertinent information is assembled in Table II.

3,3′-Diacetyl-4,4′-biphenol. A mixture of 4,4′-biphenol diacetate (5.2 g., 0.02 mol.), aluminum chloride (6.7 g., 0.05 mol.) and 50 ml. of dry chlorobenzene was heated at reflux for 24 hr. During this time hydrogen chloride was evolved and a dark yellow precipitate formed. The yellow mixture was cooled in an ice bath and 50 ml. of 3*N* hydrochloric acid was added dropwise with vigorous stirring. The chlorobenzene was then removed by steam distillation and the light brown solid remaining in the distillation flask was collected and recrystallized from 1:1 ethanol-dioxane to give 1.0 g. (19.2%) of light yellow fibrous needles, m.p. 215–216°.

C. *Infrared spectra.*[10] The infrared spectra of all the bis(*o*-hydroxyketones) were obtained in chloroform solution using sealed liquid absorption cells of approximately 0.1 mm. thickness. A Perkin-Elmer Model 21 double beam spectrophotometer with sodium chloride optics was used. Important absorption bands are listed in Table II.

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(8) (a) H. Schmidt and G. Schultz, *Ann.*, **207**, 320 (1881). (b) J. van Alphen, *Rec. trav. chim.*, **50**, 415 (1931). (c) A. Weissberger and J. W. Williams, *Z. physik. Chem.*, [B] **3**, 367 (1929). (d) A. L. Wilds, C. H. Shunk, and C. H. Hoffman, *J. Am. Chem. Soc.*, **76**, 1733 (1954).

(9) (a) J. Moir, *J. Chem. Soc.*, **91**, 1305 (1907). (b) D. Vorlander, *Z. physik. Chem.*, [A] **105**, 211 (1923).

(10) The infrared spectra were run by Mrs. Ann. V. Baker of this laboratory.

Reduction of Phthalyl and Succinyl Dichlorides with Tri-*n*-butyltin Hydride. Cyclization of γ-Oxoacyl Chlorides[1]

HENRY G. KUIVILA

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Recently van der Kerk, Noltes, and Luijten have reported that benzaldehyde is obtained by the reduction of benzoyl chloride with triphenyltin hydride (equation 1, R = phenyl).[2]

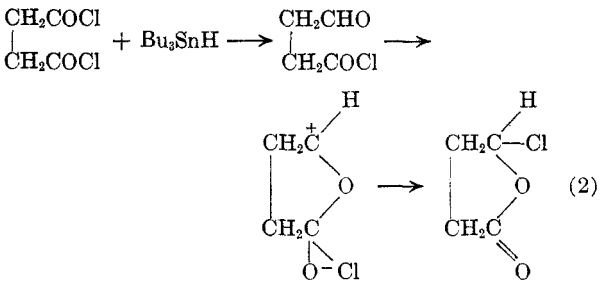
$$R_3SnH + C_6H_5COCl \longrightarrow R_3SnCl + C_6H_5CHO \quad (1)$$

We have found that a similar result is obtained with the more conveniently prepared tri-*n*-butyltin hydride. This reaction proceeds exothermically when the reactants are mixed at room temperature. Aldehydes, on the other hand, are reduced only under much more drastic conditions. Thus, a new convenient synthesis of aldehydes from acid chlorides is suggested. As part of an examination of the scope of such reductions phthalyl and succinyl chlorides have been examined as substrates.

When 1 mole of tri-*n*-butyltin hydride was added to a mole of succinyl dichloride without solvent, an exothermic reaction ensued. The reaction product, after 2 hr. at about 40°, was distilled yielding about 80% of crude product, which upon redistillation provided a product corresponding in neutral equivalent and chloride analysis to the replacement of one of the chlorines by hydrogen. The infrared spectrum showed a carbonyl band at 1810 cm.$^{-1}$, but none in the region 1635–1730 cm.$^{-1}$, nor any C—H band in the region 2700–2800 cm.$^{-1}$. The product is therefore not an aldehyde. The location of the carbonyl band is not shifted by the dilution of the chloride with 2 mol. of tri-*n*-butyltin chloride. Similar mixtures involving the tin halide and succinyl dichloride or γ-butyrolactone have carbonyl absorptions at 1785–1790 cm.$^{-1}$ or 1775 cm.$^{-1}$, respectively.

When 2 moles of hydride were used, the nature of the infrared spectrum after 2 hr. of reaction time was essentially the same as when 1 mole was used. The only difference was in broadening of the band at 1810 cm.$^{-1}$, which was due to the Sn—H band of unreacted hydride which occurs at this same frequency. Clearly the second chloride is far more difficult to reduce than the first.

The reduction product is undoubtedly γ-chloro-γ-butyrolactone, whose formation can be rationalized by the reaction sequence (2).



(2)

As there is no indication of the presence of aldehyde, the second step must be essentially irreversible. Furthermore, the cyclization must occur fairly rapidly, for the second mole of hydride does not lead to the formation of succindialdehyde, which would be expected to form fairly readily in view of the speed of reduction of the first acid chloride group.

Analogous reactions have been observed in the reaction of succinyl chloride with reagents such as diethylcadmium by Cason and Reist.[3] The products obtained are ethyl γ-ketocaproate (when diethyl ether is the solvent) and γ-ethyl-γ-caprolactone; no 3,6-octanedione is obtained. The products found can be accounted for on the basis of cyclization of initially formed γ-ketocaproyl chloride; the diketone would be formed by reaction of this (acyclic) acid chloride with another mole of diethylcadmium. An alternative mechanism proceeding through a cyclic acylonium ion can also account for the facts.[3a]

A cyclic structure has been assigned to γ-ketocaproyl chloride[3b] on the basis of the presence of a single carbonyl band at 1805 cm.$^{-1}$. Similarly,[4] four 2-benzoylbenzoyl chlorides had single carbonyl bands in the region 1790–1800 cm.$^{-1}$. These latter bands represent upward shifts of about 20 cm^{-1} from the 3-phenylphthalides. The shift from α-butyrolactone (1775 cm.$^{-1}$) to the chloro compound involves a shift of 35 cm.$^{-1}$ to a higher frequency. These examples supplement those reported earlier[5] in which electron withdrawing substituents in the γ-position cause shifts in the carbonyl bands of γ-lactones to higher frequencies.

On the basis of the examples discussed above it seems reasonable to conclude that the cyclic γ-chloro-γ-lactones are more stable thermodynamically than the acyclic tautomers, the γ-oxoacid chlorides. Furthermore the cyclization can be brought about with as weak a Lewis acid as tri-*n*-butyltin chloride, and might possibly not require a catalyst at all.

Experiments similar to those conducted with succinyl dichloride were also carried out with phthalyl dichloride. Presumably because of the

(1) It is a pleasure to acknowledge support of this work by the Office of Ordnance Research. Thanks are also due to the Metal and Thermit Corporation for samples of tri-*n*-butyltin chloride.

(2) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem.*, **7**, 356 (1957).

(3) (a) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1668 (1958); (b) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1492 (1958).

(4) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley, Inc., New York, 1958, p. 187.

presence of carbonyl impurities, the spectra of the products were not amenable to reliable interpretation. However, when 2 moles of tri-*n*-butyltin hydride were allowed to react with the acid chloride, a 55% yield of phthalide crystallized from the reaction mixture. Its formation undoubtedly results from the reduction of 3-chlorophthalide formed by way of a sequence such as (2). The ready reduction of the phthalide in the second step occurs because the chlorine is now benzylic, and therefore more susceptible to reduction than that in γ-chloro-γ-butyrolactone.

EXPERIMENTAL

Reaction between succinyl dichloride and tri-n-butyltin hydride. To 2.92 g. (18.9 mmol.) of succinyl dichloride which had been freshly distilled was added 5.50 g. (18.9 mmol.) of tri-*n*-butyltin hydride.[6]

The reactants were allowed to stand, with occasional cooling to keep the temperature below about 40°, for 2 hr. Distillation from a modified Claisen flask provided two fractions: b.p. 49–62°/0.3–0.4 mm., 1.84 g. (80%) and b.p. 102–127°/0.4 mm., 6.06 g. (98% crude tri-*n*-butyltin chloride). The first fraction was redistilled yielding a main fraction b.p. 45°/0.4 mm., 1.00 g. of γ-chloro-γ-butyrolactone.

Anal. Calcd. for $C_4H_5O_2Cl$: Cl, 29.4; neut. eq., 60.3. Found: Cl, 28.1, 28.0; neut. eq., 60.5.

Reaction between phthalyl dichloride and tri-n-butyltin hydride. A mixture of 11.0 g. (37.8 mmol.) of tri-*n*-butyltin hydride and 4.54 g. (8.9 mmol.) of phthalyl dichloride was cooled in a water bath occasionally during the first hour after preparation in order to keep the temperature below 50°. It was then allowed to stand for 5 days; 0.47 g. of crystals which had appeared were filtered off and washed with 10 ml., of petroleum ether, b.p. 30–60°. The filtrate was diluted with 20 ml. more of petroleum ether, whereupon another 0.91 g. of crystals appeared. The product melted at 72–74°, undepressed upon mixture with authentic phthalide, and had an infrared spectrum identical with that of phthalide.

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(6) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Applied Chem.*, **7**, 366 (1957).

Proton Nuclear Resonance Spectroscopy. X. Rapid Tautomerization of Formazans[1,2]

GEORGE V. D. TIERS,[1] STEVEN PLOVAN,[2,3] AND SCOTT SEARLES, JR.

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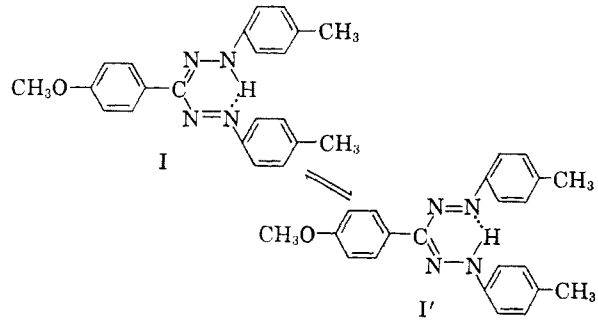
Early workers, studying the problem of tautomerism in unsymmetrically substituted formazans, reported the isolation of two tautomers[4]; however, subsequent studies[5–7] showed that only one form could be isolated. The cyclic hydrogen-bridged structure was proposed[6] in view of the chelating ability of formazans, and the failure to isolate two forms of the chelates prepared from unsymmetrical formazans. In all such studies the requirement of unsymmetrical substitution introduces the possibility of severe steric, electronic, and solvent effects upon the position of tautomeric equilibrium.

Nuclear spin resonance (NSR) spectroscopy affords a sensitive method for the detection of rapid equilibration: it is especially suitable for the study of symmetrical systems,[8] for example, 1,5-di-(4-methylphenyl)-3-(4-methoxyphenyl) formazan



(I). For such purposes it is necessary to choose cases for which all the observed NSR peaks can be assigned with confidence; for the formazan (I) the detailed assignment is given in Table I.

TABLE I

ASSIGNMENT OF NSR SHIELDING VALUES[a] FOR FORMAZAN (I)

Proton Group	Shielding Value, τ (p.p.m.)[a]	Relative No. of Protons
For the 4-Methoxyphenyl Group:		
2-H	2.10[b] | J =	2
3-H	3.20[b] | 8.9c/s	2
4-CH_3O	6.218 ± 0.002	3
For the 4-Methylphenyl Groups:		
2-H	2.59[b] | J =	4
3-H	2.93[b] | 8.5c/s	4
4-CH_3	7.684 ± 0.002	6

[a] For the definition of τ see ref. 10; the formazan, I, concentration was 8% (wt./vol.) in CCl_4. [b] "Nonequivalent doublet" (AB-type) analyzed according to ref. 8, p. 119; the coupling constant J refers to spin interaction between 2- and 3-H.

Whenever NSR assignment may be desired, it is important to avoid unsubstituted phenyl groups, and to synthesize, instead, an appropriate *para*-substituted analog; it may not be widely

(1) Contribution No. 165; Central Research Department, Minnesota Mining and Manufacturing Co., St. Paul, Minn.

(2) A portion of a dissertation submitted in partial fulfillment of the requirements for the Ph.D. degree at Kansas State University, 1959.

(3) Pan American Petroleum Foundation Fellow, 1957–58.

(4) M. Busch and R. Schmidt, *J. Prakt. Chem.*, **131**, 182 (1931).

(5) D. Jerchel and W. Woticky, *Ann.*, **605**, 191 (1957).

(6) L. Hunter and C. B. Roberts, *J. Chem. Soc.*, 820–3 (1941).

(7) R. Kuhn and D. Jerchel, *Ber.*, **74**, 941 (1941).

(8) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance*, McGraw-Hill, Inc., New York, 1959, p. 438 and p. 223.

recognized that *only infrequently* do phenyl groups give analyzable NSR patterns. *Para*-substituents having spin $^1/_2$ (F^{19}, P^{31}) introduce some complexity and should be avoided; all others (including D) appear quite satisfactory.

A further advantage is gained in the present instance by the use of "*para*-sensitive" groups such as methyl and methoxy (formyl, acetyl, and dimethylamino also are good) which give sharp NSR peaks, the exact spectral location of which is dependent upon the electrical nature of the structure attached *para* to them.[9] Thus, the 3-position in the formazan appears to be slightly electron-withdrawing, the methoxy shift being −0.048 p.p.m. relative to anisole,[10] while the *average* of the 1- and 5- positions is slightly electron-donating as judged by the positive methyl shift, +0.021 p.p.m., compared to toluene.[10]

The two apparently different *p*-tolyl groups of I in fact yield identical spectral patterns; if a symmetrical, "mesomeric" structure be ruled out, the observed equivalence requires rapid tautomerization, with an estimated lower limit for the rate constant being *ca.* 10^3 sec.$^{-1}$.[8] An alternative explanation, based on rapid intermolecular NH exchange, is excluded, as it would require a sharp NH peak (not seen), the effects of spin-spin interaction and quadrupole broadening by N^{14} being averaged to zero by such exchange.[11]

EXPERIMENTAL

The NSR equipment and techniques used were previously described.[10,12]

1,5-Di-(4-methylphenyl)-3-(4-methoxyphenyl)-formazan (I). A solution of 2.4 g. (0.01 mol.) of *p*-anisaldehyde-*p*-tolylhydrazone in 300 ml. 95% ethanol at 0° was treated with a diazonium salt solution prepared from 1.07 g. (0.01 mol.) *p*-toluidine, 2.5 ml. (0.03 mol.) 12*N* HCl and 0.76 g. (0.11 mol.) sodium nitrite, at 0°. The *p*H of the diazonium salt solution was adjusted to 6.5 by means of sodium acetate, and it was added dropwise to the vigorously stirred hydrazone solution. After 15 min. a yellow solid was filtered from the solution and allowed to stand until its color was deep red; it was twice recrystallized from ethanol, 2.6 g. (73%) being recovered as deep red needles, m p. 172–175° (uncorr.).

Anal. Calcd. for $C_{22}H_{22}ON_4$: N, 15.64%. Found: N, 16.08%.

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(9) G. V. D. Tiers, Presented at the Symposium on Nuclear Resonance Spectroscopy, Joint SAS-ASTM E-13 Meeting, New York, 1958.

(10) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(11) Ref. 8, p. 102 and p. 226.

(12) G. V. D. Tiers and F. A. Bovey, *J. Phys. Chem.*, **63**, 302 (1959).

The Tetrazole-Azidoazomethine Equilibrium. III. Reduction of Pyridotetrazoles[1]

J. H. BOYER, M. S. CHANG, AND R. F. REINISCH

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The presence of an equilibrium between pyridotetrazole (I) and 2-azidopyridine (III) with electron withdrawing substituents in the pyridine ring was established by spectrophotometric detection of both azido and tetrazolo groups in solutions of certain examples. With no substituent or with electron donating substituents, azide concentration, if present, was not detected.[2] The marked stability of pyridotetrazole in strong acid[3] may be explained by an electromeric displacement toward the electron seeking tetrazole ring. An electromeric displacement toward the pyridine ring, on the other hand, would decrease the stability of the tetrazole ring in I relative to its tautomer III, and might be realized in alkaline solutions.[4] A confirmation of the two possible electronic displacements has been found in catalytic hydrogenation of pyridotetrazole in acidic, basic and neutral media and by reduction of 7-methyl-8-nitropyridotetrazole with stannous chloride in hydrochloric acid.

A detailed catalytic reduction of the tetrazole ring has not been reported heretofore.[5] Its resistance to catalytic hydrogenation was demonstrated in the reduction of I over a noble metal to di- and tetrahydropyridotetrazole[6] (II) and in the reduction of 5-phenyltetrazole in acetic acid over platinum to 5-cyclohexyltetrazole.[7] In the present work, reduction of pyridotetrazole (I) over palladium in the presence of acetic acid to tetramethylenetetrazole (II) in nearly quantitative yield, together with a trace of 2-aminopyridine (IV) has been realized. A dihydropyridotetrazole is not detected. In con-

(1) Financial support by E. Bilhuber, Inc., Orange, New Jersey, and by Research Grants H-2295 and CY-2895 from the National Institutes of Health is gratefully acknowledged.

(2) J. H. Boyer and E. J. Miller, Jr., *J. Am. Chem. Soc.*, **81**, 4671 (1959) (Part I); J. H. Boyer and H. W Hyde, *J. Org. Chem.*, in press.

(3) Pyridotetrazole is recovered unchanged from concentrated sulfuric acid at 120° (J. H. Boyer, W. J. McCarville, D. I. McCane, and A. T. Tweedie, *J. Am. Chem. Soc.*, **75**, 5298 (1953).

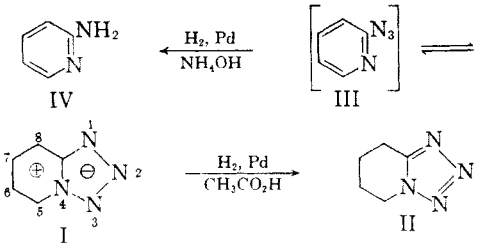
(4) Preliminary observations suggested an instability of pyridotetrazole and its derivatives in bases.[3]

(5) Ring cleavage of tetrazolium salts may occur upon catalytic reduction over palladium [D. Jerchel and R. Kuhn, *Ann.*, **568**, 185 (1950)]. R. O. Roblin, Jr., J. H. Williams, P. S. Winnek, and J. P. English, *J. Org. Chem.*, **62**, 2002 (1940) state that 5-*p*-nitrobenzenesulfonamidotetrazole is reduced over palladium to sulfanilylguanidine, but they do not give the experimental procedure.

(6) Kereszty and Wolf, German pat. **613,123** [*C. A.* **29**, 5604 (1935)]; U. S. pat. **2,008,536** [*C. A.* **29**, 5994 (1935)]. The solvent is not specified in the abstracts.

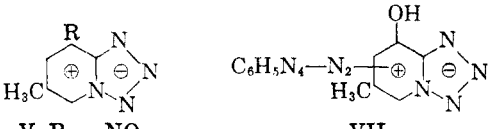
(7) B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.*, **72**, 3379 (1950).

trast, reduction in the presence of ammonium hydroxide gives 2-aminopyridine (IV) inm oderate yield with no tetramethylenetetrazole and a similar reduction in ethanol gives lower yields of both II and IV.



Stannous chloride in hydrochloric acid transforms 6-methyl-8-nitropyridotetrazole (V) into 6-methyl-8-aminopyridotetrazole (VI). Apparently tetrazole destabilization as a result of the presence of the electron attracting nitro group is ineffective in the presence of an opposing electromeric shift demanded by the acid environment.

A derivative tentatively assigned the structure of an azo compound (VII) is obtained upon treatment of diazotized VI with boiling water.



V, R = NO_2
VI, R = NH_2

VII

EXPERIMENTAL[8]

Tetramethylenetetrazole. A solution of 10.65 g. (0.09 mol.) of pyridotetrazole in 5.40 g. (0.09 mol.) of glacial acetic acid and 200 ml. of 95% ethanol was treated with hydrogen (initial pressure of 2 atm.) over 1.25 g. of 10% palladium on charcoal. Hydrogen pressure decreased to a constant value after about 4 hr. The solution, separated from catalyst, was evaporated to dryness *in vacuo*. Addition of *n*-hexane to dried and decolorized chloroform extracts of the residue precipitated 8.6 g. (85%) of tetramethylenetetrazole as colorless needles, m.p. 117–118° after recrystallization from a mixture of chloroform and *n*-hexane (lit.[9] m.p. 115–116°).

Anal. Calcd. for $C_5H_8N_4$: C, 48.38; H, 6.49; N, 45.14. Found: C, 48.65; H, 6.54; N, 45.39.

A trace of 2-aminopyridine in the filtrate was detected as the picrate, melting point and mixture melting point 215–216° (lit.[9] m.p. 216–217°).

The reduction was repeated with the substitution of 0.09 mol. of ammonium hydroxide for 0.09 mol. of glacial acetic acid. Addition of hexane to a chloroform solution of the product did not precipitate tetramethylenetetrazole. Addition of a saturated ethanolic solution of picric acid gave 7.81 g. of *2-aminopyridine* picrate, melting point and mixture melting point 216–217° after recrystallization. Based upon quantitative picrate formation this represents a 29.4% yield of 2-aminopyridine.

In another reduction, neither acid nor base was added to the ethanol solvent. A 15.8% yield of 2-aminopyridine was isolated as its picrate derivative and a 35.0% yield of tetramethylenetetrazole was obtained.

Preparation of 6-methyl-8-aminopyridotetrazole. A solution of 11.3 g. (0.05 mol.) of stannous chloride dihydrate and 15 ml. of concentrated hydrochloric acid was cooled to 5°. The temperature rose to about 60° with the addition of 1.69 g. (0.01 mol.) of 6-methyl-8-nitropyridotetrazole[10] in one portion. The solution was vigorously stirred for about 5 min. until a clear solution resulted and was then stirred in an ice bath for 1 hr. and filtered. The filtrate was treated dropwise with a solution of 40% sodium hydroxide to precipitate the amine as a fine solid, 0.92 g. (61%), m.p. 214–215° (dec.) after recrystallization from boiling water and drying *in vacuo* overnight at 80°.

Anal. Calcd. for $C_6H_7N_5$: C, 48.31; H, 4.73; N, 46.95. Found: C, 48.43; H, 4.90; N, 46.86.

Preparation of 6-methyl-8-acetamidopyridotetrazole. A solution of 0.3 g. (0.002 mol.) of 6-methyl-8-aminopyridotetrazole and 2 g. of acetic anhydride was heated for a few minutes, and cooled. The precipitate, 0.32 g. (84%), m.p. 238–239°, was recrystallized from ethanol.

Anal. Calcd. for $C_8H_9N_5O$: C, 50.25; H, 4.74; N, 36.63; O, 8.37. Found: C, 50.45; H, 4.72; N, 36.83; O, 8.53.

Preparation of 6-methyl-8-hydroxy 5(or 7)-(8′-azo-6′-methyl-pyridotetrazolo)-pyridotetrazole. A solution of 0.3 g. (0.002 mol.) of 6-methyl-8-aminopyridotetrazole, 3 g. of water and 3.6 g. (0.36 mol.) of concentrated sulfuric acid was chilled to 0–5° in an ice-salt bath with stirring. Dropwise addition of a solution of 0.15 g. (0.0022 mol.) of sodium nitrite was accompanied by an evolution of gas. After stirring for 5 to 10 min. the diazotization mixture was added slowly to 10–20 ml. of boiling water. A crude red solid after recrystallization from *N,N*-dimethylformamide gave 0.05 g. (48.4%) of 6-methyl-8-hydroxy 5(or 7)-8′-azo-6′-methyl-pyridotetrazole)-pyridotetrazole, m.p. 230° (explosive dec.) and 0.20 g. of starting material, m.p. 214–215°.

Anal. Calcd. for $C_{12}H_{10}N_{10}O$: C, 46.49; H, 3.25; N, 45.18; O, 5.16. Found: C, 46.70; H, 3.29; N, 44.61; O, 5.87.

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(8) Semimicro analyses by Alfred Bernhardt, Max Planck Institut Mülheim (Ruhr), Germany. Melting points are not corrected.

(9) W. Marckwald, *Ber.*, **27**, 1317 (1894).

(10) J. H. Boyer and W. Schoen, *J. Am. Chem. Soc.*, **78**, 423 (1956).

Hofmann Degradation of 3a-(3,4-Methylenedioxyphenyl)-1-methyloctahydroindole

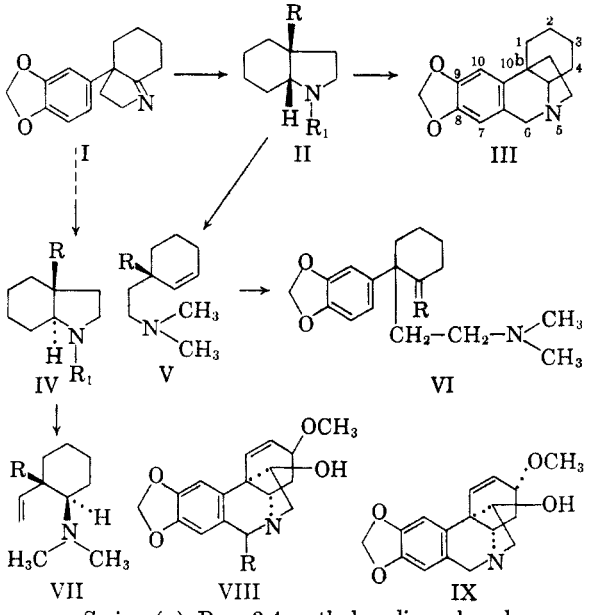
P. F. HIGHET AND W. C. WILDMAN

Received July 20, 1959

The synthesis of (±)-crinane (III) demonstrated that several Amaryllidaceae alkaloids are derivatives of 5,10b-ethanophenanthridine.[1,2] A key intermediate in this synthesis was the hexahydroindole (I) which was reduced by catalytic methods to an octahydroindole of unknown stereochemistry. It was reasoned[3] that catalytic hydrogenation of I should proceed by the addition of hydrogen to the enamine from the side opposite that occupied

(1) W. C. Wildman, *Chem. & Ind. (London)*, 1090 (1956).
(2) W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).
(3) N. Sugimoto and H. Kugita, *Pharm. Bull.*, **5**, 378 (1957).

by the methylenedioxyphenyl group. Such a process would lead to a *trans*-octahydroindole (IVa, R_1 = H). Sodium borohydride reduction of I gave the same octahydroindole as was obtained by catalytic reduction. Since this type of reduction would be expected to lead to the more stable *cis*



Series: (a). R = 3,4-methylenedioxyphenyl
(b). R = H

isomer (IIa, R_1 = H), independent evidence for the stereochemistry of the C:D ring junction was sought. Although structural studies on the alkaloids haemanthamine (VIII, R = H),[4] haemanthidine (VIII, R=OH)[5] and crinamine (IX)[4] provided degradative evidence that rings C and D of these bases were *cis* fused, independent proof based on the synthesis of III was sought for the nature of this ring fusion.

The recent studies by Booth and King[6] prompted us to examine the stereochemistry of the hydrogenation product of I by the Hofmann degradation. Hofmann degradation of *cis*-octahydro-1-methylindole (IIb, R_1 = CH_3) leads to 3-(β-dimethylaminoethyl)-cyclohexene (Vb)[7-9] while the corresponding *trans* compound (IVb, R_1 = CH_3) affords *trans*-1-dimethylamino-2-vinylcyclohexane (VIIb).[6] It seemed likely that the mode of elimination found for these simple indoles should prevail in the analogous precursor of crinane (IIa or IVa, R_1 = CH_3). By this reasoning, if the octahydroindole formed by the reduction of I were *cis* fused (IIa, R_1 = H), Va would result from the Hofmann degradation of IIa (R_1 = CH_3), while a *trans* fusion (IVa, R_1 = H) would give rise to VIIa under similar conditions.

Preliminary attempts to prepare the requisite starting material by methylation of the octahydroindole with formaldehyde and formic acid were unsuccessful. The only product isolated by this method was (±)-crinane (III), formed by a Pictet-Spengler type of cyclization to the activated aromatic nucleus. The desired *N*-methyl derivative was prepared successfully by reductive methylation of the secondary amine in the presence of formaldehyde, palladium-on-charcoal, and hydrogen. Quaternization of the product with methyl iodide and pyrolysis of the derived methohydroxide gave a product which was proved to be Va by spectral evidence and by the synthesis of the dihydro derivative (VI, R = H_2).

The methine (Va) showed no bands in the infrared spectrum attributable to a terminal methylene group but showed absorption at 3015 and 702 $cm.^{-1}$ characteristic of an unsubstituted cyclohexene. Catalytic hydrogenation of Va afforded a dihydro derivative (VI, R = H_2) which showed neither of these bands. Finally, VI (R = H_2) was synthesized in an unambiguous manner. Alkylation of 2-(3,4-methylenedioxyphenyl)-cyclohexanone[2] with β-dimethylaminoethyl chloride in the presence of sodamide gave an aminoketone (VI, R = O). Wolff-Kishner reduction of this gave a product identical with that obtained from catalytic reduction of Va.

These data support the assignment of a *cis* C:D ring fusion in (±)-crinane and the Amaryllidaceae alkaloids based on this nucleus. It is evident that the catalytic and chemical reduction product of I is IIa (R_1 = H) and that the course of the Hofmann degradation of IIa (R_1 = CH_3) parallels that of the simpler analog IIb (R_1 = CH_3). Conformational considerations consistent with the observed reaction path have been discussed earlier.[10]

EXPERIMENTAL[11]

Attempted methylation of IIa (R_1 = H) *with formic acid and formalin.* A solution of 654 mg. of IIa (R_1 = H) in 5 ml. of formic acid and 3 ml. of formalin was refluxed for 23 hr. The mixture was made basic with concentrated sodium hydroxide and extracted four times with ether. The ethereal solution was washed twice with water and twice with brine.

(4) H. M. Fales and W. C. Wildman, *Chem. & Ind.* (London), 561 (1958); *J. Am. Chem. Soc.*, **82**, 197 (1960).
(5) S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2590 (1958).
(6) H. Booth and F. E. King, *J. Chem. Soc.*, 2688 (1958).
(7) J. McKenna, *Chem. & Ind. (London)*, 406 (1954).
(8) B. Bailey, R. D. Haworth, and J. McKenna, *J. Chem. Soc.*, 967 (1954).
(9) F. E. King, J. A. Barltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945).
(10) F. E. King and H. Booth, *J. Chem. Soc.*, 3798 (1954).
(11) All melting points were observed on a Köfler microscope hot stage and are corrected. Infrared spectra were determined with either a Perkin-Elmer model 21 or a Beckman model IR-7 spectrophotometer. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

The solvent was removed under reduced pressure to give 678 mg. of an oil whose infrared spectrum resembled that of crinane. Two recrystallizations from ether gave 323 mg. of material melting at 108–111°; mixture melting point with (±)-crinane, 106–110°.[2,12]

Cis-3a-(3,4-methylenedioxyphenyl)-1-methyloctahydroindole (IIa, R_1 = CH_3). An ethanolic solution of 234 mg. of IIa (R_1 = H) was stirred under hydrogen at room temperature and atmospheric pressure in the presence of 230 mg. of 10% palladium-on-charcoal and 5 ml. of formalin. In 45 min. the mixture absorbed 20.3 ml. of hydrogen (85%). The product was filtered, concentrated and chromatographed on Merck alumina. Elution with chloroform gave 231 mg. of oil which was dissolved in acetone and treated with methyl iodide. Addition of ether precipitated 258 mg. of material, m.p. 169–175°. Four recrystallizations of the *methiodide* from chloroform–ethyl acetate gave colorless prisms, m.p. 198.5–199.5°.

Anal. Calcd. for $C_{17}H_{24}NO_2I$: C, 50.88; H, 6.03; N, 3.49. Found: C, 50.91; H, 6.04; N, 3.53.

The *picrate* was prepared in ethanol and recrystallized from acetone-ethanol and from acetone-ether to give prisms, m.p. 196–198°.

Anal. Calcd. for $C_{16}H_{21}NO_2 \cdot C_6H_3N_3O_7$: C, 54.09; H, 4.95; N, 11.47. Found: C, 53.99; H, 4.88; N, 11.57.

Hofmann degradation of IIa (R_1 = CH_3). A solution of 194 mg. of the methiodide of IIa (R_1 = CH_3) in 1:1 ethanol-water was treated with silver oxide that had been freshly prepared from 93 mg. of silver nitrate. The mixture was scratched and stirred for a few minutes, then centrifuged. The solid material was washed twice with water and once with methanol. The combined supernatant liquid was evaporated to dryness at 40–50° under reduced pressure, then heated for 25 min. at a temperature gradually increasing from 125 to 165°. The resulting residue, 130 mg., was partitioned between 0.1*N* hydrochloric acid and ether. The aqueous layers were made basic with ammonium hydroxide and extracted four times with ether. The ether extracts were washed with water and brine and concentrated under reduced pressure to give 97 mg. of oil. This was chromatographed on 10 g. of Merck alumina. Benzene elution produced 8 mg. of fore run, followed by 38 mg. of Va, then 20 mg. of material whose infrared spectrum suggested it to be slightly impure Va. Elution with 1–5% ethyl acetate gave 20 mg. of material trailing in many fractions.

The infrared spectrum (carbon tetrachloride) of Va purified in this manner showed absorption at 3012 and 702 cm.$^{-1}$. The ultraviolet absorption spectrum (ethanol) showed maxima at 234 (ϵ 4240) and 287 mμ (ϵ 4240).

1-(β-Dimethylaminoethyl)-1-(3,4-methylenedioxyphenyl)-cyclohexane (VI, R = H_2). A solution of 38 mg. of Va in ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 40 mg. of pre-equilibrated 10% palladium-on-charcoal. Absorption of hydrogen ceased after the uptake of 3.55 ml. (theor. 3.2 ml.) in 29 min. The mixture was filtered, and the solvent was removed under reduced pressure to give 40 mg. of a clear oil. The infrared spectrum (carbon tetrachloride) showed no absorption at 3012 or 702 cm.$^{-1}$. The ultraviolet absorption spectrum (ethanol) showed maxima at 235 (ϵ 4120) and 288 mμ (ϵ 3980).

The *picrate* was prepared in ethanol to yield 48 mg. of material, m.p. 108–131°. Three recrystallizations from ethanol gave 27 mg. of short prisms, m.p. 133.5–135°. On standing in a vial for 3 months, the melting point was found to be 174–176°. The infrared spectrum (chloroform) of this material was identical with that obtained by synthesis from VI (R = O), (*vide infra*).

Anal. Calcd. for $C_{17}H_{25}NO_2 \cdot C_6H_3N_3O_7$: C, 54.75; H, 5.59; N, 11.11. Found: C, 55.10; H, 5.54; N, 11.16.

2-(β-Dimethylaminoethyl)-2-(3,4-methylenedioxyphenyl)-cyclohexanone (VI, R = O). To a stirred suspension of sodamide (prepared from 690 mg. of sodium) and 20 ml. of benzene was added dropwise a solution of 2.22 g. of 2-(3,4-methylenedioxyphenyl)-cyclohexanone[2] in dry benzene. A dark brown color appeared. The mixture was refluxed for 3 hr. At the end of this time a solution of β-chloroethyldimethylamine (prepared from 10.9 g. of the amine hydrochloride) was added. The reaction mixture was refluxed for 16 hr., chilled, and treated first with ethanol, then with water. The layers were separated, and the aqueous portion was extracted twice with benzene. The benzene solution was extracted once with dilute hydrochloric acid and twice with water, then concentrated under reduced pressure to give 0.917 g. of neutral material with an infrared spectrum identical with that of the starting ketone.

The acidic solution was made basic with sodium hydroxide and extracted four times with benzene to give 1.966 g. of an oil which was chromatographed on 100 g. of alumina. Elution with 10–50% ethyl acetate in benzene and finally with ethyl acetate gave 770 mg. of a clear oil. Infrared spectra of the various chromatographic fractions showed only minor differences.

The *hydrochloride* was formed by saturating an ethanolic solution of the amine with gaseous hydrogen chloride. Three recrystallizations from ethanol–ethyl acetate gave fine white needles, m.p. 245–249° (dec.).

Anal. Calcd. for $C_{17}H_{24}NO_2Cl$: C, 62.66; H, 7.42; N, 4.30. Found: C, 62.70; H, 7.38; N, 4.37.

1-(β-Dimethylaminoethyl)-1-(3,4-methylenedioxyphenyl)-cyclohexane (VI, R = H_2). A solution of 488 mg. of VI (R = O), 2.9 g. of potassium hydroxide and 5 ml. of hydrazine hydrate in 17 ml. of diethylene glycol was refluxed for 6.5 hr. at 150–160°. The mixture was diluted with water, acidified with hydrochloric acid and extracted twice with benzene. The aqueous layer was filtered, made basic with sodium hydroxide and extracted four times with chloroform. The chloroform was evaporated under reduced pressure to leave 256 mg. of oil. The infrared spectrum of this oil showed that reduction was not complete.[13] Chromatography of the oil on 20 g. of alumina and elution with 10% ethyl acetate gave 77 mg. of a clear oil which showed no carbonyl absorption.

The *picrate* was prepared in ethanol and recrystallized three times from ethanol to give elongated prisms, m.p. 173–174°. A mixture melting point with the higher melting polymorphic picrate of VI (R = H_2) which had been obtained from the reduction of Va was 173.5–174.5°.

Anal. Calcd. for $C_{17}H_{25}NO_2 \cdot C_6H_3N_3O_7$: C, 54.75; H, 5.59; N, 11.11. Found: C, 54.97; H, 5.51; N, 11.25.

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(12) (±)-Crinane was reported[2] to melt at 97–99°. A re-examination of this material showed that it is a low melting polymorph of the (±)-crinane reported above. The higher melting form may be isolated either by sublimation of the material melting at 97–99° or by seeding a melt with the higher melting polymorph at 105°. The infrared spectra ($CHCl_3$) of the two forms are identical.

(13) More forcing conditions for the Wolff-Kishner reduction of compounds similar to VI (R = O) have led to ill-defined products lacking the methylenedioxy group, so this method of attempting to improve the yield of VI (R = H_2) was not used. However, it was established that lengthening the reaction time caused no improvement in yield.

Dissociation Constants of 2-Substituted Pyridines

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As part of a research program on pyridine chemistry, the dissociation constants of several 2-substituted pyridines were measured.

EXPERIMENTAL

The half-neutralization method was used and all *p*H measurements were made at 25 ± 0.2°. At least 2 solutions of different concentrations, half neutralized with hydrochloric acid were made for each compound, and four *p*H measurements were made on each solution; this was repeated with a fresh sample of the same solution. All measurements were made on solutions freshly made up from the pyridines immediately after their purification.

All distillations were done on an all-glass column packed with Fenske rings. This column had twelve theoretical plates when tested at atmospheric pressure with benzene–carbon tetrachloride.

Since $BH^+ \rightleftarrows B + H^+$

$K_a = a_B \cdot a_{H^+}/a_{BH^+} = c_B \cdot \gamma_B \cdot a_{H^+}/c_{BH^+} \gamma_{BH^+}$

We assume $\gamma_B = 1.00$ and $c_B = c_{BH^+}$

then $pK_a = pH + \log \gamma_{BH^+}$

The Debye-Huckel limiting law was used in the form $\log \gamma = -0.509\sqrt{\mu}/(1 + \sqrt{\mu})$

No difference in results could be found using carbon dioxide–free water or ordinary distilled water. It was found that carbon dioxide in the air did not change the measured *p*H values even for the weakest acids.

The values in Table I indicate the expected trend in +I effect:

$$(CH_2)_x\,CH_3 > CH_3 > H > CH_2C_6H_5 > CH = CH_2 > Br > Cl$$

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TABLE I

Compound	Fraction Used: B.P., °C.	Fraction Used: Pressure, mm. Hg	n_D^{30}	Conc. of Solutions mol./l.	pK_a at 25° (thermodynamic)
2-Amylpyridine	211	760	1.4848	0.00500, 0.00560	6.00 ± 0.02
2-Hexylpyridine	87	6	1.4850	0.0010	5.95 ± 0.02
2-Methylpyridine	128	760	1.4940	0.142, 0.101	5.94 ± 0.01 (lit. 5.96[a]; 6.02[b])
Pyridine[c]	115	760	1.5033	0.100, 0.005	5.25 ± 0.01 (lit. 5.23[a]; 5.25[b])
2-Benzylpyridine	123–126	5	1.5732	0.00580, 0.00184	5.13 ± 0.01
2-Vinylpyridine	42–44	10	1.5386	0.0220, 0.0128	4.98 ± 0.01
2-Bromopyridine[d]	66	10	1.5658	0.0928, 0.102	0.71 ± 0.01
2-Chloropyridine[d]	170.5	760	1.5262	0.109, 0.114	0.49 ± 0.02
					Standard deviations given

[a] A. Gero and J. Markham, *J. Org. Chem.* **16**, 1835 (1951). [b] R. Pearson and F. Williams, *J. Am. Chem. Soc.* **75**, 3073 (1953). [c] Prepared by several methods: (1) redistilled from reaction of sodium and pyridine; (2) redistilled from pyrolysis of pyridine at 700–800; (3) from zinc chloride addition compound. [d] Since this base is very weak the assumption of $C_B = C_{BH^+}$ is not valid. This pK_a was estimated from $C_{H^+} = a_{H^+}/\gamma_{H^+}$ (using $\gamma_{H^+} = \gamma_{BH^+}$ from Debye-Hückel), $C_{BH^+} = C_{HCl} - C_{H^+}$ and $C_B = C_B^0 - C_{BH^+}$ (where C_{HCl} is concentration of added hydrochloric acid and C_B^0 is initial concentration of the pyridine). Then $pK_a = pH + \log \gamma_{BH^+} + \log C_{BH^+}/C_B$.

1,3,5,7-Tetramethyl-2,4,6,8-tetracarbethoxyporphyrin[1]

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Corwin and Sydow[2] showed that it is possible to produce the copper complex of 1,3,5,7-tetramethyl-2,4,6,8-tetracarbethoxyporphyrin by the condensation of the appropriate bromomethene in the presence of cuprous chloride. Because of the importance of having a number of porphyrins with electron-attracting substituents available for study, we have attempted to improve upon the synthesis of this compound.

We have found that it is possible to prepare the free porphyrin directly without the necessity for an extra step to remove the metal. This is done by the substitution of silver powder for cuprous chloride in the condensation. The reaction is carried out in boiling terphenyl. Subsequent preparation of the silver complex has shown that silver is removed thermally under the reaction conditions, thus accounting for the occurrence of the free porphyrin under the conditions used. The mechanism of this unusual reaction is under investigation.

EXPERIMENTAL

1,3,5,7-Tetramethyl-2,4,6,8-tetracarbethoxyporphyrin. Ten grams of 3,5,4′-trimethyl-4,3′-dicarbethoxy-5′-bromodipyrrylmethene hydrobromide, 5 g. of silver powder and 15 g. of *p,p′*-terphenyl were mixed thoroughly. The mixture was heated in small amounts by a Bunsen burner flame until it started to give a thick smoky ring. This required approximately 10 seconds. After cooling, the material hardened together as a black mass. It was scraped off with a spatula,

(1) Porphyrin Studies. XVI. Paper XV, A. H. Corwin and S. D. Bruck, *J. Am. Chem. Soc.*, **80**, 4736 (1958).

(2) A. H. Corwin and V. L. Sydow, *J. Am. Chem. Soc.*, **75**, 4484 (1953).

extracted with ethylene dichloride, and filtered. The filtrate was concentrated and chromatographed on a column of Fisher's alumina. It was developed with ethylene dichloride until it was washed free from yellow material. Later, the porphyrin was eluted with chloroform. After distilling the chloroform, the porphyrin was purified by extracting with 30% hydrochloric acid. Finally it was crystallized from a mixture of chloroform and methanol. Yield, 2.1% of analytically pure porphyrin.

Anal. Calcd. for $C_{36}H_{38}O_8N_4$: C, 66.06; H, 5.81. Found: C, 66.09; H, 6.35. Spectrum in chloroform: λ 653 mμ (log ε, 3.3377); λ 596 mμ (log ε, 3.7009); λ 557 mμ (log ε, 3.7467); λ 522 mμ (log ε, 4.1196).

Silver complex. Twenty milligrams of the porphyrin was dissolved in 1 ml. of pyridine and a concentrated solution of 50 mg. of silver acetate in pyridine was added. The mixture was heated on a steam bath until it gave a pure silver complex spectrum. (Two bands) The solvent was distilled nearly to dryness under reduced pressure. The residue was washed several times with hot water and dried in a desiccator. The dry material was crystallized from a mixture of benzene and methanol. Yield, 17 mg.

Anal. Calcd. for $C_{36}H_{36}O_8N_4Ag$: C, 56.84; H, 4.76. Found: C, 57.19; H, 4.77. Spectrum in chloroform: 592, 552. In pyridine, 595, 559.

Demetallation of the silver complex. In the presence of excess silver powder the following observations were made: (a) No demetallation in boiling benzene or naphthalene. (b) Heating the silver complex in terphenyl under the conditions used for the synthesis brought about complete demetallation as judged spectroscopically with the Hartridge reversion spectroscope. The demetallation can also be brought about in this solvent by heating in a Wood's metal bath for about 2 min., the time required for the test tube to reach the boiling temperature of the terphenyl. Experiments were performed in the presence and absence of added silver and demetallation took place equally well either way.

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Antihypertensive Agents. III. Dialkylaminoalkoxypiperidines and Related Compounds

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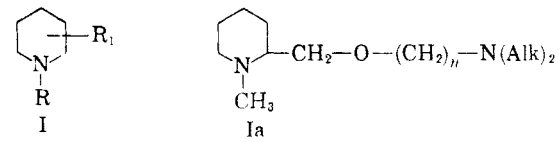
In a previous paper[1] selective effectiveness as hypotensive agents with bistertiary amines of the type I, R = CH_3, R_1 = 2—$CH_2O(CH_2)_nN(Alk)_2$, n = 2 and 3, *i.e.* (Ia), had been noted. In this report the effectiveness of 3- and 4-position analogs of Ia was evaluated. The structure (I), R_1 = 3—$O(CH_2)_nN(Alk)_2$ which retains the two-carbon



I Ia

chain between the piperidine nitrogen and the ether oxygen, characteristic of Ia, was also studied. In addition, replacement of R = CH_3 in Ia by R = $C_6H_5CH_2CH_2$— was investigated. This type of group replacement has been particularly effective in enhancing analgesic properties.[2] The compounds prepared are described in Table I.

The only compound showing even moderate hypotensive activity as the bistertiary amine was compound 7, which is related to Phillips[3] 1-methyl-3-(4′-dimethylaminobutyl)piperidine.

EXPERIMENTAL[4]

N-Alkyl-3-piperidinols. Reductive alkylation of *N*-alkyl-3-piperidinols[5] using formaldehyde and acetaldehyde, respectively, gave *N*-methyl-3-piperidinol (73%), b.p. 103–104° (40 mm.),[6] and *N*-ethyl-3-piperidinol (51%), b.p. 126–128° (40 mm.).[7]

3-(Hydroxymethyl)-1-methylpyridinium bromide. A solution of 56.8 g. (0.52 mol.) of 3-pyridinemethanol in 500 ml. of acetonitrile was cooled to −5° during the addition of 95 g. (1.0 mol.) of methyl bromide. After storage at 20° for 20 hr., 101 g. of product was separated and recrystallized (isopropanol–isopropyl ether) to give 89 g. (84%), m.p. 92–94°.

Anal. Calcd. for $C_7H_{10}BrNO$: C, 41.2; H, 4.9; N, 6.9. Found: C, 40.7; H, 5.2; N, 6.9.

1-Methanol-3-piperidinemethanol hydrobromide was prepared in 70% yield (using the method previously described[1] for the 2-hydroxymethyl analog), m.p. 113–115° (ethanol–methyl ethyl ketone).

Anal. Calcd. for $C_7H_{16}BrNO$: C, 40.0; H, 7.7; N, 6.7. Found: C, 40.3; H, 7.9; N, 6.6.

1-Ethyl-4-piperidinemethanol. A solution of 89.1 g. (0.82 mol.) of 4-pyridinemethanol and 133 g. (1.2 mol.) of ethyl bromide in 800 ml. of acetonitrile was heated under reflux for 24 hr. Removal of the solvent and seeding gave a solid which after trituration with ether yielded 170 g. of crude 4-(hydroxymethyl)-1-ethylpyridinium bromide.

The crude quaternary salt was hydrogenated directly by the method described above[1] and converted to the piperidine base with 40% sodium hydroxide. The reaction mixture was salted with potassium carbonate, extracted with ether, dried (anhydrous magnesium sulfate) and distilled to yield 4-hydroxymethyl-1-ethylpiperidine (31%) b.p. 90–92° (0.15 mm.).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.1; H, 12.0; N, 9.8. Found: C, 66.7; H, 12.0; N, 9.5.

2-Hydroxymethyl-1-phenethylpyridinium bromide. 2-Pyridinemethanol (22 g., 0.2 mol.) and 40.7 g. (0.22 mol.) of phenethyl bromide were dissolved in 250 ml. of acetonitrile

(1) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, 80, 2743 (1958).

(2) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).

(3) A. P. Phillips, *J. Am. Chem. Soc.*, **76**, 2211 (1954).

(4) Descriptive data shown in the table are not reproduced in the Experimental section.

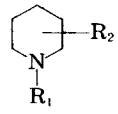
(5) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc., (Sci. Ed.)*, **46**, 333 (1957).

(6) S. Tchelitcheff, U. S. Patent **2,489,546** (Nov. 29, 1949), reports b.p. 79° (15 mm.).

(7) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Am. Chem. Soc.*, **74**, 1485 (1952), report b.p. 93–95° (15 mm.).

TABLE I

DIALKYLAMINOALKOXYALKYLPIPERIDINES



No.	R_1	R_2	Yield,[a] %	M.P.[b,c(a)] or B.P. (Mm.)	Formula	Analyses[d] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Activity
1[e]	CH_3—	3-$O(CH_2)_2N(CH_3)_2$	11	100–103 (9)								0
2	$2CH_3I$[f]		60	294–297[c(b)]	$C_{12}H_{28}IN_2O$	30.6	30.8	6.0	6.1	6.0	6.0	1+
3	C_2H_5—	3-$O(CH_2)_2N(CH_3)_2$	17	102–106 (8)	$C_{11}H_{24}N_2O$	66.0	65.6	12.1	12.3			0
4	CH_3—	3-$O(CH_2)_3N(CH_3)_2$	50	142–144 (35)	$C_{11}H_{24}N_2O$	66.0	65.8	12.1	11.8	14.0	13.5	0
5	$2CH_3I$[f]		85	214–216	$C_{13}H_{30}I_2N_2O$	32.2	32.2	6.2	6.2	5.8	5.7	1+
6	$2C_2H_5I$[g]		71	171–174	$C_{15}H_{34}I_2N_2O$	35.2	34.9	6.7	7.0			0
7	C_2H_5—	3-$O(CH_2)_3N(CH_3)_2$	38	116–118 (6)	$C_{12}H_{26}N_2O$					13.1	13.1	2+
8	$2CH_3I$[f]		52	197–200	$C_{14}H_{32}I_2N_2O$	33.8	33.8	6.5	6.5	5.6	5.2	3+
9[h]	CH_3—	3-$CH_2O(CH_2)_2N(C_2H_5)_2$	10	113 (2)								0
10	C_2H_5—	4-$CH_2O(CH_2)_2N(C_2H_5)_2$	40	106 (0.9)	$C_{14}H_{30}N_2O$	69.4	69.1	12.5	12.6	11.6	11.6	0
11	$C_6H_5CH_2CH_2$—	2-$CH_2O(CH_2)_2N(C_2H_5)_2$	4	120–124 (0.08)	$C_{20}H_{34}N_2O$	75.4	75.3	10.8	10.2			0

[a] Yields are based on distilled or recrystallized product. [b] Melting points are not corrected and were obtained on a Fisher-Johns melting point block. [c] (a) Recrystallizing solvent is ethanol unless otherwise shown; (b) methanol. [d] Analyses by Weiler and Strauss, Oxford, England. [e] Characterized as the methiodide (Compound 2). [f] Compound is the dimethiodide of bisamine immediately above. [g] Compound is the diethiodide of bisamine immediately above. [h] B. Elpern, U. S. Patent 2,773,876 (Dec. 11, 1956) reports b.p. 113–118° (3.2 mm.).

and heated under reflux for 22 hr. The solvent was removed to give 19 g. (32%), m.p. 150–154°. Recrystallization (ethanol) gave m.p. 158–159°.

Anal. Calcd. for $C_{14}H_{16}BrNO$: C, 57.2; H, 5.5; N, 4.8. Found: C, 57.4; H, 5.7; N, 5.1.

1-Phenethyl-2-piperidinemethanol hydrobromide. A mixture of 14 g. (0.048 mol.) of 2-hydroxymethyl-1-phenethylpyridinium bromide in 250 ml. of ethanol and 1.3 g. of 5% rhodium on carbon afforded complete uptake of hydrogen[1] after 3 hr. The catalyst was removed and the filtrate concentrated to dryness. Crystallization (ethanol-ether) gave 10 g., m.p. 153–154° and recrystallization (ethanol-ether) gave m.p. 157–158°.

Anal. Calcd. for $C_{14}H_{22}BrNO$: C, 56.0; H, 7.4; N, 4.7. Found: C, 56.3; H, 7.1; N, 4.9.

3-(3-Dimethylaminopropoxy)-1-ethylpiperidine (Compound 7). Sodium hydride (3.1 g., 0.13 mol.) was stirred under 50 ml. of dry toluene while a solution of 15.4 g. (0.12 mol.) of 1-ethyl-3-piperidinol in 50 ml. of toluene was added over 40 min. Stirring was continued at 20° for 2 hr. and then under reflux for 2 hr. This solution was treated over 1 hr. with the filtered solution prepared from 38.4 g. (0.24 mol.) of 3-dimethylaminopropyl chloride hydrochloride dissolved in water, made basic with 40% sodium hydroxide, extracted with 150 ml. of toluene and dried (magnesium sulfate). Reflux was continued for 6 hr. When cool, the mixture was filtered and the residue distilled to yield 9.8 g. (38%) of product, b.p. 116–118° (6 mm.).

3-(3-Dimethylaminopropoxy)-1-ethyl-1-methylpiperidinium iodide methiodide (Compound 8). Addition of 3.2 g. (0.015 mol.) of 3-(3-dimethylaminopropoxy)-1-ethylpiperidine in 10 ml. of acetonitrile to a cooled solution of 4.7 g. (0.033 mol.) of methyl iodide in 15 ml. of acetonitrile caused an immediate exothermic reaction. After 20 hr. the precipitated product (4.7 g.) was separated.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological results of the screening of the compounds and Mrs. T. Ast for technical assistance.

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6-Alkylacridizinium Derivatives[1]

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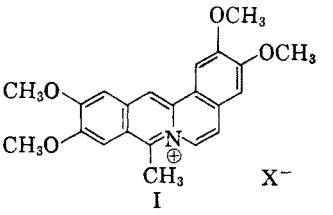
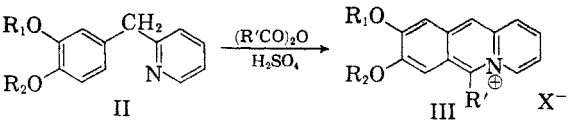
Probably the first reported compound containing the fully aromatic quinolizinium[2] nucleus was the Coralyn (I) of Schneider and Schroeter,[3,4] described in 1920. Coralyn, an 8-methyl-2,3,10,11-tetramethoxybenz[a]acridizinium salt was obtained in 90% yield by the action of sulfoacetic acid (acetic anhydride containing a small amount of sulfuric acid) on papaverine.



I

It seemed likely that 2-(3,4-dialkoxybenzyl)-pyridines (II) might be made to undergo a similar acylative cyclization, affording the first simple 6-alkylacridizinium salts III.



II III

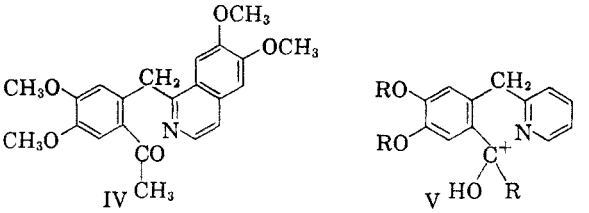
The requisite benzylpyridines (II) were prepared by reaction of 2-pyridyllithium with the appropriate aldehyde, followed by reduction of the crude carbinol. The acylative cyclization was carried out at 100° by means of sulfuric acid in a large excess of the appropriate anhydride, and the results are summarized in Table I.

TABLE I

6-ALKYL-8,9-ALKOXYACRIDIZINIUM SALTS (III)

R_1	R_2	R′	% Yield (as)	Ultraviolet Absorption Maxima, mμ (Perchlorate)		
CH_3	CH_3	CH_3	—[a]	368	382	401
C_2H_5	C_2H_5	CH_3	74[b](ClO_4)	370	384	404
C_2H_5	C_2H_5	C_2H_5	48[c]	370	385	405
—CH_2—		CH_3	25(Pic.)[d]			

[a] A 31% yield of sulfoacetate, m.p. 255–262° (dec.), was recorded, but this salt was never obtained in a state of analytical purity. [b] Product melting at 252–256° (dec.). [c] A part of the yield (25%) was obtained as the perchlorate m.p. 260–264° (dec.), the remainder (23%) as picrate, m.p. 188–192°. [d] No perchlorate of this compound was prepared.



IV V

Schneider and Schroeter[3] adduced evidence to show that the acetylative cyclization of papaverine occurred *via* acetopapaverine (IV). Probably the acylative cyclization of the 2-(3,4-dialkoxybenzyl)pyridine likewise occurs *via* a carbonyl derivative, or more exactly, *via* the conjugate acid V. The Coralyn synthesis can be regarded not only as the prototype of the Woodward synthesis of

(1) Taken in part from a thesis submitted in partial fulfillment of the requirements for the Ph.D. Degree, Duke University, 1958. This research was supported by a research grant (NSF-G2364) of The National Science Foundation.

(2) *Chemical Abstracts* nomenclature.

(3) W. Schneider and K. Schroeter, *Ber.* **53B**, 1459 (1920).

(4) W. Schneider and O. Boger, *Ber.*, **54B**, 2021 (1921).

TABLE II

6-ALKYLACRIDIZINIUM SALTS, III

R_1	R_2	R′	M.P., °C.	Formula	C Calcd.	C Obsd.	H Calcd.	H Obsd.	N Calcd.	N Obsd.
				Picrates						
CH_3	CH_3	CH_3	239–241 (dec.)[a]	$C_{22}H_{18}N_4O_9$	54.80	55.02	3.76	3.91	11.62	12.04
C_2H_5	C_2H_5	CH_3	205–206[b]	$C_{24}H_{22}N_4O_9 \cdot {}^1/_2H_2O$	55.00	54.81	4.46	4.72	10.79	10.65
C_2H_5	C_2H_5	C_2H_5	197–199[c]	$C_{25}H_{24}N_4O_9$	57.25	57.43	4.62	4.92	10.69	10.50
—CH_2—		CH_3	235–236[d]	$C_{21}H_{14}N_4O_9$	54.09	54.03	3.03	3.19	12.01	11.99
				Perchlorates						
CH_3	CH_3	CH_3	288–291[e]	$C_{16}H_{16}ClNO_6$	54.10	54.39	4.57	4.59	3.86	4.32
C_2H_5	C_2H_5	CH_3	272–274[f]	$C_{18}H_{20}ClNO_6 \cdot 3/2H_2O$	52.98	53.13	5.67	5.72	3.44	3.68
C_2H_5	C_2H_5	C_2H_5	269–270[g]	$C_{19}H_{22}ClNO_6$	57.69	57.31	5.56	5.66	3.56	3.75

[a] Needles from acetone. [b] Well formed needles from acetone-ethanol. [c] Flakes from acetone-ethanol. [d] Granules from ethanol. [e] All of the perchlorates formed needles which melted with decomposition. [f] From acetone-water. [g] From acetone-ethanol.

quinolizinium derivatives,[5–8] but also a further example of aromatic cyclodehydration,[9] one involving electrophilic attack on aromatic nitrogen rather than the usual carbon.

EXPERIMENTAL[10]

2-(3′,4′-Methylenedioxybenzyl)pyridine (II) (R_1 — R_2 = —O—CH_2O—) was prepared essentially as in the case of the known 2-(3,4-dimethoxybenzyl)pyridine[11] (II, R_1 = R_2 = OCH_3). To a solution of butyllithium prepared from 30.5 g. of *n*-butyl chloride, and maintained at a temperature of −50°, 40 g. of 2-bromopyridine was added in dry ether. The reaction mixture was stirred for 15 min., and then 42.7 g. of piperonal in dry ether was added. The temperature of the mixture was maintained at 0° for 1 hr. longer, and then allowed to come to room temperature. The reaction mixture was poured into dilute acid, the acid layer separated and made basic, and the resulting oil taken up in ether. The ethereal solution was washed, dried and concentrated and the crude residue was used directly for the reduction. A solution of the residue in 300 ml. of benzene was cooled and treated with 38 g. of thionyl chloride, the temperature being kept below 25°. After the mixture had stood for an additional hour, it was made basic with sodium hydroxide solution. The benzene layer was separated, wahed, dried and concentrated. The residue was dissolved in 250 ml. of glacial acetic acid and while this was heated on the steam bath during a 6 hr. period, 36 g. of zinc powder was added in small portions. The excess zinc was removed by filtration, the acetic acid was evaporated under reduced pressure, and the residue made alkaline with sodium hydroxide. The oil which separated was taken up in ether, and the ethereal extract washed, dried and concentrated. The residue was fractionated yielding 13.2 g. (28%) of an oil, b.p. 185–196° (3 mm.).

A *picrate* was prepared for analysis as fine yellow granules from ethanol, m.p. 143–145°.

Anal. Calcd. for $C_{19}H_{13}N_4O_9$: C, 51.70; H, 2.97; N, 12.70. Found: C, 52.00; H, 3.59; N, 12.66.

2-(3′,4′-Diethoxybenzyl)pyridine (II, R_1 = R_2 = OC_2H_5). Essentially the same procedure was used except that the aldehyde was 3,4-diethoxybenzaldehyde. The yield of 2-(3′,4′-diethoxybenzyl) pyridine, b.p. 170–180°(3 mm.) was 12.5%.

The *picrate*, prepared for analysis, crystallized from ethanol as bright yellow clusters, m.p. 157–158°.

Anal. Calcd. for $C_{22}H_{22}N_4O_9$: C, 54.40; H, 4.56; N, 11.51. Found: C, 54.36; H, 4.84; N, 11.79.

Acetylative cyclization of the benzylpyridine derivatives. One gram of the benzylpyridine derivative (II) was dissolved in 20 ml. of acetic or propionic anhydride containing 0.8 ml. of concentrated sulfuric acid. The mixture was heated on the steam bath for 2 hr., after which it was cooled, and the salt precipitated by addition of ether. The organic solvents were separated from the salt either by filtration or decantation. The crude sulfoacetate salt was dissolved in water, and perchloric acid added to precipitate the product as a *perchlorate* salt which was crystallized from an acetone-ethanol mixture.

The *picrate* was prepared by addition of an alcoholic solution of picric acid to an aqueous solution containing the crude sulfoacetate salt. The results are summarized in Table II.

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(5) R. B. Woodward and B. Witkop, *J. Org. Chem.*, **71**, 379 (1949).

(6) R. B. Woodward and W. M. McLamore, *J. Org. Chem.*, **71**, 379 (1949).

(7) A. Richards and T. S. Stevens, *Chem. and Ind.* **1954**, 905.

(8) A. Richards and T. S. Stevens, *J. Chem. Soc.*, 3067 (1958).

(9) *Cf.*, C. K. Bradsher, *Chem. Revs.*, **38**, 447 (1946).

(10) All melting points were taken on a Fisher-Johns hot stage and are uncorrected. All analyses were by Micro Tech Laboratories, Skokie, Illinois.

(11) N. Sugiomoto, *J. Pharm. Soc. Japan*, **76**, 1045 (1956).

Benzo[*b*]quinolizidine Derivatives[1]

C. K. BRADSHER AND NANCY L. YARRINGTON

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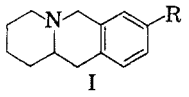
It was shown earlier[2] that benzo[*b*]quinolizidine derivatives (I, R = H) can be produced by the catalylic reduction of the acridizinium nucleus. As part of a study of the relation between structure

(1) This investigation was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

(2) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).



I

and hypotensive activity, we have prepared a few benzo[*b*]quinolizidine derivatives. It has been found that sodium borohydride may be used for the reduction of acridizinium bromide to I (R = H).

EXPERIMENTAL[3]

2-Aldoximino-1-(3-methoxy)benzylpyridinium bromide. To a flask containing 5 ml. of dimethyl formamide, 4.88 g. of pyridine 2-aldoxime and 8.04 g. of *m*-methoxybenzyl bromide were added. The flask was warmed gently on the steam bath until solution was complete, then stoppered and allowed to stand for 24 hr. at room temperature. The colorless crystals were triturated with ethyl acetate and collected. The yield was 11.41 g. (88%), m.p. 178–182°. The analytical sample melted at 180–182°.

Anal. Calcd. for $C_{14}H_{15}BrN_2O_2$: C, 52.03; H, 4.68; N, 8.67. Found: C, 52.44; H, 4.84; N, 8.55.

8-Methoxyacridizinium perchlorate. To a solution containing 1 g. of the oximino quaternary salt in 8 ml. of absolute alcohol, 6 ml. of concentrated hydrochloric acid was added, and the mixture refluxed for 5 hr. After vacuum evaporation of the solvents the residual yellow solid was washed with ethyl acetate and then dissolved in a small quantity of water. The perchlorate was precipitated by addition of perchloric acid. Recrystallization of the product from methanol yielded 0.41 g. (44%) of yellow platelets, m.p. 222–224° (lit.[4] 218–219°).

8-Hydroxyacridizinium bromide. The oximino quaternary salt (5.9 g.) was placed in 30 ml. of 48% hydrobromic acid and the mixture refluxed for 45 min. The mixture was vacuum evaporated and the residue crystallized from a concentrated ethanol solution. The yield was 3.9 g. (97%),[5] m.p. 246–248° (lit.[4] 250–252°).

8-Methoxybenzo[b]quinolizidine (I, R = OCH_3) *hydroperchlorate.* To a suspension of 5.2 g. of 8-methoxyacridizinium perchlorate in 300 ml. of methanol, 100 mg. of platinum oxide was added and hydrogenation was carried out at room temperature and atmospheric pressure until the theoretical amount of hydrogen had been absorbed. The solution was filtered, concentrated, and cooled; 4.4 g. (83%) of colorless crystals, m.p. 175–177° was obtained.

Anal. Calcd. for $C_{14}H_{20}ClNO_4$: C, 52.92; H, 6.35; N, 4.41. Found: C, 53.10; H, 6.07; N, 4.50.

8-Methoxybenzo[b]quinolizidine (I. R = OCH_3) was recrystallized from ethanol, m.p. 50–51°.

Anal. Calcd. for $C_{14}H_{19}NO \cdot {}^1/_3H_2O$: C, 75.30; H, 8.88; N, 6.27. Found: C, 75.58; H, 8.69; N, 6.15.

8-Hydroxybenzo[b]quinolizidine (I. R = OH) *hydrochloride.* The reduction of 1.7 g. of the 8-hydroxyacridizinium salt was carried out as in the case of the methyl ether. Concentration of the methanol solution yielded 1.51 g. (88%), decomposes 268–290°. The analytical sample consisted of colorless prisms, decomposes 276–318°.

Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.57; N, 5.81. Found: C, 65.37; H, 7.69; N, 5.70.

8-Hydroxybenzo[b]quinolizidine (I. R = OH) was obtained as a colorless powder, m.p. 230–231°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.82; H, 8.43; N, 6.90. Found: C, 76.51; H, 8.35; N, 7.04.

The *methiodide* was prepared in 92% yield by refluxing a methanol solution of the base for 1 hr. with excess methyl iodide. It formed colorless needles from ethanol, m.p. 274–275°.

Anal. Calcd. for $C_{14}H_{20}INO$: C, 48.72; H, 5.84; N, 4.06. Found: C, 48.56; H, 5.91; N, 4.25.

Benzo[b]quinolizidine (I. R = H) *methiodide.* (a) *From the hydrobromide.* Benzo[b]quinolizidine hydrobromide[2] was converted to the free base by action of ammonia, and the crude base obtained by ethereal extraction was methylated with methyl iodide. The product was obtained from ethanol as colorless irregular crystals, m.p. 290–291°.

(b) *From the sodium borohydride reduction product.* To a solution of 2 g. of acridizinium bromide in 45 ml. of water an aqueous suspension 0.68 g. of sodium borohydride was added. The mixture was heated on the steam bath until the evolution of hydrogen ceased and a red oil separated. The oil was taken up in ether, the solution dried and concentrated, and the residue heated with methyl iodide on the steam bath for 2 hr. The product melted at 267–268° and the melting point did not change on recrystallization. When a sample of the product was dissolved in ethanol and seeded with a single crystal of product obtained by Procedure a, the entire material crystallized in irregular clusters, m.p. 290–291°. The infrared spectrum of this material was identical with that of the product obtained by Procedure a.

Anal. Calcd. for $C_{14}H_{20}IN$: C, 51.07; H, 6.12; N, 4.25. Found[6]: C, 51.27, 50.97; H, 5.85, 5.96; N, 4.13, 4.55.

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(3) All melting points were taken on a Fisher-Johns hot stage and are uncorrected. All analyses were performed by Drs. Weiler and Strauss, Oxford, England.

(4) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).

(5) Only a 37% yield of 8-hydroxyacridizinium was reported earlier [ref. (4)] for the cyclization of crude 1-(3-methoxybenzyl)-2-formylpyridinium bromide.

(6) Values are for the product of Procedure *a* and for the low-melting form (m.p. 267–268°) obtained by Procedure *b*.

9(11)-Dehydrocortical Steroids. Synthesis of 9(11)-Anhydro-17α-hydroxycorticosterone Acetate and 9(11)-Anhydrocorticosterone Acetate

E. M. CHAMBERLIN, E. W. TRISTRAM, T. UTNE, AND J. M. CHEMERDA

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The elimination of the 11β-hydroxyl group from the steroidal nucleus to give 9(11)-dehydro compounds is easily accomplished because of the favorable conformation of the 11β-hydroxyl group and the 9α-hydrogen atom (di-axial-trans).[1] Reichstein and his co-workers[2] have reported the conversion of 11β-hydroxylated cortical steroids without a 17α-hydroxyl function to 9(11)-anhydro derivatives using phosphorus oxychloride and pyridine or refluxing acetic-hydrochloric acid mixtures. In the

(1) W. A. Cranshaw, H. B. Henbest, and E. R. Jones, *J. Chem. Soc.*, **73** (1954); H. L. Herzog, C. C. Payne, and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 930 (1954).

(2) (a) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740 (1940); (b) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **24**, 351 (1941); (c) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **26**, 715 (1943); (d) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 1316 (1943).

case of the steroidal hormones where an α,β-unsaturated ketone is present, the usual reagents for dehydration lead to complications. Graber, Haven, and Wendler[3] have reported the preparation of 17α-hydroxy-21-acetoxy-4,9(11-)pregnadiene-3-20-dione, [9(11)-anhydro-17α-hydroxycorticosterone acetate], by an indirect method from 11β-hydroxy-20-cyano-21-acetoxy-17(20)-pregnen-3-one. The dehydration of this latter compound was effected with phosphorus oxychloride and pyridine. In compounds where the Δ^4-3-ketone structure is absent, these latter authors[3] have shown that dehydration with phosphorus oxychloride-pyridine proceeds without complications to give the anhydro compound in good yields—e.g., 11β,17α-dihydroxy-21-acetoxypregnane-3,20-dione gives 17-α-hydroxy-21-acetoxy-9(11)-pregnene-3,20-dione in 73% yield.

The preparation of 9-halo derivatives of 11β,17α-dihydroxy-21-acetoxy-4-pregnen-3,20-dione (hydrocortisone acetate) demanded a ready supply of the 9(11)-anhydro compound, 17α-hydroxy-21-acetoxy-4,9(11)-pregnadien-3,20-dione, and a direct method of dehydration of the readily available hydrocortisone acetate was sought. Two reagents, methanesulfonyl chloride and methyl chlorosulfite, were found which bring about this dehydration smoothly and in good yield. One of these reagents was mentioned briefly without details in the preparation of 17α-hydroxy-21-acetoxy-1,4,9(11)-pregnatrien-3,20-dione from 11β,17α-dihydroxy-21-acetoxy-1,4-pregnadien-3,20-dione (prednisolone acetate)[4] and we are prompted to communicate our experience with this dehydration.

Initially, hydrocortisone acetate in pyridine reacted with methanesulfonyl chloride at room temperature in the course of 24 hr. to give a 30% yield of the 9(11)-anhydro compound. Further study of this reaction lead to optimum conditions whereby the dehydration was carried out with methanesulfonyl chloride in pyridine-dimethylformamide solution at 80–85° to give 75–80% yield of product.

The method appears to be generally applicable and has been employed in the dehydration of corticosterone acetate.

A more vigorous dehydrating agent was methyl chlorosulfite.[5] This reagent effected dehydration of hydrocortisone acetate in tetrahydrofuran-pyridine solution at −10 to −5° over a period of 4 hr. or in dimethylacetamide solution at 20–25° over a period of 30 min. The yield with this reagent was 65–89% of theory. It is of interest that in the dehydration of cholesterol to cholestadiene with methyl chlorosulfite reported by Berti[5] the methyl sulfonyl ester was first obtained and isolated and the dehydration was achieved only by heating at 185–270° under 20 mm. vacuum. In the present work despite our efforts to isolate the intermediate esters no trace of these intermediates could be isolated.

EXPERIMENTAL

17α-Hydroxy-21-acetoxy-4,9(11)-pregnadien-3,20-dione. (a) Methanesulfonyl chloride method. To a slurry of 10 g. (0.0247 mol.) of 11β,17α-dihydroxy-21-acetoxy-4-pregnen-3,20-dione (hydrocortisone acetate) in 50 ml. of dry dimethylformamide[6] and 8.8 ml. of dry pyridine was added dropwise with stirring 6.43 g. (4.4 ml., 0.0564 mol.) of methanesulfonyl chloride. The reaction mixture was stirred and the temperature maintained at 80–85° for 1 hr. after all the methanesulfonyl chloride had been added. At the end of the reaction period the temperature was brought to 25–30° and the mixture was diluted with 200 ml. of methanol. After cooling (ice bath) for 1/2 hr. the product was filtered and washed with methanol. Recrystallization from methylene chloride–methanol afforded 7.4 g. (77.5%) of product, m.p. 228–238°; infrared identical with an authentic sample. An analytical sample melted 232.5–236.5° (lit.[3] m.p. 231.5–234.5°).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.47; H, 7.38. Found: C, 71.08; H, 7.93.

(b) Methyl chlorosulfite method. Four grams (0.01 mol.) of 11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione (hydrocortisone acetate) was dissolved in 20 cc. of dry dimethylacetamide. To this solution was added with stirring 11 g. (0.084 mol.) of methyl chlorosulfite.[5] During the addition the temperature was kept between 20–25° by external cooling. During the course of the addition the mixture set to a semi-solid mass. When the addition of the methyl chlorosulfite was complete (30 min.), 70 ml. of methanol was added and the mixture was aged in an ice bath for 1/2 hr. The product was filtered and washed with methanol, 2.5 g. (65%), m.p. 205–225°. Recrystallized from chloroform-methanol, the product melted 237–240°. Identity was established by infrared comparison and mixed melting point.

A 4-g. sample (0.01 mol.) of 11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione was dissolved by heating in 150 ml. of dry tetrahydrofuran and the solution was cooled to −10°. Dry pyridine (8 ml.) was added. To the cooled solution was added with stirring 11.5 g. (0.088 mol.) of methyl chlorosulfite.[5] The temperature was kept between −10 and −5° during the addition of the reagent. The reaction mixture was then allowed to come to room temperature over a period of 4 hr and the product was precipitated by the addition of 150 ml. of ice water. The product was filtered after aging 1/2 hr. and washed with cold water, yield 3.45 g. (89%), m.p. 226–230°. The identity of the substance was confirmed by mixed melting point and comparison of the infrared spectrum.

21-Acetoxy-4,9(11)-pregnadien-3,20-dione. A 4-g. sample (0.013 mole) of 11β-hydroxy-21-acetoxy-4-pregnene-3,20-dione (corticosterone acetate) was dissolved in 20 ml. of dry dimethylformamide. To this solution was added 1.6 ml. of dry pyridine and 2 ml. of methanesulfonyl chloride. The reaction mixture stood at room temperature 3 days. At the end of this time 60 ml. ice water was added. The precipitated product was filtered, washed with water, and twice recrystallized from methanol, m.p. 153–157° (lit.[2d] m.p. 159–160°); infrared 5.75 μ (OAc), 5.82 μ (>C=O), 6.01 μ, 6.19 μ (—C=C—C=O), no OH band.

(3) R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, *J. Am. Chem. Soc.*, **75**, 4722 (1953).

(4) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restino, A. Borman, and F. M. Singer, *J. Am. Chem. Soc.*, **77**, 4181 (1955).

(5) Berti, *J. Am. Chem. Soc.*, **76**, 1214 (1954).

(6) The steroid initially all goes into solution and then reprecipitates as a dimethylformamide complex.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.50; H, 8.16. Found: C, 74.71; H, 8.22.

Acknowledgment. The authors are indebted to Dr. N. Trenner and Mr. R. Walker for the infrared spectra and to Mr. R. N. Boos and staff for the analytical data reported.

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16-Hydroxylated Steroids. XIII.[1] 9α-Fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione

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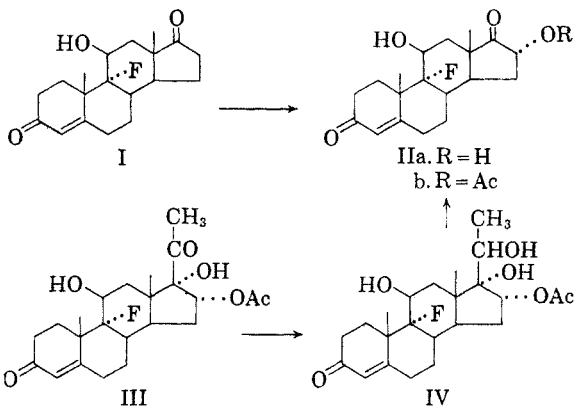
The research program of this laboratory on the preparation of 16-hydroxylated steroids has been extended to include C19-steroids. We wish to report on the synthesis of 9α-fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione (IIa).[2]

9α-Fluoro-11β-hydroxy-4-androstene-3,17-dione (I)[3] on microbiological hydroxylation with *Streptomyces roseochromogenus* (Lederle AE 409)[4] afforded 9α-fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione (IIa). The structure of the fermentation product was established as follows:

Compound IIa exhibited a positive Blue Tetrazolium test indicative of the 16,17-ketol moiety.[5] Acetylation gave the monoacetate IIb, in turn, synthesized from 16α-acetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (III).[6] Reduction of III in methanol at 0° with sodium borohydride gave 16α-acetoxy-9α-fluoro-11β,17α,20-trihydroxy-4-pregnen-3-one (IV).[7] The latter on the basis of elemental analyses was apparently obtained in a pure state. However, its ultraviolet absorption spectrum, $\lambda_{max}^{methanol}$ 240 mμ (ε 11,000), revealing a low molecular extinction coefficient,[8] indicated that reduction in part of the C3-carbonyl and/or the C4-5-double bond had occurred.[9] The material as such in methanol was treated with an aqueous solution of sodium periodate at room temperature to give after partition chromatography 16α-acetoxy-9α-fluoro-11β-hydroxy-4-androstene-3,17-dione (IIb), identical in all respects with the acetylated fermentation product.

Bioassay. Rosemberg and Dorfman[10] have recently cited 9α-fluoro-11β-hydroxy-4-androstene-3,17-dione (I) as the first instance of a highly active sodium retaining substance in the C19-series. These same investigators have now found in a preliminary assay that 9α-fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione (IIa) was inactive in the electrolyte assay (saline load, six hours) on adrenalectomized rats at 6, 25, and 100 μg. dose levels.[11]

Flow Sheet



EXPERIMENTAL

All melting points are uncorrected.

9α-Fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione (IIa). Forty 500 ml. flasks were charged with 100 ml. each of the following medium: corn steep liquor (30 g.), glucose (30 g.), soybean oil (5 g.), and calcium carbonate (5 g.) in 1 l. of distilled water. Each flask, after the addition of 25 mg. of 9α-fluoro-11β-hydroxy-4-androstene-3,17-dione (I) dissolved in 1 ml. of methanol, was inoculated with 4 ml. of a 48 hr. (28°) mycelial growth of *Streptomyces roseochromogenus* (Lederle AE 409). The fermentation was carried out for 78 hr. at 28° with shaking (rotary shaker, 240 RPM).

The pooled fermentation mixture was filtered, and the filtrate was extracted twice with 4 l.-portions of chloroform. The combined extracts were washed with water, treated with animal charcoal, dried and evaporated. The crude residue was subjected to partition chromatography on 300

(1) Paper XII, S. Bernstein, R. Littell, J. J. Brown, and I. Ringler, *J. Am. Chem. Soc.*, **81**, 4573 (1959).

(2) G. H. Thomas and R. W. Thoma, U. S. Patent **2,853,502** (Sept. 23, 1958), have also described the preparation of IIa by microbiological 16α-hydroxylation.

(3) S. Bernstein and R. H. Lenhard, *J. Am. Chem. Soc.*, **77**, 6665 (1955); J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(4) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progr. Hormone Research*, **9**, 149 (1955); R. W. Thoma, J. Fried, S. Bonanno and P. Grabowich, *J. Am. Chem. Soc.*, **79**, 4818 (1957).

(5) A. S. Meyer and M. C. Lindberg, *Anal. Chem.*, **27**, 813 (1955).

(6) S. Bernstein, J. J. Brown, L. I. Feldman, and N. E. Rigler, *J. Am. Chem. Soc.*, **81**, 4956 (1959).

(7) The reduction of the C20-carbonyl group presumably provided the 20β-hydroxyl group; see, D. K. Fukushima and E. D. Meyer, *J. Org. Chem.*, **23**, 174 (1958).

(8) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(9) F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz, *Chem. & Ind.* (London), 1482 (1954); J. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

(10) E. Rosemberg and R. I. Dorfman, *Proc. Exptl. Biol. and Med.*, **99**, 336 (1958).

(11) We wish to thank the Worcester Foundation group for carrying out this assay, the details of which will be reported by them elsewhere.

g. of Celite[12] with a ternary system consisting of 1 part water, 5 parts dioxane, and 4 parts cyclohexane. The fraction collected from 2.3–3.9 hold-back volumes (HBV) (maximum product at 3.3) (1 HBV = 485 ml.) was evaporated to afford 604 mg. of crude IIa. Two crystallizations from acetone gave pure IIa, m.p. 262–270° with previous softening and browning and with decomposition at 271°; $\lambda_{max}^{methanol}$ 237 mμ (ε 17,400); ν_{max}^{KBr} 3510, 3400, 3250, 1754, 1657, 1640–1615 (inflection) cm.$^{-1}$; $[\alpha]_D^{25}$ +157° (methanol); positive Blue Tetrazolium test.

Anal. Calcd. for $C_{19}H_{25}O_4F$ (336.39): C, 67.83; H, 7.49; F, 5.65. Found: C, 67.64; H, 7.65; F, 5.86.

16α-Acetoxy-9α-fluoro-11β,17α,20-trihydroxy-4-pregnen-3-one (IV). A solution of 350 mg. of 16α-acetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (III) in 50 ml. of methanol was cooled to 0° and treated with 47 mg. of sodium borohydride. After remaining at 0° for 1 hr., the solution was acidified with 0.2 ml. of glacial acetic acid and evaporated. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution and water. The dried extract was evaporated and the residue crystallized from acetone-petroleum ether to afford 254 mg. of crude IV, m.p. 215–219.5° with previous softening. Two additional crystallizations from the same solvent pair gave 228 mg., m.p. 214.5–217.5° with previous softening; $\lambda_{max}^{methanol}$ 240 mμ (ε 11,000); ν_{max}^{KBr} 3430, 1725, 1666, 1625, 1277, and 1253 cm.$^{-1}$; $[\alpha]_D^{25}$ −19° (acetone).

Anal. Calcd. for $C_{23}H_{33}O_6F$ (424.49): C, 65.07; H, 7.84; F, 4.48. Found: C, 64.99; H, 8.17; F, 4.19.

This material was used as such in the subsequent side chain degradation.

16α-Acetoxy-9α-fluoro-11β-hydroxy-4-androstene-3,17-dione (IIb). A. Forty milligrams of IIa in 2 ml. of pyridine was treated with 1 ml. of acetic anhydride, and the mixture was allowed to stand at room temperature overnight. The crude acetate was subjected to partition chromatography on 31 g. of Celite[12] with the system four parts petroleum ether (b.p. 90–100°), three parts ethyl acetate, four parts methanol, and two parts water. The fraction collected from 3.5–5.5 hold-back volumes (maximum product at 4.7) (1 HBV = 38 ml.) was evaporated, and the residue was crystallized from acetone-petroleum ether (b.p. 35–60°) to afford pure IIb, m.p. 248–250°. Its infrared spectrum was identical with that obtained in preparation B.

B. A solution of 380 mg. of impure 16α-acetoxy-9α-fluoro-11β,17α,20-trihydroxy-4-pregnen-3-one (IV) in 20 ml. of methanol was treated with 7.6 ml. of an aqueous solution of sodium periodate (0.1*M*). After standing at room temperature for 19 hr., the solution was poured into ice water, and the resultant precipitate was filtered and washed with water to afford 178 mg. of crude product, m.p. 227.5–236° with previous softening. Three crystallizations from acetone-petroleum ether (b.p. 60–70°) gave 129 mg. of material having a constant melting point (233–239°). Paper strip chromatography indicated approximately 75% of pure IIb together with 25% of a more polar contaminant. A 110 mg. portion of the above 129 mg. was subjected to partition chromatography on Celite[12] using a solvent system consisting of three parts of petroleum ether (b.p. 90–100°), two parts of ethyl acetate, three parts of methanol and two parts of water. The eluate from the second hold-back volume (1 HBV = 320 ml.) was evaporated and the residue crystallized from acetone-petroleum ether to afford 78 mg. of pure IIb, m.p. 246.5–249° with previous softening. One additional crystallization did not alter the melting point; $\lambda_{max}^{methanol}$ 238 mμ (ε 16,300); ν_{max}^{KBr} 3510, 1770, 1755, 1662, 1630, 1245, and 1220 cm.$^{-1}$; $[\alpha]_D^{25}$ +121° (chloroform). Paper strip chromatography indicated an homogeneous compound.

Anal. Calcd. for $C_{21}H_{27}O_5F$ (378.43): C, 66.73; H, 7.19; F, 5.02. Found: C, 67.16; H, 7.54; F, 4.75.

Acknowledgment. We wish to thank Louis M. Brancone and associates for the analyses, William Fulmor and associates for the infrared and ultraviolet absorption spectra and optical rotation data, and Robert H. Blank for the paper chromatographic analyses.

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(12) The adsorbent was specially treated Celite 545 which was slurried in 6*N* hydrochloric acid and allowed to stand overnight. It was then filtered and was washed with water, followed by a mixture of methanol and ethyl acetate. Finally, it was dried at room temperature. Celite is the trademark of Johns-Manville Company for diatomaceous silica products.

Steroidal Hormone Relatives. VIII. A Synthetic Approach to 6-Aza-equilenin[1,2]

J. H. BURCKHALTER AND JOHN A. DURDEN, JR.

Received October 3, 1959

Estrogens are carcinogenic to experimental animals which have an inherited sensitivity to the development of mammary carcinoma, and many clinicians will not employ them in the treatment of women who have a familial history of malignancy.[3] Yet, estrogens,[3] as well as androgens,[4] may be used in the treatment of inoperable breast cancer, and estrogenic materials are effective in the palliation of prostatic carcinoma and its metastases and may also be useful against lung and skin metastases.[3] Such facts have led us to propose that the aza analogs of the steroids might be of considerable interest as possible carcinolytic agents.[5] Perhaps an azasteroid would fit the enzyme site of the parent hormone in such a manner that only a carcinolytic effect would result.

The favorable effect of estrogens upon the blood levels of cholesterol and presumably upon the course of atherosclerosis[6] raises the question of whether or not an azaestrogen would retain the antiatherogenic effect of the parent hormone without exhibiting the undesirable estrogenic effect. It is possible that a nonestrogenic azasteroid would

(1) Abstracted from a portion of the Ph.D. thesis of John A. Durden, Jr., University of Kansas, 1957.

(2) This investigation was supported in part by Grant CY-3573, from the National Cancer Institute, U. S. Public Health Service.

(3) *New and Nonofficial Drugs*, J. P. Lippincott Co., Philadelphia, Pa., 1959, p. 504.

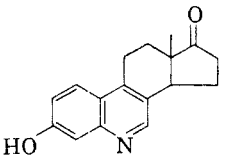
(4) *New and Nonofficial Drugs*, J. P. Lippincott Co., Philadelphia, Pa., 1959, p. 542.

(5) Application for Research Grant to the National Institutes of Health, February 26, 1957.

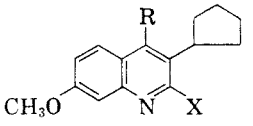
(6) H. W. Eder in *Hormones and Atherosclerosis*, G. Pincus, Ed., Academic Press, Inc., New York, N. Y., 1959, Chapter 24.

fit an enzyme site important to cholesterol synthesis in such a manner that the generation of cholesterol would be inhibited.

These considerations have induced us to undertake various syntheses designed to lead to a number of azasteroids. Recent publications from other laboratories have prompted a preliminary report of incomplete work toward a total synthesis of 6-azaequilenin (I).[7]



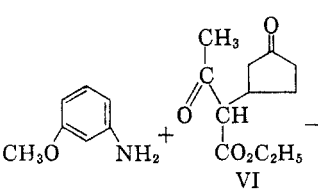
I



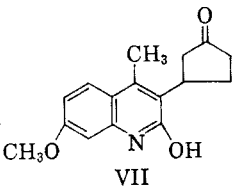
	R	X
II.	CH_2CH_3	OH
III.	CH_3	OH
IV.	CH_3	Cl
V.	CH_3	H

Model compound II was made by means of the Knorr quinoline synthesis[11] which entailed heating a mixture of *m*-anisidine and ethyl α-cyclopentylpropionylacetate[12] to give an anilide which was closed by sulfuric acid to 3-cyclopentyl-7-methoxy-4-ethylcarbostyril (II). The same reactions involving *m*-anisidine and ethyl α-cyclopentylacetoacetate[12a] gave α-cyclopentylacetoaceto-*m*-anisidide. Treatment of the anisidide with sulfuric acid gave 3-cyclopentyl-7-methoxy-4-methylcarbostyril (III). Reaction of III with phosphorus oxychloride gave the gummy 2-chloroquinoline (IV) which, through hydrogenolysis using palladium on charcoal, afforded 3-cyclopentyl-7-methoxylepidine (V) as the hydrochloride.

A closer approach to I was through the synthesis of 3-(3-oxocyclopentyl)-7-methoxy-4-methylcarbostyril (VII). Ethyl α-(3-oxocyclopentyl)-acetoacetate (VI) was synthesized by the Michael condensation using 2-cyclopentenone[13] and aceto-



VI



VII

acetic ester. From *m*-anisidine and VI in the Knorr reaction, the carbostyril (VII) was obtained. VII formed a 2,4-dinitrophenylhydrazone.

Carbostyrils II, III, and VII have very similar infrared spectra, with lactam peaks (1650 cm.$^{-1}$)[14] but only VIII has carbonyl absorption (1740 cm.$^{-1}$) which is due exclusively to the terminal ring ketonic grouping. The lepidine (V) showed no lactam absorption.

Attempts are currently being made to improve the yield of VII; and other studies are in progress toward the synthesis of 6-azaequilenin and other azasteroids.

EXPERIMENTAL

3-Cyclopentyl-7-methoxy-4-ethylcarbostyril (II). A mixture of 14 g. (0.067 mol.) of ethyl α-cyclopentylpropionylacetate[12] and 10 g. (0.067 mol.) of *m*-anisidine was heated at reflux temperature with a Bunsen burner for 5 min. After the mixture had been cooled, 40 ml. of concentrated sulfuric acid was added very slowly with stirring. During the treatment a solid separated, the mixture became very hot and the the solid redissolved while a vigorous ebullition took place. After standing 40 min. at room temperature, the reaction mixture was heated on the steam bath for 20 min. before it was poured with stirring into ice water. A purple solid separated. The suspension was made neutral with sodium hydroxide and a solid was collected on a filter and subsequently recrystallized from alcohol with charcoal treatment to yield 2 g. (11% yield) of a white solid, II, m.p. 200–201°. Further recrystallization from alcohol elevated the melting point to 204–205°.

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80. Found: C, 75.30; H, 7.70.

α-Cyclopentylacetoaceto-m-anisidide. A mixture of 19.8 g. (0.1 mol.) of ethyl α-acetylcyclopentylacetate[12a] and 12.3 g. (0.1 mol.) of *m*-anisidine[15] was heated at reflux temperature under an air condenser for 4 min. with a Bunsen burner. During this period, fumes came from the condenser. The contents of the flask were poured into a beaker, and cooling in an ice bath gave a solid which was collected on a filter. The product was triturated with Skelly B to yield 14 g. (51%) of white anisidide, m.p. 130–133°. Recrystallization from benzene-Skelly B elevated the melting point to 133–134.5°. $\lambda_{max}^{CHCl_3}$ 1680 cm.$^{-1}$ (C=O sec. amide I); 1600 cm.$^{-1}$ (sec. amide II); 1530 cm.$^{-1}$ (sec. amide II); 1280 cm.$^{-1}$ (sec. amide III).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.63; H, 7.69. Found: C, 69.53; H, 7.68.

3-Cyclopentyl-7-methoxy-4-methylcarbostyril (III). A mixture of 14.7 g. (0.07 mol.) of ethyl α-cyclopentylaceto[12a] and 9.1 g. (0.07 mol.) of *m*-anisidine[15] was heated at reflux under an air condenser with an open flame for 3 min. and was then

(7) Several steroid analogs with a five-membered heterocyclic B ring have been synthesized.[8] A 3-aza-A-homocholestanone has been prepared through partial synthesis from cholestanone,[9] and a synthetic approach has been made toward a 14-aza-D-homosteroid.[10]

(8) G. V. Bhide, M. R. Pai, N. L. Tikotkar, and B. D. Tilak, *Tetrahedron*, **4**, 420 (1958); G. V. Bhide, N. L. Tikotkar, and B. D. Tilak, *Chemistry and Industry*, 1319 (1957); R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Research (India)*, **15B**, 497, 573 (1956) [*Chem. Abstr.*, **51**, 5784, 8719 (1957)]; R. J. Collins and E. V. Brown, *J. Am. Chem. Soc.*, **79**, 1103 (1957).

(9) C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.*, 3458 (1958).

(10) N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958).

(11) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1952, Vol. 4, p. 30.

(12) Prepared by the methods of (a) H. Rydon, *J. Chem. Soc.*, 1544 (1939), and (b) F. Challenger and B. Fishwick, *J. Inst. Petrol.*, **39**, 220 (1953) [*Chem. Abstr.*, **48**, 9355 (1954)].

(13) M. Rosenblum, *J. Am. Chem. Soc.*, **79**, 3179 (1957), and K. Alder and R. Flock, *Chem. Ber.*, **89**, 1735 (1956).

(14) *Cf.* J. A. Gibson, W. Kynaston, and A. S. Lindsay, *J. Chem. Soc.*, 4340 (1955), who have shown that carbostyrils exist as 2-quinolones whose spectra confirm the amido form in neutral or acidic media. Also, G. W. Ewing and E. A. Steck, *J. Am. Chem. Soc.*, **68**, 2181 (1946), have used ultraviolet spectra to demonstrate the amido structure.

(15) F. Reverdin and A. de Luc, *Ber.*, **47**, 1537 (1914).

allowed to cool at room temperature. The mixture was then added slowly to 15 ml. of sulfuric acid preheated to 60°, at such a rate that the temperature did not rise above 90°. When addition was complete the temperature of the reaction mixture was held at 90° for 20 min. and then allowed to fall to 60° when the mixture was poured with vigorous stirring over ice. The solid which separated was collected on a filter and then recrystallized from 500 ml. of alcohol with charcoal treatment to give 5.4 g. (30% yield) of a white solid (III), m.p. 216–218°. After further recrystallization it melted at 218–219°.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.79; H, 7.44. Found: C, 74.83; H, 7.25.

α-Cyclopentylacetoaceto-*m*-anisidide which had been isolated was also converted in about 50% yield by treatment with sulfuric acid to III.

3-Cyclopentyl-7-methoxylepidine hydrochloride monohydrate (V). A mixture of 5.43 g. (0.021 mol.) of III and 5 ml. of phosphorus oxychloride was heated on a steam bath for about 30 min. until complete solution had almost taken place. The reaction mixture was heated at gentle reflux for 15 min. with a Bunsen burner and then it was poured into water with stirring. A solid separated which was collected on a filter and subsequently dissolved in chloroform. The solution was washed with water, and then dried over a sodium sulfate–sodium carbonate mixture. The drying agent was removed by filtration and the chloroform was removed *in vacuo* to leave a residual gum. The residue was dissolved in 40 ml. of glacial acetic acid. After the addition of 2 g. of anhydrous sodium acetate and 1 g. of 5% palladium on charcoal, hydrogenation was carried out at 35 lb. pressure with heat supplied to the flask by an infrared lamp. When the theoretical amount of hydrogen had been absorbed, the catalyst was removed and the volume of the filtrate was reduced. The residue was made basic with alkali. Extraction with ether and drying over a sodium hydroxide–sodium sulfate mixture gave an ether solution which was treated with hydrogen chloride gas to produce a solid. Recrystallization from alcohol gave 4 g. (70% yield) of off-white crystalline V, m.p. 210–211°.

Anal. Calcd. for $C_{16}H_{19}NO{\cdot}HCl{\cdot}H_2O$: C, 64.96; H, 7.50. Found: C, 65.05; H, 7.50.

Ethyl α-(3-oxocyclopentyl)acetoacetate (VI). A solution of 1.15 g. (0.05 atom) of sodium metal in 100 ml. of absolute alcohol was reduced in volume to dryness and the residue taken up in 4 ml. of absolute alcohol. Then a mixture of 22 g. (0.27 mol.) of 2-cyclopentenone[13] and 59.5 g. (0.46 mol.) of ethyl acetoacetate was added to the alcoholic solution with shaking. An exothermic reaction occurred. After 30 min. at room temperature, the reaction mixture was warmed at 45° for 2 hr. and then left at room temperature overnight. The reaction mixture was made neutral with 3.5 ml. of glacial acetic acid, diluted with 200 ml. of ether, and extracted twice with water. The ether extract was dried over sodium sulfate. Removal of the drying agent and distillation gave 38 g. (67% yield) of clear liquid (VI), b.p. 135° (1.5 mm.); n_D^{23} 1.4650. $\lambda_{max}^{CHCl_3}$ 1718 cm.$^{-1}$ (C=O); 1740 cm.$^{-1}$ (5-membered ring C=O); 1742 cm.$^{-1}$ (ester C=O); 1625 cm.$^{-1}$ (ester C=O chelated to enolic OH?).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.32; H, 7.79.

3-(3-Oxocyclopentyl)-7-methoxy-4-methylcarbostyril (VII). A mixture of 5 g. (0.023 mol.) of ester VI and 2.9 g. (0.024 mol.) of *m*-anisidine was heated at reflux temperature over an open flame for 2.75 min. The thick red oil was poured into a beaker and allowed to cool. The oil was then chilled in ice and treated slowly with 23 ml. of concentrated sulfuric acid with stirring. The acid solution was left in ice for about 30 min., warmed on the steam bath for 10 to 15 min. and then poured with vigorous stirring over ice whereupon a gum separated. The suspension was made basic with sodium hydroxide solution so that the mixture became warm and the gum turned slightly crystalline. The mixture was neutralized with 10% hydrochloric acid and chilled in the ice bath for 3 hr. The solid was collected on a filter. Recrystallization from a 20:1 ethyl acetate–alcohol mixture gave a white solid (VII), m.p. 177–178°, 1 g. (15% yield).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 70.56; H, 6.32.

The *2,4-dinitrophenylhydrazone* of VII was prepared and recrystallized from acetic acid,[16] m.p. 275–277° (dec.).

Anal. Calcd. for $C_{22}H_{21}N_5O_6$: C, 58.53; H, 4.69. Found: C, 58.13; H, 4.66.

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(16) By Mr. D. G. Mikolasek.

The Color of 8-Mercaptoquinoline

J. E. BANFIELD

September 22, 1959

The absorption spectrum of 8-mercaptoquinoline in ethanol and in 50% ethanol has been reported by Badger and Buttery[1] and observations concerning its thermochromic solution in chloroform containing a little ethanol were made. These workers considered that the C=C—C=S chromophore was not involved.

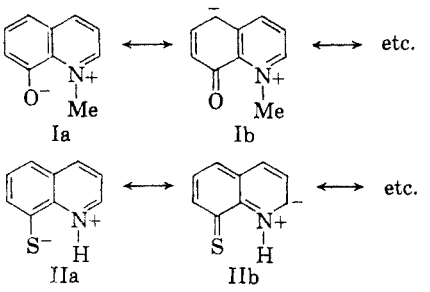
Very recently the absorption spectrum of 8-hydroxy-1-methylquinolinium anhydro salt (and of related compounds) in a number of solvents has been reported[2] together with some observations of the colors. Thus the hydrated 8-hydroxy-1-methylquinolinium hydroxide was orange, and this on dehydration changed to violet-red. The solution of the anhydro salt in water was red, in nonpolar solvents was violet, and the addition of hydroxylic solvents to the chloroform solution resulted in a progressive hypsochromic shift. End absorption in the visible was recorded for the acidic solution. A lucid explanation of these facts in terms of the resonance contributors (Ia), (Ib), *etc.*, the modification of these by hydrogen bonding at the oxygen atom, and of protonation of the oxygen atom has been presented.[2]

The generally similar shape of the spectra and the relative positions of the long wave length maxima of the 8-hydroxy-1-methylquinolinium anhydro salt (484 mμ)[2] and of the 8-mercaptoquinoline (500 mμ)[1] in ethanol together with some findings made during another investigation prompt us to record these observations in support of a parallel explanation of the properties of 8-mercaptoquinoline in terms of the resonance contributors (IIa), (IIb), *etc.* Thus the concentrated solution of 8-mercaptoquinoline in pyridine was an intense blue-violet which was changed by the addi-

(1) G. M. Badger and R. G. Buttery, *J. Chem. Soc.*, 3236 (1956).

(2) J. P. Saxena, W. H. Stafford, and Winifred L. Stafford, *J. Chem. Soc.*, 1579 (1959).

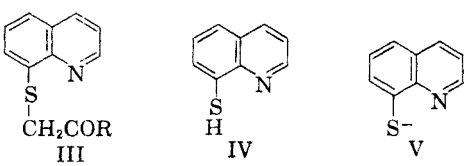
tion of ethanol to a reddish blue color; on the other hand, dilution of the concentrated solution with pyridine caused the color to be very greatly diminished.



The preparation of two *S*-alkyl type derivatives of 8-mercaptoquinoline is now reported. The reaction of phenacyl chloride with 8-mercaptoquinoline in pyridine solution gave 8-quinolyl phenacyl sulfide (III, R = C_6H_5); 8-quinolyl acetonyl sulfide (III, R = CH_3) was similarly prepared from chloroacetone and the thiol. Both of these compounds were colorless, either in the solid state or as their solution in organic solvents.

S-benzoyl 8-quinolyl sulfide, as reported previously,[3] was colorless. This compound gave a colorless solution in ethanol unchanged by the addition of water; however, this aqueous ethanolic solution gradually developed a red color, the more rapidly on warming. Thus it seems likely that the long wave-length absorption reported[1] for the benzoyl derivative in 50% ethanol should be attributed to the partial hydrolysis of this thiol ester, in which case the objection to the C=C—C=S chromophore for this substance is invalid.

Alkaline solutions of 8-mercaptoquinoline were colorless or nearly so, and the acidic solution was yellow confirming earlier observations.[3]



The above observations together with the change in the red color of the dihydrate to the pale violet color of the liquid 8-mercaptoquinoline[1] find a ready explanation in structure II. The existence in ionizing solvents of 8-mercaptoquinoline in the purple zwitterionic form is not unexpected in view of the greater acidity of thiol compounds as compared with hydroxyl compounds, this zwitterionic form being presumably modified in hydroxylic solvents and in the solid red dihydrate by hydrogen bonding. In nonpolar solvents the zwitterionic form would be relatively less stable (compare the *N*-heteroaromatic hydroxy compounds[4]) and the colorless nature of such solutions[1] finds explanation in the predominance of the tautomeric form (IV), the pale violet color of the pure liquid thus indicates an autoprotolytic equilibrium between IV and II. The effect of dilution of the pyridine solution can be attributed to a solvolytic equilibrium involving pyridinium ions and the anion (V), the latter entity accounting also for the lack of color of the aqueous alkaline solution of the thiol.

(3) A. Edinger, *Ber.*, **41**, 937 (1908).
(4) S. F. Mason, *J. Chem. Soc.*, 5016 (1957).

EXPERIMENTAL

S-Benzoyl 8-mercaptoquinoline was prepared by Edinger's method[3] and had m.p. 110° (lit.[3] 110°); preparation of this compound under nitrogen was found advantageous.

8-Quinolyl acetonyl sulfide. Chloroacetone was added to a solution of 8-mercaptoquinoline in pyridine and the solution was set aside overnight under nitrogen. The next day the mixture was stirred into water and the mixture was set aside for several days to crystallize. The solid was collected and purified by low temperature recrystallization from ethanol. The product was 8-quinolyl acetonyl sulfide, m.p. 54–54.5°.

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.28; H, 4.97; N, 6.11.

8-Quinolyl phenacyl sulfide. Phenacyl chloride in pyridine was added to an equimolecular amount of 8-mercaptoquinoline in pyridine and the mixture was kept for 24 hr. under nitrogen and then poured into water to yield a solid. This solid was recrystallized from ethanol to give 8-quinolyl phenacyl sulfide m.p. 133°.

Anal. Calcd. for $C_{17}H_{13}NOS$: C, 73.12; H, 4.69; N, 5.02. Found: C, 73.01; H, 4.70; N, 4.76.

Acknowledgment. The author is indebted to Dr. W. Zimmermann and his staff for the microanalyses.

NOTE ADDED IN PROOF: Substantially similar conclusions concerning the color of 8-mercaptoquinoline have been reached by A. Albert and G. B. Barlin [*J. Chem. Soc.*, 2384 (1959)] in a paper which appeared after the submission of this note.

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Hydrogenolytic Cleavage of Menthofuran[1]

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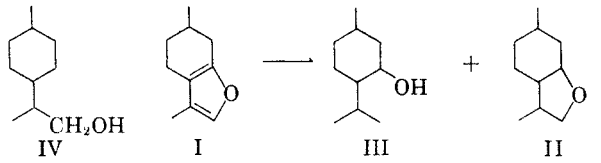
Received March 23, 1959

Recently, Wienhaus[2] carried out the catalytic hydrogenation of menthofuran (I) over platinum black in acetic acid, reporting tetrahydromenthofuran (II) as the sole product. It is known, however, that in the presence of Adams' catalyst furan compounds are not only hydrogenated to tetrahydrofurans, but often subjected to hydrogen-

(1) Abstracted partly from the Master thesis submitted by W. Tagaki, March 1, 1956, and presented at the monthly meeting of Kansai Branch of the Agricultural Chemical Society of Japan, Kyoto, January 26, 1957.
(2) H. Wienhaus and H. Dewein, *Ber.*, **91**, 256 (1958).

olysis also.[3] Thus, it appears that the hydrogenolysis of I may result either in the formation of menthol (III) or *p*-menthane-9-ol (IV).



IV I III II

IIIa. (+)-*neo*menthol
IIIb. (+)-*neoiso*menthol

Independently of Wienhaus,[2] we have carried out the catalytic hydrogenation of I using Adams' catalyst and acetic acid and have found that cleavage occurs to the extent of about 20% to give a mixture of menthols. The remaining 80% of the product was II formed by ring hydrogenation. The cleaved product was converted quantitatively to the 3,5-dinitrobenzoate. By chromatography of this ester on an alumina column it was found that the cleavage product was entirely composed of (+)-*neo*menthol (IIIa) and (+)-*neoiso*menthol (IIIb) without any *p*-menthane-9-ol, (IV). The direction of hydrogenolytic cleavage of I observed here agrees with that reported by Shuikin and Belsky[4] who used a different catalyst.

Variation of the hydrogenation temperature between 20° and 60° did not affect the extent of ring cleavage, but did change the ratio of IIIb to IIIa, as shown in Table I, from 2:1 at 20° to 1.2:1 at 60°. This result is of interest from both the stereochemical and preparative point of view, since *neoiso*menthol is considered to be the most unstable isomer[5] and is more difficult to prepare than any of the other isomeric menthols.

The formation of IIIa and IIIb in the hydrogenation substantiates the common observation regarding *cis*- addition of hydrogen to ethylenic bonds in the presence of catalysts, since in both IIIa and IIIb the hydroxyl and *iso*propyl groups are *cis* to each other. The corresponding *trans*-isomers, (−)-menthol and (+)-*iso*menthol were not obtained in the catalytic hydrogenation. On the other hand, the stereochemistry of the major product II is not certain. An attempt to correlate the steric configuration of II with that of isomeric menthol by cleaving the ether bond with acetyl chloride failed, resulting in IV. As discussed by Smith and Fuzek,[3] II is probably not an intermediate in the transformation of I into III, since II no longer reacted with hydrogen under the same experimental conditions. We are now making an effort to establish the stereochemistry of II and the result will be reported.

EXPERIMENTAL[6]

Menthofuran (I) synthesized by the method reported by Pallaud and Berna[7] showed the following constants; $[\alpha]_D^{21}$ + 93° (*c*, 9.63 in methanol), b.p. 91.5–92.5° (18 mm.).

Catalytic hydrogenation. Only the procedure at 20° is described. The reductions at 40° and 60° were carried out by the same procedure using the same amount of sample and reagent. The amount of hydrogen uptake and the content of menthol (measured by acetylation) in the product were not much affected by temperature.

TABLE I[a]

COMPOSITION (%) OF THE CRUDE MENTHYL 3,5-DINITROBENZOATE

T,[b] °C.	F-I: M.P. 150–155°	F-II: M.P. 85–145°	F-III: M.P. 95–99°	R[c]	F-III/F-I[d]
20	26	4	52	9	2.0
40	29	8	49	9	1.7
60	38	5	45	4	1.2
	32	3	64	—	2.0

[a] The bottom line represents the analysis of an authentic mixture (2:1) of (+)-*neoiso*menthyl- (m.p. 99–100°) and (+)-*neo*menthyl 3,5-dinitrobenzoate (m.p. 154–155°). [b] Hydrogenation temperature. [c] Resinous substance. [d] The accuracy was ±0.1 in duplicate analysis.

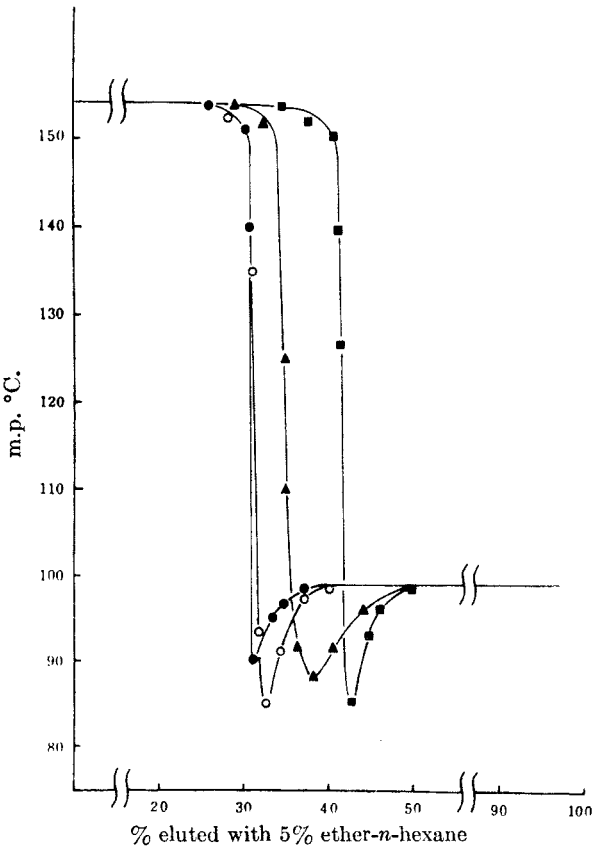


Fig. 1. Alumina chromatography of Menthyl 3,5-dinitrobenzoate (See Table I): ●, authentic mixture; ○, 20°; ▲, 40°; ■, 60°

(3) H. A. Smith and J. F. Fuzek, *J. Am. Chem. Soc.*, **71**, 415 (1949), and the references there cited.

(4) N. I. Shuikin and I. F. Belsky, *Proc. Acad. Sci. U.S.S.R. (English Translation)*, **116**, 905 (1957).

(5) E. L. Eliel, *Experimentia*, **9**, 91 (1953).

(6) All melting and boiling points are uncorrected.

(7) R. Pallaud and J. Berna, *Ind. Parfum.*, **8**, 154 (1953); *Chem. Abstr.*, **47**, 10179 (1953).

The hydrogenation temperature was controlled by the circulation of water through the jacket surrounding the hydrogenation flask. In the flask were placed freshly distilled menthofuran (I), 3.210 g., (0.0214 mol.), platinum oxide (60 mg.), and acetic acid (30 ml.). At the beginning of the shaking, the hydrogenation mixture should be colorless.[8] After 4 hr., the absorption of hydrogen ceased at 1120 ml. (0.466 mol.; measured at 20°). From the hydrogenation mixture a colorless oil (3.000 g.) was obtained, b.p. 88–100° (18 mm.) which contained 20.1% menthol mixture.

The hydrogenation product was treated with 3,5-dinitrobenzoyl chloride in pyridine and then steam-distilled. The undistilled residue solidified to give the crude 3,5-dinitrobenzoate (0.829 g.). From the distillate, tetrahydromenthofuran (II) was obtained, b.p. 91–92° (20 mm.). α_D^{17} −20.8° (homogeneous), d_4^{25} 0.9286, n_D^{25} 1.4610, MR (calcd.) 45.62, (obsd.) 45.58.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.90; H, 11.81.

The crude 3,5-dinitrobenzoate (100 mg.) was purified by passing an *n*-hexane solution of the 3,5-dinitrobenzoate through a layer of alumina (1 g.). The removal of *n*-hexane from the effluent gave colorless needles (86 mg.), while a resinous substance (9 mg.) adsorbed on the alumina was eluted with ether.

The purified 3,5-dinitrobenzoate (20.0 mg.) was chromatographed on an alumina column (alumina 15 g.; height 15 cm.) using *n*-hexane mixed with 5% ether as developing solvent. The effluent was collected in small fractions and the solvent was removed from each fraction. After the melting points had been determined, as shown in Fig. 1, the fractions were combined into three parts: Fraction I 6.0 mg. (m.p. 150–154°), Fraction II 1.0 mg. (m.p. 85–145°), and Fraction III 12.1 mg. (m.p. 95–99°). From the results obtained by the above preliminary purification and by chromatography, the composition of crude ester was calculated as shown in Table I.

When recrystallized from methanol, Fraction I and Fraction III melted at 154–155° and 99–100° respectively, and were shown to be (+)-*neo*menthyl- and (+)-*neoiso*menthyl 3,5-dinitrobenzoate, by mixed melting point determinations with authentic samples. Fraction II was a mixture of these two isomers.

Acknowledgment. The authors wish to express their sincere thanks to Prof. Sankichi Takei for his constant encouragement, and to Mr. Hiroo Ueda for supplying the authentic samples.

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(8) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **72**, 399 (1950).

Differentiation of Glyceraldehyde from Other Trioses by Means of 2,4-Dinitrophenylhydrazine[1]

SAMUEL C. SMITH, P. M. ALTHOUSE, AND J. W. SHIGLEY

Received August 11, 1959

In an effort to identify some oxidation products of glycerides by 2,4-dinitrophenylhydrazone derivatives it was discovered that the literature is rather vague concerning the 2,4-dinitrophenylhydrazone of glyceraldehyde.

Neuberg,[2] using a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid at 0°, prepared glyceraldehyde 2,4-dinitrophenylhydrazone which melted at 166–167°. Neuberg and Collatz[3] reported the 2,4-dinitrophenylosazone of glyceraldehyde to melt at 265° (dec.). Later, Neuberg and Strauss[4] reported that the bishydrazone (osazone) of methyl glyoxal can be obtained quantitatively from dihydroxyacetone and glyceraldehyde with 2,4-dinitrophenylhydrazine in hydrochloric acid. This 2,4-dinitrophenylosazone melted at 298°.[5]

In the present investigation two methods were used to study the dinitrophenylhydrazones and osazones of glyceraldehyde, dihydroxyacetone, and pyruvaldehyde (methyl glyoxal). The results appear in Table I.

Infrared spectra of the products melting at 164–166° were all similar with peaks at: 3.05, 6.15–6.20, 6.28, 7.45, 8.18, 8.70–8.90, 9.15–9.35, 10.28, 10.75–10.90, 11.73–11.95, and 12.00 μ. Infrared spectra of the products melting at 297–299° were all similar with peaks at: 3.08, 6.19, 6.27, 6.32, 6.65, 7.40–7.50, 7.60, 7.95, 8.23–8.28, 8.73, 9.20, 9.47, 10.68, 10.92, 11.90–12.00, and 13.43–13.70 μ.

The results show that glyceraldehyde 2,4-dinitrophenylhydrazone can be prepared in hydrochloric acid at 5°, but the 2,4-dinitrophenylosazone of pyruvaldehyde forms at other temperatures. In the case of dihydroxyacetone and pyruvaldehyde, however, the 2,4-dinitrophenylosazone of pyruvaldehyde forms at all the temperatures tried. This osazone which melts from 250–298° can be recrystallized from dioxane or pyridine to melt at 297–299°.

These data show that by the use of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid at 5° glyceraldehyde can be differentiated from the other trioses.

EXPERIMENTAL

Preparation of dinitrophenylhydrazones and osazones. Two methods were used to study the dinitrophenylhydrazones and osazones of glyceraldehyde (Nutritional Biochemicals #6559), dihydroxyacetone (Nutritional Biochemicals #4386), and pyruvaldehyde (methyl glyoxal), (K&K #2995L 30% soln.). The first was that of Brady and Elsmie[6] in which a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid was added to an aqueous solution of the triose. The second method was that of Allen[7] as modified

(1) This Communication has been authorized for publication on October 15, 1958, as Paper No. 2302 in the Journal Series of the Pennsylvania Agricultural Experiment Station.

(2) I. S. Neuberg, *Biochem. Z.*, **255**, 1 (1932).

(3) C. Neuberg and H. Collatz, *Biochem. Z.*, **223**, 494 (1930).

(4) C. Neuberg and E. Strauss, *Arch. Biochem.*, **11**, 457 (1946).

(5) E. Simon and C. Neuberg, *Biochem. Z.*, **232**, 479 (1931).

(6) O. L. Brady and G. V. Elsmie, *Analyst*, **51**, 77 (1926).

(7) C. F. H. Allen, *J. Am. Chem. Soc.*, **52**, 2955 (1930).

TABLE I

PROPERTIES OF VARIOUS PRODUCTS PREPARED FROM TRIOSES WITH 2,4-DINITROPHENYLHYDRAZINE

Method Temperature	HCl 5°	HCl 20°	HCl 35°	H_2SO_4 5°	H_2SO_4 20°	H_2SO_4 35°
PPt. color						
Gly[a]	Yellow	Yellow-orange	Orange	Orange	Orange	Orange
DHA[b]	Orange	Orange	[e]	[e]	Orange	[e]
Pyr[c]	Orange	[e]	[e]	[e]	Orange	[e]
Solubility in hot (1:1) 50% C_2H_5OH/C_2H_5OAc						
Gly	Complete	*ca.* 50%	*ca.* 50%	Trace	Trace	Trace
DHA	Trace	Trace			Trace	
Pyr	Trace				Trace	
M.p. material recrystallized by above						
Gly	166	166	164	—	—	—
DHA	—	—			—	
Pyr	—				—	
M.p. residue from solubility tests						
Gly	—	284[d]	289	298	298	298
DHA	253[d]	280[d]			284[d]	
Pyr	299				289[d]	

[a] Gly, glyceraldehyde. [b] DHA, dihydroxyacetone. [c] Pyr, pyruvaldehyde. [d] Recrystallized from dioxane to melt at 298°. [e] Not performed.

by Brady[8] in which 2,4-dinitrophenylhydrazine was dissolved in a small amount of concentrated sulfuric acid and the solution diluted with ethanol. This solution was added to an alcoholic solution of the triose. Each procedure was run at 5°, 20°, and 35°. The solutions were held at the required temperature for 2 hr. before mixing, and then allowed to react for 12 hr. Only the first crops of precipitate were retained.

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(8) O. L. Brady, *J. Chem. Soc.*, 1931, 756.

The Identification of $C_{12}H_8N_4O$, an Oxidation Product from α-Pyridil Monohydrazone[1]

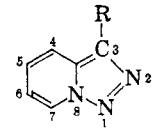
J. H. BOYER AND N. GOEBEL

Received August 17, 1959

Treatment of α-pyridil (I) with tosyl hydrazide and the resulting derivative with aqueous alkali gives a product, $C_{12}H_8N_4O$, incorrectly identified as "azipyridil" (II).[2] Chemical and physical evidence require the formulation to be that of 1-α-picolinoylpyridotriazole (III, R = α−C_5H_4NCO).

$(\alpha\text{-}C_5H_4NCO)_2$ (I)

$\alpha\text{-}C_5H_4NC{=}N_2$
$\alpha\text{-}C_5H_4NC{=}O$ (II)



III

In acid solution pyridotriazole (III. R = H) and, at higher temperatures, 1-phenylpyridotriazole (III. R = C_6H_5) react with carboxylic acids to form esters of corresponding α-pyridylcarbinols.[3] In its resistance to attack by carboxylic acids, III (R = α-C_5H_4NCO) further demonstrates lack of triazole ring reactivity towards acids when electron withdrawing groups are at the 1-position. In boiling aniline, III (R = α − C_5H_4NCO) undergoes degradation of the triazole ring and the product,[2] di(α-pyridyl) acetanilide, suggests an intermediate formation of II. Transformation of III (R = α − C_5H_4NCO) into II apparently occurs more readily in the presence of iodine or bromine, each of which gives rise to the formation of α,α-dihaloketones as nitrogen is liberated.[2]

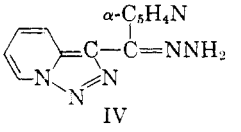
Hydrazine hydrate combines with III (R = α − C_5H_4NCO) to bring about the formation of the corresponding hydrazone (IV) and, if air is present, its oxidation product 1,1′-bipyridotriazole(V).[4]

(1) Partial support of this work under a National Institutes of Health Grant No. CY-2895 is gratefully acknowledged.

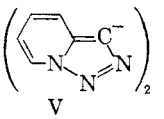
(2) B. Eistert and W. Schade, *Chem. Ber.*, 91, 1411 (1958).

(3) J. H. Boyer and L. T. Wolford, *J. Am. Chem. Soc.*, 80, 2741 (1958).

(4) J. H. Boyer, R. Borgers and L. T. Wolford, Jr., *J. Am. Chem. Soc.*, 79, 678 (1957).



IV



V

Infrared absorption data for III have been obtained from potassium bromide discs and from chloroform solution. Lack of absorption from 3.5 to 6.0 mμ clearly indicates the absence of an aliphatic diazo group in both the solid state and in solution at ordinary temperature.

EXPERIMENTAL[5]

1-α-Picolinoylpyridotriazole (III, R = C_5H_4NCO). According to the directions of Eistert and Schade[2] for the preparation of azipyridil, 1-α-picolinoylpyridotriazole (III. R = C_5H_4NCO), m.p. 151° was obtained in 66% yield.

Infrared absorption for 1-α-picolinoylpyridotriazole from (a) a potassium bromide disc (cm.$^{-1}$, % transmission): 3086, 18.5; 3040, 18.0; 1658, 7.1; 1634, 12.5; 1587, 28.6; 1572, 28.0; 1511, 7.4; 1479, 30.0; 1427, 15.2; 1416, 10.6; 1355, 29.9; 1328, 33.9; 1309, 42.2; 1271, 26.2; 1245, 27.1; 1225, 10.3; 1159, 21.7; 1151, 27.4; 1110, 39.1; 1091, 17.5; 1052, 34.9; 1010, 41.5; 993, 27.0; 940, 7.9; 890, 23.4; 812, 41.6; 768, 4.5; 752, 20.0; 742, 17.2; 723, 43.7; 703, 26.0; 673, 16.1; 648, 46.6; and (b) a chloroform solution (cm.$^{-1}$, absorptivity): 3425, 0.03; 2967, 0.15; 2445, 0.03; 1653, 0.82; 1634, 0.70; 1585, 0.34; 1572, 0.26; 1499, 0.33; 1471, 0.11; 1412, 0.40; 1359, 0.19; 1325, 0.21; 1274, 0.28; 1145, 0.36; 1107, 0.17; 1091, 0.42; 1045, 0.05; 1008, 0.31; 995, 0.36; 964, 0.06; 939, 0.70; 886, 0.50.

1-α-picolinoylpyridotriazole 3,5-dinitrobenzoate. A solution of 2.25 g. (0.01 mol.) of 1-α-picolinoylpyridotriazole and 2.12 g. (0.01 mol.) of 3,5-dinitrobenzoic acid in 75 ml. of *o*-xylene was heated at 110° for 2 hr. Upon cooling the crude salt, *1-α-picolinoylpyridotriazole 3,5-dinitrobenzoate,* m.p. 154–159° (dec.) separated in 75% yield. It recrystallized from ethyl acetate–ethanol as pale yellow needles, m.p. 158–159 (dec.).

Anal. Calcd. for $C_{19}H_{12}N_6O_7$: C, 52.30; H, 2.77; N, 19.28; O, 25.66. Found: C, 52.40; H, 2.69; N, 18.98; O, 25.68.

After treating 1.0 g. (0.002 mol.) of this salt with 10 ml. of 10% sodium hydroxide with stirring for 10 min., a solid was removed by filtration. Upon acidifying the filtrate, 0.4 g. (90%) of 3,5-dinitrobenzoic acid, m.p. and mixture m.p. 204–205°, was obtained. The solid phase from the alkaline reaction mixture was identified as 1-α-picolinoylpyridotriazole, melting point and mixture melting point 151°, 0.5 g. (90%).

Attempts to alkylate 3,5-dinitrobenzoic acid with 1-α-picolinoylpyridotriazole in tetralin at 160° led to an unidentified oil.

1,1′-Bipyridotriazole. A solution of 1.0 g. (0.005 mol.) of 1-α-picolinoylpyridotriazole and 0.16 g. (0.05 mol.) of hydrazine (as 95% aqueous hydrazine) in 30 ml. of *n*-butyl alcohol was refluxed for 2 hr. Colorless needles, 0.2 g. (17% of *1,1′-bipyridotriazole,* m.p. 245° (dec.), separated upon cooling, and after recrystallization from ethanol melted at 254–255° (dec.).

Anal. Calcd. for $C_{12}H_8N_6$: C, 61.02; H, 3.41; N, 35.55. Found: C, 61.09; H, 3.34; N, 35.60.

A mixture melting point determination with a sample prepared from a dihydrazone of α-pyridil and silver oxide[4] showed no depression. The previously reported[4] m.p. 272–274° (dec.) is in error.

Upon concentration of the solvent a second product separated from the reaction mixture in *n*-butyl alcohol as pale yellow needles, 0.6 g. (51%), m.p. 172–176°. Recrystallization from ethanol gave the *hydrazone of 1-α-picolinoylpyridotriazole,* m.p. 174–175°.

Anal. Calcd. for $C_{12}H_{10}N_6$: C, 60.49; H, 4.19; N, 35.28. Found: C, 60.53; H, 4.08; N, 35.64.

When the reaction between 1-α-picolinoylpyridotriazole and hydrazine was carried out under nitrogen, the hydrazone derivative was obtained in 90% yield with no trace of 1,1′-bipyridotriazole.

Acknowledgment. We are indebted to Mr. R. T. O'Connor, Southern Regional Research Laboratory for infrared absorption data.

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(5) Semimicro elemental analyses by Alfred Bernhardt, Mülheim (Ruhr) Germany. Melting points are uncorrected.

The Electrochemical Reduction of Michler's Ketone[1]

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Received September 15, 1959

In connection with another project, it became necessary to reduce Michler's ketone to the corresponding pinacol (*p,p*-dimethylaminodiphenylcarbinol) and to rearrange this material to the pinacolone. After rather unsuccessful attempts to prepare the pinacol by other means it was decided to reduce Michler's ketone electrochemically. The ensuing experiments resulted in some interesting results of theoretical and practical significance for electrochemical preparations and are reported herewith.

The reduction of ketones at a variety of cathodes to form pinacols has been widely used.[2a-4] Escherlich and Moest[5] found that Michler's ketone yields the pinacol with a copper electrode while both pinacol and hydrol are formed in almost equal amounts at a nickel cathode. The chief advantage of any given electrode under the usual conditions of uncontrolled cathode potentials is to limit the cathodic potential to the hydrogen overvoltage of the metal. It was therefore deemed simplest to use the method of Allen and Corwin[6] where the reduction is conducted at a controlled potential mercury cathode.

From polarographic results,[7] it is known that in acid solutions of *p*H 1.3 benzophenone is reduced

(1) Contribution No. 109 from the Research Council of Alberta.

(2) (a) K. Elbs and K. Brand, *Z. Electrochem.,* **8,** 783 (1902). (b) J. Tafel, *Z. Electrochem.,* **17,** 972 (1911).

(3) S. Swann, Jr., N. J. Leonard, and F. C. Howard, *Trans. Electrochem. Soc.,* **67,** 6 pp. preprint (1936).

(4) N. J. Leonard, S. Swann, Jr., and C. Fuller, *J. Am. Chem. Soc.,* **75,** 5127 (1953).

(5) F. Escherlich and M. Moest, *Z. Electrochem.,* **8,** 849 (1902).

(6) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.,* **72,** 114 (1950).

(7) R. Pasternak, *Helv. Chim. Acta,* **31,** 753 (1948).

TABLE I

ELECTROLYSES OF MICHLER'S KETONE[a]

Cathode[b] Potential, V.	Ketone Concn.	Acid Concn.	Stirring[c]	Yield Pinacol	Other Products
0.90	0.125*M*	1.5*N*	Rapid	70%	Hydrol
1.40	0.125*M*	1.5*N*	Rapid	5%	Hydrol
0.90	0.125*M*	1.5*N*	Slow	14%	Ether and viscous oil
1.05	0.125*M*	1.5*N*	Slow	None	Ether 90%, tar
1.40	0.125*M*	1.5*N*	Slow	None	Ethane 8%, ether 30%
1.50	0.125*M*	1.5*N*	None	None	Ethane 26%, ether tar
1.20	0.5*M*	1.5*N*	Rapid	85%	Hydrol 4%
1.20	0.5*M*	2.5*N*	Rapid	64%	Ether
1.35	0.5*M*	1.5*N*	Rapid	38%	Hydrol and tar
1.40	0.5*M*	2.2*N*	Rapid	45%	Ether 45%, tar
0.95	0.125 *I*	0.75 in 50% isopropyl alcohol	Rapid	74%	Recovered ketone
1.05	0.125*M*	Same	Rapid	77%	Ether
1.05	0.125*M*	Same	Slow	None	48% ether, tar

[a] 200-ml. solution. [b] Cathode area, 50 cm.^{2} [c] Temp., 20–25°.

in one electron step. In controlled potential electrolyses Pasternak showed that only benzopinacol is isolated, whereas at *p*H 4.3 a mixture of benzpinacol and benzhydrol was produced and at *p*H 8.6 mainly benzhydrol was produced. Polarographic investigation of Michler's ketone showed that in 1.5*M* hydrochloric acid a one-electron reduction occurred at a half-wave potential of −0.72 volt in solutions of $7.5 \times 10^{-4}M$ to 1×10^{-2} *M*. This indicated that electrolyses conducted with cathodic potentials of −0.90V should result in good yields of pinacol. However, the work of Allen and Corwin[8] indicated that higher yields of pinacol and lower yields of the hydrol were obtained in the reduction of *p*-aminoacetophenone with potentials as high as −1.5 volts despite the fact that polarographic results indicated that a potential of −1.1 volt would be adequate.

The results of a number of reductions of Michler's ketone under varied conditions are summarized in Table I. High pinacol yields are favored by higher concentrations of ketones, comparatively low voltages and rapid stirring. Increasing the acid concentration from 1.5*N* to 2.5*N* resulted in a decreased pinacol yield and favored formation of the ether. Lower acid concentration which might be beneficial were not investigated because of solubility considerations. While the effect of diluting the electrolyte with isopropyl alcohol seemed to increase the specificity of the reduction at −0.95 volt, the results at −1.05 volts indicate quite clearly that the same factors were operative in producing side reactions. Very high cathodic potentials with no stirring resulted in appreciable yields of the ethane. Because of the possibility of pinacol-pinacolone rearrangement, the temperature was maintained in the 20–25° range although Allen, Fearn, and Levine[8] found that high temperatures favored pinacol formation.

Isomerization of the pinacol to the pinacolone. First attempts to prepare the pinacol resulted in the isolation of some pinacolone as contaminating material. It was determined that this material arose from isomerization of the pinacol hydrochloride when this material was isolated according to the method of Allen and Corwin. In subsequent experiments the electrolyzed solution was neutralized with sodium bicarbonate, the precipitated pinacol extracted with chloroform and precipitated with benzene, care being exercized not to heat any of the solutions. That isomerization of the pinacol did not take place during the electrolysis was indicated by the fact that no pinacolone was detected with the latter isolation technique. However, some isomerization of the pinacol occurred when heated on the steam cone for 2 hr. in 2*N* hydrochloric acid although 50% of the starting material was recovered unchanged. On the other hand, warming the pinacol to 50° for 15 min. in glacial acetic acid resulted in complete destruction of the pinacol and a higher yield of pinacolone. Heating for longer periods resulted in extensive decomposition of the pinacolone. The facile rearrangement of the pinacol in acetic acid but not in hydrochloric acid is presumably due to the fact that the free amine groups in acetic acid solution labilize the system toward the pinacol-pinacolone rearrangement.[9] On the other hand, in hydrochloric acid these amino groups exist as cations which stabilize the system towards rearrangement.

From the polarographic results it is certain that the primary electrode process is a rapid one electron reduction of Michler's ketone to form a ketyl radical. The results reported in Table I demon-

(8) M. J. Allen, J. E. Fearn, and H. A. Levine, *J. Chem. Soc.*, 2220 (1952).

(9) W. E. Bachmann and H. R. Steinberger, *J. Am. Chem. Soc.*, **56**, 170 (1934).

TABLE II

DIAGNOSTIC BANDS[a] OF MICHLER'S KETONE AND REDUCTION PRODUCTS[b]

Ketone	1361 (st)	1321 (st)	1289 (st)	1230	1183 (st)	1169	1064	947	927 (st)	833 (st)	819	768 (st)	682
Hydrol	3570	1349 (st)	1227	1182	1162 (st)	1058	1018	939	948	813 (st)	797 (st)		750
Pinacol	3540	1348 (st)	1227	1206	1156		1058	1032	948	813 (st)	797 (st)		757
Pinacolone	1665 (st)	1349 (st)	1242	1163	1060	1027	948	822	805 (st)	765	747		674 (st)
Ether	1348 (st)	1226	1184	1162 (st)	1131	1060 (Broad)		948	816 (st)	800	756		
Ethane (Nujol)	1620	1521	1354	1236	1206	1168	1123	1064	950	805	793		752

[a] Cm.$^{-1}$ [b] Carbon disulfide solution.

strate that this radical forms a complex[10a] with the electrode which has been formulated by Brewster[10b] according to Equation 1:

$$Ar_2C{=}O \xrightarrow[Hg^-]{H^+} Ar_2COH \quad (Hg) \qquad (1)$$

Under the influence of stirring, the free radical is apparently freed from the surface of the electrode and dimerization occurs to form the pinacol according to Equation 2:

$$2Ar_2COH\ (Hg) \longrightarrow 2Ar_2\dot{C}OH \longrightarrow Ar_2COH\ |\ Ar_2COH \qquad (2)$$

This mechanism explains why high yields of pinacol are only obtained with rapid stirring. Slow stirring or dilute solutions, both of which inhibit dimerization, may present an opportunity for further reduction. In particular, higher cathodic potentials encourage reduction to the hydrol, which is easily converted to the ether in acid solutions, and to the ethane. This occurs very easily in the case of Michler's ketone. These results are at variance with the results of Corwin for *p*-aminoacetophenone where high pinacol yields were favored by higher cathodic potentials.

A recent paper by Mandell, Powers, and Day[11] has produced convincing evidence of a rate controlling reaction for the second step of the reduction of phenyl ketones in alkaline solutions. The existence of a stereospecific reaction indicated the existence of a complex between the ketyl radical and the mercury surface. The effect of stirring reported here gives independent substantiation to the existence of such a complex and demonstrates that the mechanism is operative in acid solution.

EXPERIMENTAL

The electrolyses were carried out in a 600-ml. beaker with a layer of mercury, stirred by a magnetic stirrer, as cathode. The beaker was cooled to 20–25° by means of a copper water bath through which tap water flowed. The anolyte was 1.5*N* hydrochloric acid containing hydrazine as an anodic depolarizing agent. The anolyte compartment was made from an alundum thimble 4.5 × 16 cm. outside dimensions soaked in sodium silicate followed by sulfuric acid accorded to Allen and Corwin. The cathode potential was controlled manually.

After completion of electrolyses as indicated by a fall of the current to a low value, or evolution of hydrogen, or both the solution was poured into a sodium bicarbonate solution, extracted with chloroform, and the chloroform solution dried over sodium sulfate, and reduced in volume at reduced pressure to produce a 10% solution. To the dried chloroform solution was added three volumes of benzene and the solution cooled in the refrigerator. The pinacol, filtered off and

(10) (a) No attempt is made herein to define the actual nature of such a complex. Presumably it is not an adsorption complex because the polarographic results indicate a normal diffusion wave. (b) J. H. Brewster, *J. Am. Chem. Soc.*, **76**, 6361 (1954).

(11) L. Mandell, R. M. Powers, and R. A. Day, Jr., *J. Am. Chem. Soc.*, **80**, 6284 (1958).

dried melted at 192–193° when carried out under optimum conditions. Reduction of volume to a small volume and addition of ethyl alcohol precipitates the ether. Identification of material was largely by means of infrared analyses in carbon disulfide solution. Diagnostic bands of isolated compounds are listed in Table II.

Preparation of pinacolone. A 2-g. sample of pinacol was dissolved in 40 ml. acetic acid and warmed to 50° on steam cone for 15 min. The acetic acid solution was poured into water, neutralized with sodium carbonate, and extracted with benzene. The benzene extract was dried over sodium sulfate, reduced in volume and diluted with petroleum ether 40–60°. Yield of crude pinacolone m.p. 220° 1.6 g. After recrystallization from benzene–petroleum ether, it melted at 230–232°.

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Chondroitin Sulfate Modifications. II.[1] Peracetylated Sodium Chondroitin Sulfate A

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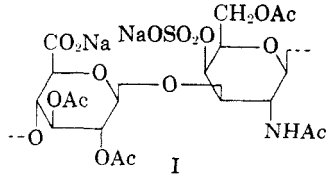
The acetylation of the acidic polysaccharides, pectin[3] and hyaluronic acid,[4] as effected with pyridine and acetic anhydride in formamide, has been reported. We find that this acetylating system can be applied to sodium chondroitin sulfate A under conditions in which the reaction is entirely homogeneous. It is essential that all moisture be excluded. The polysaccharide salt is peracetylated without desulfation and the product (I), after purification by precipitation methods and dialysis, can be isolated as a white, fluffy powder on freeze-drying. This polymeric peracetate is remarkable in being readily soluble in water, formamide and 1:1 water-ethanol. It is insoluble in acetone, chloroform, ethanol, and ether. It may be readily de-*O*-acetylated to yield the original material and can thus be of use in the purification of the polysaccharide.



I

(1) Part I, *J. Am. Chem. Soc.*, **82**, in press (1960).

(2) National Science Foundation Research Associate under Grant NSF G584 to The Ohio State University.

(3) J. F. Carson, Jr., and W. D. Maclay, *J. Am. Chem. Soc.*, **67**, 787 (1945).

(4) Z. Hadidian and N. W. Pirie, *Biochem. J.*, **42**, 266 (1948); R. W. Jeanloz and E. Forchielli, *J. Biol. Chem.*, **186**, 495 (1950).

EXPERIMENTAL

Peracetylated sodium chondroitin sulfate A (I). An amount of 3.8 g. of sodium chondroitin sulfate A, purified essentially as described previously,[5] was finely pulverized and dried over phosphoric anhydride at 70° and 0.05 mm. for 24 hr. This dry powder was dissolved in 24 ml. of dry, freshly distilled formamide by shaking overnight in a sealed flask. To this solution was added, with agitation, 24 ml. of dry, freshly distilled pyridine followed by 10 ml. of acetic anhydride. The sealed solution was shaken at room temperature for 12 hr. when a further quantity of 13 ml. of acetic anhydride was added, and shaking was continued for a total of 24 hr., during which time the color of the solution became a medium red-brown. The solution was then poured with stirring into 500 ml. of ethanol at 0° and then 400 ml. more ethanol was added to yield a white, flocculent precipitate which was collected by filtration and washed with ethanol. The product was further purified by pouring its solution in 100 ml. of water into 500 ml. of ethanol. Precipitation was effected on the addition of 3–5 ml. of a saturated aqueous sodium chloride solution. This procedure was twice repeated and the final product was dissolved in 100 ml. of water and dialyzed for 2 days against distilled water. Recovery of the product as a fluffy, white, amorphous solid was effected by freeze-drying; yield 3.5 g. (72%), $[\alpha]_D^{30}$ −25° (*c* 1.14, water).

This material was insoluble in acetone, chloroform, ether, ethanol, and methanol but was soluble in water, formamide and 1:1 (by vol.) water-ethanol. It was non-reducing toward Benedict solution and exhibited a positive sulfate test only after hydrolysis with dilute hydrochloric acid. The ninhydrin test for the free amino group was negative; positive tests were obtained for uronic acid and hexosamine. Infrared absorption spectral examination showed the strong acetate ester peak at 1740 cm.$^{-1}$ The prominent bands at 3500 cm.$^{-1}$ and 1670 cm.$^{-1}$ may be attributed to the water of hydration.[6]

Anal. Calcd. for $C_{12}H_{12}NaO_6(NHCOCH_3)(OCOCH_3)_{3.25}(OSO_2ONa\cdot 2H_2O)_{0.75}$: C, 38.38; H, 4.52; N, 2.18; Na, 6.28; CH_3CO, 28.52. Found: C, 37.83; H, 4.53; N, 2.34; Na, 6.14; CH_3CO,[7] 28.05.

De-O-acetylation of peracetylated sodium chondroitin sulfate A. An amount of 600 mg. of the above-described peracetylated sodium chondroitin sulfate A was added at 0° to a filtered solution of 3.0 g. of barium hydroxide octahydrate in 50 ml. of water, and the resultant solution was maintained at 0–5° for 1.5 hr. The solution was then carbonated, filtered, and barium ion was removed exactly with sulfuric acid. The centrifuged, neutral solution was dialyzed against distilled water for 48 hr. and its solid content was recovered as a white powder by freeze-drying; yield 300 mg. (64%), $[\alpha]_D^{32}$ −16° (*c* 1.08, water). The product exhibited a negative ninhydrin reaction for the free amino group.

Anal. Calcd. for $C_{12}H_{16}NaO_6(NHCOCH_3)(OH)_{3.25}(OSO_2ONa\cdot 2H_2O)_{0.75}$: N, 2.77; ash (as sulfate), 24.62; CH_3CO, 8.52. Found: N, 2.50; ash, 24.42; CH_3CO,[7] 8.15.

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(5) M. L. Wolfrom and K. Onodera, *J. Am. Chem. Soc.*, **79**, 4739 (1957). In footnote 23 of this reference the product is designated incorrectly as sodium chondroitin sulfate C. Our preparation contained 0.8 sulfate group per disaccharide unit.

(6) S. A. Barker, E. J. Bourne, and D. H. Whiffen, *Methods of Biochem. Anal.*, **3**, 213 (1956).

(7) A. Chaney and M. L. Wolfrom, *Anal. Chem.*, **28**, 1614 (1956).

Formation of Linear Polymers from Diene Monomers by a Cyclic Polymerization Mechanism. IV. Synthesis and Polymerization Studies of Some Doubly-Unsaturated, Unsymmetrical Monomers[1]

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Current interest in the polymerization of symmetrical dienes by an alternating intramolecular-intermolecular mechanism has led to extensive studies in this field.[3] Previous work[3] in these Laboratories has successfully extended the scope of this reaction to unsymmetrical dienes. We now wish to report the synthesis and results of the polymerization studies of a number of unsaturated derivatives of crotyl and vinylacetic acid, additional examples of unsymmetrical, doubly-unsaturated monomers.

EXPERIMENTAL[4]

Monomers. The *esters of crotonic acid* were prepared by refluxing a benzene solution (200 ml.) of *trans*-crotonic acid (0.5 mol.), the appropriate alcohol (0.55 mol.), and *p*-toluenesulfonic acid (1.0 g.) under a Dean-Stark trap until water evolution ceased (*ca.* 24 hr.). The reaction mixtures were worked up as previously described.[3]

The *esters of vinylacetic acid* were prepared by the dropwise addition of vinylacetyl chloride[5] (0.2 mol.) to a stirred solution of the appropriate alcohol (0.22 mol.) and pyridine (0.21 mol.) in 125 ml. of dry ether. The temperature of the reaction mixture was maintained at 0–5° throughout the addition, after which the cooling bath was removed and the mixture stirred an additional 4 hr. One hundred milliliters of water was added, and the ether layer washed with saturated sodium bicarbonate solution, water, and dried over anhydrous sodium sulfate. Distillation afforded the desired ester.

N-Allylcrotonamide was prepared by the dropwise addition of a solution of 0.5 mol. of crotonyl chloride in 50 ml. of dry ethylene dichloride to a cooled (0°), stirred solution of 1.01 mol. of allyl amine in 400 ml. of dry ethylene dichloride.[6] When addition was complete the mixture was allowed to warm to room temperature and stirred overnight. The work-up was identical with that of the above vinylacetates.

TABLE I

PHYSICAL PROPERTIES OF MONOMERS

$CH_3CH{=}CHC({=}O)X$ (I)

$CH_2{=}CHCH_2C({=}O)X$ (II)

Compound	Yield, %	B.P., °/Mm.	n_D^{22}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ia. X = $-OCH_2CH{=}CH_2$[a]	—	63–64°/22	1.4452	—	—	—	—
Ib. X = $-OCH_2CH{=}CHCH_3$[b]	33	84–86°/22	1.4484	68.54	68.77	8.63	8.77
Ic. X = $-OCH_2C(CH_3){=}CH_2$	41	77.3–77.5°/22	1.4491	68.54	68.49	8.63	8.79
Id. X = $-OCH_2C{\equiv}CH$	37	79.5–80.5°/25	1.4583	67.73	67.53	6.41	6.50
Ie. X = $-NCH_2CH{=}CH_2$[c]	83	90–91°/0.8	1.4911	67.16	67.32	8.86	8.91
IIa. X = $-OCH_2CH{=}CH_2$	48	58–58.5°/27	1.4313	66.64	66.76	7.99	8.15
IIb. X = $-OCH_2CH{=}CHCH_3$	56	78–79°/27	1.4374	68.54	68.25	8.63	8.81
IIc. X = $-OCH_2C(CH_3){=}CH_2$	53	73–74°/27	1.4351	68.54	68.42	8.63	8.88

[a] V. P. Golendeev, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 1408 (1940) [*Chem. Abstr.*, **35**, 3607[6] (1941)] reports b.p. 88–89°/70 mm., n_D^{20} 1.4465. [b] F. C. Frostick, Jr., B.Phillips, and P. S. Starcher, *J. Am. Chem. Soc.*, **81**, 3350 (1959), report b.p. 85–87°/25 mm., n_D^{30} 1.4495. [c] N: Calcd., 11.19. Found, 11.15.

The infrared spectra (liquid films) of the monomers were consistent with their assigned structures. Physical data are recorded in Table I.

Polymerizations were carried out in bulk under dry nitrogen using 5–10 g. samples of monomer and 2% by weight of the appropriate initiator [benzoyl peroxide or azobisisobutyronitrile]. The solid polymers were isolated and purified as previously described.[3] Benzoyl peroxide-initiated polymerizations were run at 100°; those using azobisisobutyronitrile were maintained at 75°. Data concerning the polymerizations is summarized in Table II.

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under Contract Number AF 18(603)-116. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2a) Post-doctoral fellow, 1958–1959; (b) Present address: Department of Chemistry, Marshall College, Huntington, W. Va.

(3) The previous paper in this series [M. D. Barnett, A. Crawshaw, and G. B. Butler, *J. Am. Chem. Soc.*, **81**, 5946 (1959)] contains many pertinent references.

(4) All boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 21 double beam spectrophotometer. Analyses were carried out by Galbraith Laboratories, Knoxville, Tenn., or by Weiler and Strauss, Oxford, England.

(5) G. H. Jeffery and A. J. Vogel, *J. Chem. Soc.*, 658 (1948).

(6) W. S. Weaver and W. M. Whaley, *J. Am. Chem. Soc.*, **69**, 515 (1947).

TABLE II

POLYMERIZATION STUDIES

Monomer	Polymer (Approximate Values) % Residual Alcohol Bond	% Residual Acid Bond	% Cyclization	Approximate % Conversion	Gel Time (hr.)	Inherent Viscosity (g. polymer/100 ml. solution)	Observations
Ia[a]	15	60	25	10	110	0.046 (0.198)	—
Ib	—	—	—	—	—	—	No polymer with 2% Bz_2O_2[d] at 100° for 45 days or 2% AIBN[e] at 75° for 14 days
Ic[b]	11	58	31	10	[c]	0.039 (0.207)	—
Id	—	—	—	—	—	—	No solid polymer with 2% Bz_2O_2 at 100° for 29 days
Ie	—	—	—	—	—	—	No polymer with 2% Bz_2O_2 at 100° for 14 days or 2% AIBN at 75° for 14 days
IIa	—	—	—	—	—	—	No solid polymer with 2% Bz_2O_2 at 100° for 22 days or 2% AIBN at 25° for 11 days
IIb	—	—	—	—	—	—	No polymer with 2% Bz_2O_2 at 100° for 25 days or 2% AIBN at 75° for 12 days
IIc	—	—	—	—	—	—	No solid polymer with 2% Bz_2O_2 at 100° for 25 days or 2% AIBN at 75° for 12 days

[a] Calcd. for $(C_7H_{10}O_2)_n$: C, 66.64; H, 7.99. Found: C, 66.37; H, 7.90. [b] Calcd. for $(C_8H_{12}O_2)_n$: C, 68.54; H, 8.63. Found: C, 68.37; H, 8.29. [c] No gelation after 32 days at 100° using 2% Bz_2O_2. [d] Benzoyl peroxide. [e] Azobisisobutyronitrile.

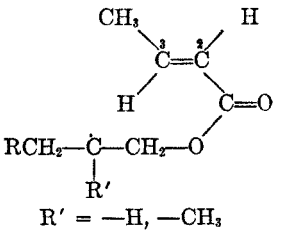
Residual unsaturation was determined as previously described[3] (Table II).

Inherent viscosity measurements were carried out in glacial acetic acid at 30.0° using a modified Ubbelohde viscometer (Table II).

Results and discussion. As indicated in Table II only allyl crotonate (Ia) and β-methallyl crotonate (Ic) gave solid, titratable polymers. Crotyl crotonate (Ib), crotyl vinylacetate (IIb) and *N*-allylcrotonamide (Ie) gave no polymeric material; allyl vinylacetate (IIa), β-methallyl vinylacetate (IIc) and propargyl crotonate (Id) afforded only viscous oils which resisted crystallization.

The relatively low degree of cyclization in poly(allyl crotonate) and poly(β-methallyl crotonate) is not surprising in view of the great difference in reactivities between the alcohol and acid bonds. This effect of differences in bond reactivities as reflected in linear *vs.* cyclopolymerization has been noted earlier.[3]

In addition to the anticipated absorption in the C=C stretching (1640–1655 cm.$^{-1}$) and carbonyl (1725–1740 cm.$^{-1}$) regions the infrared spectra (solid film from carbon tetrachloride) of the solid polymers showed a strong band at 1770–1772 cm.$^{-1}$ characteristic of a 5-membered lactone ring.[7] These findings were surprising, for although molecular models indicated somewhat less steric hindrance to attack of the initially-formed free radical at C_2 of



the acid (5-membered lactone ring) rather than at C_3 (6-membered lactone ring), attack at C_3 should be favored by virtue of the resonance-stabilized radical formed at C_2.

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(7) H. K. Hall and R. Zbinden, *J. Am. Chem. Soc.*, 80, 6428 (1958).

Preparation of Hexaphenylcyclotrisiloxane by the Reaction of Diphenyldichlorosilane with Zinc Oxide

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In recent papers,[1] the senior author has described some methods which involve direct synthesis of

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hexaphenylcyclotrisiloxane (hereafter called trimer) from diphenyldichlorosilane (DPDS).

It has now been found that the trimer can be obtained readily by the reaction of DPDS with zinc oxide: When one mol. of DPDS was added to one and one half to two mol. of zinc oxide in inert solvents, reaction occurred exothermally. Trimer was obtained from the reaction product in a yield of 96 % (mean). Zinc chloride was determined as zinc hydroxide by neutralization with aqueous base.

Stoichiometry supports the following equation:

$$ZnO + (C_6H_5)_2SiCl_2 \longrightarrow ZnCl_2 + 1/3[(C_6H_5)_2SiO]_3$$

Other anhydrous reagents[2] (cupric oxide, lead oxide, silver oxide, manganese dioxide, cupric sulfate, ferric sulfate, zinc sulfate, nickel sulfate, ferric oxalate, cupric carbonate basic, etc.) were found to react with DPDS in substantially similar manner.

EXPERIMENTAL

Reagents. Purified-grade diphenyldichlorosilane was received from the Shin-etsu Chemical Industrial Co. Reagent-grade zinc oxide was finely powdered after prolonged drying. Methyl acetate was purified according to the ordinary method.

Procedure. A typical procedure is as follows: When a solution of diphenyldichlorosilane in methyl acetate (50 g., 0.2 mol., of DPDS, dissolved in 100 ml. of methyl acetate) was added portion-wise to a shaking flask which contained 24 g., 0.3 mole, of zinc oxide and 200 ml. of methyl acetate, an exothermic reaction occurred gradually. After the addition of DPDS was complete, the reaction mixture was gently refluxed for about 10 min., the color change of crystal violet[3] was used to determine completion of the reaction.

Benzene (200 ml.) was added to the reaction mixture to dissolve the silicon-containing product, and the resulting mixture, cooled to room temperature, was filtered by suction. The filtrate was shaken with about 400 ml. of distilled water to remove zinc chloride.

The top layer was separated, ethanol (200 ml.) was added to it, and the solution was evaporated to dryness on a water bath. A white crystalline mass melting at 177–180° and mixed with a small amount of oily liquid, was obtained. Further purification was effected by recrystallization from ethyl acetate, whereby 38 g. (97%) of pure trimer melting at 188–189° was obtained as elongated hexagonal plates.

Anal. Calcd. for $C_{36}H_{30}Si_3O_3$: Si, 14.16; OH/mol., 0.00; mol. wt., 594. Found: Si, 14.8; OH/mol., 0.0 (Karl Fischer titration[4]); mol. wt., 580–600 (Rast).

The x-ray powder pattern of the trimer obtained showed the major part to be orthorhombic trimer[5] and a minor amount to be triclinic trimer.[5]

From the bottom layer, 19 g. (96%) of zinc hydroxide was obtained by aqueous treatment with ammonium hydroxide using phenolphthalein as an indicator.

Although some other oxides and sulfates were also found to produce trimer and chlorides, respectively, most effective results (highest yield of trimer, greatest simplicity in procedure) were achieved by using zinc oxide as a reactant, whereby the marked dehydrating effect of the chloride resulted in almost a quantitative formation of the trimer.

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Synthesis of Tetra(perfluoroalkoxy)silanes

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The first reported synthesis of a tetraalkoxysilane was made by von Ebelman.[1] Since that time many tetraalkoxysilanes have been reported in literature.[2,3,4,5] Reaction 1 is most generally used for the preparation of these compounds:[6,7]

$$4SiCl_4 + 10\ ROH \longrightarrow ROSiCl_3 + (RO)_2SiCl_2 + (RO)_3SiCl + (RO)_4Si + 10HCl \quad (1)$$

A modification of the method of Helferich and Hausen[8] was employed to make a number of previously unreported tetra(perfluoroalkoxy)silanes. The method consisted of reacting tetrachlorosilane and a 10% molar excess of perfluorinated alcohols in an anhydrous medium at −10°. Hydrogen chloride produced during the reaction was removed by refluxing and by purging the reaction mixture with dry inert gas. The desired silanes were recovered by vacuum distillation.

Molar excesses of alcohol were used, not only to promote the formation of the tetra-substituted silanes, but also to prevent any reaction between silicon tetrachloride and the tetra-substituted silanes during refluxing or distillation.[9]

$$SiCl_4 + Si(OR)_4 \longrightarrow 2Cl_2Si(OR)_2 \quad (2)$$

Before distillation, the crude mixture of silanes was percolated through a column of activated, dry silica gel to remove the acidic materials which

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TABLE I

PROPERTIES OF TETRA(PERFLUOROALKOXY)SILANES

R	B.P./Mm. Hg	$(RO)_4Si$ F.P.[a]	d_4^{20a} and	$d_4^{71.1}$	n_D^{20}	Viscosity, cp.[a] 20.0 and	71.1
$CF_3—CH_2—$[b]	155.5–157/743	−25	1.5107	1.4089	1.30206	2.2089	1.240
$HCF_2CF_2CH_2—$	117–118/4	<−68	1.5927	1.5100	1.33174	18.92	3.583
$CF_3(CF_2)_2CH_2—$	96–97/4	<−68	—	1.5740	1.30088	7.613	1.931
$H(CF_2—CF_2)_2CH_2—$	156–159/2.5	<−68	1.8150	1.6440	1.32622	42.75	5.820
$H(CF_2—CF_2)_3CH_2—$	201–204/3	<−68	—	1.7181	—	108.8	12.23
$H(CF_2—CF_2)_4CH_2—$	235–240/2.5[c]	—	—	—	—	—	—

[a] Freezing points, densities, and viscosities were determined by T. M. Verdura. [b] Pennsalt Chemicals Corp. Booklet DC-1254, *Trifluoroethanol*, b.p. 60–61/25 mm. [c] Material decomposed during distillation.

are deleterious to hydrolytic stability. The mechanism that has been postulated[10] for this hydrolyzation is as follows:

$$\equiv SiOR + H_2O \longrightarrow ROH + \equiv SiOH \longrightarrow {}^1/_2 \equiv SiOSi\equiv + {}^1/_2H_2O \quad (3)$$

The corresponding alcohol and polymeric siloxanes are produced, leading to the precipitation of insoluble polymers or, ultimately, of silica.

All the compounds listed in Table I, except tetra (1,1-dihydrotrifluoroethoxy)silane, are new compounds.

EXPERIMENTAL[11]

Starting materials. Tetrahydrofuran (Eastman Kodak Co., white label) was refluxed over calcium hydride until no more bubbles evolved upon further calcium hydride addition. The tetrahydrofuran was then distilled from the calcium hydride through a 1/2 by 12 inch Vigreux column, and the portion distilling at 64–64.5° collected. Water content was less than 0.003% by test with Karl Fischer reagent.[12] *Tetrachlorosilane* (Tech. Grade) was purified by distillation. *1,1-Dihydrotrifluoroethanol* (Pennsalt Chemicals Corp.) was distilled from anhydrous calcium sulfate (Drierite), and the portion distilling at 72–72.5° collected. *1,1-Dihydroheptafluorobutanol* (Minnesota Mining & Mfg. Co.) was distilled, and the portion distilling at 74–74.6° collected. The *trihydroperfluoroalcohols*[13] (du Pont) were used as received. The inert gases used for purging of the reaction mixtures were dried by passage through Linde molecular sieve, Type 4A.

Apparatus. The all-glass apparatus used in the preparations and distillations was protected from atmospheric moisture by Drierite-filled tubes.

Tetra (1,1-dihydrotrifluoroethoxy)silane. While 220.1 g. (2.2 mol.) of 1,1-dihydrotrifluoroethanol was rapidly stirred, 84.9 g. (0.50 mol.) of tetrachlorosilane was added over a period of 1 hr. After the addition was completed, the solution was refluxed for 2 hr., while hydrogen chloride was evolved at a decreasing rate. The reaction mixture was cooled to 25° and percolated through an anhydrous silica gel column, using dry tetrahydrofuran as eluant. The product was then distilled through a 1/2 by 12 inch Vigreux column, and the clear fraction boiling at 155.5–157° (743 mm.) was collected.

Tetra (1,1,3-trihydrotetrafluoropropoxy)silane. The preparation of this compound will illustrate the method used for the preparation of the remaining compounds listed in Table I. A solution of 290.5 g. (2.2 mol.) of 1,1,3-trihydrotetrafluoropropanol in an equal volume of tetrahydrofuran was cooled to −14°. While this solution was vigorously stirred, a solution of 84.9 g. (0.5 mol.) of tetrachlorosilane in an equal volume of tetrahydrofuran was added over a 1-hr. period. During the addition the solution temperature was maintained below −10°. The solution was then refluxed for 2 hr. with the generation of copious amounts of hydrogen chloride. The heat source was removed and the solution purged with a dry inert gas for 2 hr. Tetrahydrofuran and excess alcohol were removed under vacuum at room temperature, and the residue vacuum distilled through a 1/2 by 12 inch Vigreux column. The clear colorless fluid distilling at 117–118° (4 mm.) was collected.

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(13) The author wishes to thank A. C. Haven of du Pont who supplied samples of alcohols.