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# A Direct Synthesis of DL-Baikiain

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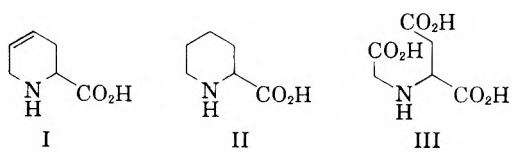
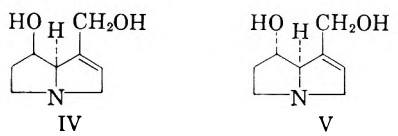
A convenient synthesis of DL-baikiain (DL-1,2,3,6-tetrahydro-2-pyridinecarboxylic acid, I) from *cis*-1,4-dichloro-2-butene and acetamidomalonic ester is described.

The presence of a levorotatory, unsaturated, secondary $\alpha$-amino acid in the heartwood of Rhodesian teak (*Baikiaea plurijuga*) was first reported in 1950 by King, King, and Warwick.[1] Various experiments by these investigators established the structure of this substance, to which the name "baikiain" was given, as L(−)-1,2,3,6-tetrahydro-2-pyridinecarboxylic acid (I). Thus, on catalytic reduction it took up one mole of hydrogen and furnished L(−)-pipecolic acid (II), while on ozonolysis it afforded *N*-carboxymethyl-L-aspartic acid (III). In addition, there was described a synthetic route to baikiain, which, because of the exceedingly low yield in the last step, was admitted to be only partially successful and certainly of very limited preparative value.



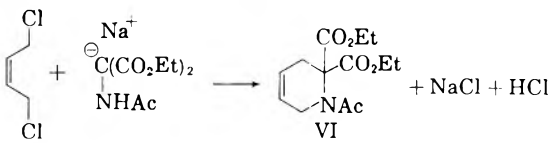
I II III



IV V

Our interest in developing a flexible synthetic approach to the fully oxygenated unsaturated *Senecio* bases[2] retronecine (IV) and heliotridine (V) from the $\Delta^4$-dehydropipecolic acid structure (I) prompted us to seek a more direct route to biakiain than that explored by King and coworkers. In this latter connection, Dobson and Raphael[3] have recently published a synthesis of DL-baikiain somewhat related to our own, but which is much lengthier. These authors, by employing an eight-step sequence starting from 1,4-dichloro-2-butyne, were able to prepare DL-baikiain in an over-all yield of about 8%.

The synthesis now reported utilizes the condensation of *cis*-1,4-dichloro-2-butene with the sodium salt of diethyl acetamidomalonate to furnish an intermediate (VI) capable of being converted to baikiain:



VI

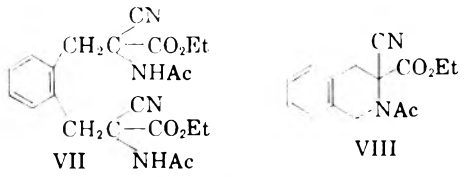
This approach finds analogy in the observation of Burckhalter and Stevens[4] that the reaction of *o*-xylylene dibromide with two molar equivalents of ethyl sodioacetamidocyanoacetate yields not only the diester VII (30%) but also the tetrahydroisoquinoline derivative VIII (43%):

(1) F. E. King, T. J. King, and A. J. Warwick, *J. Chem. Soc.*, 3590 (1950); F. E. King and T. J. King, *Chem. & Ind. (London)*, 489 (1953); *cf.* W. R. Carruthers and R. H. Farmer, *Chem. & Ind. (London)*, 641 (1953).

(2) For a recent review of the structure and stereochemistry of the pyrrolizidine alkaloids, see F. L. Warren, *Record Chem. Progr.*, **20**, 15 (1959).

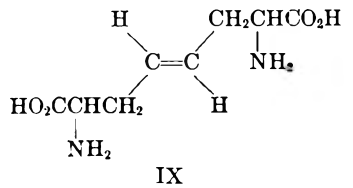
(3) N. A. Dobson and R. A. Raphael, *J. Chem. Soc.*, 3642 (1958).

(4) J. H. Burckhalter and V. C. Stevens, *J. Am. Chem. Soc.*, **73**, 56 (1951).



VII VIII

Initially, the use of *cis*-1,4-dibromo-2-butene in our alkylation studies was contemplated, but the extreme ease with which this substance is known to isomerize, thereby giving rise to *trans* olefinic products,[5] foreshadowed difficulties with this choice. Consequently, it was not surprising that, in the mixture resulting from the hydrolysis and decarboxylation of the material produced by the reaction of this dihalide with diethyl sodioacetamidomalonate at 25–45° in benzene–dimethyl sulfoxide (15:1), merely trace amounts of baikiain could be detected. The major product appeared to be the *dl* or possibly the *meso* form[4] of the *trans* diamino dicarboxylic acid IX, whose structure was confirmed by ozonolysis to DL-aspartic acid. The *trans* configuration of the double bond in IX is assigned on the basis of the strong absorption at 10.3 $\mu$ in its infrared spectrum (absent in the spectrum of DL-baikiain).



IX

In sharp contrast to the foregoing results, the alkylation of diethyl acetamidomalonate with *cis*-1,4-dichloro-2-butene under the same conditions proceeded as desired, without detectable isomerization of the double bond. As already indicated, this dihalide served to produce the cyclic diester VI, which was not isolated but was hydrolyzed directly with base. The resulting product was then decarboxylated in hydrochloric acid solution to furnish, after appropriate concentration and extraction, DL-baikiain hydrochloride, in 29% over-all yield from the dichlorobutene. Isolation of the free amino acid was accomplished by the action of silver carbonate on the hydrochloride.

Besides being identical with natural L(−)-baikiain[1] (I) in crystalline appearance, paper chromatographic behavior, and ninhydrin color test, our synthetic product was further characterized by hydrogenation to DL-pipecolic acid (II) and by ozonolysis leading to the trimethyl ester of *N*-carboxymethyl-DL-aspartic acid (III). The identity of these products was confirmed by direct comparisons with authentic preparations. Infrared spectra of the *N*-benzoyl derivative of the synthetic baikiain and of the methyl ester of this derivative were indistinguishable from the respective spectra of the same compounds prepared from the natural material. However, the spectra of the synthetic and the natural amino acid (in Nujol or as potassium bromide pellets) showed considerable differences, as did those of the corresponding hydrochlorides.[6]

Studies to extend this work to the synthesis of the oxygenated pyrrolizidine bases present in the *Senecio* alkaloids are now in progress.

## EXPERIMENTAL

Melting points were determined on a microscope hot stage calibrated against standard substances. Infrared spectra were taken on a Perkin-Elmer Infracord spectrophotometer. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

DL-*Baikiain hydrochloride.* To a suspension of 7.2 g. (0.30 mole) of sodium hydride in 250 ml. of dry benzene and 35 ml. of dimethyl sulfoxide (Stepan Chemical Co.), a solution of 34.9 g. (0.16 mole) of diethyl acetamidomalonate (Winthrop Laboratories, 1450 Broadway, New York 18, N. Y.) in 200 ml. of dry benzene was added under nitrogen, with stirring, over a period of 1 hr. The reaction temperature was then raised to 50° and maintained at this temperature for 2 hr. to complete the formation of the sodio derivative (cessation of hydrogen evolution). With stirring continued, the mixture was then cooled to 25°, and 19.2 g. (0.15 mole) of *cis*-1,4-dichloro-2-butene[7] in 25 ml. of dry benzene was added under nitrogen, over a period of 2 hr. After being stirred for 2.5 hr. at 25° and then for an additional 14 hr. at 45°, the reaction mixture was treated with 30 ml. of absolute ethanol to consume unchanged sodium hydride. The resulting suspension was filtered, and the insoluble solids were washed with an additional 100 ml. of alcohol. The solvents were then evaporated under aspirator vacuum on the steam bath, the residue mixed with 180 ml. of water containing 12 ml. of acetic acid, and the resulting mixture extracted with three 100-ml. portions of ether. Removal of the ether at reduced pressure from the combined extracts left an oily, tan-colored product which could not be made to crystallize. This was taken up in 40 ml. of ethanol, 100 ml. of 2.5*N* aqueous sodium hydroxide was added, and the solution heated at reflux for 4 hr. under a nitrogen atmosphere. During this operation two phases slowly separated. The mixture was then cooled in an ice bath, while 50 ml. of conc. hydrochloric acid was added, with shaking (gas evolution). The resulting solution was refluxed for 0.5 hr. (darkening of color) and then evaporated to dryness *in vacuo* on the steam bath. The residual solids, which gave a yellow color with ninhydrin test solution, were then extracted with two 200-ml. portions of refluxing absolute ethanol, each for 0.25 hr., and filtered while hot. Concentration and cooling of the combined, dark-colored ethanolic extracts furnished 7.1 g. (29% over-all yield) of DL-baikiain hydrochloride as glistening, white prisms, m.p. 255–261° (dec.). Purification by crystallization from methanol–ethyl acetate afforded 6.9 g. of colorless product, m.p. 262–264° (dec.) (rapid heating) (lit.[3] 264°, dec.).

*Anal.* Calcd. for $C_6H_9O_2N\cdot HCl$ (163.61): C, 44.05; H, 6.16; N, 8.56; Cl, 21.67. Found: C, 44.31; H, 6.32; N, 8.69; Cl, 21.44.

An ascending paper chromatogram of this product with phenol-water as the mobile phase gave a yellow-brown

(5) A. E. Blood and C. R. Noller, *J. Org. Chem.*, **22**, 844 (1957); see also ref. 10.

(6) In private correspondence with us Professor Raphael has indicated that the identity of the potassium bromide infrared spectra mentioned in ref. 3 actually referred only to the *N*-benzoyl derivatives.

(7) L. H. Amundsen, R. H. Mayer, L. S. Pitts, and L. A. Malentacchi, *J. Am. Chem. Soc.*, **73**, 2118 (1951).

ninhydrin spot with an $R_f$ value of 0.85, identical in position, shape, and color with that produced by L(−)-baikiain.[1,8] The infrared spectrum of the synthetic product in Nujol or as a potassium bromide pellet differed significantly from the published spectrum[8] of the optically active compound.

*DL-Baikiain* (I). Treatment of 300 mg. of the above hydrochloride with 350 mg. of silver carbonate in 5 ml. of water, with stirring, for 10 min., followed by filtration of the mixture, evaporation of the solvent, and recrystallization of the residue from methanol-acetone, provided 210 mg. (90% yield) of DL-baikiain as small, elongated prisms, m.p. 251–254° (dec.) (lit.[3] 273–274° dec.).

*Anal.* Calcd. for $C_6H_9O_2N$ (127.14): C, 56.68; H, 7.14; N, 11.02. Found: C, 56.54; H, 7.33; N, 10.77.

A mixed melting point of this substance with natural L(−)-baikiain,[1] m.p. 270–273° (dec.), was 255–261° (dec.). The paper chromatographic behavior was identical with that of L(−)-baikiain. Nujol and potassium bromide pellet infrared spectra showed a number of similarities but were quite different from those of the natural material.[6]

*N-Benzoyl-DL-baikiain.* The procedure described by King, *et al.*,[1] for the preparation of the *N*-benzoyl derivative of L(−)-baikiain was followed. The crude product, obtained in 80% yield, recrystallized from water to form irregular, flattened needles, m.p. 172–173° (lit.[3] 179–180°).

*Anal.* Calcd. for $C_{13}H_{13}O_3N$ (231.24): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.63; H, 5.89; N, 5.85.

The infrared spectrum of this substance in chloroform solution or as a potassium bromide pellet[3] was identical with that of *N*-benzoyl-L(−)-baikiain. The spectra of the respective methyl esters (diazomethane) in carbon disulfide or chloroform solution were likewise indistinguishable.

*DL-Baikiain hydrochloride methyl ester.* This derivative was obtained in 85% yield from DL-baikiain hydrochloride by the procedure of King, *et al.*,[1] for the preparation of L(−)-baikiain hydrochloride methyl ester. It crystallized from ethanol-acetone as fine prisms, m.p. 183–184°.

*Anal.* Calcd. for $C_7H_{11}O_2N \cdot HCl$ (177.58): C, 47.34; H, 6.76; N, 7.89; Cl, 19.97. Found: C, 47.13; H, 6.82; N, 7.75; Cl, 19.69.

*Hydrogenation experiments. A.* The reduction of 100 mg. (0.61 mmole) of DL-baikiain hydrochloride over Adams' catalyst according to the procedure of King, *et al.*,[1] for the hydrogenation of L(−)-baikiain hydrochloride, resulted in the uptake of 14.7 ml. of hydrogen in 10 min. at 25° and 745 mm. (theory 15.3 ml.). Separation of the catalyst, evaporation of the solvent, and recrystallization of the residue from ethanol-benzene gave DL-pipecolic acid hydrochloride, m.p. 257–260°, undepressed on admixture with an authentic sample, m.p. 259–261°, prepared by hydrogenation of picolinic acid hydrochloride.[9] Ascending paper strip chromatograms (phenol-water) of both samples gave identical deep violet ninhydrin spots with an $R_f$ value of 0.87 (lit.[8] 0.895).

*B.* A solution of 0.2312 g. (1.0 mmole) of *N*-benzoyl-DL-baikiain in 15 ml. of ethanol was mixed with 0.1 g. of 10% palladium-charcoal (Adams' platinum catalyst[1] led to over-reduction) and shaken under hydrogen at 25° and 747 mm. The reduction was complete in 25 min., with an uptake of 22.8 ml. of hydrogen (theory 24.9 ml.). After filtration and concentration of the solution, colorless prisms, crystallizing as a solvate from benzene–petroleum ether (b.p. 40–60°), were obtained. After being dried at 100° these melted at 125.5–127°, undepressed on admixture with an authentic sample of *N*-benzoyl-DL-pipecolic acid, m.p. 126–127° (lit.[9] 126–127°), prepared by benzoylation[9] of DL-pipecolic acid.

*Trimethyl N-carboxymethyl-DL-aspartate.* The procedure and scale recorded by King, *et al.*,[1] for the preparation of the L form of this substance were employed. From 1.8 g. of methyl bromoacetate and 3.8 g. of dimethyl DL-aspartate, a colorless crude product was obtained which, after work-up, afforded 2.1 g. (76% yield from the bromoacetate) of the trimethyl ester of *N*-carboxymethyl-DL-aspartic acid (III) as an oily liquid, b.p. 124° (0.06 mm.), $n_D^{23}$ 1.4498 [L-ester[1] b.p. 120° (bath) (0.1 mm.)].

*Anal.* Calcd. for $C_9H_{15}O_6N$ (233.22): C, 46.35; H, 6.48; N, 6.01. Found: C, 46.56; H, 6.45; N, 6.31.

The *picrate* was prepared in ethanol and recrystallized from ethanol-ether to give clusters of light yellow needles, m.p. 137–138° (L-picrate[1] m.p. 137°).

*Anal.* Calcd. for $C_9H_{15}O_6N \cdot C_6H_3O_7N_3$ (462.33): C, 38.97; H, 3.92; N, 12.12. Found: C, 39.02; H, 4.15; N, 12.32.

The picrolonate crystallized from ether containing a small amount of ethanol as deep yellow hexagonal prisms, m.p. 126–127° (L-picrolonate[1] m.p. 182°).

*Anal.* Calcd. for $C_9H_{15}O_6N_4 \cdot C_{10}H_8O_5N_4$ (497.42): C, 45.87; H, 4.66; N, 14.08. Found: C, 45.92; H, 4.94; N, 14.36.

*Ozonolysis of DL-baikiain hydrochloride.* The procedure described by King, *et al.*,[1] for the ozonolysis of L(−)-baikiain hydrochloride was employed on one-half scale, esentially without change. After esterification of the ozonization product with methanol there was obtained 270 mg. of a redistilled, pale yellow oil, b.p. 120–125° (0.1 mm.). Its infrared spectrum was practically identical with that of authentic trimethyl *N*-carboxymethyl-DL-aspartate described above. The picrate deposited from ethanol-ether as light yellow needles, m.p. 137–138°, undepressed on admixture with the foregoing authentic preparation. The picrolonate crystallized from the same solvent pair as deep yellow hexagonal prisms, m.p. 126–127°, likewise undepressed on admixture with the authentic sample noted above.

*trans-2,7-Diamino-4-octenedioic acid* (IX). The already-presented description of the preparation of DL-baikiain hydrochloride was duplicated on the same scale, save that *cis*-1,4-dibromo-2-butene[10] was used in place of the dichloro derivative. The crude hydrolysis-decarboxylation product gave a strong blue-violet ninhydrin color test and had an $R_f$ value of 0.35 when chromatographed on paper with phenol-water. Baikiain (yellow spot with an $R_f$ of 0.85) was also detected on the chromatogram. Purification by extraction with hot alcohol from the inorganic contaminants was only partially successful. Ion exchange chromatography, however, did facilitate the isolation. Absorption of 2.0 g. of the crude hydrochloride (total yield 4.5 g.) on a well washed column of Dowex-50 (20 × 300 mm.), followed by washing with water until sodium chloride was no longer eluted, and then elution with 1.2 l. of 3*N* hydrochloric acid, afforded, after concentration of the amino acid fraction (last 850 ml.), 1.2 g. of the colorless *bis* (?) hydrochloride of the *dl* or *meso* form of *trans*-2,7-diamino-4-octenedioic acid (IX), which crystallized from methanol-water as small, flattened needles, m.p. *ca.* 235–240° (dec.). Attempted purification by repeated recrystallization from hot methanol-acetone resulted in extensive loss of hydrogen chloride, leading finally to the *free* amino acid, which deposited as fine, difficultly-soluble granules, m.p. 355–360° (dec.) (darkening at 320°). The analysis appeared to indicate that partial dehydration had also occurred.

*Anal.* Calcd. for $C_8H_{14}O_4N_2$ (202.21): C, 47.52; H, 6.98; N, 13.86. Found: C, 48.35; H, 7.32; N, 14.35; Cl, nil.

The infrared spectrum (Nujol) of this product indicated the presence of a *trans*-1,2-disubstituted olefinic linkage (strong band at 10.3 $\mu$). Ozonolysis of a 2.0-g. sample of a partially purified sample of the hydrochloride, followed by esterification of the ozonization product with methanol, as in the degradation of baikiain,[1] furnished 0.8 g. of a colorless liquid, b.p. 85–90° (0.1 mm.), $n_D^{23}$ 1.4425. The infrared spectrum of this material indicated it to be substantially identical with dimethyl DL-aspartate, an authentic sample of which

(8) R. M. Zacharius, J. F. Thompson, and F. C. Steward, *J. Am. Chem. Soc.*, **76**, 2908 (1954).

(9) C. M. Stevens and P. B. Ellman, *J. Biol. Chem.*, **182**, 75 (1950).

(10) A. Vallette, *Ann. chim.*, (12) **3**, 644 (1948).

was found to have b.p. 85–90° (0.1 mm.) and $n_D^{23}$ 1.4420. Passage of anhydrous hydrogen chloride into an ether solution of this ester deposited the *hydrochloride* of *dimethyl* DL-*aspartate*, which crystallized from ethanol–ethyl acetate as slightly hygroscopic, colorless, hard prism clusters, m.p. 115–116.5°, undepressed on admixture with an authentic specimen prepared from DL-aspartic acid.

*Anal.* Calcd. for $C_6H_{11}O_4N \cdot HCl$ (197.63): C, 36.46; H, 6.12; N, 7.09. Found: C, 36.67; H. 6.17; N, 7.10.

*Acknowledgment.* We are deeply grateful to Dr. F. E. King, F.R.S., British Celanese Ltd., for supplying a generous comparison sample of *L*(−)-baikiain and to Professor Joseph H. Burckhalter for giving much helpful advice and encouragement during the course of this work. We also wish to thank the University of Kansas for providing a grant from the General Research Fund and the General Aniline and Film Corp. for furnishing *cis*-2-butene-1,4-diol.

LAWRENCE, KAN.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT CENTER OF THE FOOD MACHINERY AND CHEMICAL CORPORATION]

# α-Oximinoketones. V. The Synthesis of 5-Cyano-2-oximinovaleric Acid and DL-Lysine from 2,6-Dioximinocyclohexanone[1]

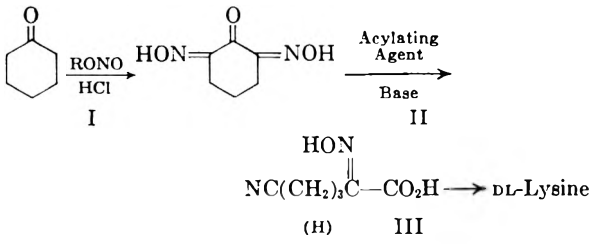
ARTHUR F. FERRIS, GRANNIS S. JOHNSON,[2] FRANCIS E. GOULD, AND HAROLD K. LATOURETTE

*Received September 4, 1959*

A new three-step synthesis which gives DL-lysine monohydrochloride in 20% overall yield from cyclohexanone has been developed. The reaction sequence is: (1) conversion of cyclohexanone to 2,6-dioximinocyclohexanone by the action of methyl nitrite, (2) partial cleavage of 2,6-dioximinocyclohexanone to 5-cyano-2-oximinovaleric acid by the action of acylating agent and aqueous base, and (3) reduction of 5-cyano-2-oximinovaleric acid to DL-lysine by catalytic hydrogenation.

The importance of L-lysine as an essential amino acid in the diet of man and some higher animals and its relative scarcity in most of the common cereal proteins have led to many attempts to prepare this amino acid synthetically. Perhaps the largest number of published syntheses have proceeded from ε-caprolactam (most commonly prepared by Beckmann rearrangement of cyclohexanone oxime).[3] Other favorite starting materials have been malonic ester[4–6] or its derivative, acetamidomalonic ester.[7,8] Several elegant syntheses have been based on oxygen-containing heterocyclic materials such as acrolein dimer (3,4-dihydro-2H-pyran-2-carboxaldehyde)[9] or furfural.[10–12]

The need for a better method of preparing DL-lysine than any of those described has led to an extended effort in this laboratory to realize the deceptively simple three-step synthesis shown in equation form below:




This research is described in this and the next two papers of this series.

The preparation of 2,6-dioximinocyclohexanone (Step I) was described first by Borsche[13] and has been studied more recently by Treibs and coworkers.[14] The reduction of the ethyl ester of 5-cyano-2-oximinovaleric acid has been carried out successfully,[4–6] so that it seemed logical to believe that step III could be made to succeed. The critical step thus appeared to be II, which may be described as a partial "second order" Beckmann rearrangement, wherein it was desired to bring about rearrangement at one oxime group but not at the

(1) A preliminary account of this and the next two papers in this series was published in *Chem. & Ind. (London)*, 996 (1959).

(2) Present address: General Aniline and Film Co., Linden, N. J.

(3) R. J. Wineman, E. T. Hsu, and C. E. Anagnostopoulos, *J. Am. Chem. Soc.*, **80**, 6233 (1958); W. C. Francis, J. R. Thornton, J. C. Werner, and T. R. Hopkins, *J. Am. Chem. Soc.*, 80, 6238 (1958). Previous work is summarized in these papers.

(4) E. Fischer and F. Weigert, *Ber.*, **35**, 3772 (1902).

(5) H. Borsook, C. L. Deasy, A. J. Haagen-Smit, G. Keighley, and P. H. Lowy, *J. Biol. Chem.*, **176**, 1383 (1948).

(6) P. Olynyk, D. B. Camp, A. M. Griffith, S. Woislowski, and R. W. Helmkamp, *J. Org. Chem.*, **13**, 465 (1948).

(7) M. Servigne and E. Szarvasi, *Compt. rend.*, **238**, 1595 (1954).

(8) D. T. Warner and O. A. Moe, *J. Am. Chem. Soc.*, **70**, 2763, 3918 (1940).

(9) R. R. Whetstone and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5280 (1951).

(10) A. O. Rogers, R. D. Emmick, L. W. Tyran, L. B. Phillips, A. A. Levine, and N. D. Scott, *J. Am. Chem. Soc.*, **71**, 1837 (1949).

(11) R. Gaudry, *Can. J. Research*, **26B**, 387 (1948).

(12) H. Conroy, U. S. Patents **2,786,848** and **2,786,850**, March 26, 1957; H. Conroy and W. J. Paleveda, U. S. Patent **2,786,849**, March 26, 1957.

(13) W. Borsche, *Wallach Fest.*, 301 (1909); *Chem. Abstr.*, **5**, 883 (1911).

(14) A. Treibs and D. Dinelli, *Ann.*, **517**, 152 (1935); A. Treibs and A. Kuhn, *Chem. Ber.*, **90**, 1691 (1957).

other. Although the second order Beckmann rearrangement is well enough known to be discussed in several general references[15-17] and to have been the subject of at least one careful study,[18] no record was found of any attempt to carry out the reaction only once in a system capable of reacting twice. The fact that the intermediate α-oximino acid should react further to give a nitrile, carbon dioxide, and water under acylating conditions is well documented.[19] In addition, at the time that this work was undertaken, it was not completely certain that aliphatic and cycloaliphatic α-oximino ketones existed completely in the *anti* form, an essential feature of the proposed synthesis.[18] However, the work of Taylor[20] on the metal complexes of α-oximino ketones made it appear reasonable to assume before experiments were undertaken that 2,6-dioximinocyclohexanone existed in the *anti* form.

As expected, step I of the synthesis presented no serious problems. The treatment of cyclohexanone with methyl nitrite in the presence of hydrochloric acid, a modification[21] of the Borsche[13] synthesis, gave 2,6-dioximinocyclohexanone consistently in about 75% yield.

Before serious study of step II was undertaken, preliminary experiments were carried out to establish with certainty the configuration of 2,6-dioximinocyclohexanone. 2-Oximinocyclohexanone was prepared from 2-carbethoxycyclohexanone[22] by the method of Geissman and Schlatter,[23] and it was subjected to the second order Beckmann rearrangement. The action of benzenesulfonyl chloride and aqueous base gave a 71% yield of 5-cyanovaleric acid, identified by hydrolysis to adipic acid. Very recently Murakami and Tokura[24] have shown that 2-oximino-1-tetralone is cleaved by thionyl chloride in liquid sulfur dioxide to *o*-(2-cyanoethyl)benzoic acid, but unfortunately the results of their work had not been published at the time that our preliminary experiments were carried out. In a second experiment, 2,6-dioximinocyclohexanone was treated with three equivalents of benzenesulfonyl chloride and base, and a 50% yield of glutaronitrile was obtained. (Borsche[25] tentatively identified glutaronitrile as one of the products obtained by the action of base on 2,6-dibenzoyloximinocyclohexanone.) The fact that these reactions all give nitriles and not isonitriles[18] indicated that 2,6-dioximinocyclohexanone and the other cyclic α-oximino ketones possess the desired *anti* configuration. This left little doubt that the proposed synthesis was feasible, and the key problem then became the question of stopping the rearrangement at the desired intermediate point.

Two major lines of approach to the problem of partial rearrangement were taken: The first consisted of attempting to induce a chemical difference between the two oximino groups so that one would react and the other would not; the second consisted of using a deficiency of acylating agent in the rearrangement, accepting the necessity of recovering and recycling a considerable amount of starting material, and hoping thus to save a considerable portion of the intermediate 5-cyano-2-oximinovaleric acid from attack. All attempts to use the first approach failed. Although simple α-oximino ketones can be alkylated easily,[26] only tars were obtained in experiments designed to produce monoalkyl derivatives of 2,6-dioximinocyclohexanone. Tarry products were obtained likewise in efforts to reduce the dioxime to 2-amino-6-oximinocyclohexanone or derivatives thereof.

The second approach proved to be more fruitful. When 2,6-dioximinocyclohexanone was dissolved in aqueous base and treated with a deficiency of acylating agent, 5-cyano-2-oximinovaleric acid was formed. The most difficult problem in connection with this step was that of finding a method of isolation for the very water soluble product. The first successful method of isolation was based on the observation of Aymaretto[27] that complexes of α-oximino acids with copper, nickel, or cobalt ions were soluble in base but insoluble in dilute acids. Thus, in working up the reaction mixtures from the partial rearrangement (or, probably better, partial cleavage[28]) the solutions were acidified, the unchanged 2,6-dioximinocyclohexanone which precipitated was removed by filtration, and a solution of nickel sulfate was added to precipitate the nickel complex of 5-cyano-2-oximinovaleric acid. Some acylating agents were considerably more effective in the partial cleavage reaction than others, the best being acetic anhydride, which gave yields of nickel complex as high as 68% (based on 2,6-dioximinocyclohexanone not recovered). The best yield obtained with benzenesulfonyl chloride was only 35%, and with phosphorus oxychloride 15%. Free 5-cyano-2-oximinovaleric acid was obtained

(15) A. H. Blatt, *Chem. Revs.*, **12**, 218 (1933).
(16) V. Migrdichian, *Org. Synthesis*, Vol. 1, Reinhold Publishing Corp., New York, 1957, p. 376.
(17) E. F. Degering, *An Outline of Organic Nitrogen Compounds*, University Lithoprinters, Ypsilanti, Mich., 1950, p. 184.
(18) A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934).
(19) R. E. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, J. Wiley and Sons, Inc., New York, 1953, p. 598.
(20) T. W. J. Taylor and E. K. Ewbank, *J. Chem. Soc.*, 2818 (1926); T. W. J. Taylor, *J. Chem. Soc.*, 2018 (1931).
(21) O. Touster, *Org. Reactions*, **7**, 351 (1953).
(22) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, *Org. Syntheses*, Coll. Vol. II, 531 (1943).
(23) T. A. Geissman and M. J. Schlatter, *J. Org. Chem.*, **11**, 771 (1946).
(24) D. Murakami and N. Tokura, *Bull. Chem. Soc. Japan*, **31**, 1044 (1958). We are indebted to Dr. Tokura for sending us a copy of this publication.
(25) Ref. 13, p. 305.
(26) A. F. Ferris, *J. Org. Chem.*, **24**, 1726 (1959).
(27) M. Aymaretto, *Gazz. chim. ital.*, **57**, 648 (1927).
(28) A. F. Ferris, *J. Org. Chem.*, **25**, 12 (1960).

from the nickel complex by treating a solution of the complex in aqueous base with dimethylglyoxime, removing the precipitated nickel dimethylglyoxime by filtration, evaporating the filtrate under reduced pressure, treating the residue with ethanolic hydrochloric acid, removing sodium chloride by filtration, evaporating the filtrate, and recrystallizing the crude acid from chloroform. The yield of pure 5-cyano-2-oximinovaleric acid obtained by this technique was 57% based on nickel complex; hence, the overall yield based on 2,6-dioximinocyclohexanone was 38%.

The yield of step II was improved considerably by the development of better techniques of isolation. The best method was based on saturating the acidified reaction mixture with an inorganic salt and then extracting with a normally water soluble solvent. When isopropanol was used as the solvent the crude extract contained some inorganic salt and had to be purified further by extraction with ether. Pure 5-cyano-2-oximinovaleric acid was precipitated from the ether solution by the addition of hexane or chloroform. The yield of partial cleavage product from 2,6-dioximinocyclohexanone was 62% with this recovery system. A similar system based on ethyl acetate as the extracting solvent gave a somewhat poorer yield, 53%.

In view of the report[6] that catalytic hydrogenation of ethyl 5-cyano-2-oximinovalerate to DL-lysine proceeds readily, serious difficulty had not been anticipated in step III of the proposed synthesis. In actual fact, however, finding a combination of catalyst and solvent which would bring about the hydrogenation of 5-cyano-2-oximinovaleric acid to lysine proved very difficult. As had been anticipated, acetic anhydride, the solvent used[6] in the reduction of the ethyl ester, could not be used because it rearranged the acid to glutaronitrile, carbon dioxide being evolved. A number of other catalyst-solvent systems commonly used in the hydrogenation of nitriles and/or oximes[29,30] were tried without success, including platinum and palladium-on-charcoal in ethanolic hydrochloric acid, and Raney nickel and precious metal catalysts in ethanolic ammonia. The nickel complex of 5-cyano-2-oximinovaleric acid was found to be soluble in ethanolic ammonia, and attempts were made to hydrogenate it in the presence of a variety of catalysts, all without success. In most of these failures hydrogen was taken up—in many instances the theoretical amount—but in no case was the product lysine. Although the nature of the products was not investigated, it seemed probable that the failures could be attributed to the condensation reactions leading to secondary amines which are well known complications[29,30] in many reductions of nitriles to primary amines.

(29) H. Adkins and R. L. Shriner in H. Gilman, *Organic Chemistry*, Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, 1943, p. 809.

(30) Ref. 19, p. 658.

It was ultimately found that the combination of platinum (from *in situ* reduction of platinum oxide) as catalyst and acetic acid as solvent led to uptake of the theoretical amount of hydrogen and to isolation of lysine as the monohydrochloride upon treating the reaction mixture with hydrochloric acid. The classic technique of Eck and Marvel[31] was used in the isolation of the DL-lysine monohydrochloride. A study of the reduction ultimately raised the yield of DL-lysine monohydrochloride to 43%. At this point in the development of the new lysine synthesis, the overall yield of lysine from cyclohexanone was 20%.

Since the hydrogenation of the ethyl ester of 5-cyano-2-oximinovaleric acid had been reported[6] to proceed in much better yield (73%) than that obtained in this study with the acid, conversion of the acid to the ester followed by hydrogenation of the ester seemed to offer an opportunity to improve the over-all yield of the process. Because of the ease with which the acid is decomposed in acidic media, conventional esterification techniques could not be used. However, by adding a little thionyl chloride to a solution of the acid in ethanol and allowing the mixture to stand at room temperature for a few days,[32] ethyl 5-cyano-2-oximinovalerate was prepared in 61% yield. When hydrogenated in acetic anhydride in the presence of platinum this material was reduced, and DL-lysine monohydrochloride was obtained upon hydrolysis of the reaction mixture with hydrochloric acid. However, even in an extended series of experiments it was never possible to duplicate the reported yield of 73%.[6] A number of variations involving changes in amount of solvent and catalyst gave yields consistently in the range of 50–57%. Thus, by proceeding through the ester the yield of lysine from 5-cyano-2-oximinovaleric acid was 35%, and over-all from cyclohexanone, 16%. The route involving hydrogenation of the acid is to be preferred, since it gave a better over-all yield of lysine in fewer steps.

## EXPERIMENTAL[33,34]

*2,6-Dioximinocyclohexanone.* To a solution of 491 g. (5.00 moles) of cyclohexanone in 2500 ml. of ether was added 100 ml. of concentrated hydrochloric acid. The solution was cooled to 10°, and nitrogen was passed slowly through it for 10–15 min. Then, with nitrogen flow continuing, methyl nitrite was passed in slowly from an external generator. The methyl nitrite was generated by adding a solution of 320 ml. (5.75 moles) of concentrated sulfuric acid in 575 ml. of water dropwise to a mixture of 845 g. (11.25 moles) of sodium nitrite, 400 g. (12.50 moles) of methanol, and 750 ml. of water. The temperature was maintained at 5–15° by ex-

(31) J. C. Eck and C. S. Marvel, *Org. Syntheses*, **Coll. Vol. II**, 374 (1943).

(32) K. Freudenberg and W. Jakob, *Ber.*, **74**, 1001 (1941).

(33) All melting points are uncorrected.

(34) Most of the microanalyses were carried out by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

ternal cooling while the methyl nitrite was passed in over about 5 hr. A yellow solid precipitated as the reaction proceeded. When all the methyl nitrite had been added the cooling bath was removed, and the mixture was allowed to warm to about 25°. Any tendency for the temperature to rise above this point was controlled by intermittent cooling. After 3 hr. at 25° the hydrochloric acid was neutralized by the addition of 100 ml. of pyridine. (If the product was to be used within a few days for the next step of the reaction, neutralization was not necessary.) The yellow solid product was recovered by suction filtration, and was washed on the filter with 500 ml. of acetone. It was sucked as dry as possible, and then was dried further in a vacuum desiccator. There was obtained 612 g. (78%) of yellowish brown 2,6-dioximinocyclohexanone, pure enough for use in the next step of the reaction. For an analytical sample, a portion of the crude product was recrystallized four times from 2:1 methanol-water. The final product was a mass of fine yellow needles which showed no definite melting point, but charred slowly in the range of 160–200° when heated in a capillary.

*Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.95. Found: C, 46.22; H, 5.17; N, 17.77.

*5-Cyano-2-oximinovaleric acid.* To a solution of 200 g. (5.0 moles) of sodium hydroxide in 2000 ml. of water was added 156.1 g. (1.0 mole) of 2,6-dioximinocyclohexanone. The temperature was held at 20–25° while the oxime dissolved to give an orange-brown solution. With vigorous stirring 51.1 g. (0.5 mole) of acetic anhydride was added over 30 min., the temperature being held at 20–30°. After stirring for 1 hr., a solution of 150 ml. of concentrated sulfuric acid in 150 ml. of water was added slowly, the temperature being held at 20–25°. Unchanged 2,6-dioximinocyclohexanone precipitated and was recovered by filtration, washed with two 100-ml. portions of water, and dried. Recovered 2,6-dioximinocyclohexanone amounted to 88.5 g. The filtrate, amounting to 2530 ml., was saturated with sodium sulfate and extracted once with 1000 ml. of isopropanol and once with 500 ml. The combined isopropanol solution was concentrated *in vacuo* at 50° to a slurry. The slurry was extracted with four 400-ml. portions of ether, the ether solution was dried, and the ether was evaporated at reduced pressure. There was obtained 42.0 g. of 5-cyano-2-oximinovaleric acid, m.p. 105° dec., a 54% yield based on acetic anhydride and a 62% yield based on 2,6-dioximinocyclohexanone not recovered. A portion of this material was recrystallized by being taken up in hot ethyl acetate (5 ml./g. solid) and precipitated by addition of two volumes of a 3:1 hexane-chloroform mixture. The recrystallized acid melted at 109–110° dec.

*Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.95; neut. equiv., 156.1. Found: C, 46.44; H, 4.92; N, 17.94; neut. equiv., 155.1.

*Ethyl 5-cyano-2-oximinovalerate.* To a solution of 31.0 g. (0.20 mole) of 5-cyano-2-oximinovaleric acid in 400 ml. of absolute ethanol was added 5.5 g. (0.046 mole) of thionyl chloride. The mixture was allowed to stand at room temperature. Each day a 1 ml. aliquot was removed, diluted with water, and titrated with 0.1*N* sodium hydroxide. When the acidity remained constant (9 days) the ethanol was removed by distillation at reduced pressure at 40–50°. The solid residue was recrystallized twice from carbon tetrachloride to give 20.0 g. (61%) of pure ethyl 5-cyano-2-oximinovalerate, m.p. 74–75°, (lit.,[4] m.p. 74°).

*Reduction of 5-cyano-2-oximinovaleric acid.* In a solution of 7.8 g. (0.10 mole) of 5-cyano-2-oximinovaleric acid in 100 ml. of glacial acetic acid was suspended 0.6 g. of platinum oxide (Adams' catalyst), and the mixture was shaken at room temperature with hydrogen at 50 p.s.i. After 8 hr. the theoretical amount of hydrogen had been taken up. The catalyst was filtered from the reaction mixture, and the acetic acid was evaporated under reduced pressure at 40–50°. The residue was treated with 25 ml. of concentrated hydrochloric acid, and the excess was evaporated under reduced pressure. This treatment was repeated, and after evaporation to dryness there remained 7.9 g. of solid. This was taken up in 100 ml. of boiling 95% ethanol, and a solution of 10 ml. of pyridine in 10 ml. of 95% ethanol was added. A white solid separated slowly. After several days standing the solid was recovered by filtration and dried. It amounted to 3.9 g. (43%) of DL-lysine monohydrochloride, m.p. 258–262°. The infrared spectrum of this product was identical with that of an authentic sample of DL-lysine monohydrochloride.

*Reduction of ethyl 5-cyano-2-oximinovalerate.* In a solution of 36.8 g. (0.20 mole) of ethyl 5-cyano-2-oximinovalerate in 200 ml. of acetic anhydride was suspended 3.0 g. of platinum oxide, and the mixture was shaken at room temperature with hydrogen at 50 p.s.i. In about 8 hr. the theoretical amount of hydrogen was taken up. The catalyst was filtered from the reaction mixture and washed with 25 ml. of acetic anhydride. The filtrate was heated with 300 ml. of water at 50°, and the mixture was stirred until it became homogeneous. Then 450 ml. of concentrated hydrochloric acid was added, and the resulting solution was heated under reflux for 16 hr. The water and hydrochloric acid were evaporated at reduced pressure at 50–60°. The resulting sirup was treated twice with 100-ml. portions of concentrated hydrochloric acid evaporating to a sirup after each treatment. The final sirup was dissolved in 200 ml. of boiling 95% ethanol. The solution was cooled to room temperature and 800 ml. of ether was added. A white precipitate of DL-lysine dihydrochloride formed. The supernatant liquid was decanted, and the solid was dissolved in 850 ml. of hot absolute ethanol. To the hot solution was added 48 ml. of pyridine in 100 ml. of hot ethanol. A white solid precipitated at once. The solution was held for 16 hr. at 5° to complete the precipitation, then the solid was recovered by filtration and dried. It amounted to 21.0 g. (57%) of DL-lysine monohydrochloride, m.p. 256–260°. Its infrared spectrum was identical with that of an authentic sample of DL-lysine monohydrochloride.

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PRINCETON, N. J.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT CENTER OF THE FOOD MACHINERY AND CHEMICAL CORPORATION]

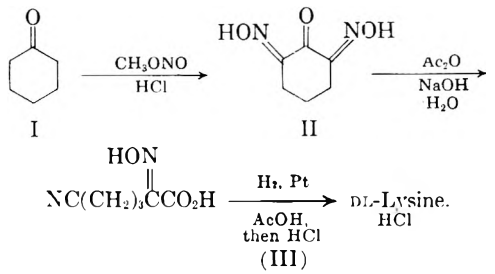
# α-Oximinoketones. VI. Synthesis of Alkyl 5-Cyano-2-oximinovalerates and DL-Lysine from 2,6-Diacyloximinocyclohexanones[1]

ARTHUR F. FERRIS, GRANNIS S. JOHNSON,[2] AND FRANCIS E. GOULD

*Received October 1, 1959*

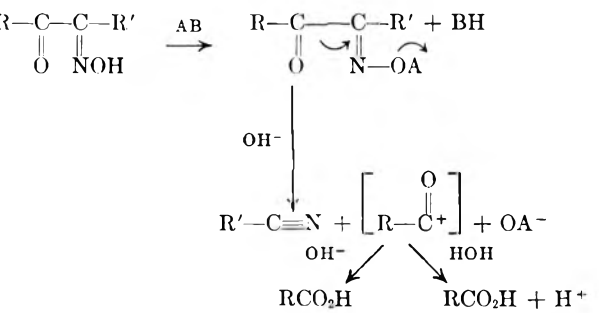
An improved version of the previous synthesis of lysine from cyclohexanone[1] gave the yields indicated in the following four steps: (1) nitrosation of cyclohexanone to 2,6-dioximinocyclohexanone (75%); (2) acetylation of 2,6-diacetoximinocyclohexanone (76%); (3) cleavage with sodium ethoxide in ethanol to ethyl 5-cyano-2-oximinovalerate (88%); and hydrogenation to DL-lysine (57%). The overall yield was 29%. A study of the "second order" Beckmann rearrangement in alcohols (step 3) was made, and the mechanistic implications of the results are discussed. The key to improved yields in this step was the discovery that alkyl 5-cyano-2-oximinovalerates are resistant to further rearrangement by acylating agents and base.

The previous paper in this series[1] described the synthesis of DL-lysine in 20% over-all yield from cyclohexanone by the three-step sequence shown below:

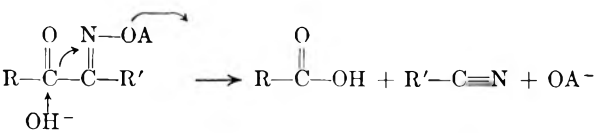



The over-all yield was the result of yields of 75% in step I, 62% in step II, and 43% in step III. In contrast to 5-cyano-2-oximinovaleric acid, its ethyl ester was reduced to lysine in 57% yield. However, a rather low yield on esterification of the acid (61%) reduced the over-all yield in step III to 35%. Thus the over-all conversion to lysine by proceeding through the ester was actually a little poorer than when the acid was hydrogenated. It was obvious, therefore, that a substantial improvement in the over-all lysine process would be realized if an ester of 5-cyano-2-oximinovaleric acid instead of the free acid could be obtained in step II. It should be noted also that although the yield in the partial "second order" Beckmann rearrangement (step II) was fairly good, it was attained by using only half the amount of acetic anhydride theoretically necessary for the desired single cleavage, which necessitated recovery and recycling of a considerable portion of the 2,6-dioximinocyclohexanone charged to the reaction.

In attempting to devise a method for obtaining an ester of 5-cyano-2-oximinovaleric acid instead of the free acid in step II, it was pertinent to reconsider the mechanism of the second order Beckmann rearrangement of α-oximino ketones.[3] It has been suggested previously[4] that this rearrangement involves acylation of the oxime; the concurrent departure of the acylate anion and shift of an electron pair from a position between the carbonyl carbon and the oxime carbon to a position between the latter carbon and the nitrogen, thus cleaving the carbon — carbon bond and forming a nitrile and an oxocarbonium cation; and finally combination of the cation with solvent or with the anion which initiated the rearrangement:




It is equally possible on the basis of previous work to regard the final two steps as concerted, that is, to assume that in the rearrangement the acylated α-oximino ketone is attacked at the carbonyl carbon by the anion of the base as the acylate ion departs. In fact, attack by the anion might even be regarded as the initiating step in the rearrangement:




This view appears to be that held by Green and Saville.[5] Whatever the exact sequence of the last two steps, it was grasped that on the basis of this

(1) Paper V of this series: A. F. Ferris, G. S. Johnson, F. E. Gould, and H. K. Latourette, *J. Org. Chem.*, in press.

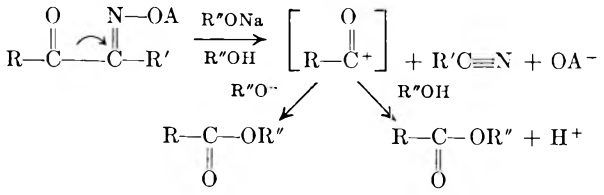
(2) Present address: General Aniline and Film Corp., Linden, N. J.

(3) Helpful discussion of this mechanism with R. Miller, E. R. Gilmont, B. R. Franko, and H. Stange of this laboratory is gratefully acknowledged.

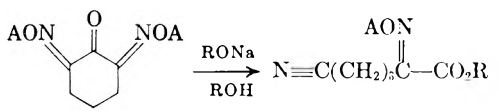
(4) A. F. Ferris, *J. Org. Chem.*, in press.

(5) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956).

mechanism the treatment of a preformed α-acyloximino ketone with a solution of a metal alkoxide in an alcohol should give an ester product in the second order rearrangement:



This concept applied to a 2,6-diacyloximinocyclohexanone should give the acyl derivative of the desired ester in step II;



It was expected that a deficiency of alkoxide would have to be used to avoid attack on the alkyl 5-cyano-2-acyloximinovalerate, just as it had been necessary to use a deficiency of acylating agent in the earlier preparation of 5-cyano-2-oximinovaleric acid.[1]

The first 2,6-diacyloximinocyclohexanone was prepared by Borsche[6] by treating 2,6-dioximinocyclohexanone with benzoyl chloride in the presence of pyridine. Repeating this preparation gave 2,6-dibenzoyloximinocyclohexanone in 47% yield. The melting point of this compound, 186–187°, was considerably higher than that reported by Borsche, 170–172°, but it seems probable that our material was the same as his, since our melting point was taken on a Fisher-Johns block while his was almost certainly taken in a capillary. A more practical acylated product was prepared by treating 2,6-dioximinocyclohexanone with a 3:1 excess of acetic anhydride containing a catalytic amount of mineral acid. A 76% yield of 2,6-diacetoximinocyclohexanone, m.p. 177.5–178.5°, was obtained.

When 2,6 - diacetoximinocyclohexanone was treated with a solution of sodium ethoxide in ethanol the result was in part that which had been expected, and in part unexpected. The product was an ethyl ester, but it was ethyl 5-cyano-2-oximinovalerate, not the expected ethyl 5-cyano-2 acetoximinovalerate. The acetyl group which should have been on the α-oximino group had been removed by solvolysis. Further, it soon became apparent that the use of a deficiency of base was not necessary, since ethyl 5-cyano-2-oximinovalerate was obtained in very good yield (88%) when the equivalent amount or even an excess of base was used. The failure of ethyl 5-cyano-2-acetoximinovalerate to be cleaved might be explained by assuming that the rearrangement did not have time to take place because of very rapid solvolysis, but this seems very unlikely in view of the fact that oxime esters normally rearrange very rapidly and exothermically in the presence of base.[4,7] Further, when 2,6-diacetoximinocyclohexanone was treated with a suspension of an equivalent of sodium methoxide in benzene, methyl 5-cyano-2-acetoximinovalerate, a stable and readily isolable compound, was obtained in 62% yield. In contrast, attempts to dissolve 5-cyano-2-oximinovaleric acid in acetic anhydride, even in the absence of base, led to rapid rearrangement.[1] Even more vigorous rearrangement occurred in the presence of base, when the ammonium salt of 5-cyano-2-oximinovaleric acid was added to acetic anhydride. Ethyl 5-cyano-2-oximinovalerate has been shown[1,8] to dissolve without decomposition in acetic anhydride prior to hydrogenation. It must be concluded that ethyl 5-cyano-2-acetoximinovalerate is solvolyzed in ethanol because, like the acetates of *syn*-benzoin oxime and *syn*-benzil monoxime,[7] it has very little tendency to undergo rearrangement.

The fact that an acylated α-oximino ester, presumably in the *anti* configuration since it is derived from a material in which both oxime groups appear to be *anti* to the carbonyl,[1] fails to be cleaved under conditions which lead to rapid cleavage of acylated α-oximino acids and ketones is a most striking one. At the present time this behavior must be listed with the similar behavior of the acetates of *syn*-benzoin oxime and *syn*-benzil monoxime as not capable of ready interpretation from the standpoint of mechanism. From a synthetic point of view, the stability of ethyl 5-cyano-2-oximinovalerate is most useful, since it permits the cleavage of 2,6-diacetoximinocyclohexanone in good yield without the necessity for recycling starting material.

Some additional experiments directed toward extending the synthesis were only partially successful. A solution of sodium hydroxide in ethanol could be substituted for the solution of sodium ethoxide, but the yield of ethyl 5-cyano-2-oximinovalerate was reduced to 72%. 2,6-Dibenzoyloximinocyclohexanone was cleaved also by sodium ethoxide in ethanol, but the yield was only 60%.

None of the experiments thus far discussed shed any light on the sequence of events in the second order rearrangement: that is, they did not indicate whether the reaction was initiated by departure of the acylate anion, by attack of the base anion, or by a concerted attack and departure. Experiments with a variety of weaker bases did provide an indication of the probable sequence. Weak bases were found to be catalysts for the rearrangement in series of qualitative experiments wherein suspensions of 2,6-diacetoximinocyclohexanone in ethanol

(6) W. Borsche, *Wallach Fest.*, 301 (1909); *Chem. Abstr.*, **5**, 883 (1911).

(7) A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934).

(8) P. Olynyk, D. B. Camp, A. M. Griffith, S. Woislowski, and R. W. Helmkamp, *J. Org. Chem.*, **13**, 465 (1948).

were treated with various bases, and a rapid rise in temperature was taken as an indication of reaction. By this means sodium acetate, sodium cyanide, sodium carbonate, and several amines were shown to be catalysts for the reaction. In a quantitative experiment it was found that when 2,6-diacetoximinocyclohexanone was slurried in ethanol and treated with excess sodium acetate there was obtained in very good yield a mixture of ethyl 5-cyano-2-oximinovalerate and ethyl 5-cyano-2-acetoximinovalerate in about equal amounts. With excess diethylamine or *n*-butylamine in ethanol the only product was ethyl 5-cyano-2-oximinovalerate in yields of 76% and 79% respectively. Similarly, when 2,6-diacetoximinocyclohexanone was slurried in isopropanol and treated with *n*-butylamine, isopropyl 5-cyano-2-oximinovalerate was obtained in 83% yield. The infrared spectra of the ester products from the amine-catalyzed reactions indicated that they contained traces of amides. Attempts to prepare the amides in quantity by treating 2,6-diacetoximinocyclohexanone in dioxane with diethylamine and *n*-butylamine gave only tars. The fact that an ester was obtained when 2,6-diacetoximinocyclohexanone was cleaved with sodium acetate in ethanol might be explained on the basis of initiation of the rearrangement by base attack on the carbonyl carbon, since it is possible to postulate that an intermediate mixed anhydride was obtained and then reacted with solvent to give the observed product. The similar result with amines, however, seems to be explainable only on the assumption that the first step of the reaction was the departure of the acylate anion and shift of the electron pair, and that this was followed by reaction of the oxocarbonium ion formed by the cleavage with the alcohol solvent. Since there appears to be no noteworthy difference between the amine-catalyzed, the alkoxide-catalyzed, and the hydroxide-catalyzed reactions, it seems reasonable to suppose that all second order Beckmann rearrangements follow this sequence.

On the basis of the work described in this paper, the preferred route to lysine is a four-step combination of reactions reported herein and in the previous paper,[1] including nitrosation of cyclohexanone with methyl nitrite (75%), acetylation of 2,6-dioximinocyclohexanone with acetic anhydride (76%), cleavage of 2,6-diacetoximinocyclohexanone with sodium ethoxide in ethanol (88%), and reduction of ethyl 5-cyano-2-oximinovalerate by catalytic hydrogenation (57%). This sequence gave an over-all yield of 29%, better than the 20% of the first sequence, and had the additional advantage of not requiring recycle of 2,6-dioximinocyclohexanone.

## EXPERIMENTAL[9]

*2,6-Dibenzoyloximinocyclohexanone.* To a stirred solution of 56.0 g. (0.40 mole) of benzoyl chloride and 24.0 g. (0.30 mole) of pyridine in 200 ml. of benzene was added 15.6 g. (0.10 mole) of 2,6-dioximinocyclohexanone over 15 min. The temperature rose from 26 to 41°. The mixture was held at 45–50° by application of heat for 30 min., then was cooled to 20°. A solid precipitated and was recovered by suction filtration. The filter cake was washed with benzene and alcohol and was dried *in vacuo*. There was obtained 17.0 g. (47%) of 2,6-dibenzoyloximinocyclohexanone, m.p. 186–187°.

*Anal.* Calcd. for $C_{20}H_{16}O_5N_2$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.92; H, 4.70; N, 7.65.

*2,6-Diacetoximinocyclohexanone.* To a stirred solution of 1 ml. of concentrated sulfuric acid in 612 g. (6 moles) of acetic anhydride was added portionwise 156 g. (1 mole) of 2,6-dioximinocyclohexanone. The addition required 45 min. The temperature rose from 27 to 55°, and then was held at 50–55° by external cooling. After addition was complete, the temperature was held at 50° for 30 min. by application of heat. The reaction mixture was cooled to 25°, and the precipitate which formed was recovered by filtration, washed with three 200-ml. portions of benzene, and dried. The lemon yellow crystals of 2,6-diacetoximinocyclohexanone amounted to 183 g. (76%), m.p. 177.5–178.5° dec.

*Anal.* Calcd. for $C_{10}H_{12}O_5N_2$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.96; H, 5.13; N, 11.64.

*Ethyl 5-cyano-2-oximinovalerate.* (a) *From 2,6-dibenzoyloximinocyclohexanone and sodium ethoxide in ethanol.* A solution of 0.6 g. (0.025 g.-atom) of sodium in 100 ml. of absolute ethanol was prepared. A slurry of 8.5 g. (0.0233 mole) of 2,6-dibenzoyloximinocyclohexanone in 150 ml. of absolute ethanol was prepared, and the sodium ethoxide solution was added to the slurry with cooling to maintain the temperature at 20–30°. Addition required 15 min., and stirring was continued for an additional 30 min. The excess alcohol was distilled off at reduced pressure and at a temperature not exceeding 50°. The residue was taken up in 50 ml. of hot carbon tetrachloride and filtered to remove solid which failed to dissolve. After drying, the insoluble solid weighed 3.0 g. (theory for sodium benzoate, 3.6 g.). Solid crystallized from the carbon tetrachloride filtrate on cooling and was recovered by filtration and dried. There was obtained 2.8 g. (60%) of ethyl 5-cyano-2-oximinovalerate, m.p. 72–74°. (Lit.,[10] m.p. 74°.)

(b) *From 2,6-diacetoximinocyclohexanone and sodium ethoxide in ethanol.* A solution of sodium ethoxide in ethanol was prepared by dissolving 11.5 g. (0.50 g.-atom) of sodium in 500 ml. of absolute ethanol. This solution was cooled to 20°, and a slurry of 120.0 g. (0.50 mole) of 2,6-diacetoximinocyclohexanone in 500 ml. of absolute ethanol was added, the temperature being held at 20–30° by external cooling. After the addition was complete and there was no further tendency for the temperature of the reaction mixture to rise, the alcohol was evaporated at reduced pressure at 40–50°. The resulting slurry was taken up in 1000 ml. of ether, and the mixture was filtered to remove solid which failed to dissolve. The filter cake was washed with 100 ml. of ether, and the filtrate and washings were combined and washed with 500 ml. of saturated sodium bicarbonate solution. The ether solution was dried over anhydrous magnesium sulfate, stirred with decolorizing charcoal, and filtered. The ether was evaporated under reduced pressure, and the residue was dried *in vacuo*. There was obtained 81.0 g. (88%) of ethyl 5-cyano-2-oximinovalerate, m.p. 74–75°.

(c) *From 2,6-diacetoximinocyclohexanone and diethylamine in ethanol.* In 300 ml. of absolute ethanol was slurried 24.0 g. (0.10 mole) of 2,6-diacetoximinocyclohexanone. With vigorous stirring, 24.0 g. (0.33 mole) of diethylamine was added, the temperature being held at 20–30° by external cooling. The clear brown solution obtained was evaporated under

(9) All melting points are uncorrected.

(10) E. Fischer and F. Weigert, *Ber.*, **35**, 3772 (1902).

reduced pressure on a hot water bath, and the residue was taken up in 300 ml. of ether. The ether solution was washed with 150 ml. of saturated sodium bicarbonate solution, treated with decolorizing charcoal, and dried over anhydrous magnesium sulfate. The ether was evaporated under reduced pressure to leave 14.0 g. (76%) of ethyl 5-cyano-2-oximinovalerate, m.p. 73°.

(d) *From 2,6-diacetoximinocyclohexanone and n-butylamine in ethanol.* With vigorous stirring 14.6 g. (0.20 mole) of *n*-butylamine was added to a slurry of 24.0 g. (0.10 mole) of 2,6-diacetoximinocyclohexanone in 200 ml. of absolute ethanol. The temperature rose rapidly from 25 to 55° during the addition of the first few ml. of the amine, then dropped off slowly as the rest was added. After addition was complete, the resulting clear solution was evaporated under reduced pressure on a hot water bath. The residue was taken up in 500 ml. of ether, and the ether solution was washed with dilute hydrochloric acid and saturated sodium bicarbonate solution. It was then treated with decolorizing charcoal and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure left 14.5 g. (79%) of ethyl 5-cyano-2-oximinovalerate, m.p. 70°. The infrared spectrum of this material showed that it contained a trace of amide.

*Methyl 2-acetoximino-5-cyanovalerate.* A mixture of 800 ml. of dry benzene, 120 g. (0.5 mole) of 2,6-diacetoximinocyclohexanone, and 27 g. (0.5 mole) of sodium methoxide was stirred vigorously. In 1 hr. the temperature rose from 27 to 65°. The mixture was cooled to 45°, and the temperature rose in 15 min. to 51°. The mixture was cooled to 40°, and no further increase in temperature occurred. A test with *p*H paper showed that the mixture was neutral, and it was cooled to room temperature and filtered. After drying the filter cake weighed 40 g. (theory for sodium acetate, 41 g.). The benzene was evaporated at reduced pressure at 50°, and the residue was held under vacuum for 24 hr. to insure removal of all volatile material. There remained 66 g. (62%) of methyl 2-acetoximino-5-cyanovalerate, a brown oil. After standing for several days the oil partially crystallized. The mixture of liquid and solid was recrystallized from a mixture of equal volumes of ethyl acetate and cyclohexane to give 33 g. (31%) of white crystalline methyl 2-acetoximino-5-cyanovalerate, m.p. 48°. The infrared spectrum of this solid was essentially identical to that of the oil.

*Anal.* Calcd. for $C_9H_{12}O_4N_2$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.80; H, 5.73; N, 13.50.

*Action of sodium acetate in ethanol on 2,6-diacetoximinocyclohexanone.* With vigorous stirring 5.0 g. (0.0610 mole) of anhydrous sodium acetate was added to a slurry of 10.0 g. (0.0416 mole) of 2,6-diacetoximinocyclohexanone in 30 ml. of absolute ethanol. The temperature rose rapidly to 80°, then dropped slowly. After standing an hour the mixture was heated to 60° under reduced pressure to evaporate the ethanol. The residue was taken up in 100 ml. of ether, and the solid which failed to dissolve was removed by filtration. The filtrate was washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The ether was evaporated under reduced pressure to leave 7.8 g. of white solid, m.p. 50–56°. Comparison of the infrared spectrum of this material with those of ethyl 5-cyano-2-oximinovalerate and methyl 2-acetoximino-5-cyanovalerate indicated that this material was composed of about equal amounts of ethyl 5-cyano-2-oximinovalerate (theory, 7.7 g.) and ethyl 2-acetoximino-2-cyanovalerate (theory, 9.4 g.).

*Isopropyl 5-cyano-2-oximinovalerate from 2,6-diacetoximinocyclohexanone and n-butylamine in isopropanol.* The procedure described for the analogous reaction in ethanol was followed using an equal volume of isopropanol. There was obtained 16.5 g. (83%) of isopropyl 5-cyano-2-oximinovalerate, a brownish oil. After standing several days the oil crystallized. A portion of the solid was recrystallized from a 5:1 cyclohexane–ethyl acetate mixture to give white crystals of isopropyl 5-cyano-2-oximinovalerate, m.p. 55–56°.

*Anal.* Calcd. for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.14. Found: C, 54.43; H, 7.24; N, 14.09.

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PRINCETON, N. J.

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[CONTRIBUTION FROM THE WHITMORE LABORATORY OF THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

# The Five Monocarboxylic Acids of Phenanthrene[1,2]

*Received September 2, 1959*

JOSEPH A. DIXON AND D. D. NEISWENDER, JR.[3]

The syntheses, melting points, ultraviolet and infrared spectra of the five monocarboxylic acids of phenanthrene are reported.

During a study of the synthesis and properties of alkylphenanthrenes it was found that many of the best synthetic routes to these hydrocarbons involve substitution reactions on phenanthrene or a partially hydrogenated phenanthrene. Such reactions frequently produce mixtures of isomers and it is necessary for identification to convert the substitution products to known structures. The monocarboxylic acids of phenanthrenes are a logical set of reference structures, as many functional groups can be converted readily to the carboxylic acid group.

Although syntheses and melting points of the five isomeric phenanthrene monocarboxylic acids have been reported,[4–18] examination of the literature

(1) Taken in part from the dissertation submitted by D. D. Neiswender in partial fulfillment of the requirements for the Ph.D. degree at The Pennsylvania State University.

(2) Presented in part before the Division of Organic Chemistry at the 133rd National Meeting of the American Chemical Society, San Francisco, California, April, 1958.

(3) American Petroleum Institute Fellow, 1955–1957. Present address: Research and Development Laboratories, Socony Mobil Oil Co., Inc. Paulsboro, New Jersey.

(4) L. F. Fieser, *J. Am. Chem. Soc.* **54**, 4110 (1932).

(5) J. R. Dice and P. A. Smith, *J. Org. Chem.* **14**, 179 (1949).

reveals the following: The structural assignments of the 2- and 3- acids depend on the validity of the separation and identification of the mixture of acids obtained upon sulfonation of phenanthrene by Werner in 1902;[19] the reported melting points of a given monocarboxylic acid may differ as much as 11°; the 2- and 3- and 9- acids all melt in the range 250° to 270°; and the infrared and ultraviolet spectra have not been reported.

Because of this, the acids have been synthesized by unambiguous routes and their melting points, and infrared and ultraviolet spectra determined.

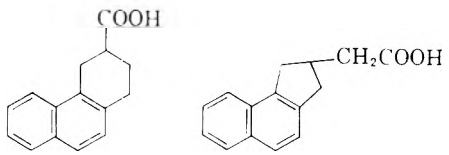
Each of the acids was purified by fractional distillation of the methyl ester, crystallization of the fractions, saponification of the purified ester, and crystallization of the acid.

Phenanthrene-1-carboxylic acid[4-7] and phenanthrene-4-carboxylic acid[10-12] were prepared from 4-(α-naphthyl)butanoic acid and 4-(β-naphthyl)-butanoic acid respectively by an excellent synthetic route designed by Rutherford and Newman.[20] When the naphthylbutanoic acids were prepared by Friedel-Crafts acylation of naphthalene, only the *beta* acid could be separated from the mixture of isomers. Fractional crystallization, fractional neutralization of the acids, and fractional acidification of the sodium salts failed to yield the *alpha* acid free of the *beta* acid.[21] Therefore, the 4-(α-naphthyl)butanoic acid was prepared by Wolff-Kishner reduction of the keto acid obtained from the reaction of α-naphthylmagnesium bromide with succinic anhydride.

The 2-phenanthrene carboxylic acid[8,9] was the only isomer prepared by a substitution reaction on phenanthrene. Acetylation of 9,10-dihydrophenanthrene,[6] dehydrogenation with sulfur and haloform oxidation yielded this acid. As treatment of 2-acetyl-9,10-dihydrophenanthrene with hypochlorite led to diphenyl-2,2′,3-tricarboxylic acid,[22] the dehydrogenation was performed prior to the oxidation.

3-Phenanthrene carboxylic acid[8,9] was synthesized from 1-keto-1,2,3,4-tetrahydrophenanthrene carboxylic acid[23] (I). Clemmensen reduction, conversion to the methyl ester, dehydrogenation with sulfur and saponification yielded the 3-acid.

The cyclization of (1-naphthylmethyl)succinic acid may lead to either I or II.[23] In the present work, catalysis by hydrogen fluoride or by sulfuric acid led to the formation of I, but the yield was significantly higher from the reaction in which hydrogen fluoride was used. The structure of the product was established by the infrared spectrum[24] and by reduction and dehydrogenation of the keto-acid to the phenanthrene acid.




I II

9-Phenanthrene carboxylic acid was prepared by carbonation of the Grignard reagent from 9-bromophenanthrene.[15,16] In addition the Diels-Alder adduct of acrylic acid and 1,1′-bicyclohexenyl was dehydrogenated with sulfur at 150-210° to produce the same acid. This established that almost completely hydrogenated phenanthrene carboxylic acids could be dehydrogenated easily and in good yield without migration or loss of the carboxylic group.

The melting points of the five phenanthrene carboxylic acids and the corresponding methyl esters are listed in Table I. In Figs. 1 and 2 are shown the infrared and ultraviolet spectra respectively.

The melting points of the esters agree well with previously reported values. However, the melting points observed in this laboratory of four of the acids were significantly higher than the literature values. For each acid, the melting point was determined both on a Nalge-Axelrod hot stage and in a capillary tube immersed in a stirred oil bath. The thermometers were checked against one calibrated by the National Bureau of Standards.

Examination of the infrared spectrum in the 6-15 micron region appears to be the best procedure for identification of an unknown phenanthrene acid.

## EXPERIMENTAL

*Infrared spectra.* The spectra of the acids were obtained with a Perkin-Elmer Recording Infrared Spectrophotometer,

(6) W. E. Bachmann and C. H. Boatner, *J. Am. Chem. Soc.* **58**, 2097 (1936).
(7) W. E. Bachmann and N. C. Deno, *J. Am. Chem. Soc.* **71**, 3062 (1949).
(8) H. Gilman and T. H. Cook, *J. Am. Chem. Soc.* **62**, 2813 (1940).
(9) E. Mosettig and J. van de Kamp, *J Am. Chem. Soc.* **52**, 3704 (1930).
(10) O. Kruber, *Ber.* **67B**, 1000 (1934).
(11) L. F. Fieser, M. F. Fieser, and E. B. Hershberg, *J. Am. Chem. Soc.* **58**, 2322 (1936).
(12) M. F. Ansell and D. H. Hey, *J. Chem. Soc.* 2874 (1950).
(13) A. F. McKay and H. F. Brownell, *J. Org. Chem.* **15**, 648 (1950).
(14) M. A. Goldberg, E. P. Ordas, and G. Carsch, *J. Am. Chem. Soc.* **69**, 260 (1947).
(15) E. W. Shoppee, *J. Chem. Soc.* 37 (1933).
(16) W. E. Bachmann, *J. Am. Chem. Soc.* **56**, 1363 (1934).
(17) D. H. Hey and J. M. Osbond, *J. Chem. Soc.* 3164 (1949).
(18) T. A. Beissman and R. W. Tess, *J. Am. Chem. Soc.* **62**, 514 (1940).
(19) A. Werner, *Ann.* **321**, 248 (1902).
(20) K. G. Rutherford and M. S. Newman, *J. Am. Chem. Soc.* **79**, 213 (1957).
(21) M. S. Newman, R. B. Taylor, T. Hodgson, and A. B. Garrett, *J. Am. Chem. Soc.* **69**, 1784 (1947) and references therein.
(22) D. D. Neiswender, W. B. Moniz, and J. A. Dixon, to be published.
(23) J. C. Bardahn, D. Nasipuri, and R. N. Adhya, *J. Chem. Soc.* 355 (1956).
(24) L. F. Fieser and M. F. Fieser, *Natural Products Related to Phenanthrene*, Reinhard Publ. Corp., New York, 1949, p. 202.

Model 21. Pellets containing 200.0 mg. of anhydrous, high purity potassium bromide and 1.0 mg. of the acid were used in obtaining the spectra. A pellet containing 200.0 mg. of potassium bromide was placed in the reference beam.

*Ultraviolet spectra.* These spectra were obtained using a Beckman Model DU Spectrophotometer equipped with a Spectracord. The solubility of the acids in *n*-hexane was too low ($<1 \times 10^{-6}$ *M*); therefore absolute ethanol was used as a solvent. Concentrations in the range of $10^{-5}$ *M* were used.

*Anal.* Calcd. for $C_{15}H_{10}O_2$: C, 81.1; H, 4.5; neut. equiv. 222. Found: C, 80.8; H, 4.4; neut. equiv. 221.

*2-Acetyl-9,10-dihydrophenanthrene.* This ketone was prepared by the method of Burger and Mosettig[25] and was purified by fractional distillation through a 36″ spinning band column (obtained from Nester and Faust, Exton, Pa.). Yield 58%, b.p. 152° (0.21 mm.), $n_D^{25} = 1.6581$.

*2-Acetylphenanthrene.* Powdered sulfur (8.9 g., 0.28 mole) and 2-acetyl-9,10-dihydrophenanthrene (61.6 g., 0.28 mole)

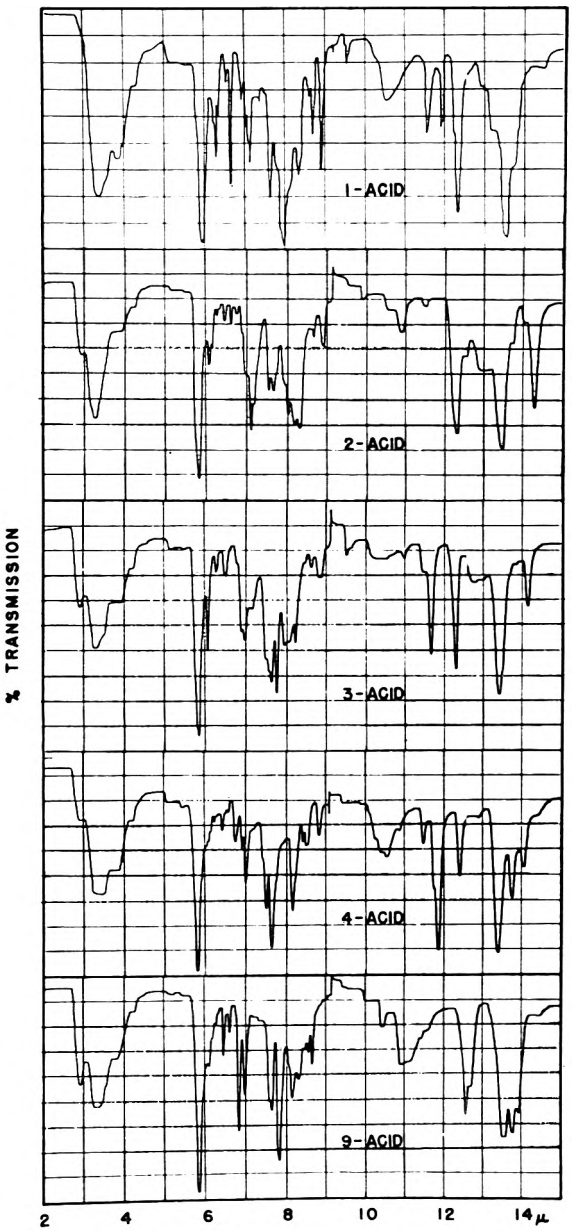



Fig. 1. Infrared spectra of the monocarboxylic acids of phenanthrene

*Phenanthrene-1-carboxylic acid.* This acid was prepared from 4-(α-naphthyl)butanoic acid by the synthetic route designed by Rutherford and Newman[20] for the synthesis of phenanthrene-4-carboxylic acid. The crude methyl ester was fractionally distilled in a Piros-Glover Spinning Band column (obtained from H. S. Martin Co., Evanston, Illinois). After two crystallizations from methanol the methyl 1-phenanthrene carboxylate had m.p. 55.0–55.7°.

*Anal.* Calcd. for $C_{16}H_{12}O_2$, saponification equiv. 236. Found, 233. Saponification of the ester yielded the acid, m.p. 234.7–235.2°.

were heated at 230–260° for 2 hr. A small Claisen head was attached to the flask and the crude ketone was distilled (97% yield; b.p. 195–200° at 1.5 mm).

*Phenanthrene-3-carboxylic acid.* 2-Acetylphenanthrene (30 g., 0.14 mole) was oxidized by treatment with refluxing Clorox (*ca.* 5% sodium hypochlorite) for 24 hr. The unchanged ketone (9.2 g.) was filtered and the filtrate acidified. The crude acid which precipitated weighed 16.4 g.,

(25) A. Burger and E. Mosettig, *J. Am. Chem. Soc.* **57**, 2731 (1935); **58**, 1857 (1936).

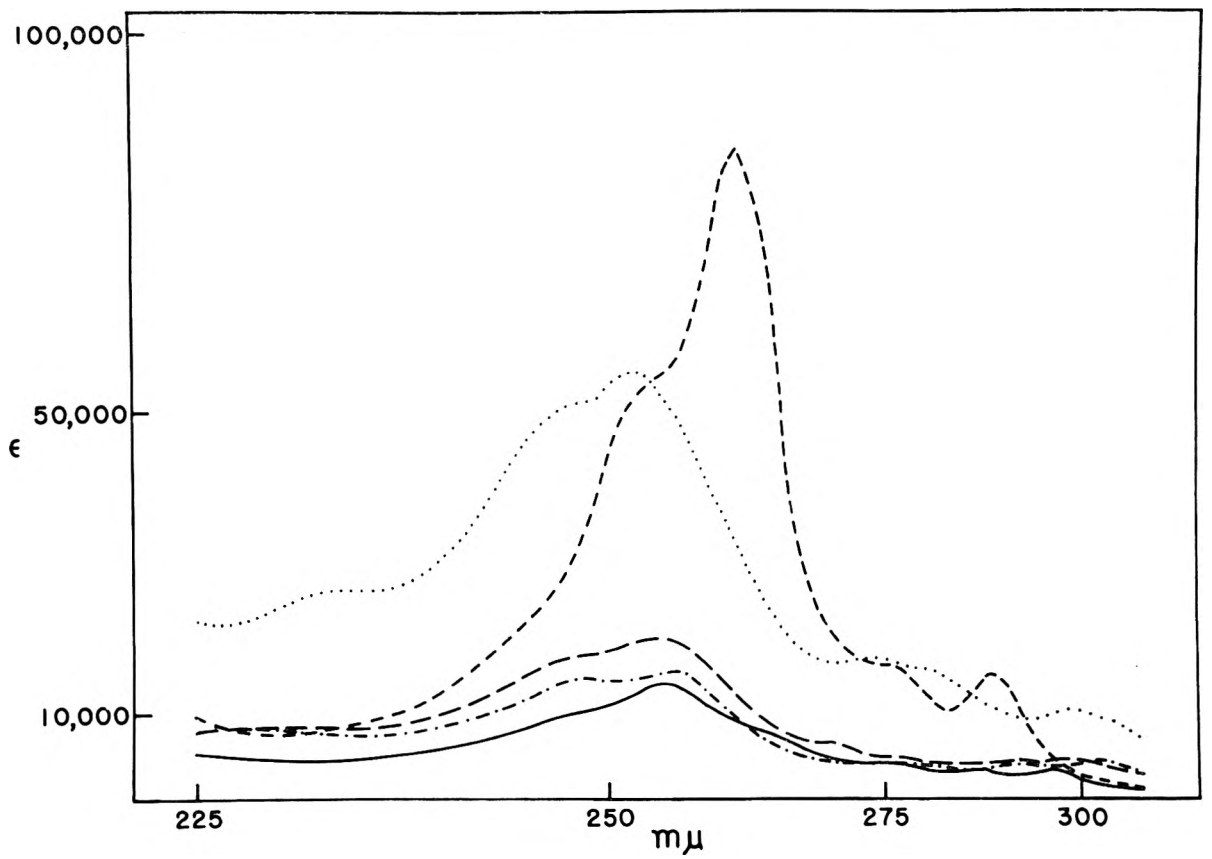



Fig. 2. Ultraviolet absorption spectra: 1-phenanthrene carboxylic acid (. . . . . ); 2-phenanthrene carboxylic acid (———); 3-phenanthrene carboxylic acid (—·—·); 4-phenanthrene carboxylic acid (———); 9-phenanthrene carboxylic acid (- - - -); all in absolute ethanol

78% yield based on ketone consumed; m.p. 262–265°. The crude acid was added to an ethereal solution of diazomethane and the resulting ester was purified by distillation through a Piros-Glover spinning band column and by recrystallization of the distillation fractions from methanol, m.p. 96.7–98.2°, b.p. 176° (0.40 mm.).

*Anal.* Calcd. for $C_{16}H_{12}O_2$: Saponification equiv. 236. Found: 239. Pure phenanthrene-2-carboxylic acid was obtained by saponifying the ester with 0.4*N* potassium hydroxide in diethylene glycol and recrystallizing the acid from ethanol, m.p. 267.8–268.5°.

*Anal.* Calcd. for $C_{15}H_{10}O_2$: C, 81.1; H, 4.5; neut. equiv. 222. Found: C, 80.8; H, 4.5; neut. equiv. 220.

*(1-Naphthylmethyl)succinic acid.*[23] Recrystallization did not remove the 3-(1-naphthyl)propanoic acid which formed as a byproduct in this synthesis. The mixture of acids was converted to the methyl esters and the desired dimethyl (1-naphthylmethyl)succinate was separated by fractional distillation, m.p. 93–95°.

*Anal.* Calcd. for $C_{17}H_{18}O_4$: Saponification equiv. 143. Found: 142.

The dimethyl ester was saponified. The diacid was crystallized from acetone-hexane; m.p. 182.5–184.0°; 45% yield based on the crude mixture of acids.

*1-Keto-1,2,3,4-tetrahydrophenanthrene-3-carboxylic acid.* Previous workers[23] cyclized the diacid to the keto acid using 85% sulfuric acid. However, this method gave only a 50% yield of the desired ketoacid. Use of anhydrous hydrogen fluoride resulted in an 85–90% yield. The diacid (31 g.) was dissolved in 300 ml. of anhydrous hydrogen fluoride and the latter was allowed to evaporate overnight. After washing the residue thoroughly with water, the solid product was recrystallized from ethanol, yield 25 g. m.p. 225–226°. The melting point was not depressed by addition of the cyclization product obtained using 85% sulfuric acid.

*Anal.* Calcd. for $C_{15}H_{12}O_3$: Neut. equiv., 240. Found: Neut. equiv., 237.

Strong ketonic carbonyl absorption was observed at 5.93 $\mu$[24] (corresponding absorptions for 7-butyl-1-tetralone and 1-indanone were observed at 5.90 $\mu$ and 5.82 $\mu$ respectively).

The ketone was reduced by the Clemmensen reduction[26]; m.p. 209.5–210°, yield 36%.

*Phenanthrene-3-carboxylic acid.* The methyl ester of 1,2,3,4-tetrahydro-3-phenanthrene carboxylic acid (7.8 g.) (prepared by direct esterification with methanol) and sulfur (2.1 g.) were heated at 240° for 40 min. Vacuum distillation gave 5.6 g. (75%) of distillate, b.p. 165–170° (0.3 mm.), m.p. 88–93°; repeated recrystallizations from hexane raised the melting point to 95.1–95.6°.

*Anal.* Calcd. for $C_{16}H_{12}O_2$: Saponification equiv. 236. Found: 240.

The purified ester was quantitatively saponified with 0.4*N* potassium hydroxide in diethylene glycol. After several recrystallizations from ethanol, the acid melted at 278.5–280.0°.

*Anal.* Calcd. for $C_{15}H_{10}O_2$: C, 81.1; H, 4.5; neut. equiv. 222. Found: C, 80.6; H, 4.7; neut. equiv. 221.

*Phenanthrene-4-carboxylic acid.* The synthesis of this acid was described by Rutherford and Newman.[20] The methyl phenanthrene-4-carboxylate was purified by fractional distillation, b.p. 155–160° at 0.10 mm. Saponification of the ester yielded the acid, m.p. 174.5–175.5°.

(26) E. L. Martin; *Org. Reactions*, **Vol. I**, 166 (1942).

TABLE I

MELTING POINTS OF THE PHENANTHRENE CARBOXYLIC ACIDS AND METHYL ESTERS

| Isomer | Acid | | Methyl Esters | |
|---|---|---|---|---|
| | Found | Lit. | Found | Lit. |
| 1 | 234.7–235.2 | 228–233[4–7] | 55.0–55.7 | 57[4] |
| 2 | 267.8–268.5 | 254–260.3[8, 9, 10] | 96.7–98.2 | 96.0–96.5[9] |
| 3 | 278.5–280.0 | 269–272[8, 9, 19] | 95.1–95.6 | 94.5–95.0[9] |
| 4 | 174.5–175.5 | 170–174.5[10, 11, 20] | 83.0–84.0 | 84.8–85.5[20] |
| 9 | 259.2–260.0 | 246–256[8, 13–18] | 116.2–116.8 | 115.5–116.0[9, 17] |

*Anal.* Calcd. for $C_{16}H_{10}O_2$: C, 81.1; H, 4.5; neut. equiv. 222. Found: C, 81.1; H, 4.5; neutralization equiv. 223.

*1,1′-Bicyclohexenyl.* The conjugated diene was prepared by dehydrating 195 g. of 1,1′-dihydroxy-1,1′-dicyclohexyl[27] over 19 g. of anhydrous copper sulfate at 130–150°. As the diene formed it distilled from the mixture; yield 177 g. (96%). After purification by washing with dilute sodium bicarbonate and fractional distillation the diene weighed 122 g. (77%), b.p. 87° (0.84 mm.), $n_D^{25}$ 1.5349.

*1,2,3,4,5,6,7,8,9,9a,10,10a-Dodecahydrophenanthrene-9-carboxylic acid.* Acrylic acid (25 g.), 1,1′-bicyclohexenyl (27 g.), and 100 ml. of 95% ethanol were refluxed for 24 hr. On cooling, 24.3 g. (52%) of snow-white crystals precipitated, m.p. 168–170°.

*Anal.* Calcd. for $C_{15}H_{22}O_2$: Neut. equiv. 234. Found: 233.

A second crop of crystals (14 g.) had a lower melting point and is believed to have been contaminated with the ethyl ester.

*Phenanthrene-9-carboxylic acid.* The dodecahydrophenanthrene-9-acid. (16.1 g.) and powdered sulfur (13.2 g.) were heated for 3 hr. at 150–210°. The product was dissolved in 5% sodium carbonate solution. After filtration, the acid was recovered by acidification of the filtrate. Ten grams of the crude acid was converted to the methyl ester with diazomethane. The ester was fractionally distilled through a Piros-Glover spinning band column (b.p. 162° at 0.22 mm.). Repeated recrystallization from methanol of the best distillation fractions yielded 1.6 g. (16%) of ester, m.p. 116.2–116.8°.

*Anal.* Calcd. for $C_{16}H_{12}O_2$: Saponification equiv. 236. Found: 232. Saponification of the ester with 0.4*N* potassium hydroxide in diethylene glycol and three recrystallizations from ethanol gave colorless needles, m.p. 259.2–260.0°.

*Anal.* Calcd. for $C_{15}H_{10}O_2$: C, 81.1; H, 4.5; neut. equiv. 222. Found: C, 81.9; H, 4.5; neut. equiv. 221.

*Acknowledgment.* The authors thank the American Petroleum Institute for the generous support of this research.

The synthesis of the phenanthrene-1-carboxylic acid by Gerald Yarnell is gratefully acknowledged.

UNIVERSITY PARK, PA.

(27) E. E. Gruber and R. Adams, *J. Am. Chem. Soc.* **57**, 2555 (1935).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

# Synthesis of β-Hydroxy Esters from Ethyl Acetate and Ketones or Aldehydes by Means of Lithium Amide. Some Results with Other Esters[1]

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*Received September 21, 1959*

Ethyl acetate was condensed with various ketones or aldehydes including certain α,β-unsaturated ketones or aldehydes by means of two equivalents of lithium amide in liquid ammonia to form the corresponding β-hydroxy esters. In general the yields were good. This method is considered more convenient than that involving the Reformatsky reaction. The products were saponified and/or dehydrated to give derivatives. The condensations of certain other esters with ketones or aldehydes were effected with one or two equivalents of lithium amide.

It has been previously shown[2] that lithio *t*-butyl acetate, prepared from molecular equivalents of the ester and lithium amide in liquid ammonia, can be condensed satisfactorily with various ketones or aldehydes in ether to form the β-hydroxy esters. For example, this aldol type of condensation was realized with the lithio ester and acetophenone in 76% yield (Equation 1).

$$CH_3COOC(CH_3)_3 \xrightarrow{LiNH_2} LiCH_2COOC(CH_3)_3 \xrightarrow[2.\ acid]{1.\ C_6H_5COCH_3} C_6H_5C(CH_3)OHCH_2COOC(CH_3)_3 \quad (1)$$

It has similarly been observed[3] that even ethyl acetate can be condensed satisfactorily with acetophenone,[3] cyclohexanone,[3] or fluorenone[4] provided an extra equivalent of lithium amide is employed.

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

(2) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, **73**, 2972 (1951); *J. Am. Chem. Soc.*, **75**, 1068 (1953).

(3) C. R. Hauser and J. K. Lindsay, *J. Am. Chem. Soc.*, **77**, 1050 (1955).

(4) C. R. Hauser and D. Lednicer, *J. Org. Chem.*, **22**, 1248 (1957).

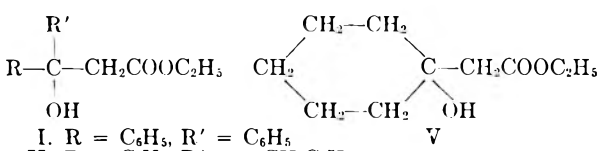
TABLE I

β-HYDROXY ESTERS FROM ETHYL ACETATE WITH KETONES OR ALDEHYDES BY MEANS OF TWO EQUIVALENTS OF LITHIUM AMIDE IN LIQUID AMMONIA

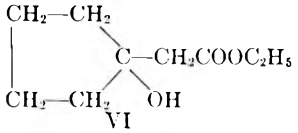
| Ketone or Aldehyde | β-Hydroxy Ester | Yield, % | M.P. or B.P. Found | Mm. | Reported | Mm. |
|---|---|---|---|---|---|---|
| Benzophenone | Ethyl β-hydroxy-β,β-diphenylpropionate (I) | 84 | M.p. 85–86[a] | | 87[b] | |
| 4-Methyl benzophenone | Ethyl β-hydroxy-β-tolyl-β-phenylpropionate (II) | 88 | M.p. 56–57[a] | | [c] | |
| Acetophenone | Ethyl β-hydroxy-β-phenylbutyrate (III) | 66 | 146–148 | 15 | 146–147 | 15[d] |
| 3-Pentanone | Ethyl β-hydroxy-β,β-diethylpropionate (IV) | 65 | 99–102 | 13–14 | [e] | |
| Cyclohexanone | Ethyl 1-hydroxycyclohexylacetate (V) | 69 | 124–126 | 18 | 124–126 | 18[f] |
| Cyclopentanone | Ethyl 1-hydroxycyclopentylacetate (VI) | 31 | 99–102 | 9 | 105–107 | 11[g] |
| Benzaldehyde | Ethyl β-hydroxy-β-phenylpropionate (VII) | 37 | 154–156 | 12 | 151–154 | 11–12[h] |
| Anisaldehyde | Ethyl β-hydroxy-β-anisylpropionate (VIII) | 28 | 182–186 | 17 | [c] | |
| Benzalacetone | Ethyl β-hydroxy-β-styrylbutyrate (IX) | 65 | 188–191 | 20 | 192 | 20[i] |
| Benzalacetophenone | Ethyl β-hydroxy-β-phenyl-β-styrylpropionate (X) | 93 | M.p. 74–75[a] | | [c] | |
| Cinnamaldehyde | 5-Phenylpentadienoic acid (XI)[j] | 20[k] | M.p. 165–166[l] | | 165[m] | |

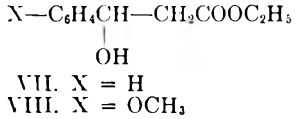
[a] Recrystallized from ethanol. [b] H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1907). [c] See Experimental. [d] S. Lindenbaum, *Ber.*, **50**, 1270 (1917). [e] Product reported by G. A. R. Kon and K. S. Nargund, *J. Chem. Soc.*, 2461 (1932), and by S. Reformatsky, *J. prakt. Chem.*, **54**, 469 (1896), but no b.p. was given. [f] O. Wallach, *Ann.*, **347**, 328 (1906). [g] O. Wallach, *Ann.*, **323**, 159 (1902). [h] C. R. Hauser and D. S. Breslow, *Org. Syntheses*, **21**, 51 (1951). [i] E. P. Kohler and G. L. Heritage, *Am. Chem. J.*, **43**, 484 (1910). [j] Crude ester decomposed upon attempted purification and was therefore saponified and isolated as the α,β-unsaturated acid. [k] Yield based on starting cinnamaldehyde. [l] Recrystallized from benzene. [m] J. J. Sudborough and J. M. Gittens, *J. Chem. Soc.*, **95**, 315 (1909).

It has now been found that the latter method also is quite general. Thus, the several types of β-hydroxy esters I–XI were synthesized from ethyl acetate and the appropriate ketone or aldehyde by a modification of the earlier procedure. The yields and other data are summarized in Table I.

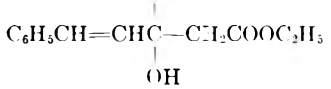


I. R = $C_6H_5$, R′ = $C_6H_5$
II. R = $C_6H_5$, R′ = $p$-$CH_3C_6H_4$
III. R = $C_6H_5$, R′ = $CH_3$
IV. R = $C_2H_5$, R′ = $C_2H_5$

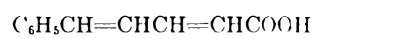




VII. X = H
VIII. X = $OCH_3$



IX. R = $CH_3$
X. R = $C_6H_5$



XI. (ester not isolated)

In the earlier procedure[3] the condensations were initiated in liquid ammonia, but completed in refluxing ether (two hours). In the present work the condensations were completed in liquid ammonia. The general procedure involved the addition of ethyl acetate to two molecular equivalents of lithium amide in liquid ammonia, followed after fifteen to twenty minutes by one equivalent of the ketone or aldehyde. After one hour the reaction mixture was neutralized with ammonium chloride.[5]

In certain condensations such milder reaction conditions appear to be required to avoid the dehydration of the β-hydroxy ester. Thus, whereas the β-hydroxy esters IV and VII were obtained in the condensations of ethyl acetate with diethyl ketone and benzaldehyde under the present conditions, only the dehydration product of IV and a mixture of the β-hydroxy ester VII and its dehydration product (determined spectrophotometrically) were isolated when the reaction mixture was refluxed in ether.

(5) No significant difference in the yield (81–84%) of β-hydroxy ester I was observed when the neutralization was carried out by adding solid ammonium chloride to the reaction mixture, by pouring the reaction mixture into a solution of ammonium chloride in liquid ammonia, or by replacing the ammonia by ether followed by acidification with cold dilute hydrochloric acid.

TABLE II

DERIVATIVES OF KNOWN β-HYDROXY ESTERS

| β-Hydroxy Ester | Treatment | Product | M.p. or b.p. ° Found | Mm. | Reported | Mm. |
|---|---|---|---|---|---|---|
| I | Saponification | β-Hydroxy-β,β-diphenylpropionic acid | M.p. 210–211[a] | | 212[b] | |
| I | Sapon., Dehyd. (Method A) | β-Phenylcinnamic acid | M.p. 161–162[a] | | 162[b] | |
| III | Dehyd. (Method B) | Ethyl β-methylcinnamate | 146–149 | 17 | 146–148 | 17[c] |
| III | Dehyd., Sapon. | β-Methylcinnamic acid | M.p. 97–98[a] | | 97–98[c] | |
| IV | Dehyd. (Method B) | Ethyl β,β-diethylacrylate | 74–78 | 13 | 77 | 14[e] |
| IV | Dehyd., Sapon. | β,β-Diethylacrylic acid | 128–131 | 23 | 129 | 23[e] |
| V | Saponification | Cyclohexanolacetic acid | M.p. 63–64[f] | | 62–64[g] | |
| VI | Dehyd. (Method C) | Ethylcyclopentylideneacetate | 82–84 | 11 | 82–84 | 11[g] |
| VI | Dehyd., Sapon. | Cyclopentylideneacetic acid | M.p. 49–50[a] | | 49–50[g] | |
| VII | Saponification | Cinnamic acid | M.p. 132–133[h] | | 133[i] | |
| IX | Dehyd., Sapon. (Method D) | β-Methyl-β-styrylacrylic acid | M.p. 153–153.5[j] | | 153[k] | |

[a] Recrystallized from 1:1 methanol-water. [b] H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1910). [c] S. Lindenbaum, *Ber.*, **50**, 1270 (1917). [d] Recrystallized from 60–90° petroleum ether. [e] G. A. R. Kon and K. S. Nargund, *J. Chem. Soc.*, 2461 (1932). [f] Recrystallized from 1:1 benzene-ligroin. [g] O. Wallach, *Ann.*, **347**, 328 (1906). [h] Recrystallized from benzene. [i] Heilbron, *Dictionary of Organic Compounds*, Vol. I, Oxford University Press, N. Y. (1953) p. 586. [j] Recrystallized from 1:1 ethanol-water. [k] E. P. Kohler and G. L. Heritage, *Am. Chem. J.*, **43**, 484 (1910).

It can be seen from Table I that the yields of β-hydroxy esters I–IV from typical aromatic and aliphatic ketones were good to excellent, those of β-hydroxy esters V and VI from the cyclic ketones fair to good, those of β-hydroxy esters VII and VIII from the aromatic aldehydes fair, and those of IX and X from the α,β-unsaturated ketones good to excellent. The β-hydroxy ester from cinnamaldehyde was not isolated; it was converted to the α,β-unsaturated acid XI in an overall yield of 20%.

These yields are in general comparable to those reported for the Reformatsky reactions, which have usually been employed for the synthesis of β-hydroxy esters. We believe the present method is more convenient than the latter process.

The known β-hydroxy esters were identified by conversion to appropriate derivatives through saponification and/or dehydration. The results are summarized in Table II. In general the yields of the derivatives were good to excellent (50–85%). The new β-hydroxy esters were identified similarly including analysis (see Experimental).

The condensation of ethyl acetate with the α,β-unsaturated ketones or aldehydes was of special interest since 1,4- as well as 1,2- addition was conceivable. That the latter mode of addition occurred was indicated by the infrared absorption spectra which gave absorption at 2.7 μ for the hydroxyl group, which would not be present in the event of 1,4- addition.

The strucutre of the β-hydroxy ester IX was established by dehydration and saponification to form the corresponding α,β-unsaturated acid (see Table II). Since attempts to convert β-hydroxy ester X to a suitable derivative were unsatisfactory, this structure must be considered only tentative. The structure of the α,β-unsaturated acid obtained through ethyl acetate and cinnamaldehyde was established as XI by comparison of the melting point and infrared spectrum with an authentic sample prepared from cinnamaldehyde and ethyl malonate, followed by dehydration, saponification, and decarboxylation.[6]

Attempts to condense ethyl acetate with *p*-nitroacetophenone or *p*-nitrobenzaldehyde employing two equivalents of lithium amide and using the inverse addition procedure were unsatisfactory, since only tars were produced or the starting nitro compounds were recovered. The Reformatsky reaction has likewise been reported unsuitable with nitro ketones or aldehydes.[7] However, *t*-butyl acetate has been condensed successfully with certain nitro ketones as aldehydes employing one equivalent of lithium amide.[2]

It should be mentioned that an attempt to condense ethyl acetate with benzophenone by means of one equivalent of lithium amide following the general procedure was unsuccessful, although this condensation was realized to form β-hydroxy ester I in 20% yield when a mixture of equivalents of the ester and ketone was added to one equivalent of the reagent. The similar addition of a mixture of the ester and ketone to two equivalents of the reagent produced the β-hydroxy ester I in 43% yield, which is considerably less than that (84%) obtained by the general procedure.

*Results with other esters.* Isopropyl acetate and *t*-butyl acetate were condensed with benzophenone by means of two equivalents of lithium amide by the general procedure to form β-hydroxy esters

(6) B. S. Bansal and K. C. Pandya, *J. Indian Chem. Soc.*, **24**, 443 (1947).

(7) R. L. Shriner, *Org. Reactions*, Vol. I, 2 (1942).

XII and XIII in yields of 80% and 87% respectively.

$(C_6H_5)_2C(OH)CH_2COOR$ XII. R = $CH(CH_3)_2$
XIII. R = $C(CH_3)_3$

The condensation of *t*-butyl acetate with benzophenone was also effected by means of one equivalent of lithium amide in liquid ammonia following the general procedure to form β-hydroxy ester XIII in 71% yield. *t*-Butyl acetate has previously been condensed with various ketones or aldehydes by means of one equivalent of the reagent[2] but benzophenone was not then studied.

Ethyl propionate was condensed with benzophenone by means of two equivalents of lithium amide by the general procedure to form β-hydroxy ester XIV in 21% yield:

$(C_6H_5)_2C(OH)CH(CH_3)COOC_2H_5$
XIV

*t*-Butyl propionate has previously been condensed with acetone and acetophenone in yields of 53–58% by means of one equivalent of lithium amide.[2]

The present method failed to effect the condensation of ethyl phenylacetate with benzophenone under the usual conditions and, when forcing conditions were employed, the ester underwent self-condensation to produce ethyl α,γ-diphenylacetoacetate (60%). Ethyl phenylacetate was recently[2] condensed with benzaldehyde by means of one equivalent of lithium amide to form β-hydroxy ester XV in 34% yield. The present method employing two equivalents of lithium amide gave only a 15% yield of this β-hydroxy ester:

$C_6H_5CHOHCH(C_6H_5)COOC_2H_5$
XV

## EXPERIMENTAL[8]

*β-Hydroxy esters from ethyl acetate and ketones or aldehydes by lithium amide. General procedure.* In a 1-l. three-necked round bottom flask, equipped with a ball-sealed stirrer, separatory funnel and condensor, was placed 400 ml. of commercial, anhydrous liquid ammonia. To the stirred liquid was added a small piece of lithium metal. After the appearance of the blue color (almost immediately) a few crystals of ferric nitrate were added, followed by small portions of lithium metal until a total of 0.42 mole had been added. After the blue color had been discharged and a grey suspension of lithium amide had formed (about 20 min.), a solution of 0.2 mole (17.6 g.) of ethyl acetate and 50 ml. of anhydrous ether was added during 1 min. After stirring for 20 min., 0.20 mole of the ketone or aldehyde was added during 1 min. At the end of 1 hr. stirring the reaction mixture was neutralized by adding 0.42 mole of solid ammonium chloride. The liquid ammonia was then driven off by means of a hot water bath while adding 200–300 ml. of ether. When the ammonia had been removed, 200 ml. of cold water was added. The ether layer was separated and washed with 1*N* sulfuric acid, saturated sodium bicarbonate solution, and then water, and combined with the ether extracts of the aqueous layers. The ether solution was dried over magnesium sulfate and the solvent was removed. The residue was then either vacuum distilled, or recrystallized from the appropriate solvent. The results are summarized in Table I.

The known β-hydroxy esters formed were identified, in addition to boiling point or melting point, by the preparation of certain derivatives given in Table II.

*Derivatives of known β-hydroxy esters* (Table II). Saponifications, unless otherwise stated, were accomplished by refluxing the β-hydroxy esters with 20% aqueous sodium hydroxide for 3 hr. Dehydrations were effected by the methods listed below.

*Method A.* Dehydration was effected by refluxing a mixture of the acid, acetic anhydride, and sodium acetate for 3 hr. Water was then added and the acetic acid and anhydride were removed by distillation. The residue was dissolved in sodium carbonate solution, filtered and acidified to give the unsaturated acid.

*Method B.* The β-hydroxy ester was refluxed for 3–4 hr. with three volumes of benzene containing excess phosphorus oxychloride. Water was then added to the cooled mixture and the benzene layer was separated, dried over magnesium sulfate, and then distilled.

*Method C.* The β-hydroxy ester was heated at 130° for 60 min. with solid potassium bisulfate. The resulting mixture was vacuum distilled to yield the unsaturated ester.

*Method D.* The β-hydroxy ester was dehydrated by refluxing with 5*N* hydrochloric acid for 15 hr. The cooled solution was extracted by ether and the ether evaporated to a residue which was saponified by treatment with 3% methanolic potassium hydroxide for 20 hr. at room temperature.

*New β-hydroxy esters prepared by the general procedure. Ethyl-β-hydroxy-β-tolyl-β-phenyl propionate* (II). The ether residue was stirred with 95% ethanol in an ice bath to form a white solid, which upon recrystallization two times from ethanol melted at 56–57°. The infrared spectrum showed weak hydroxyl absorption at 2.75 μ and ester carbonyl absorption at 5.82 μ.

*Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.73; H, 7.16.

A mixture of 5 g. of III was dehydrated using Method A (see below) and then saponified to yield 1.7 g. (41%) of β-tolyl cinnamic acid, m.p. 139–140° after recrystallization from ethanol water (lit.,[9] m.p. 140°).

*Ethyl-β-hydroxy-β,β-diethyl propionate* (IV). Distillation of the ether residue gave a colorless liquid b.p. 99–102° (13–14 mm.). The infrared spectrum showed strong hydroxyl absorptions at 2.7 μ and ester carbonyl absorption at 5.75 μ.

*Anal.* Calcd. for $C_9H_{18}O_3$: C, 62.39; H, 10.47. Found: C, 62.64; H, 10.90.

For derivatives see Table II.

*Ethyl-β-hydroxy-β-anisyl propionate* (VIII). Distillation of the ether residue gave 23 g. (28%) of viscous liquid b.p. 182–186° (17 mm.). Much dark red nondistillable residue remained after the distillation. The product showed hydroxyl absorption at 2.75 μ and the ester carbonyl absorption at 5.7 μ in the infrared.

*Anal.* Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.74. Found: C, 69.31; H, 7.62.

Saponification of 8 g. of VI gave 5.5 g. (80% of β-anisyl acrylic acid, m.p. 172–173° (lit.,[10] m.p. 172–173°).

*Ethyl-β-hydroxy-β-phenyl-β-styryl propionate* (X). Evaporation of the ether layer in the general procedure yielded a solid which was recrystallized from 95% ethanol to give X, m.p. 74–75° in 95% yield. The infrared shows weak hydroxyl absorption at 2.75 μ and ester carbonyl absorption at 5.72 μ.

*Anal.* Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.34; H, 6.84.

Attempts to prepare derivatives of X by use of the methods described above all led to intractible materials.

*Simultaneous addition of ethyl acetate and benzophenone to*

(8) Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(9) J. V. Braun, G. Manz, and E. Reinsch, *Ann.*, **468**, 291 (1929).

(10) E. Knoevenagel, *Ber.*, **31**, 2606 (1898).

*lithium amide*. Lithium amide was prepared from 1.4 g. (0.2 mole) of lithium in 400 ml. of liquid ammonia. After 20 min. stirring a mixture of 17.6 g. (0.2 mole) of ethyl acetate and 36.4 g. (0.2 mole) of benzophenone in 150 ml. of anhydrous ether was added. After stirring for 1 hr. the mixture was neutralized and worked up as in the general procedure. By fractional crystallization from ethanol with cooling there was obtained 11.0 g. (20%) of β-hydroxy ester I, m.p. 85–86°, and 21 g. (58%) of benzophenone, m.p. 45–46°.

The above procedure was repeated, except that 0.4 mole of lithium amide was employed rather than 0.2 mole. From the resulting reaction mixture was obtained 25.1 g. (46%) of β-hydroxy ester I, m.p. 84–85°, and 20.0 g. (55%) of recovered benzophenone m.p., 45–46°.

*Isopropyl-β-hydroxy-β,β-diphenyl propionate* (XII). The general procedure was followed using 1.7 g. (0.24 mole) of lithium, 12.5 g. (0.12 mole) of isopropyl acetate, and 21.6 g. (0.12 mole) of benzophenone. The ether residue was recrystallized from ethanol to yield 27.2 g. (80%) of the ester as colorless, rod-shaped crystals, m.p. 101–102°.

*Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.93; H, 7.03.

A 3.0 g. sample of XII was added to 10 ml. of ice cold concentrated sulfuric acid. After standing for 15 min., chipped ice was added and a viscous tan material separated. The material was treated with dilute sodium hydroxide solution and extracted by ether. The aqueous layer was separated and acidified to give 0.7 g. (53%) of β-phenyl cinnamic acid, m.p. 162–163° after recrystallization from a 1:1 methanol-water mixture (lit.,[11] m.p. 162°).

*t-Butyl-β-hydroxy-β,β-diphenyl propionate* (XIII). The general procedure was followed using 1.2 g. (0.34 mole) of lithium, 20 g. (0.17 mole) of *t*-butyl acetate, and 31.5 g. (0.17 mole) of benzophenone. Evaporation of the ether fraction yielded a solid which, upon recrystallization from 95% ethanol gave 36.4 g. (87%) crystalline ester XII, m.p. 93–94° after recrystallization from ethanol (lit.,[12] m.p. 92–93°).

*Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.47; H, 7.43. Found: C, 76.23; H, 7.54.

Repetition of the above reaction using one instead of two equivalents of lithium amide gave XII in 71% yield.

Dehydration was accomplished by adding 3 g. of XIII to 10 ml. of ice-cold concentrated sulfuric acid. After 15 min. the slurry was poured onto chipped ice to precipitate a yellow solid. The solid was dissolved in sodium hydroxide solution and the yellow coloration was removed by ether extraction. Acidification of the aqueous layer precipitated 1.9 g. (90%) of β-phenyl cinnamic acid, m.p. 161–162° after recrystallization from 1:1 methanol-water mixture (lit.,[11] m.p. 162°).

*Ethyl-β-hydroxy-β,β-diphenyl isobutyrate* (XIV). The general procedure was followed using 1.7 g. (0.24 mole) of lithium, 12.5 g. (0.12 mole) of ethyl propionate and 22.2 g. (0.12 mole) of benzophenone. The oily ether residue was cooled with stirring in an ice bath to give 7.3 g. (21%) of the ester, m.p. 98–99°.

*Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.02; H, 7.09. Found: C, 76.03; H, 7.27.

*Ethyl-β-hydroxy-α β-diphenyl propionate* (XV). The general procedure was not used here, the reaction previously reported[2] being repeated exactly except that two equivalents of lithium amide were used rather than one. The reaction was carried out using 2.91 g. (0.42 mole) of lithium, 33 g. (0.2 mole) of ethyl phenyl acetate and 21.5 g. (0.2 mole) of benzaldehyde. Distillation of the ether residue gave 8 g. (15%) of ester b.p. 171–176° (3 mm.) (lit.,[2] b.p. 170–175° (2 mm.)).

DURHAM, N. C.

(11) H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1910).

(12) K. Sisido, H. Nozaki, and O. Kurihara, *J. Am. Chem. Soc.*, **74**, 6254 (1952).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

# Reactions of Nitroalkanes with Olefin Oxides

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Acidic mononitroalkanes react with olefin oxides in the presence of pyridine. The products depend upon the nature of the nitroalkane. Nitromethane gives a 1-(2-hydroxyalkyl)pyridinium nitrite and tars, while nitroethane yields 3,4,5-trimethylisoxazole, 1-(2-hydroxyalkyl)pyridinium nitrite, tars and a possible trace of nitroalcohol. Secondary nitroalkanes yield, depending on the steric requirements of the substituted groups, ketones, ketone oximes, 1-(2-hydroxyalkyl)pyridinium nitrite, ditertiary *vic*-dinitroalkane, 1,3-nitroalcohol and tars.

Condensation reactions of acidic mononitroalkanes are known to involve a nucleophilic attack of the corresponding nitronate anion upon an electron deficient center. As olefin oxides usually undergo ring opening by a nucleophilic displacement, one might expect nitroalkanes to condense with olefin oxides to yield as one possible product a 1,3-nitroalcohol:

$$RR'CHNO_2 + \overline{CH_2{-}CHR''O} \rightleftharpoons RR'{-}\overset{NO_2}{\overset{|}{C}}{-}CH_2{-}\overset{OH}{\overset{|}{C}}H{-}R''$$

(1) From the Ph.D. Thesis of Frank J. Donat.

The 1,3-nitroalcohols have not been previously described. In fact, the only reaction of nitroalkanes and olefin oxides appearing in the literature reports an oxime as the principal product.[3a] The role of the olefin oxide is further obscured by the known base-induced transformations of nitroalkanes to oximes.[3b,3c,4,5]

(2) Present address: B. F. Goodrich Chemical Co., Brecksville, Ohio.

(3a) Hanns Ufer, Ger. **877,303**. (3b) E. M. Nygaard, U. S. Patent **2,401,267**. (3c) E. M. Nygaard and T. T. Noland, U. S. Patent **2,401,269**.

(4) E. M. Nygaard, J. H. McCracken, and T. T. Noland U. S. Patent **2,370,185**.

(5) H. Wetz and J. Weise, Ger. **837,692**.

TABLE I

EFFECTS OF VARYING THE NITROALKANE AND THE OLEFIN OXIDE IN THEIR REACTION IN THE PRESENCE OF PYRIDINE

$$6\ RR'CHNO_2 + 1R''\underset{\diagdown\ \diagup}{O}CH{-}CH_2 \xrightarrow[\text{1. 5 hr. at 90°C; 2. 16 hr. at room temp.}]{C_5H_5N} \text{Products}$$

| Nitroalkane | Olefin Oxide | Products and Yields[a] |
|---|---|---|
| Nitromethane | Ethylene oxide | 1-(2-Hydroxyethyl)pyridinium nitrite: 7%. Nitroalcohol: infrared indicates a possible trace. Tars: 5 g. |
| Nitromethane | Propylene oxide | 1-(2-Hydroxypropyl)pyridinium nitrite: 3.3%. Nitroalcohol: possible trace indicated by infrared. Tars: 4 g. |
| Nitroethane | Ethylene oxide | 1-(2-Hydroxyethyl)pyridinium nitrite: 9%. 3-Nitro-1-butanol: 1.3%. 3,4,5-Trimethylisoxazole: 16.2%. Tars: 9.1 g. Acetaldehyde: 20% based on unreclaimed ethylene oxide. |
| Nitroethane | Propylene oxide | 1-(2-Hydroxylpropyl)pyridinium nitrite: 5.94%. Nitroalcohol: 0.9%. 3,4,5-Trimethylisoxazole: 1.8%. Tars: 14.6 g. |
| 2-Nitropropane | Ethylene oxide | 1-(2-Hydroxyethyl)pyridinium nitrite: 23%. 3-Nitro-3-methyl-1-butanol: 7.5%. 2,3-Dinitro-2,3-dimethylbutane: 8.4%. Acetaldehyde: 23.0% based on theory for ethylene oxide. Acetone: 23% based on theory. Acetone oxime: 35%. Tars: 29.3 g. |
| 2-Nitropropane | Propylene oxide | 1-(2-Hydroxypropyl)pyridinium nitrite: 17.6%. 4-Nitro-4-methyl-2-pentanol: 15%. 2,3-Dinitro-2,3-dimethylbutane: 14.8%. Acetone: 15%. Acetone oxime: 29%. Tars: 25.2 g. |
| 2-Nitrobutane | Ethylene oxide | 1-(2-Hydroxyethyl)pyridinium nitrite: 21.1%. 3-Nitro-3-methyl-1-pentanol: 5.1%. 2-Butanone: 22.6%. 2-Butanone oxime: 33.2%. Tars: 40 g. |
| Nitrocyclohexane | Ethylene oxide | 1-(2-Hydroxyethyl)pyridinium nitrite: 4.5%. Cyclohexanone: 6.1%. Cyclohexanone oxime: 4.9%. Tars: 11.2 g. |

[a] All percentages are calculated on the basis of one mole of nitroalkane going to products.

The present investigation then was undertaken to determine the nature of the reaction of an olefin oxide with a nitroalkane. The results of our study are summarized in Table I. Pyridine appears to be unique in being able to induce extensive reaction other than tar formation. Therefore pyridine was used extensively as a catalyst for the system.

The olefin oxides differ slightly in reactivity but give essentially similar products. Propylene oxide appears to be slightly less reactive than ethylene oxide in some instances. Preliminary work on styrene oxide indicates that it is even less reactive than propylene oxide. The three oxides might, therefore, be arranged in the following series based on their reactivity: Ethylene > propylene > styrene.

One of the major differences, as might be expected, is the nature of the products from nitromethane, nitroethane, and the secondary nitroalkanes. Nitromethane, for example, in the presence of aqueous alkali, has been reported to react vigorously and completely to yield methazonic acid, nitrite anion, hydrogen cyanide, and resin.[6,7,8,9] We found that nitromethane undergoes only a limited amount of reaction with either ethylene or propylene oxide in the presence of pyridine. The main product is 1-(2-hydroxyalkyl)pyridinium nitrite.The other products are tar and possibly a trace of nitroalcohol (indicated by infrared spectroscopy) formed by the condensation of nitromethane with the olefin oxide. No cyanide was observed. The formation of methazonic acid, however, cannot be ruled out, even if it were not detected, as methazonic acid is unstable and would polymerize under the conditions of our reaction. Preliminary studies indicate that a much more complete reaction of nitromethane occurs upon standing for long periods at room temperature. Under these conditions an excellent yield of 1-(2-hydroxypropyl)pyridinium nitrite is obtained. Large amounts of tars are also formed, but again no cyanide or methazonic acid could be detected.

Nitroethane appears to be somewhat more reactive than nitromethane and yields 1-(2-hydroxyethyl)pyridinium nitrite, 3,4,5-trimethylisoxazole, acetaldehyde (when ethylene oxide is used), tars, and a small amount of nitroalcohol. The acetaldehyde probably arises directly from the rearrangement of ethylene oxide, although some may result from loss of nitrite ion. Nitroalcohol formation again appears to be a minor reaction and the main products are the 3,4,5-trimethylisoxazole, and pyridinium nitrite.

The secondary nitroalkanes 2-nitropropane, 2-nitrobutane, and nitrocyclohexane all yield similar products. 2-Nitropropane and 2-nitrobutane show about the same reactivity and are by far the most reactive nitroalkanes studied. These are also the only two nitroalkanes which yield appreciable amounts of nitroalcohol. The products from 2-nitropropane include 1-(2-hydroxyethyl)pyridinium nitrite, 3-nitro-3-methyl-1-butanol, 2,3-dinitro-2,3-dimethyl-

(6) W. R. Dunstan and F. R. S. Goulding, *J. Chem. Soc.*, **77**, 1262 (1900).
(7) P. Friese, *Ber.*, **9**, 394 (1876).
(8) M. T. Lecco, *Ber.*, **9**, 705 (1876).
(9) W. Meister, *Ber.*, **40**, 3435 (1907).

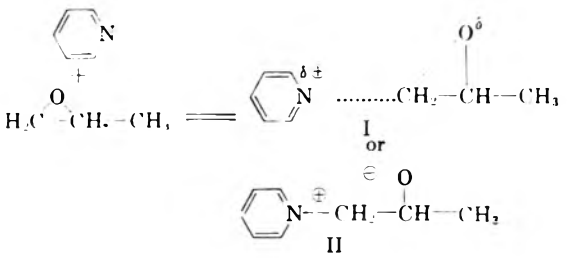
butane, acetone, acetone oxime, and tars. The acetaldehyde probably arises from the rearrangement of the ethylene oxide under the conditions of the reaction. Another significant fact is that the nitrite ion, as in the case with primary nitroalkanes, forms 1-(2-hydroxyalkyl)pyridinium nitrite.

2-Nitrobutane with ethylene oxide is seen to yield 1-(2-hydroxyethyl)pyridinium nitrite, 3-nitro-3-methyl-1-pentanol, 2-butanone and 2-butanone oxime. Unlike 2-nitropropane, however, it does not yield acetaldehyde or a ditertiary vic-dinitroalkane. This latter material is believed to arise from an oxidative dimerization of the secondary nitroalkane. Steric hinderance probably inhibits this dimerization in the case of 2-nitrobutane.

Nitrocyclohexane, unlike either 2-nitropropane or 2-nitrobutane, reacts only to a limited extent with ethylene oxide yielding small amounts of 1-(2-hydroxyethyl)pyridinium nitrite, cyclohexanone, and cyclohexanone oxime. The lack of reactivity in this case is probably due to the steric hindrance of the cyclohexane ring to an $S_N2$ attack on the carbon containing the nitro or isonitro group.

The similarity of some of the products found in our study to those obtained from the normal base induced transformations of nitroalkanes suggests a similar reaction mechanism. Dunstan[6,10] found that anhydrous bases are without effect on nitroalkanes, while aqueous or alcoholic bases cause extensive reaction. An analogous situation arises in our study. We have learned that anhydrous pyridine by itself is unable to induce significant transformations in either nitromethane or 2-nitropropane while pyridine plus an olefin oxide produces extensive reaction. We might, therefore, expect the olefin oxide to be taking the place of water or alcohol in these latter reactions. If the situation were this simple, however, pyridine should yield the same $\beta$-dioxime from nitroethane which has been reported by Lippincott[11] as being formed under the mild conditions of an aqueous organic base. Obviously the catalyst, if we may call it that, is much more nucleophilic than pyridine and may even approach the nucleophilicity of hydroxyl ion. Direct comparison with the work of Lippincott should probably not be made because his reactions were carried out at room temperature whereas we used a temperature of 90°.

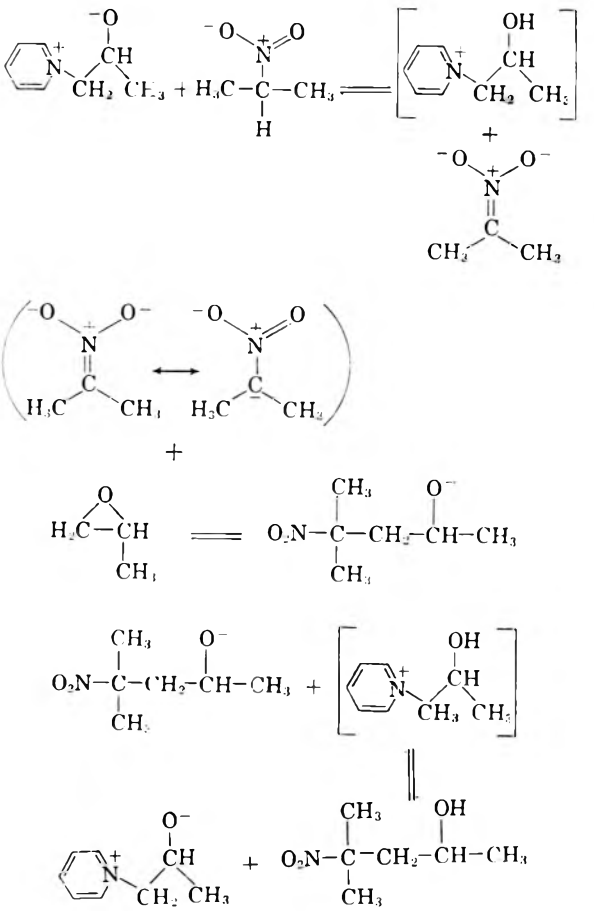
Considering these factors, along with the formation of 1-(2-hydroxyalkyl)pyridinium nitrite in each reaction, we might expect the nucleophilic intermediate to arise from a combination of pyridine with olefin oxide. Such a combination might lead to a complex I or to an internal pyridine salt (II):



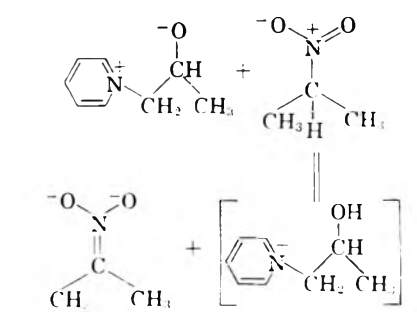
I or II

Either (I) or (II) might then serve as a catalyst and reagent for the reactions we observed in our study. For example, we might picture the role of this intermediate in the 2-nitropropane-propylene oxide system as follows:

(a) Nitroalcohol formation[12]:



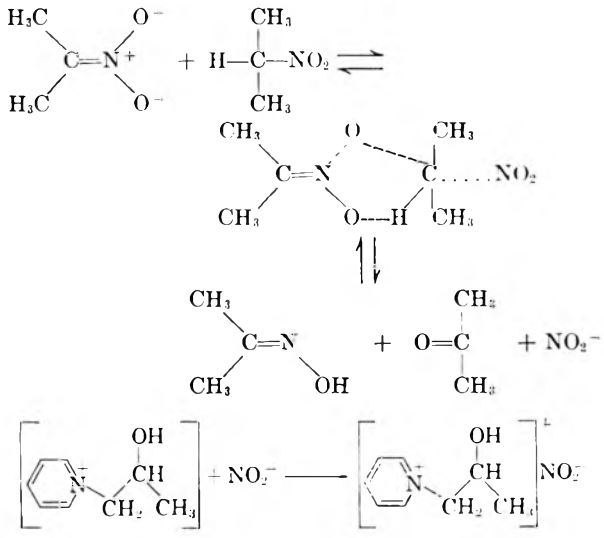
(b) Pyridinium nitrite, acetone and acetone oxime formation



(10) W. R. Dunstan and T. S. Dymond, *J. Chem. Soc.*, 410 (1890).

(11) S. B. Lippincott, *J. Am. Chem. Soc.*, 62, 2604 (1940).

(12) Structure II is arbitrarily used in all the illustrations.



The ditertiary vic-dinitroalkane can also be postulated in a similar manner.

## EXPERIMENTAL

*Reagents.* The olefin oxides, nitroalkanes, and pyridine were each thoroughly dried over an appropriate drying agent and then carefully fractionated. Only those fractions which boiled over a range of 1° or less were chosen for our investigation.

*Apparatus.* The apparatus consisted of a three-necked, 2-l., round-bottomed flask equipped with an Ace Trubore stirrer and Teflon paddle, a dry ice-acetone cold finger, a thermometer, and a dropping funnel. The cold finger was connected to a liquid nitrogen cold trap and then through a drying tube to the atmosphere. The dropping funnel was surrounded by a jacket packed with Dry Ice to prevent the loss of low boiling olefin oxide.

*General experimental procedure.* All of the reactions were carried out in the following manner: 5 moles of nitroalkane and 1 mole of pyridine were added to the reaction flask. The mixture was stirred and heated to 90°, then 1 mole of olefin oxide dissolved in 1 mole of nitroalkane was added dropwise. The addition generally required about 3 hr. However, stirring and heating were continued a total of 5 hr., measured from the start of the olefin oxide addition. The reaction mixture was allowed to stand an additional 16 hr. at room temperature.

The low boiling materials were removed at low temperature under vacuum and collected over liquid nitrogen. These light ends, which usually consisted of olefin oxide, aldehyde, and ketone were then fractionated at atmospheric pressure. The oxides were identified by boiling points and comparison of their infrared spectra with those of authentic samples, while the aldehydes and ketones were identified by their boiling points, by the melting points of their 2,4-dinitrophenylhydrazone derivatives, and by comparison of their infrared spectra with those of authentic samples.

Next, the excess nitroalkane was removed at reduced pressure keeping the pot temperature below 50°. The residue was poured into an excess of dry ether (about 4 l.). The solution was vigorously shaken and then allowed to stand until it became clear. A deep red oil precipitated from the solution. The ether was removed by decantation and the residual oil placed under vacuum. This oil, now very viscous (Fraction A, see analysis below) consists mainly of 1-(2-hydroxyalkyl)pyridinium nitrite. In those reactions involving a nitroalkane, styrene oxide, and pyridine, the 1-(2-phenyl-2-hydroxyethyl)pyridinium nitrite crystallized directly from the reaction mixture and could be removed by filtration.

The ether solution decanted from Fraction A was treated with anhydrous hydrogen chloride to precipitate an orange-brown oil and some colorless crystals. This material designated Fraction B (see analysis below) consisted of pyridine hydrochloride and tars. From reactions involving secondary nitroalkanes, ketone oxime hydrochlorides were also present.

The ether solution, now a much lighter amber color, was evaporated to remove ether. As ether was being removed, 2,3-dinitro-2,3-dimethylbutane precipitated from those reaction systems utilizing 2-nitropropane. After recrystallization from petroleum ether, the 2,3-dinitro-2,3-dimethylbutane was identified by its melting point 209–210°, mixed melting point, comparison of its infrared spectrum with that of an authentic sample, and elemental analysis.

*Anal.* Calcd. for $C_6H_{12}N_2O_4$: C, 40.90; H, 6.87; N, 15.90. Found: C, 41.00: H, 6.97; N, 15.93.

The residue, after removal of all of the ether, was distilled under high vacuum. In some cases a vacuum of less than 1 micron was employed and all distillates were collected over Dry Ice in acetone or liquid nitrogen. The first fraction usually consisted of nitroalkane, while the constitution of subsequent fractions depended upon the nitroalkane and olefin oxide used in the particular reaction. These fractions contained 3,4,5-trimethylisoxazole, 1,3-nitroalcohol, glycol, and 2,3-dinitro-2,3-dimethylbutane. A black tar remained as pot residue. The pot temperatures were never permitted to rise above 80° and, in most cases, were kept below 60°. The infrared spectra of all fractions were examined and those fractions which seemed most likely to contain nitroalcohol were used to prepare *p*-nitrobenzoate and 3,5-dinitrobenzoate ester derivatives. These derivatives were analyzed for carbon, hydrogen, and nitrogen.

4-Nitro-4-Methyl-2-Pentanol

| Ester | M.P. | Analyses |
|---|---|---|
| *p*-Nitrobenzoate | 115–116° | Calcd. for $C_{13}H_{16}N_2O_6$: C, 52.02; H, 5.44; N, 9.45. Found: C, 51.91; H, 5.21; N, 9.28 |
| 3,5-Dinitrobenzoate | 138–139° | Calcd. for $C_{13}H_{15}N_3O_8$: C, 45.75; H, 4.43; N, 12.31. Found: C, 45.30; H, 4.15; N, 12.43 |
| 3-Nitro-3-methyl-1-butanol: | | |
| *p*-Nitrobenzoate | 94–94.5° | Calcd. for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.92. Found: C, 50.54; H, 5.20; N, 10.21 |
| 3,5-Dinitrobenzoate | 125–125.3° | Calcd. for $C_{12}H_{13}N_3O_8$: C, 44.04; H, 4.00; N, 12.87. Found: C, 43.51; H, 4.25; N, 13.01 |
| 3-Nitro-3-methyl-1-pentanol: | | |
| *p*-Nitrobenzoate | 78.8–79° | Calcd. for $C_{13}H_{16}N_2O_6$: C, 52.02; H, 5.44; N, 9.46. Found: C, 51.86; H, 4.95; N, 9.82 |
| 3,5-Dinitrobenzoate | 83.3–84° | Calcd. for $C_{13}H_{15}N_3O_8$: C, 45.75; H, 4.42; N, 12.31. Found: C, 44.90; H, 4.25; N, 12.52 |

In those cases where the nitroalcohol was contaminated with glycol, the ester derivatives of the glycol were found to be much less soluble in petroleum ether than the ester derivatives of the nitroalcohols. These glycols which were derived from its corresponding olefin oxide were identified by the melting points of their ester derivatives and also by elemental analysis of these same derivatives.

The 3,4,5-trimethylisoxazole was purified by precipitating the cadmium complex, washing the solid complex with anhydrous alcohol until the supernatant liquid became colorless and then regenerating the trimethylisoxazole by warming the complex with water. The water solution was then extracted with ether and the ether solution dried over

anhydrous magnesium sulfate and distilled. The final identification of the 3,4,5-trimethylisoxazole was accompanied by comparing its boiling point and infrared spectrum with that of an authentic sample prepared by treating nitroethane with aqueous sodium hydroxide. The melting point of our material was found to be 3° which compares favorably with the melting point of 3–4° reported in the literature.[10]

*Analysis of fraction A.* The fraction was dried over phosphorus pentoxide under vacuum, at room temperature, for about 1 week. When styrene oxide was employed as the olefin oxide, the 1-(2-phenyl-2-hydroxyethyl)pyridinium nitrite (m.p. 179.6–179.9°) crystallized from the reaction mixture directly and was purified by recrystallization from absolute alcohol or dry dimethylformamide. In this case the pyridinium nitrite was analyzed directly for nitrite ion, nitrogen, carbon and hydrogen.

*Anal.* Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38; $NO_2^-$, 18.45. Found: C, 63.67; H, 5.63; N, 11.17; $NO_2^-$, 18.68.

When the pyridinium nitrite was obtained as an oil, it was very difficult to isolate a pure crystalline product. In these cases the amount of pyridinium nitrite in the sample was determined by titrating small portions of Fraction A with standard potassium permanganate.[13]

To obtain analytical data, the nitrite (which is very hygroscopic) was converted to the chloride, which is somewhat easier to handle, and purified in this form. The conversion and purification were carried out as follows: The crude pyridinium nitrite was taken up in water and then treated with freshly regenerated Rohm and Haas Amberlite IR-120 sulfonic acid-type ion exchange resin. When the evolution of nitrogen oxides had ceased, the solution was filtered and the resin which now contained the pyridinium salt was washed repeatedly with water and then once with acetone. The resin was then warmed with 10% hydrochloric acid to remove the pyridinium salt, and the acid solution was evaporated to 40° under vacuum. When about 10 ml. of residue remained, absolute alcohol was added and again the solution was evaporated under vacuum. This process was repeated until a viscous oil remained and all acid had been removed. The oil residue, after being dried under vacuum in the presence of phosphorus pentoxide for 1 week, was taken up in a minimum of absolutely dry dimethylformamide, sealed in a vial, then placed under refrigeration (about −10°) for 1 week. Crystals were filtered under dry nitrogen and then recrystallized from dry dimethylformamide (m.p. 127–127.4°).

*Anal.* Calcd. for $C_7H_{10}NOCl$: Cl, 22.22. Found: Cl, 22.06.

*Analysis of fraction B.* Two procedures were used in analyzing the fraction obtained from the treatment of the ether solution of the reaction mixture with anhydrous hydrogen chloride. In those cases where this fraction consisted mainly of pyridine hydrochloride, as for example from nitromethane and nitroethane, it was treated with aqueous sodium bicarbonate and the organic material was extracted into ether. Ether was removed and the residue fractionated.

The second procedure was used on those samples known to contain oxime hydrochlorides as well as pyridine hydrochloride. In this second procedure, a portion of Fraction B, which had been dried for 1 week in a vacuum desiccator over phosphorus pentoxide, was vacuum distilled. The oxime hydrochloride readily distilled as a colorless liquid which solidified in the receiver. The oximes were identified by comparing the melting points and mixed melting points of both the oxime hydrochloride and oxime with those of compounds of known structure.

CLEVELAND 6, OHIO

(13) W. C. Pierce and E. L. Haensch, *Quantitative Analysis*, John Wiley and Sons, Inc., New York, 1945, pp. 196–197.

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

# Cyclic Dienes. XXV. Synthesis of an Epoxydiene[1,2]

WILLIAM J. BAILEY AND CHARLES E. KNOX[3]

*Received September 16, 1959*

An epoxydiene, 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane, was prepared by the pyrolysis of an epoxydiacetate at 500°. The structure of the diene was proved by analysis, ultraviolet and infrared spectra, hydrolysis to a solid dihydroxydiene and conversion to two solid Diels-Alder adducts. The diene could be polymerized by a free radical mechanism to a benzene-soluble polymer of high molecular weight. Treatment of this linear polymer with a diamine produced a hard epoxy resin.

In this series of articles the preparation of a variety of cyclic dienes has been reported, but with the exception of 9,10-dimethylene-1,7-dioxacyclohendecane-2,6-dione[4] and thiophene 1-dioxide[5] all contained only carbon and hydrogen. It was of interest to extend this series to include a variety of cyclic dienes containing polar groups. Of particular interest was a cyclic diene containing an epoxy group, since the polymers from such a monomer would combine the characteristics of a diene polymer with those of an epoxy resin. For these reasons the synthesis of the epoxydiene, 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane (III) was undertaken.

Although $\Delta^4$-cyclohexene-1,2-dimethanol diacetate (I) had been prepared previously by a two-step procedure,[6] a shorter procedure was developed by use of an effectively one-step reductive acetylation with lithium aluminum hydride and acetic anhydride.[4,7] In this procedure diethyl $\Delta^4$-cyclohexane-1,2-dicarboxylate was reduced in the usual

(1) Previous paper in this series, *J. Am. Chem. Soc.*, **81**, 5598 (1959).

(2) Presented in part before the Division of High Polymers, 128th Meeting, ACS, Miami, Fla., April 1957.

(3) Office of Naval Research Fellow, 1955–57.

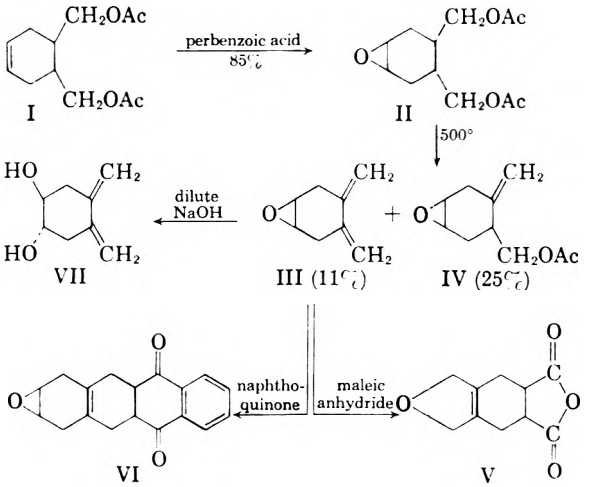
(4) W. J. Bailey and W. R. Sorenson, *J. Am. Chem. Soc.*, **78**, 2287 (1956).

(5) W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.*, **76**, 1932 (1954).

(6) W. J. Bailey and J. Rosenberg, *J. Am. Chem. Soc.*, **77**, 73 (1955).

(7) W. J. Bailey and M. J. Stanek, Abstracts of the 127th National Meeting of the American Chemical Society, Cincinnati, Ohio, April 1955, p. 30N.

way with lithium aluminum hydride but, instead of the usual hydrolysis, the reaction mixture was treated directly with acetic anhydride to produce an 82% yield of the diacetate I. The epoxidation of I was accomplished in an 85% yield with perbenzoic acid. Of the methods available for the preparation of perbenzoic acid, the procedure of Kergomard and Bijou[8] was preferred. According to this simple procedure benzoyl chloride was treated with 35% hydrogen peroxide plus sodium hydroxide to give a chloroform solution of perbenzoic acid in 75 to 82% yields.




Since the pyrolysis of esters had been used successfully for the synthesis of highly unsaturated compounds, it was hoped that pyrolysis under controlled conditions would not isomerize the epoxide ring. For example, the pyrolysis of esters was used successfully to prepare 1,2-dimethylene-4-cyclohexene,[6] isomeric with *o*-xylene, and 1,4-dimethylene-2-cyclohexene,[9] isomeric with *p*-xylene. However, pyrolysis of an epoxide either in the liquid phase or over catalysts usually results in the rearrangement to an aldehyde or ketone. For example, pyrolysis of 2,3-epoxypentane gave methyl *n*-propyl ketone,[10] while simple distillation of 1,1-diphenyl-1,2-propylene oxide at atmospheric pressure gave $\alpha,\alpha$-diphenylacetone.[11] Pyrolysis of cyclohexene oxide in the vapor phase at high temperatures or in the presence of catalysts gave a variety of products, including cyclohexanone, water, and cyclohexadiene.[12]

The pyrolysis of the epoxydiacetate II over Pyrex helices at 500° under such conditions that very little carbonization occurred and 64% of two molar equivalents of acetic acid was liberated did produce an 11% yield of the desired epoxydiene, 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane (III). At the same time, a 25% yield of the olefin acetate IV and a 7% recovery of starting material were realized. The yield of diene III, based on unrecovered II and IV, was, therefore, only 16%. However, the reason for the low yield apparently was not rearrangement of the epoxide group but rather polymerization of III either during pyrolysis or subsequent treatment. Distillation of III always gave some polymeric residue.

The structure of III was indicated by spectral data as well as conversion to several solid derivatives. The presence of conjugated double bonds exocyclic to a six-membered ring was indicated by an $\epsilon$ maximum of 4500 at 225 m$\mu$ in the ultraviolet spectrum of III determined in cyclohexane. Although this maximum occurs at slightly longer wave lengths than that in the spectrum of 1,2-dimethylenecyclohexane (218 m$\mu$),[13] it occurs at a substantially shorter wave length than predicted from Woodward's rules[14] (237 m$\mu$). This difference can be rationalized by the assumption that the attached three-membered ring changes the conformation of the six-membered ring so that the two methylene groups are more nearly planar.[15] The infrared spectrum of the epoxydiene showed a strong band at 893 cm.$^{-1}$, indicating the presence of methylene groups, and strong bands at 873, 1065, and 1232 cm.$^{-1}$, indicating the presence of an epoxide group.

Diels-Alder adducts V and VI were prepared from 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane and maleic anhydride and naphthoquinone, respectively. The structure of the maleic anhydride adduct V was indicated by analysis and by infrared spectrum; bands at 848, 1061, and 1226 cm.$^{-1}$ indicated the presence of the three-membered oxygen ring and bands at 808, 952, 1448, 1788, and 1848 cm.$^{-1}$ indicated the presence of the anhydride ring.

The hydrolysis of the epoxydiene III in very dilute sodium hydroxide gave, as the main product, polymer; however, a small amount of *trans*-1,2-dimethylenecyclohexane-4,5-diol (VII) was isolated from the product. The structure of the dihydroxydiene was indicated by an $\epsilon$ max. of 3200 at 222 m$\mu$ in the ultraviolet spectrum determined in iso-octane. The infrared spectrum of VII, determined on a Nujol mull, showed bands at 1065 and 3400 cm.$^{-1}$, indicating the presence of secondary hydroxyl groups, and a band at 905 cm.$^{-1}$, indicating the presence of methylene groups.

In a standard peroxide-catalyzed emulsion system, 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane (III) gave solid white polymer that was completely soluble in benzene but insoluble in methanol.

(8) A. Kergomard and J. Bijou, *Bull. soc. chim. France*, 1956, 486.

(9) W. J. Bailey and R. Barclay, *J. Am. Chem. Soc.*, 81, 5393 (1959).

(10) M. Favorskii, M. Chichonkin, and I. Ivanov, *Compt. rend.*, 199, 1229 (1934).

(11) J. Levy and LaGrave, *Compt. rend.*, 180, 1032 (1925).

(12) F. O. Rice and A. L. Stallbaumer, *J. Am. Chem. Soc.*, 64, 1527 (1942).

(13) W. J. Bailey and H. R. Golden, *J. Am. Chem. Soc.*, 76, 5418 (1954).

(14) R. B. Woodward, *J. Am. Chem. Soc.*, 64, 72 (1942).

(15) W. J. Bailey and W. B. Lawson, *J. Am. Chem. Soc.*, 79, 1444 (1957).

Although the polymer did not possess a definite softening point, it became slightly discolored and resinous between 180° and 200°, suggesting that cross linking had taken place. An infrared spectrum of the polymer showed no band at 893 cm.$^{-1}$, indicating almost complete 1,4-addition during polymerization; the strong bands corresponding to the epoxy group, 868, 1061, and 1217 cm.$^{-1}$, were, however, still present. When the epoxydiene III was polymerized in bulk with benzoyl peroxide, a rubbery polymer resulted. When this soluble polymer was cross linked with ethylenediamine, a very hard epoxy resin resulted.

It must be concluded that in the vapor state the 1,2-disubstituted three-membered epoxide ring is more stable than the ester group. It is likely that, in contrast to the noncatalyzed cyclic mechanism proposed for ester pyrolysis, the rearrangement of the epoxide ring is acid or base catalyzed. Thus, the vapor-phase pyrolysis will tend to minimize any catalyzed reaction and allow for the synthesis of a large variety of polyfunctional or strained compounds.

## EXPERIMENTAL[16]

*$\Delta^4$-Cyclohexene-1,2-dimethanol diacetate* (I). In a 12-l., three-necked flask, equipped with stirrer, reflux condenser, and dropping funnel, was placed 100 g. (2.63 moles) of lithium aluminum hydride in 6 l. of anhydrous ether. While the flask was externally cooled by an ice bath, 500 g. (2.22 moles) of diethyl $\Delta^4$-cyclohexene-1,2-dicarboxylate, b.p. 103° (0.6 mm.), $n_D^{25}$ 1.4606 [reported[17] b.p. 129–131° (5 mm.), $n_D^{25}$ 1.4605–1.4610], in 2 l. of anhydrous ether was added dropwise over a 5-hr. period with stirring. After addition of the diester was complete, the reaction mixture was heated under reflux for 5 days. (If the reaction mixture coagulated so that the reaction mixture could not be stirred, heating was carried out without stirring until the complex could be broken—heating for 2 days usually was sufficient.)

The ether was removed by distillation and replaced with 4500 ml. of anhydrous di-*n*-butyl ether until a reaction temperature of 120° was reached. After the reaction mixture was cooled to 60°, 600 ml. of glacial acetic acid was added dropwise. Stirring was discontinued when the reaction mixture solidified. After the mixture was heated for 24 hr. and then cooled, the solid complex was dispersed and the stirring was continued. Acetic anhydride (2500 ml.) was added slowly to the hot mixture and the heating was continued for several days. After the reaction mixture was cooled and filtered, the solvent and excess reactants were removed *in vacuo*. The residue was fractionated through a 12-inch Vigreux column to give 411 g. (82%) of $\Delta^4$-cyclohexene-1,2-dimethanol diacetate (I), b.p. 103–105° (0.2 mm.), $n_D^{25}$ 1.4765 (reported b.p. 121–128° (1.0 mm.)).

*7-Oxabicyclo[4.1.0]heptane-3,4-dimethanol diacetate* (II). By a modification of the method of Kergomard and Bijou,[8] 50 g. (0.5 mole) of 35% hydrogen peroxide solution was added to a solution of 40 g. (1.0 mole) of sodium hydroxide in 300 ml. of water and 300 ml. of absolute alcohol at 0 to 4°. After the mixture was agitated for 10 min., 72 g. (0.5 mole) of benzoyl chloride was added while the temperature was maintained below 5°. Agitation was continued with external cooling until the reaction mixture became only slightly cloudy (usually 1–2 hr.), thus ensuring nearly complete reaction of the benzoyl chloride. The reaction mixture was filtered under vacuum into a cold filter flask to remove any benzoyl peroxide. The filtrate containing some sodium peroxide gave perbenzoic acid by the addition of cold 10% sulfuric acid solution to a definite acid end point (Congo red or methyl orange). Successive extractions of the acidified filtrate with 150, 75, and 50 ml. of cold chloroform gave a chloroform solution of perbenzoic acid. (It is usually advantageous to add crushed ice to the aqueous solution to avoid a temperature rise during the extraction.) The concentration of perbenzoic acid in the chloroform solution was determined by the potassium iodide titration method on an aliquot. The yield was 75 to 82% of theoretical.

To a 1-l., three-necked flask, fitted with stirrer, dropping funnel, and reflux condenser, and containing a cold chloroform solution of perbenzoic acid (0.377 mole) was added dropwise a solution of 85.2 g. (0.377 mole) of $\Delta^4$-cyclohexene-1,2-dimethanol diacetate (I) in 200 ml. of chloroform at a rate such that the temperature of the reaction mixture did not rise above 10°. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 18 hr. After the reaction mixture was washed with several portions of a 10% sodium carbonate solution (until all the benzoic acid was removed) and then with water, it was dried over anhydrous magnesium sulfate. After the solvent was removed by distillation in a partial vacuum, the residue was distilled through a 12-inch, helix-packed column to yield 77.2 g. (85%) of 7-oxabicyclo[4.1.0]heptane-3,4-dimethanol diacetate (II), b.p. 121–125° (0.3 mm.), $n_D^{25}$ 1.4705.

*Anal.* Calcd. for $C_{12}H_{18}O_5$: C, 59.47; H, 7.49. Found: C, 59.66; H, 7.38.

*3,4-Dimethylene-7-oxabicyclo[4.1.0]heptane* (III). At the rate of 0.33 g. per min., 145.6 g. (0.606 mole) of 7-oxabicyclo[4.1.0]heptane-3,4-dimethanol diacetate (II) was added dropwise to a Vycor tube packed with Pyrex helices and externally heated at 500° in an apparatus described previously.[18] Charring was minimized by sweeping the system continuously with a slow stream of oxygen-free nitrogen. The yellow pyrolysate in ether was washed free of acetic acid with water and dried over anhydrous sodium carbonate. (Titration of aliquots of the aqueous washings indicated that 65% of two molar equivalents of acetic acid had been liberated.) The pyrolysate was fractionated through a 12-inch, helix-packed column to yield 7.9 g. (11%) of 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane (III), b.p. 65–68° (10 mm.), $n_D^{25}$ 1.4970; 27.3 g. (25%) of 3-methylene-7-oxabicyclo[4.1.0]heptane-4-methanol acetate (IV), b.p. 81–86° (0.8 mm.); and 10.4 g. (7% recovery) of unchanged 7-oxabicyclo[4.1.0]heptane-3,4-dimethanol diacetate (II). There remained 37.5 g. of a dark polymeric residue in the distilling flask. The yield of III, based on unrecovered II and IV, was 16%.

*Anal.* Calcd. for $C_8H_{10}O$: C, 78.62; H, 8.25. Found: C, 78.40; H, 8.50.

*6,7-Epoxy-$\Delta^{9(10)}$-decalin-2,3-dicarboxylic anhydride* (V). A mixture of 0.53 g. (0.0044 mole) of 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane (III) and 0.43 g. (0.0044 mole) of maleic anhydride was heated under reflux in 25 ml. of ether for 25 min. The Diels-Alder adduct, which precipi-

(16) The authors are indebted to Miss Kathryn Gerdeman and Miss Jane Swan for the microanalyses and to Dr. Ellis Lippincott, Dr. Asa Leifer, Dr. Rudolph Schroeder, and Mr. Charles E. White for the infrared spectra and aid in their interpretation. The infrared spectra of the monomers were determined with a rock salt prism in a Beckman IR-4 spectrophotometer, while the spectrum of the polymer was determined on a Perkin-Elmer Model 12-C spectrophotometer modified for double-pass operation. The ultraviolet spectra were determined on a Beckman DU spectrophotometer. All melting points are corrected.

(17) A. C. Cope and E. C. Herrick, *Org. Syntheses*, **30**, 29 (1950).

(18) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, **21**, 543 (1956).

tated from the hot mixture, was removed by filtration to give 0.9 g. (95%) of 6,7-epoxy-$\Delta^{9(10)}$-decalin-2,3-dicarboxylic anhydride (V), m.p. 190.5–191.5°.

*Anal.* Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.50. Found: C, 65.60; H, 5.76.

*2,3-Epoxy-1,2,3,4,5,5a,6,11,11a,12-decahydronaphthacene-6,11-dione* (VI). To a solution of 0.52 g. (0.0033 mole) of 1,4-naphthoquinone in 25 ml. of dry toluene was added 0.60 g. (0.005 mole) of 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane (III) and the solution was heated under reflux for 2 days. The solvent was removed by distillation to give a yellow solid. Two recrystallizations from 95% ethanol gave 0.87 g. (70%) of VI as yellow needles, m.p. 165.5–170°, which became slightly discolored on exposure to air.

*Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.00; H, 5.75.

*trans-1,2-Dimethylenecyclohexane-4,5-diol* (VII). Crude 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane (III) (33 g.) was treated with a solution of 24 g. of sodium hydroxide in 800 ml. of water for 15 hr. at 40–50°. After the mixture was cooled to room temperature, 15 g. of acetic acid was added and the aqueous solution was extracted continuously with ether for 24 hr. After the ether solution was dried over anhydrous magnesium sulfate and the solvent was removed by distillation, some low boiling liquids were removed from the residue under partial vacuum. The remaining residue was a polymeric resin, which was insoluble in ether, benzene, methanol, and acetone.

Extraction of the residue in hot acetone, followed by filtration of the mixture, gave a white resin, softening point 165–167°. Evaporation of the acetone filtrate gave a white solid, which was dissolved in methanol. Addition of the solution to a large excess of benzene and concentration of this solution to one-half its original volume (essentially removing the methanol) gave 20 mg. of *trans*-1,2-dimethylenecyclohexane-4,5-diol (VII) as a white powder, m.p. 214–215°.

*Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found: C, 68.39; H, 8.59.

*Emulsion polymerization of 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane* (III). In a 2-oz. screw-cap bottle were placed 2.06 g. of 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane (III), 0.10 g. of sodium stearate, 0.02 g. of lauryl mercaptan, 0.007 g. of potassium persulfate and 3.80 g. of water. The bottle was rotated in a water bath maintained at 63° for 26 hr., at which time the emulsion had broken. After acidification of the mixture with dilute hydrochloric acid and removal of the solid by filtration, the solid was dissolved in 60 ml. of benzene and a trace of 1,3,5-trinitrobenzene was added as an inhibitor. The benzene solution was poured slowly into 250 ml. of cold methanol with stirring and the white flocculent polymer precipitated. Filtration, followed by drying, gave 0.77 g. (37% conversion) of poly-3,4-dimethylene-7-oxabicyclo[4.1.0]heptane. The polymer did not exhibit a definite softening point, although discoloration and signs of cross linking of the polymer occurred at 180°. The polymer showed signs of considerable discoloration at 230°. This decomposition probably resulted from cross linking of the epoxide groups, as the heated polymer displayed hard, brittle properties which were not present in the original polymer.

Determination of the viscosity of the polymer at 25° in a chloroform solution in an Ostwald viscometer gave an intrinsic viscosity of 0.326.

*Combined peroxide-catalyzed and epoxide polymerization of 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane* (III). When 0.57 g. of 3,4-dimethylene-7-oxabicyclo[4.1.0]heptane (III) was polymerized in bulk with a catalytic quantity of benzoyl peroxide at steam-bath temperature for 13 hr., the resulting polymer was very viscous and displayed some elasticity at room temperature. After a small amount of ethylenediamine was added to this polymer, the mixture was heated for 2 hr. on a steam bath. There resulted a very hard amber-colored resin which adhered to the walls of the glass container.

COLLEGE PARK, MD.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

# Cyclopentenes and Cyclopentanes. II. Synthesis from Isophorone[1]

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Synthesis of 1,1,3,3-tetramethylcyclopentane, 1,1,2,4-tetramethylcyclopentane and 1,1,3,4-tetramethylcyclopentane from isophorone has been accomplished. Several intermediate compounds, tetramethylcyclopentenes, trimethylcyclohexenes polymethyladipic acids, cyclohexanones cyclopentanones and cyclohexanediols were prepared and characterized. The methods described are adaptable to large scale use.

The tetramethylcyclopentanes comprise a little known group of hydrocarbons. Of the seven possible structural isomers only one (1,1,2,3-tetramethylcyclopentane[3]) has been reported as synthesized, and no effort was made to determine the hydrocarbon's geometrical configuration. 1-*trans*-2-*cis*-3-*trans*-4-Tetramethylcyclopentane and 1,1-3-*trans*-4-tetramethylcyclopentane have been identified in a representative petroleum.[4] If all of the geometrical isomers are counted, sixteen different tetramethylcyclopentanes are possible.

Previously,[5,6] isophorone (3,5,5-trimethyl-2-cy-

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(3) J. F. Eykman, *Chem. Weekblad*, **3**, 692 (1906).

(4) F. D. Rossini and A. J. Streiff, Paper presented to Section V of the Fifth World Petroleum Congress, N. Y. (1959).

TABLE I

PHYSICAL PROPERTIES FOR SOME HYDROCARBONS SYNTHESIZED

| Compound | F.P., °C. | B.P., °C. | $d_4^{20}$ | $n_D^{20}$ | Purity, Mole % |
|---|---|---|---|---|---|
| 1,1,3,3-$(CH_3)_4$ Cyclopentane | −88.29 | 117.96 | 0.7509 | 1.4125 | 99.0 + 0.5 |
| 1,1,3,4-$(CH_3)_4$ Cyclopentane (*trans*) | −93.94 | 121.4–121.6 | 0.7489 | 1.4120 | 98.5 + 0.5 |
| 1,1,3,4-$(CH_3)_4$ Cyclopentane (*cis*) | −106.49 | 132.9–133.0 | 0.7670 | 1.4204 | 98.0 + 0.5 |
| 1,1,2,4-$(CH_3)_4$ Cyclopentane (*cis* and *trans*) | −118.91 | 129.41–129.45 | 0.7648 | 1.4194–1.4196 | — |
| 3,3,5,5-$(CH_3)_4$ Cyclopentene | −64.23 | 107.03 | 0.7484 | 1.4154 | — |
| 3,3,5-$(CH_3)_3$ Cyclohexene | −85.39 | 131.33 | 0.7888 | 1.4386 | 99.5 + 0.2 |
| 3,5,5-$(CH_3)_3$ Cyclohexene | −91.97 | 133.58 | 0.7941 | 1.4406 | 97.8 + 0.2 |

clohexenone) had been used as a starting material for a variety of trimethylcyclopentanes. Paper I of our series[7] describes syntheses based on cyclopentadiene. The present work extends the use of isophorone to the synthesis of five tetramethylcyclopentanes (two as a mixture of geometrical isomers), one tetramethylcyclopentene, and, incidentally, two trimethylcyclohexenes.

The synthesis of 1,1,3,3-tetramethylcyclopentane from isophorone was made possible by the discovery of M. S. Kharasch and P. O. Tawney[8a] that, in the presence of cuprous chloride, methyl Grignard reagent undergoes 1,4-addition to isophorone, and 3,3,5,5-tetramethylcyclohexanone is obtained. When this ketone was oxidized by nitric acid it yielded 2,2,4,4-tetramethyladipic acid, which upon destructive distillation was converted to a new ketone, 2,2,4,4-tetramethylcyclopentanone. This ketone was converted to 1,1,3,3-tetramethylcyclopentane in two ways: (1) direct reduction by a modification of the Wolff-Kishner procedure, and (2) reduction by catalytic hydrogenation, dehydration, and re-hydrogenation. The products obtained were of about the same purity. Method 2 produced two new olefins in the dehydration step: 3,3,5,5-tetramethylcyclopentene and another, tentatively identified as 1,3,3,5-tetramethylcyclopentene (which could be formed by retropinacolic rearrangement).

1,1,2,4 - Tetramethylcyclopentane and 1,1,3,4,-tetramethylcyclopentane were synthesized by a similar series of reactions. 3,3,5-Trimethylcyclohexanone and 3,3,5-trimethylcyclohexanol were oxidized by nitric acid to produce a mixture of 2,2,4-trimethyladipic acid and 2,4,4-trimethyladipic acid, which was ketonized without separation or purification, yielding cyclic ketones.

2,2,4-Trimethylcyclopentanone, the lower boiling of the cyclic ketones, was separated in good purity by high-efficiency distillation, and 2,4,4-trimethylcyclopentanone was isolated through its sodium bisulfite addition product. The purified ketones were condensed individually with methyl Grignard reagent to produce 1,2,2,4-tetramethylcyclopentanol and 1,2,4,4-tetramethylcyclopentanol, respectively. Dehydration of the latter and hydrogenation of the resulting olefin mixture produced 1,1,3,4-tetramethylcyclopentanes. The 1,2,2,-4-tetramethylcyclopentanol was treated with anhydrous hydrogen chloride to obtain the corresponding organic chloride which was then reduced with sodium in liquid ammonia to produce 1,1,2,4-tetramethylcyclopentane; some retropinacolic-type rearrangement probably took place during the hydrochlorination but the same hydrocarbon product would result. These quite different methods of reduction were chosen because it was believed that they would produce approximately equimolar mixtures of the geometrical isomers from which each individual isomer might be isolated in quantity.

In the case of the 1,1,3,4-tetramethylcyclopentanes, the mixture was distilled at about 25-plate efficiency to separate it into nearly equal amounts of *trans* isomer and *cis* isomer, with the properties shown in Table I.

The mixture of 1,1,2,4-tetramethylcyclopentanes was fractionated at about 25-plate efficiency, and 94% of the distillate had a boiling range of only 0.04° and a refractive index ($n_D^{20}$) range of only 0.0002. Inasmuch as both of the possible geometric isomers were undoubtedly present,[8b] it was concluded that the boiling points of the two must be similar. This appears plausible when other such pairs are compared: for example, the two 1,3-dimethylcyclopentanes boil only 0.96° apart and the 1-methyl-3-ethylcyclopentanes 0.6° apart.

An alternative method of synthesizing relatively pure samples of the trimethyladipic acids and pure trimethylcyclopentanones was developed. Dehydration of 3,3,5-trimethylcyclohexanol gave 3,3,5-

(5) S. F. Birch and E. A. Johnson, *J. Chem. Soc.*, 1493 (1951).

(6) George Slomp, Doctoral Dissertation, the Ohio State University, 1949. Also presented before the Organic Division of the American Chemical Society in September, 1950, in Chicago, Ill.

(7) Grant Crane, C. E. Boord, and A. L. Henne, *J. Am. Chem. Soc.*, **67**, 1237 (1945).

(8a) M. S. Kharasch and P. O. Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941).

(8b) An equimolar mixture of the *cis* and *trans* isomers of 1,3-dimethylcyclopentane had been obtained by reduction of 1-chloro-1,3-dimethylcyclopentane by sodium in liquid ammonia (unpublished work of this laboratory).

trimethylcyclohexene and 3,5,5-trimethylcyclohexene (new compounds) which were separated by distillation and individually oxidized to the known 2,2,4-trimethyladipic acid and 2,4,4-trimethyladipic acid, respectively, thus establishing their structures. These acids were then converted to ketones separately to produce pure samples of 2,2,4-trimethylcyclopentanone and 2,4,4-trimethylcyclopentanone, respectively.

## EXPERIMENTAL

*3,3,5,5-Tetramethylcyclohexanone.* The procedure followed in this synthesis was similar to one published.[8] To 770 ml. of filtered 2.14*M* methylmagnesium bromide (1.65 moles) contained in a 2-l., three-neck flask fitted with a Hershberg stirrer, thermometer, bulb condenser, and dropping funnel was added 0.0165 mole of cuprous chloride. Redistilled isophorone (Union Carbide Chemicals Co.) was added dropwise while maintaining the temperature at 10–15°, until 191 g. (1.38 moles) had been added. Stirring was continued for 1 hr. longer under reflux, and the mixture was allowed to stand overnight at room temperature. The reaction was quenched by pouring it into a mixture of 100 g. of glacial acetic acid and 800 g. of cracked ice. The ether layer was separated and the aqueous layer was extracted twice with 50 ml. of ether. The combined ether solutions were washed twice with 10% sodium bicarbonate, water, and saturated sodium chloride solution, successively. After drying over anhydrous sodium sulfate, the ether was removed by rapid distillation and the remaining material was fractionated at 10 mm. pressure and 10:1 reflux ratio on a 1.6 × 55 cm. column packed with 3/16-in. glass helices. The fractions boiling at 72–74°, 10 mm. amounted to 162.5 g. (76.5% yield) of tetramethylcyclohexanone. Properties determined were: b.p. 195–196°, $n_D^{20}$ 1.4520–1.4522; (lit.,[8] b.p. 196–197°, $n_D^{20}$ 1.4520).

*2,2,4,4-Tetramethyladipic acid.* Oxidation of 3,3,5,5-tetramethylcyclohexanone was accomplished in all-glass apparatus consisting of a 1-l., multi-neck flask fitted with a pressure-compensating dropping funnel, a propeller-type stirrer, a multibulb reflux condenser, and a thermometer well. The flask was charged with 480 ml. (5.0 moles) of 50% nitric acid and 1.0 g. of ammonium metavanadate, and the vigorously stirred mixture was heated to 65°. Then, 145.8 g. (0.945 mole) of 3,3,5,5-tetramethylcyclohexanone was dropped in at a carefully controlled rate and an exothermal reaction occurred with foaming and evolution of nitrogen oxides; the temperature was maintained at 60–65° by surrounding the flask with cold water. When about half of the ketone had been added, solid tetramethyladipic acid began to separate. Stirring was continued for 0.5 hr. after addition was complete, while reaction temperature was maintained by surrounding the flask with hot water. By the end of this time, no more gases were evolved, and the spent reaction mixture was allowed to cool to room temperature. The crude 2,2,4,4-tetramethyladipic acid, filtered and washed with water, amounted to 188 g. (98% yield); it melted at 118–119°, neut. equiv. 100.9 (theory 101.1).

A small amount of the acid was purified by recrystallization from water, and this sample (m.p. 119.0–119.5°) had a neut. equiv. of 101.2.

*Anal.* Calcd. for $C_{10}H_{18}O_4$: C, 59.38 H, 8.97. Found: C, 59.34; H, 8.95.

The di-*p*-toluide of the acid was prepared and it recrystallized as needles (m.p. 125–126°) from ethyl alcohol.

*2,2,4,4-Tetramethylcyclopentanone.* In a typical run, 177 g. (0.875 mole) of 2,2,4,4-tetramethyladipic acid was converted to the ketone by heating to about 250–255° with 20 g. of manganese carbonate and 20 g. of barium hydroxide. The crude ketone (70% yield), after washing and drying, was distilled at about 20-plate efficiency to produce relatively pure 2,2,4,4-tetramethylcyclopentanone (61% yield). Physical properties determined for a center fraction were: b.p. 165.38°, $d_4^{20}$ 0.8651, $n_D^{20}$ 1.4305, f.p. −55.19° (f.p. range, 2.2°).

*Anal.* Calcd. for $C_9H_{16}O$: C, 77.08; H, 11.50. Found: C, 77.05; H, 11.48.

Semicarbazone, m.p. 189–189.5°.

*Anal.* Calcd. for $C_{10}H_{19}ON_3$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.88; H, 9.68; N, 21.28.

*1,1,3,3-Tetramethylcyclopentane by direct reduction.* To obtain the hydrocarbon, 107.5 g. (0.756 mole) of the corresponding ketone was reduced with 90 ml. of 85% hydrazine and 120 g. of potassium hydroxide in 600 ml. of diethylene glycol by the modified Wolff-Kishner method of Huang-Minlon.[9] The reactants were combined in a 2-l. round bottom flask which was fitted with a thermometer reaching nearly to the bottom and a reflux condenser with a take-off side arm. After the mixture was refluxed for 1 hr. take-off was commenced and the temperature was maintained at 170–175° by adjusting the rate at which water and hydrocarbon were distilled; the reaction was finished in about 2 hr. and distillation ceased.

The hydrocarbon layer in the distillate was separated and washed with dilute hydrochloric acid, water, and saturated salt solution; the 78 g. of crude product was dried over anhydrous sodium sulfate and fractionated at about 20-plate efficiency to yield 75.5 g. (77.5%) of 1,1,3,3-tetramethylcyclopentane with the properties shown in Table I.

*1,1,3,3-Tetramethylcyclopentane by indirect reduction.* In a typical run, 67.0 g. (0.477 mole) of 2,2,4,4-tetramethylcyclopentanone was hydrogenated over 10 g. of reduced nickel-on-kieselguhr at 200° and 1900 p.s.i.g. in a 300-ml. rocking autoclave to produce 62 g. (91%) of a compound presumed to be the corresponding 2,2,4,4-tetramethylcyclopentanol (b.p.$_{745}$ 174.4–175.0°, $n_D^{20}$ 1.4431–1.4428). The material crystallized as white needles, m.p. 32.5–33.0° (uncorr.).

The tetramethylcyclopentanol was dehydrated by passing it through a 2.5 × 100 cm. tube filled with 8–14 mesh activated alumina at 300°. From 96.0 g. (0.675 mole) of carbinol, 64 g. (95% yield) of crude olefins was obtained after separation and drying. Distillation at 20-plate efficiency indicated 87% of the olefin mixture was 3,3,5,5-tetramethylcyclopentene: b.p.$_{760}$ 107.03°, $n_D^{20}$ 1.4154. The remaining 13% of the distillate (b.p.$_{744}$ 122°, $n_D^{20}$ 1.430) was rearranged olefin(s), most likely 1,3,3,5-tetramethylcyclopentene. The desired cycloparaffin was produced by hydrogenating 26.8 g. (0.215 mole) of the 3,3,5,5-tetramethylcyclopentene over 5 g. of nickel-on-kieselguhr. The reaction was carried out at 150° and 1900 p.s.i.g. in a 300-ml. rocking autoclave fitted with a 100-ml. glass liner. Distillation at 20-plate efficiency gave 22.5 g. (83% yield) of 1,1,3,3-tetramethylcyclopentane (b.p.$_{745}$ 117.2–117.4°, $n_D^{20}$ 1.4125). A center fraction had virtually the same properties as the previous sample (Table I).

*3,3,5-Trimethylcyclohexanol (dihydroisophorol).* In a typical run, 1855 g. (13.7 moles) of isophorone was hydrogenated to saturation over 90 g. of nickel-on-kieselguhr at 250° in a 3-l. rocking autoclave at pressures of 1600–2000 p.s.i.g. The product was decanted from the catalyst while warm, and formed white crystalline needles which were not further purified. The yield was nearly quantitative.

*3,3,5-Trimethylcyclohexanone (dihydroisophorone).* Isophorone was hydrogenated as in the preceding section except that the temperature was held at 95–105° and treatment was suspended when the calculated amount of hydrogen had been absorbed. At this point, the rate of absorption had decreased nearly to zero. The bomb was cooled, and the liquid material was decanted from the catalyst and used without further purification. The yield was nearly quantitative.

*Mixed 2,2,4- and 2,4,4-trimethyladipic acids.* These acids were produced from a mixture of dihydroisophorone and

(9) Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2487 (1946).

dihydroisophorol by the same procedure described for 2,2,4,-4-tetramethyladipic acid, but on a larger scale. Presence of the ketone in the mixture prevented crystallization in the addition funnel.

The excess nitric acid was neutralized by a minimum amount of sodium hydroxide, with stirring. A color change from green to orange occurred at the point of equivalency, and the 2,2,4- and 2,4,4-trimethyladipic acids separated as an oil which partially crystallized upon standing; the yields of crude mixed acids were essentially quantitative in several runs.

*2,2,4- and 2,4,4-Trimethylcyclopentanones.* The crude mixture of trimethyladipic acids was converted to a ketone mixture by dry distillation with 10% of its weight of barium hydroxide. This reaction was performed, without mechanical stirring, in a 5-l. Pyrex flask heated to temperatures (260–290°) at which the trimethylcyclopentanones were formed at a steady rate and distilled off through a Vigreux column. The distillate consisted of the crude trimethylcyclopentanone mixture and a water layer which yielded additional crude ketone when saturated with sodium chloride. Based on the trimethylcyclohexanone-hexanol starting material, 80 to 85% yields of crude ketones were obtained over the two steps.

Pure 2,4,4-trimethylcyclopentanone was obtained from the crude ketone mixture through its sodium bisulfite addition compound (2,2,4-trimethylcyclopentanone does not form such a compound, due to steric hindrance). In a typical run, 400 ml. (355 g.) of the crude ketones was added to 2000 ml. of 40% sodium bisulfite and 300 ml. of absolute alcohol, and the mixture was stirred until a finely crystalline precipitate formed. From the precipitate (filtered, washed with ether, and dried) the 2,4,4-trimethylcyclopentanone was regenerated by steam distillation over an excess of sodium bicarbonate, 20 to 55 g. of ketone being obtained. This yield could have been substantially increased, but the product would have been less pure. Distillation of the product of several such runs gave 2,4,4-trimethylcyclopentanone with the following properties: b.p. 161.29°, $d_4^{20}$ 0.8772, $n_D^{20}$ 1.4312, m.p. −25.64°; semicarbazone m.p. 160.1–160.6°. (Lit.,[5] b.p. 161.5°, $d_4^{20}$ 0.8765, $n_D^{20}$ 1.4313, m.p. −25.6°.)

Even though the 2,2,4- and 2,4,4-trimethylcyclopentanones boil about 5° apart, fractional distillation is not recommended for their separation because considerable self-condensation may occur. In the present work, however, a quantity (8.3 moles) of pure 2,2,4-trimethylcyclopentanone was obtained by distillation of some of the crude ketone mixture at better than 100-plate efficiency. Most of the 2,4,4-trimethylcyclopentanone in the mixture was sacrificed, thereby. The distilled 2,2,4-trimethylcyclopentanone had the following properties: b.p. 156.1°, $d_4^{20}$ 0.8737, $n_D^{20}$ 1.4293, f.p. −40.36°; semicarbazone m.p. 175.1 to 176.0°. (Lit.,[5] b.p. 155.6°, $d_4^{20}$ 0.8730, $n_D^{20}$ 1.4294, f.p. −40.6°.)

*1,1,3,4-Tetramethylcyclopentane.* The purified 2,4,4-trimethylcyclopentanone (5.05 moles) was condensed with methyl Grignard reagent in the customary manner to produce 1,2,4,4-tetramethylcyclopentanol (4.47 moles, 89% yield); the carbinol after distillation under reduced pressure had the following properties: b.p. 65 to 76°/18 mm., $n_D^{20}$ 1.4411–1.4405.

The distilled carbinol was dehydrated over activated alumina at 325° to produce a mixture (486 g. or 4.4 moles) of crude tetramethylcyclopentenes. After distillation and redistillation at about 20-plate efficiency, there was obtained 271 g. (43% yield from ketone) of tetramethylcyclopentenes with the following properties: b.p. 121.0–126.5°/745 mm., $n_D^{20}$ 1.4331–1.4409.

The tetramethylcyclopentene mixture (271 g.) was hydrogenated to saturation over nickel-on-kieselguhr catalyst at 150°. The hydrogenate was filtered free of catalyst, after which it was treated exhaustively with 10% sodium permanganate solution, and steam distilled; the crude 1,1,3,4-tetramethylcyclopentane (after drying) weighed 190 g., a 30% yield from the ketone. Distillation of the product at 25-plate efficiency separated it into the *trans* isomer (b.p. 121.4–121.6°) and the *cis* isomer (b.p. 132.9–133.0°) in the ratio of 55:45.

*1,1,2,4-Tetramethylcyclopentane.* The purified 2,2,4-trimethylcyclopentanone (8.3 moles) was condensed with methyl Grignard reagent to produce 1,2,2,4-tetramethylcyclopentanol (b.p. 54–71°/20 mm., $n_D^{20}$ 1.4298–1.4491); the yield of distilled product was 6.8 moles, or 82% (from ketone).

The 1,2,2,4-tetramethylcyclopentanol (6.8 moles) was saturated with anhydrous hydrogen chloride at ice temperature to produce the corresponding chloride; the yield of crude chloride was 1090 g., or 100%.

The 1-chloro-1,2,2,4-tetramethylcyclopentane was converted to the cycloparaffin by sodium in liquid ammonia. The chloride (6.8 moles) was added rapidly to a solution of 17 g.-atoms of sodium in 4 l. of liquid ammonia, in a 12-l. flask equipped with a Dry Ice–cooled reflux condenser, Hershberg stirrer, and dropping funnel. Rapid stirring was continued for 1/2 hr. after addition was complete; then, powdered ammonium nitrate was added from a side-flask to destroy unreacted sodium. The amount of nitrate required (1.8 moles) indicated 5.4 atoms of excess sodium, *i.e.*, that reaction with the chloride had consumed about 85% of the theoretical amount. Then, 7 moles of powdered ammonium chloride was added to neutralize the by-product, sodium amide, and the reaction mixture was quenched with as much water as the reserve capacity of the flask would permit. The hydrocarbon layer was washed twice with water, and then was steam distilled and dried; the yield of crude tetramethylcyclopentane was 59% (from ketone). The crude product was highly unsaturated to bromine, so it was resaturated with anhydrous hydrogen chloride and retreated with sodium in liquid ammonia. The product was agitated with successive portions of potassium permanganate solution until the purple color persisted, when it was again steam distilled; the yield of dried, saturated hydrocarbon was 425 g. (50% from ketone). The olefin-free 1,1,2,4-tetramethylcyclopentane was fractionally distilled at 25-plate efficiency, but was not separated into its geometric isomers thereby, the distillate showing only 0.04° boiling range (Table I).

*3,3,5- and 3,5,5-Trimethylcyclohexene.* To dehydrate dihydroisophorol, 2.2 kg. of the carbinol (2500 ml., 15.4 moles) was placed with 8 g. of *p*-toluenesulfonic acid in a 3-l. pot attached to a column having about 15-plate efficiency. Enough heat was applied to obtain reflux, and the olefins were distilled, along with water, as they were formed. The organic distillate was dried over anhydrous sodium sulfate to obtain 1.85 kg. (95% yield) of mixed olefins. Fractionation of 5 kg. of such product at better than 100-plate efficiency yielded about 55% of the charge as 3,3,5-trimethylcyclohexene and about 36% as 3,5,5-trimethylcyclohexene; the properties of the two cyclohexenes are shown in Table I. The cyclo-olefins were definitely identified by stepwise oxidation to the corresponding trimethyladipic acids:

*3,3,5-Trimethylcyclohexane-1,2-diol.* For the oxidation of the cycloolefins, the hydroxylation method of D. Swern *et al.*[10] was followed, with certain modifications. For the hydroxylation of 3,3,5-trimethylcyclohexene, 308 ml. of 87% formic acid was placed in a 1-l., multi-neck flask fitted with an efficient stirrer, a condenser, a thermometer well, and a dropping funnel. Stirring was started, and 155 g. (1.25 moles) of purified 3,3,5-trimethylcyclohexene was added. The mixture was warmed to 45° and 159.5 g. (1.27 moles) of 27% hydrogen peroxide was added as rapidly as possible while maintaining the reaction temperature at 45–47° by cooling with an ice bath. After addition was complete, the mixture was stirred overnight at 40° and at the end of this time, no hydrogen peroxide remained and two

(10) D. Swern, G. N. Billen, and J. T. Scanlan, *J. Am. Chem. Soc.*, **68**, 1504 (1946).

layers were in evidence. The lower (acid) layer was separated and then neutralized with 322 g. of potassium hydroxide. By continuous ether extraction of this layer, 3 g. of material was recovered and added to the upper (mono- and/or diformic ester) layer. The ester material was saponified by refluxing for 5 hr. with 90 g. of potassium hydroxide and 100 ml. of water. Upon cooling to room temperature, the upper (glycol) layer solidified and weighed 199.5 g. The lower (aqueous) layer yielded 4.5 g. of additional glycol on continuous extraction with ether. The glycol (204 g.) was distilled under reduced pressure to yield 152 g., b.p.$_7$ 120–122° and 13 g., b.p.$_7$ 122–125° (combined yield 84%). A small amount of glycol from the 120–122° fraction was recrystallized from benzene, and this sample of 3,3,5-trimethylcyclohexane-1,2-diol melted at 102.4–102.8°.

*Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.11; H, 10.91.

*3,5,5-Trimethylcyclohexane-1,2-diol.* 3,5,5-Trimethylcyclohexene (155 g., 1.25 moles) was oxidized in exactly the same manner as its isomer, with 159.5 g. of 27% hydrogen peroxide solution (1.27 moles) in 308 ml. of 87% formic acid. There was obtained 167.3 g. (85% yield) of a mixture of geometrical isomers of the glycol (b.p.$_7$ 120–130°). A small amount of material from a center fraction (b.p.$_7$ 124–125°) was recrystallized to yield white needles; m.p. 58.3–58.7°.

*Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.77; H, 11.77.

*2,2,4-Trimethyladipic acid from 3,3,5-trimethylcyclohexane-1,2-diol.* 3,3,5-Trimethylcyclohexane-1,2-diol (158 g., 1.0 mole) was placed with 100 ml. of water in a 3-l. flask fitted with an efficient stirrer and a baffle to aid mixing. The mixture was warmed to 45°, and 400 g. of sodium permanganate in 1800 ml. of water was added, portionwise, with enough cooling to maintain temperature at 45–50°.

The reaction mixture was then made slightly alkaline with 20% sodium hydroxide (about 30 ml. being required), and permanganate solution was added until no more was consumed (about 90 ml. additional required). A small amount of sodium bisulfite was then added (enough to destroy the purple color), and the reaction mixture was filtered, hot, through a Buchner funnel. The filter cake (manganese dioxide) was rinsed with 100 ml. of hot water, then removed from the funnel and leached by boiling with 200 ml. more water, after which it was refiltered. Both batches of filtrate were evaporated (individually) to about one-half volume; they were then cooled and acidified to *p*H 2 with hydrochloric acid. A small amount of carbon dioxide was evolved and the solution became cloudy just before the desired *p*H was reached. The mixtures were held at −5° overnight, to crystallize. The first filtrate yielded 175.5 g. of white crystalline acid and the second filtrate, obtained by leaching the solid manganese dioxide with more water, yielded 10 g. more, corresponding to a 98.7% of crude acids having a neutralization equivalent of 101.1 (theory, 94.11). The acid was recrystallized once from water to yield 170 g. (92% yield) of 2,2,4-trimethyladipic acid; neut. equiv. 94.3, m.p. 100.1 to 100.4°, (lit.[5], m.p. 101.1 to 101.5°).

*Anal.* Calcd. for $C_9H_{16}O_4$: C, 57.42; H, 8.57. Found: C, 57.45; H, 8.58.

*2,4,4-Trimethyladipic acid from 3,5,5-trimethylcyclohexane-1,2-diol.* In exactly the same manner as its isomer, 3,5,5-trimethylcyclohexane-1,2-diol (152.1 g., 0.96 mole) was oxidized to yield 120 g. of crystalline acids from the first filtrate and 15.5 g. from the second filtrate. The total yield was 65.8% of crystalline material having a neutralization equivalent of 97.0 (theory, 94.11). The aqueous layers were combined and upon continuous ether extraction yielded 51.4 g. (28.4%) of oil with a neutralization equivalent of 116.0, bringing the total yield of crude acid up to 94.2%. This oily acid did not crystallize when seeded and held at −5° for 1 week. The crystalline acids were recrystallized once from water and there was obtained 115 g. (63.7% yield) of 2,4,4-trimethyladipic acid having a neutral equivalent of 94.3, m.p. 69.7 to 70.0°, (lit.,[5] m.p. 68.6 to 69.2°).

*Anal.* Calcd. for $C_9H_{16}O_4$: C, 57.42; H, 8.57. Found: C, 57.40; H, 8.56.

*Trimethylcyclopentanones from pure trimethyladipic acids.* The pure 2,2,4- and 2,4,4-trimethyladipic acids were distilled, separately, with barium hydroxide and manganous carbonate as described under 2,2,4,4-tetramethylcyclopentanone. The yields of purified 2,2,4- and 2,4,4-trimethylcyclopentanone were 67% and 78%, respectively, and the properties of these samples were virtually identical with those of the corresponding ketones isolated earlier from their mixture.

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[CONTRIBUTION FROM THE R & E DIVISION, MONSANTO CHEMICAL COMPANY]

# Methylcyclopentadiene Isomers

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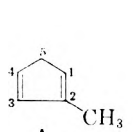
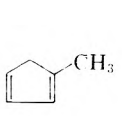
The three methylcyclopentadiene isomers, 1-, 2-, and 5-methylcyclopentadiene were separated by vapor phase chromatography over 2,4-dimethylsulfolane substrate and identified *via* their ultraviolet absorption maxima. Five methylcyclopentadiene dimer isomers were separated by vapor phase chromatography over silicone oil substrate. They were identified as far as the parent monomers are concerned by dimerizing monomer mixtures of known isomer concentration. Composition of the dimer isomers approaches statistical distribution. Infrared spectra of the monomer isomers are included.

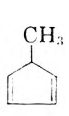
Commercial methylcyclopentadiene is a by-product of thermal cracking of petroleum hydrocarbons. Pyrolysis of the commercial methylcyclopentadiene dimer yields a mixture of isomeric methylcyclopentadienes and some cyclopentadiene. Three isomers of monomeric methylcyclopentadiene are possible: 2-methyl (A), 1-methyl (B), and 5-methylcyclopentadiene (C). Only Diels-Alder adducts of two of these isomers, presumably those of 1-methyl and 2-methylcyclopentadiene have been separated.[2,3] Structures were not as-




A




B




C

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signed with certainty to any of the parent dienes.[3] Attempts to prepare 5-methylcyclopentadiene produced a mixture of the other two monomers. Separation of the pure isomers by vapor phase chromatography over dinonylphthalate substrate was reported by McLean to be unsatisfactory. In the present work the three isomers of methylcyclopentadiene monomer have been separated by vapor phase chromatography and identified.

The two monomeric isomers A and B comprising commercial methylcyclopentadiene (the by-product of thermal cracking) have been successfully resolved using 2,4-dimethylsulfolane substrate. Methylcyclopentadiene monomer obtained by the catalytic dehydrogenation of methylcyclopentane contained beside A and B the third isomer, 5-methylcyclopentadiene, representing only about 3% of the total methylcyclopentadiene monomer. The ratio of the first two isomers was the same as in the methylcyclopentadiene obtained by pyrolyzing the commercial dimer. The distribution of the monomer isomers obtained by dehydrogenating methylcyclopentane is as follows: 2-methylcyclopentadiene 51.7%, 1-methylcyclopentadiene 45.3% and 5-methylcyclopentadiene 3.0%. The three methylcyclopentadiene monomer isomers were identified via the wavelengths of the absorption maxima in their ultraviolet spectra. The absorption maximum of unsubstituted cyclopentadiene is at 240 mμ. It can be predicted on theoretical grounds that the bathochromic shifts of simple substituents in the 1-and 2- positions of the butadienyl system are in the ratio of 3:1.[4] A methyl group in the 1- or 2- position will cause a bathochromic shift of 9 or 3 mμ respectively.[5] Substitution on the saturated carbon atom (5-position) should not increase the wavelength of the absorption maximum. In non alternate ring systems (rings containing odd numbers of carbon atoms) inductive effects may cause a hypsochromic shift, *i.e.*, a decrease of the wavelength of the ultraviolet absorption maximum.

Maxima at 244 and 249.6 mμ were found for the first two isomers. For the third isomer, present only in minor quantities, the exact position of the maximum was obscured by impurities present in the sample. It was between 235 and 240 mμ. Cyclopentadiene absorbed at 240 mμ. The commercial methylcyclopentadiene monomer (a mixture of the first two isomers) absorbed at 247 mμ.[6] Ultraviolet absorptions are summarized in Table I. Infrared spectra of the three monomeric isomers are illustrated in Fig. 1. The spectrum of cyclopentadiene is included for comparison. No isomerization of the monomeric isomers was observed on standing.

TABLE I

ULTRAVIOLET ABSORPTIONS OF THE METHYLCYCLOPENTADIENE MONOMER ISOMERS

| Compound | UV Absorption Predicted | UV Absorption Measured |
|---|---|---|
| 2-Methylcyclopentadiene | 243 | 244 |
| 1-Methylcyclopentadiene | 249 | 249.6 |
| 5-Methylcyclopentadiene | 240 | 235–240 |
| Cyclopentadiene | 240 | 240 |

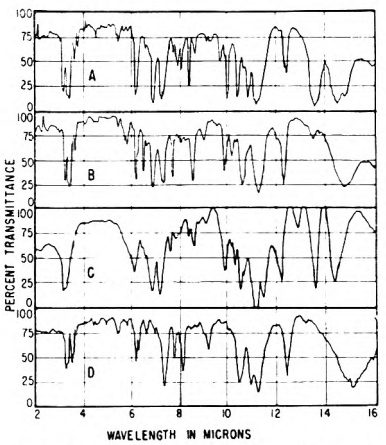


Fig. 1. Infrared spectra of the methylcyclopentadiene isomers and of cyclopentadiene monomer

A = 2-methylcyclopentadiene
B = 1-methylcyclopentadiene
C = 5-methylcyclopentadiene
D = cyclopentadiene

*Dimer isomers.* The dimerization tendency of methylcyclopentadiene is well known. Dimerization is measurable above 0° and it is practically completed within two hours at 60°. Above 172° dedimerization occurs and the monomers are recovered. No dimerization was observed below −20° over a prolonged time, or in very dilute alcoholic solution. A difference was noted in the rates of dimerization at room temperature of 1-methylcyclopentadiene and 2-methylcyclopentadiene; the latter dimerizes faster and the residual monomeric fraction gets richer in 1-methylcyclopentadiene. During five days the ratio of 2-methylcyclopentadiene to 1-methylcyclopentadiene in the residual monomeric fraction decreased from 1.08 to 0.46. This difference of rates was also observed by Craven.[2] The dimerization rate of cyclopentadiene is faster than that of the methylcyclopentadiene isomers.

Methylcyclopentadiene dimer isomers were resolved by vapor phase chromatography with D.C. 550 Silicone Oil on $C_{22}$ Firebrick substrate at 107°. The different dimer isomers were identified as far as the parent monomers are concerned by dimerizing monomer mixtures with known concentrations of the various isomers. By comparing the dimer compositions with the distribution of the monomer isomers in the initial mixture the

(2) W. J. Craven, Ph.D. Thesis, Cornell University, 1955.
(3) S. McLean, Ph.D. Thesis, Cornell University, 1958.
(4) D. Peters, *J. Chem. Soc.*, 1761 (1959).
(5) H. Booker, L. K. Evans, and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940).
(6) J. S. Powell and K. C. Edson, *Anal. Chem.*, 20, 510 (1948).

TABLE II

DISTRIBUTION OF THE METHYLCYCLOPENTADIENE DIMER ISOMERS RESULTING FROM DIMERIZING MONOMER ISOMER MIXTURES OF KNOWN CONCENTRATION

| Monomer Composition before Dimerization Mole % | | | | Composition of the Dimer-Fraction after Dimerization Mole % | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Exp. No. | 2-MCPD[a] (A) | 1-MCPD[b] (B) | CPD[c] (D) | AA | iso-AA (or iso-AB) | BB | AB | AD, BD | DD |
| 1 | 95 | 5 | — | 86.7 | 6.4 | 1.5 | 5.4 | — | — |
| 2 | 80 | 20 | — | 61.7 | 3.2 | 5.9 | 29.2 | — | — |
| 3 | 35 | 65 | | 14.5 | 1.0 | 34.5 | 50.0 | — | — |
| 4 | 51.5 | 45.1 | 3.4 | 33.5 | 6.7 | 18.4 | 37.8 | 2.3 | 1.3 |
| 5 | — | — | 100.0 | — | — | — | — | — | 100.0 |
| | Commercial Dimer (Enjay) | | | 33.6 | 10.2 | 18.6 | 33.4 | 2.5 | 1.7 |

[a] 2-Methylcyclopentadiene. [b] 1-Methylcyclopentadiene. [c] Cyclopentadiene.

identity of the dimer isomers was determined. The composition of the dimer isomers approaches statistical distribution. Slight deviations are due to the higher dimerization rate of 2-methylcyclopentadiene and to the formation of trimers. Five dimer isomers were characterized. They are the simple dimers of cyclopentadiene, 1-methylcyclopentadiene and 2-methylcyclopentadiene, and two "codimers" resulting from the addition of two different monomers (i.e., 2-methylcyclopentadiene + 1-methylcyclopentadiene, and cyclopentadiene + any methylcyclopentadiene isomer). The sixth dimer isomer could be either any isomeric simple dimer of 2-methylcyclopentadiene or less likely any isomeric codimer of 2-methylcyclopentadiene + 1-methylcyclopentadiene (Table II).

The dimers have the same *endo*-dicyclopentadiene skeleton: No attempts were made to locate

the positions of the methyl substituents. The dimer isomers did not have any characteristic absorption in the ultraviolet region. The available quantity of 5-methylcyclopentadiene was insufficient for dimerization studies.

Trimers and higher polymers are formed simultaneously with the dimers. They were observed during the vapor phase chromatographic analyses.

## EXPERIMENTAL[7]

The monomeric isomers were separated with a Perkin-Elmer Vapor Fractometer, Model 154 over 30% tetrahydro-2,4-dimethyl thiophene-1,1-dioxide (2,4-dimethylsulfolane) on $C_{22}$ Firebrick (mesh 30–60) in a 6 ft. long 1/4" stainless steel column at 34°. The carrier gas was helium with 23 ml/min flow rate at 5 p.s.i. inlet pressure. The outlet line of the instrument was equipped with small glass cold-traps cooled to −70° with Dry Ice. Twenty to twenty-five runs with sample sizes from 0.01 to 0.02 ml. gave sufficient material for infrared and ultraviolet analyses. Retention time ratios to cyclopentadiene as standard monomer of the methylcyclopentadiene monomer isomers and other conjugated diolefins over 2,4-dimethylsulfolane at 34° are listed in Table III. At temperatures above 40° the difference in the retention time of methylcyclopentadiene isomers decreases and the resolution declines. The same instrument with the same column and the same carrier gas was used for the separation of the methylcyclopentadiene dimer isomers. 10% D.C. Silicone Oil on $C_{22}$ Firebrick (mesh 40-60) substrate was used at 107° column temperature. Attempts to

TABLE III

RETENTION TIME RATIOS OF METHYLCYCLOPENTADIENE MONOMER ISOMERS AND OTHER CONJUGATED DIOLEFINS OVER 2,4-DIMETHYLSULFOLANE AT 34°

| Compound | Retention Time Ratio |
|---|---|
| Butadiene | 0.22 |
| Isoprene | 0.54 |
| 1-*trans*-3-Pentadiene | 0.71 |
| 1-*cis*-3-Pentadiene | 0.79 |
| Cyclopentadiene | 1.00 (by definition) |
| 2-Methylcyclopentadiene | 2.52 |
| 1-Methylcyclopentadiene | 2.85 |
| 5-Methylcyclopentadiene | 3.29 |

TABLE IV

RETENTION TIME RATIOS OF METHYLCYCLOPENTADIENE DIMER ISOMERS OVER D.C. 550 SILICONE OIL AT 107°

| | Compound | Retention Time Ratio |
|---|---|---|
| DD | Cyclopentadiene dimer | 1.00 (by definition) |
| AD, BD | Cyclopentadiene-methylcyclopentadiene codimer | 1.29 |
| BB | 1-Methylcyclopentadiene dimer | 1.43 |
| AB | 1-Methylcyclopentadiene-2-methylcyclopentadiene codimer | 1.77 |
| AA | 2-Methylcyclopentadiene dimer | 2.10 |
| iso-AA | Isomeric 2-methylcyclopentadiene dimer (?) | 2.52 |

(7) Ultraviolet spectra were obtained in ethanolic solution using a Cary Model 11 Spectrophotometer. Infrared spectra were obtained of the undiluted hydrocarbons employing a Baird Model B Infrared Spectrophotometer. Commercial methylcyclopentadiene was obtained from the Enjay Corporation.

resolve the dimer isomers with 30% D.C. 710 Silicone Oil substrate were unsuccessful. Retention time ratios to cyclopentadiene dimer as standard, of the methylcyclopentadiene dimer isomers over D.C. 550 Silicone Oil at 107° are included in Table IV.

*Dimerization.* Methylcyclopentadiene monomer mixtures of desired composition were kept in a 60° waterbath. Dimerization was practically complete within 2–3 hr.

*Acknowledgments.* The author thanks Donald R. Beaseeker for his contributions in the interpretation of the spectral data, and William D. Ross for his assistance in the vapor phase chromatographic analyses.

EVANSTON, ILL.

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[CONTRIBUTION FROM THE ORGANIC BASIC RESEARCH LABORATORY, THE DOW CHEMICAL COMPANY]

# Preparation of Ketals from 2,2-Dimethoxypropane[1]

N. B. LORETTE AND W. L. HOWARD

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Methods are given for preparing symmetrical and mixed ketals by alkoxyl and ketone interchanges between 2,2-dimethoxypropane and alcohols, ketones, and other ketals. Properties of twenty-one ketals are given.

Acetone dimethyl acetal (2,2-dimethoxypropane) is now readily available[2] and transketalization methods have been developed by which it can be used to prepare a variety of other ketals. The methods comprise interchanging the alkoxyl or ketone groups in a slightly acid medium, and both kinds of groups can, in effect, be interchanged simultaneously in the same mixture. Both symmetrical and mixed ketals, $RR'C(OR'')_2$ and $RR'C(OR'')OR'''$, can be obtained in good yields by proper choice of conditions. Occasional instances of the use of alkoxyl interchange are found in the literature[3] but the reaction does not seem to have been studied extensively. The ketone interchanges are similar to the reactions with orthoesters studied by MacKenzie and Stocker.[3a] Mixed ketals have been obtained previously in isolated instances.[4] The use of 2,2-dimethoxypropane in preparing ketals avoids the necessity of obtaining the less accessible orthoesters or substituted acetylenes required by previous methods.[3]

Acidification of a mixture of 2,2-dimethoxypropane and an alcohol quickly establishes the equilibria (1), (2), and (3).

$$(CH_3)_2C(OCH_3)_2 + ROH \rightleftharpoons (CH_3)_2C(OCH_3)OR + CH_3OH \quad (1)$$

$$(CH_3)_2C(OCH_3)OR + ROH \rightleftharpoons (CH_3)_2C(OR)_2 + CH_3OH \quad (2)$$

$$2(CH_3)_2C(OCH_3)OR \rightleftharpoons (CH_3)_2C(OR)_2 + (CH_3)_2C(OCH_3)_2 \quad (3)$$

By distilling the methanol formed, the position of equilibrium can be shifted far in the direction of the new ketals. Methanol and 2,2-dimethoxypropane form a binary azeotrope (b.p. 61°, 56.5% dimethoxypropane by weight), but this is easily broken by using hexane or benzene as a solvent. With the methanol these hydrocarbons form lower-boiling azeotropes which are practically free of 2,2-dimethoxypropane. By their use the reactions can be brought nearly to completion at moderate temperatures without appreciable loss of 2,2-dimethoxypropane. These azeotrope relations also exist at reduced pressures so that low reaction temperatures can be maintained for preparing heat-sensitive ketals.

The mixed ketals are obtained from reaction (1) by using only one mole of alcohol per mole of 2,2-dimethoxypropane or other ketal. However, the simultaneous occurrence of reaction (3) limits the yield of the mixed ketal. If R is a lower primary alkyl radical, the methoxyl and alkoxyl groups will be distributed statistically as in the redistribution reaction of Calingaert and Beatty[5] and the theoretical yield of mixed ketal will be 50%. With the alkyl radical sterically or electronically considerably different from methyl, yields of the mixed ketals can exceed 50%. The higher symmetrical ketal is a usual by-product of the preparation of the mixed ketal. Two or more moles of alcohol per mole of 2,2-dimethoxypropane give predominantly the symmetrical ketal with small amounts of mixed ketal depending on the completeness of removal of the methanol.

The redistribution in reaction (3) has been demonstrated in both directions with acetone methyl and allyl ketals. The final ratio of mixed to symmetrical ketals was 2:1:1. In a simple mixture of ketals of the same ketone the redistri-

(1) Presented in part at the Gordon Research Conference on Organic Reactions and Processes, July 1958.

(2) The Dow Chemical Company, Midland, Mich.

(3) Reviews are given in (a) C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, **20**, 1695 (1955) and (b) R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, John Wiley and Sons, Inc., New York, 1953, Chap. 8.

(4) (a) C. D. Hurd and M. A. Pollack, *J. Am. Chem. Soc.*, **60**, 1905 (1938); (b) R. Alquier, *Bull. soc. chim.*, **10**, 197 (1943).

(5) G. Calingaert and H. A. Beatty, *Organic Chemistry, An Advanced Treatise*, Vol. II, 2nd ed., H. Gilman, Ed., John Wiley and Sons, Inc., New York, 1947, Chap. 24.

bution of alkoxyl groups occurred rapidly in all of the examples studied. However, when a mixture of acetone dimethyl ketal and cyclohexanone dipropyl ketal was acidified and allowed to stand for thirty minutes before being made basic, distillation of the mixture resulted in almost quantitative recovery of the starting materials. But with methanol added to the mixture under the same conditions, six ketals and propyl alcohol were obtained in approximately the amounts required by the redistribution reaction. This behavior strongly suggests that a protonated alcohol molecule figures prominently in the mechanism of this reaction. The fact that the reaction evidently requires the presence of alcohol when the alkylidene groups are different but not when they are alike is still puzzling.[5a]

Methyl ketals of other ketones are obtained by acidifying a mixture of a ketone, methanol, and 2,2-dimethoxypropane and removing the acetone by distillation as it is formed. The reaction is very slow when care is taken to exclude alcohols or water, but it is fast when methanol is present. The rate increases with alcohol concentration. It therefore appears that the interchange proceeds by the coupled reactions

$$RR'CO + 2CH_3OH \rightleftharpoons RR'C(OCH_3)_2 + H_2O \quad (5)$$

$$H_2O + (CH_3)_2C(OCH_3)_2 \rightleftharpoons 2CH_3OH + (CH_3)_2CO. \quad (6)$$

There is evidence that ketals decompose to some extent to alcohols and unsaturated ethers on acidification,[6,7] reaction (7)

$$RCH_2C(R')(OR'')_2 \longrightarrow RCH{=}C(R')OR'' + R''OH \quad (7)$$

and these traces of alcohol may account for the slow reaction observed when mixtures initially free of alcohol and water are acidified. In its requirement for alcohol this reaction resembles that of orthoesters and ketones.[3a,8] MacKenzie and Stocker propose an elaborate mechanism for the interaction of alcohols, ketones, and orthoesters,[3a] and it is quite possible that some ketal is formed in that way. A similar mechanism may also exist for the reaction of alcohols, ketones, and ketals. However, it is now known that ketals can be prepared in good yield and at least moderate (10–40%) conversion[9] directly from ketones and alcohols. The concept of coupled reactions of hydrolysis of one ketal (or orthoester) by the water resulting from direct formation of another ketal provides an alternate and possibly more likely mechanism for these reactions.

Ketals of ketones other than acetone and alcohols other than methanol can be made in a single reaction mixture by coupling their formation, reaction (8), with the hydrolysis of 2,2-dimethoxypropane, reaction (6). By conducting the reaction in benzene, both acetone and methanol can be simultaneously removed by distillation to shift the equilibrium, because of the proximity of the boiling points of acetone and the benzene–methanol azeotrope. Some mixed ketal, $RR'C(OCH_3)OR''$, may be obtained in this procedure, depending on the equilibrium constant of reaction (8) and the effectiveness of the distillation apparatus. Other interchanges such as reactions (1), (2) and (3) undoubtedly occur simultaneously in this procedure. This reaction closely resembles that of ketones, orthoesters, and alcohols studied by MacKenzie and Stocker.[3a]

$$RR'CO + 2R''OH \rightleftharpoons RR'C(OR'')_2 + H_2O \quad (8)$$

Under acid conditions ketals can be decomposed according to reaction (7)[3a,6,7] and in some cases this reaction occurs at an appreciable rate at temperatures in the vicinity of 50°. Because they boil at low temperatures, the lower unsaturated ethers so produced will distill from the reaction zone and constitute a serious loss if they are formed in appreciable amounts. Both the lower and higher ethers will also polymerize in the presence of acid, especially if R is H. Therefore, the preparative reactions of this paper are best carried out under mild conditions, and the acid catalyst should be neutralized before isolation of the products.

Other ketals than those of acetone or methanol can enter these exchange reactions. Ketals of aliphatic, alicyclic, and aromatic ketones and a variety of alcohols have been used. Other functional groups which are stable to the mild conditions of acidity and temperature used can be present and ketals containing these groups can be produced. Cyclohexanone dimethyl ketal can be obtained in good yield from methanol and cyclohexanone,[9b] and in high yield when the reaction is coupled with the hydrolysis of 2,2-dimethoxypropane. It enters the alcohol interchange reactions readily and is a good starting material for other ketals of cyclohexanone. Dimethyl ketals of acetophenone, butanone, and the pentanones have been prepared and react similarly. Combinations of these ketone and alcohol interchanges thus provide a general method for the preparation of many ketals. The properties and method of preparation of a number of ketals obtained in this way are given in Table I.

(5a) The referee has pointed out that a possible explanation may lie in the relative ease of formation of unsaturated ethers from the ketals involved. Such ethers are possible intermediates in transketalizations of this type.

(6) D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **57**, 544 (1935).

(7) H. P. Crocker and R. H. Hall, *J. Chem. Soc.*, **1955**, 2052.

(8) H. E. Carswell and H. Adkins, *J. Am. Chem. Soc.*, **50**, 235 (1928).

(9) (a) J. H. Brown, Jr., and N. B. Lorette, The Dow Chemical Company, U. S. Patent, **2,827,494**, March 18, 1958. (b) R. E. McCoy, A. W. Baker, and R. S. Gohlke, *J. Org. Chem.*, **22**, 1175 (1957). (c) N. B. Lorette, W. L. Howard, and J. H. Brown, Jr., in press, *J. Org. Chem.*

TABLE I

PREPARATION AND PROPERTIES OF KETALS RR'C(OR'')OR'''

| Ketone | Ketal R'' | Ketal R''' | Method | Yield, % | B.P.° | mm. | $n_D$ (T) | Density g./ml. (T) | $\Delta H_v$[a] kcal./g.-mole | Analyses Calcd. C | Calcd. H | Found[b] C | Found[b] H |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acetone | $CH_3$ | $C_2H_5$ | A[m] | 37 | 54 | 160 | 1.3811 (25) | 0.834 (25) | 8.4 | 61.0 | 11.9 | 61.1 | 11.8 |
| | $C_2H_5$ | $C_2H_5$ | A | 82 | 45 | 60 | 1.3861 (25)[c] | | 9.4 | | | | |
| | $CH_3$ | $C_3H_7$ | B | 34 | 58 | 82 | 1.3902 (25) | 0.835 (25) | 10.8 | 63.6 | 12.2 | 63.8 | 12.1 |
| | $C_3H_7$ | $C_3H_7$ | A (B)[m] | 78 (20) | 78 | 54 | 1.3995 (25)[d] | 0.828 (25) | 11.7 | | | | |
| | $CH_3$ | $C_4H_9$ | B | 34 | 59 | 33 | 1.3980 (25) | 0.836 (25) | 10.9 | 65.7 | 12.4 | 65.6 | 12.5 |
| | $C_4H_9$ | $C_4H_9$ | A | 82 | 89 | 20 | 1.4105 (25)[e] | 0.831 (25) | 13.6 | 70.2 | 12.9 | 70.2 | 13.0 |
| | $CH_3$ | Allyl | B (C) | 66 (48) | 49 | 50 | 1.4040 (24) | 0.859 (22) | 9.8 | 64.6 | 10.8 | 64.8 | 10.8 |
| | Allyl | Allyl | A | 75 | 59 | 20 | 1.4228 (25) | 0.866 (25)[f] | 11.7 | 69.2 | 10.3 | 69.5 | 10.5 |
| | $CH_3$ | $CH_2CH_2Cl$ | A[m] | 37 | 61 | 20 | 1.4219 (25) | 1.022 (25) | | 47.2 | 8.6 | 47.0 | 8.6[g] |
| | $CH_2CH_2Cl$ | $CH_2CH_2Cl$ | A | 70 | 75 | 2 | 1.4513 (24) | 1.132 (24) | | 41.8 | 7.0 | 42.1 | 7.1[h] |
| | $CH_3$ | $CH_2CH_2OCH_3$ | A | 55 | 40 | 8 | 1.4025 (24) | 0.915 (24) | | 56.7 | 10.9 | 56.5 | 10.5 |
| | $CH_2CH_2OCH_3$ | $CH_2CH_2OCH_3$ | A[m] | 27 | 82 | 7 | 1.4123 (24) | 0.959 (25) | | 56.2 | 10.5 | 56.2 | 10.7 |
| Butanone | $CH_3$ | Allyl | B (E)[m] | 41 (14) | 68 | 50 | 1.4146 (24) | 0.867 (24) | 10.9 | 66.6 | 11.2 | 66.7 | 11.2 |
| | Allyl | Allyl | E | 39 | 94 | 50 | 1.4300 (24) | 0.872 (24) | 11.8 | 70.6 | 10.7 | 70.8 | 10.9 |
| 3-Pentanone | Allyl | Allyl | E | 57 | 87 | 20 | 1.4343 (25) | 0.877 (25) | 12.1 | 71.7 | 10.9 | 71.8 | 10.9 |
| Acetophenone | $C_3H_7$ | $C_3H_7$ | E | 63 | 62 | 1[i] | 1.4752 (25) | 0.937 (25) | | 75.6 | 10.0 | 75.7 | 10.0 |
| Cyclopentanone | Allyl | Allyl | E | 53 | 98 | 20 | 1.4535 (24) | 0.930 (24) | 13.5 | 72.5 | 10.0 | 72.5 | 10.2 |
| Cyclohexanone | $CH_3$ | $CH_3$ | D | 95 | 63 | 20 | 1.4370 (25) | 0.947 (25)[j] | 11.2 | | | | |
| | $CH_3$ | $C_3H_7$ | C | 50 | 87.5 | 19 | 1.4388 (22) | 0.922 (25) | | 69.7 | 11.7 | 70.1 | 12.2[k] |
| | $C_3H_7$ | $C_3H_7$ | A | 86 | 103 | 12 | 1.4393 (24) | 0.900 (25) | 13.6 | 71.9 | 12.1 | 72.2 | 12.2 |
| | Allyl | Allyl | E | 74 | 98 | 10 | 1.4633 (24) | 0.936 (24)[l] | 13.6 | | | | |

[a] Heat of vaporization calculated from Cox charts. [b] Average of duplicates which agreed within 0.3%. [c] Lit.[7] b.p. 113°, $n_D^{20}$ 1.3886. [d] Lit.[7] b.p. 91° (95), $n_D^{20}$ 1.4026. [e] Lit.[10] b.p. 64° (3), $n_D^{20}$ 1.4120. [f] Lit.[4a] b.p. 61° (26), $n_D^{20}$ 1.4254, $d_4^{20}$ 0.870. [g] Cl: Calcd. 23.2; found 23.1. [h] Cl: Calcd. 35.3; found 35.1. [i] Lit.[13] b.p. 112–115° (10). [j] Lit.[11] b.p. 54–56° (13), $n_D^{19.2}$ 1.4416, $d_4^{19.2}$ 0.9528. [k] Analyzed 95% pure by vapor chromatography; mass and infrared spectra consistent with assigned structure. [l] Lit.[11] b.p. 106–108° (13), $n_D^{17.5}$ 1.4632, $d_4^{17.5}$ 0.9410. [m] Signifies that ketal was obtained as by-product of indicated method.

## EXPERIMENTAL

*Materials.* Acetone dimethyl acetal (2,2-dimethoxypropane) supplied by The Dow Chemical Company was used as received. The other materials were commercial products. The acid catalyst usually was *p*-toluenesulfonic acid monohydrate (Eastman Kodak Co.). The materials were used without being dried, except that where indicated the *p*-toluenesulfonic acid was dried by recrystallization from a toluene solution. Yields could possibly be improved in some cases by careful drying of the reactants.

*Alcohol interchange with 2,2-dimethoxypropane. Method A. Acetone dibutyl ketal.* Butyl alcohol (489 g., 6.60 moles), 2,2-dimethoxypropane (312 g., 3.00 moles), benzene (1.0 l.), and *p*-toluenesulfonic acid (0.2 g.) were combined and the mixture was distilled with fractionation, giving 570 ml. of distillate boiling from 57° to 59°. Addition of a l. of water to the distillate left 340 ml. of benzene phase, indicating the initial presence of 230 ml. of water-soluble material (theoretical for methanol, 243 ml.). The reaction mixture was cooled and a solution of 0.5 g. of sodium methoxide in 25 ml. of methanol was added rapidly with stirring in order to achieve nearly instantaneous neutralization. Distillation was resumed and the pressure was reduced as necessary so that the temperature in the flask did not exceed 130°. The following fractions were collected for examination: I, b. 36–45° (18 mm.), $n_D^{25}$ 1.3992, 62 g.; II, b. 45–88° (18 mm.), 9 g.; III, b. 88° (18 mm.) to 90° (19.5 mm.), $n_D^{25}$ 1.4105, 460 g.; residue, 31 g. Fraction I was recovered butyl alcohol and fraction III was acetone dibutyl ketal, 82% yield (lit.: b.p. 64.0° (2.3 mm.), $n_D^{20}$ 1.4128;[3a] and b.p. 64–64.5 (3 mm.), $n_D^{20}$ 1.4120[10]).

*Mixed ketals by alcohol interchange. Method B. Butanone allyl methyl ketal.* Allyl alcohol (58 g., 1.0 mole), butanone dimethyl ketal (118 g., 1.00 mole), 200 ml. of benzene, and 0.2 g. of *p*-toluenesulfonic acid were combined and distilled at atmospheric pressure with fractionation until the head temperature was 61° at which time 110 ml. of distillate had been obtained. The distillation was interrupted and the reaction solution was made basic by the addition of 0.3 g. of sodium methoxide dissolved in 10 ml. of methanol. Distillation was continued at atmospheric pressure until the temperature in the flask reached 122°, at which time the pressure was reduced to 100 mm. The following three fractions were obtained (principal component, boiling range at 100 mm., mid-range boiling point, number of moles): butanone dimethyl ketal, 42–68°, 51°, 0.17; butanone allyl methyl ketal, 68–102°, 84°, 0.41; butanone diallyl ketal, above 102°, 111° (third plateau on boiling point curve, distillation stopped), 0.30 (distillate plus residue; the refractive index of the residue at 24° was 1.4310, compared to $n_D^{24}$ 1.4300 for butanone diallyl ketal). The losses comprised 0.12 mole of butanone moiety and 0.25 mole of methoxyl indicating a loss of 0.12 mole of the lower symmetrical ketal, probably by pyrolysis to unsaturated ether. The yield of mixed ketal was 41%, or 82% of the theoretical 0.50 mole predicted by the redistribution reaction.

*Mixed ketals from symmetrical ketals. The redistribution reaction with ketals. Method C.* a. *Acetone allyl methyl ketal.* Acetone dimethyl ketal (208 g., 2.00 moles) and acetone diallyl ketal (312 g., 2.00 moles) were mixed and acidified with 0.1 g. of *p*-toluenesulfonic acid. After 15 min. at 24° the solution was made basic by the addition of 0.3 g. of sodium methoxide dissolved in 10 ml. of methanol. Fractional distillation on a 1000 × 25 mm. column packed with ⅛-in. glass helices gave 99 g. (0.95 mole) of acetone dimethyl ketal boiling at 43° (200 mm.), 250 g. (1.92 moles) of acetone allyl methyl ketal boiling at 81° (200 mm.), and 148 g. (0.95 mole) of acetone diallyl ketal boiling at 77° (50 mm.). The redistribution reaction requires a mole ratio of 1:2:1. The yield of mixed ketal was thus 96%.

b. *Disproportionation of mixed ketals.* Acetone allyl methyl ketal (520 g., 4.00 moles) was acidified with 0.2 g. of *p*-toluenesulfonic acid and allowed to stand for 15 min. at 24°. It was then made basic by adding 0.3 g. of sodium methoxide in 10 ml. of methanol and distilled at 200 mm., giving 103 g. (0.99 mole) of acetone dimethyl ketal boiling at 43° and 262 g. (2.02 moles) of acetone allyl methyl ketal at 81°. The distillation residue ($n_D^{24}$ 1.4233, 161 g.) was shown by infrared spectroscopy to be essentially pure acetone diallyl ketal (1.03 moles).

In a similar manner 4.00 moles of acetone butyl methyl ketal gave 0.98, 1.95, and 0.97 moles of the three ketals. During the acid phase of the reaction a sample withdrawn after 8 min. and made basic had the same infrared spectrum as the final reaction solution which was made basic after 1 hr. The reaction is evidently completed in 8 min. or less.

*Methyl ketals from ketones and 2,2-dimethoxypropane. Method D.* a. *Cyclohexanone dimethyl ketal.* Cyclohexanone (196 g., 2.00 moles), 2,2-dimethoxypropane (250 g., 2.40 moles), 200 ml. of methanol (156 g., 4.87 moles), and 0.05 g. of *p*-toluenesulfonic acid were mixed and distillate was removed as fast as possible through a 1200 × 19 mm. column packed with ⅛-in. glass helices while the head temperature was kept below 58°. The reflux ratio at first was 3:2, but was raised to 19:1 as the distillation progressed. After 268 ml. of distillate had been collected, the head temperature could not be kept below 58° so it was allowed to rise to 63° at which time a total of 298 ml. (236 g.) of distillate (A) had been obtained. The odor of 2,2-dimethoxypropane was very strong in the distillate boiling at 61° (the boiling point of its azeotrope with methanol) indicating its presence in excess at the end of the period of acetone production. The distillation was interrupted and the reaction solution was made basic by the addition of 0.1 g. of sodium methoxide dissolved in 10 ml. of methanol. Distillation was resumed at reduced pressure giving an additional 62 g. of methanol in the receiver and 22 g. in the cold trap. The remaining solution was distilled at about 45 mm. giving the following fractions: I, 27 g., b.p. 68–80° (44 mm.), $n_D^{22}$ 1.4420, [37% cyclohexanone and 63% cyclohexanone dimethyl ketal (by infrared analysis)]; II, 230 g., $n_D^{22}$ 1.4380, b.p. 80° (44 mm.) to 82° (47 mm.), [pure cyclohexanone dimethyl ketal (lit.,[11] b.p. 54–56° (13 mm.), $n_D^{19.2}$ 1.4416)]; III, 25 g., $n_D^{22}$ 1.4390, (distillation residue and column holdup, slightly impure ketal). The distillation was taken to dryness, leaving only the trace residue of salts; fraction III was obtained by allowing the fractionating column to drain back into the flask, adding ether to wash the column, and evaporating the ether on the steam bath. There was a loss of 8 g. The total yield of the ketal was 95%, and 5% of the cyclohexanone was recovered.

The 236 g. of distillate A from the acid solution was redistilled, giving 134 g. boiling from 54–56.5°, 77 g. boiling from 56.5–63.5° (methanol–ketal azeotrope, b.p. 61°), and a residue of 10 g. ($n_D^{22}$ 1.3307, methanol). The azeotrope[12] of acetone and methanol boiling at 55.5° is 88% acetone by weight, indicating 118 g. of acetone in the 134 g. fraction (theor. acetone 116 g.).

b. *The effect of alcohol concentration.* Three moles each of cyclohexanone and 2,2-dimethoxypropane were mixed, acidified with dried *p*-toluenesulfonic acid and allowed to stand for 41 hr. at room temperature. The solution was made basic and distilled on the 1200 × 19 mm. fractionating column. After only 33 ml. had distilled, the material distilling was mainly 2,2-dimethoxypropane, indicating practically no production of acetone. A similar solution, but containing in addition 2 moles of methanol per mole of cyclohexanone, was acidified as before and made basic after 4 hr. Distillation gave a 70% yield of pure cyclohexanone dimethyl ketal and an additional 8% in forerun and residue. Attempts to shift the equilibrium by distilling ace-

(10) H. B. Dykstra, *J. Am. Chem. Soc.*, **57**, 2255 (1935).

(11) B. Helferich and J. Hausen, *Ber.*, **57B**, 795 (1924).

(12) L. H. Horsley and co-workers, *Azeotropic Data*, American Chemical Society, Washington, D. C., 1952, p. 29.

tone from acidified mixtures of cyclohexanone and 2,2-dimethoxypropane, even at reduced pressure and with acid concentrations of the order of 0.001 *M*, resulted in the formation of unsaturated ethers and methanol, and thus made it impossible to keep the reaction mixture free of the alcohol. Yields of 20–50% of the ketal were obtained in these cases, depending on the treatment.

The first 100 ml. of distillate from a mixture of 1.0 mole of acetophenone, 1.5 moles of 2,2-dimethoxypropane, 410 ml. of hexane, and 0.2 g. of *p*-toluenesulfonic acid contained 28% (vol.) of isopropenyl methyl ether and 1.0% acetone, while in a second experiment with the same amounts of ketone and ketal but with 2.0 moles of methanol and only 330 ml. of hexane (to make equal dilutions in both cases) the first 100 ml. of distillate contained 20% acetone and less than 1% isopropenyl methyl ether.

c. *Redistribution with acetone dimethyl ketal and cyclohexanone dipropyl ketal.* An equimolecular mixture of acetone dimethyl ketal (52 g., 0.50 mole) and cyclohexanone dipropyl ketal (100 g.) was acidified with 10 mg. of *p*-toluenesulfonic acid and allowed to stand at 24° for 30 min. It was then made basic by the addition of 100 mg. of sodium methoxide in 5 ml. of methanol. Fractional distillation gave first the azeotrope of methanol and acetone dimethyl ketal, then the remainder of the acetone dimethyl ketal, and finally the cyclohexanone dipropyl ketal. Total recoveries of the two ketals were 96% and 99% respectively. No more than traces of the other possible ketals were shown by either the distillation curves or refractive index measurements.

Another equimolecular mixture of these ketals was made as before and 10 g. of methanol and 10 mg. of *p*-toluenesulfonic acid were added. After 30 min. at 24° the solution was made basic in the same manner. Distillation of the solution gave the following fractions (boiling range, mid-range boiling point, and composition of fraction given): I, 36–40.5° (303 mm.), 39° (303 mm.), azeotrope of methanol and 2,2-dimethoxypropane; II, 40.5–65° (303 mm.), 47° (303 mm.), azeotropes of methanol and propyl alcohol with 2,2-dimethoxypropane; III, 65° (303 mm.) to 50° (81 mm.), 45° (81 mm.), azeotrope of propyl alcohol and acetone methyl propyl ketal; IV, 50–71° (81 mm.), 58° (81 mm.), acetone methyl propyl ketal; V, 71–93° (81 mm.), 88.5° (81 mm.), acetone dipropyl ketal; VI, 93° (81 mm.) to 75° (19 mm.), 60.5° (19 mm.), cyclohexanone dimethyl ketal; VII, 75–87.5° (19 mm.), 87.5° (19 mm.), cyclohexanone methyl propyl ketal; VIII, above 87.5° (19 mm.), ——, residue and column holdup (isolated by washing the packed column with ether and evaporating the ether, and identified as a mixture of the methyl propyl and dipropyl ketals of cyclohexanone by infrared spectroscopy). The mid-range boiling points were taken from well defined plateaus on the distillation curve, except for fraction II which gave no plateau. From the known composition of the azeotropes and by means of infrared spectrophotometric analyses the following recoveries were determined (given in gram-moles): methanol 0.24 (including 0.12 added when inactivating the catalyst), propyl alcohol 0.19, and the six ketals in order of increasing molecular weight 0.14, 0.25, 0.09, 0.15, 0.25, 0.10.

*Ketals from ketone, alcohol, and 2,2-dimethoxypropane. Method E. Acetophenone dipropyl ketal.* A solution of acetophenone (120 g., 1.00 mole), propyl alcohol (480 g., 8.00 moles), 2,2-dimethoxypropane (156 g., 1.5 moles), 300 ml. of hexane, and 0.2 g. of *p*-toluenesulfonic acid was distilled through a 1000 × 25 mm. column packed with 1/8-in. glass helices with the reflux ratio being adjusted so that the head temperature remained below 50°. After each 150–200 ml. of distillate was obtained, an equal volume of hexane was added to the boiling solution until 530 ml. of distillate had been collected. The still-head temperature then slowly rose to 64° at which time the total distillate volume was 770 ml. The reaction mixture was made basic by rapidly adding 0.2 g. of sodium methoxide in 10 ml. of methanol. Distillation was resumed and the pressure was reduced as necessary in order to keep the temperature in the flask below 100–110°. After a forerun which included some acetone dipropyl ketal, a residue of 190 ml. ($n_D^{25}$ 1.4820) remained. After two distillations through a 3-in. column packed with Berl saddles, this residue gave 141 g. of acetophenone dipropyl ketal, b.p. 61° (1 mm.), $n_D^{25}$ 1.4750, 63% yield (lit.[13] b.p. 112–115° (10 mm.)).

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FREEPORT, TEX.

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[CONTRIBUTION FROM THE ORGANIC BASIC RESEARCH LABORATORY, THE DOW CHEMICAL COMPANY]

# Ketals of Monohydric Secondary Alcohols[1]

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Alkoxyl interchange between secondary alcohols and simple ketals gives ketals containing secondary alkoxyl groups in good yields. Such ketals can also be made by the addition of secondary alcohols to $\alpha,\beta$-unsaturated ethers and by disproportionation reactions. Ketals with secondary alkoxyl groups can be prepared directly from ketones and secondary alcohols by coupling the reaction with the hydrolysis of another ketal. Mixed ketals in which the alkoxyl groups may be either both secondary or only one secondary and one primary can also be made by these methods.

The preparation of ketals of primary alcohols by alcohol interchange reactions with dimethyl ketals has been discussed in a previous paper.[2] This reaction has now been extended to include the preparation of ketals of monohydric secondary alcohols. There are two previous references in the literature to the successful preparation of ketals of this type. Stevens, McLean, and Weinheimer[3] obtained relatively unstable $\alpha$-hydroxyketals by

(1) Presented in part at the Gordon Research Conference on Organic Reactions and Processes, July 1958.

(2) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1960).

(3) C. L. Stevens, R. L. McLean, and A. J. Weinheimer, *Chem. & Ind.* (London), **1957**, 1321; *J. Am. Chem. Soc.*, **80**, 2276 (1958).

the addition of secondary alcohols to epoxyethers. These authors pointed out that this reaction is an alcohol interchange with an intramolecular ketal, and they ascribed the driving force for the reaction to the opening of the epoxide ring. Reichle has obtained diisopropyl ketals from cyclic ketones and triisopropyl orthoformate.[4] A recent patent[5] states that secondary and tertiary alcohols will react with allene to form the corresponding acetone ketals, but no examples of such compounds are given. Also without examples, an older patent[6] states that ketals can be formed with secondary alcohols. Other attempts to prepare ketals with secondary alkoxyl radicals were not successful.[7]

In the interchange reaction with secondary alcohols, ketals of primary alcohols give symmetrical ketals of the secondary alcohols and mixed ketals containing one secondary and one primary alkoxyl group. Mixed ketals in which the different alkoxyl groups are both secondary can be prepared by alcohol interchange with a symmetrical ketal and a secondary alcohol or by disproportionation between two symmetrical ketals, Reaction 1.

$$R_2C(OR')_2 + R_2C(OR'')_2 \rightleftharpoons 2R_2C(OR')OR'' \quad (1)$$

No special driving force for the alcohol interchange reaction is needed other than that provided by the removal of the by-product alcohol by distillation. The equilibrium of Reaction 1 is rapidly attained after the addition of a trace of strong acid.

The addition of alcohols to $\alpha,\beta$-unsaturated ethers to give ketals has been demonstrated with secondary alcohols. The product ketal may contain one primary and one secondary alkoxyl group, or both alkoxyl groups may be secondary, depending on the nature of the alkoxyl group in the ether. Symmetrical ketals are obtained along with the mixed ketals because of the simultaneous occurrence of the disproportionation Reaction 1. The yields of ketals by this method have been shown to be nearly quantitative both by isolation of the reaction products and by infrared spectroscopy. An absorption band (6.1$\mu$) due to the carbon-carbon double bond of the ether almost completely disappears, and the spectrum of the ketal appears. The loss of the 6.1-$\mu$ absorption band was demonstrated with mixtures of the following ethers and alcohols: 1-cyclohexen-1-yl methyl and ethyl ethers, isopropenyl methyl, ethyl, and propyl ethers, and isopropyl, *sec*-butyl, 2-pentyl, and cyclohexyl alcohols. Disappearance of the 6.1-$\mu$ absorption band and appearance of the spectrum of a known ketal occurred with cyclohexyl isopropenyl ether and cyclohexanol, isopropenyl methyl ether and isopropyl alcohol, and 1-cyclohexen-1-yl methyl ether and isopropyl alcohol. These properties also served to identify 1-cyclohexen-1-yl isopropyl ether (not isolated) as the principal constituent of a distillate fraction obtained in the forerun during the preparation of cyclohexanone diisopropyl ketal by alcohol interchange. The addition reaction did not occur with *t*-butyl alcohol.

The readily available ketals, 2,2-dimethoxypropane[8] and 1,1-dimethoxycyclohexane,[2,9] were usually used as starting materials for the alcohol interchange reactions, and the methanol produced was removed azeotropically with hexane or benzene.[2] In general, equilibrium concentrations of the methanol and product ketals have been lower, thus necessitating more tedious distillations, than in the preparation of ketals of primary alcohols. For this reason somewhat lower than the best attainable yields have been accepted to avoid long reaction times. Decomposition to unsaturated ethers is more serious when the ketals contain secondary alkoxyl groups, and conversions to these ethers are greater and lead to greater losses during long distillations from acid solutions. The ethers can often be recovered, however, and used in addition reactions to prepare the same or other ketals. The product ketals were isolated and purified by distillation from alkaline media, or in some cases by crystallization.

In the preparation of mixed ketals yields of mixed and symmetrical ketals usually were in approximate accord with the requirements of the redistribution reaction of Calingaert and Beatty,[10] when the alkoxyl radicals were both secondary (isopropyl and cyclohexyl). When they were not of the same order (methyl and isopropyl) the disproportionation equilibria favored the mixed ketal. This is further evidence of the relatively greater difficulty of formation of ketal groupings with secondary alcohols and the greater stability of primary alkoxyl groups in ketal linkage.

Interchange of ketone groups, similar to alcohol interchange, probably does not occur directly at an appreciable rate although an apparent transketonation can be accomplished if alcohol is present. When equimolar amounts of acetone diisopropyl ketal, cyclohexanone, and isopropyl alcohol were acidified and kept for thirty minutes at room temperature, infrared analysis showed the appearance of cyclohexanone diisopropyl ketal and acetone in considerable amounts. However, when equimolar amounts of acetone diisopropyl acetal and cyclohexanone, without alcohol, were treated in the same manner, no cyclohexanone diisopropyl ketal

(4) W. T. Reichle, *Dissertation Abstr.*, **19**, 3134 (1959); private communication.

(5) E. U. Elam and R. H. Hasek, Eastman Kodak Co., U. S. Patent **2,875,252**, February 24, 1959.

(6) W. H. Carothers and H. B. Dykstra, E. I. du Pont de Nemours and Co., U. S. Patent **2,124,686**, July 26, 1938.

(7) C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, **20**, 1695 (1955).

(8) 2,2-Dimethoxypropane is available from The Dow Chemical Co., Midland, Mich.

(9) R. E. McCoy, A. W. Baker, and R. S. Gohlke, *J. Org. Chem.*, **22**, 1175 (1957).

(10) G. Calingaert and H. A. Beatty, *Organic Chemistry, an Advanced Treatise*, Vol. II, 2nd ed., H. Gilman, Ed., John Wiley & Sons, New York, 1947, Chap. 24.

was detectable in the spectrum after thirty minutes. Absorptions due to small amounts of isopropenyl isopropyl ether and isopropyl alcohol were present, however, and the intensity of absorptions due to acetone diisopropyl ketal had decreased. After 130 minutes absorption shoulders due to cyclohexanone diisopropyl ketal had begun to appear and they were stronger after 190 minutes. At least part of the observed slow formation of the cyclohexanone ketal can be accounted for by the presence of isopropyl alcohol from the decomposition of the acetone ketal indicated by the spectrum after thirty minutes, since it has been shown that the cyclohexanone ketal is formed rapidly when an equimolar amount of isopropyl alcohol is present; and this also indicates that its rate of formation depends on the alcohol concentration. Evidently the cyclohexanone ketal is formed only slowly if at all by direct interchange. From measurements of the ultraviolet absorption spectra of acidified mixtures of several ketones and isopropyl alcohol, Wheeler concluded that no reaction occurred.[11] The apparent transketonation just described indicates that ketones and secondary alcohols do react to form ketal and water to a small extent, and that coupling of this reaction with the hydrolysis of another ketal to remove water will provide enough driving force to shift the equilibrium of ketal formation considerably in the direction of ketal. We believe that this is the first evidence of the existence of the reaction of formation of a ketal directly from a ketone and a monohydric secondary alcohol.

As with ketals of primary alcohols,[2] ketals of secondary alcohols can be prepared by the simultaneous reaction of a ketone, a secondary alcohol, and another ketal such as 2,2-dimethoxypropane or 1,1-dimethoxycyclohexane. A mixture of cyclohexanone, isopropyl alcohol, and 2,2-dimethoxypropane gave yields of 57% of cyclohexanone isopropyl methyl ketal and 17% of cyclohexanone diisopropyl ketal. A number of concurrent and interrelated reactions (2) undoubtedly occur in

$$R(OCH_3)_2 + i\text{-}C_3H_7OH \rightleftharpoons R(OCH_3)(O\text{-}i\text{-}C_3H_7) + R(O\text{-}i\text{-}C_3H_7)_2 + CH_3OH \quad (2)$$

$$R'{=}O + CH_3OH \rightleftharpoons R'(OCH_3)_2 + H_2O$$
$$R'{=}O + i\text{-}C_3H_7OH \rightleftharpoons R'(O\text{-}i\text{-}C_3H_7)_2 + H_2O$$
$$R'(OCH_3)_2 + i\text{-}C_3H_7OH \rightleftharpoons R'(OCH_3)(O\text{-}i\text{-}C_3H_7) + R'(O\text{-}i\text{-}C_3H_7)_2 + CH_3OH$$
$$H_2O + R(O\text{-}i\text{-}C_3H_7)_2 \rightleftharpoons R{=}O + i\text{-}C_3H_7OH$$
$$H_2O + R(OCH_3)_2 \rightleftharpoons R{=}O + CH_3OH, \text{ etc.}$$

(R = isopropylidene; R′ = cyclohexylidene)

this mixture and ultimately lead to the isopropyl ketals of cyclohexanone. The water produced is consumed by the hydrolysis of the acetone ketals, and the equilibria are shifted in the direction of the cyclohexanone isopropyl ketals by the removal of acetone and methanol by distillation. This is a convenient preparative method which utilizes readily available starting materials.[8,9]

All of the ketals of secondary alcohols so far prepared undergo the same endothermic hydrolysis that is characteristic of the ketals of primary alcohols. Examination of the hydrolyzates from the hydrolytic degradation of two of these ketals showed only the ketone and alcohol, thus providing additional evidence for the acetal structure. The hydrolysis was essentially quantitative with the stoichiometric amount of water at room temperature, indicating a large hydrolysis constant and thus a very small constant for the reverse reaction of ketal formation. This observation corroborates Wheeler's failure to detect the reverse reaction with isopropyl alcohol and ketones[11] and suggests that the reason was lack of sensitivity of his method.

Suitable combinations of these preparative reactions and those of our previous paper[2] afford methods for the convenient preparation of many ketals of secondary alcohols from readily available starting materials. Table I gives the properties of some of these ketals which have already been obtained.

## EXPERIMENTAL

*Materials.* Acetone dimethyl acetal (2,2-dimethoxypropane) supplied by The Dow Chemical Co. was used as received. Cyclohexanone dimethyl acetal was prepared from methanol and cyclohexanone directly[9] or with added 2,2-dimethoxypropane.[2] The *p*-toluenesulfonic acid was used as the monohydrate (Eastman Kodak Co.) except where noted. The other materials were commercial products and were used without drying. The isopropyl alcohol used contained 0.2% water.

*Alcohol interchange. Method A. a. Acetone isopropyl methyl and acetone diisopropyl ketal.* A solution composed of 832 g. (8.00 moles) of 2,2-dimethoxypropane, 1349 g. (23.2 moles) of isopropyl alcohol, 3500 ml. (2403 g.) of hexane, and 0.05 g. of *p*-toluenesulfonic acid was set for distillation through a glass Oldershaw fractionating column approximately 1 meter long and having 30 trays. The column was fitted with a magnetically controlled liquid-dividing take-off head actuated by an electric timer. The timer was powered by a Wheelco "Capacitrol" arranged to respond to the temperature in the still head. The Capacitrol was set to operate the timer and thus remove distillate at head temperatures below 50°, in order to collect the azeotrope of methanol and hexane, b.p. 48°. At first a reflux ratio of 10 was satisfactory but it soon had to be increased to 20 and then to 50. Finally, with the timer set at 2% take-off, distillate was collected intermittently whenever the temperature in the still head fell below 50° and actuated the timer through the Capacitrol. The distillation required 13 days and 1866 g. of distillate was collected before the rate of distillation was deemed impracticably slow and the process stopped. The solution was cooled and 0.4 g. of sodium dissolved in 24 g. of isopropyl alcohol was added.

The mixture was then distilled through a 1200 × 19 mm. column packed with 1/8-in. glass helices and fitted with a vapor-dividing head with similar automatic controls. The azeotrope of hexane and isopropyl alcohol was first obtained (boiling range 57–65°), and during the distillation an additional 2 l. of hexane was added to accomplish the removal of the remaining alcohol. The distillation was finished at reduced pressure, finally giving the three fractions: (a) 31 g. boiling from 53° (350 mm.) to 47.5° (164 mm.), (b) 91 g. boiling from 47.5° (164 mm.) to 63° (52 mm.), (c) 798 g.

(11) O. H. Wheeler, *J. Am. Chem. Soc.*, 79, 4191 (1957).

TABLE I

PROPERTIES OF KETALS $R_2C(OR')OR''$

| Ketone | Ketal R′ | Ketal R″ | Method | Yield, % | B.P. °C. | mm. | $n_D$ (T) | Density g./ml. (T) | Analyses Calcd. C | Calcd. H | Found[a] C | Found[a] H |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acetone | $CH_3$ | *i*-$C_3H_7$[b] | C | 42 | 47 | 68 | 1.3882 (25) | 0.833 (25) | 63.6 | 12.2 | 63.6 | 12.2 |
| Acetone | *i*-$C_3H_7$ | *i*-$C_3H_7$[c] | A | 65 | 62 | 50 | 1.3987 (23) | 0.827 (25) | 67.5 | 12.6 | 67.4 | 12.4 |
| Acetone | $CH_3$ | *sec*-$C_4H_9$[d] | A | 38 | 61 | 50 | 1.3986 (25) | 0.836 (25) | 65.7 | 12.5 | 65.8 | 12.6 |
| Acetone | *sec*-$C_4H_9$ | *sec*-$C_4H_9$ | A | 10 | 67 | 12 | 1.4122 (25) | 0.833 (25) | 70.2 | 12.9 | 70.2 | 12.9 |
| Acetone | *i*-$C_3H_7$ | *cy*-Hex[e] | B | 39 | 116–118 | 41 | 1.4383 (24) | 0.896 (25) | 71.9 | 12.1 | 72.0 | 12.1 |
| Acetone | *cy*-Hex | *cy*-Hex[f] | A | 49 | 110–115 | 3 | 1.4673 (24) | 0.950 (25) | 75.0 | 11.7 | 75.1 | 11.9 |
| Cyclohexanone | $CH_3$ | *i*-$C_3H_7$ | A[g] | 57 | 68 | 8 | 1.4390 (24) | 0.918 (24) | 69.7 | 11.7 | 69.8 | 11.8 |
| Cyclohexanone | *i*-$C_3H_7$ | *i*-$C_3H_7$ | A[g] | 33 | 85 | 8 | 1.4410 (24) | 0.905 (24) | 72.0 | 12.1 | 72.2 | 12.0 |
| Cyclohexanone | *cy*-Hex | *cy*-Hex[h] | A | 29 | 150–160 | 3 | 1.4903 (26) | — — | 77.1 | 11.5 | 77.1 | 11.6 |

[a] Average of duplicates. [b] Heat of vaporization, $\Delta H_v$, 9.6 kcal./g. mole. [c] $\Delta H_v$, 11.1 kcal./g. mole. [d] $\Delta H_v$, 10.4 kcal./g. mole. [e] Mol. wt.: calcd. 200, found 198 (cryo.). [f] M.p. 25°; density and refractive index values are for supercooled liquid; mol. wt.: calcd. 240, found 236 (cryo.). [g] For yields by method D, see text. [h] M.p. 43–43.5°; refractive index value for supercooled liquid; isolated by crystallization.

boiling at 63–64.5° (52 mm.), $n_D^{23}$ 1.3987, and 27 g. of residue. Fractions a and b and the residue were combined, 100 ml. of hexane and 50 ml. of *cis*-decalin were added, and the mixture was washed with water and dried. Distillation of this solution gave two fractions (d) 35 g. boiling from 41–50° (51 mm.), $n_D^{22}$ 1.3909, and (e) 21 g. boiling from 50–67° (51 mm.), $n_D^{22}$ 1.3988.

Fractions c and e were identified as acetone diisopropyl ketal, yield 819 g. (5.12 moles) or 65% based on 7.85 moles of 2,2-dimethoxypropane (8.00 moles less 0.15 mole for the amount of water introduced with the isopropyl alcohol). Fraction d was acetone isopropyl methyl ketal, 0.27 mole, 3.4%. In other runs in which the distillation of the hexane-methanol azeotrope was carried on for only 3–4 days, yields of the two ketals were each about 30%. Benzene is not so satisfactory as hexane as the azeotroping agent in this process because it leads to increased losses of isopropenyl isopropyl ether whose boiling point is near that of the benzene-methanol azeotrope.

All of the distillate fractions were collected and worked up. Of 6194 g. of material taken, 5624 g. was recovered and 570 g. lost. Alcohols were washed from the hexane distillates with water and recovered by distillation, yielding 10.3 moles of methanol and 11.4 moles of isopropyl alcohol. By difference, unrecovered isopropyl alcohol was 11.4 moles. Isopropenyl methyl ether, 1.40 moles (17.8% on the same basis as for the ketals), was recovered from the hexane-methanol distillate. No 2,2-dimethoxypropane was recovered.

*b. Acetone cyclohexyl isopropyl ketal and cyclohexyl isopropenyl ether.* One mole each of acetone diisopropyl ketal (160 g.) and cyclohexanol (100 g.) were added to 500 ml. of hexane and acidified with 0.05 g. of *p*-toluenesulfonic acid. The solution was fractionally distilled at atmospheric pressure, giving 362 g. of distillate of boiling range 57–61°. (Sixty g. of isopropyl alcohol was obtained as its azeotrope with water[12] by washing this distillate with water and distilling the aqueous phase.) The reaction solution was then cooled and made basic by the instantaneous addition of 0.1 g. of sodium methoxide in 10 ml. of methanol. Distillation was resumed and the remaining hexane was removed, first at atmospheric and finally at reduced pressure to keep the flask temperature below 100°. Two forerun fractions consisted of 16 g. of acetone diisopropyl ketal, b.p. 47–56° (25 mm.), $n_D^{22}$ 1.4013, and 37 g. of a mixture, b.p. 56° (25 mm.) to 86° (12 mm.), $n_D^{22}$ 1.4507, which was mainly cyclohexyl isopropenyl ether with a small amount of cyclohexanol (determined by infrared spectroscopy). The next fraction boiling at 87.5° (13 mm.), $n_D^{22}$ 1.4398, was 30.5 g. of acetone cyclohexyl isopropyl ketal. The distillation was stopped overnight but the system remained under vacuum.

When the distillation was resumed 34 g. of material distilled at 50° (11 mm.), $n_D^{22}$ 1.4519, $d_{25}$ 0.893 g./ml., and was identified as cyclohexyl isopropenyl ether. Another 4 g., b.p. 50–55° (11 mm.), $n_D^{22}$ 1.4542, distilled leaving a dry flask. A residue of 41 g. was obtained as column holdup. Evidently a pyrolysis had occurred. A similar unpredictable pyrolysis was observed in other runs, usually occurring spontaneously during the distillation of the ketal and making it impossible to continue the distillation.

The yield of acetone cyclohexyl isopropyl ketal was 15% by this procedure, or 30% of the amount predicted by the redistribution reaction. In a similar experiment with half-mole quantities of the reactants, the residue after the removal of the hexane was separated into two crude fractions by rapid distillation at room temperature, first at 25 mm. and finally at 1 mm., with a final short heating to 50°. Analysis of these fractions and the residue by infrared spectroscopy showed the presence of 0.22 mole of acetone cyclohexyl isopropyl ketal and 0.10 mole of acetone di-

(12) L. H. Horsley and co-workers, *Azeotropic Data*, American Chemical Society, Washington, D. C., 1952, p. 7.

cyclohexyl ketal. The redistribution reaction predicts 0.25 and 0.125 mole, respectively. Fractional distillation of the residue, which contained the cyclohexyl ketals, gave 25 g. of the mixed ketal before pyrolysis interfered, making the isolated yield 25%.

*Identification of cyclohexyl isopropenyl ether.* The following data identify the material of the preceding experiment, b.p. 50° (11 mm.), as cyclohexyl isopropenyl ether.

*Anal.* Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50; mol. wt., 140. Found: C, 76.93, 77.25; H, 11.54, 11.80; mol. wt., 143 (cryo.).

Calculated as the ether, 0.005 mole (0.70 g.) of the unknown was added to 0.005 mole (0.50 g.) of cyclohexanol and the solution was acidified with a trace of *p*-toluenesulfonic acid. An exothermic reaction occurred, and the product solidified when placed in the refrigerator, remelting over a range ending at about 22° (melting point of acetone dicyclohexyl ketal, 25°). The infrared spectrum of the product mixture was essentially the same as that of acetone dicyclohexyl ketal, band for band, except that trace absorptions corresponding to the strongest bands of cyclohexanol indicated about 1–2% of this impurity. Absence of absorptions at 6.06, 7.8, and 12.6 $\mu$, all characteristic of the ether, showed that conversion of the ether was practically quantitative.

*Mixed ketals by disproportionation of symmetrical ketals. Method B. a. Acetone cyclohexyl isopropyl acetal.* Half-mole quantities of acetone diisopropyl ketal (80 g.) and acetone dicyclohexyl ketal (120 g.) were combined and acidified with 0.05 g. of *p*-toluenesulfonic acid dissolved in 10 ml. of isopropyl alcohol. The mixture soon became quite pink and then faded to a yellowish color during about 20 min. at room temperature (*cf.* MacKenzie and Stocker[7]). The acid catalyst was then neutralized by the rapid addition of a solution of 0.1 g. of sodium methoxide in 10 ml. of methanol. Fractional distillation of the mixture gave 35 g. of acetone diisopropyl ketal, b.p. 44–64° (36 mm.), $n_D^{24}$ 1.3978; 24 g. of unidentified material, b.p. 64–114° (36 mm.), $n_D^{24}$ 1.4471; 77.5 g. of acetone cyclohexyl isopropyl ketal, b.p. 116–118° (41 mm.), $n_D^{24}$ 1.4383; and a residue of 48 g. of acetone dicyclohexyl ketal, $n_D^{25}$ 1.4650 (estimated nearly pure by infrared spectroscopy). The ketals were isolated in approximately the mole ratio required by the redistribution reaction, 1.1:2.0:1.0, but the recoveries were only about 80%.

*b. Disproportionations involving both primary and secondary alkoxyl groups.* Acetone isopropyl methyl ketal (142 g., 1.07 moles) was acidified with 0.01 g. of solid *p*-toluenesulfonic acid. Discoloration occurred in the vicinity of the crystals as they dissolved, but there was little further darkening of the solution. The refractive index was the same (1.3882) before, directly after, and 5 days after the addition of the acid. After 5 days at room temperature (about 24°) 0.05 g. of solid sodium methoxide was added and the mixture was distilled. The following fractions were obtained: (a) acetone dimethyl ketal, 21 g., b.p. 41–48° (205 mm.), $n_D^{24}$ 1.3767; (b) transition, 13 g., b.p. 48–73° (205 mm.), $n_D^{24}$ 1.3844; (c) acetone isopropyl methyl ketal, 61 g., b.p. 73–74° (205 mm.), $n_D^{24}$ 1.3890; transition, 7 g., b.p. 40–59° (40 mm.), $n_D^{24}$ 1.3954; (d) acetone diisopropyl ketal, 6 g., b.p. 59° (40 mm.), $n_D^{24}$ 1.3981; and (e) residue. The residue was distilled without fractionation and gave an additional 20 g. of acetone diisopropyl ketal, b.p. 61.5° (42 mm.), $n_D^{24}$ 1.3984. The cold trap contained 11 g. of material identified as a mixture of isopropenyl methyl ether and isopropyl alcohol. Estimating the compositions of the transition fractions by linear interpolation of refractive indices and summing gives a mole ratio of the ketals of 1.0:2.2:0.65 which deviates somewhat from the 1:2:1 required by the redistribution reaction and, considering also the material in the cold trap, favors the mixed ketal.

In another experiment equimolar amounts of cyclohexanone dimethyl ketal (1.44 g.) and cyclohexanone diisopropyl ketal (2.00 g.) were mixed and acidified with a few crystals of *p*-toluenesulfonic acid. After 3 hr. at room temperature the infrared spectrum of the mixture was determined and compared with the spectra of mixtures of known concentrations of the three possible ketals, made up from the pure materials and adjusted to be equimolar in the symmetrical ketals. The spectrum of the acidified mixture closely matched that of the known sample in which the mole ratio of cyclohexanone dimethyl, isopropyl methyl, and diisopropyl ketals was 1.0:4.7:1.0, showing considerable deviation from the 1:2:1 requirement of the redistribution reaction. Acidification of a sample of cyclohexanone isopropyl methyl ketal gave the same spectrum after 30 min. at room temperature, demonstrating attainment of the equilibrium from the other direction. The spectra of the acidified mixtures differed from that of the known mixture in having absorption bands due to small amounts of hydroxyl, carbonyl, and unsaturation (6.06 $\mu$).

*Addition of secondary alcohols to unsaturated ethers. Method C. a. Acetone isopropyl methyl ketal.* Isopropenyl methyl ether (60 g., 0.83 mole) was added dropwise to isopropyl alcohol (120 g., 2.0 moles) acidified with 0.035 g. of *p*-toluenesulfonic acid. External cooling was used to keep the temperature below 20° and the addition required about 30 min. The mixture was then made basic by the instantaneous addition of a solution of 0.05 g. of sodium methoxide in 5 ml. of methanol. The reaction product was washed with 600 ml. of water in three portions, and separation gave 82.5 g. of organic phase. The aqueous solution was extracted with 100 ml. of 45–60° petroleum ether which was separated and combined with the first organic phase. After being dried with potassium carbonate, the ether solution was distilled, giving 18.5 g. of acetone dimethyl ketal, 46.5 g. (42%) of acetone isopropyl methyl ketal, b.p. 45°/59 mm., $n_D^{25}$ 1.3876, and 31 g. of residue identified by refractive index, $n_D^{25}$ 1.3977, as acetone diisopropyl ketal.

*b.* The preparation of *acetone dicyclohexyl ketal* by this method has been given in connection with the identification of cyclohexyl isopropenyl ether. It can be isolated by crystallization from acetone or methanol at low temperature, m.p. 25°

*Simultaneous reaction of ketone, secondary alcohol, and a ketal. Method D. a. Evidence for the coupling of the reaction of formation of one ketal and the hydrolysis of another.* Equimolar amounts of cyclohexanone (2.0 g.), isopropyl alcohol (1.2 g.), and acetone diisopropyl ketal (3.2 g.) were mixed and the solution was divided into two parts. One part was used as a control sample, and the other was acidified with a small amount of *p*-toluenesulfonic acid and its infrared spectrum was determined after 30 min. Comparison of this spectrum and that of the control with those of authentic samples showed the following compositions by volume: found in the control sample, 23% cyclohexanone, 48% acetone diisopropyl ketal (calcd. from the amounts taken, 28.6% and 50.6% respectively), no acetone, no ketal of cyclohexanone; found in the acidified sample, 29% cyclohexanone diisopropyl ketal and 16% acetone diisopropyl ketal. Acetone and cyclohexanone were both present in the acidified sample, but they were not determined for want of unobstructed absorption bands in the spectrum.

To determine whether acetone diisopropyl ketal and cyclohexanone react at an appreciable rate by a direct interchange, an equimolar mixture of cyclohexanone (4.0 g.) and acetone diisopropyl ketal (6.5 g.) was made up and divided as before. One part was acidified with a similar amount of *p*-toluenesulfonic acid which had been dissolved in boiling toluene, further boiled, recrystallized by cooling, and stored under petroleum ether. Infrared spectra were determined on samples of this solution after 30, 130, and 190 min. The spectrum of the control indicated 38% (vol.) cyclohexanone (13.4 $\mu$) and 62% acetone ketal (11.4 $\mu$). The acidified sample after 30 min. still contained 38% cyclohexanone, but the acetone ketal had decreased to 48% and new bands at 6.06 and 7.8 $\mu$ and at 10.5 $\mu$ indicated 9% isopropenyl isopropyl ether and 6% isopropyl alcohol. Strong bands at 8.05, 8.7, and 9.3 $\mu$ characteristic

of cyclohexanone diisopropyl ketal were absent. In the spectrum after 130 min. weak absorption bands due to the cyclohexanone ketal had appeared and the absorption bands of cyclohexanone and the acetone ketal had become weaker. These trends continued in the same direction in the spectrum of the 190-min. sample, in which the concentration of cyclohexanone diisopropyl ketal was estimated at about 10%.

*b. Cyclohexanone isopropyl methyl ketal and cyclohexanone diisopropyl ketal.* A solution of cyclohexanone (98 g., 1.0 mole), isopropyl alcohol (264 g., 4.40 moles), 2,2-dimethoxypropane (125 g., 1.20 mole), benzene (250 ml.), and *p*-toluenesulfonic acid (0.05 g.) was distilled on a good fractionating column at a pressure of 270 mm. with automatic controls set to remove distillate when the temperature in the still head was below 34°. After about 24 hr. this temperature could not be maintained with a 50:1 reflux ratio, so the distillation was stopped. The volume of the distillate was 226 ml. and contained 109 ml. of water-soluble material. The reaction solution was made basic by adding a solution of 0.1 g. of sodium in 20 ml. of isopropyl alcohol. Infrared analysis showed that less than 2% of the cyclohexanone remained unchanged. Distillation was resumed and after 412 ml. of forerun had distilled, 99 g. (57.5%) of cyclohexanone isopropyl methyl ketal was obtained in the boiling range 47–70° (8 mm.), $n_D^{24}$ 1.4388. The residue was identified by infrared spectroscopy as practically pure cyclohexanone diisopropyl ketal, yield 34 g. (17%). Similar yields were obtained using hexane as solvent instead of benzene.

*Hydrolytic degradation.* Equimolar amounts of acetone di-*sec*-butyl ketal (11.5 g.) and water (1.10 g.) were mixed and acidified with a tiny crystal of *p*-toluenesulfonic acid introduced on the bulb of a thermometer. The temperature began to decrease and the mixture suddenly became homogeneous. The infrared spectrum of the solution, determined after 30 min., indicated the presence of 29% (vol.) acetone and 70% *sec*-butyl alcohol (calcd., 29% and 71%). None of the absorption bands of the ketal was present.

Cyclohexanone dicyclohexyl ketal was hydrolyzed in an equal weight of purified dioxane with a 10% excess of water, and the infrared spectrum of the solution was determined. Absorption bands characteristic of cyclohexanol and cyclohexanone were present, but the bands of the ketal were absent.

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[CONTRIBUTION NO. 1054 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

# The Synthesis of Nitrogen-Containing Ketones. X. The Mechanism of the Acylation of Pyridine Derivatives[1,2]

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A new mechanism is proposed for the course of the acylation of pyridine derivatives. Evidence in its support is presented.

As a result of previous work from this laboratory,[4–7] the following series of reactions was proposed, using a 2-alkylpyridine as an example, to rationalize the results which were obtained when 2-picoline and certain related 2-alkylated tar bases were acylated with esters in the presence of the basic condensing agent, BM.

$$\underset{\text{I}}{2\text{-}C_5H_4NCH_2R} + BM \longrightarrow \underset{\text{II}}{(2\text{-}C_5H_4NCHR)^-M^+} + HB \quad (1)$$

$$\text{II} + R'CO_2C_2H_5 \longrightarrow \underset{\text{III}}{2\text{-}C_5H_4NCHR(COR')} + MOC_2H_5 \quad (2)$$

$$\text{III} + \text{II} \begin{cases} \xrightarrow{a} \underset{\text{IV}}{[2\text{-}C_5H_4NCR(COR')]^-M^+} + \text{I} \\ \xrightarrow{b} \underset{\text{V}}{(2\text{-}C_5H_4NCHR)_2C(OM)R'} \end{cases} \quad (3)$$

An acid-base reaction occurs between I and the basic condensing agent, BM, to give the metalated pyridine derivative, II (equation 1). *Then it is assumed* (Equation 2) *that the free ketone,* III, *is formed by the reaction of* II *with the ester.* Finally, III may react with II in two ways: (1) III and II may undergo an acid-base reaction to give the anion of the ketone, IV, and I (Equation 3a) and (2) a carbinol may be formed as its metallic salt, V, by the addition of II across the carbonyl group of III (Equation 3b). Thus, when the lithium derivatives of 2-picoline,[4,5] quinaldine,[5] 2,6-lutidine,[5] 2-ethylpyridine,[7] and 2-isobutylpyridine[7] were acylated with esters only ketones of type III (where R′ is aromatic or heterocyclic) or mixtures of ketones and carbinols of type V (where M = H and R′ is aliphatic) were obtained. When

(1) For paper IX in this series, see S. Raynolds and R. Levine, *J. Am. Soc.*, in press.

(2) This paper is based on part of the thesis presented by S. R. to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

(3) Monsanto Chemical Co. Research Fellow for the academic year 1958–59.

(4) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

(5) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

(6) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **77**, 4926 (1955).

(7) C. Osuch and R. Levine, *J. Org. Chem.* 21, 1099 (1956).

TABLE I

ACYLATION OF 2-PICOLINE AND 2-BENZYLPYRIDINE TO GIVE KETONES, $2-C_5H_4NCHRCOR'$, AND CARBINOLS, $(2-C_5H_4NCHR)_2C(OH)R'$, USING 2:2:1 MOLAR RATIO OF TAR BASE: CONDENSING AGENT: ETHYL ESTER

| Run No. | R | R' | Condensing Agent | Solvent | Temp. | Ketone, % Yield | M.P. or B.P. | mm. | Carbinol, % Yield | M.P. or B.P | Mm. | K/C |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | $CH_3$ | $C_6H_5Na$ | $C_6H_6$ | 5 | 59 | 75–78[a,b] | 2 | 28 | 148–152[a,c] | 2 | 2.1 |
| 2 | H | $C_2H_5$ | $C_6H_5Na$ | $C_6H_6$ | 5 | 55 | 83–86[a,d] | 2 | 33 | 153–156[a,e] | 1 | 1.7 |
| 3 | H | $C_2H_5$ | SDIA[f] | $C_6H_6$ | 5 | 48 | 73–75 | 0.77 | 22 | 135–140 | 0.68 | 2.2 |
| 4 | H | $C_2H_5$ | $C_6H_5Li$ | $(C_2H_5)_2O$ | 35[g] | 62 | 83–86 | 2 | 12 | 153–156 | 1 | 5.2 |
| 5 | H | $C_2H_5$ | LDIA[h] | $(C_2H_5)_2O$ | 35[g] | 62 | 83–86 | 2 | 2 | 135–140 | 0.68 | 31.0 |
| 6 | H | $C_2H_5$ | $C_6H_5Li$ | $C_6H_6$ | 5 | 64 | 83–86 | 2 | 4 | 153–155 | 1 | 16.0 |
| 7 | H | $C_2H_5$ | $C_6H_5Na$ | $(C_2H_5)_2O$[i] | 35[g] | 34 | 83–85 | 2 | 24 | 153–156 | 1 | 1.4 |
| 8 | H | $C_6H_5$ | $C_6H_5Na$ | $C_6H_6$ | 5 | 80 | 148–155[a] | 2 | 0 | | | ∞ |
| 9 | H | $C_6H_5$ | $C_6H_5Li$ | $(C_2H_5)_2O$ | 35[g] | 80 | 149–155 | 2 | 0 | | | ∞ |
| 10 | $C_6H_5$ | $CH_3$ | $C_6H_5Li$ | $(C_2H_5)_2O$ | 35[g] | 93 | 145–150[j] | 2.74 | 0 | | | ∞ |
| 11 | $C_6H_5$ | $C_2H_5$ | $C_6H_5Li$ | $(C_2H_5)_2O$ | 35[g] | 22 | 128–132<br>76–78[k,l] | 0.28 | 60 | 146–147[m,n] | | 0.37 |
| 12 | $C_6H_5$ | $C_2H_5$ | SDIA[f] | $C_6H_6$ | 5 | 82 | 128–132 | 0.27 | 0 | | | ∞ |
| 13 | $C_6H_5$ | $C_2H_5$ | $C_6H_5Na$ | $C_6H_6$ | 5 | 81 | 128–132 | 0.28 | 0 | | | ∞ |
| 14 | $C_6H_5$ | $C_2H_5$ | LDIA[h] | $(C_2H_5)_2O$ | 35[g] | 54 | 128–132 | 0.28 | 37 | 146–147 | | 1.5 |
| 15 | $C_6H_5$ | $C_2H_5$ | $C_6H_5Li$ | $C_6H_6$ | 5 | 64 | 128–132 | 0.28 | 0 | | | ∞ |
| 16 | $C_6H_5$ | $C_2H_5$ | $C_6H_5Na$ | $(C_2H_5)_2O$[i] | 35[g] | 68 | 128–132 | 0.28 | 0 | | | ∞ |
| 17 | $C_6H_5$ | $(CH_3)_2CH$ | $C_6H_5Li$ | $(C_2H_5)_2O$ | 35[g] | 81 | 133–135[o,p] | 0.30 | 0 | | | ∞ |
| 18 | $C_6H_5$ | $C_6H_5$ | $C_6H_5Li$ | $(C_2H_5)_2O$ | 35[g] | 60 | 190–195<br>125.0–125.7[p,q] | 0.5 | 16 | 137.8–138.8[r,s] | | 3.75 |
| 19 | $C_6H_5$ | $C_6H_5$ | $C_6H_5Na$ | $C_6H_6$ | 5 | 62 | 180–185 | 0.25 | 0 | | | ∞ |
| 20 | $C_6H_5$ | $C_6H_5$ | SDIA[f] | $C_6H_6$ | 5 | 82 | 180–185 | 0.25 | 0 | | | ∞ |

[a] See ref. 4. [b] Picrate, m.p. 134–135° (from 95% ethanol); lit.[4] m.p. 140–141°; *Anal.* Calcd. for $C_{14}H_{12}N_4O_8$: C, 46.16; H, 3.82. Found: C, 46.46; H, 3.63. [c] Dipicrate, m.p. 213–214°. [d] Picrate, m.p. 143.2–143.6°. [e] Dipicrate, m.p. 193.5–195°. [f] SDIA = sodium diisopropylamide. [g] Reaction effected in refluxing ether. [h] LDIA = lithium diisopropylamide. [i] The sodium derivative of the tar base was prepared in benzene, which was then replaced by ether. [j] *Anal.* Calcd. for $C_{14}H_{13}NO$: C, 79.60; H, 6.20. Found: C, 79.20; H, 6.30. Picrate, m.p. 133.8–134.5° (from 95% ethanol). *Anal.* Calcd. for: $C_{20}H_{16}N_4O_8$: C, 54.55; H, 3.66. Found: C, 54.18; H, 3.59. [k] From 95% ethanol. *Anal.* Calcd. for $C_{15}H_{15}NO$: C, 79.96; H, 6.71. Found: C, 79.98; H, 6.70. [l] Picrate, m.p. 117.5–119.2° (from a 60–70° petroleum ether-benzene mixture). *Anal.* Calcd. for $C_{21}H_{18}N_4O_8$: C, 55.51; H, 3.99. Found: C, 55.28; H, 4.05. [m] Recrystallized from 95% ethanol. *Anal.* Calcd. for: $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64. Found: C, 82.51; H, 6.77. [n] Picrate, m.p. 133.0–133.5° (from 95% ethanol). *Anal.* Calcd. for $C_{39}H_{32}N_8O_{15}$: C, 63.56; H, 4.69. Found: C, 63.78; H, 5.12. [o] *Anal.* Calcd. for $C_{16}H_{17}NO$: C, 80.32; H, 7.16. Found: C, 80.74; H, 7.49. [p] From 60–70° petroleum ether. *Anal.* Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53. Found: C, 83.27; H, 5.92. [q] Picrate, m.p. 139.2–139.9° (from 95% ethanol). *Anal.* Calcd. for $C_{25}H_{18}N_4O_8$: C, 59.76; H, 3.61. Found: C, 59.62; H, 3.71. [r] From a 60–70° petroleum ether-benzene mixture. *Anal.* Calcd. for $C_{31}H_{26}N_2O$: C, 84.13; H, 5.92. Found: C, 83.80; H, 5.86. [s] Attempts to prepare a crystalline picrate failed.

TABLE II

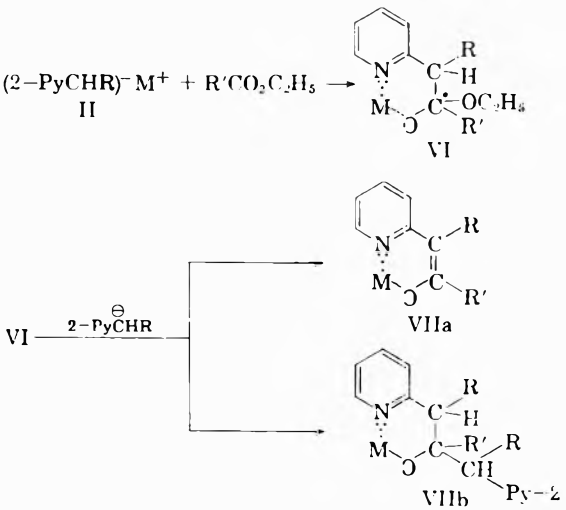
REACTIONS OF KETONES, 2-$C_5H_4NCHR(COC_2H_5)$, I, WITH TAR BASES, 2-$C_5H_4NCH_2R$, II, IN THE PRESENCE OF CONDENSING AGENTS, $C_6H_5M$, III, TO GIVE CARBINOLS, $(2\text{-}C_5H_4NCHR)_2C(OH)C_2H_5$, IV

| R | M | Molar Ratio III:II:I | Solvent | Temp. | Carbinol, IV % Yield | Ketone, I % Recovered |
|---|---|---|---|---|---|---|
| H | Na | 1:1:1 | $C_6H_6$ | 5 | 13 | 81 |
| H | Na | 2:2:1 | $C_6H_6$ | 5 | 23 | 73 |
| $C_6H_5$ | Li | 1:1:1 | $(C_2H_5)_2O$ | 35[a] | 6 | 73 |
| $C_6H_5$ | Li | 2:2:1 | $(C_2H_5)_2O$ | 35[a] | 3 | 94 |

[a] Reaction effected in refluxing ether.

mixtures were formed, the ketone was found to be the major product.

In the present paper new data are presented which necessitate a revision of the mechanism which has just been described. *It is now suggested that when* II *and the ester react they do not give the free ketone directly. Instead, they react to give the adduct,* VI. Intermediate VI can then react with the anion II in two ways: (1) elimination of ethanol gives directly the enol derivative, VIIa, of the ketone and (2) displacement of ethoxide ion at C* by the anion II gives the metallic derivative, VIIb, of the carbinol. When the reaction is processed, VIIa and VIIb give the free ketone and carbinol, respectively.




A consideration of the following seven factors lends support to the revised mechanism.

*1. Interaction of Metalated Pyridine Derivatives with Free Ketones.* The original mechanism of Levine et al.[4–7] implies that, in those reactions where mixtures of ketones and carbinols are obtained, comparable amounts of the products should be obtained when either the metalated pyridine derivative is treated with an ester or the free ketone is treated with the metalated pyridine derivative. To test this argument several experiments were performed. From the interaction of two equivalents of 2-picolylsodium (prepared from 2-picoline and phenylsodium in benzene) and one equivalent of ethyl propionate (Table I, Run 2) there were isolated 1-(2-pyridyl)-butanone-2, VIII (55%, III where R = hydrogen and R′ = ethyl) and ethyl-di-(2-picolyl)carbinol, IX (33%, V where R = hydrogen, R′ = ethyl and M = hydrogen). In addition, treatment of the free ketone, VIII, with one and two equivalents or 2-picolylsodium (Table II, Runs 1 and 2) gave 13% and 23% yields respectively of carbinol, IX. Thus, the 13% yield of IX which was obtained from the interaction of equivalents of VIII and 2-picolylsodium was only about one-third as much (33%) as would be expected from the reaction of 2-picolylsodium (two equivalents) with ethyl propionate (one equivalent) if IX arises exclusively from the interaction of VIII with 2-picolylsodium. It is not too surprising that a higher yield (23%) of IX (Table II, Run 2) was obtained when a 2:1 molar ratio of 2-picolylsodium:VIII was employed than when a 1:1 molar ratio of reactants was used as in the former reaction more 2-picolylsodium is available for reaction with VIII.

That a ketone is not necessarily the intermediate from which the total amounts of the carbinols are formed in the reactions of 2-picoline and its derivatives with esters is even more forcibly supported by the following results. When 2-benzylpyridine (two equivalents) was acylated with ethyl propionate (one equivalent) using phenyllithium (two equivalents) as the condensing agent (Table I, Run 11), there was obtained a mixture of 1-phenyl-1-(2-pyridyl)-butanone-2, X, (22%, III where R = phenyl and R′ = ethyl) and 1,3-di-(2-pyridyl)-1,3-diphenyl-2-ethylpropanol-2, XI (60%, V where R = phenyl, R′ = ethyl and M = hydrogen). However, when the free ketone, X, was treated with the lithium derivative of 2-benzylpyridine, no more than 3% of carbinol, XI, was obtained (Table II, Runs 3 and 4).

The data which have just been presented suggest that although part of the carbinols, IX and XI, may have been formed by the reactions of the free ketones VIII and X with 2-picolylsodium and the lithium derivative of 2-benzylpyridine, respectively, the major amounts of these products are formed in some other way.

*2. The Effects of the Size of the Alkyl Group, R′, in the Acylating Ester, $R'CO_2C_2H_5$.* The ketone to carbinol ratio (K/C) which is found in the acylation of a tar base anion with an ester appears to result from a competition between the elimination and substitution reactions which were mentioned above. The size of R′ in the acylating ester and thus in the adduct VI might be expected to have definite

effects on the K/C ratio. It might be anticipated that *the elimination reaction would be aided by bulky R′ groups*, as the acetal-like carbon atom (C*) of VI is bonded to four other atoms in this adduct and to only three other atoms in the free ketone, III. The elimination is thus accompanied by a relief of steric strain. It might also be anticipated that *the substitution reaction would be hindered by the presence of bulky R′ groups*, as they would increase the crowding around C*, and it should be more difficult for substitution to take place by a backside attack of the tar base anion at this carbon atom. *Thus, it can be concluded that the K/C ratio should be increased as the steric requirements of R′ are increased.*

This mechanistic picture is of use in understanding the earlier results which were obtained in this laboratory. Thus, it is not surprising that when an ether solution of 2-picolyllithium[4] was acylated with a series of ethyl esters, $RCO_2C_2H_5$, the K/C ratio increased from 1.29 to 7.40 when R was increased[8] in size from methyl to ethyl to isopropyl to isobutyl. Similar results were obtained in the acylation of 2,6-lutidyllithium.[5]

In the present study it was found that the acylation of an ether solution of the lithium derivative of 2-benzylpyridine with three aliphatic ethyl esters of increasing steric requirements gave results (Table I, Runs 10, 11 and 17) which were unexpected from a consideration of the above discussion concerning the K/C ratios which were found in the acylation of 2-picoline[4] and 2,6-lutidine.[5] These experiments show that as R′ is increased in size from methyl to ethyl to isopropyl a minimum in ketone formation and a maximum in carbinol formation occur when R′ is of intermediate size, *i.e.*, when R′ is ethyl (Table I, Run 11). These results suggest that two opposing factors are in operation, one of which is primarily responsible for preventing carbinol formation in the case of ethyl acetate (Table I, Run 10) and the other which prevents carbinol formation in the case of ethyl isobutyrate (Table I, Run 17). A molecular model of the adduct which is formed between the lithium derivative of 2-benzylpyridine and ethyl isobutyrate (VI, where R = phenyl, R′ = isopropyl and M = lithium) shows that the approach of another molecule of the lithium derivative of 2-benzylpyridine to the backside of the acetal-type carbon, C*, would be very difficult and hence it might be anticipated that little or no carbinol should be formed. It is not too surprising that a slight change in the steric situation as occurs in changing the acylating ester from ethyl isobutyrate (Table I, Run 17, K/C = ∞) to ethyl propionate (Table I, Run 11, K/C = 0.37) would have a very pronounced effect on the K/C ratio, as C* of VI is very crowded in both cases.[9]

From the above considerations it might be anticipated that a very low K/C ratio, *i.e.*, a high yield of carbinol, should be obtained in the acylation of 2-benzylpyridine with ethyl acetate, as C* in the initially-formed adduct (VI, R = phenyl, R′ = methyl and M = lithium) should be less sterically hindered than C* in the adduct which is formed between the lithium derivative of 2-benzylpyridine and ethyl propionate. However, contrary to these expectations, no carbinol was obtained in the acylation of 2-benzylpyridine with ethyl acetate (Table I, Run 10, K/C = ∞).

The following theory is presented to rationalize the results which have been obtained. It is suggested that the lithium derivative of 2-benzylpyridine reacts with ethyl acetate to give the chelated structure VI (R = phenyl, R′ = methyl, and M = lithium), which is sufficiently stable[10] to resist rupture and subsequent backside attack by the 2-benzylpyridine anion at C*—hence no carbinol is produced. When ethyl propionate is used as the acylating ester, a less stable chelate ring is formed, which does not interfere appreciably with the substitution reaction by which carbinol is formed. Finally, if a chelate is formed when ethyl isobutyrate is used as the acylating ester, the chelate is less stable than that which is formed in the ethyl propionate reaction and carbinol formation does not occur because of steric crowding at C*. Thus, in the acylation of the lithium derivative of 2-benzylpyridine, the K/C ratio appears to depend on a delicate balance between the importance of the stability of the initially-formed chelate VI and the steric situation at C*.[11]

*3. The Importance of Pyridine Ring Substitution.* It is important to stress that in the present investigation and in previous studies which were performed in this laboratory[4-7], when mixtures of ketones and carbinols were obtained from the reaction of a tar base with an ester, the tar base is always 2-picoline or a derivative of 2-picoline. Thus, the reactions of the anions of 3-picoline,[12,13] 4-picoline,[13,14] and cer-

(8) These results were originally[1] explained as being due to the increase in steric interference in the reactions between the initially-formed free ketones and 2-picolyllithium as R′ increases in size.

(9) The same changes in the relatively unstrained adducts which are believed to be present when 2-picolyllithium is acylated with ethyl propionate and ethyl isobutyrate[4] would be expected to result in the relatively small changes in the K/C ratios which were observed, *viz.*, 2.28 and 3.75, respectively.

(10) It is not unreasonable to assume the formation of this stable chelate, as it has been shown [G. A. Guter and G. S. Hammond, *J. Am. Chem. Soc.*, **78**, 5166 (1956)] that lithium ions can be separated from sodium and potassium ions by their preferential chelation with the beta-diketone, dipivaloylmethane.

(11) Numerous examples are known in the field of chelate chemistry in which large differences in ring stability are caused by small structural changes [A. E. Martell and M. Calvin, *Chemistry of the Metal Chelate Compounds*, Prentice-Hall Inc. (1952)].

(12) A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Am. Chem. Soc.*, **78**, 674 (1956).

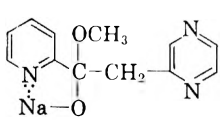
(13) S. Raynolds and R. Levine, *J. Am. Chem. Soc.*, **82**, 472 (1960).

tain of their derivatives[13,14] with esters give only ketones. Why carbinol formation should be so critically dependent on the location of the side chain in the pyridine ring is not apparent from the previously reported[4] mechanism for these acylations, which was summarized at the start of this paper.

However, if it is assumed that most of the carbinol produced in any reaction arises from structure VI, the results which were obtained can be explained. That the acylations of 2-picoline and 2-benzylpyridine give higher yields of carbinols than the corresponding reactions in which the free ketones, 1-(2-pyridyl)-butanone-2 and 1-(2-pyridyl)-1-phenylbutanone-2 are treated with metallic derivatives of 2-picoline and 2-benzylpyridine (see the discussion of factor 1 above) is not unreasonable, for the necessary intermediate adduct VI, from which most of the carbinols are subsequently formed, cannot be produced in the reactions of ketones with the organometallic compounds. It is also suggested that the adducts which are formed from the metallic derivatives of 3- and 4-picoline and their derivatives with esters have open chain rather than chelated structures analogous to VI, as such chelated structures would involve the formation of highly strained seven- and eight-membered rings.

The following results of Behun and Levine[15] lend further support to the argument that pyridine ring substitution plays an important role in carbinol formation. Thus, the acylation of pyrazylmethylsodium with a series of aliphatic, aromatic, and heterocyclic[16] esters gave good to excellent yields of ketones in all cases. Only one reaction, *viz.*, when the acylating ester was methyl picolinate, gave a mixture of ketone (2-pyridyl pyrazylmethyl ketone, 42.6%) and carbinol (2-pyridyl-bis(pyrazylmethyl) carbinol, 22.8%).

The intermediate XII, which is comparable to VI, can be formed when the acylating ester is methyl picolinate; hence some carbinol is formed in this reaction. Because of the strain which would be involved it is very unlikely that structures comparable to XII would be produced when the acylating ester is methyl nicotinate or isonicotinate; thus only ketones are formed in these reactions. It is also important to stress that a chelated structure comparable to VI would be very unlikely to involve the nitrogen atoms of the pyrazine ring when methylpyrazine is acylated, as these atoms are only weakly basic.[17]



XII

It is also important to note that when 2-pyridyl pyrazylmethyl ketone was treated with pyrazylmethylsodium recovered ketone and no carbinol were obtained. Thus, it appears that a fairly basic nitrogen atom as part of a relatively unstrained quasi five- or six-membered ring (Structure VI or XII) is necessary for carbinol formation to occur.

4. *Molar Ratio of Reactants.* The mechanism for the acylation of alkylpyridines as originally formulated[4] and as revised in the present paper accounts for the facts that higher yields of products (i.e., only ketone or a mixture of ketone and carbinol) are obtained from the reactions of esters with metallic derivatives of alkylpyridines, which carry at least two lateral $\alpha$-hydrogen atoms, when a 2:2:1 molar ratio of alkylpyridine:condensing agent:ester is used than when a 1:1:1 molar ratio of reactants is employed. Thus, the 80% yield of 2-phenacylpyridine which was obtained using a 2:2:1 molar ratio of 2-picoline:phenyllithium:ethyl benzoate dropped to 61% when a 1:1:1 molar ratio of reactants was employed.[4,18] The first mole of alkylpyridine anion is used to make one mole of the adduct VI.[15] Then, a second mole of the alkylpyridine anion is required for (1) participating in the substitution reaction with VI to give the metalated derivative of the carbinol, VIIb, and/or (2) producing the anion, VIIa, of the free ketone, III, which is formed by eliminating ethanol from VI.

5 *Effect of Solvents on the K/C Ratio.* We have also found that changes in basicity of the solvent have marked effects on the ketone/carbinol (K/C) ratio. If one considers the two solvents, ethyl ether and benzene, the use of ether rather than benzene as the solvent should emphasize the nucleophilic character of the alkylpyridine anion which is involved in the reaction in question. The effect should be more pronounced when the lithium derivative of an alkylpyridine is employed than when the analogous sodium compound is used, as the lithium ion tends to coordinate with ether to a greater extent than does the sodium ion.[19] It might be anticipated that a higher K/C ratio should be obtained when the lithium derivative of a tar base is acylated with an ester in benzene as the solvent than when this derivative is acylated in ether as the solvent. The use of either benzene or ether as the solvent in the acylation of the sodium derivative of a tar base would be expected to result in only a slight change in the K/C ratio, as the sodium ion has a very slight tendency

(14) C. Osuch and R. Levine, *J. Org. Chem.*, **22**, 939 (1957).

(15) J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5157 (1959).

(16) These were methyl furoate, methyl 2-thenoate, and three isomeric methyl pyridinecarboxylates.

(17) The *p*Ka values of pyridine and pyrazine are 5.23 and 0.6 respectively, (A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948)).

(18) In connection with this discussion the reader is referred to a paper by Raynolds and Levine (see ref. 1) on the acylation of 1-(2-pyridyl)-3-dimethylaminopropane (which has two lateral alpha-hydrogen atoms) and 1-(2-pyridyl)-1-phenyl-3-dimethylaminopropane (which has only one lateral alpha-hydrogen atom).

(19) See pages 191–194 of the reference in footnote 11.

to coordinate with either ether or benzene. In support of these ideas it has been found that the acylation of 2-picolyllithium with ethyl propionate gave a K/C ratio of 5.2 using ether as the reaction solvent (Table I, Run 4) and a value of 16.0 (Table I, Run 6) using benzene as the solvent. In similar experiments involving the propionylation of the lithium derivative of 2-benzylpyridine, the K/C ratio in ether was 0.37 (Table I, Run 11) and ∞ in benzene (Table I, Run 15). Furthermore, the propionylation of 2-picolylsodium in ether (Table I, Run 7) and in benzene (Table I, Run 2) gave essentially the same K/C ratios, *viz.*, 1.4 and 1.7, respectively. Similar results were obtained in the propionylation of the sodium derivative of 2-benzylpyridine in ether (Table I, Run 16) and benzene (Table I, Run 13).

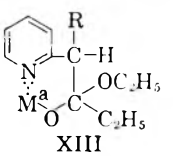
The acylations of 2-picoline and 2-benzylpyridine with ethyl propionate using both lithium diisopropylamide and sodium diisopropylamide as condensing agents were also studied to see what effects the diisopropylamine which is formed by the metalation of the pyridine derivative has on the course of these reactions.

$$2\text{-}C_5H_4NCH_2R + MN(i\text{-}C_3H_7)_2 \longrightarrow 2\text{-}C_5H_4NCHRM + HN(i\text{-}C_3H_7)_2$$

R = H and $C_6H_5$; M = Li and Na

A comparison of Runs 4 and 5 with Runs 2 and 3 (Table I) reveals that the presence of diisopropylamine has a more pronounced effect on the K/C ratio when 2-picolyllithium is propionylated than in the analogous reaction involving 2-picolylsodium. Similar results were obtained (compare Runs 11 and 14 with Runs 12 and 13 in Table I) in the acylation of 2-benzylpyridine with ethyl propionate.

The intermediate XIII is believed to be involved in these reactions.

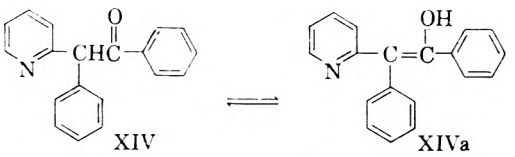


XIII

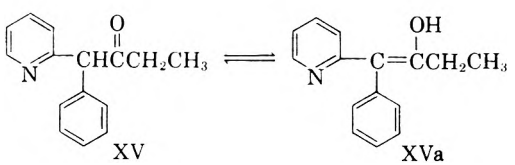
The greater the extent to which $M^a$ is coordinated with diisopropylamine, the less stable chelate XIII should be; therefore, the elimination reaction should occur more readily and the K/C ratio should increase. The solvation effects should be very pronounced when lithium is the metal which is used in these reactions (compare Runs 4 and 5 with Runs 11 and 14 in Table I). Furthermore, when the sodium derivative of 2-picoline was propionylated (Runs 2 and 3 in Table I) and the sodium derivative of 2-benzylpyridine was propionylated (Runs 12 and 13 in Table I) and benzoylated (Runs 19 and 20 in Table I), the presence of diisopropylamine had only a slight effect on the K/C ratio in the case of 2-picoline and no effect was noticed with 2-benzylpyridine, as it would be expected that the sodium ion would be solvated only slightly with diisopropylamine.

The results of the propionylation of 2-benzylpyridine are especially striking as the acylation of its sodium derivative in the absence (Run 12, Table I) or the presence (Run 13, Table I) of diisopropylamine gives a high yield of only ketone while the acylation of the lithium derivative gives mixtures of ketones and carbinol in which the carbinol is the major product in the absence of diisopropylamine (Run 11, Table I) and the ketone is the major product in the presence of diisopropylamine (Run 14, Table I).

6. *Effects of Changing R′ in the Acylating Ester,* $R'CO_2C_2H_5$, *from Alkyl to Phenyl.* When an ether solution of 2-picolyllithium is acylated with ethyl propionate and ethyl benzoate, the K/C ratio increases from 5.2 (Run 4, Table I) to ∞ (Run 9, Table I) respectively. Similar results were obtained when an ether solution of the lithium derivative of 2-benzylpyridine was acylated with ethyl propionate (Run 11, Table I, K/C = 0.37) and ethyl benzoate (Run 18, Table I, K/C = 3.75). That the K/C ratio of 3.75 which was observed in the benzoylation of the lithium derivative of 2-benzylpyridine in ether is so much larger than that (0.37) which was observed in its propionylation may be understood from a consideration of the structures of the ketones XIV and XV which are formed.



XIV XIVa



XV XVa

Structures XIVa and XVa are resonance stabilized, as both have an enolic double bond in conjugation with the benzene and pyridine rings which are located on the same carbon atom. In addition XIV and XIVa are further resonance stabilized in the following ways: (a) the carbonyl group in XIV is conjugated with the benzene ring to which it is bonded and (b) the enolic double bond of XIVa is conjugated with two benzene rings as well as the pyridine ring. Such added stabilization is not possible in structures XV and XVa. Thus, it appears that the considerably greater K/C ratio which was observed in the benzoylation of the lithium derivative of 2-benzylpyridine than was observed in its propionylation is due to the formation of the highly resonance stabilized ketone, XIV–XIVa, which is subsequently converted to its anion by another mole of the anion of 2-benzylpyridine.

A similar explanation can be used to account for the results which were observed in the propionylation and benzoylation of 2-picolyllithium. As the

ketones which are derived from the acylation of 2-picoline with aliphatic esters are not resonance stabilized to the same extent as is 2-phenacylpyridine, it is not unreasonable that the already relatively high K/C ratios which are obtained when 2-picoline is acylated with aliphatic esters[20] are further increased so that K/C = ∞ when the acylating ester is ethyl benzoate.

*7. The Effects of Changing the Metal and R from Hydrogen to Phenyl in the Pyridine Derivatives,* $2 - C_5H_4NCH_2R$. The data in Table I indicate that higher yields of carbinols, *i.e.*, lower K/C ratios, are observed when 2-picolylsodium is propionylated (Table I, Runs 2 and 7) than when 2-picolyllithium is propionylated (Table I, Runs 4 and 6). It might be expected that when M = lithium the chelated adduct VI (R = hydrogen, and R′ = ethyl) would be formed very readily and be more stable than the analogous adduct when M = sodium. Therefore, it is not surprising that a higher K/C ratio is obtained when M = lithium than when M = sodium.

If a stable chelate ring is indeed formed from the reaction of ethyl propionate and 2-picolyllithium, it might seem unreasonable that any carbinol is formed in this reaction, as such a ring would interfere with the backside attack of the 2-picolyllithium on C* of VI, the route by which carbinol is formed. However, it should be emphasized that 2-picolyllithium is a relatively strong base and it might be expected to rupture the chelate ring to some extent and thus form some carbinol. Also, in spite of the fact that 2-picolyllithium is a strong base, the predominant reaction of the chelate which is formed between 2-picolyllithium and ethyl propionate is one of elimination to give the ketone, 1-(2-pyridyl)-butanone-2, as the major product.

A very different situation prevails when 2-benzylpyridine is acylated with ethyl propionate. The data discussed above in factor 2 suggest that when M is lithium, the chelate VI (R is phenyl and R′ is ethyl) is probably less stable than the analogous chelate which is formed in the propionylation of 2-picolyllithium. As the 2-benzylpyridine anion is undoubtedly a considerably weaker base than the anion of 2-picoline, the substitution reaction by which the carbinol is formed from VI and the weakly basic 2-benzylpyridine anion would be expected to be much slower than the corresponding reaction between ethyl propionate and the more strongly basic 2-picoline anion. However, although the lithium derivative of 2-benzylpyridine is a weaker base than 2-picolyllithium, the propionylation of these lithium reagents gives a lower K/C ratio in the 2-benzylpyridine acylation (Table I, Run 11, K/C = 0.37) than in the 2-picoline acylation (Table I, Run 4, K/C = 5.2). This is due to the probability that the chelate VI, where R = phenyl, R′ = ethyl, and M = lithium, is less stable than the analogous chelate which is formed from 2-picolyllithium and ethyl propionate (VI, where R = hydrogen, R′ = ethyl and M = lithium), with the result that it undergoes substitution very extensively and gives a high yield of carbinol even with the weakly basic lithium derivative of 2-benzylpyridine.

A consideration of the adducts of type VI which are formed from ethyl propionate and the lithium and sodium derivatives of 2-benzylpyridine suggests that more carbinol should be formed from the adduct which is more stable and less likely to undergo a rapid elimination reaction to form the ketone. The lithium adduct would be expected to be more stable than the sodium adduct, as lithium forms bonds which are more covalent than those which are formed by sodium. Therefore, as the data in Table I (Runs 11, 13, 15 and 16) indicate. Higher yields of ketone are obtained when M is sodium than when it is lithium regardless of the solvent which is used.

As the 2-benzylpyridine anion is a weak base, its ability to initiate a nucleophilic attack on the initially-formed adduct between the 2-benzylpyridine anion and ethyl propionate should be increased by the use of a solvent such as ether, which would emphasize the nucleophilic character of the 2-benzylpyridine anion by solvating the metal with which it is associated. A solvent such as benzene would make the lithium derivative of 2-benzylpyridine appear to be a weaker base than it is in ether, as the benzene would not aid in its ionization. Therefore, the benzene solvent would not aid the attack of the lithium derivative of 2-benzylpyridine on the initially-formed adduct between the organolithium compound and ethyl propionate. Thus, one would expect the lowest K/C ratio, *i.e.*, the highest yield of carbinol (Table I, Run 11) from the reaction of the lithium derivative of 2-benzylpyridine with ethyl propionate in ether.

Thus, the following three conditions must be fulfilled in order to form carbinol from the acylation of a 2-alkylpyridine with an ester:

(a) The attacking tar base anion must be nucleophilic enough to overcome the energy barrier to substitution. In the case of weakly basic anions, the nucleophilicity may be emphasized by the use of appropriate solvents.

(b) The elimination reaction, by which ketone is formed, must be slow enough to allow the substitution reaction to compete successfully with it, especially when a weakly basic anion is involved.

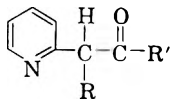
(c) The chelate ring of the initially-formed adduct between the metallic derivative of the tar base and the acylating ester must not be so stable that it interferes with the backside attack of the metallic derivative of the tar base on the acetal-like carbon atom (C* in VI) of the adduct, the route by which carbinol is formed.

In the acylation of 2-benzylpyridine with ethyl propionate these conditions are best met when the metal is lithium and the solvent is ethyl ether. Car-

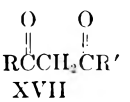
(20) See ref. 4 and the discussion of factor 2 above.

binol is not formed when the lithium derivative of 2-benzylpyridine is acylated with ethyl propionate in benzene as the solvent, as condition (a) is violated. The adduct formed by the reaction of the sodium derivative of 2-benzylpyridine with ethyl propionate in both ether and benzene would be expected to undergo elimination so rapidly that the already slow substitution reaction (because of the weakly basic nature of the 2-benzylpyridine anion) cannot compete with it and therefore only ketone is formed. The data (Table I, Runs 18 and 19) on the benzoylation of the lithium and sodium derivatives of 2-benzylpyridine are also consistent with the above arguments.

Finally, it is of interest to note that ketones, XVI, which are formed by the lateral acylation of 2-picoline and 2-benzylpyridine are structurally analogous to β-diketones, XVII.



R = H and $C_6H_5$
R′ = alkyl and $C_6H_5$
XVI



XVII

Although ketones, XVI differs from the β-diketones, XVII, in that the azomethine linkage which is present in XVI is replaced by a carbonyl group in XVII, both of these classes of compounds chelate with cupric ion. Furthermore, Hauser *et al.*[21] have recently obtained evidence in support of the postulate that an adduct, which is structurally analogous to VI, is formed as an intermediate in the base-catalyzed acylation of the lithium and sodium derivatives of ketones with esters to give β-diketones.

(21) D. G. Hill, J. Burkus, and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 602 (1959).

## EXPERIMENTAL[22]

In this section three typical experiments are described.

(a) *Reaction of the lithium derivative of 2-benzylpyridine with 1-phenyl-1-(2-pyridyl)-2-butanone, X.* The previously described[4] procedure for acylating 2-picolyllithium was followed except that the ester was replaced by ketone, X. Thus, from an ether solution of phenyllithium (0.1 mole), 2-benzylpyridine (0.1 mole, 17.0 g.), and 1-phenyl-1-(2-pyridyl)-2-butanone (0.05 mole, 11.3 g.), there was isolated 0.8 g. (3%) of 1,3-diphenyl-2-ethylpropanol-2, m.p. 146–147° alone and when mixed with an authentic sample. There were also recovered 16.4 g. of 2-benzylpyridine, b.p. 95–98° at 0.22 mm., and 10.6 g. of X, b.p. 128–130° at 0.28 mm.

(b) *Reaction of 2-benzylpyridine, sodium diisopropylamide and ethyl benzoate.* Sodium diisopropylamide (0.1 mole) was prepared by the reaction of a suspension phenylsodium (0.1 mole) in benzene with diisopropylamine (0.1 mole, 10.1 g.) using the previously described procedure.[23] Then, 2-benzylpyridine (0.1 mole, 17.0 g.) and ethyl benzoate (0.05 mole, 7.5 g.) were added and the reaction was conducted and processed using the procedure which has been described[23] for similar reactions. In this way, there were obtained 11.1 g. (82%) of α-phenyl-α-(2-pyridyl) acetophenone, b.p. 180–185° at 0.25 mm., and 9.2 g. of recovered 2-benzylpyridine, b.p. 95–98° at 0.22 mm.

The reactions involving the use of lithium diisopropylamide as the metalating agent were effected as described previously.[23]

(c) *Reaction of 2-benzylpyridine, phenylsodium and ethyl propionate in ethyl ether.* 2-Benzylpyridine (0.1 mole, 17.0 g.), dissolved in an equal volume of anhydrous benzene, was added to a suspension of phenylsodium (0.1 mole) in benzene and the mixture was stirred for 1 hr. at 30°. Nitrogen was allowed to enter the flask slowly while the benzene was removed by distillation at reduced pressure (100 mm.) using a warm water bath to heat the reaction vessel. After removing as much benzene as possible, approximately 200 ml. of anhydrous ethyl ether was added and the mixture was refluxed for 15 min. Ethyl propionate (0.05 mole, 5.1 g.), dissolved in an equal volume of anhydrous ether, was added and the mixture was refluxed for 1 hr. After the usual processing there were isolated 7.6 g. (68%) of 1-phenyl-1-(2-pyridyl)-2-butanone, b.p. 128–132° at 0.28 mm., and 8.0 g. (48%) of recovered 2-benzylpyridine, b.p. 95–98° at 0.22 mm.

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(22) The 2-picoline and 2-benzylpyridine were supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

(23) S. Raynolds and R. Levine, *J. Am. Chem. Soc.*, **82**, 472 (1960).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

# Aroylations of β-Diketones at the Terminal Methyl Group to Form 1,3,5-Triketones. Cyclizations to 4-Pyrones and 4-Pyridones

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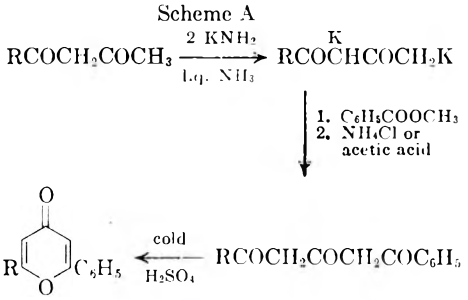
Several β-diketones were aroylated at the terminal methyl group with aromatic esters by means of two molecular equivalents of potassium amide in liquid ammonia to form 1,3,5-triketones. The triketone from 2-acetylcyclohexanone and methyl benzoate evidently consisted of two isomeric forms which were interconvertible. The triketones were cyclized with acid to form 4-pyrones, and with ammonia or methylamine to give 4-pyridones. These reactions furnish convenient methods of synthesis of such compounds. Mechanisms are considered.

Recently[2] acetyl- and benzoylacetones were benzoylated at the terminal methyl group to form the corresponding 1,3,5-triketones, which were cyclized to give pyrones (Scheme A, R = $CH_3$ or $C_6H_5$).[3]

Scheme A

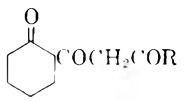



In the present investigation this novel mode of aroylation of β-diketones and the cyclization of the resulting 1,3,5-triketones were found to be quite general. The triketones were also cyclized with ammonia to form 4-pyridones.

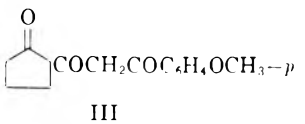
*Aroylations of β-diketones to form 1,3,5-triketones.* Acetyl- and benzoylacetones were aroylated not only with methyl benzoate but also with other appropriate aromatic esters to form triketones Ia–f. Similarly, 2-acetylcyclohexanone, 2-acetylcyclopentanone, and *o*-hydroxyacetophenone were aroylated with the appropriate esters to give triketones IIa–b, III and IV respectively. The results are summarized in Tables I and II.

$RCOCH_2COCH_2COR'$

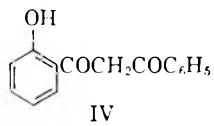
Ia. R = $CH_3$, R′ = $C_6H_5$
Ib. R = $CH_3$, R′ = $C_6H_4Cl$-*p*
Ic. R = $C_6H_5$, R′ = $C_6H_5$
Id. R = $C_6H_5$, R′ = $C_6H_4Cl$-*p*
Ie. R = $C_6H_5$, R′ = $C_6H_4OCH_3$-*p*
If. R = $C_6H_5$, R′ =


IIa. R = $C_6H_5$
IIb. R = $C_6H_4OCH_3$-*p*




III




IV

The general procedure for effecting these condensations involved the addition of the β-diketone to two molecular equivalents of potassium amide in liquid ammonia, followed by one-half of an equivalent of the ester. These proportions of the reactants were chosen to comply with the following three-step mechanism, which is an adaptation of that involved in the acylations of ketones with esters by alkali amides to form β-diketones.[4]

$$RCOCH_2COCH_3 + 2KNH_2 \xrightarrow{\text{liq. } NH_3} \underset{K}{RCOCHCOCH_2K} + 2NH_3 \quad (a)$$

$$\underset{K}{RCOCHCOCH_2K} + R'COOCH_3 \longrightarrow \underset{K}{RCOCHCOCH_2COR'} + KOCH_3 \quad (b)$$

$$\underset{K}{RCOCHCOCH_2COR'} + \underset{K}{RCOCHCOCH_2K} \longrightarrow \underset{K}{RCOCHCOCHCOR'} + \underset{K}{RCOCHCOCH_3} \quad (c)$$

Although essentially all of the β-diketone is first converted to its dipotassio salt (step a), only half of this salt may condense with the ester (step b) as the other half effects the conversion of the resulting monopotassio salt of the triketone to its dipotassio salt (step c). Therefore half of the starting β-diketone is regenerated as its monosodio salt in this last step. Actually most of this regenerated β-diketone may be recovered on acidification, a fact that supports the three step mechanism given above.

It can be seen from Table I that the yields of the triketones were fairly good to good (40–62%), ex-

(1) National Science Foundation Predoctoral Fellow, 1958–1960.

(2) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

(3) For the present purpose only carbanion resonance forms of the potassium salts are considered, although other resonance forms may contribute more to the structure of the molecule.

(4) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 62–63, 114 (1954).

TABLE I

YIELDS OF 1,3,5-TRIKETONES FROM β-DIKETONES AND ESTERS BY MEANS OF POTASSIUM AMIDE

| β-Diketone | Ester | Triketone | M.P.,°[a] | Yield, %[b] |
|---|---|---|---|---|
| Acetylacetone | Methyl benzoate | 1-Phenyl-1,3,5-hexanetrione (Ia) | 105–109[c,d] | 53[e] |
| Acetylacetone | Methyl *p*-chlorobenzoate | 1-(*p*-Chlorophenyl)-1,3,5-hexanetrione (Ib) | 97–98[f] | 52 |
| Benzoylacetone | Methyl benzoate | 1,5-Diphenyl-1,3,5-pentanetrione (Ic) | 106–110[g,h] | 57–62[i,j] |
| Benzoylacetone | Methyl *p*-chlorobenzoate | 1-(*p*-Chlorophenyl)-5-phenyl-1,3,5-pentanetrione (Id) | 106–107.5[h] | 47 |
| Benzoylacetone | Methyl anisate | 1-(*p*-Methoxyphenyl)-5-phenyl-1,3,5-pentanetrione (Ie) | 121–122[k] | 61[l] |
| Benzoylacetone | Ethyl nicotinate | 1-Phenyl-3-pyridyl-1,3,5-pentanetrione (If) | 90–91[m] | 40 |
| 2-Acetylcyclohexanone | Methyl benzoate | 1-(2-Oxocyclohexyl)-3-phenyl-1,3-propanedione (IIa) | 83–86[n,h]<br>100–110[q,m] | 37–44[o,p] |
| 2-Acetylcyclohexanone | Methyl anisate | 1-(*p*-Methoxyphenyl)-3-(2-oxocyclohexyl)-1,3-propanedione (IIb) | 86–90[r,s] | 45[t] |
| 2-Acetylcyclopentanone | Methyl anisate | 1-(*p*-Methoxyphenyl)-3-(2-oxocyclopentyl)-1,3-propanedione (III) | 91–95[u] | 42[t] |
| *o*-Hydroxyacetophenone | Methyl benzoate | *o*-Hydroxydibenzoylmethane (IV) | 117–122[v,f] | 14[t] |

[a] Melting points given are for analytical samples in the cases of new compounds. [b] Yields are based on the ester. The melting point range for the product from which the yield was determined was usually slightly greater than that given in the table. [c] Reported m.p.:[2] 107–108° and 106–107°.[16] [d] Recrystallized from methanol or 95% ethanol. [e] Reported[2] yield, 60%. [f] Recrystallized from methanol. [g] Reported[2, 15] m.p. 107–108°. The melting point was changed to 110–115° by recrystallizing from acidic ethanol. See experimental and note g., Table II. [h] Recrystallized from 95% ethanol. [i] Reported[2] yield, 58%. [j] A 96% crude yield of the theoretically regenerated benzoylacetone was recovered. [k] Recrystallized from benzene. [l] An 86% crude yield of the theoretically regenerated benzoylacetone was recovered. [m] Recrystallized from a mixture of ethanol and water. [n] α-Form, the purest fraction isolated. [o] Yield includes both α- and β-forms. [p] A 92% yield of the theoretically regenerated 2-acetylcyclohexanone was recovered. [q] β-Form, the purest fraction isolated. [r] A small amount of crystals, m.p. 80–105°, was also obtained. [s] Recrystallized from methanol or *n*-hexane. [t] Crude yield. [u] Recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°). [v] Crude. Reported[19] m.p. 117–120° for crude material.

TABLE II

INFRARED DATA, ENOL TESTS, AND ANALYSES FOR 1,3,5-TRIKETONES

| Triketone | Color of Crystals | Infrared Spectra,[a,b] μ μ | Enol Test[c] | Empirical Formula | Analyses,[a] % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|
| Ia[d] | Straw yellow | 6.24, 6.37 | Green | — | — | — | — | — |
| Ib | Pale green | 6.19, 6.37 | Green | $C_{12}H_{11}O_3Cl$[e] | 60.39 | 60.64 | 4.64 | 4.83 |
| Ic[f] | Brown[g] | 6.24, 6.37 | Green | — | — | — | — | — |
| Id | Yellow | 6.24, 6.40 | Green | $C_{17}H_{13}O_3Cl$[h] | 67.9 | 67.78 | 4.36 | 4.35 |
| Ie | Bright yellow | 6.24, 6.37 | Green | $C_{18}H_{16}O_4$ | 72.96 | 73.26 | 5.44 | 5.61 |
| If[i] | Yellow | 6.26, 6.40 | Green | $C_{16}H_{13}O_3N$[j] | 71.90 | 72.09 | 4.90 | 5.07 |
| IIa α-form[k] | Brown | 6.24, 6.35[l] | Green[m] | $C_{15}H_{16}O_3$ | 73.75 | 73.70 | 6.60 | 6.78 |
| β-form[k] | Pale yellow | 6.14, 6.28, 6.39[n] | Reddish-brown | $C_{15}H_{16}O_3$ | 73.75 | 73.79 | 6.60 | 6.58 |
| IIb | Brownish-yellow | 6.24,[o] 6.30, 6.40 | Green | $C_{16}H_{18}O_4$ | 70.05 | 70.29 | 6.61 | 6.51 |
| III | Pale green | 6.13[o] 6.30 | Green | $C_{15}H_{16}O_4$ | 69.21 | 69.02 | 6.20 | 6.11 |
| IV | Yellow | 6.24, 6.37 | Reddish-brown | — | — | — | — | — |

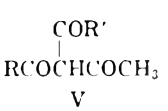
[a] Reference 33. [b] Absorption bands found in the enol-chelate region from 5.5 μ to 6.5 μ. All bands are strong unless noted otherwise. [c] Color produced with ethanolic ferric chloride. [d] Ultraviolet spectrum:[33] $\lambda_{max}$ = 246 mμ, 337 mμ; log ε = 3.80 (8 × $10^{-5}$ *M* solution), 4.16. [e] *Anal.* Calcd. for $C_{12}H_{11}O_3Cl$: Cl, 14.96. Found: 14.71. [f] Ultraviolet spectrum:[33] $\lambda_{max}$ = 247 mμ, 374 mμ; log ε = 4.04, 4.50. [g] Yellow crystals were obtained when Ic was recrystallized from acidic ethanol. See experimental and note g. Table I. [h] *Anal.* Calcd. for $C_{17}H_{13}O_3Cl$: Cl, 11.79. Found: 11.95. [i] Amphoteric. See experimental. [j] *Anal.* Calcd. for $C_{16}H_{13}O_3N$: N, 5.24. Found: 5.20. [k] The purest fraction isolated. [l] The same infrared spectrum was obtained in carbon tetrachloride solution as in the potassium bromide pellet. [m] Changed to reddish-brown on standing. [n] Showed a strong hydroxyl band at 3.00 μ. The infrared spectrum of a carbon tetrachloride solution, however, was identical with that of the α-form. [o] Shoulder.

cept that (14%) for compound IV. Although these yields were based on the ester, at least certain of them would not be much less if based on the β-diketone used minus that recovered (see notes j, l, and p of Table I).

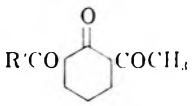
As the conversion yield of a ketone to a β-diketone may often be improved by the use of an extra equivalent of alkali amide,[4] it seemed possible that the conversion yield of a β-diketone to a triketone might be improved similarly. In this procedure step e in the above mechanism would be effected by an extra equivalent of alkali amide, thereby avoiding the regeneration of half of the β-diketone. Accordingly, benzoylacetone was added to three molecular equivalents of potassium amide in liquid ammonia, followed by two equivalents of

methyl benzoate.[5] Triketone Ic was obtained in 37% yield based on the diketone. Although this conversion yield is a little higher than that (about 30% based on the diketone) obtained in the general procedure, only 21% of the crude diketone was recovered as compared to 48% recovered in the general procedure (see note j, Table I). The general procedure seems to provide a slightly cleaner reaction, but this second method may prove more satisfactory in cases where the diketone is very expensive and difficult to recover.

The structures of the triketones were established by cyclization to 4-pyrones and 4-pyridones as described in the next two sections. These results showed that the triketones did not have such a structure as V, which could not have been converted to these cyclic products. Neither could the triketones from 2-acetylcyclohexanone and 2-acetylcyclopentanone have been the ring-methylene aroylation products, for example, VI, which should not be expected to cyclize readily to give a 4-pyrone



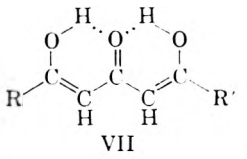
V



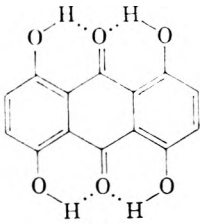
VI

or a 4-pyridone for steric reasons. This is in agreement with the previous alkylations of 2-acetylcyclohexanone and 2-acetylcyclopentanone with benzyl chloride, in which the terminal methyl group and not the ring-methylene group was involved in the condensation.[6]

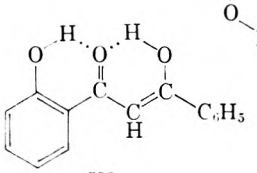
It can be seen from Table II that for all of the triketones studied the infrared bands in the carbonyl and enol-chelate region from 5.5$\mu$ to 6.5$\mu$ were above 6$\mu$, indicating a considerable shift in the carbonyl absorption. Except for a weak band at 2.9$\mu$ in all the spectra run in potassium bromide pellets (attributed to moisture in the potassium bromide), only the $\beta$-form of triketone IIa gave a strong band at 3$\mu$ showing the presence of a free hydroxyl group. That no hydroxyl band was being masked by the potassium bromide was demonstrated in the case of triketones Ia and Ic, which showed no bands near 3$\mu$ when their spectra were determined in mineral oil mulls. These spectra suggest an enol-chelate structure such as VII for the triketones. This structure is similar to those proposed for 1,4,5,8-tetrahydroxyanthraquinone (VIII)[7] and for *o*-hydroxydibenzoylmethane (IX),[8] the keto form of which would be IV.



VII



VIII



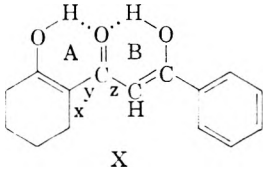
IX

The enol-chelate absorption of VIII was reported as 1592 cm.$^{-1}$ (6.27$\mu$) and 1577 cm.$^{-1}$ (6.34$\mu$)[7] which is comparable with the bands given in this region for the triketones listed in Table II. The spectra in this region are complicated by the absorption of the phenyl group, and the correct assignment of the individual bands is difficult.[9] Ultraviolet spectra for triketones Ia and Ic are given in notes d and f of Table II.

It can further be seen from Table II that the triketones produced green enol tests with ethanolic ferric chloride, except the $\beta$-form of triketone IIa and compound IV, which gave reddish-brown enol tests. $\beta$-Diketones of the type $RCOCH_2COR'$ generally give cherry red enol tests.[10] The metal chelating properties of the triketones should be interesting.[11]

Triketone IIa was obtained in two forms, designated $\alpha$ and $\beta$, which differed in their melting points, solubilities, colors, infrared spectra, and enol tests (see Tables I and II). Although neither form was isolated as a sharply melting solid, the infrared spectrum of the samples of each prepared for analysis indicated that they were not contaminated appreciably with one another. Yet each could be converted to the other (see experimental).

From its properties, the $\alpha$-form appears to have the enol-chelate type of structure X similar to that (VII) represented above for other triketones.



X

(5) While only one equivalent of this ester would theoretically be required, an extra equivalent was employed in accordance with the corresponding procedure for the acylation of ketones; see ref. 4, page 114.

(6) T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, 81, 1160 (1959).

(7) H. Bloom, L. H. Briggs, and B. Cleverley, *J. Chem. Soc.*, 178 (1959). See also ref. 9, pp. 142–144.

(8) E. H. Holst, Ph.D. thesis, 1955, Pennsylvania State University. Private communication from W. C. Fernelius, Department of Chemistry, Pennsylvania State University. See also ref. 9, p. 143.

(9) See L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2d. ed., John Wiley and Sons, New York, N. Y., 1958, p. 64.

(10) See G. T. Morgan, H. D. K. Drew, and C. R. Porter, *Ber.*, 58, 333 (1925); C. R. Hauser and J. T. Adams, *J. Am. Chem. Soc.*, 66, 345 (1944).

(11) Samples of triketones Ia and Ic have been sent to W. C. Fernelius of Pennsylvania State University, who is studying the metal derivatives of these triketones.

It is the least polar form judging from solubilities in ethanol and carbon tetrachloride, and its infrared spectrum more nearly resembles those of the other triketones. The more polar β-form could possibly be a conformational isomer in which the planarity of enol-chelate ring A in formula X is disrupted by rotation about bond y, thus freeing the hydroxyl group and accounting for the 3.00 μ band in the infrared spectrum. The eclipsed interaction between bonds x and z would be expected to oppose the stabilizing effect of the hydrogen bonding in ring A. A similar eclipsed interaction has been suggested to occur in 3-methylacetylacetone, the enol form of which shows an hydroxyl band at 2.94μ, whereas the enol form of acetylacetone shows only a weak band at that frequency.[12,13] The possibility that the β-form of IIa was a cyclic hemiacetal analogous to the intermediate shown in equation 2 has not been ruled out. However, such a structure would be expected to absorb at a shorter wave length than that observed in the carbonyl region (see Table II), and it would not be expected to give a positive enol test.

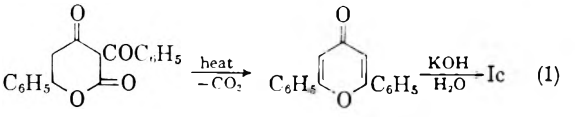
Triketone Ic was obtained both as brown and as bright yellow crystals (see note g, Table I), but the two samples gave identical infrared spectra.

It should be mentioned that two isomeric forms of the triketone 3,5,7-nonanetrione have been reported by Deshapande.[14] One form was converted to the other having a different color and a different molar refractive index.

In contrast to the β-diketones listed in Table I, no triketone was isolated when trifluoroacetylacetone or dimedone (1,1-dimethylcyclohexane-3,5-dione) was treated with methyl benzoate under similar conditions. The dimedone was largely recovered.

Whereas methyl benzoate and the other aromatic esters listed in Table I served as satisfactory aroylating agents, an attempt to effect the propionylation of the dipotassio salt of benzoylacetone with phenyl propionate was unsuccessful. As the starting β-diketone was mainly recovered, its dipotassio salt appears to have merely ionized an α-hydrogen of the ester, thereby rendering both reactants ineffective.

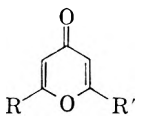
The present method of synthesis of 1,3,5-triketones is considered more convenient than that described previously involving the base catalyzed ring - opening of a 4 - pyrone.[15–18] The latter method may be illustrated for the symmetrical triketone Ic starting with dehydrobenzoyl acetic acid (Equation 1).



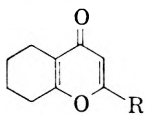
(1)

However, for the special case of compound IV, our method appears not to be as satisfactory as that involving the base catalyzed rearrangement of the *O*-benzoyl derivative of *o*-hydroxyacetophenone.[19]

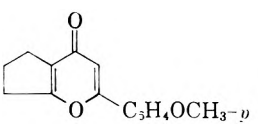
*Cyclization of 1,3,5-triketones to form 4-pyrones.* Triketones Ia–f were cyclized by means of cold sulfuric acid[20] to form 4-pyrones XIa–f. Similarly triketones IIa–b, III and IV gave pyrones XIIa–b, XIII and flavone XIV respectively. The results are summarized in Tables III and IV.



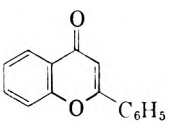

XIa. R = $CH_3$, R′ = $C_6H_5$
XIb. R = $CH_3$, R′ = $C_6H_4Cl$-*p*
XIc. R = $C_6H_5$, R′ = $C_6H_5$
XId. R = $C_6H_5$, R′ = $C_6H_4Cl$-*p*
XIe. R = $C_6H_5$, R′ = $C_6H_4OCH_3$-*p*
XIf. R = $C_6H_5$, R′ = 3-Pyridyl




XIIa. R = $C_6H_5$
XIIb. R = $C_6H_4OCH_3$-*p*




XIII




XIV

The mechanism of the reaction presumably involves the cyclization of an enol form of the triketone to give a hemiacetal type of structure, which undergoes dehydration. This may be illustrated with the symmetrical triketone Ic (Equation 2). For the other triketones, which are unsymmetrical, the reaction may follow two paths leading to the same pyrone, depending upon whether the 1- or 3-keto group is involved in the enolization.

(12) See G. S. Hammond, *Steric Effects in Organic Chemistry*, M. S. Newman, ed., John Wiley and Sons, New York, N. Y., 1956, p. 446–447.

(13) Molecular models show that the interference of the eclipsing groups is greater in triketones IIa and IIb than in triketones III and IV. While III may have a β-form (see note r, Table I), III and IV give no such indication.

(14) S. S. Deshapande, Y. V. Dingankar, and D. N. Kopil, *J. Ind. Chem. Soc.*, **11**, 595 (1934).

(15) K. Balenović and R. Munk, *Archiv. Kem.*, **18**, 41 (1946); *Chem. Abstr.* **42**, 2926a (1948).

(16) S. Ruhemann, *J. Chem. Soc.*, **93**, 1281 (1908).

(17) G. Soliman and I. E. El-Kholy, *J. Chem. Soc.*, 1755 (1954).

(18) In this laboratory 2-methyl-6-phenyl-4H-pyran-4-one (XIa) was opened with barium hydroxide according to Ruhemann's procedure[16] to form triketone Ia in 46% yield.

(19) T. S. Wheeler, *Org. Synthesis*, **32**, 72 (1952).

(20) Triketone Ic was first cyclized in this manner by Balenović; see ref. 15.

TABLE III

CYCLIZATION OF 1,3,5-TRIKETONES TO FORM 4-PYRONES

| Triketone | Pyrone | Recrystallization Solvent | M.P.°[a] | Yield, %[b] |
|---|---|---|---|---|
| Ia | 2-Methyl-6-phenyl-4H-pyran-4-one (XIa) | *n*-Hexane | 85–87[c,d] | 60 |
| Ib | 2-(*p*-Chlorophenyll)-6-methyl-4H-pyran-4-one (XIb) | Methanol-water, or ethanol-pet. ether[e] | 111–112.5 | 90 |
| Ic | 2,6-Diphenyl-4H-pyran-4-one (XIc) | Ethanol-water | 138.5–141.5[f] | 91[g] |
| Id | 2-(*p*-Chlorophenyl)-6-phenyl-4H-pyran-4-one (XId) | Ethanol-water | 159–160[h] | 90 |
| Ie | 2-(*p*-Methoxyphenyl)-6-phenyl-4H-pyran-4-one (XIe) | Ethanol-water, or ethanol-benzene | 162.5–164[i] | 88 |
| If | 2-Phenyl-6-(3-pyridyl)-4H-pyran-4-one (XIf) | Ethanol-water | 157–158 | 91 |
| IIa[j] | 5,6,7,8-Tetrahydroflavone (XIIa) | Ethanol-water | 121–123 | 70–76 |
| IIb | 4′-Methoxy-5,6,7,8-tetrahydroflavone (XIIb) | Ethanol-water | 148–150[k] | 70 |
| III | Cyclopenteno[b]-6-(*p*-methoxyphenyl)-4H-pyran-4-one (XIII) | Ethanol-water | 160–162 | 59[l] |
| IV | Flavone (XIV) | Ethanol-water | 96–98[m] | 63 |

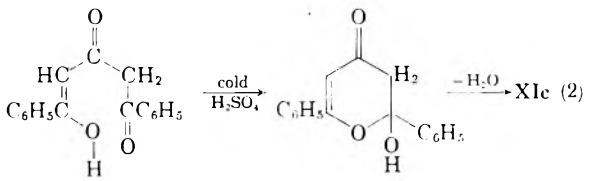
[a] Melting points given are for analytical samples in the cases of new compounds. [b] The melting point range for the product from which the yield was determined was usually greater than that given in the table. [c] Reported[36] m.p. 87–88°. [d] Isolated first as a low melting solid, (see Experimental). [e] B.p. 30–60°. [f] Reported m.p.[2] 138.5–141.5° and 139–141°.[15] [g] Reported yield,[2] 94%. [h] Reported[17] m.p. 160°. [i] Reported[17] m.p. 160–161°. [j] Both the α- and β-forms of IIa gave the same pyrone. [k] Isolated first as a high melting salt (see experimental). [l] Crude yield was 86%. [m] Reported m.p. 97°; H. Simonis, *Z. Angew. Chem.*, **39**, 1461 (1926).

TABLE IV

INFRARED AND ULTRAVIOLET SPECTRA AND ANALYSES FOR 4-PYRONES

| Pyrone | Infrared Spectra[a,b,c] μ | μ | μ | Ultraviolet Spectra[a] $\lambda_{max}$, mμ | log ε | Empirical Formula | Analyses,[a] % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| XIa | 6.00s, 6.19s | | | 272[d] | 4.31[d] | — | — | — | — | — |
| XIb | 6.03s, 6.18m, 6.26m | | | 278 | 4.31 | $C_{12}H_9O_2Cl$[e] | 65.32 | 65.06 | 4.11 | 4.02 |
| XIc | 6.05 s, 6.17 m–w, 6.28 m–w, 6.36 m–w | | | 254, 281[f] | 4.31, 4.36[f] | — | — | — | — | — |
| XId | 6.03 s, 6.25 s, 6.37 w | | | 260, 283 | 4.35, 4.39 | — | — | — | — | — |
| XIe | 6.09 s, 6.26 s, 6.39 m | | | 268, 313 | 4.41, 4.32 | — | — | — | — | — |
| XIf[g] | 6.09 s, 6.29 m | | | 250, 282 | 4.22, 4.31 | — | — | — | — | — |
| XIIa | 6.05 s, 6.20 s | | | 272 | 4.35 | $C_{15}H_{14}O_2$ | 79.62 | 79.58 | 6.24 | 6.17 |
| XIIb | 6.05 s, 6.21 s | | | 301 | 4.35 | $C_{16}H_{16}O_3$ | 74.98 | 74.77 | 6.29 | 6.39 |
| XIII | 6.04 s, 6.23 s, 6.37 m | | | 302 | 4.37 | $C_{15}H_{14}O_3$ | 74.36 | 74.45 | 5.83 | 6.05 |
| XIV | 6.07 s, 6.27 w, 6.36 w | | | 250, 293 | 4.32, 4.40 | — | — | — | — | — |

[a] Reference 33. [b] s = strong, m = medium, w = weak. [c] Absorption bands found in the region from 5.5 μ to 6.5 μ. [d] Reported[21] ultraviolet spectrum: $\lambda_{max}$ = 274 mμ; log ε = 4.32. [e] *Anal.* Calcd. for $C_{12}H_9O_2Cl$: Cl, 16.07. Found: 16.13. [f] Reported[21] ultraviolet spectrum: $\lambda_{max}$ = 257 mμ, 283 mμ; log ε = 4.36, 4.41. [g] Satisfactory analysis was obtained only for a picrate (see Experimental).

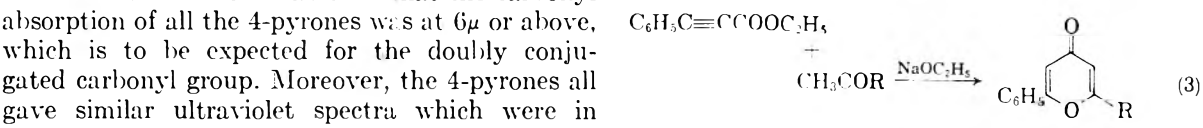


(2)

It can be seen from Table III that the yields of the 4-pyrones were good to excellent (59–91%). Both the α- and β-forms of triketone IIa gave the same pyrone XIIa in equally good yields.

It can be seen from Table IV that the carbonyl absorption of all the 4-pyrones was at 6μ or above, which is to be expected for the doubly conjugated carbonyl group. Moreover, the 4-pyrones all gave similar ultraviolet spectra which were in agreement with those reported earlier[21] for XIa and XIc (see notes d and f, Table IV) and which seemed to be characteristic of the 4-pyrone structure. The pyrone structure of XIIa was further supported by aromatization of the cyclohexane ring to form flavone (XIV).

The present method of synthesis of 4-pyrones through the triketones compares favorably with earlier methods in most cases and is an improvement in some. One of the better previous methods involved the Claisen type of acylation of ketones with ethyl phenylpropiolate accompanied by cyclization (Equation 3).[17]



(3)

(21) P. Franzosini, G. Traverso, and M. Sanesi, *Ann. Chim. (Rome)*, **45**, 128–140 (1955).

TABLE V

CYCLIZATION OF 1,3,5-TRIKETONES TO FORM 4-PYRIDONES

| Triketone | Pyridone | Recryst. Solvent | M.P.,°[a] | Yield,[b] % |
|---|---|---|---|---|
| Ia | 2-Methyl-6-phenyl-4-(1H)-pyridone (XVa) | Water[c] | 175–177[d] | quant. |
| Ib | 2-(*p*-Chlorophenyl)-6-methyl-4(1H)-pyridone (XVb) | Methanol | 236–237[e] | 70 |
| Ic | 2,6-Diphenyl-4(1H)-pyridone (XVc) | Benzene | 175–179[f] | 45[g] |
| Id | 2-(*p*-Chlorophenyl)-6-phenyl-4(1H)-pyridone (XVd) | Ethanol | 208–212 | 30[g,h] |
| Ie | 2-(*p*-Methoxyphenyl)-6-phenyl-4(1H)-pyridone (XVe) | Ethanol | 219–222 | 16[g] |
| IIa[i] | 2-Phenyl-5,6,7,8-tetrahydro-4(1H)-quinolone (XVIa) | Ethanol | 266–269[j] | 76 |
| IIb | 2-(*p*-Methoxyphenyl)-5,6,7,8-tetrahydro-4(1H)-quinoline (XVIb) | Propanol-water | 289–291[e] | 75 |
| III | Cyclopenteno[b]-6-(*p*-methoxyphenyl)-4(1H)-pyridone (XVII) | —[k] | >300[e] | 70[h] |

[a] Melting points given are for analytical samples in the cases of new compounds. [b] The melting point range for the product from which the yield was determined was usually greater than that given in the table. [c] Water solution formed a gell when cooled (see experimental). [d] Crude residue. Reported[16] m.p. 177–178°. Part of the recrystallized material melted at 176–180° and the remainder at 189–191° (see experimental). [e] This melting point was obtained after sublimation *in vacuo*. [f] Reported[27] m.p. 178°. [g] Most of the unchanged triketone was recovered from the reaction mixture. [h] Crude yield. [i] α-Form was used. [j] Decomposes. [k] Attempts to recrystallize XVII from various solvents were unsuccessful.

TABLE VI

INFRARED AND ULTRAVIOLET SPECTRA AND ANALYSES FOR 4-PYRIDONES

| Pyridone | Infrared Spectra[a,b,c] μ | μ | μ | Ultraviolet Spectra[a] $\lambda_{max}$, mμ | log ε | Empirical Formula | Analyses,[a] % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XVa | 6.16 s, 6.34 s, 6.55 b | | | 238 | 4.40 | — | — | — | — | — | — | — |
| XVb | 6.16 s, 6.36 m-s, 6.52 s | | | 243 | 4.47 | $C_{12}H_{10}ONCl$ | 65.61 | 65.51 | 4.59 | 4.74 | 6.38 | 6.49 |
| XVc | 6.18 s, 6.35 s, 6.54 s | | | 246 | 4.48 | — | — | — | — | — | — | — |
| XVd | 6.19 s, 6.38 s, 6.56 s | | | 251 | 4.41 | $C_{17}H_{12}ONCl$ | 72.47 | 72.32 | 4.30 | 4.34 | 4.97 | 5.10 |
| XVe | 6.17 s, 6.34 m, 6.49 s | | | 256 | 4.41 | $C_{18}H_{15}O_2N$ | 77.96 | 77.90 | 5.45 | 5.26 | 5.05 | 5.13 |
| XVIa | 6.15 s, 6.30 w, 6.54 s | | | 241, 268 | 4.45, 4.21 | $C_{15}H_{15}ON$ | 79.97 | 79.70 | 6.71 | 6.59 | 6.22 | 6.13 |
| XVIb | 6.15 s, 6.31 w, 6.57 s | | | 251, 272 | 4.40, 4.30 | $C_{16}H_{17}O_2N$ | 75.27 | 75.22 | 6.71 | 6.86 | 5.49 | 5.48 |
| XVII | 6.19 s, 6.36 w, 6.52 s, 6.59 s | | | 251, 275 | 4.38, 4.26 | $C_{15}H_{15}O_2N$ | 74.66 | 74.84 | 6.27 | 6.04 | 5.81 | 6.04 |

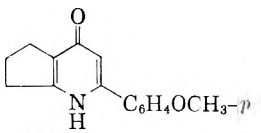
[a] Reference 33. [b] s = strong, m = medium, w = weak, b = broad. [c] Absorption bands found in the region from 5.5μ to 6.6μ.

It should be mentioned that long ago Feist[22] prepared the symmetrical 4-pyrone XIc by the decarboxylation of dehydrobenzoylacetic acid (see Equation 1). Recently, Neelakantan[23] reported that this 4-pyrone can be prepared in excellent yield by condensing ethyl benzoate with acetone in the presence of sodium ethoxide, but no details were given.

It should be pointed out that 4-pyrones such as XIIa-b apparently can not be prepared by the reduction of flavones, as the direct reduction of flavone will occur first in the oxide ring.[24]

*Cyclizations of 1,3,5-triketones with ammonia to form 4-pyridones.* Triketones Ia–e were converted to pyridones XVa–e by treatment with ethanolic ammonia.[25] Similarly triketones IIa–b and III gave pyridones XVIa–b and XVII respectively. The results are summarized in Tables V and VI.

XVa. R = $CH_3$, R′ = $C_6H_5$ XVIa. R = $C_6H_5$
XVb. R = $CH_3$, R′ = $C_6H_5Cl$-*p* XVIb. R = $C_6H_4OCH_3$-*p*
XVc. R = $C_6H_5$, R′ = $C_6H_5$
XVd. R = $C_6H_5$, R′ = $C_6H_4Cl$-*p*
XVe. R = $C_6H_5$, R′ = $C_6H_4OCH_3$-*p*

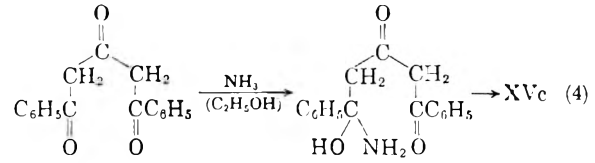


XVII

These reactions appear to be initiated by the addition of the ammonia to the 1- or 3-carbonyl group of the triketone to form a ketone-ammonia type of intermediate,[26] which undergoes cyclization and dehydration to produce the 4-pyridone.

(22) F. Feist, *Ber.*, **23**, 3726 (1890).
(23) L. Neelakantan, *J. Org. Chem.*, **22**, 1584 (1957).
(24) See S. Wawzonek, *Heterocyclic Compounds*, Vol. 2, R. C. Elderfield, ed., John Wiley and Sons, New York, 1951, pp. 256–57.
(25) Apparently this method has not previously been employed with triketones, although triketone Ia has been cyclized with aqueous ammonia to form XVa in unreported yield.[16]
(26) This intermediate might also arise from the conjugate addition of ammonia to an enol form of the triketone.

This may be represented with the symmetrical triketone Ic (Equation 4).

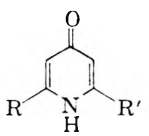


(4)

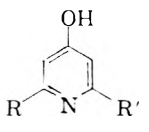
Although the 4-pyridone XVc has previously been prepared from 4-pyrone XIc and ethanolic ammonia,[27] the pyrone was apparently not an intermediate in the present reaction, as the conditions employed by us failed to effect the conversion of this pyrone or of pyrone XIe to the corresponding 4-pyridones.

It can be seen from Table V that the yields were good to excellent for most of the 4-pyridones. The low yield (16%) obtained from triketone Ie could probably be improved, as most of the unchanged triketone was recovered. The present method appears more convenient than the earlier methods which proceed through 4-pyrones.[22,27-30]

It can be seen from Table VI that the 4-pyridones give slightly larger extinction coefficients than the 4-pyrones in the ultraviolet region. This may indicate that the 4-pyridones have the quinoid nucleus (tautomer XVIII) rather than the benzenoid nucleus (tautomer XIX). In line with this the extinction coefficient of 1,2,6-trimethyl-4-(1H)-pyridone has been reported[31] as about 14,000, which is close to that for 2,6-dimethyl-4H-pyran-4-one, whereas that for the benzenoid structure in 2,6-dimethyl-4-methoxypyridine is less than 1500.[31]

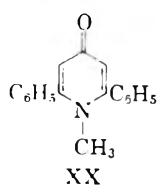


XVIII

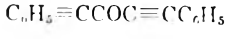


XIX

Finally triketone Ic was cyclized with methylamine to form the *N*-methyl-4-pyridone XX in 42% yield. This compound has previously been prepared by the reaction of methylamine with the unsaturated ketone XXI, but no yield was reported.[32]



XX



XXI

At least certain of the other 1,3,5-triketones prepared in this work could presumably also be cyclized with primary amines to form corresponding *N*-alkyl or *N*-aryl derivatives.

The *N*-methyl pyridone XX reacted with an equivalent of methyl iodide to form an ether insoluble salt, but the site of the alkylation (nitrogen or oxygen) was not determined.

## EXPERIMENTAL[33]

*β-Diketones and esters.* 2-Acetylcyclohexanone and 2-acetylcyclopentanone were prepared by the boron fluoride catalyzed acetylation of cyclohexanone and cyclopentanone respectively.[34] Methyl *p*-chlorobenzoate was prepared by the esterification of *p*-chlorobenzoic acid and methanol by means of sulfuric acid. The other β-diketones and esters were obtained from commercial sources and usually redistilled or recrystallized.

*Preparation of the dipotassio salts of β-diketones.* To a stirred solution of 0.4 mole of potassium amide in 500–600 ml. of commercial anhydrous liquid ammonia[2] was added 0.2 mole of the β-diketone. Solids were added through a powder funnel, and liquids as a solution in about 50 ml. of anhydrous ether. Acetylacetone was first converted into its ammonium salt by carefully pouring some liquid ammonia into an ether solution of this diketone. A vigorous reaction occurred to precipitate a voluminous white solid. This slurry was then poured into the potassium amide solution through a powder funnel, rinsing the last bit in with some dry ether. Care should be taken to exclude moisture during this operation. Other β-diketones showed little or no reactivity towards the liquid ammonia and could be added directly to the potassium amide solution.

The solution was stirred for 20–60 min. and then considered to contain 0.2 mole of the dipotassio β-diketone. Benzoylacetone formed a yellowish green solution, 2-acetylcyclopentanone a green solution, and acetylacetone and 2-acetylcyclohexanone greyish white suspensions. *o*-Hydroxyacetophenone formed a white precipitate unless the solution was more dilute.

*Aroylation of dipotassio β-diketones to form 1,3,5-triketones* (Tables I and II). To a stirred solution or suspension of 0.2 mole of a dipotassio β-diketone in 500 ml. of liquid ammonia was added, during 1 or 2 min., 0.1 mole of an ester dissolved in about 50 ml. of anhydrous ether. After stirring for 30–90 min. longer, the reaction mixture was neutralized and worked up by one of the procedures described below.

In the preparations of triketones Ia–b, IIa–b, III, and IV, the liquid ammonia of the reaction mixture was evaporated as an equal volume of ether was added. The resulting ethereal suspension was then poured with stirring into a slight excess of cold, dilute acetic acid. After shaking thoroughly, the two layers were separated, care being taken that the aqueous layer was weakly acidic. The ethereal layer was washed with water, followed by sodium bicarbonate solution, and dried over Drierite. The solvent was removed and the residue was recrystallized directly to give the triketone, or the β-diketone was first removed by distillation *in vacuo* and the residue then recrystallized.

(27) L. Neelakantan, *J. Org. Chem.*, **23**, 741 (1958).

(28) See H. S. Mosher, *Heterocyclic Compounds*, Vol. 1, R. C. Elderfied, ed., John Wiley and Sons, New York, N. Y., 1950, pp. 472–474.

(29) W. Borsche and W. Peter, *Ann.*, **453**, 148 (1927).

(30) S. S. Deshapande, *J. Ind. Chem. Soc.*, **9**, 303 (1932).

(31) R. C. Gibbs, J. R. Johnson, and E. C. Hughes, *J. Am. Chem. Soc.*, **52**, 4895 (1930).

(32) J. Chauvelier, *Bull. Soc. Chim. France*, **21**, 734 (1954).

(33) Melting points were taken on a Fisher-Johns melting point apparatus which had been calibrated with melting point standards. Infrared spectra were determined with a Perkin-Elmer Infracord by the potassium bromide pellet method unless stated otherwise. Ultraviolet spectra were determined with a Warren Spectracord spectrophotometer using $2 \times 10^{-5}$ *M* solutions in 95% ethanol with a 1 cm. sample cell. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

(34) See ref. 4, p. 131.

In the preparations of triketones Ic–d, the liquid ammonia reaction mixture was neutralized by adding an excess (25 g.) of solid ammonium chloride.[35] The liquid ammonia was then evaporated as an equal volume of ether was added. The resulting ethereal suspension was shaken with water, and the two layers were separated. The ethereal layer was dried over Drierite, and the solvent removed under reduced pressure. The residue was recrystallized directly to give the triketone. When triketone Ic was recrystallized from ethanol, dark brown crystals were obtained having a melting point of 106–110°. If a small amount of concentrated hydrochloric acid were added to the hot, dark ethanol solution, the solution became clearer and, upon cooling, bright yellow crystals formed, m.p. 110–115°. Both solids had the same crystalline form and identical infrared spectra both in potassium bromide pellets and in mineral oil mulls.

In the preparation of triketone Ie, the reaction mixture was neutralized similarly with ammonium chloride, and the liquid ammonia was replaced by ether. The resulting ethereal suspension was shaken with water to dissolve the inorganic salts. The remaining suspension of the triketone, which was only slightly soluble in the ether, was filtered and recrystallized from benzene.

In the preparation of triketone If the reaction mixture was neutralized with ammonium chloride, the liquid ammonia replaced by ether, and the ethereal suspension shaken with dilute hydrochloric acid (30 ml. of conc. hydrochloric acid diluted). A yellow insoluble salt was formed which was filtered from the ether and water layers. The salt was neutralized by shaking in a separatory funnel with ether and aqueous sodium bicarbonate. These two layers were separated, and the ethereal layer was dried over Drierite. The solvent was removed under reduced pressure, and the residue was recrystallized from an ethanol water mixture to give triketone If. The triketone was amphoteric, being soluble in aqueous sodium carbonate or sodium hydroxide, and forming an insoluble salt with hydrochloric acid.

*Isolation of α and β forms of triketone IIa.* The two forms of IIa were obtained relatively free of each other (as shown by their infrared spectra) only with difficulty, and neither gave a very sharp melting point. The general procedure was followed up to the point of removing the solvent and distilling out the excess 2-acetylcyclohexanone, except that the reaction mixture was stirred in ether for an hour before neutralizing it with aqueous acetic acid. The residue from the distillation was taken up in hot 95% ethanol, and on cooling the α-form crystallized in brown crystals, m.p. 83–86° in the purest sample obtained. The β-form was fractionally precipitated from the filtrate of the α-form by the gradual addition of water. The best fraction obtained was a white solid, m.p. 100–110°.

The α-form softened after standing several months. It gave a green color with ethanolic ferric chloride, which on standing changed to the reddish brown color given by the β-form. By dissolving the α-form in hot ethanol, some of the β-form could be obtained upon the addition of water. The infrared spectrum of the α-form in the carbonyl and enol-chelate region, determined both in carbon tetrachloride solution and in potassium bromide pellets, showed strong bands at 6.24 μ and 6.35 μ (see Table II). Neither spectrum showed a band in the hydroxyl region around 3 μ (except for the weak absorption at 2.9 μ arising from moisture in the potassium bromide, which was present in all spectra made by the potassium bromide pellet method).

The β-form gave a reddish brown color with ethanolic ferric chloride. The infrared spectrum determined in potassium bromide showed strong bands at 6.14 μ, 6.28 μ, and 6.39 μ in the carbonyl and enol-chelate region (see Table II), and a strong hydroxyl band was present at 3.00 μ. The spectrum of a carbon tetrachloride solution, however, was identical with that of the α-form. The residue left after evaporation of the solvent from a carbon tetrachloride solution of the β-form gave a green color with ethanolic ferric chloride, characteristic of the α-form. The analytical data are given in Table II. Both forms were cyclized to the same pyrone XIIa.

*Cyclizations of 1,3,5-triketones to form 4-pyrones* (Tables III and IV). A 1-g. sample of the triketone was dissolved in 10 ml. of conc. sulfuric acid at 0°C. After 10 min. at this temperature, the solution was poured into ice water. The resulting precipitate was collected on a funnel, washed with water, and recrystallized from an appropriate solvent to give the 4-pyrone.

In the cyclization of triketone Ia, there was first obtained a solid, m.p. 50–53°, which was apparently a hydrate of the pyrone XIa. This solid was dissolved in hot benzene, and the solvent evaporated to dryness on the steam bath. The residue was recrystallized from *n*-hexane to give the pyrone XIa, m.p. 85–87° (reported[36] m.p. 87–88°). The picrate prepared from either the hydrate or the free pyrone melted at 155–158°, and the melting point was not depressed on mixing the two samples.

The product from the cyclization of triketone If gave analyses between those calculated for pyrone XIf and its monohydrate even after several recrystallizations from ethanol-water. It was converted to a picrate, which melted at 217–223° dec., after three recrystallizations from methyl cellosolve.

*Anal.* Calcd. for $C_{22}H_{14}O_9N_4$ (picrate): N, 11.71. Found: 11.88.

In the cyclization of triketone IIb, there was first obtained a solid, m.p. 250–260° dec., which was apparently the salt of pyrone XIIb. This solid was refluxed with ethanol for several minutes, cooled, and water then added to precipitate the free pyrone XIIb, m.p. 148–150°. The addition of two drops of conc. sulfuric acid to an acetone solution of 0.3 g. of the pyrone precipitated the salt, m.p. 254–258° dec.

*Dehydrogenation of 4-pyrone XIIa to form flavone* (XIV). A 1-g. sample of pyrone XIIa was mixed with 1 g. of 5% palladium on charcoal in a small round bottomed flask equipped with a condenser, and the mixture was heated at 200° for 2 hr. The residue was cooled, taken up in ether, and the catalyst was removed by filtration. The ether was evaporated and the residue was then taken up in a small amount of benzene and placed on an alumina column. Elution successively with 200–300 ml. of petroleum ether (b.p. 30–60°), benzene, and finally ethanol produced sufficient fractionation so that an early fraction contained 0.05 g. (5% yield) of flavone (XIV), m.p. 95–97° after recrystallization from *n*-hexane. A mixed melting point with an authentic sample of flavone prepared from IV was not depressed, and the infrared spectra of the two samples were identical.

*Cyclization of 1,3,5-triketones with ammonia to form 4-pyridones* (Tables V and VI). To 1 g. of the triketone dissolved in 50 ml. of absolute ethanol was slowly added commercial, anhydrous liquid ammonia until the flask was cold. The solution was evaporated to dryness by heating in an open beaker over a steam bath, and the process was then repeated with the residue. In the preparation of XVe, *n*-propyl alcohol was used as a solvent instead of ethanol. The pyridone was isolated from the residue by recrystallization from an appropriate solvent (See Table V). In some cases purification was effected by vacuum sublimation.

In the preparation of 4-pyridone XVa, the crude residue melted at 175–177° (reported[16] m.p. 177–178°). The pyridone could be recrystallized from hot water, but if the water solution were allowed to cool, it formed a gel from which no crystals could be obtained. This behavior was also

(35) When triketone Ia was neutralized in liquid ammonia using this procedure, Hauser and Harris[2] obtained a 38% yield of triketone Ia and a 16% yield of 2-methyl-6-phenyl-4-(1H)-pyridone (XVa). By neutralizing in ether with acetic acid they obtained a 60% yield of triketone and no pyridone.

(36) S. Ruhemann, *J. Chem. Soc.*, **93**, 431 (1908).

observed by Ruhemann.[16] However, only part of the recrystallized pyridone melted at 176–180°, the rest melting at 189–190°.

*Cyclization of triketone Ic with methylamine to form 4-pyridone* XX. Methylamine was bubbled into an ethanolic solution of 9.3 g. of triketone Ic, and the solvent was then removed on the steam bath. The oily residue was recrystallized from a mixture of benzene and hexane to give 3.9 g. (42%) of 2,6-diphenyl-1-methyl-4(1H)-pyridone (XX), m.p. 185–188° (reported[32] m.p. 187°). The infrared spectrum in the region 5.5–6.5 $\mu$ showed a strong band at 6.16 $\mu$, a medium band at 6.47 $\mu$, and a weak band at 6.37 $\mu$. Ultraviolet spectrum: $\lambda_{max}$ = 237 m$\mu$, 270 m$\mu$: log $\epsilon$ = 4.39, 4.26.

A 1.8-g. sample of this compound was added to 7 ml. of acetonitrile, and a few drops of methanol were added to dissolve all the solid. An excess (2 ml.) of methyl iodide was added, and the solution was allowed to stand overnight at room temperature. Ether was added to precipitate 1.7 g. (61%) of the methiodide of 4-pyridone XX (white crystals), m.p. 123–129° dec. The product was recrystallized by dissolving it in methanol and adding ether. Three recrystallizations changed the melting point to 129–137° dec. The infrared spectrum in the region 5.5–6.5 $\mu$ showed a strong band at 6.15 $\mu$, and a medium band at 6.36 $\mu$. Ultraviolet spectrum: $\lambda_{max}$ = 279 m$\mu$; log $\epsilon$ = 4.06; broad shoulder at 232–239 m$\mu$, log $\epsilon$ = 4.40.

*Anal.* Calcd. for $C_{19}H_{18}ONI$: C, 56.59; H, 4.50; N, 3.47. Found: C, 56.32; H, 4.77; N, 3.40.

DURHAM, N. C.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

# Infrared Spectra of the Nitrile *N*-Oxides: Some New Furoxans

RICHARD H. WILEY AND B. J. WAKEFIELD

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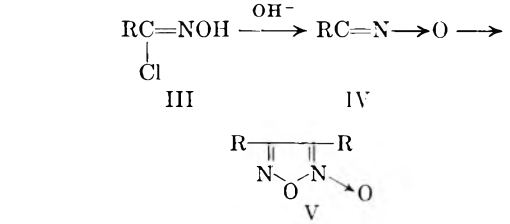
A number of arylnitrile *N*-oxides have been prepared in carbon tetrachloride solution and their infrared spectra studied. Absorption bands at 2295 cm.$^{-1}$ and 1370 cm.$^{-1}$ characteristic of the triple bond and *N*-oxide linkages of the nitrile oxide group have been identified. Several new diaryl furoxans have been obtained by dimerization of these nitrile *N*-oxides and two new aliphatic nitrile oxides have been obtained in solution.

The nitrile *N*-oxides (IV) are somewhat unstable compounds formed by the action of dilute alkali on hydroxamic chlorides as indicated in the reaction scheme:[1–9] and the assignment of a proper



structure has received considerable attention.[6,10–12] They are highly reactive toward olefinic linkages to form isoxazoles[13] and they dimerize readily to furoxans[5] (V). Because of the ease with which they dimerize very little is known about their physical properties. A few appropriately substituted types; *e.g.*, *p*-chlorobenzonitrile *N*-oxide, dimerize slowly and the physical properties of these compounds have been studied.[12,14,15] Others, such as benzonitrile *N*-oxide, dimerize rapidly during isolation and are difficult to characterize. The lowest molecular weight recorded[6,7] for benzonitrile *N*-oxide is 134, whereas theory requires 119, indicating that partial dimerization occurs before the molecular weight can be determined.

We have now devised a procedure for recording the spectra of the less stable nitrile *N*-oxides in carbon tetrachloride solution. The nitrile *N*-oxides were prepared from the hydroxamic chlorides obtained by the route given above. The oximes were prepared by standard methods[16] and were chlorinated at 0° in 8*N* hydrochloric acid[17] or in organic solvents. The hydroxamic chlorides were not purified as the melting points of the crude products agreed well with recorded values. The hydroxamic chlorides were dissolved or suspended in carbon

(1) O. Piloty and H. Steinbock, *Ber.*, **35**, 3114 (1902).
(2) H. Rheinboldt, *Ann.*, **451**, 169 (1926).
(3) B. G. Gowenlock and W. Lüttke, *Quart. Revs.*, **12**, 321 (1958).
(4) A. Werner, *Ber.*, **27**, 2846 (1894).
(5) R. Koreff, *Ber.*, **19**, 176 (1886).
(6) H. Wieland, *Ber.*, **40**, 418 (1907).
(7) H. Wieland, *Ber.*, **40**, 1667 (1907).
(8) H. Wieland, *Ann.*, **367**, 61 (1909).
(9) G. S. Skinner, *J. Am. Chem. Soc.*, **46**, 734 (1924).
(10) H. Wieland, *Ber.*, **42**, 803 (1909).
(11) K. von Auwers, *Ber.*, **61**, 1041 (1928).
(12) G. Speroni, *Ricerca sci.*, **27**, 1199 (1957).
(13) P. Grünanger and I. Grasso, *Gazz. chim. ital.*, **85**, 1250, 1271 (1955) and many previous papers. See also: A. Quilico in R. H. Wiley, L. C. Behr, A. Quilico, and R. L. McKee, *Five Membered O-N Heterocycles*, Interscience Publishers, Inc., New York, in press.
(14) S. Califano, R. Moccia, R. Scarpati, and G. Speroni, *J. Chem. Phys.*, **26**, 1777 (1957).
(15) S. Califano, R. Scarpati, and G. Speroni, *Atti. accad. nazl. Lincei Rend., Classe sci. fis. mat. e nat.*, **23**, 263 (1958).
(16) R. P. Linstead and B. C. L. Weedon, *Guide to Qualitative Organic Chemical Analysis*, Butterworths Scientific Publications, London, 1956.
(17) G. W. Perold, A. P. Steyn, and F. V. K. von Reiche, *J. Am. Chem. Soc.*, **79**, 462 (1957).

tetrachloride at 0° and the solutions were shaken with dilute icecold aqueous sodium hydroxide or sodium carbonate. The carbon tetrachloride layers were separated, dried at 0°, and used for the spectroscopic studies. The nitrile *N*-oxides thus prepared are listed in Table I. The identities of the nitrile *N*-oxides were confirmed, in most cases, by isolating the furoxans formed on standing. Strongly electron-donating substituents in the aromatic nucleus facilitated chlorination of the ring with the result that *o*-methoxybenzaldoxime gave 5-chloro-2-methoxybenzonitrile *N*-oxide and salicylaldoxime gave 3,5-dichloro-2-hydroxybenzonitrile *N*-oxide. In order to confirm these structures, *o*-methoxybenzaldehyde and salicylaldehyde were chlorinated to give 5-chloro-2-methoxybenzaldehyde and 3,5-dichloro-2-hydroxybenzaldehyde respectively. The oximes from these aldehydes gave the same furoxanes as those from *o*-methoxybenzaldehyde and salicylaldoxime. 2,4-Dimethoxybenzaldoxime gave a solution of a nitrile *N*-oxide but no pure furoxan could be obtained and it is probable that a mixture of chlorinated products was formed.

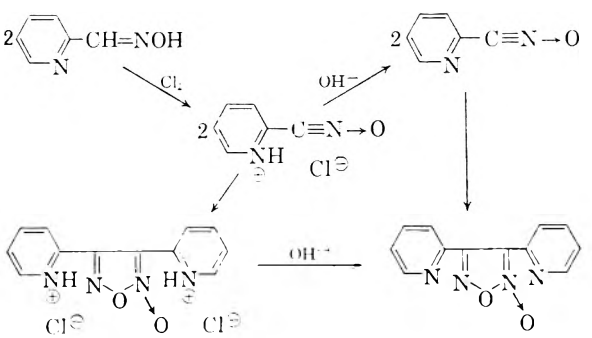
TABLE I

INFRARED ABSORPTION OF NITRILE *N*-OXIDES IN CARBON TETRACHLORIDE

| *N*-oxide | Maxima[a] |
|---|---|
| Benzonitrile *N*-oxide | 2288s, 1712m, 1368vs, 1098s, 1029w, 835w |
| *p*-Phenylbenzonitrile *N*-oxide[b] | 2294, 1376, 1211, 1103, 836 |
| *p*-Methylbenzonitrile *N*-oxide | 2294m, 1704m, 1616w, 1368s, 1253w, 1208w, 1182w, 1098m, 850m |
| *o*-Nitrobenzonitrile *N*-oxide[b] | 2304, 1536, 1393, 1346, 1121, 1070, 857, |
| *m*-Nitrobenzonitrile *N*-oxide[b] | 2294, 1546, 1391, 1357, 1134 |
| *m*-Chlorobenzonitrile *N*-oxide | 2288s, 1595w, 1567m, 1422m, 1370vs, 1235w, 1126m, 1088m, 999w, 964w, 880w |
| *p*-Chlorobenzonitrile *N*-oxide | 2294s, 1597m, 1495m, 1374vs, 1100vs, 1016m, 935m, (826s)[c] |
| 2,4-Dichlorobenzonitrile *N*-oxide | 2299, 1590, 1391, 1372, 1124, 1100, 1045, 873 |
| 5-Chloro-2-methoxybenzonitrile *N*-oxide | 2294m, 1486s, 1464m, 1414m, 1366w, 1346m, 1287w, 1274w, 1253w, 1125m, 1107w, 1075m, 1027m, 902w, 803w |
| 3,5-Dichloro-2-hydroxybenzonitrile *N*-oxide[b] | 2299, 1704, 1672, 1471, 1422, 1353, 1326, 1163, 870 |
| 2,3-Dichloro-2-methylbutyronitrile *N*-oxide | 2294vs, 1733w, 1460m, 1385s, 1168w, 1131m, 1071s |
| 4,5-Dichloro-2,2-dimethylpentanonitrile *N*-oxide | 2288s, 1721s, 1460s, 1401m, 1393s, 1236s, 1211m, 1152s |

[a] Frequencies in cm.$^{-1}$. Intensities indicated by the abbreviations w (weak), m (medium), s (strong), vs (very strong). [b] Dilute solution. Intensities of bands not estimated. [c] Partly obscured by solvent absorption.

The extreme readiness with which hydrogen chloride is eliminated from hydroxamic chlorides is demonstrated by the behavior of oximes containing basic groups. On chlorination, *p*-dimethylaminobenzaldoxime, pyridine-2-aldoxime, and pyridine-4-aldoxime gave white solids, insoluble in organic solvents and very soluble in water. The aqueous solutions were acid to litmus and gave an immediate precipitate with silver nitrate solution. When aqueous solutions of these substances were made alkaline at 0°, nothing was extracted from the solution with carbon tetrachloride. If the aqueous phases were allowed to stand, the furoxans were formed. If the white solids were allowed to stand and then treated with alkali, the furoxans were again obtained. It is postulated that the hydroxamic chlorides are formed only momentarily from oximes containing basic groups and that the white solid product obtained is the hydrochloride of the nitrile *N*-oxide. Addition of alkali gives the water-soluble nitrile *N*-oxide which forms the furoxan on standing. Alternatively, the hydrochloride dimerizes on standing and addition of alkali liberates the furoxan. These reactions are formulated for pyridine-2-aldoxime:



A carbon tetrachloride solution of benzodinitrile *N*-oxide was not obtained by treating *p*-benzenedihydroxamic chloride (from terephthaldoxime) with alkali. The dinitrile *N*-oxide was apparently insoluble in carbon tetrachloride and rapidly formed a high molecular weight polymeric product presumably having alternating benzene and furoxan rings in the chain.

The frequencies and approximate intensities of the principal infrared absorption bands of the carbon tetrachloride solutions of the nitrile *N*-oxides are recorded in Table I. Carbon tetrachloride and chloroform were considered the most suitable solvents for this study. Since it has been noted[18] that the hydrogen atom in chloroform may interact with *N*-oxides, carbon tetrachloride was used. In some cases the nitrile *N*-oxides were only sparingly soluble in carbon tetrachloride. The following infrared absorption bands have been recorded[14] for three comparatively stable nitrile *N*-oxides in carbon tetrachloride: 2,4,6-trimethylbenzonitrile

(18) R. H. Wiley and S. Slaymaker, *J. Am. Chem. Soc.*, 79, 2233 (1957).

*N*-oxide, 2287 cm.$^{-1}$, 1348 cm.$^{-1}$; 2,3,5,6-tetramethylbenzonitrile *N*-oxide, 2288 cm.$^{-1}$, 1346 cm.$^{-1}$; *p*-chlorobenzonitrile *N*-oxide, 2292 cm.$^{-1}$, 1377 cm.$^{-1}$ (*cf.* Table I).

In some cases (benzonitrile *N*-oxide, *p*-methylbenzonitrile *N*-oxide, 3,5-dichloro-2-hydroxybenzonitrile *N*-oxide, and the two aliphatic compounds), bands near 1710 cm.$^{-1}$ indicated that the solutions were contaminated by traces of aldehyde which may have been formed by hydrolysis of the oximes by hydrochloric acid during the chlorination stage. No other impurities have been detected. Traces of oxime or of unreacted hydroxamic chloride would have been extracted by alkali and the furoxans were almost completely soluble in carbon tetrachloride.

All the nitrile *N*-oxides give a strong and remarkably constant band near 2295 cm.$^{-1}$; the slight variations in frequency are not significantly larger than the experimental error. Absorption in the 2300 cm.$^{-1}$ to 2100 cm.$^{-1}$ region is characteristic of triple bond stretching vibrations. Acetylenes absorb at 2140–2100 cm.$^{-1}$ (monosubstituted) or 2260–2190 cm.$^{-1}$ (disubstituted; often very weak).[19] Nitriles absorb at 2260–2240 cm.$^{-1}$ (saturated aliphatic), 2240–2220 cm.$^{-1}$ (aromatic) or 2235–2215 cm.$^{-1}$ ($\alpha,\beta$-unsaturated aliphatic).[19] Azides absorb at 2160–2120 cm.$^{-1}$ [19] and acid azides give two peaks between 2250 cm.$^{-1}$ and 2140 cm.$^{-1}$.[20] The only other compounds with peaks in this region are the isocyanates which absorb at 2275–2263 cm.$^{-1}$.[21] Although nitrile *N*-oxides absorb close to the region of triple bond stretching for other compounds, their absorption is at a significantly higher frequency. This band is therefore regarded as highly characteristic of the arylnitrile *N*-oxides. The frequency difference between the nitrile *N*-oxides and the isocyanates is not large but is still significant and the nitrile *N*-oxides and the isocyanates may be distinguished by other features of their infrared spectra. A band near 1350 cm.$^{-1}$ was attributed[14] to N—O stretching vibrations. Vibrations of this type have been reported over a wide range of frequencies. Pyridine *N*-oxides give one or two strong bands between 1300 cm.$^{-1}$ and 1235 cm.$^{-1}$ (as high as 1319 cm.$^{-1}$ in one case) in carbon tetrachloride[22,23] or in chloroform.[24,25] Pyrimidine *N*-oxides show a strong band in the range 1300 cm.$^{-1}$ to 1255 cm.$^{-1}$. [18] Within these ranges the frequencies vary considerably for different ring substituents. For the furoxans, a doublet in the range 1475–1410 cm.$^{-1}$ has been attributed to the *N*-oxide group and a band in the 1360–1300 cm.$^{-1}$ region is regarded as being due to a ring N—O vibration.[26] The *N*-oxides of tertiary aliphatic amines absorb at 970–950 cm.$^{-1}$.[27] It seems clear that the absorption frequency of the *N*-oxide function depends greatly on the nature of the N—O bond and may lie anywhere between the normal N—O single bond stretching frequency (near 900 cm.$^{-1}$ [28]) and the normal N:O double bond stretching frequency (1621 cm.$^{-1}$ to 1488 cm.$^{-1}$).[3] It has been shown, indeed, that a graph of N—O stretching frequency against N—O bond length gives a smooth curve.[3] All the nitrile *N*-oxides we have studied have a strong absorption band near 1370 cm.$^{-1}$. In most cases this is the strongest band in the spectrum. The frequency of this absorption is near the upper end of the range for N—O stretching vibrations and this fact suggests that the N—O bond in the nitrile N-oxides must possess considerable double-bond character. The hybridization of the bonds in the nitrile N-oxides is illustrated by the three possible electronic structures:

$$\mathrm{R{-}C{\equiv}\overset{+}{N}{-}O^{-}} \qquad \mathrm{R{-}\overset{-}{C}{=}\overset{+}{N}{=}O} \qquad \mathrm{R{-}\overset{+}{C}{=}N{-}\overset{-}{O}}$$

The last structure, involving a large charge-separation, would be expected to contribute little to the hybrid although it becomes significant in addition reactions. The second structure, however, may make a large contribution to the hybrid. The infrared spectrum of the nitrile *N*-oxides is clearly correlated with the accepted structure for these compounds. It was not possible to correlate the position of the 1370 cm.$^{-1}$ band with the nature of the nuclear substituents. When strongly electron-donating substituents were present in the original oxime, the nucleus of the resulting nitrile *N*-oxide was chlorinated. It may be significant, however, that the band occurred at the highest frequencies (over 1390 cm.$^{-1}$) in the nitrobenzonitrile *N*-oxides.

The 1370 cm.$^{-1}$ band is less useful for identification of the nitrile *N*-oxide group than that at 2290 cm.$^{-1}$ as many other groups give bands in this region. The high intensity of the band increases its usefulness, however, and distinguishes the nitrile *N*-oxides from the isocyanates which give a very strong band at 2275–2263 cm.$^{-1}$ but only a weak band near 1370 cm.$^{-1}$ [3] The unexpected nature of the isocyanate spectrum is accounted for by mechanical coupling of the C:N and C:O stretching vibrations.[14,29]

(19) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd Ed., Wiley, New York, 1958.

(20) E. Lieber and E. Oftedahl, *J. Org. Chem.*, **24**, 1014 (1959).

(21) W. H. T. Davison, *J. Chem. Soc.*, 3712 (1953).

(22) H. Shindo, *Pharm. Bull. (Japan)*, **4**, 460 (1956).

(23) H. Shindo, *Pharm. Bull. (Japan)*, **6**, 117 (1958).

(24) A. R. Katritzky and J. N. Gardner, *J. Chem. Soc.*, 2192 (1958).

(25) A. R. Katritzky and A. R. Hands, *J. Chem. Soc.*, 2195 (1958).

(26) N. E. Boyer, G. M. Czernik, H. S. Gutowsky, and H. R. Snyder, *J. Am. Chem. Soc.*, **77**, 4238 (1955).

(27) R. Mathis, R. Wolf, and F. Gallais, *Compt. rend.*, **242**, 1873 (1956).

(28) S. Califano and W. Lüttke, *Z. physik. Chem.*, **6**, 83 (1956).

(29) R. C. Lord and F. A. Miller, *Applied Spectroscopy*, **10**, 115 (1956).

The other bands in the infrared spectra of the nitrile *N*-oxides may be correlated with known structural features of the nucleus and the substituents. The exception is the strong band near 1100 cm.$^{-1}$ given by several of the compounds studied. Bands in the range 1225–950 cm.$^{-1}$ have been correlated with the out-of-plane deformation vibrations of the nuclear hydrogen atoms in substituted benzenes.[19] Such bands are usually weak and it seems unreasonable to assign the strong 1100 cm.$^{-1}$ band to such a structural feature. The band is particularly prominent in the spectra of *p*-substituted benzonitrile *N*-oxides and it also appears in the aliphatic types. We have not at present correlated this band with any molecular vibration.

The procedures outlined for the preparation of the arylnitrile *N*-oxides has been applied to two new aliphatic types. It is recognized that the reactions involved cannot be successfully accomplished with aliphatic aldehydes having $\alpha$-hydrogen atoms.[7–9] Trimethylacetonitrile *N*-oxide is the only aliphatic nitrile *N*-oxide known and its infrared spectrum has been recorded.[15] We have converted tiglic aldoxime to 2,3-dichloro-2-methylbutyronitrile *N*-oxide and 2,2-dimethyl-4-pentenaldoxime to 4,5-dichloro-2,2-dimethylpentanonitrile *N*-oxide. Characteristic infrared absorption bands were observed at 2294 cm.$^{-1}$ and 1385 cm.$^{-1}$ for the former and 2288 cm.$^{-1}$ and 1393 cm.$^{-1}$ for the latter. Neither of these nitrile *N*-oxides nor their furoxans were isolated in an analytically pure form. The carbon tetrachloride solutions of the *N*-oxides showed only traces of carbonyl and no olefinic absorption in accordance with the structures assigned but indicative of impurities.

There is still some disagreement about the structure of the furoxans, but the 1,2,5-oxadiazole 2-*N*-oxide formulation (V) is generally used and is accepted for the present work. The chemistry of the furoxans has recently been reviewed.[30] Most of the furoxans prepared in the course of the present work are new compounds. Data pertaining to them are recorded in Table II. In many cases the furoxans could be prepared simply by digesting the hydroxamic chloride with excess dilute aqueous sodium hydroxide or sodium carbonate. A cleaner product was obtained by preparing a solution of the nitrile *N*-oxide in an organic solvent and allowing the solution to stand at room temperature for twenty-four to forty-eight hours. Ether was used as the solvent rather than carbon tetrachloride as the nitrile *N*-oxides were more soluble in ether. No pure furoxan could be prepared from 2,4-dimethoxybenzaldoxime. A mixture of chlorinated materials was obtained. When *o*-nitrobenzohydroxamic chloride was treated with dilute aqueous sodium carbonate at 0°, a white solid, m.p. 70–75°, was obtained. On standing for one hour at room temperature this became brown and after standing overnight was a black tar. No pure furoxan was isolated. The solution of *o*-nitrobenzonitrile *N*-oxide was obtained normally (see above). It is known, however, that *o*-nitrobenzaldoxime undergoes unusual transformations with alkali.[31]

The infrared absorption spectra of a number of diaryl and diaroylfuroxans have been studied and correlations of bands with their structural features have been made.[26] The spectra of the furoxans which we have prepared show features similar to those reported[26,33] and are extremely complex.

## EXPERIMENTAL

Infrared spectra were measured with a Baird recording double beam spectrometer. Melting points were measured in open capillaries and are uncorrected. Analyses were by Micro Tech Laboratories, Skokie, Ill.

*Aldehydes.* The aldehydes used were commercially available materials, with the exception of *p*-phenylbenzaldehyde, 5-chloro-2-methoxybenzaldehyde, and 3,5-dichloro-2-hydroxybenzaldehyde.

*p-Phenylbenzaldehyde.* Biphenyl was formulated with carbon monoxide and hydrogen chloride in the presence of aluminum chloride and cuprous chloride.[34] The crude product was converted to the oxime without purification.

*5-Chloro-2-methoxybenzaldehyde.* *o*-Methoxybenzaldehyde (5 g.) was dissolved in chloroform (25 ml.) and chlorine was passed into the ice cold solution for 90 min. The solution was allowed to stand for 1 hr. at room temperature and the solvent was evaporated under reduced pressure. The residue was recrystallized from aqueous acetic acid to give 5-chloro-2-methoxybenzaldehyde (4 g.; 63%), m.p. 80–81° (lit.,[35] m.p. 81°).

*3,5-Dichloro-2-hydroxybenzaldehyde.* Salicylaldehyde was chlorinated as described above, to give 3,5-dichloro-2-hydroxybenzaldehyde[36] (65% yield), m.p. 93–94° (lit.,[36] m.p. 95°).

*Oximes.* Benzaldoxime, pyridine-2-aldoxime, and pyridine-4-aldoxime were commercially available materials. The other oximes were prepared by a standard method[16] using an ethanolic solution of hydroxylamine acetate. The yields and melting points were as follows: *p*-phenylbenzaldoxime, 70% yield from biphenyl, m.p. 147–149° (lit.,[37] m.p. 149–150°); *p*-methylbenzaldoxime, 23%, m.p. 76–78° (lit.,[16] m.p. 79°); *o*-nitrobenzaldoxime, 70%, m.p. 102–103° (lit.,[37] m.p. 102–103°); *m*-nitrobenzaldoxime, 82%, m.p. 125° (lit.,[37] m.p. 121–123°); *m*-chlorobenzaldoxime, 92%, m.p. 72–72.5°, (lit.,[37] m.p. 70–71°); *p*-chlorobenzaldoxime, 90%, m.p. 107–109° (lit.,[37] m.p. 110°); 2,4-dichlorobenzaldoxime, 58%, m.p. 134–136° (lit.,[37] m.p. 136–137°); *p*-dimethylaminobenzaldoxime, 91%, m.p. 144–145° (lit.,[37] m.p. 144°); *o*-methoxybenzaldoxime, 58%, m.p. 100–101° (lit.,[37] m.p. 92°); 2,4-dimethoxybenzaldoxime, 83%, m.p. 107–108° (lit.,[38] m.p. 106°); salicylaldoxime, 50%, m.p. 62–63° (lit.,[37] m.p. 63°); terephthaldehydedioxime, 76%,

(30) J. V. R. Kaufmann and J. P. Picard, *Chem. Revs.*, **59**, 429 (1959).

(31) O. L. Brady and R. F. Goldstein, *J. Chem. Soc.*, 1921 (1926).

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(33) J. H. Boyer, U. Toggweiler, and G. A. Stoner, *J. Am. Chem. Soc.* **79**, 1748 (1957).

(34) D. H. Hey, *J. Chem. Soc.*, 2476 (1931).

(35) Buu-Hoï, *Compt. rend.* **221**, 202 (1945).

(36) H. Biltz and K. Stepf, *Ber.*, **37**, 4027 (1904).

(37) I. M. Heilbron, ed. *Dictionary of Organic Compounds*, 3rd Ed., Oxford University Press, New York, 1953.

(38) L. Gattermann, *Ann.* **357**, 369 (1907).

TABLE II

3,4-DIARYLFUROXANS

| Ar | M.P.[a] | Formula | Analysis | |
|---|---|---|---|---|
| | | | N, Calcd. | N, Found |
| Phenyl | 113–114[b] | | | |
| *p*-Phenylphenyl | 159–160 | $C_{26}H_{18}N_2O_2$ | 7.14 | 7.04 |
| *p*-Methylphenyl | 142–143[c] | | | |
| *m*-Nitrophenyl | 182–184[d] | | | |
| *m*-Chlorophenyl | 96–97 | $C_{14}H_8N_2O_2Cl_2$ | 9.12 | 9.31 |
| *p*-Chlorophenyl | 180–181 | $C_{14}H_8N_2O_2Cl_2$ | 9.12 | 9.19 |
| 2,4-Dichlorophenyl | 159–160 | $C_{14}H_6N_2O_2Cl_4$ | 7.80 | 7.80 |
| 5-Chloro-2-methoxyphenyl | 183–184 | $C_{16}H_{12}N_2O_4Cl_2$ | 7.70 | 7.70 |
| 3,5-Dichloro-2-hydroxyphenyl | 195 | $C_{12}H_6N_2O_4Cl_4$ | 6.87 | 6.93 |
| *p*-Dimethylaminophenyl | 143–144 | $C_{18}H_{22}N_4O_3$[e] | 16.36 | 16.45 |
| 2-Pyridyl | 169.5–170.5 | $C_{12}H_8N_4O_2$ | 23.33 | 24.11[f] |
| 4-Pyridyl | 140–141 | $C_{12}H_8N_4O_2$ | 23.33 | 23.09 |

[a] All the furoxans decomposed, though some only slowly, at their melting points. [b] Lit. m.p. 114–115° (ref. 32). [c] Lit. m.p. 143–144 (ref. 2). [d] Lit. m.p. 183–185 (ref. 7). [e] Including one molecule of water of crystallization. [f] The discrepancy was confirmed by a repeat analysis of another sample. The properties of this compound were otherwise normal and no explanation of this result can be offered.

m.p. 201–202° (lit.,[16] m.p. 200°); 3,5-dichloro-2-hydroxybenzaldoxime, 63%, m.p. 194° (lit.,[36] m.p. 195°); tiglic aldoxime, 43%, m.p. 42–43° (lit.,[37] m.p. 43°).

*5-Chloro-2-methoxybenzaldoxime* was prepared in 71% yield, m.p. 139–140°.

*Anal.* Calcd. for $C_8H_8NO_2Cl$: N, 7.55. Found: N, 7.53.

*2,2-Dimethyl-4-pentenaldoxime*, b.p. 85°/17 mm., $n_D^{25}$ 1.4565 was prepared from 2,2-dimethyl-4-pentenal[39] in 27% yield.

*Anal.* Calcd. of $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.83; H, 10.20; N, 10.95.

*Nitrile N-oxides.* A typical preparation of a carbon tetrachloride solution of a nitrile *N*-oxide is described. Solutions of benzonitrile *N*-oxide, *p*-phenylbenzonitrile *N*-oxide, *p*-methylbenzonitrile *N*-oxide, *o*-nitrobenzonitrile *N*-oxide, *m*-nitrobenzonitrile *N*-oxide, *m*-chlorobenzonitrile *N*-oxide, *p*-chlorobenzonitrile *N*-oxide, 2,4-dichlorobenzonitrile *N*-oxide, and 5-chloro-2-methoxybenzonitrile *N*-oxide were prepared from the corresponding oximes by this procedure. *o*-Methoxybenzaldoxime gave the same product as 5-chloro-2-methoxybenzaldoxime. Salicylaldoxime and 3,5-dichloro-2-hydroxybenzaldoxime both gave 3,5-dichlorobenzonitrile *N*-oxide; sodium carbonate was used instead of sodium hydroxide for the dehydrochlorination step.

Tiglic aldoxime gave 2,3-dichloro-2-methylbutyronitrile *N*-oxide and 2,2-dimethyl-4-pentenaldoxime gave 4,5-dichloro-2,2-dimethylpentanonitrile *N*-oxide identified by their infrared spectra. Attempts to isolate the products or furoxans derived from them gave only decomposition products. The infrared spectra of the nitrile *N*-oxides have been recorded in Table I.

The melting points (all with decomposition) of the crude hydroxamic chlorides were as follows: benzohydroxamic chloride, m.p. approx. 45° (lit.,[17] m.p. 42–48°); *p*-methylbenzohydroxamic chloride, m.p. 68–71° (lit.,[2] m.p. 69–70°); *o*-nitrobenzohydroxamic chloride, m.p. 90–93° (lit.,[4] m.p. 92–94°); *m*-nitrobenzohydroxamic chloride, m.p. 96–96° (lit.,[4] m.p. 94–95°); *m*-chlorobenzohydroxamic chloride, m.p. 75–80°; *p*-chlorobenzohydroxamic chloride, m.p. 82–86°; 2,4-dichlorobenzohydroxamic chloride, m.p. 100–105°; 5-chloro-2-methoxybenzohydroxamic chloride, m.p. 115–125°; 3,5-dichloro-2-hydroxybenzohydroxamic chloride, m.p. 172–174°; 1,4-benzenedihydroxamic chloride, m.p. 183–186° (lit.,[2] m.p. 188°). The aliphatic hydroxamic chlorides were liquids.

*p-Phenylbenzonitrile N-oxide.* *p*-Phenylbenzaldoxime (10 g.) was chlorinated in 8*N* hydrochloric acid (50 ml.) at 0°.[17] The resulting suspension was filtered and the crude *p*-phenylbenzohydroxamic chloride (11 g.; 94%) m.p. 125–127° dec. was used for the next stage. A portion was recrystallized from cyclohexane to give pure *p*-phenylbenzohydroxamic chloride, m.p. 129–130°.

*Anal.* Calcd. for $C_{13}H_{10}NOCl$: N, 6.05. Found: N, 6.09.

*p*-Phenylbenzohydroxamic chloride (1 g.) was suspended in spectro-grade carbon tetrachloride (20 ml.). The suspension was cooled to 0° and 14% aqueous sodium hydroxide (6 ml.) was added dropwise with shaking. The mixture was kept at 0° and shaken occasionally for 30 min. The carbon tetrachloride layer (5 ml.) was withdrawn by means of a pipet and was allowed to stand over anhydrous calcium chloride at 0° for 30 min. The solution was used for infrared studies as quickly as possible.

*Furoxans.* Typical procedures for preparing the furoxans are described. Most of the furoxans could be prepared by the method used for 3,4-di(*p*-biphenylyl)furoxan. The method described for 3,4-di(*m*-chlorophenyl)furoxan was more satisfactory and was used to prepare 3,4-diphenylfuroxan, 3,4-di(*p*-methylphenyl)furoxan, 3,4-di(*m*-nitrophenyl)furoxan, 3,4-di(*p*-chlorophenyl)furoxan, 3,4-di(2,4-dichlorophenyl)furoxan, 3,4-di(5-chloro-2-methoxyphenyl)furoxan and 3,4-di(3,5-dichloro-2-hydroxyphenyl)furoxan. The methods described for 3,4-di(2-pyridyl)furoxan were used also for 3,4-di(4-pyridyl)furoxan and for 3,4-di(*p*-dimethylaminophenyl)furoxan. The melting points and analyses of the furoxans are recorded in Table II.

*3,4-Di(p-biphenylyl)furoxan.* *p*-Phenylbenzohydroxamic chloride (2 g.) was warmed on a steam bath with an excess of concd. aqueous sodium carbonate for 30 min. Carbon dioxide was evolved. The solution was cooled and filtered and the solid was washed with water and air dried. The crude product (1 g.; 78%), m.p. 151–153°, was recrystallized from aqueous ethanol and from benzene to give pure 3,4-di(*p*-biphenylyl)furoxan, m.p. 159–160°. For analysis, see Table II.

*3,4-Di(m-chlorophenyl)furoxan.* *m*-Chlorobenzohydroxamic chloride (from 1.5 g. of *m*-chlorobenzaldoxime) was dissolved in ether (30 ml.). The solution was cooled in ice and an excess of 10% aqueous sodium hydroxide was added dropwise, with shaking. The solution was shaken occasionally for 30 min., at 0°. Sufficient ether was added to dissolve a white precipitate which formed and the ether layer was separated and dried over anhydrous sodium sulfate. The ether solution was allowed to stand for 48 hr. at room temperature, was evaporated and the residue (1 g.; 66%), m.p. 75–80°, was recrystallized from aqueous ethanol to give pure 3,4-di(*m*-chlorophenyl)furoxan, m.p. 96–97°. For analysis, see Table II.

(39) K. C. Brannock, *J. Am. Chem. Soc.*, 81, 3379 (1959).

*3,4-Di(2-pyridyl)furoxan.* Pyridine-2-aldoxime (2 g.) was dissolved in 8*N* hydrochloric acid (15 ml.) at 0°. Chlorine was passed into the ice cold solution for 20 min. An excess of concd. aqueous sodium carbonate was added and the solution was warmed on a steam bath for 30 min. The solution was filtered and the brown solid was recrystallized from benzene/cyclohexane and from water to give 3,4-di(2-pyridyl)furoxan (0.5 g.; 27%), m.p. 169–170.5°. For analysis, see Table II.

Pyridine-2-aldoxime was dissolved in carbon tetrachloride or in ether, and chlorine was passed into the ice-cold solution for 20 min. The solution was filtered and the white solid was retained. The white solid was insoluble in organic solvents but soluble in water to give an acid solution.

The white solid was suspended in spectro-grade carbon tetrachloride and an excess of 10% aqueous sodium hydroxide was added to the ice-cold suspension. The mixture was allowed to stand at 0°, with occasional shaking, for 20 min. Part of the carbon tetrachloride layer was removed. The infrared spectrum of this solution showed only very weak absorption. On standing, the aqueous solution deposited 3,4-di(2-pyridyl)furoxan, m.p. 165–168° after recrystallization from water.

A portion of the white solid was allowed to stand at room temperature for 48 hr. It was then dissolved in water and the ice-cold solution was made alkaline. 3,4-Di(2-pyridyl)-furoxan, m.p. 163–168° after recrystallization from water, was precipitated.

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

# The Basic Strength of Pyrrole

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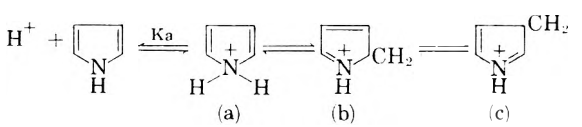
The $pK_a$ of pyrrole has been determined spectrophotometrically using the Hammett $H_0$ indicator method and is found to be −0.27. The problems caused by the acid-catalyzed polymerization of pyrrole have been overcome by a back-extrapolation method and a differential plot.

It has long been recognized that pyrrole is a very weak base although no reliable measurement of its $pK_a$ value has been made. Hall[1] established a relationship between the basicity constants of a series of bases in a nonaqueous solvent and water, and showed that by titrating the bases in glacial acetic acid, the $pK_a$ values of certain bases, which could not be determined in aqueous solutions, could be predicted. Pyrrole was dissolved in glacial acetic acid and titrated conductometrically with perchloric acid; by inspecting the titration curve obtained, the approximate $pK_a$ of pyrrole was reported to be +0.4. More recently, Tamres and co-workers[2] found that for a series of closely related compounds there was a linear relationship between the acidity constants and the ability of these compounds to form hydrogen bonds. For a number of compounds related to pyridine it was shown that $\Delta\nu = 14.8\ pK_a + 136$, where $pK_a$ is the acid dissociation constant of the compound and $\Delta\nu$ the frequency shift in cm.$^{-1}$ of the oxygen-deuterium stretching frequency in the infrared spectrum of methyl deuteroalcohol solutions. In the presence of pyrrole, $\Delta\nu$ was 161 cm.$^{-1}$ and therefore the $pK_a$ of pyrrole is 1.7 if the above linear relationship is applicable. However, too much reliance cannot be placed on acid dissociation constants obtained from studies on hydrogen bonding for a number of reasons. For example, different steric and solvation effects will be involved with different pyridine bases; there is also a fundamental difference between protonation of a pyridine type molecule where electrostatic forces are primarily involved, and hydrogen bond formation with such a compound in which a covalent bond is formed.[2] Moreover, in most pyridine type bases protonation takes place at the nitrogen atom, whereas in pyrrole it is possible that protonation takes place at a carbon atom. If carbon protonation occurs[3] the above relationship between $\Delta\nu$ and $pK_a$ is less likely to be valid.

In spite of the fact that pyrrole is an extremely weak base a certain amount of the protonated species (a), (b), or (c) is formed when pyrrole is




added to mineral acids. The protonated ion of pyrrole is highly unstable and undergoes polymerization very readily, one of the chief products of polymerization being the trimer, 2,5-dipyr-

(1) N. F. Hall, *J. Am. Chem. Soc.*, **52**, 5115 (1930).

(2) M. Tamres, S. Searles, E. M. Leighly, and D. W. Mohrman, *J. Am. Chem. Soc.*, **76**, 3983 (1954).

(3) H. A. Potts and G. F. Smith, *J. Chem. Soc.*, 4018 (1957).

rolylpyrrolidine.[3] The formation of polymers even in moderately strong acid solutions has been the main difficulty in the direct determination of the $pK_a$ of the very weak base, pyrrole. This paper is concerned chiefly with the elimination of the experimental difficulties caused by polymerization and the determination of the $pK_a$ of pyrrole by a spectrophotometric method.

## EXPERIMENTAL

*Materials.* A sample of pyrrole was kindly supplied by Ansul Chemical Company, Wisconsin. The compound had the following physical constants: B.p. 131° at 760 mm. pressure; $n_D^{20}$ 1.5091. Perchloric acid obtained from General Chemical Company, New York, was used to prepare a 6*M* stock solution. This solution was diluted appropriately and used in all the spectrophotometric measurements.

*Apparatus.* A Cary Model 14 spectrophotometer with 1 cm. silica cells was used for most of the preliminary work. Subsequent determinations were carried out with a Beckman Model DU spectrophotometer fitted with a photomultiplier attachment using matched 1 cm. silica cells.

*Absorption spectrum of pyrrole.* A stock solution containing 0.0522 g. pyrrole per l. of water was used to make up a series of solutions which ranged from 0.1 to 1.1*M* in perchloric acid, each solution being $6.22 \times 10^{-5}M$ in pyrrole. The absorption spectra of these solutions were determined using the Cary spectrophotometer. Fig. 1 shows the variation of the ultraviolet absorption spectrum of pyrrole with acidity, for three of the solutions used. The absorption maximum was 204 ± 1 mμ for all solutions; there was no measurable shift of the absorption maximum with variation in concentration of perchloric acid.

*Variation of the absorption spectrum of pyrrole with time.* Twenty-five-ml. portions of a stock aqueous solution of pyrrole containing 0.0506 g. pyrrole per l. were pipetted into a series of volumetric flasks containing water and perchloric acid. The final strength of the perchloric acid ranged from 5.0*M* to 0.10*M*. The time of mixing for all the solutions was kept constant. The absorbance of the solutions containing a constant amount of pyrrole was read at 205 mμ in a 1 cm. silica cell, and absorbance readings were taken at definite time intervals in order to determine the concentration of acid below which polymerization was not appreciable (Table I). All measurements were made at 25 ± 1°.

## RESULTS

Fig. 1 shows that the absorbance of the protonated form of pyrrole is appreciably greater than that of pyrrole. Therefore, it should be possible to determine the molar absorptivity of the cationic species of pyrrole, which is a proton donor, as well as the molar absorptivity of pyrrole, a proton acceptor, by measuring the absorbance of a solution at a sufficiently high and at a sufficiently low acidity, respectively. The molar absorptivity of the unprotonated pyrrole was readily measured in solutions that were 0.10 to 0.40*M* in perchloric acid. Preliminary experiments had shown that in solutions that were greater than 2.0*M* in perchloric acid, the protonated form of pyrrole was the predominant species present. However, if the solutions were greater than 1*M* in perchloric acid polymerization takes place (Table I), thus making the direct determination of the molar absorptivity

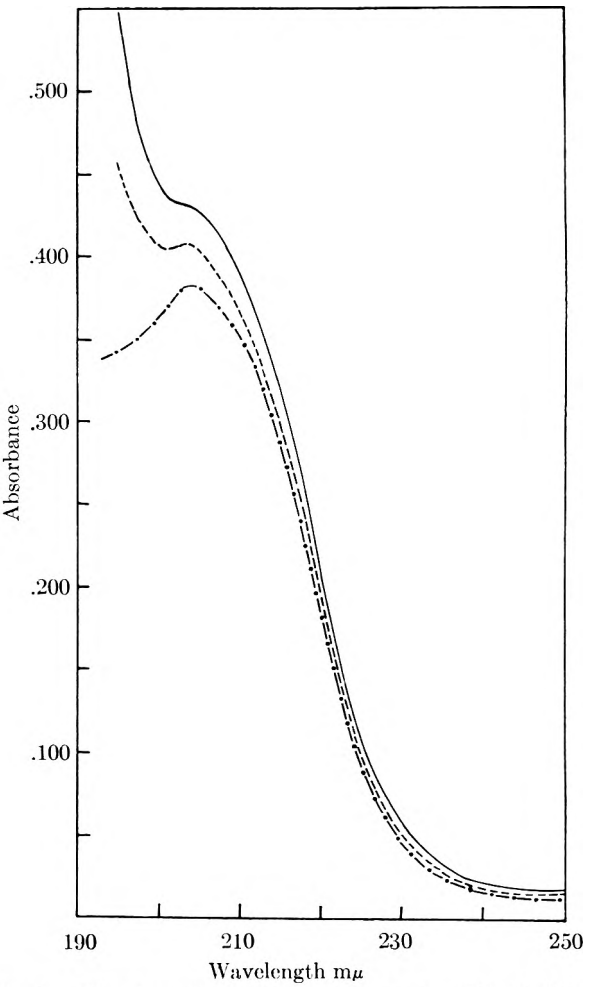



Fig. 1. The absorption spectrum of pyrrole ($6.22 \times 10^{-5}$ M) in perchloric acid solutions. Legend.——1.00 M acid; ---- 0.500 M acid; —·— 0.100 M acid

of the protonated species impossible. An approximate value of the molar absorptivity of the protonated form of pyrrole was obtained by plotting the absorbance values of the solutions against time and extrapolating to zero time. In the case of solutions that were 1.0 to 2.0*M* in perchloric acid, the absorbance decreased relatively slowly with time and it was possible to extrapolate these values readily to zero time. If the perchloric acid concentration was greater than 2.0*M* there was a very rapid decrease in absorbance with time, thus introducing a great degree of uncertainty in the extrapolation. The best value for the molar absorptivity of the protonated form of pyrrole that was obtained by the extrapolation method was 7425, at 205 mμ.

One of the most convenient methods of determining significant $pK_a$ values of very weak bases is to make use of the $H_0$ acidity scale.[4] If the ionization of the protonated form of pyrrole is represented by

$$BH^+ \overset{Ka}{\rightleftharpoons} B + H^+$$

(4) M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

TABLE I

VARIATION OF THE ABSORBANCE OF AN ACID SOLUTION OF PYRROLE ($7.54 \times 10^{-5} M$) WITH TIME

| Molarity of Perchloric Acid / Time in Min. | 5.00 | 3.00 | 2.00 | 1.20 | 1.10 | 1.00 | 0.950 | 0.900 |
|---|---|---|---|---|---|---|---|---|
| | | | | Absorbance at 205 mμ | | | | |
| 0 | 0.562[a] | 0.558[a] | 0.560[a] | 0.522[a] | 0.505[a] | 0.497[a] | 0.490[a] | 0.487[a] |
| 4 | 0.475 | 0.518 | 0.555 | 0.512 | — | — | — | — |
| 5 | — | — | — | — | 0.504 | 0.495 | 0.490[a] | 0.487 |
| 6 | 0.460 | 0.495 | — | — | — | — | — | — |
| 8 | 0.450 | 0.485 | — | — | — | — | — | — |
| 10 | 0.450 | 0.477 | 0.540 | 0.504 | — | — | — | — |
| 20 | 0.450 | 0.470 | 0.528 | 0.498 | 0.498 | — | 0.486 | 0.486 |
| 30 | 0.450 | 0.467 | 0.520 | — | — | — | — | — |
| 40 | — | — | — | 0.488 | 0.494 | — | 0.484 | 0.485 |
| 50 | — | — | 0.510 | — | — | — | — | — |
| 60 | — | — | 0.506 | 0.486 | 0.492 | 0.493 | — | — |

[a] Absorbance values extrapolated to zero time.

the absorbance of a solution containing both ionic species is given by

$$\epsilon.C = \epsilon_{BH^+} \cdot C_{BH^+} + \epsilon_B \cdot C_B$$

where the total concentration of pyrrole in the solution is given by

$$C = C_{BH^+} + C_B$$

$C_{BH^+}$ and $C_B$ are the concentrations in moles per liter, of the forms $BH^+$ and B and $\epsilon$, $\epsilon_{BH^+}$, and $\epsilon_B$ the molar absorptivities at 205 mμ of a mixture of the two forms, of the protonated species and of the unprotonated species of pyrrole respectively. The ratio of the ionized to the unionized forms of pyrrole could be written as

$$\frac{C_{BH^+}}{C_B} = \frac{\epsilon_B - \epsilon}{\epsilon - \epsilon_{BH^+}}$$

This ionization ratio is related to the acid ionization constant of pyrrole and the acidity function of the medium by the equation

$$H_0 = pK_a + \log \frac{C_B}{C_{BH^+}}$$

or

$$H_0 = pK_a + \log \frac{\epsilon - \epsilon_{BH^+}}{\epsilon_B - \epsilon}$$

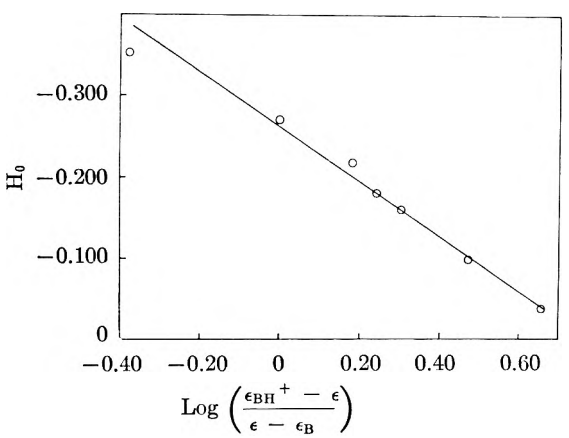



Fig. 2. Determination of $pK_a$ using a linear plot

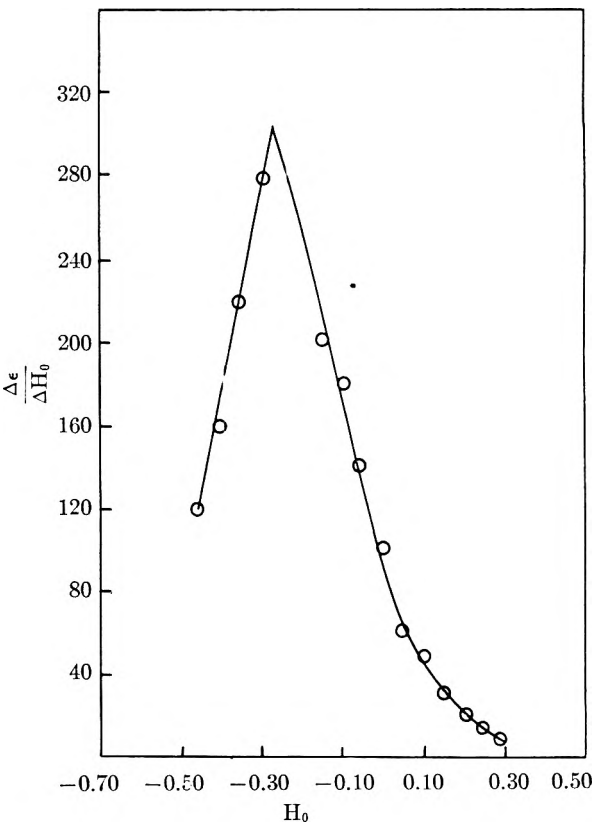



Fig. 3 Determination of $pK_a$ using a differential plot

As the values of $H_0$ at selected molarities of perchloric acid have been determined,[4] the value of $pK_a$ can be calculated by a number of methods. If $H_0$ is plotted against $\epsilon$, the value of $H_0$ at which $\epsilon = (\epsilon_{BH^+} + \epsilon_B)/2$ gives $pK_a$; or if $H_0$ is plotted against log $(\epsilon - \epsilon_{BH^+})/(\epsilon_B - \epsilon)$ the intercept of the straight line obtained will give $pK_a$ (Fig. 2). However, there is some uncertainty about the exact value of $\epsilon_{BH^+}$ since pyrrole polymerizes very rapidly in solutions that are greater than $2M$ in perchloric acid. It is possible to determine the $pK_a$ of pyrrole even though the exact value of $\epsilon_{BH^+}$ is not known. If $d\epsilon/dH_0$ is plotted against $H_0$ the

value of $H_0$ at which $d\epsilon/dH_0$ reaches a maximum gives $pK_a$ (Fig. 3). All values of $H_0$ were obtained from tables.[4] The value of $pK_a$ for pyrrole obtained from plots of the type shown in Figs. 2 and 3 is $-0.27$.

## DISCUSSION

The ultraviolet absorption spectrum of pyrrole in hexane consists of a strong band at 210 mμ ($\epsilon$ = 15,000) and a very weak band at 240 mμ ($\epsilon$ = 300).[5] The high intensity absorption is probably due to $\pi \rightarrow \pi^*$ transitions but the low intensity band cannot be attributed to the presence of $n \rightarrow \pi^*$ transitions in pyrrole. It has been reported that this low intensity band was not observed in the spectra of a number of $\alpha$ and $\beta$-alkyl pyrroles in ethanol.[6] On the other hand *N*-methylpyrrole has an absorption band in the 240 mμ region[7]; this is probably due to the reduction in electronegativity of the nitrogen atom caused by the electron-releasing properties of the methyl group. This facilitates the participation of the nitrogen 2*p* electrons in conjugation with the $\pi$-electrons in the pyrrole ring. Fig. 1 shows the ultraviolet spectra of pyrrole in aqueous solutions containing perchloric acid. In no case was a low intensity band in the 240 mμ region obtained. Therefore, on the basis of the ultraviolet spectra alone, it is apparently not possible to decide whether carbon protonation or nitrogen protonation occurs in pyrrole in the presence of acids.

The chemical reactions of pyrrole indicate that it is aromatic in character, the electrons on the nitrogen atom being delocalized on the four carbon atoms, thereby making the nitrogen atom a very poor proton acceptor. This, of course, implies that pyrrole should be a very weak base. This work has shown that pyrrole whose $pK_a$ is $-0.27$ is a weaker base than has been expected. Unfortunately no $pK_a$ values exist for related compounds for purposes of comparison. It would be of interest to determine the $pK_a$ values of substances such as indole or carbazole, which should also be very weakly basic, and also the acid dissociation constants of substituted pyrroles, notably *N*-methylpyrrole.

*Acknowledgment.* The authors are grateful to Dr. D. H. McDaniel and Dr. E. McC. Arnett for helpful discussions in connection with this work.

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(5) Menczel, *Z. physik. Chem.*, **125**, 161 (1927).
(6) G. H. Cookson, *J. Chem. Soc.*, 2789 (1953).
(7) G. Milazzo, *Gazzetta*, **74**, 152 (1944).

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[CONTRIBUTION FROM THE SCIENTIFIC LABORATORY, FORD MOTOR COMPANY]

# Studies in the Synthesis of 2,5-Diphenylpyrrole

ALFRED KREUTZBERGER AND PAUL A. KALTER

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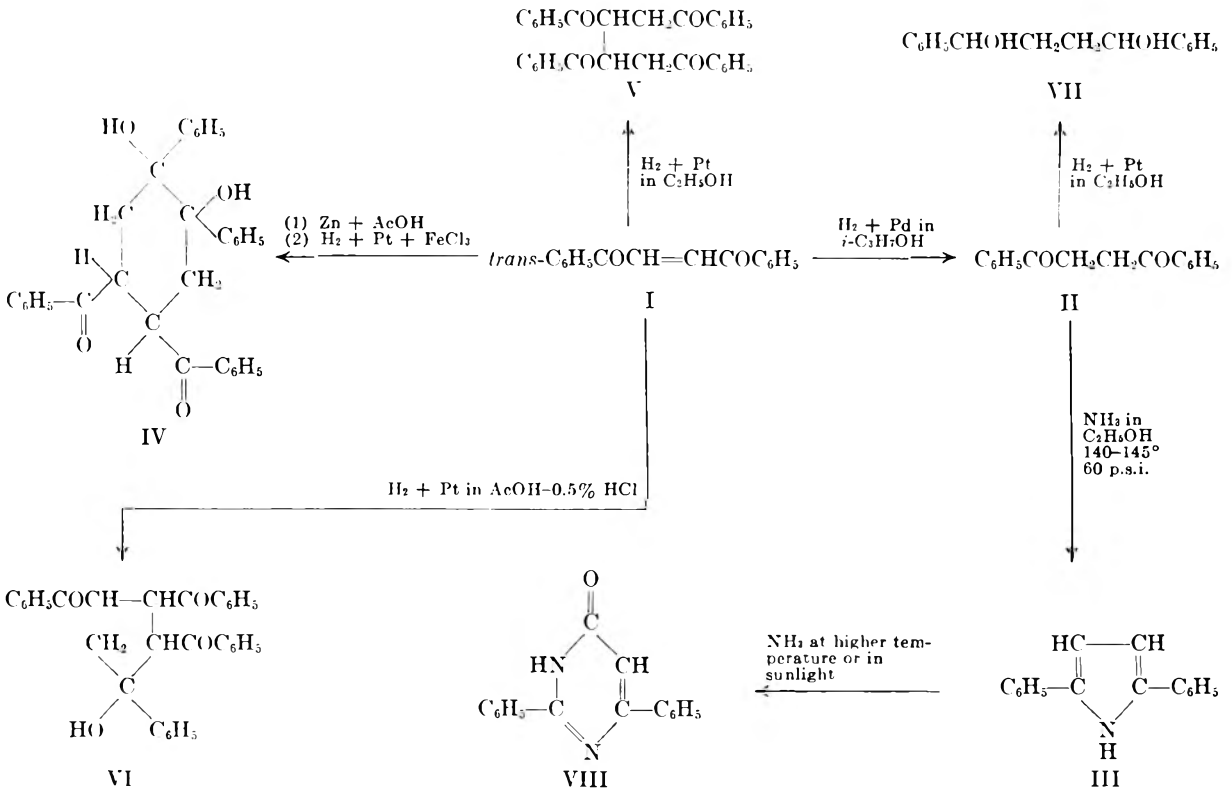
The synthesis of 2,5-diphenylpyrrole (III) from *trans*-1,4-diphenyl-2-butene-1,4-dione (I) *via* 1,4-diphenyl-1,4-butanedione (II) has been elaborated. Optimum conditions for the conversion of I to II have been found to be the palladium catalyzed pressure hydrogenation of I in isopropyl alcohol at room temperature. The pyrrole ring most effectively may be formed from II with ammonia under pressure at 140–145°.

The relative stability of 2,5-diphenylpyrrole (III) prompted us to include this compound in our investigations on new polymerizable heterocyclic compounds. Principally, there are two small-scale procedures for the synthesis of III, namely, by the ring-closing action of ammonia or ammonium acetate on either 1,4-diphenyl-1,4-butanedione[1,2] (II) or ethyl phenacylbenzoylacetate.[2] For the planned investigations it was necessary to elaborate a route by which a pure grade of III could economically be synthesized in larger quantities. Such a path lay in the reaction sequence starting with *trans*-1,4-diphenyl-2-butene-1,4-dione (I), converting this into II and finally ring-closing this to III.

Chief difficulties in this reaction sequence were encountered particularly with the conversion of I into II. Although a variety of methods for reducing I to II is known, the procedures either require costly reagents or give low yields or furnish II along with other by-products. The latter are frequently the result of a pronounced tendency of I to take a bimolecular course under certain reducing conditions. Thus, even in such reductions of I that superficially appear to proceed smoothly, for instance those effected by zinc,[3,4] we found as by-product a colorless compound melting at 159°. It has twice the molecular weight of I but does not respond to any carbon-carbon double bond agents and is most probably 4,5-dibenzoyl-1,2-diphenyl-1,2-cyclohexanediol (IV).[5]

(1) A. F. Holleman, *Ber.* **20**, 3361 (1887).
(2) S. Kapf and C. Paal, *Ber.* **21**, 3061 (1888).
(3) C. Paal and H. Schulze, *Ber.* **33**, 3798 (1900).
(4) C. F. H. Allen, D. M. Young, and M. R. Gilbert, *J. Org. Chem.* **2**, 240 (1937).
(5) C. Weygand and W. Meusel, *Ber.* **76**, 498 (1943).




Moreover, in one of the most simple and attractive reducing methods of I, the catalytic hydrogenation, II is accompanied most of the time by products of higher melting point ranges. Among the products resulting from the platinum catalyzed reduction of I, 1,2,3,4-tetrabenzoylbutane (V),[5,6] 1-phenyl-2,3,4-tribenzoyl-1-cyclopentanol (VI)[6] and IV[7] have been identified. Based on the fact that small amounts of acid effect normal hydrogenation of the double bond in pseudocodeine,[8] a method was worked out[6] by which I was said to be catalytically reducible in ethylacetate at atmospheric pressure furnishing a 90–95% yield of II. However, even under these conditions II is formed along with considerable amounts of higher melting materials. In view of the fact that II in the presence of platinum will undergo further reduction to 1,4-diphenyl-1,4-butanediols (VII),[6] we have investigated reductions of I with palladium catalysts. Our experiments have led to finding a set of conditions under which a 67% yield of pure II may be obtained. These conditions may be summarized as carrying out the palladium catalyzed reduction of I in isopropyl alcohol at room temperature and an initial hydrogen pressure of 60 p.s.i.

A very effective means of following the course and testing the completion of reduction was by infrared spectroscopy. The infrared spectrum of I has been obtained previously[9] but covered the range of 700–1600 cm.$^{-1}$ only. Furthermore, the sample had been mulled in mineral oil so that the region between 1470–1570 cm.$^{-1}$ could not be evaluated since this was obliterated by strong bands of mineral oil itself. Because of this, it proved to be necessary for our purpose to measure the infrared spectra of I and II over the full range of 700–4000 cm.$^{-1}$ and to use the potassium bromide dispersion method. Upon comparing the two infrared spectra of I and II, it becomes apparent that, aside from several joint absorption bands, the two compounds exhibit several individual marked frequencies by which their authenticity and purity may be identified. To the absorption bands that both compounds have in common belong all those associated with the aromatic nucleus, namely, the =C—H stretching mode at 3010–3030 cm.$^{-1}$, the C=C skeletal in-plane vibrations at 1590–1600 cm.$^{-1}$ and 1440–1450 cm.$^{-1}$, the 990–1020 cm.$^{-1}$ bands typical of substituted aromatic rings, and the CH out-of-plane deformations between 710–800 cm.$^{-1}$. Another band common to both I and II is the carbonyl stretching absorption at 1180–1190 cm.$^{-1}$ exhibited by most aromatic ketones.[10]

Since the time of the controversy whether the lower melting isomer of I were assigned the *cis* or *trans* configuration,[11,12] considerable work has been

(6) R. E. Lutz and F. S. Palmer, *J. Amer. Chem. Soc.* **57**, 1957 (1935).

(7) H. Keller, R. Pasternak, and H. v. Halban, *Helv. Chim. Acta* **29**, 512 (1946).

(8) R. E. Lutz and L. F. Small, *J. Amer. Chem. Soc.* **54**, 4715 (1932).

(9) L. P. Kuhn, R. E. Lutz, and C. R. Bauer, *J. Amer. Chem. Soc.* **72**, 5058 (1950).

(10) N. B. Colthup, *J. Opt. Soc. Amer.* **40**, 379 (1950).

(11) C. Paal and H. Schulze, *Ber.* **35**, 168 (1902).

(12) I. Smedley, *J. Chem. Soc.* **95**, 219 (1909).

done on this question. However, the infrared spectrum does not seem to have been consulted in this respect. Yet it contains strong bands at 970, 1290, and 1310 cm.$^{-1}$ which arise from —CH=CH— deformation vibrations. Of these, the first has been shown to be an out-of-plane deformation mode appearing with trans double bonds only,[13] while the latter two are commonly associated with —CH=CH— in-plane deformation vibrations of *trans* disubstituted ethylenes.[14] The strong absorption at 1640 cm.$^{-1}$ in the spectrum of I may be assigned to the stretching vibration of the carbonyl group, this being in conjugation with the ethylenic C=C link.

According to the common rule that the carbonyl group of saturated ketones absorbs at a frequency that is about 40 cm.$^{-1}$ higher than that of a C=C conjugated C=O group, one would expect a shift to 1680 cm.$^{-1}$ upon hydrogenating I to II. The infrared spectrum of II indeed confirms this expectation. In addition to this, two more bands typical of saturated ketones[10,15] appear in the spectrum of II, namely, at 1220 and 1350 cm.$^{-1}$. Of course, in successful hydrogenation experiments the aforementioned bands arising from —CH=CH— vibrations must not show up any more. Instead, the C—H stretching band due to the newly formed —$CH_2$—$CH_2$— group appears at 2910 cm.$^{-1}$.

Our investigations of a suitable method for synthesizing III on a larger scale resulted in finding that the ring-closing reaction of II by means of ammonia, a method initiated by Holleman and later improved through introduction of a pressure technique by Allen *et al.*,[4] is best suited. However, we also found that the temperature in this reaction step is critical, in that with increasing temperature a red discoloration of the reaction mixture accompanied by the formation of a higher melting compound becomes prevailing. This thermal effect is most probably identical with the light-induced action of ammonia on III resulting in a ring expansion with formation of 2,6-diphenyl-4(3)-pyrimidone (VIII).[16] Optimum temperature for the ammonia-pressure-conversion of II to III has now been found to be at 140–145°.

(13) R. S. Rasmussen and R. R. Brattain, *J. Phys. Chem.* **15**, 131 (1947).

(14) N. Sheppard and G. B. B. M. Sutherland, *Proc. Roy. Soc.* **A196**, 195 (1949).

(15) S. A. Francis, *J. Chem. Phys.* **19**, 942 (1951).

## EXPERIMENTAL[17]

*1,4-Diphenyl-1,4-butanedione* (II). The *trans*-1,4-diphenyl-2-butene-1,4-dione (I) used was a commercial grade which, prior to hydrogenation, was recrystallized from ethanol and exhibited then a melting point of 111–112°.

A suspension of 75 g. (0.3 mole) of I, 1 g. of 10% palladium on powdered charcoal catalyst, and 20 ml. of conc. hydrochloric acid in 2000 ml. of isopropyl alcohol was agitated at room temperature in an autoclave[18] under an initial hydrogen pressure of 60 p.s.i. until an amount of 0.95–1.0 mole of hydrogen had been taken up (approx. 15 min.). Then the mixture is heated to boiling and filtered hot. Upon cooling, 51 g. (67% yield) of long white needles of II was obtained, m.p. 147–148°. A specimen prepared for analysis and the infrared spectrum by recrystallization from absolute ethyl alcohol melted at 148–149°.

*Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.73; H, 5.80.

*2,5-Diphenylpyrrole* (III). To 1000 ml. of absolute ethyl alcohol saturated with dry ammonia gas under ice cooling was added 150 g. (0.6 mole) of powdered II and the mixture heated in a sealed pressure vessel[18] for 6 hr. at 140–145°. After cooling, the reaction contents were poured into 2000 ml. of water when III was precipitated as a pale yellow solid. Vacuum-filtered and dried, it amounted to 134 g. (97% yield based on II) and melted at 142–144°. It could best be purified by recrystallization from a 4:1 ethyl alcohol-water mixture; silver gray scales, m.p. 143–144°.

*Anal.* Calcd. for $C_{16}H_{13}N$: C, 87.63; H, 5.98; N, 6.39. Found: C, 87.49; H, 6.01; N, 6.50.

The infrared measurements were made on a Perkin-Elmer double beam spectrophotometer, Model 137. The spectra refer to potassium bromide disks.

DEARBORN, MICH.

(16) S. Capuano and L. Giammanco, *Gazz. chim. ital.* **85**, 217 (1955).

(17) All melting points were determined using a Fisher-Johns melting point apparatus.

(18) The autoclave used was a "Magne Dash High Pressure" type (Autoclave Engineers, Inc., Erie, Pennsylvania) constructed of 316 stainless steel and agitated by magnetic action of a dasher.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF LOYOLA UNIVERSITY]

# Synthesis of Some Substituted Pyridines[1]

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*Received October 23, 1959*

Three related series of bicyclic substituted pyridines have been prepared, differing from one another in the size of the carbocyclic ring fused in the 2,3-position. The cyclopentane, cyclohexane, and cycloheptane rings were the carbocyclic rings fused in the 2,3-positions. Other substituent groups have been placed in the 5-position, the 6-position, or the 5- and 6-positions of the pyridine nucleus. Evidence is also presented showing that it is possible to reduce selectively nitriles to primary amines or secondary amines, by adjusting the acidity of the solution.

The compounds synthesized during the present investigation were prepared in order to correlate the effect of the variation of substituents on the pyridine ring with changes in the infrared absorption spectra. In addition, these compounds might prove useful physiologically as they are related to some vitamins. The bioassays, which are being conducted, and the study of the infrared spectra will be reported elsewhere.

The general synthetic reaction scheme is illustrated in Fig. 1. The reactions were standard in nature, except for the hydrogenations, which are discussed later in this paper.

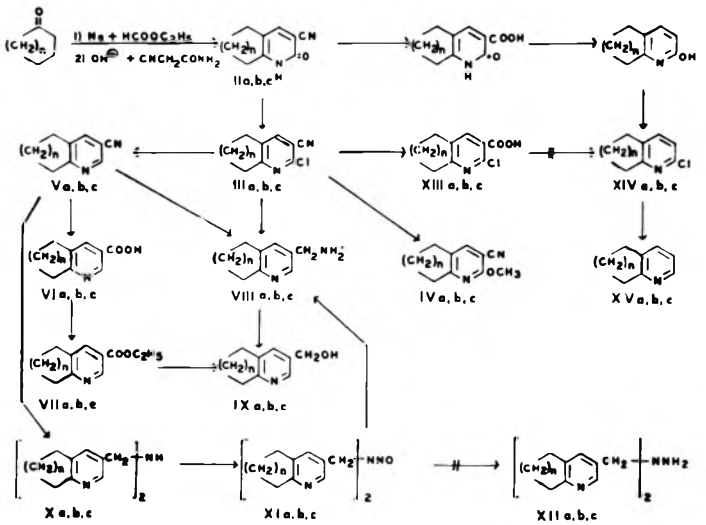

Fig. 1. Reaction scheme. For "a" compounds $n = 1$. For "b" compounds $n = 2$. For "c" compounds $n = 3$

## EXPERIMENTAL

Compounds II through III were prepared as reported previously.[4]

*6,7-Dihydro-2-methoxy-3-cyano-1,5-pyrindine* (IVa). To 33 ml. of freshly prepared 1*N* sodium methoxide was added 3.0 g. of IIIa dissolved in 20 ml. of absolute alcohol. The flask containing the solution was stoppered loosely and placed on a hot plate at about 60° for 2 hr. The solution was filtered while warm to remove most of the sodium chloride, cooled in an ice bath and the white crystalline product was filtered. The solution developed a grayish color as the reaction proceeded. The yield was 2.5 g. (86%), m.p. 114–114.5° after one recrystallization from methanol.

*Anal.* Calcd. for $C_{10}H_{10}N_2O$: N, 16.1. Found: N, 16.1.

*6,7-Dihydro-3-cyano-1,5-pyrindine* (Va). To 160 ml. of a 1% solution of sodium hydroxide in absolute ethanol was added 3.0 g. of IIIa. To this solution was added 2.0 g. of a catalyst consisting of 5% palladium on charcoal. The mixture was hydrogenated using the Parr pressure reaction apparatus, under about 25 p.s.i. hydrogen pressure. The theoretical amount of hydrogen was taken up in 3 min., and after 1 more min. the shaker was turned off, 3 ml. concentrated hydrochloric acid was added, and the mixture filtered. The catalyst was washed three times with small portions of 95% ethanol. The resulting solution was evaporated at reduced pressure, and about 10 ml. of water containing 3 ml. concentrated hydrochloric acid added. The solution was filtered and brought to a *p*H of about 5 to precipitate the product. The white crystals were filtered and air dried. The yield in a typical run was 2.1 g. (87%), m.p. 88°. The product would not form a picrate.

*Anal.* Calcd. for $C_9H_8N_2$: N, 19.4. Found: N, 19.4.

*6,7-Dihydro-1,5-pyrindine-3-carboxylic acid* (VIa). This acid was prepared by refluxing 1.5 g. Va for 8 hr. with 20 ml. of 6*N* hydrochloric acid. After refluxing, the solution was cooled and 50% aqueous sodium hydroxide added dropwise

(1) Abstracted from the dissertation of Edith M. Godar submitted in February of 1959 to the Graduate School of Loyola University, Chicago, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Dreyfus Foundation Fellow, 1956–58.

(3) To whom all inquiries should be sent.

(4) E. M. Godar and R. P. Mariella, *J. Am. Chem. Soc.*, 79, 1402 (1957).

until a precipitate formed. This occurred at about *p*H 5. The precipitate was filtered, washed with several small portions of water, and air dried. Yield, 1.5 g. (88.5%), m.p. 223–225°.

*Anal.* Calcd. for $C_9H_9NO_2$: N, 8.6. Found: N, 8.3.

*6,7-Dihydro-3-carboethoxy-1,5-pyrindine* (VIIa). To 15 ml. of absolute ethanol in a 50-ml. flask was added 1.5 g. of Va. Then 6.8 ml. of conc. sulfuric acid was added and the reaction mixture heated at reflux for 12 hr. The solution was cooled, filtered, and made alkaline with 20% aqueous sodium hydroxide. The alkaline solution was extracted with three small portions of ethyl ether, the ether layer dried, and evaporated. Yield after one recrystallization from 95% ethanol was 1.3 g. (65.5%), m.p. 42°. This compound would not form a picrate.

*Anal.* Calcd. for $C_{11}H_{13}NO_2$: N, 7.3. Found: N, 7.1.

*6,7-Dihydro-3-aminomethyl-1,5-pyrindine dihydrochloride* (VIIIa). To a solution of 2.4 g. of Va in 100 ml. of absolute ethanol was added 3.0 g. of 5% palladium and 4.0 ml. of conc. hydrochloric acid. The pressure reaction flask containing the mixture was placed in the Parr hydrogenation apparatus and shaken at about 35 p.s.i. of hydrogen. The theoretical uptake occurred in about 3 min. and the shaking was continued for another 10 min. with no further reaction. The flask was removed from the apparatus and the contents filtered through a Buchner funnel. The catalyst was washed three times with 95% ethanol and the washings added to the filtrate. The ethanolic solution was evaporated under reduced pressure. Absolute ethanol was added during the evaporation in small portions until the amine dihydrochloride precipitated from the solution. At this time about 50 ml. of absolute ethyl ether was added and the powdery white crystals filtered from the solution. The dihydrochloride was allowed to dry in air. The yield in a typical reaction was 2.5 g. (85%), m.p. 208–210°.

*Anal.* Calcd. for $C_9H_{14}Cl_2N_2$: N, 12.7. Found: N, 12.7.

VIIIa *may also be prepared from* IIIa *as follows.* To about 160 ml. of a 1% solution of sodium hydroxide in absolute ethanol containing 2.0 g. of 5% palladium on charcoal was added 3.0 g. of IIIa. The mixture was placed in the low pressure hydrogenation apparatus and shaken at about 25 p.s.i. until one third of the theoretical amount of hydrogen was consumed. This occurred in 2 min. and the shaking was continued for 1 min. more. The shaker was turned off, 8 ml. of conc. hydrochloric acid was added and the hydrogenation was resumed. The theoretical amount of hydrogen was taken up in about 5 min. and the shaking was allowed to proceed for another 5 min. The bottle was removed from the apparatus and the contents filtered through a Buchner funnel. The precipitate was washed three times with 95% ethanol. The ethanol solution was evaporated as described above. The yield in a typical reaction was 2.8 g. (76%). The infrared spectrum of this compound was identical with that of the compound prepared by the alternate method.

*6,7-Dihydro-3-hydroxymethyl-1,5-pyrindine hydrochloride* (IXa). A solution of 2.2 g. of the dihydrochloride of VIIIa in approximately 40 ml. of water was prepared. A solution of 3.4 g. sodium nitrite in about 40 ml. of water was also prepared. These solutions were placed in separate burets whose tips were immersed in 150 ml. of 20% hydrochloric acid in a 250-ml. beaker and run in slowly at room temperature. The reagents were added at a slow enough rate to keep the evolution of nitrogen oxides to a minimum. The solution was stirred until the evolution of gas ceased. Then it was heated to boiling for several minutes. The solution was evaporated under reduced pressure with the concurrent addition of absolute ethanol. When all the water had been displaced the remaining salts were extracted three times with hot absolute ethanol and the ethanol filtered. The resulting solution was reduced in volume and the hydrochloride of the alcohol completely precipitated by the addition of 25 ml. of absolute ethyl ether. The solution was filtered and the white crystalline solid dried in a desiccator. Yield 1.3 g. (60%), m.p. 130°.

*Anal.* Calcd. for $C_9H_{12}ClNO$: N, 7.6. Found: N, 7.8.

IXa may also be prepared from the corresponding ester VIIa, by reduction with lithium aluminum hydride. One-tenth g. of VIIIa was dissolved in 5 ml. anhydrous ether and 1.0 ml. of 0.584*N* lithium aluminum hydride in ether added. The mixture was stirred for several minutes and several drops of 50% aqueous sodium hydroxide solution added. The mixture was extracted several times with 2–3 ml. portions of ether and the ether evaporated. Yield 0.055 g. (71%). The infrared spectrum of the hydrochloride of this compound was identical with that of the compound prepared by the alternate method.

*Di([6,7-dihydro-1,5-pyrindine-β-yl]methyl) amine* (Xa). A pressure bottle containing 3.0 g. of IIIa, 6 g. of ammonium carbonate, 2.0 g. of a catalyst consisting of 5% palladium on charcoal and about 80 ml. absolute ethanol was placed in the Parr low pressure hydrogenation apparatus and the contents shaken under a hydrogen pressure of about 15 p.s.i. The reaction was complete in 40 min. The solution was filtered and the catalyst washed three times with small portions of 95% ethanol. The ethanol was evaporated under reduced pressure with the concomitant addition of absolute ethanol to displace any water present. The amine hydrochloride precipitated from ethanol and was filtered. The free amine was obtained by dissolving the hydrochloride in dilute hydrochloric acid and making the resultant solution basic with sodium hydroxide. The alkaline solution was extracted with ether until no more oil was apparent; the ether solution was dried with anhydrous potassium carbonate. Upon evaporation of the ether the free amine was obtained, m.p. 118°, yield, 2.1 g. (89.5%).

*Anal.* Calcd. for $C_{18}H_{21}N_3$: N, 15.0. Found: N, 15.0.

*Di([6,7-dihydro-1,5-pyrind-β-yl]methyl)-N-nitrosamine* (XIa). To 1.5 g. of the monohydrochloride of Xa in a 25-ml. Erlenmeyer flask was added 6.7 ml. of a 10% solution of sodium nitrite in conc. sulfuric acid. The resulting solution was placed on a hot plate at about 50° for 1 hr. After this time the acid mixture was poured over about 100 g. ice and the solution allowed to come to room temperature. It was heated to boiling to expel any fumes from unreacted nitrite. The solution was cooled and neutralized with 50% aqueous sodium hydroxide. A precipitate formed which was allowed to settle overnight, and was filtered from the solution and washed with a small amount of water. The yield was 1.2 g. (82%), melting point after one recrystallization from absolute ethanol was 146–148°.

*Anal.* Calcd. for $C_{18}H_{20}N_4O$: C, 70.0; H, 6.5; N, 18.2. Found: C, 69.6; H, 6.4; N, 18.9.

The nitrosamine was difficult to purify as such, but readily formed a *dipicrate*, m.p. 203.5–204.5°. This was analyzed by titration in glacial acetic acid using perchloric acid as the titrant.

*Anal.* Calcd. for $C_{30}H_{26}N_{10}O_{14}$: Equivalent weight 384. Found: 387.

*Attempted preparation of di([6,7-dihydro-1,5-pyrind-β-yl]-methyl)hydrazine* (XIIa). To 7.2 ml. of 0.584*N* lithium aluminum hydride was added a solution of 1.2 g. of XIa in 20 ml. of dry ethyl ether. The mixture was stirred for an hour after all the reagents had been added. The excess hydride was decomposed with water and 0.3 g. sirupy phosphoric acid was added. The resulting mixture was extracted three times with ether. After the ether was evaporated 1.1 g. of an oil was recovered, which proved to have an infrared spectrum identical with that of the free base of compound VIIIa, and was therefore a primary amine. No hydrazine was obtained, although a small amount of the starting compound was recovered.

*6,7-Dihydro-2-chloro-1,5-pyrindine-3-carboxylic acid* (XIIIa). To 25 ml. of a 5% aqueous solution of sodium hydroxide in a 50-ml. flask was added 1.5 g. of IIIa. The mixture was heated under reflux for 4 hr. The solution was cooled and acidified. The white precipitate which formed was filtered and washed several times with small portions of water. Yield, 1.5 g. (96%), m.p. 206–208°.

*Anal.* Calcd. for $C_9H_8ClNO_2$: N, 7.1. Found: N, 7.2.

*Attempted preparation of 6,7-dihydro-2-chloro-1,5-pyrindine* (XIVa). This compound had been previously prepared by another route,[4] but it was thought that it could be prepared also by the decarboxylation of compound XIIIa. When an attempt was made to decarboxylate this compound by heating above the melting point, only hydrochloric acid was evolved. All attempts to separate material from the residue yielded only unchanged chloropyrindine. No attempts were made to identify the material resulting from the removal of hydrochloric acid from the molecule.

The remaining two series of compounds were prepared by the same methods as used for the 6,7-dihydropyrindines. Therefore, the yields and physical constants are noted here:

*6,7,8,9-Tetrahydro-2-methoxy-3-cyanoquinoline* (IVb). (79%), m.p. 106–106.5°.

*Anal.* Calcd. for $C_{11}H_{12}N_2O$: N, 14.9. Found: N, 15.0.

*6,7,8,9-Tetrahydro-3-cyanoquinoline* (Vb). (96%), m.p. 81–82°.

*Anal.* Calcd. for $C_{10}H_{10}N_2$: N, 17.7. Found: N, 17.6.

*6,7,8,9-Tetrahydroquinoline-3-carboxylic acid* (VIb). (89.5%), m.p. 240° dec.

*Anal.* Calcd. for $C_{10}H_{11}NO_2$: N, 7.9. Found: N, 7.9.

*6,7,8,9-Tetrahydro-3-carboethoxyquinoline* (VIIb). (67%), $b_{1.1}$ 126°.

*Anal.* Calcd. for $C_{12}H_{15}NO_2$: N, 6.8. Found: N, 6.9.

*6,7,8,9-Tetrahydro-3-aminomethylquinoline dihydrochloride* (VIIIb). (71.5%), m.p. 227–230°.

*Anal.* Calcd. for $C_{10}H_{16}Cl_2N_2$: N, 11.9. Found: N, 11.9.

*6,7,8,9-Tetrahydro-3-hydroxymethylquinoline hydrochloride* (IXb). (70%), m.p. 147°.

*Anal.* Calcd. for $C_{10}H_{14}ClNO$: N, 7.0. Found: N, 7.1.

*Di-([6,7,8,9-tetrahydroquinol-β-yl]methyl)amine* (Xb). (88%), m.p. 79–80°.

*Anal.* Calcd. for $C_{20}H_{25}N_3$: N, 13.7. Found: N, 13.8.

*Di-([6,7,8,9-tetrahydroquinol-β-yl]methyl)-N-nitrosamine* (XIb). (81.5%), m.p. 100–101°, picrate m.p. 180–182°. This compound was analyzed as the picrate, as the amine was difficult to obtain in crystalline form.

*Anal.* Calcd. for $C_{32}H_{30}N_{10}O_{15}$: N, 17.6. Found: N, 17.6.

*6,7,8,9-Tetrahydro-2-chloroquinoline-3-carboxylic acid* (XIIIb). (91.6%), m.p. 179–180°.

*Anal.* Calcd. for $C_{10}H_{10}ClNO_2$: N, 6.6. Found: N, 6.7.

*6,7,8,9-Tetrahydro-2-methoxy-3-cyano-5-cyclohepta(b)pyridine* (IVc). This compound formed much more slowly than did the other two compounds of this type, as evidenced by the time of appearance of color in the solution. The solution developed only a slight yellow color during the course of the reaction. (68%) after two recrystallizations from methanol. M.p. 82–84°.

*Anal.* Calcd. for $C_{12}H_{14}N_2O$: N, 13.9. Found: N, 13.8.

*6,7,8,9-Tetrahydro-3-cyano-5-cyclohepta(b)pyridine* (Vc). (98%), m.p. 89–90°.

*Anal.* Calcd. for $C_{11}H_{12}N_2$: N, 16.3. Found: N, 16.1.

*6,7,8,9-Tetrahydro-5-cyclohepta(b)pyridine-3-carboxylic acid* (VIc). (90%), m.p. 218°.

*Anal.* Calcd. for $C_{11}H_{13}NO_2$: N, 7.3. Found: N, 7.5.

*6,7,8,9-Tetrahydro-3-carboethoxy-5-cyclohepta(b)pyridine* (VIIc). (78.5%), m.p. 52°.

*Anal.* Calcd. for $C_{13}H_{17}NO_2$: N, 6.4. Found: N, 6.5.

*6,7,8,9-Tetrahydro-3-aminomethyl-5-cyclohepta(b)pyridine dihydrochloride* (VIIIc). (86.5%), m.p. 226–227°.

*Anal.* Calcd. for $C_{11}H_{18}Cl_2N_2$: N, 11.2. Found: N, 11.0.

*6,7,8,9-Tetrahydro-3-hydroxymethyl-5-cyclohepta(b)pyridine hydrochloride* (IXc). (80%), m.p. 127–128°.

*Anal.* Calcd. for $C_{11}H_{16}ClNO$: N, 6.6. Found: N, 6.6.

*Di-([6,7,8,9-tetrahydro-5-cyclohepta(b)pyrid-β-yl]methyl) amine* (Xc). (82.5%), m.p. 86–87°.

*Anal.* Calcd. for $C_{22}H_{29}N_3$: N, 12.5. Found: N, 12.6.

*Di-([6,7,8,9-tetrahydro-5-cyclohepta(b)pyrid-β-yl]methyl)-N-nitrosamine* (XIc). (84%), m.p. 168.5–169°.

*Anal.* Calcd. for $C_{22}H_{28}N_4O$: N, 15.4. Found: N, 15.6.

*6,7,8,9-Tetrahydro-2-chloro-5-cyclohepta(b)pyridine-3-carboxylic acid* (XIIIc). (92.5%), m.p. 168–170°.

*Anal.* Calcd. for $C_{11}H_{12}ClNO_2$: N, 6.2. Found: N, 6.4.

*Discussion of hydrogenation procedures.* The first attempts to convert the cyanochloropyridines to aminomethylpyridines were made by the use of the procedure employed by Perez-Medina, Mariella, and McElvain.[5] These authors had used this method successfully to reduce some monocyclic cyanochloropyridines to the corresponding primary amines.

When this procedure (palladium on charcoal in acidic solution) was used with the bicyclic cyanochloropyridines, it was found that the uptake of hydrogen was very slow, the yields poor, several products were formed, and about half of the starting material was recovered.

Similar reductions in strongly basic solutions or in the presence of an excess of ammonium carbonate resulted in a reasonable rate of reduction (one hour and a half) with the formation of the *corresponding secondary amines.*

It was also discovered that in a slightly basic or neutral solution, the hydrogenations of the bicyclic cyanochloropyridines proceeded rapidly to about one third of theoretical and stopped. When an excess of acid was then added, the remainder of the theoretical amount of hydrogen was absorbed quickly. From this it follows that the halogen is rapidly removed in base (two to three minutes) and the nitrile easily and quickly reduced (three to six minutes) in acid to form the primary amine.

In order to check these procedures a series of halogen compounds were hydrogenated in the presence of sodium hydroxide. The compounds used were chlorobenzene, whose halogen was completely removed in forty-five minutes; bromobenzene, four minutes; iodobenzene, three minutes; and 2-bromopyridine in six minutes. Samples of benzonitrile and nicotinonitrile did not absorb hydrogen under the basic conditions used.

Using the acidic ethanolic medium the following nitriles were reduced to primary amines: nicotinonitrile in twenty-five minutes, 6,7-dihydro-3-cyano-1,5-pyrindine in five minutes, 6,7,8,9-tetrahydro-3-cyanoquinoline in ten minutes, and 6,7,8,9-tetra-3-cyano-5-cyclohepta(b)pyridine in three minutes.

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

# Synthesis of Isoquinoline Alkaloids. II. The Synthesis and Reactions of 4-Methyl-3-pyridinecarboxaldehyde and Other 4-Methyl-3-substituted Pyridines[1,2]

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The synthesis of 4-methyl-3-pyridinecarboxaldehyde has been accomplished by an unequivocal route. The syntheses of several new 4-methyl-3-substituted pyridines have been carried out and the methods for the preparation of others have been improved.

In general, isoquinoline compounds are prepared from 2-arylethylamine derivatives or alkyl aldimine compounds (both containing a preformed benzene ring) by intramolecular cyclization.[4] This investigation is directed toward the synthesis of isoquinoline compounds from a preformed pyridine nucleus. Such a route would allow the introduction of complex substituents in the 6- and 7-positions at a late stage in the synthesis and would be particularly applicable to certain of the bisbenzylisoquinoline alkaloids. For this purpose, 4-methyl-3-pyridinecarboxaldehyde, X, presents two reactive functional groups, a $\gamma$-methyl group and a carbonyl, which could conceivably be converted into carbons five and eight of the isoquinoline molecule.

3-Cyano-4-methylpyridine, V, was chosen as a starting point for the synthesis of the desired aldehyde. The preparation of this nitrile was carried out by ring closure[5] followed by synthetic operations. This is in contrast to the reported synthesis[6,7] which involved substitution reactions on a pyridine nucleus. Thus, 3-cyano-2,6-dihydroxy-4-methylpyridine, III, which had been previously prepared in low yield by Guareschi[8] and Hope,[9] was obtained, as a salt, in yields of 85 to 95% by the condensation of ethyl acetoacetate and cyanoacetamide in the presence of a mole of piperidine or potassium hydroxide. In contrast to previous work,[9] the intermediate piperidinium or potassium salts, I and II, were isolated. This isolation might have been the reason for our near quantitative yields. The proposed structures of these salts are based upon their water solubility, elemental analysis, and the fact that I can be obtained by neutralization of 3-cyano-2,6-dihydroxy-4-methylpyridine with piperidine. The dihydroxypyridine, III, itself was obtained in essentially quantitative yield by the acidification of the salts. The conversion of 3-cyano-2,6-dihydroxy-4-methylpyridine to the corresponding 3-cyano-2,6-dichloro-4-methylpyridine, IV, in yields of 89 to 97% was effected by a fivefold excess of phosphorus oxychloride at elevated temperature. The dichloride did not form a hydrochloride or a picrate. Hydrogenolysis of 3-cyano-2,6-dichloro-4-methylpyridine proceeded satisfactorily in the presence of palladium (from palladium chloride) to give 3-cyano-4-methylpyridine, V, in yields of about 87%. The overall yield for the three steps was 66 to 80%.

Attempts to prepare 4-methyl-3-pyridinecarboxaldehyde, X, directly from the nitrile, V, failed. Controlled lithium aluminum hydride reduction,[10] sodium aluminum triethoxyhydride reduction,[11] Stephen's reduction,[12] and a modified Stephen's reduction[13] yielded only traces of the aldehyde, isolated as the 2,4-dinitrophenylhydrazone. Therefore, a somewhat more involved and indirect approach based upon ethyl 4-methyl-3-pyridinecarboxylate, VII, was followed.

4-Methyl-3-pyridinecarboxylic acid (homonicotinic acid, XI) had been prepared by the oxidation of 4-methylquinoline (lepidine)[14] and by the strong base[6] or strong acid[7] hydrolysis of 3-cyano-4-methylpyridine, V. In view of the difficulties in-

(1) Paper I: J. M. Bobbitt and T.-t. Chou, *J. Org. Chem.*, **24**, 1106 (1959).

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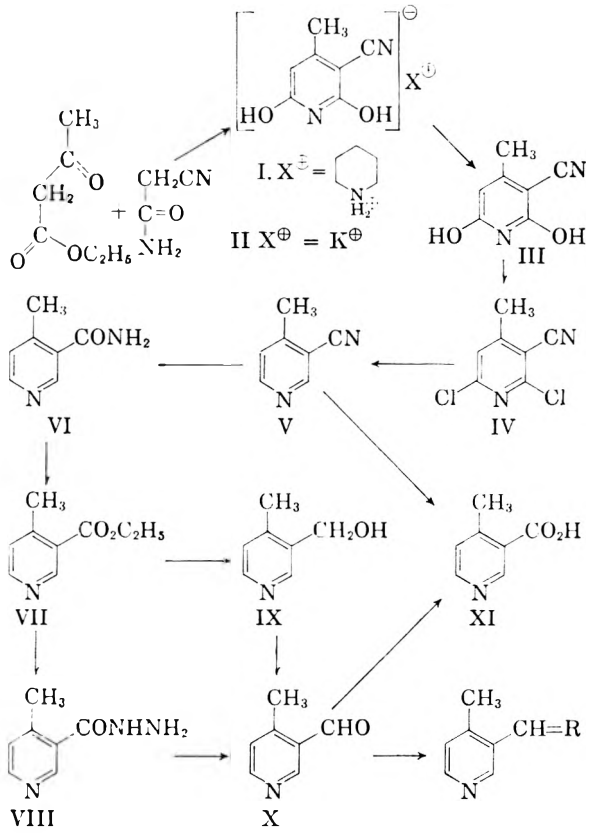
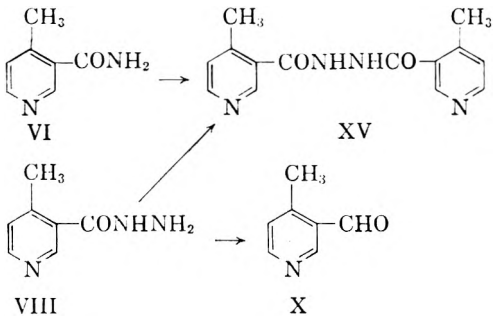


XII. R = O—CH₂
O—CH₂
XIII. R = $C(CO_2C_2H_5)_2$
XIV. R = $NN(CH_3)_2$

volved in these reactions, it was of interest to study the direct conversion of the nitrile, V, to ethyl 4-methyl-3-pyridinecarboxylate. The conversion was accomplished successfully with sulfuric acid in absolute alcohol at elevated temperatures and pressures, although the ester, VII, was obtained in yields of only 48% and was contaminated by traces of nitrile. A better preparation of this ester involved the conversion of the nitrile to 4-methyl-3-pyridinecarboxamide, VI, by partial hydrolysis in the presence of Amberlite IRA-400 (over 90%)[15] followed by alcoholysis in absolute ethanol and anhydrous hydrogen chloride.[16] The ester was obtained in yields of 75 to 85% and its infrared spectrum showed the complete absence of any nitrile or amide impurity. The amide was characterized as a picrate and a hydrochloride and the physical constants of the ester agreed with those in the literature.[17]

The preparation of 4-methyl-3-pyridinecarboxhydrazide, VIII, was undertaken, as it was reported[18] that periodate oxidation of nicotinic acid hydrazide gave reasonable yields of nicotinaldehyde. The conversion of ethyl 4-methyl-3-pyridinecarboxylate, VII, to the hydrazide, VIII, proceeded smoothly in yields of about 90%, and oxidation of the hydrazide with sodium metaperiodate gave low but isolable yields (22 to 30%) of 4-methyl-3-pyridinecarboxaldehyde, X. Repeated attempts to increase this yield were not successful.

The attempted conversion of 4-methyl-3-pyridinecarboxamide to the hydrazide, VIII, by the transamidation reaction of Galat and Elion[19] was not successful but yielded interesting results. Thus, the fusion of 4-methyl-3-pyridinecarboxamide with hydrazine dihydrochloride gave, in 13% yield, 1,2-bis(4-methyl-3-pyridinoyl)hydrazine, XV. Confirmation of this result was established by an alternate synthesis of XV from 4-



methyl-3-pyridinecarboxhydrazide, VIII, by mercuric oxide oxidation.[20] It was observed that this oxidation yielded not only the diacylhydrazine, XV, but the desired aldehyde, X, which could be isolated in yields of 27 to 30% as its 2,4-dinitrophenylhydrazone. However, the reaction was considered inadequate as a preparative method for the aldehyde.

Finally, ethyl 4-methyl-3-pyridinecarboxylate was reduced in good yield (80%) to 3-hydroxymethyl-4-methylpyridine, IX, with lithium aluminum hydride.[21,22] This carbinol was converted to 4-methyl-3-pyridinecarboxaldehyde in 52 to 64% yield by oxidation with lead tetraacetate.[21] The aldehyde was characterized as a 2,4-dinitrophenylhydrazone, an oxime, a semicarbazone and a dimethylhydrazone, XIV.[23] The aldehyde is soluble in ether, chloroform, benzene, ethanol, and partially soluble in water, but is insoluble in hexane.

4-Methyl-3-pyridinecarboxaldehyde, X, is extremely easily oxidized by air to 4-methyl-3-pyridinecarboxylic acid, XI. This reaction con-

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(23) The dimethylhydrazone was prepared because it had been reported [R. H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, **22**, 204 (1957)] that the dimethylhydrazone of nicotinaldehyde has some antitumor activity.

stitutes a structure proof, as the acid isolated is identical in all respects with an authentic sample prepared by the acid hydrolysis[7] of 3-cyano-4-methylpyridine. 2 - Methyl - 3 - pyridinecarboxaldehyde has been reported[24] to form a self condensation product on standing. Although 4-methyl-3-pyridinecarboxaldehyde is very easily oxidized, no dimerization product was observed.

The cyclic ethylene acetal, XII, and ethyl (4-methyl-3-pyridal)malonate, XIII, were prepared in order to explore the reactions of this new aldehyde and to test possible synthetic approaches to 6,7-disubstituted isoquinolines. The acetal, XII, was prepared (66%) by the procedure of Salmi[25] although it was necessary to modify the isolation method somewhat. The acetal was characterized as a picrate. Ethyl (4-methyl-3-pyridal)malonate, XIII, was prepared (69%) according to the method of Allen and Spangler[26] for the preparation of ethyl benzalmalonate. This ester, XIII, appears to hydrolyze and decarboxylate with great ease, as attempts to prepare its picrate yielded a compound whose analysis agrees closely with that of the picrate of β-(4-methyl-3-pyridyl)acrylic acid.

## EXPERIMENTAL[27]

*3-Cyano-2,6-dihydroxy-4-methylpyridine*, III; *piperidine method.*[28] A mixture of 210 g. (2.5 moles) of cyanoacetamide, 316 ml. (325 g., 2.5 moles) of ethyl acetoacetate, 250 ml. (213 g., 2.5 moles) of freshly distilled piperidine, and 800 ml. of methanol was refluxed until crystals began to separate from the reaction mixture and then for 1 hr. more (total time, about 24 hr.). The mixture was allowed to cool and the crystalline salt was separated by filtration and washed thoroughly with methanol to yield 348 g. of the white piperidinium salt of 3-cyano-2,6-dihydroxy-4-methylpyridine, m.p. 229–235° (dec.). The salt gave a deep blue coloration with 5% alcoholic ferric chloride and turned pink in moist air.

*Anal.* Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.25; H, 7.28; N, 17.86. Found: C, 61.28; H, 7.37; N, 17.81.

A compound identical with the above salt in all respects was formed by heating equimolar amounts of piperidine and 3-cyano-2,6-dihydroxy-4-methylpyridine in ethanol.

The salt was dissolved in warm water, filtered, and allowed to cool. Additional water was added, if needed, to dissolve any precipitate and the solution was cautiously acidified with concentrated hydrochloric acid and allowed to cool. The product was separated by filtration, washed with methanol, water, and methanol again, and dried at 60° to yield 257 g., m.p. 295–300° (dec.), lit.,[8,9] chars at 300–304°, m.p. 316–319° (dec.). An additional 97.5 g. (total, 354.5 g., 94.5%) was obtained by acidification of the filtrate from the piperidinium salt. A sample recrystallized from ethanol-water melted at 315–320° (dec.). The compound gave a blue-green coloration with aqueous potassium nitrite, a violet color with 5% ferric chloride solution and turned green on standing in moist air.

*3-Cyano-2,6-dihydroxy-4-methylpyridine; potassium hydroxide method.* A mixture of 336 g. (4 moles) of cyanoacetamide, 507 ml. (520 g., 4 moles) of ethyl acetoacetate, and 850 ml. of methanol was warmed to attain solution and 275 g. (4.18 moles) of potassium hydroxide dissolved in 200 ml. of methanol was added (during 2 hr.) with stirring. During the addition, a white precipitate formed and enough methanol was added to prevent caking. The mixture was heated at reflux temperature and stirred for 8 hr., and the product was removed from the cooled reaction mixture by filtration and washed with methanol. The 3-cyano-2,6-dihydroxy-4-methylpyridine monopotassium salt thus formed was dissolved in warm water, filtered, cooled, acidified with concentrated hydrochloric acid, and isolated as described above. The yield of the pyridinediol, III, varied from 404 to 544 g. (68 to 90%).

*3-Cyano-2,6-dichloro-4-methylpyridine*, IV.[28] 3-Cyano-2,6-dihydroxy-4-methylpyridine (50 g., 0.33 mole) and phosphorus oxychloride (120 ml., 201 g., 1.3 moles) were placed in a glass-lined stainless steel autoclave and maintained at 180° for 4–6 hr. After cooling, the contents were transferred cautiously and with stirring onto cracked ice. The crystalline product was removed by filtration, washed thoroughly with water and dried at 60°. The yield of crude yellow product varied from 55 to 60 g. (88 to 96%), m.p. 109–110°. The analytical sample, m.p. 110–110.5°, was recrystallized twice from ethanol.

*Anal.* Calcd. for $C_7H_4N_2Cl_2$: C, 44.92; H, 2.14; N, 14.97; Cl, 37.90. Found: C, 45.19; H, 2.20; N, 14.95; Cl, 37.86.

*3-Cyano-4-methylpyridine*, V.[28] Crude 3-cyano-2,6-dichloro-4-methylpyridine, (40 g., 0.214 mole), anhydrous sodium acetate (35 g., 0.43 mole), 200 ml. of methanol and 0.5 g. of palladium chloride[29] were shaken with hydrogen (50 p.s.i.) until no more hydrogen was taken up. The catalyst and residue were removed by filtration and washed several times with methanol. The filtrates from ten of these reductions were combined and the methanol was distilled through a 3-ft. Vigreux column. The residue was dissolved in 500 ml. of water, neutralized with solid sodium bicarbonate and extracted with ether. The ether solution was dried over anhydrous sodium sulfate, the solvent was removed, and the oily residue was distilled to yield 219 g. (87%) of 3-cyano-4-methylpyridine, b.p. 79–82°/3 mm., m.p. 45–46°, lit., b.p. 64°/1–2 mm.,[7] m.p. 43–44°.[6] The *picrate* melted at 185–186.5°, lit.[7] 184.5–185.5°, and the *hydrochloride* sublimed at 188–190° and decomposed at 211°, lit.,[7] sublimes 208–209°.

*4-Methyl-3-pyridinecarboxamide*, VI. Amberlite IRA-400-OH (70 g.), 60 g. (0.51 mole) of 3-cyano-4-methylpyridine, and 350 ml. of water were stirred at reflux temperature for 3 hr. The warm mixture was filtered and the filtrate was evaporated on a steam bath to yield 62 g. (89%) of 4-

(24) A. Dornow and H. Bormann, *Chem. Ber.*, **82**, 216 (1949).

(25) E. J. Salmi, *Ber.*, **71**, 1803 (1938).

(26) C. F. H. Allen and F. W. Spangler, *Org. Syntheses*, Coll. Vol. III, 377 (1955).

(27) All melting points were taken on a Kofler Micro Hot Stage Apparatus and are corrected. The analyses were performed by Geller Laboratories of Barconia, N. Y., and Drs. Weiler and Strauss of Oxford, England. We would like to thank the Rohm and Haas Co. of Philadelphia, the Kay-Fries Co. of West Haverstraw, N. J., and the General Aniline and Film Co. of Easton, Pa., for gifts of Amberlite IRA-400, cyanoacetamide, and diglyme (dimethyldiethyleneglycol) respectively.

(28) This is a modification of a procedure used [T. R. Govindachari, K. Nagarajan, and S. Rajappa, *J. Chem. Soc.*, 551 (1957)] for the synthesis, in poor yield, of 3-cyano-2,6-dihydroxy-4-ethylpyridine and ultimately 3-cyano-4-ethylpyridine.

(29) Commercial palladium chloride gave erratic results. Best results were obtained with freshly prepared palladium chloride. See F. P. Treadwell and W. T. Hall, *Analytical Chemistry*, 9th ed., John Wiley and Sons, New York, 1955, p. 525.

methyl-3-pyridinecarboxamide, m.p. 165–167°.[30] The analytical sample, m.p. 167–167.5°, was recrystallized twice from ethanol.

*Anal.* Calcd. for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.42; H, 5.91; N, 20.77.

A *hydrochloride* was prepared in ethanol with anhydrous hydrogen chloride. After three recrystallizations from absolute ethanol, it exhibits m.p. 239–241° (dec).

*Anal.* Calcd. for $C_7H_9N_2Cl$: C, 48.64; H, 5.24; N, 16.24; Cl, 20.54. Found: C, 48.53; H, 5.44, N, 16.01, Cl, 20.49.

A *picrate*, m.p. 217–217.5° was prepared in ethanol and recrystallized three times from the same solvent.

*Anal.* Calcd. for $C_{13}H_{11}N_5O_8$: C, 42.74; H, 3.04; N, 19.17. Found: C, 43.18; H, 3.31; N, 19.23.

*Ethyl 4-methyl-3-pyridinecarboxylate*, VII, *from 3-cyano-4-methylpyridine*. Concentrated sulfuric acid (33 ml.) was added, with stirring, to 25 g. (0.21 mole) of the nitrile, V, in 90 ml. of absolute ethanol and the mixture was maintained at 130° for 14–16 hr. in a glass-lined autoclave. After cooling, the reaction mixture was poured onto 200 g. of cracked ice and the alcohol was removed under vacuum. The resulting aqueous solution was neutralized with sodium bicarbonate and extracted with several portions of ether. The ether solution was dried over anhydrous sodium sulfate, the ether was distilled, and the residue was distilled to yield 16.7 g. (48%) of ester, b.p. 60–62°/0.3–0.5 mm. The infrared spectrum showed that a small amount of nitrile was present.

*Ethyl 4-methyl-3-pyridinecarboxylate*, VII, *from 4-methyl-3-pyridinecarboxamide*, VI. 4-Methyl-3-pyridinecarboxamide (65 g., 0.48 mole) in 3500 ml. of refluxing absolute ethanol[16] was stirred and anhydrous hydrogen chloride was passed in for 5 hr. The solution was heated under reflux with occasional introduction of more hydrogen chloride until solid ammonium chloride precipitated (about 30 hr.). Three liters of alcohol was distilled and the residue was evaporated to dryness under vacuum. The solid residue was dissolved in 300 ml. of water, cautiously neutralized with solid sodium bicarbonate, and extracted with several portions of ether. The combined ether extracts were dried over sodium sulfate, the ether was removed, and the residue was distilled to yield 66.7 g. (85%) of ethyl 4-methyl-3-pyridinecarboxylate, b.p. 96–98°/6 mm., lit.[17] 118°/12 mm., $n_D^{20}$ 1.5059, $d_{25}^{25}$ 1.087. The *picrate* melted at 138.5–140°, lit.[17] 137°.

*4-Methyl-3-pyridinecarboxhydrazide*, VIII. Ethyl 4-methyl-3-pyridinecarboxylate (38.5 g., 0.23 mole) and 100 ml. of 48% hydrazine hydrate containing 5 ml. of absolute ethanol were heated under reflux for 20 hr., cooled, and the precipitated product was removed by filtration, washed with cold water and dried *in vacuo* to yield 32 g. (91%) of product, m.p. 173–175°. The analytical sample, m.p. 176.5–177.3° was recrystallized twice from methanol.

*Anal.* Calcd. for $C_7H_9N_3O$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.41; H, 5.98; N, 27.97.

*1,2-Bis(4-methyl-3-pyridinoyl)hydrazine*, XV, *from* VI. Analogous to the transamidation method of Galat and Elion,[19] a mixture of 5 g. (0.037 mole) of 4-methyl-3-pyridinecarboxamide and 7.7 g. (0.073 mole) of hydrazine dihydrochloride was ground and heated to the melting point until bubbling and foaming subsided. Absolute ethanol (25 ml.) was added to the cooled mixture which was then filtered to remove ammonium chloride. The filtrate was neutralized with aqueous sodium bicarbonate and evaporated to dryness on a steam bath. The residue was extracted with boiling absolute ethanol and the extract was filtered, concentrated, and cooled to yield, after recrystallization from ethanol-water, 1.3 g. (13%) of white crystalline product, m.p. 249–249.5°.

*Anal.* Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.13; H, 5.23; N, 20.87.

1,2-Bis(4-methyl-3-pyridinoyl)hydrazine was also prepared in 15% yield by oxidation with mercuric oxide of 4-methyl-3-pyridinecarboxhydrazide according to a described procedure.[20]

*Oxidation of 4-methyl-3-pyridinecarboxhydrazide*, VIII, *with mercuric oxide. 4-Methyl-3-pyridinecarboxaldehyde 2,4-dinitrophenylhydrazone.* To a stirred mixture of 2.8 g. (0.013 mole) of yellow mercuric oxide, 20 ml. of ethanol, and 1.0 g. of sodium bicarbonate, was added 1.0 g. (0.0066 mole) of 4-methyl-3-pyridinecarboxhydrazide in 50 ml. of ethanol (during 10 min.). The mixture turned dark brown and was heated at reflux for 0.5 hr. The cooled mixture was filtered and the precipitated mercurous oxide was washed with absolute ethanol. One half of the alcoholic filtrate was treated with 250 ml. of a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. The 2,4-dinitrophenylhydrazone which precipitated amounted to 0.28 g. (28%) m.p. 250–255°. After two recrystallizations from absolute ethanol and a vacuum sublimation, the analytical sample melted at 255.5–256°.

*Anal.* Calcd. for $C_{13}H_{11}N_5O_4$: C, 51.83; H, 3.68; N, 23.25. Found: C, 52.11; H, 4.05; N, 23.11.

*3-(Hydroxymethyl)-4-methylpyridine*, IX. Lithium aluminum hydride (23 g., 0.61 mole) was triturated with ether,[22] suspended in 1000 ml. of dry ether and heated, with stirring under reflux for 3 hr. in an atmosphere of nitrogen. A solution of 76 g. (0.46 mole) of ethyl 4-methyl-3-pyridinecarboxylate in 500 ml. of dry ether was added dropwise within 1.5 hr. The reaction mixture was cooled to 0° and decomposed by the cautious addition of 125 ml. of water. The ether layer was decanted and dried over anhydrous potassium carbonate. The remaining solid was extracted with three portions of boiling methanol. The methanol was removed under vacuum from the combined methanol extracts, the residue extracted with chloroform, and the resulting extract dried over potassium carbonate. The respective solvents were removed from the chloroform and ether layers and the combined residues were fractionated through a Wheeler Column (GV 130) to yield 45 g. (80%) of 3-(hydroxymethyl)-4-methylpyridine as a colorless liquid, b.p. 125–127°/1.5–2 mm., which solidified, m.p. 44–46°.

*Anal.* Calcd. for $C_7H_9NO$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.20 H, 7.38; N, 11.54.

When this reduction was carried out at 0°,[21] a gummy mass formed during ester addition and the reaction mixture was difficult to stir.

The *hydrochloride* was prepared by passing dry hydrogen chloride into an ethereal solution of the carbinol and was crystallized three times from ethanol, m.p. 191–192°.

*Anal.* Calcd. for $C_7H_{10}ClNO$: C, 52.67; H, 6.27; N, 8.77; Cl, 22.21; Found: C, 52.96; H, 6.24; N, 8.59; Cl, 21.91.

The *picrate*, m.p. 160.5–162° was prepared in ethanol and recrystallized twice from the same solvent.

*Anal.* Calcd. for $C_{13}H_{12}N_4O_8$: C, 44.32; H, 3.43; N, 15.91. Found: C, 44.38; H, 3.36; N, 15.72.

*4-Methyl-3-pyridinecarboxaldehyde*, X, *from 4-methyl-3-pyridinecarboxhydrazide.* In a manner similar to the procedure of Wingfield, Harlan, and Harmer,[18] approximately 60 ml. of concentrated ammonium hydroxide was added in small portions to a cooled (0°) solution of 16.2 g. (0.076 mole) of sodium metaperiodate in 250 ml. of water. To the cooled, resultant slurry was added 10 g. of 4-methyl-3-pyridinecarboxhydrazide (0.066 mole) in 105 ml. of 8% ammonium hydroxide; the mixture was stirred, with cooling, for an additional 10 min. and allowed to stand at 25° for 20 min. in an atmosphere of nitrogen. A solution of 17.5 g. (0.069 mole) of barium acetate in 150 ml. of water was added, the slurry was filtered, and the filtrate was made nearly neutral with acetic acid. The solution was made basic with solid sodium bicarbonate and extracted with chloroform. The chloroform extracts were dried over an-

(30) This compound has been reported[7] to melt at 146.5–147°, but no nitrogen analysis was given. For this reason, a complete analyses and the preparation of two derivatives are reported. The compound was also prepared from the nitrile by the action of hydrogen peroxide by the method of Noller, *Org. Syntheses*, **Coll. Vol. II,** 586 (1943).

hydrous sodium sulfate. The chloroform was removed under vacuum and the residue was distilled through a six-inch, semimicro Vigreux column to yield 1.8 g. (22%) of 4-methyl-3-pyridinecarboxaldehyde, b.p. 62–64°/3 mm. The analytical sample, b.p. 109–110°/11 mm., was distilled through a Wheeler Column.

*Anal.* Calcd. for $C_7H_7NO$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.20; H, 6.24; N, 11.79.

*4-Methyl-3-pyridinecarboxaldehyde*, X, *from 3-(hydroxymethyl)-4-methylpyridine.* According to the general method of Mićović and Mihailović,[21] lead tetraacetate (107 g., 0.24 mole), and 450 ml. of sodium-dried benzene were heated to reflux in a dry nitrogen filled atmosphere. The heat was removed, and 29.5 g. (0.24 mole) of 3-(hydroxymethyl)-4-methylpyridine in 100 ml. of dry benzene was added dropwise during 10 min. After considerable foaming, the reaction subsided and was heated under reflux for 1.5 hr. After cooling, the tan lead acetate was removed by filtration and was washed with benzene. The benzene filtrate and washings were combined and neutralized by shaking with 10% potassium carbonate. The aqueous layer was washed with chloroform until no further aldehyde was obtained (2,4-dinitrophenylhydrazine solution). The combined benzene and chloroform solutions were dried over sodium carbonate, concentrated under vacuum, and the residue was distilled to yield 18.5 g. (64%) of 4-methyl-3-pyridinecarboxaldehyde, b.p. 62–64°/3 mm.

The *oxime*, m.p. 177.5–180.5° was prepared in water by conventional methods and recrystallized three times from ethanol.

*Anal.* Calcd. for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.61; H, 6.26; N, 20.34.

The *semicarbazone* was prepared by conventional methods and recrystallized three times from absolute ethanol, m.p. 195.5–198.5°.

*Anal.* Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 53.87; H, 5.93; N, 31.14.

The *dimethylhydrazone*, XIV, was prepared from 1,1-dimethylhydrazine by the method of Wiley, Slaymaker, and Kraus,[23] b.p. 90–99°/0.5 mm. The distillate which solidified on standing was recrystallized from pentane (by cooling to 0°) or acetone (by cooling to −50°), m.p. 49.5–51°.

*Anal.* Calcd. for $C_9H_{13}N_3$: C, 66.22; H, 8.03; N, 25.75. Found: C, 66.15; H, 8.06; N, 25.50.

*4-Methyl-3-pyridinecarboxylic acid*, XI, *from 4-methyl-3-pyridinecarboxaldehyde*, X. A portion of aldehyde, X, (about 0.5 g.) was allowed to stand uncovered in air for 2 hr., and the solid which formed was washed with acetone and recrystallized from absolute ethanol to yield 4-methyl-3-pyridinecarboxylic acid, m.p. 213.5–215.5° (dec.), lit.,[7] 215–216°. A mixture melting point of this material and a sample prepared by the method of Webb and Corwin[7] was undepressed.

*2-(4-Methyl-3-pyridyl)-1,3-dioxolane*, XII, (*ethylene acetal of the aldehyde*). A modification of the method of Salmi[25] was used. A mixture of 5 ml. (5.5 g., 0.09 mole) of ethylene glycol, 4 g. (0.033 mole) of 4-methyl-3-pyridinecarboxaldehyde, 30 ml. of dry benzene and a few crystals of *p*-toluenesulfonic acid was refluxed in an atmosphere of nitrogen until a maximum amount of water had collected in an appropriately arranged Dean-Stark water separation apparatus. After cooling, 50 ml. of benzene was added and the solution was washed with 10% sodium carbonate solution. The aqueous solution was in turn washed with chloroform and the combined chloroform and benzene solutions were dried over sodium carbonate and the solvents were evaporated. The residue was heated with 60 ml. of 5% sodium hydroxide solution containing 30 ml. of 3% hydrogen peroxide (ethanol added to maintain solution) to 70–80° for 15 min. (to remove unreacted aldehyde). Another portion of peroxide (20 ml.) was added and the solution was heated for 10 min. more. The alcohol and excess peroxide were removed under vacuum and the liquid residue was extracted with chloroform. The chloroform extract was dried over potassium carbonate and evaporated under vacuum to a residue which on fractionation (Wheeler Column) yielded 3.6 g. of acetal (66%), b.p. 111–113°/2 mm., $n_D^{20}$ 1.5280, $d_{25}^{25}$ 1.154.

*Anal.* Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.15; H, 6.63; N, 8.48.

The *picrate*, m.p. 181.5–184° was prepared in ethanol and recrystallized three times from the same solvent.

*Anal.* Calcd. for $C_{15}H_{14}N_4O_9$: C, 45.69; H, 3.58; N, 14.21. Found: C, 45.82; H, 3.90; N, 14.14.

*Ethyl (4-methyl-3-pyridal) malonate*, XIII. According to the general method of Allen and Spangler[26] a mixture of 5 ml. of freshly distilled ethyl malonate (8.78 g., 0.055 mole), 50 ml. of dry benzene, 4 g. of 4-methyl-3-pyridinecarboxaldehyde (0.033 mole), and a few drops of piperidine was refluxed in an atmosphere of nitrogen until a maximum of water had collected in an appropriately arranged Dean-Stark tube. After the solution had cooled, ether was added and the mixture was extracted with 3*N* hydrochloric acid. The acid extract was washed with ether, made basic with solid sodium carbonate, and again extracted with ether. The ether extract was dried over potassium carbonate and fractionated to yield 6.0 g. (69%) of ethyl (4-methyl-3-pyridal)malonate, b.p. 139–143°/0.5 mm., $n_D^{20}$ 1.5241.

*Anal.* Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.83; H, 6.32; N, 5.53.

The *picrate* was prepared in ethanol, m.p. 107–110.5°. Two recrystallizations for ethanol yielded a new substance, m.p. 136–138.5°, which appeared to be β-(4-methyl-3-pyridyl)acrylic acid picrate.

*Anal.* Calcd. for $C_{20}H_{20}N_4O_{11}$ (expected picrate): C, 48.78; H, 4.09; N, 11.37. Calcd. for $C_{15}H_{12}N_4O_9$ [β-(4-methyl-3-pyridyl)acrylic acid picrate]: C, 45.92; H, 3.08; N, 14.28. Found: C, 45.89; H, 3.72; N, 14.34.

STORRS, CONN.

[CONTRIBUTION FROM EASTERN LABORATORY, EXPLOSIVES DEPARTMENT, E. I. DU PONT DE NEMOURS AND COMPANY]

# Nitrogen-Substituted Derivatives of 2,5-Pyridinedicarboxylic Acid

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The *N*-methyl and *N*-oxide derivatives of 2,5-pyridinedicarboxylic acid were prepared. 2,5-Dicarboxy-*N*-methylpyridinium betaine reacted with potassium ferricyanide in a basic solution to yield 5-carboxy-*N*-methyl-2-pyridone. 2,5-Dicarboxypyridine-*N*-oxide reacted with benzoyl chloride to give 5-carboxy-2-pyridine and with acetic anhydride to give 3-carboxy-4-pyridone.

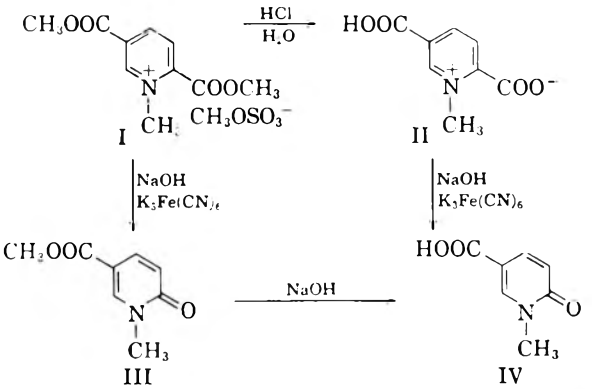
Many of the reactions of pyridine compounds are dependent on the presence of the nitrogen atom which exerts its influence as a center of electron attraction in the pyridine nucleus and as the site for the formation of reactive ammonium salts and *N*-oxides from which numerous transformations are possible. *N*-Alkyl pyridinium salts are prepared from alkyl iodides and pyridine by a vigorous exothermic reaction which is initiated at room temperature. The pyridine monocarboxylic acids are alkylated only under more severe conditions. *N*-Ethylnicotinium iodide was prepared by the reaction of potassium nicotinate with ethyl iodide at 150°.[1] 2-Methyl-6-phenylpyridine-3-carboxylic acid was not alkylated by alkyl halides, but its ethyl ester was alkylated by methyl sulfate.[2]

In our work, the pyridine dicarboxylic acid, 2,5-pyridinedicarboxylic acid (isocinchomeronic acid), was not alkylated by dimethyl sulfate in refluxing toluene or xylene solutions. However, the dimethyl ester of the acid was alkylated smoothly by dimethyl sulfate in a refluxing benzene solution to yield 2,5-dicarbomethoxy-*N*-methylpyridinium methosulfate (I). The dimethyl ester was not alkylated by methyl iodide at 130–140° in a chloroform solution.

2,5-Dicarbomethoxy-*N*-methylpyridinium methosulfate was hydrolyzed in a concentrated hydrochloric acid solution to give 2,5-dicarboxy-*N*-methylpyridinium betaine (II). The methyl betaine was insoluble in organic solvents but was slightly soluble in hot water, from which it was crystallized. The 5-carboxyl group could not be esterified by refluxing the betaine in a methanol solution with a sulfuric acid or a cation-exchange resin catalyst.

A characteristic reaction of *N*-alkyl pyridinium compounds is oxidation to pyridones by mild oxidizing agents, such as potassium ferricyanide, in basic solutions.[3]

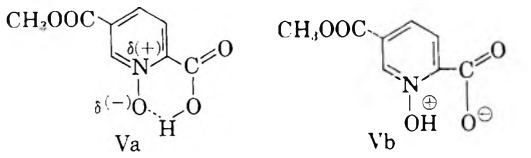
2,5 - Dicarbomethoxy - *N* - methylpyridinium methosulfate reacted rapidly and exothermically with potassium ferricyanide in basic solution. The 2-carbomethoxy group of the pyridinium methosulfate was eliminated as carbon dioxide and methanol, and the ester, 5-carbomethoxy-*N*-methyl-2-pyridone (III), and the acid, 5-carboxy-*N*-methyl-2-pyridone (IV), were formed. An exothermic reaction also occurred when the betaine, II, was oxidized by potassium ferricyanide in a basic solution, and 5-carboxy-*N*-methyl-2-pyridone was isolated as the sole product.




When zinc powder was added to an aqueous solution of 2,5-dicarbomethoxy-*N*-methylpyridinium methosulfate at room temperature, a yellow unstable solid was formed in a slightly exothermic reaction. The yellow crystalline product rapidly decomposed at room temperature and was not characterized.

Pyridine-*N*-oxides usually are prepared readily by the oxidation of pyridine compounds by 30% hydrogen peroxide in acetic acid solutions. The *N*-oxide of nicotinic acid has been prepared by this procedure.[4] 2,5-Pyridinedicarboxylic acid was not oxidized to the *N*-oxide by this method. However, its dimethyl ester was oxidized by 30% hydrogen peroxide in an exothermic reaction which was initiated at 100° to give 5-carbomethoxy-2-carboxypyridine-*N*-oxide (V). Only the monoester could be isolated from the reaction mixture. The monoester was saponified readily to 2,5-dicarboxypyridine-*N*-oxide. The facile hydrolysis of the 2-carbomethoxy group may be attributed to the inductive effect of the *N*-oxide function and to the stabilization of the acid by hydrogen bonding (Va) or by zwitterion formation (Vb).

(1) E. Winterstein and A. B. Weinhagen, *Z. physiol Chem.*; 100, 170 (1917).
(2) H. Nienberg, *Chem. Ber.*, 68, 1474 (1935).
(3) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, New York, N. Y., 1950, Vol. I, p. 415.
(4) G. R. Clemo and H. Koenig, *J. Chem. Soc.*, S231-2 (1949).

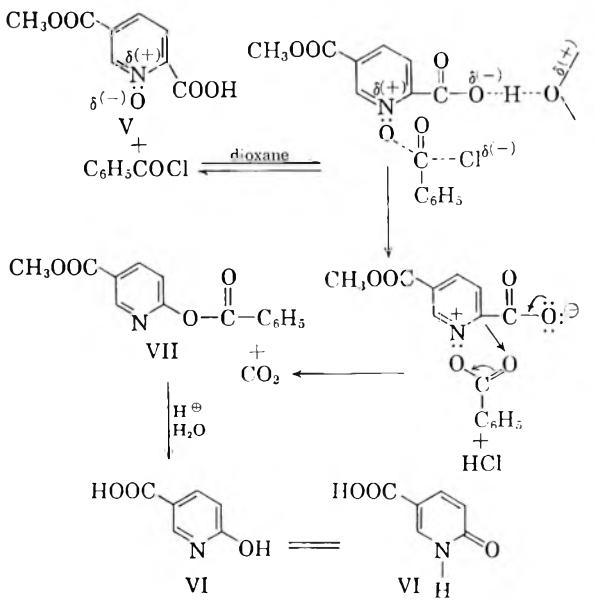


Va Vb

Substitution reactions, such as nitration, which are difficult to effect on the pyridine ring, have been carried out readily with the pyridine oxides.[5] 5 - Carbomethoxy - 2 - carboxypyridine - *N* - oxide was not nitrated in a mixture of sulfuric and nitric acids at 130°.

When benzoyl chloride was added to a dioxane solution of 5-carbomethoxy-2-carboxypyridine-*N*-oxide at 90°, a rapid exothermic reaction occurred in which carbon dioxide was evolved. After the reaction product had been hydrolyzed, 5-carboxy-2-pyridone (VI) was isolated. The 5-carboxy-2-pyridone was identical with a sample of 5-carboxy-2-pyridone which was prepared by the carboxylation of 2-pyridone by the method of Tschitschibabin.[6]

The carboxypyridone was not formed, however, when a benzene solution of 5-carbomethoxy-2-carboxypyridine-*N*-oxide and benzoyl chloride was refluxed. A polar solvent, therefore, appears to be necessary to effect the reaction. The formation of the pyridone may be rationalized by the following mechanism:



As the oxygen atom of the *N*-oxide function with its partial negative charge reacts with benzoyl chloride at the carbonyl function, dioxane solvates the acid hydrogen and an unstable intermediate zwitter ion is formed. Resonance of the positive charge in the ring places a partial positive charge at the $\alpha$-carbon. By an intramolecular rearrangement with simultaneous decarboxylation, carbon dioxide is eliminated and 2-benzoxy-5-carbomethoxypyridine (VII) is formed.

The reaction of pyridine-*N*-oxide with acetic anhydride to give 2-pyridone was demonstrated by Katada.[7]

The reaction of 5-carbomethoxy-2-carboxypyridine-*N*-oxide with acetic anhydride was initiated at 45° and was exothermic. Carbon dioxide was evolved from the reaction mixture. A crystalline ester whose elemental analysis corresponded to that of an acetoxycarbomethoxypyridine (VIII) was isolated. The acetoxycarbomethoxypyridine was hydrolyzed by water at room temperature to give a compound (IX), m.p. 82–84°, whose elemental analysis corresponded to that of a carbomethoxypyridone. The acetoxycarbomethoxypyridone was hydrolyzed in a hydrochloric acid solution to give an acid (X), m.p. 245–247° dec., whose elemental analysis corresponded to that of a carboxypyridone. However, this acid was not the same as the 5-carboxy-2-pyridone, m.p. 303.4–303.7° dec., produced by the reaction of the *N*-oxide (V) with benzoyl chloride.

A consideration of the possible structures for the product of the reaction of the *N*-oxide (V) with acetic anhydride (Table I) led to the conclusion that the product was 3-carboxy-4-pyridone, rather than the expected 5-carboxy-2-pyridone.

TABLE I

MELTING POINTS OF CARBOXYPYRIDONES AND THEIR ESTERS

| Carboxypyridone | M.P. of Acid | M.P. of Methyl Ester |
|---|---|---|
| 3-Carboxy-2-pyridone | 225° | 153° |
| 5-Carboxy-2-pyridone | 301–302° | 164° |
| 6-Carboxy-2-pyridone | 282° | — |
| 3-Carboxy-4-pyridone | 250° | — |
| Reaction product | 245–247° | 82–84° |

The ultraviolet spectra of the products obtained from the reaction of the *N*-oxide (V) with acetic anhydride and with benzoyl chloride provided additional evidence for the proposed structures. The spectra of 3-carboxy-4-pyridone, 3-carbomethoxy-4-pyridone, and 3-carbomethoxy-4-acetoxypyridine were very similar to the spectrum recorded for 1 - methyl - 3 - carboxy - 5,6,7,8 - tetrahydroquinolone,[8] whereas the spectra of 5-carboxy-2-pyridone and *N*-methyl-5-carboxy-2-pyridone were very similar to the spectra recorded for 5-carboxy-6-methyl-2-pyridone[9] and 1-methyl-5-carbamyl-2-

(5) F. E. Cislak, *Ind. Eng. Chem.*, **47**, 800 (1955). E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(6) E. A. Tschitschibabin and A. W. Kirssanow, *Ber.*, **57**, 1161 (1924).

(7) M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947).

(8) R. D. Brown and F. N. Lahey, *Austral. J. Sci. Research*, **A3**, 623 (1950).

(9) F. Ramirez and A. P. Paul, *J. Am. Chem. Soc.*, **77**, 1035 (1955).

pyridone[10] (Table II). The two maximum intensity absorption bands in the spectra of the 3-carboxy-4-pyridone derivatives occur at shorter wave lengths than do the maximum absorptions of the 5-carboxy-2-pyridone derivatives. The intensities of the bands of the spectra of 4-pyridone[11] and of the 3-carboxy-4-pyridone derivatives were much greater than the intensities of the bands in the spectra of 2-pyridone[11] and its carboxylated derivatives.

TABLE II

ULTRAVIOLET SPECTRA OF PYRIDONES[a]

| Compound | $\lambda_{max}$ (m$\mu$) | $\epsilon_{max}$ |
|---|---|---|
| 3-Carboxy-4-pyridone | 267; 220 | 13,320; 26,800 |
| 3-Carbomethoxy-4-pyridone | 268; 223 | 13,540; 27,850 |
| 3-Carbomethoxy-4-acetoxypyridine | 271; 224 | 19,240; 43,400 |
| 1-Methyl-3-carboxy-5,6,7,8-tetrahydro-4-quinolone[b,c] | 262; 220 | 9,120; 28,800 |
| N-Methyl-4-hydroxypyridine[d] | 262 | 18,200 |
| 4-Pyridone[d] | 256 | 14,100 |
| 5-Carboxy-2-pyridone | 298, 256 | 4,170; 14,500 |
| N-Methyl-5-carboxy-2-pyridone | 300; 255 | 5,370; 15,800 |
| 5-Carboxy-6-methyl-2-pyridone[b,e] | 300; 268 | 6,000; 14,500 |
| 1-Methyl-5-carbamyl-2-pyridone[f] | 300; 260 | — |
| 2-Pyridone[d] | 297; 227 | 9,000; 10,000 |

[a] All spectra taken in neutral methanol solution except as marked. [b] In ethanol. [c] See ref. 8. [d] See ref. 11. [e] See ref. 9. [f] See ref. 10.

The infrared spectra of 3-carboxy-4-pyridone and of 5-carboxy-2-pyridone show marked differences. Broad absorbances in the 4.0 $\mu$ and 5.0–5.7 $\mu$ regions of the spectrum of 3-carboxy-4-pyridone, which are not found in the spectrum of 5-carboxy-2-pyridone, indicate strong intramolecular hydrogen bonding between hydroxyl and carboxyl functions. Such bonding is possible if the hydroxyl and carboxyl functions are attached to adjacent carbons. The disappearance in the spectrum of 3-carboxy-4-pyridone of the strong absorptions found at 6.05 and 6.2 $\mu$ in the spectrum of 5-carboxy-2-pyridone also suggests that the former exists largely in the form of the hydroxypyridine.

When the *N*-oxide (V) was treated with an equimolar quantity of acetic anhydride in a dioxane solution, 3-carboxy-4-pyridone again was formed. Even the reaction of the *N*-oxide (V) with acetyl chloride in a dioxane solution produced 3-carboxy-4-pyridone instead of the product, 5-carboxy-2-pyridone, produced by the reaction of the *N*-oxide with benzoyl chloride.

2,5-Bis(*N*,*N*-diethylcarboxamido)pyridine-*N*-oxide was prepared by the oxidation of 2,5-bis-(*N*,*N*-diethylcarboxamido)pyridine by hydrogen peroxide in a glacial acetic acid solution. This *N*-oxide, from which carbon dioxide can not be eliminated readily, did not react with acetic anhydride.

(10) W. E. Knox and W. I. Grossman, *J. Biol. Chem.*, **168**, 1363 (1947).

(11) H. Specker and H. Gawrosch, *Chem. Ber.*, **75**, 1338 (1942).

## EXPERIMENTAL

*Dimethyl 2,5-pyridinedicarboxylate.* A solution of 501 g. (3.0 moles) of 2,5-pyridinedicarboxylic acid, 3200 ml. of methanol, and 480 ml. of concd. sulfuric acid was refluxed for 6 hr. After the reaction mixture had been neutralized with 4500 ml. of a 25% aqueous sodium carbonate solution, it was extracted with two 1000-ml. portions of chloroform. The chloroform extracts yielded 430 g. (69% yield) of dimethyl 2,5-pyridinedicarboxylate, m.p. 162–163°.

*2,5-Dicarbomethoxy-N-methylpyridinium methosulfate* (I). A mixture of 19.5 g. (0.1 mole) of dimethyl 2,5-pyridinedicarboxylate, 100 ml. of benzene, and 20 g. (0.16 mole) of dimethyl sulfate was refluxed for 3 hr. An oil separated from the benzene solution as the reaction mixture was refluxed; this oil formed a solid crystalline mass when it was cooled. When this material was crystallized from acetone, 26 g. of white crystals, m.p. 88–89°, was obtained.

*Anal.* Calcd. for $C_{11}H_{15}O_8NS$: C, 41.12; H, 4.71; N, 4.36. Found: C, 41.06, 41.24; H, 4.29, 4.41; N, 4.35, 4.18.

Quaternization of the dimethyl 2,5-pyridinedicarboxylate did not occur when a mixture of 19.5 g. (0.1 mole) of the ester, 60 ml. of chloroform, and 20 g. (0.14 mole) of methyl iodide was heated at 130–140° for 4 hr. in a glass-lined bomb.

*2,5-Dicarboxy-N-methylpyridinium betaine* (II). I, which had been obtained by refluxing a solution of 39.0 g. (0.20 mole) of dimethyl 2,5-pyridinedicarboxylate, 200 ml. of xylene, and 30.0 g. (0.24 mole) of dimethyl sulfate for 2 hr., was refluxed with 100 ml. of concentrated hydrochloric acid for 3 hr. When the hydrochloric acid solution was cooled, 20 g. (55% yield) of 2,5-dicarboxy-*N*-methylpyridinium betaine precipitated from the solution. II was insoluble in organic solvents and cold water and sparingly soluble in hot water. When II was crystallized from hot water, white crystals which melted at 170° dec. were obtained.

*Anal.* Calcd. for $C_8H_7O_4N$: C, 53.02; H, 3.90; N, 7.73; neut. equiv., 181. Found: C, 53.50, 53.52; H, 3.95, 3.94; N, 7.51, 7.55; neut. equiv., 177, 179.

Only a trace of II was formed when a mixture of 33.4 g. (0.20 mole) of 2,5-pyridinedicarboxylic acid, 28 g. (0.22 mole) of dimethyl sulfate, and 200 ml. of toluene was refluxed for 28 hr. Most of the 2,5-pyridinedicarboxylic acid was recovered.

*Attempted esterification of* II. When II was refluxed in a methanol solution in the presence of sulfuric acid or a Dowex 50-X12 cation exchange resin for 5–7 hr., no esterification occurred and II was recovered.

*Oxidation of* I *by potassium ferricyanide.* When 16.1 g. (0.05 mole) of I was added gradually to a stirred solution of 33.0 g. (0.10 mole) of potassium ferricyanide, 6.02 (0.15 mole) of sodium hydroxide, and 100 ml. of water, an exothermic reaction occurred. The temperature of the reaction mixture was maintained at 35–40°. After the reaction was completed, the aqueous solution was extracted with four 40-ml. portions of chloroform. One gram of 5-carbomethoxy-*N*-methyl-2-pyridone (III) was obtained from the chloroform extracts. After III was crystallized from hot water three times, it melted at 138.3–139.2°.

*Anal.* Calcd. for $C_8H_9O_3N$: C, 57.46; H, 5.33; N, 8.39. Found: C, 57.56, 57.82; H, 5.25, 5.47; N, 8.42, 8.35.

When the extracted aqueous reaction mixture was acidified, carbon dioxide was evolved and the acid, 5-carboxy-*N*-methyl-2-pyridone (IV) precipitated. After IV was recrystallized from water and from ethanol, white crystals, m.p. 241–243°, were obtained.

*Anal.* Calcd. for $C_7H_7O_3N$: C, 54.91; H, 4.61; N, 9.15. Found: C, 55.21, 55.33; H, 4.56, 4.63; N, 8.92, 9.04.

III and IV are reported to melt at 139° and 237–238°, respectively.[12]

An exothermic reaction occurred also when a solution of 3.4 g. (0.085 mole) of sodium hydroxide and 10 ml. of water was added to a solution of 3.8 g. (0.021 mole) of II, 13.9 g. (0.042 mole) of potassium ferricyanide, and 50 ml. of water. The sodium hydroxide solution was added at a rate such that the temperature of the reaction mixture did not exceed 43°. When the basic solution was acidified, carbon dioxide was evolved and IV, m.p. 240.5–241.5°, precipitated.

III and IV were not formed by the oxidation of I by 30% hydrogen peroxide in aqueous basic solutions. Instead, black tars were obtained.

*Reduction of* I *by zinc dust.* When 25 g. of zinc dust was slowly added to a solution of 21.3 g. (0.066 mole) of I in 50 ml. of water, a slightly exothermic reaction took place and a yellow solid precipitated. The yellow solid was extracted with chloroform. After the chloroform solution was distilled, a black tar containing crystalline material remained. The yellow crystalline material was recovered by crystallizing the residues from ethanol. When the crystals stood overnight in a closed vial at room temperature, they decomposed to a black tar.

*5-Carbomethoxy-2-carboxypyridine-N-oxide* (V). When the temperature of a solution of 117 g. (0.60 mole) of dimethyl 2,5-pyridinedicarboxylate, 300 ml. of glacial acetic acid, and 150 ml. of 30% hydrogen peroxide was raised to 100°, an exothermic reaction was initiated which maintained the temperature of the reaction mixture at 105° for 15 min. without the application of outside heat. The solution was heated at 100° for 1.5 hr. after the exothermic reaction ceased. When the reaction mixture was chilled, 96.5 g. (80% yield) of V precipitated. After V had been recrystallized from 95% ethanol, it melted at 151° dec.

*Anal.* Calcd. for $C_8H_7O_5N$: C, 48.72; H, 3.58; N, 7.10. Found: C, 48.72, 48.94; H, 3.37, 3.56; N, 7.00, 7.11.

When an aqueous solution of V was titrated with a sodium hydroxide solution, one equivalent of base was rapidly neutralized. A second equivalent of base was neutralized as the ester group was saponified.

*Anal.* Calcd. for $C_8H_7O_5N$: sapon. equiv., 98.6. Found: sapon. equiv., 98.4, 98.5.

When a mixture of 16.7 g. (0.10 mole) of 2,5-pyridinedicarboxylic acid, 50 ml. of glacial acetic acid, and 50 ml. of 30% hydrogen peroxide was refluxed for 8 hr., no *N*-oxide was formed.

V was saponified to the disodium salt of 2,5-dicarboxypyridine-*N*-oxide when it was heated for 15 min. in 40 ml. of 10% sodium hydroxide solution. When the basic solution was acidified with concd. hydrochloric acid, the free acid, 2,5-dicarboxypyridine-*N*-oxide precipitated. The 2,5-dicarboxypyridine-*N*-oxide melted at 242–244° dec.

*Anal.* Calcd. for $C_7H_5O_5N$: neut. equiv., 91.6. Found: neut. equiv., 92.2, 92.1.

*Reaction of* V *with benzoyl chloride.* Eight grams (0.57 mole) of benzoyl chloride was added in one portion to a solution of 10 g. (0.51 mole) of V and 50 ml. of dioxane at 90°. The rapid reaction which resulted raised the temperature of the reaction mixture to reflux (100°), and carbon dioxide was evolved rapidly. After the dioxane had been distilled from the reaction mixture, a heavy oil was left. Benzoic acid was extracted from the oily mixture with an aqueous 10% sodium carbonate solution. The brown oil remaining after the extraction was refluxed for 1 hr. with a 15% hydrochloric acid solution. When the hydrochloric acid solution was chilled, 5-carboxy-2-pyridone (VI) precipitated as a crystalline solid which melted at 303.4–303.7° dec. after recrystallization from water.

*Anal.* Calcd. for $C_6H_5O_3N$: C, 51.80; H, 3.62; N, 10.07. Found: C, 52.36, 52.58; H, 3.63, 3.70; N, 9.44, 9.65.

An authentic sample of VI was prepared by the carboxylation of 2-pyridone by the method of Tschitschibabin.[6] A mixture of 10 g. (0.105 mole) of 2-pyridone and 40 g. of dry, powdered potassium carbonate was heated in a bomb at 200° under a carbon dioxide pressure of 400 p.s.i.g. for 4 hr. When an aqueous solution of the contents of the bomb was acidified with hydrochloric acid, 6.9 g. of VI precipitated from the solution. After VI had been crystallized from water, it melted at 302–303° dec. and was identical with the VI produced by the reaction of V with benzoyl chloride.

When a solution of V, benzoyl chloride, and benzene was refluxed, there was no evidence of the occurrence of a reaction.

*Reaction of* V *with acetic anhydride.* When a mixture of 30 g. (0.152 mole) of V and 90 ml. of acetic anhydride was heated to 45°, a reaction started, and carbon dioxide was evolved. The exothermic reaction carried the temperature of the reaction mixture to 70°. The reaction was complete after 10 min. A crystalline solid (VIII) whose elemental analysis corresponded to that of an acetoxycarbomethoxypyridine was left after the acetic anhydride had been distilled under high vacuum. After the solid had been crystallized from benzene, it melted at 100–101.5°.

*Anal.* Calcd. for $C_9H_9O_4N$: C, 55.37; H, 4.65. Found: C, 55.71, 55.92; H, 4.70, 4.56.

When an acetic anhydride solution of VIII evaporated at room temperature and was exposed to the atmosphere for a week, it hydrolyzed to give a carbomethoxypyridine (IX), m.p. 82–84°. IX was crystallized from a benzene–petroleum ether mixture.

*Anal.* Calcd. for $C_7H_7O_3N$: C, 54.91; H, 4.61; N, 9.15. Found: C, 55.10, 55.22; H, 4.57, 4.65; N, 8.78, 8.88.

IX was hydrolyzed to 3-carboxy-4-pyridone (X) when it was refluxed for 1.5 hr. in a concd. hydrochloric acid solution. When the hydrochloric acid solution was partly neutralized with sodium carbonate, X precipitated as a white solid, which melted at 245–247° dec. after it was recrystallized from water.

*Anal.* Calcd. for $C_6H_5O_3N$: C, 51.80; H, 3.62; N, 10.06. neut. equiv., 139. Found: C, 51.92, 52.13; H, 3.51, 3.54; N, 9.36, 9.39; neut. equiv., 137.2, 136.7.

A solution of 10 g. (0.05 mole) of V, 50 ml. of dioxane, and 5.3 g. (0.05 mole) of acetic anhydride was heated at 85°. Carbon dioxide was evolved as the exothermic reaction proceeded. After the dioxane had been distilled under reduced pressure, the residue was hydrolyzed in a 15% aqueous hydrochloric acid solution. The product (4.5 g., 70% yield) melted at 243–245° after recrystallization from water.

*Reaction of* V *with acetyl chloride.* A mixture of 10 g. (0.05 mole) of V, 50 ml. of dioxane, and 5 g. (0.065 mole) of acetyl chloride reacted vigorously with evolution of carbon dioxide. The heavy oil which was left after dioxane had been distilled under reduced pressure was heated at 100° for 1 hr. in a 15% hydrochloric acid solution. The volume of the solution was reduced to 15 ml. When the solution was cooled, 4 g. (64% yield) of a crystalline product, m.p. 241–243°, was obtained.

*Attempted nitration of* V. V was not nitrated when 5.0 g. of V was heated at 110–130° for 3 hr. with 15 ml. of concentrated sulfuric acid and 15 ml. of nitric acid. Instead, hydrolysis of V to 2,5-dicarboxypyridine-*N*-oxide occurred.

*2,5-Bis(N,N-diethylcarboxamido)pyridine-N-oxide* (XI). A mixture of 62.5 g. (0.225 mole) of 2,5-bis(*N,N*-diethylcarboxamido)pyridine (which was prepared by the reaction of diethylamine and the dichloride of 2,5-pyridinedicarboxylic acid), 200 ml. of glacial acetic acid, and 100 ml. of 30% hydrogen peroxide was refluxed for 3 hr. After the

(12) H. V. Pechmann and W. Welsh, *Ber.*, **17**, 2395 (1884).

solvents had been distilled under reduced pressure, a white solid, m.p. 166.5–167.4°, remained.

*Anal.* Calcd. for $C_{15}H_{22}O_3N_2$: C, 61.41; H, 7.90; N, 14.32. Found: C, 61.46, 61.60; H, 7.83, 7.86; N, 13.86, 13.89.

XI did not react in a refluxing solution of acetic anhydride. The starting material was recovered after 4 hr. of heating in the acetic anhydride solution.

*Acknowledgment.* The author is indebted to L. J. Lohr and R. W. Warren, who prepared the infrared and ultraviolet spectra and assisted in their interpretation.

GIBBSTOWN, N. J.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS COMPANY]

# 3-Indolepropionic Acid

HERBERT E. JOHNSON AND DONALD G. CROSBY

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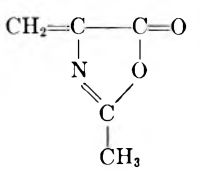
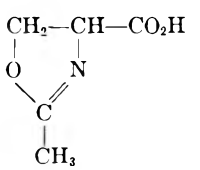
3-Indolepropionic acid has been prepared in 56% yield by the reaction of indole with acrylic acid in the presence of acetic anhydride.

3-Indolepropionic acid has, over a period of years, been the subject of many investigations concerning its plant growth regulating properties. More recently, its use as a starting material for the synthesis of lysergic acid has been described.[1] There are various procedures by which 3-indolepropionic acid may be synthesized, and, until the present investigation, the most convenient of these consisted of the hydrolysis of 3-indolepropionitrile obtained from the reaction of indole and acrylonitrile.[2]

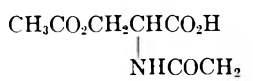
The reaction of acrylic acid with indole at 130° is reported to give a quantitative yield of 1-indolepropionic acid.[2] α-Acetamidoacrylic acid, however, reacts with indole in the presence of acetic anhydride to give acetyltryptophan.[3]



I



II

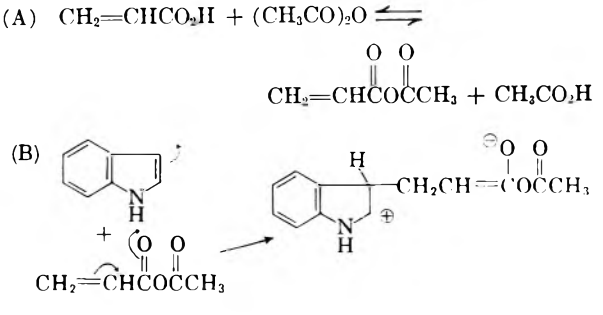


III

When acrylic acid and indole were allowed to react in acetic acid solution containing acetic anhydride, 3-indolepropionic acid could be isolated in 56% yield from the reaction mixture. The quantity of anhydride necessary for the reaction to take place was not critically investigated, but it was found that 0.20 equivalent (based on indole) was not sufficient. For convenience, at least two equivalents were usually employed, one equivalent being somewhat less satisfactory.

The role of acetic anhydride in the reaction still remains uncertain. Snyder and MacDonald[3] suggested that α-acetamidoacrylic acid is possibly converted by the anhydride present into an intermediate azlactone (I), oxazoline (II), or diacetylserine (III). On the basis of model experiments, these intermediates were rejected as unlikely, and no other explanations were presented. I and II are not possible intermediates in the present synthesis of 3-indolepropionic acid. III is considered improbable, as acetic acid would not be expected to add to acrylic acid under the reaction conditions.

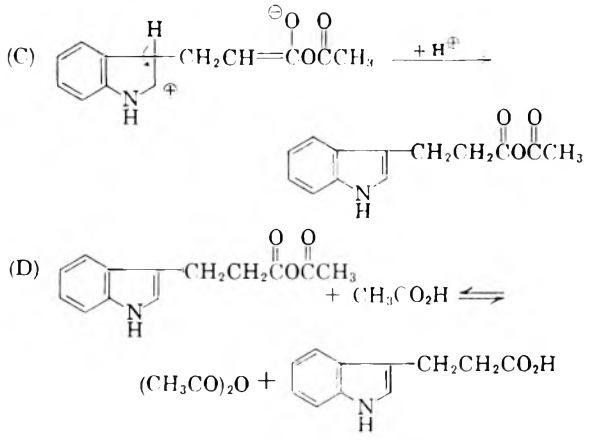
A mechanism consistent with the addition of both acrylic acid and α-acetamidoacrylic acid to the 3-position of indole places the anhydride in the role of forming a mixed anhydride with the acrylic acid. This mixed anhydride, or an acryloyl cation produced by its dissociation, is the reactive species that adds to the 3-position (Equations A–D).



(1) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.*, **78**, 3087 (1956). E. C. Kornfeld, G. B. Kline, and E. J. Fornefeld, U. S. Patent **2,796,419**.

(2) W. Reppe and H. Ufer, German Patent **698,273**; French Patent **48,570**, addition to French Patent **742,358**.

(3) H. R. Snyder and J. A. MacDonald, *J. Am. Chem. Soc.*, **77**, 1257 (1955); U. S. Patent **2,810,727**.



The equilibrium represented in (A) is apparently an over-simplification, as the seemingly excessive amount of acetic anhydride that is necessary for the reaction to proceed satisfactorily is not anticipated. Other factors therefore must predominate, and it is speculated that the quantity of acetic acrylic anhydride present at any one time is small. The possibility of (B) being a slow reaction and the equilibrium of (D) not being readily attained is considered to be of minor importance.

As would be expected on the basis of the proposed mechanism, acrylic anhydride and indole in acetic acid solution react to give 3-indolepropionic acid. Also, methyl acrylate and acrylonitrile are unreactive toward indole in the presence of acetic acid and acetic anhydride under the above reaction conditions.

## EXPERIMENTAL[4]

*3-Indolepropionic Acid:* (a). *By the reaction of indole, acrylic acid and acetic anhydride.* A solution of 60 g. (0.51 mole) of indole in 240 ml. of acetic acid containing 100 ml. (1.0 mole) of acetic anhydride and 80 g. (1.1 moles) of acrylic acid was heated at 90° for 3 hr. The reaction mixture was allowed to stand overnight at 25° and then all volatile material quickly removed by distillation under reduced pressure. A dark viscous residue remained which was added to a solution of 60 g. (1.5 moles) of sodium hydroxide in 500 ml. of water without external cooling. The mixture was then allowed to cool and the insoluble material removed by filtration. Acidification of the filtrate with concentrated hydrochloric acid precipitated 3-indolepropionic acid. The product was isolated by filtration and dried to give 54 g. (56%) of light-tan material, m.p. 128–131°. A sample was crystallized from water as long nearly-colorless needles, melting point and mixed melting point with an authentic sample prepared by the hydrolysis of 3-indolepropionitrile, 135–136°, lit.,[5] m.p. 133–134°.

(b). *By the reaction of indole, acrylic anhydride, and acetic acid.* Twenty-three grams (0.20 mole) of indole, 25 g. (0.20 mole) of acrylic anhydride, and 100 ml. of acetic acid were allowed to react according to the above procedure to give 17 g. (45%) of 3-indolepropionic acid, m.p. 124–126°. The infrared spectrum of this material is identical to the infrared spectrum of an authentic sample of 3-indolepropionic acid.

*Acknowledgment.* The authors wish to thank Mr. C. R. McClure for his able assistance.

SOUTH CHARLESTON, W. VA.

(4) All melting points are corrected.

(5) A. Ellinger, *Chem. Ber.*, **38**, 2884 (1905).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF NEW MEXICO]

# Cinnoline Chemistry. V. 4-Mercaptocinnolines and Related Compounds[1,2]

RAYMOND N. CASTLE, HELEN WARD, NOEL WHITE, AND KIKUO ADACHI

*Received July 16, 1959*

4-Mercaptocinnoline, 6,7-dimethoxy-4-mercaptocinnoline and a number of alkyl and heterocyclic derivatives of these compounds have been prepared for antitumor screening. 4,6,7-Trimethoxycinnoline and 4-ethoxy-6,7-dimethoxycinnoline were also prepared. The infrared spectra of most of these compounds were determined.

The antileukemic activity of 6-mercaptopurine prompted the preparation of the mercaptocinnolines and related compounds. 4-Mercaptocinnoline (I) was prepared by the action of thiourea on 4-chlorocinnoline. The intermediate, which precipitated from the methanolic solution, was assumed to be the thiouronium salt and was readily converted into 4-mercaptocinnoline by heating with sodium hydroxide solution. 6,7-Dimethoxy-4-mercaptocinnoline (II) was prepared in the same manner. 4-Mercaptocinnoline was prepared in nearly quantitative yield by allowing phosphorus pentasulfide to react with 4-hydroxycinnoline in dry pyridine solution. 6,7-Dimethoxy-4-mercaptocinnoline was prepared in somewhat poorer yield in the same manner. 4-Methylmercaptocinnoline (III) was prepared by allowing I to react with methyl iodide in alkaline solution. 6,7-Dimethoxy-4-methylmercaptocinnoline (IV) was prepared in a similar fashion.

4-Bicinnolyl sulfide (V) was prepared by allowing

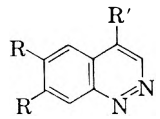
(1) Paper IV in this series, R. N. Castle, D. B. Cox, and J. F. Suttle, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 135 (1959).

(2) This investigation was supported in part by Grant CY-4327 from the National Cancer Institute, Public Health Service. Presented before the Division of Medicinal Chemistry, 136th Meeting of the American Chemical Society, September 1959, Atlantic City.

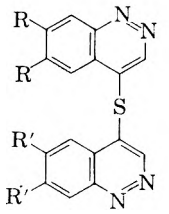
4-mercaptocinnoline to react with 4-chlorocinnoline in the presence of sodium methoxide in methanol solution. 4,4′-Bis(6,7-dimethoxycinnolyl) sulfide (VI) and 4-cinnolyl 4′-(6′,7′-dimethoxycinnolyl) sulfide (VII) were prepared by a similar procedure. 4-Cinnolyl 2-quinoxalyl sulfide (VIII) and 4-(6,7-dimethoxycinnolyl) 2-quinoxalyl sulfide (IX) were prepared similarly by allowing 2-chloroquinoxaline to react with the appropriate mercaptocinnolines.

4,6,7-Trimethoxycinnoline (X) was prepared by allowing sodium methoxide in dry methanol to react with 4-chloro-6,7-dimethoxycinnoline. 6,7-Dimethoxy-4-ethoxycinnoline (XI) was prepared in a similar manner from sodium ethoxide and 4-chloro-6,7-dimethoxycinnoline.

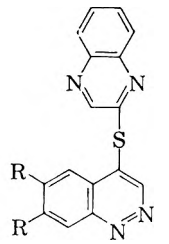
Evidence for the constitution of these compounds was obtained from the methods of synthesis and from the infrared spectra.



I. R = H, R′ = SH
II. R = $OCH_3$, R′ = SH
III. R = H, R′ = $SCH_3$
IV. R = $OCH_3$, R′ = $SCH_3$
X. R, R′ = $OCH_3$
XI. R = $OCH_3$, R′ = $OC_2H_5$



V. R, R′ = H
VI. R, R′ = $OCH_3$
VII. R = H, R′ = $OCH_3$



IX. R = $OCH_3$
VIII. R = H

## EXPERIMENTAL

The analyses were by Weiler and Strauss, Oxford, and by the Tanabe Seiyaku Company, Ltd., Tokyo.[3] The melting points are uncorrected.

*4-Mercaptocinnoline.* A mixture of 1.1 g. of 4-chlorocinnoline and 1.0 g. of thiourea dissolved in 8 ml. of dry methanol was warmed and swirled for about 10 min. The mixture became a yellow semisolid mass which was dissolved by the addition of more absolute methanol. After filtration and vacuum evaporation, fine yellow crystals separated, m.p. 146–148°. This material was heated for 35 min. on a steam bath with 4 ml. of 2.5*N* sodium hydroxide solution. The cooled solution was acidified with dilute acetic acid and the orange-yellow semisolid mass filtered, m.p. 188–192°, yield 0.7 g. A sample for analysis was recrystallized from glacial acetic acid, m.p. 200–201°.

*Anal.* Calcd. for $C_8H_6N_2S$: C, 59.23; H, 3.73; N, 17.27. Found: C, 58.97; H, 3.81; N, 16.99.

Ten grams of 4-hydroxycinnoline and 60 g. of phosphorus pentasulfide were added to 650 ml. of dry, freshly distilled C. P. pyridine. This mixture was refluxed for 5 hr., and then the excess pyridine was removed by vacuum distillation until near dryness. About 400 g. of crushed ice was added to the cooled residue and the mixture was allowed to stand for 0.5 hr. After 2 hr. heating on the steam bath, the deep red solution was allowed to stand overnight in the refrigerator. Deep red needles (9.8 g.) separated, m.p. 191–198°. A sample purified for analysis by repeated solution in ammonium hydroxide and precipitation with acetic acid melted at 203–205°. The mixed melting point with the sample described above was 202–205°.

*Anal.* Calcd. for $C_8H_6N_2S$: C, 59.23; H, 3.73. Found: C, 58.77; H, 3.99.

*6,7-Dimethoxy-4-mercaptocinnoline.* One gram of thiourea and 1.1 g. of 4-chloro-6,7-dimethoxycinnoline were dissolved in 10 ml. of dry methanol and the solution refluxed on the steam bath for 7 min. At this time a solid began to separate which amounted to 1.1 g., m.p. 175–179° crude. This product was heated for 40 min. on a steam bath with 7 ml. of 2.5*N* sodium hydroxide solution. After cooling the solution was acidified with dilute acetic acid. One gram of yellow powder was obtained, m.p. 211–213°. A sample for analysis was prepared by recrystallization from glacial acetic acid, m.p. 213–217°.

*Anal.* Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.54. Found: C, 54.16; H, 4.39.

A mixture of 7.0 g. of 6,7-dimethoxy-4-hydroxycinnoline and 30.0 g. of phosphorus pentasulfide in 325 ml. of dry, freshly distilled C. P. pyridine was refluxed for 4 hr. The pyridine was removed by distillation in vacuum on a steam bath and the residue was taken nearly to dryness. About 200 g. of crushed ice and water was added and the mixture was allowed to stand overnight, then heated 2 hr. on a steam bath. After standing 24 hr. in the refrigerator the crystalline product amounted to 6.4 g., m.p. 213–215°. A purified sample melted at 216–217° alone and when admixed with the analytical sample described above.

*4-Methylmercaptocinnoline.* To a solution of 1.62 g. (0.01 mole) of 4-mercaptocinnoline in 50 ml. of 10% sodium hydroxide solution was added 1.42 g. (0.01 mole) of methyl iodide. The mixture was stirred an additional 0.5 hr. at 25°, whereupon a greenish crystalline solid separated. The solid was extracted into about 100 ml. of chloroform. This solution was dried over magnesium sulfate and the residue obtained by evaporation. The residue was dissolved in ether and the insoluble impurities were removed by filtration. Upon evaporation 1.1 g. (63%) of yellow needles melting at 93–95° were obtained. An analytical specimen was obtained by crystallization from cyclohexane, m.p. 98°.

When the above procedure was repeated using the same quantities of materials except that two molar proportions of methyl iodide were used, the yield was 1.3 g. (74%) of product melting at 93–95°.

*Anal.*: Calcd. for $C_9H_8N_2S$: C, 61.35; H, 4.62; N, 15.90. Found: C, 61.60; H, 4.55; N, 15.85.

*6,7-Dimethoxy-4-methylmercaptocinnoline.* To a solution of 1.0 g. of 6,7-dimethoxy-4-mercaptocinnoline in 25 ml. of 10% sodium hydroxide solution was added 0.7 g. (one molar equivalent) of methyl iodide. The mixture was stirred at 25° for 0.5 hr. At this time a solid separated which was extracted into chloroform and dried over magnesium sulfate. The dried filtrate was subjected to chromatography through alumina, using chloroform as the eluent. A yield of 0.38 g. (37%) of yellow crystals was obtained, m.p. 205–210°.

(3) The authors are indebted to Drs. S. Yamada and K. Abe for their kindness in providing certain of these analyses.

An analytical sample prepared by crystallization from benzene melted at 215–217°.

*Anal.* Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.00; H, 5.34; N, 11.64.

*4,4'-Bicinnolyl sulfide.* A solution of 2.0 g. of 4-chlorocinnoline, 2.0 g. of 4-mercaptocinnoline and 0.67 g. of sodium methoxide in 35 ml. of dry methanol was refluxed for 1.75 hr. The product, 3.5 g. (97%), separated from the hot solution, m.p. 180–181°. A sample purified for analysis by crystallization from ethanol melted at 181°.

*Anal.* Calcd. for $C_{16}H_{10}N_4S$: C, 66.21; H, 3.47; N, 19.31. Found: C, 66.07; H, 3.51; N, 18.90.

*4,4'-Bis(6,7-dimethoxycinnolyl) sulfide.* A solution of 1.4 g. of 4-chloro-6,7-dimethoxycinnoline, 1.4 g. of 6,7-dimethoxy-4-mercaptocinnoline, and 0.34 g. of sodium methoxide in 23 ml. of dry methanol was refluxed for 2.5 hr., whereupon the solid product separated from the hot solution. There was obtained 2.4 g. of crude product, m.p. 210–215°. An analytical sample was prepared by crystallization from a large volume of ethanol, m.p. 220–225°.

*Anal.* Calcd. for $C_{20}H_{18}N_4SO_4$: C, 58.52; H, 4.42; N, 13.65. Found: C, 58.70; H, 4.62; N, 13.34.

*4-Cinnolyl 4'-(6',7'-dimethoxycinnolyl) sulfide.* A solution of 2.8 g. of 4-chloro-6,7-dimethoxycinnoline, 2.0 g. of 4-mercaptocinnoline, and 0.67 g. of sodium methoxide in 45 ml. of dry methanol was refluxed for 3.5 hr., at which time a solid product separated amounting to 4.24 g., m.p. 193°. The analytical sample was crystallized from ethanol, m.p. 193°.

*Anal.* Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99. Found: C, 61.62; H, 4.29; N, 15.70.

*4-Cinnolyl 2-quinoxalyl sulfide.* A solution of 1.5 g. of 2-chloroquinoxaline, 1.5 g. of 4-mercaptocinnoline and 0.5 g. of sodium methoxide in 26 ml. of dry methanol was refluxed for 8.5 hr. Only 0.25 g. of product was obtained, which after purification by crystallization from ethanol melted at 153–154°, pale yellow needles.

*Anal.* Calcd. for $C_{16}H_{10}N_4S$: C, 66.21; H, 3.47; N, 19.31. Found: C, 66.02; H, 3.69; N, 18.97.

*4-(6,7-Dimethoxycinnolyl) 2-quinoxalyl sulfide.* A solution of 1.5 g. of 2-chloroquinoxaline, 2.1 g. of 6,7-dimethoxy-4-mercaptocinnoline, and 0.5 g. of sodium methoxide in 26 ml. of dry methanol was refluxed for 2.25 hr. The solid product amounted to 1.85 g., m.p. 210°. A sample purified for analysis by crystallization from ethanol melted at 210°.

*Anal.* Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99. Found: C, 61.33; H, 4.18; N, 16.30.

*4,6,7-Trimethoxycinnoline.* A solution of 1.0 g. of 4-chloro-6,7-dimethoxycinnoline and 0.5 g. of sodium methoxide in 30 ml. of absolute methanol was refluxed for 2.5 hr. The solution was allowed to cool and stand overnight whereupon 0.74 g. (76%) of product separated, m.p. 210° dec. An analytical sample was prepared by crystallization from methanol, m.p. 210° dec.

*Anal.* Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49. Found: C, 59.74; H, 5.76.

*4-Ethoxy-6,7-dimethoxycinnoline.* A solution of 1.0 g. of 4-chloro-6,7-dimethoxycinnoline and 0.5 g. of sodium ethoxide in 30 ml. of absolute ethanol was refluxed for 2 hr. Some solid product separated during the heating period and additional material separated on standing overnight at room temperature. Upon purification of the nonhomogeneous solid by repeated crystallization from ethanol, 0.15 g. of 4-chloro-6,7-dimethoxycinnoline was recovered together with 0.3 g. of product, m.p. 185–187°.

*Anal.* Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.95. Found: C, 61.67; H, 6.17; N, 11.90.

Infrared spectra were determined on all compounds except 4-ethoxy-6,7-dimethoxycinnoline and 4-cinnolyl-4'-(6',7'-dimethoxycinnolyl) sulfide. All these compounds show the characteristic cinnoline absorption band[1] in the 6.3 $\mu$ region, although the absorption is weak in some instances. These spectra were determined as Nujol mulls on the Perkin-Elmer Infracord.

ALBUQUERQUE, N. M.

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[CONTRIBUTION FROM THE BOUND BROOK LABORATORIES, AMERICAN CYANAMID COMPANY]

# Some Carboxaldazines and *s*-Triazoles of the Anthraquinone Series

ERWIN KLINGSBERG

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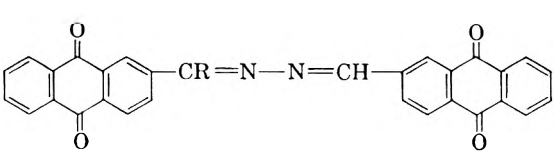
2-Anthraquinonecarboxaldazine (I) reacts with chlorine to give the $\alpha$-monochloro derivative (II) or 2-cyanoanthraquinone (VI), depending on conditions. 1,1'-Dichloro-2-anthraquinonecarboxaldazine (XI) behaves similarly. II reacts with amines to give aminoaldazines or triazoles.

The present paper describes the results of an investigation into the preparation and reactions of certain chlorinated anthraquinonecarboxaldazines, undertaken with a view to the synthesis of anthraquinonyltriazoles.[1]

Stollé,[2,3] found that benzaldazine takes up one or two atoms of chlorine, according to conditions, to give the monochloro derivative $C_6H_5CCl{:}N{-}N{:}CHC_6H_5$ or the dichloro derivative $C_6H_5CCl{:}N{-}N{:}CClC_6H_5$. The behavior of 2-anthraquinonecarboxaldazine (I) is somewhat different. While it

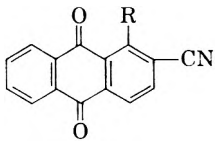


| | R = |
|---|---|
| I | H |
| II | Cl |
| III | $NH_2$ |
| IV | NHMe |
| V | $NMe_2$ |

does react with chlorine in nitrobenzene at 100–140° to give the monochloro derivative (II), a second atom of chlorine could not be introduced. When the reaction temperature was raised to 160–165°, a poor yield of unidentified product was obtained.

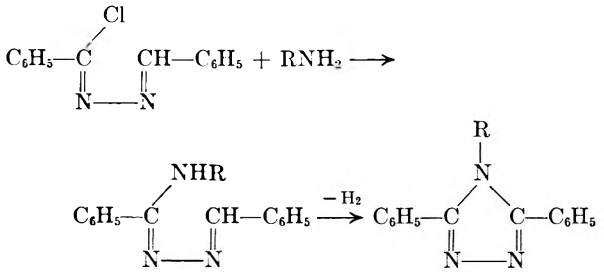
(1) E. Klingsberg, *J. Am. Chem. Soc.* **80**, 5786 (1958).
(2) R. Stollé, *J. Prakt. Chem.* **85**, 386 (1912).
(3) R. Stollé and Fr. Helwerth, *Ber.*, **47**, 1132 (1914).

Chlorination in *o*-dichlorobenzene at this temperature gave a good yield of 2-cyanoanthraquinone (VI); this cleavage reaction, giving benzonitrile from benzaldazine, was also observed by Stollé.[2]



R =
VI H
VII Cl

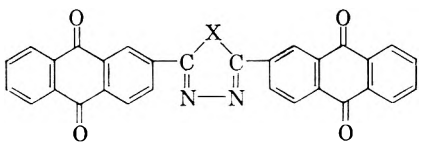
Monochlorobenzaldazine reacts with ammonia and primary amines to give *s*-triazoles by spontaneous air-dehydrogenation of the initial reaction product[3]:



R = H, alkyl, phenyl

Again, the anthraquinone derivatives behaved somewhat differently. The reaction product with ammonia had the open-chain structure (III), as shown by infrared absorption in the NH stretching region at 2.95 and 3.04 $\mu$, characteristic of primary amines. Thus, dehydrogenation did not occur even though aminolysis was conducted in nitrobenzene at 180–190°. The structure of the product was confirmed by nitrosylsulfuric acid degradation under mild conditions to 2-anthraquinonecarboxaldehyde; this behavior would be expected of III but not of a triazole.

Similarly the methylamine reaction product, an orange solid, m.p. 329–330°, had the open-chain structure (IV), as shown by a single infrared absorption band in the NH stretching region at 2.94 $\mu$ and absorption at 6.60 $\mu$ in the NH deformation region. Confirmation of structure was afforded by treatment with potassium hydroxide in diethylene glycol monoethyl ether at 155°. The product was a pale yellow neutral solid, m.p. 358–360°. Analysis showed that it contained two less hydrogen atoms than the starting material, and as it showed no absorption at 2.94 $\mu$ and much weaker absorption at 6.60 $\mu$, this was clearly the triazole (VIII). Under these conditions III was not cyclized, but



X =
VIII $NCH_3$
IX $NC_6H_5$
X O

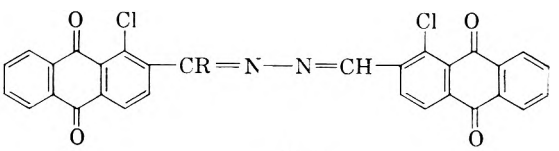
was recovered unchanged.

The reaction product of II with aniline was also lacking in absorption near 2.9 and 6.5 $\mu$, and was thus the triazole IX, formed by spontaneous cyclodehydrogenation during aminolysis. It was recovered unchanged after treatment with potassium hydroxide in diethylene glycol monoethyl ether at 155°.

The dimethylamine reaction product is, of course, incapable of cyclodehydrogenation and must be V.

The oxadiazole (X) was prepared by cyclodehydration of 1,2-bis(2-anthraquinonecarbonyl)hydrazine in oleum or polyphosphoric acid.

Attention was then turned to the 1-chloro derivatives of this series of compounds. 1-Chloro-2-anthraquinonecarboxaldehyde was prepared by the excellent procedure of Hershberg and Fieser[4] and converted to the aldazine (XI). In its behavior on



R =
XI H
XII Cl

chlorination, it resembles I. At 95° in nitrobenzene it took up a single atom of chlorine to give XII. The occurrence of chlorination in the side-chain rather than the nucleus was proved by sulfuric acid degradation to 1-chloro-2-anthraquinonecarboxylic acid and 1-chloro-2-anthraquinonecarboxaldehyde; the latter was not isolated as such but was converted to the aldazine (XI) under the conditions of the degradation. Chlorination of XI in *o*-dichlorobenzene at higher temperatures caused cleavage to 1-chloro-2-cyanoanthraquinone (VII).

Aminolysis of the side-chain chlorine atom in XII was not successful with ammonia, aniline, or other amines. Relatively mild reaction conditions gave unchanged starting material, while more severe conditions caused decomposition. Apparently the nuclear and side-chain atoms are too similar in reactivity to permit selective displacement.

## EXPERIMENTAL[5]

*2-Anthraquinonecarbonyl chloride 2-anthraquinonylmethylenehydrazone* (II). A mixture of 0.50 g. (1.07 mmoles) of 2-anthraquinonecarboxaldazine (I) and 20 ml. of nitrobenzene was heated in an oil bath at 125–135° and subjected for 3 hr. to a vigorous stream of chlorine. The internal temperature of the mixture was 110–115°. The product was then cooled, filtered, and washed with a little benzene. Yield, 0.50 g. (93%) of bright yellow solid, m.p. 321–325° dec. On crystallization from chlorobenzene, the m.p. fell to 316–319° dec.

*Anal.* Calcd. for $C_{30}H_{15}ClN_2O_4$: C, 71.6; H, 3.0; Cl, 7.1; N, 5.6. Found: C, 71.7; H, 3.2; Cl, 7.4; N, 5.8.

*2-Cyanoanthraquinone* (VI). A mixture of 0.20 g. (0.43 mmole) of 2-anthraquinonecarboxaldazine (I) and 3 ml. of

(4) E. B. Hershberg and L. F. Fieser, *J. Am. Chem. Soc.*, **63**, 2561 (1941).

(5) Melting points are corrected.

*o*-dichlorobenzene was heated in an oil bath at 160–165° and treated with a stream of chlorine for 2 hr. The mixture, at first thick, slowly dissolved to an almost colorless solution. The yellow product that separated on cooling was filtered and washed with benzene. Yield, 0.20 g., m.p. 216–217°. It was purified by crystallization from acetic acid, without change in melting point.

*Anal.* Calcd. for $C_{15}H_7NO_2$: C, 77.3; H, 3.0; N, 6.0; O, 13.7. Found: C, 77.3; H, 3.3; N, 6.0; O, 13.6.

*2-Anthraquinonecarboxamide 2-anthraquinonylmethylenehydrazone* (III). A steady stream of ammonia was passed for 5 hr. through a suspension of 0.55 g. (1.10 mmoles) of II in 10 ml. of nitrobenzene in an oil bath at 210–220°; the internal temperature was 175–180°. The mixture was then cooled, diluted with a little alcohol, and filtered, giving 0.49 g. (91%) of orange product unmelted at 365°. It was purified by crystallization from dimethylformamide.

*Anal.* Calcd. for $C_{30}H_{17}N_3O_4$: C, 74.5; H, 3.5; N, 8.7; O, 13.3. Found: C, 74.9; H, 3.4; N, 8.8; O, 12.8.

This compound showed infrared absorption at 2.95 and 3.04 $\mu$. It was recovered unchanged (elemental and infrared analysis) after being stirred for 2 hr. in potassium hydroxide and diethylene glycol monoethyl ether at 155–160°.

A solution of 0.37 g. (0.77 mmole) of III and 0.11 g. (1.6 (mmoles) of sodium nitrite in 10 ml. conc. sulfuric acid was stirred overnight at room temperature and then for 2.5 hr. at 70–75°. The reaction product was recovered by drowning on ice, filtering, and washing. Digestion with hot aqueous sodium bisulfite, followed by filtration and acidification, gave 2-anthraquinonecarboxaldehyde, m.p. 185–187°.

*N,N-Dimethyl-2-anthraquinonecarboxamide 2-anthraquinonylmethylenehydrazone* (V). A steady stream of dimethylamine was passed for 4 hr. through a suspension of 0.52 g. (1.04 mmoles) of II in 10 ml. of nitrobenzene in an oil bath at 190°. The solid dissolved, giving a deep red solution. After completion of the reaction, the mixture was cooled, diluted with a little alcohol, and filtered, giving 0.42 g. (79%) of orange product, m.p. 258–60°. It was crystallized from amyl alcohol without change in melting point. It showed no absorption in the 2.9 $\mu$ region.

*Anal.* Calcd. for $C_{32}H_{21}N_3O_4$: C, 75.2; H, 4.1; N, 8.2; O, 12.5. Found: C, 75.0; H, 4.2; N, 8.3; O, 12.7.

*N-Methyl-2-anthraquinonecarboxamide 2-anthraquinonylmethylenehydrazone* (IV). This was prepared from methylamine in a way exactly similar to that for the corresponding dimethylamino derivative. It crystallized from dimethylformamide as an orange solid, m.p. 329–330°.

*Anal.* Calcd. for $C_{31}H_{19}N_3O_4$: C, 74.9; H, 3.8; N, 8.5; O, 12.9. Found: C, 74.6; H, 3.9; N, 8.8; O, 12.6. This compound showed infrared absorption at 2.94 and 6.60 $\mu$.

*3,5-Bis(2-anthraquinonyl)-4-methyl-s-triazole* (VIII). A mixture of 0.24 g. of IV, 0.50 g. potassium hydroxide, and 20 ml. of diethylene glycol monoethyl ether was stirred 1.5 hr. in an oil bath at 145° and 1.5 hr. at 155°. Cooling, dilution with water, and filtration gave 0.16 g. (67%) of buff solid, m.p. 346–349° dec. Crystallization from 25 ml. of dimethylformamide gave 0.11 g. of very pale yellow solid, m.p. 358–360°. This was crystallized from *o*-dichlorobenzene without further change in melting point.

*Anal.* Calcd. for $C_{31}H_{17}N_3O_4$: C, 75.1; H, 3.4; N, 8.5. Found: C, 75.0; H, 3.4; N, 8.5.

This substance showed no absorption near 2.9 $\mu$, and much weaker absorption at 6.60 $\mu$ than the starting material.

*3,5-Bis(2-anthraquinonyl)-4-phenyl-s-triazole* (IX). A mixture of 1.0 g. (2.0 mmoles) of II, 0.20 ml. (0.20 g.; 2.1 mmoles) of aniline, and 7–8 ml. of nitrobenzene was stirred for 1.5 hr. in an oil bath at 165°. The product was then cooled, filtered, and washed with benzene. Yield, 0.4 g. of orange yellow solid. An additional crop of 0.2 g. was obtained from the mother liquor. The total amount, 0.6 g., represented a 55% yield. It crystallized from diethylene glycol monoethyl ether or *o*-dichlorobenzene as an orange solid, m.p. 373–375° dec.

*Anal.* Calcd. for $C_{36}H_{19}N_3O_4$: C, 77.5; H, 3.4; N, 7.5; O, 11.6. Found: C, 77.4; H, 3.5; N, 7.5; O, 11.5.

It showed no infrared absorption in the 2.9 and 6.5 $\mu$ regions. It was recovered unchanged (melting point and infrared comparison) after being stirred 1.5 hr. in diethylene glycol monoethyl ether and potassium hydroxide at 155°. 3-(2-Anthraquinonyl)-4,5-diphenyl-*s*-triazole[1] behaved similarly.

*2,5-Bis(2-anthraquinonyl)-1,3,4-oxadiazole* (X). A mixture of 0.50 g. of 1,2-bis(2-anthraquinonecarbonyl)hydrazine[1] and 5 ml. of polyphosphoric acid was stirred in an oil bath at 175–180° for 4 hr., cooled, diluted, and filtered. The product was washed neutral and dried. Yield, 0.49 g. of gray solid unmelted at 370°. Crystallization from *o*-dichlorobenzene and then dimethylformamide gave a silvery-buff solid.

*Anal.* Calcd. for $C_{30}H_{14}N_2O_5$: C, 74.7; H, 2.9; N, 5.8. Found: C, 74.7; H, 2.9; N, 6.1.

Unlike the starting material, this compound showed no absorption at 3.22 and 6.44 $\mu$ and only weak absorption at 6.33 $\mu$.

The starting material (0.50 g.) was also cyclodehydrated by stirring for 3.5 hr. at room temperature in 10 ml. of 30% oleum. The product was diluted with sulfuric acid followed by ice, filtered, washed neutral, and dried, giving 0.41 g. of cream-colored solid unmelted at 370°. This was purified in the same way and proved identical by infrared and elemental analysis.

*1-Chloro-2-anthraquinonecarboxaldazine* (XI). A solution of 11.0 g. (0.041 mole) of 1-chloro-2-anthraquinonecarboxaldehyde[4] in 600 ml. of glacial acetic acid was stirred and refluxed in a 1000-ml. three necked flask. Efficient stirring was necessary. A solution of 1.5 ml. (1.5 g.; 0.025 mole) of 85% hydrazine hydrate in 20 ml. of acetic acid was then added dropwise over a 20-min. period. After being stirred and refluxed 10 min. longer, the yellow product was filtered hot and washed with ethanol. Yield, 10.5 g. (96%), m.p. 313–314° dec. A small specimen was crystallized from nitrobenzene (200 ml. per g.) for analysis; m.p. 317–319°.

*Anal.* Calcd. for $C_{30}H_{14}Cl_2N_2O_4$: C, 67.2; H, 2.6; Cl, 13.2; N, 5.2. Found: C, 67.0; H, 2.7; Cl, 13.1; N, 5.4.

*1-Chloro-2-anthraquinonecarbonyl chloride 1-chloro-2-anthraquinonylmethylenehydrazone* (XII). A mixture of 0.70 g. (1.3 mmoles) of XI and 20 ml. of nitrobenzene was heated in an oil bath at 110–115° and subjected to a vigorous stream of chlorine for 6 hr. The internal temperature of the mixture was about 95°. It was then cooled, diluted with a little benzene, and filtered. The bright yellow product was washed with benzene and dried. Yield 0.58 g. (78%), m.p. 269–270° dec. dependent somewhat upon the rate of heating. Crystallization from xylene raised the melting point to about 276–277° dec.

*Anal.* Calcd. for $C_{30}H_{13}Cl_3N_2O_4$: C, 63.1; H, 2.3; Cl, 18.6; N, 4.9; O, 11.2. Found: C, 62.8; H, 2.4; Cl, 18.2; N, 5.0; O, 11.3.

A solution of 0.24 g. of this compound in 2.0 ml. of conc. sulfuric acid was stirred at 125° for 2.5 hr. and then cooled and drowned on ice. The yellow product was filtered and washed. Digestion in warm dilute ammonium hydroxide, followed by filtration and acidification of the filtrate, gave 0.08 g. of very pale yellow 1-chloro-2-anthraquinonecarboxylic acid, m.p. 273–275°, unaffected by admixture with an authentic specimen. Identification was confirmed by infrared comparison.

The ammonia-insoluble fraction was freed from traces of aldehyde by digestion with warm dilute sodium bisulfite solution, leaving 0.12 g. of yellow product m.p. 292–295°. Crystallization from 20 ml. of nitrobenzene gave 0.05 g. of 1-chloro-2-anthraquinonecarboxaldazine (XI), m.p. 311–311½°, unaffected by admixture with an authentic specimen. Identification was confirmed by infrared comparison.

*1-Chloro-2-cyanoanthraquinone* (VII). A steady stream of chlorine was passed for 15 min. through a mixture of 0.30 g. (0.57 mmole) of 1-chloro-2-anthraquinonecarboxaldazine

(XI) and 5 ml. of *o*-dichlorobenzene heated in an oil bath at 155°. A clear solution was obtained after 5 min. A yellow solid separated on cooling; this was filtered and washed with benzene; yield, 0.20 g. (67%), m.p. 247–250°, raised to 248–251° on crystallization from toluene. By mixed melting point and infrared comparison, this was identical with an authentic sample.

*Acknowledgement.* The author is indebted to Miss J. L. Gove for spectral data and to O. E. Sundberg and his associates for microanalyses.

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[CONTRIBUTION FROM THE DEPARTMENTS OF SURGERY AND CHEMISTRY, SINAI HOSPITAL OF BALTIMORE, INC., AND THE JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND, AND THE DEPARTMENT OF PATHOLOGY, UNIVERSITY OF LONDON, ENGLAND.]

# Preparation of Nitrotetrazolium Salts Containing Benzothiazole[1]

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In order to take advantage of the favorable influence for histochemistry of the *p*-nitrophenyl group at *N*-2 and the potential of chelating heavy metals by the thiazole-(2) group at *N*-3 in tetrazolium salts, a variety of mono and ditetrazolium salts incorporating these features were prepared. The simplest analogue (II) was found to chelate well and was reduced readily by dehydrogenase systems of mammalian tissues. Its redox potential was close to that of INT and Nitro-BT. The benzothiazole-(2) group in the C-5 position did not participate in chelation.

The discovery that a *p*-nitro group in the *N*-2 phenyl ring of tetrazolium salts confers favorable properties on the readiness with which they accept hydrogen from various dehydrogenase systems[2,3] and the discovery that a formazan containing a dimethylthiazole group at the N-3 position (MTT) chelates well with cobalt,[4,5] suggested to us that it would be worthwhile to prepare N-3 and C-5 benzothiazole derivatives of tetrazolium salts containing in addition a *p*-nitrophenyl group at N-2. It was also hoped that the remarkable substantive properties for protein in histochemical methodology[6] exhibited by Nitro-BT [2,2′-di-*p*-nitrophenyl-5,5′-diphenyl-3,3′-(3,3′-dimethoxy-4,4′-biphenylene) ditetrazolium chloride] could be duplicated in benzothiazole analogues of dinitroditetrazolium salt. Although Nitro-BT and a 5-*m*-iodophenyl analogue of Nitro-BT have been used to demonstrate dehydrogenases with electron microscopy,[7] there should be an advantage to using nitrotetrazolium salts that yield formazans of high substantivity and capable of chelating metals of high atomic number. The development of such agents should make possible precise intramitochondrial localization of dehydrogenase activity with the electron microscope. For this purpose benzothiazole groups were introduced into the N-3 and C-5 positions and *p*-nitrophenyl groups were placed at N-2. Ditetrazolium salts were also prepared with benzothiazol and *p*-nitrophenyl groups, related to BT and Nitro-BT.

The formazan (I) was obtained by coupling *p*-nitrobenzene diazonium chloride with benzothiazolylhydrazone-(2) of benzaldehyde in the presence of alkali. Attempts to prepare I by coupling diazotized 2-aminobenzothiazole with *p*-nitrophenylhydrazone of benzaldehyde failed. Oxidation of I with *N*-bromosuccinimide in ethyl acetate[8] gave the tetrazolium bromide, which was converted to the corresponding chloride (II) by treatment with silver chloride. Oxidation of I with isoamyl nitrite and glacial acetic acid resulted in the formation of a tetrazolium salt (III) containing two nitroso groups.[9] Attempts to remove these nitroso groups with ethanolic hydrochloric acid[9] resulted in the formation of IV which did not react like a tetrazolium salt.

Similarly, benzothiazolylhydrazone-(2) of benzothiazole-2-aldehyde[10] on treatment with *p*-nitrobenzene diazonium chloride gave a formazan (V), which on oxidation with *N*-bromosuccinimide in ethyl acetate gave a tetrazolium bromide which was converted with silver chloride to the corresponding tetrazolium chloride (VI). Oxidation of V with isoamyl nitrite and glacial acetic acid gave a nitroso derivative (VII) which on treatment

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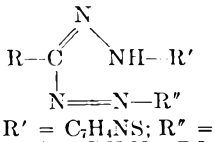
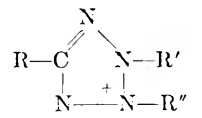
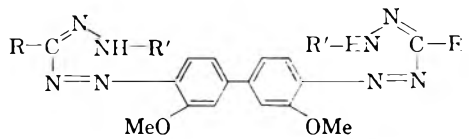


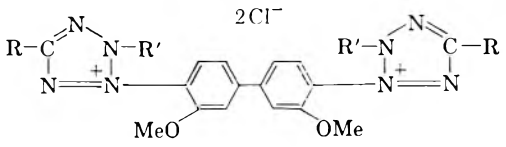
I. R = $C_6H_5$; R′ = $C_7H_4NS$; R″ = $p$-$NO_2$-$C_6H_4$
V. R = $C_7H_4NS$; R′ = $C_7H_4NS$; R″ = $p$-$NO_2$-$C_6H_4$
IX. R = $C_7H_4NS$; R′ = $p$-$NO_2$-$C_6H_4$; R″ = $o$-OMe-$p$-($m$-OMe-$C_6H_4$)-$C_6H_3$
XIII. R = $C_6H_5$; R′ = $C_7H_4NS$; R″ = $o$-OMe-$p$-($m$-OMe-$C_6H_4$)-$C_6H_3$



II. R = $C_6H_5$; R′ = $C_7H_4NS$; R″ = $p$-$NO_2$-$C_6H_4$
VI. R = $C_7H_4NS$; R′ = $C_7H_4NS$; R″ = $p$-$NO_2$-$C_6H_4$



X. R = $C_7H_4NS$; R′ = $p$-$NO_2$-$C_6H_4$
XIV. R = $C_6H_5$; R′ = $C_7H_4NS$



XII. R = $C_7H_4NS$; R′ = $p$-$NO_2$-$C_6H_4$
XV. R = $C_6H_5$; R′ = $C_7H_4NS$

with alcoholic hydrochloric acid gave a crystalline compound (VIII) which has not been identified.

The C-5 benzothiazole analogue of Nitro-BT was prepared from the $p$-nitrophenylhydrazone of benzothiazole-2-aldehyde[10] and tetrazotized 3,3′-dimethoxybenzidine at −20 to −35° as reported for Nitro-BT.[7] The resulting mixture of mono and diformazans (IX and X) were separated by extraction with benzene or methanol in a Soxhlet apparatus for a week. From the extracts, the monoformazan (IX) was obtained and purified by the usual procedure.[7] The diformazan (X) which remained in the thimble could be purified for analysis by crystallization from pyridine. It was much more soluble than the very insoluble diformazan from Nitro-BT.[2] Oxidation of X was effected with $N$-bromosuccinimide in dioxane and the resulting bromide (XI) was converted to the chloride (XII) with silver chloride.

The N-2 benzothiazole analogue of BT(XIV) was prepared from benzaldehyde, 2-benzothiazolylhydrazone and tetrazotized orthodianisidine. It was oxidized to the ditetrazolium bromide salt (XVa) with $N$-bromosuccinimide in chloroform and converted to the chloride (XV) with silver chloride. The nitroso acetate (XVI) was obtained on oxidation of XIV with isoamylnitrite.

In histochemical experiments with frozen sections of rat tissue, the benzothiazole tetrazolium salt (II) was very rapidly reduced by dehydrogenase systems as would be expected from its high position in Table I. The resulting formazan formed a black stable chelate with cobaltous ions which crystallized too readily for practical histochemical use. The other benzothiazole derivatives did not form chelates with cobalt under the conditions of the study. Investigation of other ions which do not inhibit the dehydrogenases significantly will be made.

## EXPERIMENTAL

*2-Benzothiazolyl-(2)-3-p-nitrophenyl-5-phenylformazan* (I). Benzaldehyde, 2-benzothiazolylhydrazone (3.15 g.) was dissolved in tetrahydrofuran (250 ml.). $p$-Nitroaniline (1.72 g.) was suspended in 50% hydrochloric acid (9.0 ml.), and was diazotized with an aqueous solution of sodium nitrite (0.90 g.), at 0°. The diazotized solution was then added to the tetrahydrofuran solution at −20 to −25°. An aqueous solution of potassium hydroxide (20%) was added immediately in portions until the solution became alkaline to litmus. The solution turned deep blue. The solution was stirred for 4 hr. and was allowed to stand overnight at room temperature. It was diluted with a large volume of water, the precipitate was collected, washed with hot water, and crystallized from dilute tetrahydrofuran in shining violet needles, m.p. 204–205°. Yield (3.2 g.; 64%).

*Anal.* Calcd. for $C_{20}H_{14}O_2N_6S$: N, 20.89. Found: N, 21.20.

*2-Benzothiazolyl-(2)-3-p-nitrophenyl-5-phenyltetrazolium bromide* (IIa). The formazan (I) (0.50 g.) was refluxed with ethyl acetate (150 ml.), and filtered. To the filtrate was then added a solution of $N$-bromosuccinimide (0.23 g.) in ethyl acetate (20 ml.). On shaking for some time the color of the solution turned yellow. After the addition of a few drops of conc. aqueous hydrobromic acid, the solution was cooled to 0°. The yellow precipitate was collected (0.30 g.; 50%). It was crystallized by solution in hot water with the addition of a few drops of hydrobromic acid, in shining yellow plates, m.p. 215° dec. The bromide was sparingly soluble in water.

*Anal.* Calcd. for $C_{20}H_{13}O_2N_6SBr$: Br, 16.62. N, 17.47; Found: Br, 16.30. N, 17.30.

*2-Benzothiazolyl-(2)-3-p-nitrophenyl-5-phenyltetrazolium chloride* (II). The tetrazolium bromide (IIa) (0.10 g.) was refluxed in water (150 ml.) with freshly precipitated silver chloride for 10 hr. The mixture was filtered and the filtrate was evaporated on a steambath. The precipitate crystallized from a little water containing a few drops of hydrochloric acid in shining yellow plates, m.p. 190° dec. after shrinking at 180°. Yield (0.04 g.: 45%).

*Anal.* Calcd. for $C_{20}H_{13}O_2N_6SCl$: Cl 8.13. N, 19.24. Found: Cl, 8.40, N, 19.42.

*Oxidation product of* I *with isoamylnitrite* (III). The formazan (1.10 g.) was dissolved in boiling glacial acetic acid (50 ml.). The solution was cooled to room temperature, isoamylnitrite (5.0 ml.) was added, and the solution was reheated on a steambath until the color of the solution bleached to golden yellow. On cooling a yellow crystalline precipitate appeared. It was collected and washed with a little ether, yield 1.10 g. It crystallized from glacial acetic acid in yellow needles, m.p. 229–230° dec. Nitrogen analysis revealed two nitroso groups. The carbon and hydrogen analysis was not done because the specimen exploded during combustion analysis.

*Anal.* Calcd. for $C_{20}H_{11}N_6O_2S \cdot C_2H_3O_2 \cdot 2$ NO: N, 21.62. Found: N, 21.36.

This tetrazolium salt (III) could be reduced to the original formazan.

*Anal.* Calcd. for $C_{20}H_{14}O_2N_6S$: N, 20.89. Found: N, 21.31.

*Compound* IV. The tetrazolium salt (III, 50 mg.) was suspended in absolute alcohol (30 ml.). A stream of dry hydrochloric acid gas was passed for half an hour with external water cooling. The solution was refluxed on a steambath for half an hour and was concentrated to about 15 ml. On cooling very pale yellow crystals appeared, which crys-

TABLE I

COMPARISON OF POLAROGRAPHIC RESULTS WITH A VARIETY OF TETRAZOLIUM SALTS[a]
(E 1/2, *p*H 7.0, 22°)

| Compound | Formula | Volts |
|---|---|---|
| II | 2-Benzothiazolyl-(2)-3-*p*-nitrophenyl-5-phenyl tetrazolium chloride | −0.04 |
| Nitro-BT | 2,2′-Di-*p*-nitrophenyl-3,3′-(3,3′-dimethoxy-4,4′-biphenylene)-5,5′-diphenyl ditetrazolium chloride | −0.05 |
| VI | 2-Benzothiazolyl-(2)-3-*p*-nitrophenyl-5-benzothiazolyl-(2)-tetrazolium chloride | −0.07 |
| INT | 2-*p*-Nitrophenyl-3-*p*-iodophenyl-5-phenyltetrazolium chloride | −0.09 |
| 4,5-MTT | 3,5-Diphenyl-2-(4,5-dimethylthiazolyl-(2) tetrazolium bromide | −0.11 |
| 5-MTT | 3,5-Diphenyl-2-(5-methylthiazolyl-(2)-tetrazolium bromide | −0.12 |
| XII | 2,2′-Di-*p*-nitrophenyl-3,3′-(3,3′-dimethoxy-4,4′-biphenylene)-5,5′-dibenzothiazolyl-(2)-ditetrazolium chloride | −0.15 |
| BT | 2,2′-Diphenyl-3,3′-(3,3′-dimethoxy-4,4′-biphenylene)-5,5-diphenyl ditetrazolium chloride | −0.16 |
| NT | 2,2′-Diphenyl-3,3′-(4,4′-biphenylene)-5,5′-diphenyl ditetrazolium chloride | −0.17 |
| TTC | Triphenyl tetrazolium chloride | −0.46 |
| Tellurite | | −0.95 |

[a] Acknowledgement for help in obtaining these results is due Mrs. B. Lamb, Research Department, Evershed and Vignoles Limited, London, England. Measurements were made with a Tinsley recording polarograph and a dropping mercury electrode. The tetrazolium salts were made up to a calculated concentration of $10^{-4}$ *M* in 0.1*M* phosphate buffer, *p*H 7.2, so that the final *p*H was 7.0.

tallized from alcohol in stout prismatic needles, m.p. 183° dec. The compound was insoluble in water, and it did not produce the dark color of formazan when a crystal of sodium sulphide was added to its solution in aqueous alcohol.

*Benzothiazole-2-aldehyde-2-benzothiazolylhydrazone.* (Va). This compound was prepared from equivalents by mixing alcoholic solutions of 2-hydrazinobenzothiazole (5%) and benzothiazole-2-aldehyde (20%). It crystallized from dioxane in yellow needles, m.p. 270° dec. after shrinking at 265°.

*Anal.* Calcd. for $C_{15}H_{10}N_4S_2$: N, 18.06. Found: N, 17.87.

*2-Benzothiazolyl-(2)-3-p-nitrophenyl-5-benzothiazolyl-(2)-formazan* (V). The hydrazone (Va, 1.24 g.) was dissolved in a mixture of tetrahydrofuran (40 ml.) and dimethylformamide (15 ml.). The solution was cooled to −20 to −30°. A diazotized solution of *p*-nitroaniline (0.55 g.) was added and the solution was made alkaline by the addition of aqueous sodium hydroxide (20%). After stirring for 6 hr. the solution was poured into water and was allowed to stand overnight at room temperature. The precipitate was collected (0.78 g., 43%). It crystallized from dilute dioxane in red needles, m.p. 259° dec.

*Anal.* Calcd. for $C_{21}H_{13}O_2N_7S_2$: N, 21.35. Found: N, 21.43.

*2-Benzothiazolyl-(2)-3-p-nitrophenyl-5-benzothiazolyl-(2)-tetrazolium-bromide* (VIa). To the refluxing solution of formazan (V, 1.0 g.) in ethyl acetate (200 ml.) was added a solution of *N*-bromosuccinimide (0.8 g.) in ethyl acetate. After some time a yellow solution was obtained. It was allowed to remain overnight and the precipitate was collected (0.4 g.). The precipitate was refluxed with alcohol containing water (about 30%), and filtered. The filtrate was evaporated and the substance obtained (0.25 g.) was crystallized from alcohol-water to which was added a few drops of hydrobromic acid, in brownish yellow prisms, m.p. 212° dec.

*Anal.* Calcd. for $C_{21}H_{12}N_7O_2S_2Br$: Br, 14.86; N, 18.22. Found: Br, 15.16; N, 17.98.

*2-Benzothiazolyl-(2)-3-p-nitrophenyl-5-benzothiazolyl-(2)-tetrazolium chloride* (VI). The bromide (VIa) was converted to the chloride (VI) by treatment with silver chloride in exactly the same manner as described for the chloride (II).

The chloride crystallized from water containing a few drops of methanol and a few drops of hydrochloric acid in orange-yellow needles, m.p. 199–200° dec.

*Anal.* Calcd. for $C_{21}H_{12}O_2N_7S_2Cl$: Cl, 7.19; N, 19.85. Found: Cl, 7.01; N, 19.60.

*Oxidation of V with isoamylnitrite* (VII). Oxidation of (V, 0.1 g.) was carried out exactly in the same manner as that of I, with isoamylnitrite (8 drops) and glacial acetic acid (10 ml.); yield (0.09 g.). The product (VII) crystallized from glacial acetic acid in stout yellow prismatic needles m.p. 211° dec. This acetate salt contained a nitroso group. It was reduced to a formazan by color test.

*Anal.* Calcd. for $C_{21}H_{11}N_7S_2O_2 \cdot C_2H_3O_2 \cdot NO$: N, 20.51. Found: N, 20.62.

*Compound* (VIII). The tetrazolium salt (VII, 0.1 g.) was, suspended in absolute alcohol (15 ml.) and a stream of dry hydrochloric acid was passed through it with external cooling. The substance slowly went into solution and reprecipitated on further passage of the gas as an orange precipitate. On concentration the orange color changed to pink, which also occurred on just standing. It crystallized from alcohol or acetone in pale pink needles, m.p. 196–197° dec. On recrystallization colorless crystals were obtained. This compound failed to yield a formazan on reduction. Analysis gave N, 25.73; 25.31.

*p-Nitrophenylhydrazone of benzothiazole-2-aldehyde.* This compound was prepared from equivalents by mixing alcoholic solutions of benzothiazole-2-aldehyde (20%) and *p*-nitrophenylhydrazine (10%). It crystallized from dioxane in orange-yellow needles, m.p. 256° dec.

*Anal.* Calcd. for $C_{14}H_{10}N_4O_2S$: N, 18.79. Found: N, 18.79.

*2-p-Nitrophenyl-3-(3,3′-dimethoxy-4-biphenylyl)-5-benzothiazolyl-(2)-formazan (IX), and 2,2′-di-p-nitrophenyl-3,3′-(3,3′-dimethoxy-4,4′-biphenylene)-5,5′-dibenzothiazolyl-(2)-diformazan* (X). The *p*-nitrophenylhydrazone of benzothiazolyl 2-aldehyde (0.98 g.) was dissolved in tetrahydrofuran (80 ml.), and dioxane (20 ml.). The solution was cooled to −20 to −25°. *o*-Dianisidine hydrochloride (0.52 g.) was suspended in water (2 ml.), and conc. hydrochloric acid (0.5 ml.). It was tetrazotized with an aqueous solution of sodium nitrite (0.25 g.) at 0°. The tetrazotized solution was then added to the above solution, followed by the addition of 15 ml. of sodium hydroxide (20%). It was stirred for 6 hr., at room temperature. It was then poured into a large volume of water. The precipitate obtained was collected, washed with methanol (100 ml.), with hot water, and again with methanol. To separate mono and diformazans it was extracted with benzene in a Soxhlet apparatus for a week, and with methanol or ethyl acetate for 2 days. Very faint pink color stained the final extract. The precipitate in the thimble weighed (0.70 g.; 51%). It was very sparingly soluble in pyridine. It crystallized from pyridine in dark-colored small needles; m.p. 294° dec.

*Anal.* Calcd. for $C_{42}H_{30}O_6N_{12}S_2$: N, 19.58. Found: N, 19.00.

The benzene and ethyl acetate extracts were evaporated and the monoformazan (0.20 g.; 23%) crystallized from benzene in dark prisms, m.p. 233° dec.

*Anal.* Calcd. for $C_{28}H_{22}O_4N_6S$: N, 15.61. Found: N, 15.59.

*2,2'-di-p-Nitrophenyl-3,3'-(3,3'-dimethoxy-4,4'-biphenylene)-5,5'-dibenzothiazolyl-(2)-ditetrazolium bromide* (XI). The diformazan(X, 0.1 g.) was powdered and suspended in glacial acetic acid (15 ml.). *N*-Bromosuccinimide (0.25 g.) was added, and the suspension was heated to boiling. The heating was stopped as soon as the color of the solution changed to yellow. The solution was filtered and the filtrate was evaporated in the hood at room temperature. The residue was extracted with boiling water, filtered, and evaporated on a steam bath, after the addition of a few drops of aqueous hydrobromic acid. It crystallized from its solution in hot water after the addition of a few drops of hydrobromic acid in a pale yellow powder; yield (0.1 g.). The substance did not melt up to 250° but turned brown at 162°.

*Anal.* Calcd. for $C_{42}H_{28}N_{12}O_6S_2Br_2$: Br, 15.68; N, 16.47. Found: Br, 15.58; N, 16.79.

*2,2'-di-p-Nitrophenyl-3,3'-(3,3'-dimethoxy-4,4'-biphenylene)-5,5'-dibenzothiazolyl-(2)-ditetrazolium chloride* (XII). The bromide (XI; 0.1 g.) was suspended in distilled water (500 ml.). Freshly precipitated silver chloride (from 1 g. of silver nitrate) was added and the solution was refluxed on a metal bath for 8 hr. It was filtered, and the filtrate was evaporated on a steam bath; yield (0.08 g.). It dissolved in alcohol containing water and crystallized on concentration in yellow prismatic plates. The compound did not melt but became dark at 163–164°, after turning brown at 150°.

*Anal.* Calcd. for $C_{42}H_{28}N_{12}O_6S_2Cl_2 \cdot 6H_2O$: C, 48.50; H, 3.84; Cl, 6.83; N, 16.16. Found: C, 48.48; H, 3.86; Cl, 6.74; N, 15.90.

*2-Benzothiazolyl-(2)-3-(3,3'-dimethoxy-4-biphenylyl)-5-phenyl-formazan (XIII), and 2-2'-dibenzothiazolyl-(2)-3,3'-(3,3'-dimethoxy-4,4'-biphenylene)-5,5'-diphenyldiformazan* (XIV). A tetrazotized solution of *o*-dianisidine hydrochloride (0.32 g.) was added to a solution of benzaldehyde, 2-benzothiazolylhydrazone (0.50 g.) in tetrahydrofuran (30 ml.) at −20 to −25°. This was followed by the addition of aqueous potassium hydroxide (3.0 g. in water 15 ml.). After stirring for 4 hr. at room temperature, the reaction mixture was poured into water. The precipitate was filtered, washed with hot water, dried, and extracted with methanol in a Soxhlet apparatus, for 4 days. The residue (XIV) in the thimble weighed (0.18 g., 23%). It crystallized from pyridine in dark needles with a golden luster, m.p. 278° dec.

*Anal.* Calcd. for $C_{42}H_{32}O_2N_{10}S_2$: N, 18.13. Found: N, 18.00.

The methanolic extracts (XIII) were evaporated to dryness (0.30 g., 60%). This residue was further extracted with carbon tetrachloride in a Soxhlet. Carbon tetrachloride was distilled, and the residue was purified by precipitation from its benzene solution with petroleum ether in red needles, m.p. 156–58° dec.

*Anal.* Calcd. for $C_{28}H_{23}O_2N_5S$: N, 14.19. Found: N, 14.24.

*2,2'-Dibenzothiazolyl-(2)-3,3'-(3,3'-dimethoxy-4,4'-biphenylene)-5,5'-diphenyl ditetrazolium bromide* (XVa). The diformazan (XIV, 0.1 g.) was suspended in chloroform (60 ml.). *N*-Bromosuccinimide (0.4 g.) was added and the suspension was refluxed on a steambath for 2 to 3 hr. Refluxing was usually stopped when the color of the solution became yellow. The chloroform solution was concentrated to a small volume (10 to 15 ml.) and diluted with dry ether. The yellow precipitate obtained was collected (0.11 g.). The precipitate was dissolved in alcohol, treated with norite, and filtered. The precipitate obtained on dilution with dry ether was collected and extracted with boiling distilled water. The clear yellow filtrate was evaporated after the addition of a drop of aqueous hydrobromic acid. It was purified by crystallization in yellow prismatic plates from its aqueous solution on addition of aqueous hydrobromic acid. The substance was dried in a vacuum desiccator over phosphorus pentoxide; m.p. 148° dec., yield (0.085 g.).

*Anal.* Calcd. for $C_{42}H_{30}N_{10}S_2O_2Br \cdot H_2O$: C, 53.17; H, 3.37; Br, 16.86; N, 14.77. Found: C, 53.15; H, 3.54; Br, 17.26; N, 14.90.

*2,2'-Dibenzothiazolyl-(2)-3,3'-(3,3'-dimethoxy-4,4'-biphenylene)-5,5'-diphenyl ditetrazolium chloride* (XV). The bromide (XVa) was converted to the chloride in exactly the same manner as described for the preparation of XII. For crystallization, the compound was dissolved in alcohol containing a little water, concentrated to a small volume after the addition of a drop of hydrochloric acid, and cooled. It crystallized in golden yellow plates, m.p. 129–130° dec.

*Anal.* Calcd. for $C_{42}H_{30}N_{10}S_2O_2Cl \cdot H_2O$: C, 58.66; H, 3.72; N, 16.29. Found: C, 58.97; H, 3.85; N, 16.60.

*Compound* XVI. The diformazan (XIV; 0.1 g.) was oxidized with glacial acetic acid (4 ml.) and isoamylnitrite (5 drops) on the steambath. After most of the diformazan had dissolved, the yellow solution was filtered and diluted with ether. The precipitate (0.06 g.) was purified by repeated precipitation from its methanolic solution with ether, m.p. 167° dec. This yellow powder was poorly soluble in water, contained two nitroso groups, and was reducible to a formazan by color test.

*Anal.* Calcd. for $C_{42}H_{30}N_{10}O_2S_2 \cdot 2\ C_2H_3O_2 \cdot 2\ NO$; N, 17.72. Found: N, 17.70.

*Histochemical Experiments.* The tetrazolium salts were dissolved in water and diluted with standard media for succinic dehydrogenase[6] and DPN diaphorase[5] to a final concentration of 0.1 mg./ml. Frozen sections of liver, kidney, and stomach of the rat were examined. Chelation was demonstrated by including $Co^{2+}$ in the incubation media at a concentration of $10^{-3}M$.

Reduction in the DPN diaphorase and succinic dehydrogenase systems occurred almost instantaneously with salt II and very rapidly with salt VI. This is consistent with their high position in Table I. Chelation with cobaltous ions to an almost black product in intracellular organelles occurred with II, but extensive crystallization occurred soon thereafter on storage, obscuring intracellular detail. Chelation was poor with VI and absent with XII. Nevertheless, XII gave intra-mitochondrial diformazan deposits similar to Nitro-BT, even though this diformazan was not as substantive for protein as the diformazan from Nitro-BT and was extractable from tissue sections with ethanol. This would indicate that the striking substantive properties exhibited by the diformazan of Nitro-BT is easily lost on structural changes such as introducing *ortho* or *para* iodo groups into the C-5 phenyl ring (7) or a benzothiazolyl -(2) group into the C-5 position. These experiments indicate that the benzothiazolyl -(2) group in the C-5 position not only does not favor chelation as it does in the N-3 position, but appears to inhibit chelation of a second benzothiazolyl -(2) group in the N-3 position. Salt II appears to be the most promising member of the present series for histochemistry by virtue of its readiness to accept electrons from the dehydrogenase systems and its readiness to chelate. Further exploration of the results of chelation with other metal ions would be worthwhile in order to eliminate the crystalline character of the chelate.

BALTIMORE, MD.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

# Synthesis of Some Imidazo[4,5-*d*]pyridazines and Imidazo[4,5-*d*]triazolo[4,3-*b*]pyridazines

JOHN A. CARBON

*Received June 23, 1959*

4-Amino- and 7-amino-1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine (VIa and b) have been prepared as possible adenosine antimetabolites. Treatment of 1-benzyl-4,7-dichloroimidazo[4,5-*d*]pyridazine (VII) with ethanolic hydrazine hydrate resulted in conversion to the corresponding 4-hydrazino compound (VIII). The latter material could be readily cyclized to 6-benzyl-5-chloroimidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (IX). The halogen atom in IX has proven to be quite reactive, and was replaced with a variety of nucleophilic agents. Reduction of IX with sodium in liquid ammonia gave 5-aminoimidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (X), while a similar reduction of VIII gave 4-hydrazinoimidazo[4,5-*d*]pyridazine (XII).

Recently, we reported on the synthesis of several compounds containing the imidazo[4,5-d]pyridazine ring system as potential antagonists of purine metabolism.[1] We have now extended this work to include 4 (and 7)-amino-1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine (VIa, b) isomeric with the naturally occurring nucleoside, adenosine. Also, the compound, 1-benzyl-7-chloro-4-hydrazinoimidazo[4,5-*d*]pyridazine (VIII), has offered a ready access to compounds containing the previously unknown imidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine ring system, *e.g.* X.

Treatment of 4-aminoimidazo[4,5-*d*]pyridazine hydrochloride (I) with benzoyl chloride in refluxing pyridine gave an excellent yield of the 4-benzamido compound (II), which was converted to the chloromercuri derivative (III) using the so-called Fox modification[2] to avoid traces of mercuric oxide in the product. Condensation of the chloromercuri derivative (III) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (IV), using the excellent general method of Kissman, Pidacks, and Baker,[3] gave a mixture of crude blocked nucleosides (Va, b). Catalytic debenzoylation in refluxing methanolic sodium methoxide gave a mixture of nucleosides (VIa, b), which were isolated at this stage as a mixture of their picrate salts. The free nucleosides were regenerated with IRA-400 (carbonate form),[4] and the resulting mixture separated by fractional crystallization from water.

The two compounds thus obtained, 4-amino-1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine (VIa) and the isomeric 7-amino compound (VIb), were assigned structures on the basis of a comparison of their ultraviolet absorption spectra[5] with those of 4-amino-1-methyl- and 7-amino-1-methylimidazo[4,5-*d*]pyridazine[1] (Table I). It seems highly probable that both VIa and b possess a $C_1$-$C_2$-*trans*-configuration, in view of the rule postulated by Baker *et al.*[6] on the stereochemistry of nucleoside formation.

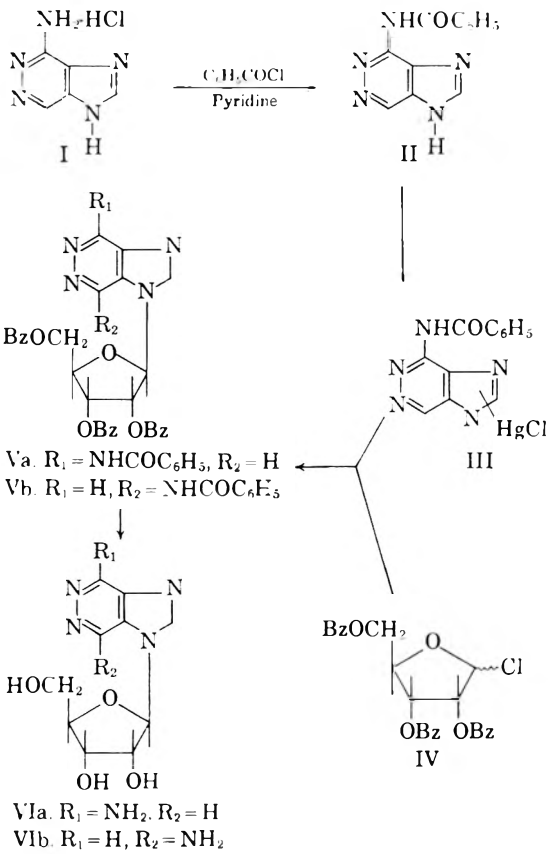



TABLE I

COMPARISON OF ULTRAVIOLET ABSORPTION MAXIMA

| Imidazo[4,5-*d*]pyridazine | $\lambda_{max}$, mμ 0.10*N* HCl | 0.10*N* NaOH |
|---|---|---|
| 4-Amino-1-β-D-ribofuranosyl- | 258 | 254 |
| 4-Amino-1-methyl[a] | 258 | 255 |
| 7-Amino-1-β-D-ribofuranosyl- | 308 | 310 |
| 7-Amino-1-methyl[a] | 263 | 261 |

[a] See ref. 1.

(1) J. A. Carbon, *J. Am. Chem. Soc.*, **80**, 6083 (1958).

(2) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

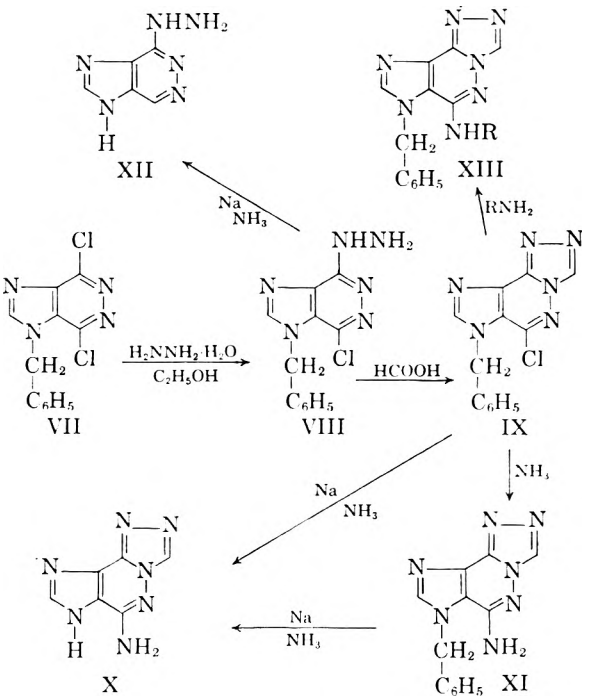
(3) H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1954).

(4) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

The conversion of 1-benzyl-4,7-dichlorimidazo-[4,5-*d*]pyridazine[1] (VII) to 1-benzyl-7-chloro-4-hydrazinoimidazo[4,5-*d*]pyridazine (VIII)[7] was readily accomplished by treatment with hydrazine hydrate in refluxing ethanol. The latter compound (VIII) could be ring-closed with boiling formic acid to give 6-benzyl-5-chloroimidazo[4,5-*d*]triazolo(4,3-*b*]pyridazine (IX). This type of ring closure has been previously observed with other hydrazino-substituted pyridazines[8] and phthalazines.[9]

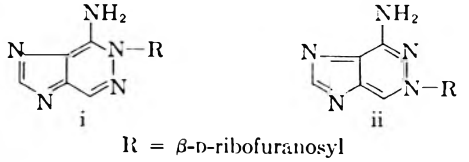
Our previous work[1] has shown that 1-benzyl-7-chloro-4-substituted-imidazo[4,5-*d*]pyridazines may be successfully reduced with sodium in liquid ammonia to give the corresponding 4-substituted compound in which the 1-benzyl and 7-chloro groupings have been removed. An attempt to apply this reaction to IX to form the unsubstituted imidazo[4,5-*d*]triazolo[4,3-6]pyridazine ring system resulted instead in replacement of the halogen atom at the 5-position by ammonia and normal cleavage of the benzyl grouping to form 5-amino-imidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (X). The structure of the latter compound (X) was proved by treatment of IX with ethanolic ammonia to form 5-amino-6-benzylimidazo[4,5-*d*]triazolo-[4,3-6]pyridazine (XI), followed by sodium in liquid ammonia reduction of XI to give a material identical in all respects with X.

The sodium in liquid ammonia reduction of VIII proceeded normally, however, to give a good yield of 4-hydrazinoimidazo[4,5-*d*]pyridazine (XII). This apparently increased reactivity of the halogen atom in the imidazo[4,5-*d*]triazolo[4,3-*b*]-pyridazine (IX) over that shown by the imidazo-[4,5-*d*]pyridazine (VIII) was borne out by other experiments. For example, treatment of IX with ethanolic ammonia, benzyl amine, or hydrazine hydrate at 80–100° resulted in the facile formation of the corresponding 5-amino (XI), 5-benzylamino (XIII, R = $CH_2C_6H_5$), or 5-hydrazino (XIII, R = $NH_2$) compound. However, when similar reactions were attempted on compound VIII, the starting material was invariably recovered unchanged. These results are not surprising, considering the loss of aromaticity of the pyridazine ring in IX as compared with the completely aromatic ring system in VIII.




The compounds reported in this paper are being screened for antitumor activity at the Sloan-Kettering Institute for Cancer Research. The results of these tests will be reported elsewhere.

(5) The comparatively high absorption maximum of VIb (308 mμ) as compared with that of 7-amino-1-methylimidazo[4,5-*d*]pyridazine (263 mμ) can possibly be attributed to the interactions between the amino group and the closely adjacent and rather bulky sugar residue. For example, 6-dimethylamino-9-ethylpurine has an absorption maximum at 277 mμ, while with the corresponding 7-ethyl compound, the maximum falls at 295 mμ [B. R. Baker *et al.*, *J. Org. Chem.*, **19**, 638 (1954)]. Another possibility would be that ribosidation had occurred on one of the pyridazine nitrogens to give a structure such as i or ii. Although we




R = β-D-ribofuranosyl

cannot exclude these structures for VIb, they appear to be rather unlikely, particularly since ribosidation of a vast number of purines has failed to give any products alkylated on a pyrimidine nitrogen.

(6) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(7) Although two isomers are theoretically possible from this reaction, depending upon which chlorine atom is replaced, we consistently obtained only one product. The structure was assigned as shown (VIII) mainly on the basis of steric considerations, as replacement at the 7-position is probably hindered by the close proximity of the 1-benzyl group.

(8) J. Druey and B. H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).

(9) N. Takahayashi, *J. Pharm. Soc. Japan, Pure Chem. Sect.*, **75**, 1242 (1955); **76**, 765, 1296 (1956).

## EXPERIMENTAL[10]

*4-Benzamidoimidazo[4,5-d]pyridazine* (II). 4-Aminoimidazo[4,5-*d*]pyridazine hydrochloride[1] (I) (17.2 g., 0.10 mole) was suspended in 100 ml. of dry pyridine and 30 g. (0.22 mole) of benzoyl chloride carefully added with stirring. The mixture was refluxed for 30 min., excess pyridine removed *in vacuo*, and the residual semisolid mass boiled with 200 ml. of ethanol for 10–15 min. The white product was filtered with suction and recrystallized from *N*,*N*-dimethylformamide-water to obtain 22.3 g. (93.3%) of colorless needles, m.p. 298–299° dec.

*Anal.* Calcd. for $C_{12}H_9N_5O$: C, 60.24; H, 3.79; N, 29.28. Found: C, 60.24; H, 3.91; N, 29.17.

(10) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus.

*Chloromercuri-4-benzamidoimidazo[4,5-d]pyridazine* (III). To 500 ml. of 50% aqueous ethanol containing 23.08 g. (0.085 mole) of mercuric chloride was added 20.3 g. (0.085 mole) of 4-benzamidoimidazo[4,5-*d*]pyridazine (II); then, with vigorous mechanical stirring, 49 ml. of 10% aqueous sodium hydroxide was slowly dropped in at a rate such that the yellow mercuric oxide color disappeared before the next drop was added. Stirring was continued an additional 30 min., 20 g. of Celite[11] was added, and the mixture filtered with suction. The product was washed with water, then with ethanol, and dried *in vacuo* at 50°. The white powder thus obtained weighed 57 g. (including 20 g. of Celite[11]). 92% of theory.

*4-Amino-1-β-D-ribofuranosylimidazo[4,5-d]pyridazine* (VIa) *and 7-amino-1-β-D-ribofuranosylimidazo[4,5-d]pyridazine* (VIb). A stirred mixture of 37 g. (0.078 mole) of chloromercuri-4-benzamidoimidazo[4,5-*d*]pyridazine (III), 20 g. of Celite,[11] and 1200 ml. of xylene was distilled until all moisture was removed. A solution of 37.5 g. (0.078 mole) of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[3,12] in 200 ml. dry xylene was added and the mixture was stirred and refluxed for 2 hr., then filtered with suction while still hot. The filter cake was washed well with 300 ml. of hot chloroform. The xylene filtrate was evaporated to dryness *in vacuo* and the residue was dissolved in 200 ml. of chloroform. The combined chloroform extracts were washed with 500 ml. of 30% aqueous potassium iodide, then with 500 ml. of water, dried over anhydrous magnesium sulfate, clarified with decolorizing carbon, and finally evaporated to dryness *in vacuo* to leave 50.2 g. of crude blocked nucleosides (V) as a brown syrup.

The 50.2 g. of crude blocked nucleosides from above was mixed with 500 ml. of methanol, 50 ml. of 1*N* methanolic sodium methoxide added, and the resulting mixture was refluxed for 30 min., a clear solution being formed at the boiling point. The solution was cooled, neutralized with 2.5 ml. of glacial acetic acid, evaporated to dryness *in vacuo*, and the residue partitioned between 200 ml. of water and 200 ml. of chloroform. The separated aqueous layer was washed with an additional 100 ml. of chloroform and then evaporated to dryness *in vacuo* below 50°. A solution of the resulting sirup in 100 ml. of methanol was treated with 300 ml. of 10% methanolic picric acid, kept overnight in the cold, and the resulting yellow precipitate filtered with suction and washed with two 100-ml. portions of water.

The crude picrate from above was suspended in 2000 ml. of water and treated with 200 g. of IRA-400 (carbonate form) at 60° with mechanical stirring until the picrate had all disappeared and the solution was colorless. After filtering with suction and washing the resin with water, the combined filtrates were evaporated to dryness *in vacuo* below 50°, and the residual colorless solid was separated into two ribosides by fractional crystallization from water.

The least water-soluble of the two compounds, *7-amino-1-β-D-ribofuranosylimidazo[4,5-d]pyridazine* (VIb), was obtained as colorless needles from water, m.p. 218–220° dec.; yield, 1.93 g. (9.9%); $[\alpha]_D^{26}$ −22° (0.50% in water). This material traveled as a single spot ($R_f$ 0.39) on paper using water-saturated butanol as solvent.[13]

*Anal.* Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.95; H, 4.91; N, 26.21; O, 23.93. Found: C, 44.88; H, 5.04; N, 26.18; O, 23.66.

The more water soluble of the two ribosides, *4-amino-1-β-D-ribofuranosylimidazo[4,5-d]pyridazine* (VIa), consisted of colorless tiny needles when recrystallized from ethanol, or precipitated from a little water by the addition of acetone, m.p. 229–230° dec.; yield, 0.57 g. (2.9%); $[\alpha]_D^{26}$ −48° (0.50% in water). Paper chromatography using water-saturated butanol revealed only a single spot of $R_f$ 0.22.[13]

*Anal.* Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.95; H, 4.91; N, 26.21; O, 23.93. Found: C, 44.96; H, 5.12; N, 26.16; O, 23.66.

*1-Benzyl-7-chloro-4-hydrazinoimidazo[4,5-d]pyridazine* (VIII). 1-Benzyl-4,7-dichloroimidazo[4,5-*d*]pyridazine (VII)[1] (27.9 g., 0.10 mole) was suspended in 200 ml. of ethanol, 12.5 g. (0.25 mole) of hydrazine hydrate added, and the mixture refluxed for 5 hr. After cooling, the product was filtered with suction and recrystallized from *N,N*-dimethylformamide-water (1:1) with Norit to give 17.3 g. (62.9%) of colorless needles, m.p. 191.5–192.0° dec.

*Anal.* Calcd. for $C_{12}H_{11}ClN_6$: C, 52.47; H, 4.04; N, 30.59. Found: C, 52.49; H, 4.12; N, 30.65.

*6-Benzyl-5-chloroimidazo[4,5-d]triazolo[4,3-b]pyridazine* (IX). Thirty-three grams (0.12 mole) of 1-benzyl-7-chloro-4-hydrazinoimidazo[4,5-*d*]pyridazine (VIII) was refluxed with 150 ml. of 98% formic acid for 1 hr., the excess formic acid removed *in vacuo*, and the residual yellow syrup stirred with 250 ml. of water until solidified. The product was filtered with suction, washed with water, and recrystallized from *N,N*-dimethylformamide-water (2:3) to obtain colorless prismatic needles, m.p. 208–209°; yield 29 g. (85%).

*Anal.* Calcd. for $C_{13}H_9ClN_6$: C, 54.84; H, 3.19; Cl, 12.45; N, 29.52. Found: C, 55.05; H, 3.46; Cl, 12.58; N, 29.87.

*5-Amino-6-benzylimidazo[4,5-d]triazolo[4,3-b]pyridazine* (XI).[14] Eighteen grams (0.063 mole) of 6-benzyl-5-chloroimidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (IX) was treated with 50 ml. of ethanol containing 15 ml. of liquid ammonia in a sealed autoclave at 100° for 4 hr. The product was isolated by suction filtration, washed with water, and recrystallized from *N,N*-dimethylformamide-water to obtain 12.5 g. (74.6%) of pale yellowish prisms, m.p. 279–282°.

*Anal.* Calcd. for $C_{13}H_{11}N_7$: C, 58.86; H, 4.18; N, 36.96. Found: C, 58.38; H, 4.07; N, 36.85.

*5-Aminoimidazo[4,5-d]triazolo[4,3-b]pyridazine* (X). A. To 22 g. (0.077 mole) of 6-benzyl-5-chloroimidazo[4,5-*d*]-triazolo[4,3-*b*]pyridazine (IX) in 500 ml. of liquid ammonia was carefully added, with vigorous mechanical stirring, 7.6 g. (0.33 g. atom) of metallic sodium. The sodium was added in small pieces over a 1-hr. period. The deep blue solution was neutralized by the careful addition of 18.7 g. (0.35 mole) of ammonium chloride and finally allowed to evaporate to dryness. The residual yellow-orange solid was washed with ether, dissolved in 200 ml. of warm dilute ammonium hydroxide, decolorized with Norit, and precipitated by neutralization with hydrochloric acid to give 4.1 g. (33%) of a cream-colored powder, m.p. >350°. As this material was insoluble in all of the common solvents, it was purified for analysis by dissolving in aqueous ammonia, filtering, and reprecipitating with acetic acid, m.p. >350°.

*Anal.* Calcd. for $C_6H_5N_7$: C, 41.13; H, 2.88; N, 55.99. Found: C, 41.12; H, 3.04; N, 55.39.

B. A similar reduction of 5-amino-6-benzylimidazo[4,5-*d*]-triazolo[4,3-*b*]pyridazine (XI) (8.4 g., 0.0317 mole) in 300 ml. of liquid ammonia with 1.59 g. (0.069 g. atom) of sodium, followed by neutralization with 3.85 g. (0.072 mole) of ammonium chloride gave 5.0 g. (90.2%) of the same product (X), m.p. >350°.

*Anal.* Calcd. for $C_6H_5N_7$: C, 41.13; H, 2.88; N, 55.99. Found: C, 41.11; H, 3.18; N, 55.95.

The infrared spectra of the products from A and B were identical in all respects.

*4-Hydrazinoimidazo[4,5-d]pyridazine* (XII). 1-Benzyl-7-chloro-4-hydrazinoimidazo[4,5-*d*]pyridazine (VIII) (17.1 g., 0.062 mole) was mixed with 500 ml. of liquid ammonia, and 6.2 g. (0.27 g. atom) of small pieces of sodium metal were added over a 1-hr. period. The reaction mixture was stirred vigorously throughout this addition. After stirring for an additional half-hour, the solution was carefully neutralized with 16 g. (0.30 mole) of ammonium chloride and

(11) Johns-Manville Co.

(12) R. K. Ness, H. W. Diehl, and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **76**, 763 (1954).

(13) Paper chromatograms were run by the ascending technique using strips of Whatman No. 1 paper. The spots were visualized by means of an ultraviolet lamp.

(14) This preparation was carried out by M. Freifelder and G. R. Stone of our Laboratories.

finally allowed to evaporate to dryness. The residual brown solid was washed with ether, suspended in 200 ml. of warm water, enough conc. hydrochloric acid added to dissolve the product, decolorized with Norit, and the filtrate adjusted to *p*H 8 with 10% sodium hydroxide. The white product was filtered with suction, washed well with water, and dried *in vacuo* at 50°, yield 7.0 g. (75%), m.p. >350°. Further purification was achieved by precipitation of the product by neutralization of a solution in aqueous hydrochloric acid.

*Anal.* Calcd. for $C_6H_6N_6$: C, 40.00; H, 4.03; N, 55.97. Found: C, 40.13; H, 3.92; N, 56.29.

The *monohydrochloride* was prepared by dissolving the free base in aqueous hydrochloric acid, evaporating to dryness *in vacuo*, and recrystallizing the residual colorless solid from aqueous ethanol to obtain colorless leaflets, m.p. >350°.

*Anal.* Calcd. for $C_3H_7ClN_6$: C, 32.18; H, 3.78; Cl, 18.99; N, 45.05. Found: C, 32.62; H, 4.03; Cl, 18.92; N, 45.59.

*6-Benzyl-5-benzylaminoimidazo[4,5-d]triazolo[4,3-b]pyridazine* (XIII, R = $CH_2C_6H_5$). One gram (0.0035 mole) of 6-benzyl-5-chloroimidazo[4,5-d]triazolo[4,3-b]pyridazine (IX) was mixed with 15 ml. of ethanol and 2 ml. of benzylamine and refluxed for 3 hr. The clear solution was cooled, and the almost colorless product which separated was isolated by suction filtration. Recrystallization from *N,N*-dimethylformamide-water or methyl cellosolve-water gave colorless prisms, m.p. 238–239°, yield 0.80 g. (64.5%).

*Anal.* Calcd. for $C_{20}H_{17}N_7$: C, 67.59; H, 4.82; N, 27.59. Found: C, 67.66; H, 5.04; N, 27.33.

*6-Benzyl-5-hydrazinoimidazo[4,5-d]triazolo[4,3-b]pyridazine* (XIII, R = $NH_2$). One gram (0.0035 mole) of 6-benzyl-5-chloroimidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (IX), 25 ml. of ethanol, and 0.50 g. (0.010 mole) of hydrazine hydrate was mixed and refluxed for 2.5 hr. The precipitate of yellow needles which separated on cooling was filtered with suction and recrystallized from *N,N*-dimethylformamide containing a little ethanol to obtain yellow needles, m.p. 268–269° dec., yield 0.60 g. (61%). This material was extremely insoluble in the common organic solvents with the exception of hot *N,N*-dimethylformamide or hot nitrobenzene. It could be dissolved in aqueous hydrochloric acid but was apparently destroyed, as neutralization only precipitated an oil which could not be crystallized.

*Anal.* Calcd. for $C_{13}H_{12}N_8$: C, 55.70; H, 4.32; N, 39.98. Found: C, 56.02; H, 4.53; N, 40.07.

*Acknowledgment.* The author would like to thank Mr. E. F. Shelberg and his staff for the microanalyses, Dr. D. J. Campbell and Mr. F. Chadde for the ultraviolet absorption spectra, and Mr. W. Washburn and his staff for the infrared absorption spectra.

NORTH CHICAGO, ILL.

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[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE AND CO.]

# *dl*-18-nor-D-Homosteroids

ROBERT R. BURTNER AND ROBERT E. GENTRY[1]

*Received October 8, 1959*

Several 17a-ethynyl and alkyl derivatives of *dl*-18-nor-D-homosteroids were prepared. None of the 17a-alkyl compounds was significantly active as an anabolic agent.

The enhanced anabolic activity of the 17-alkyl-19-nortestosterones compared with the analogous compounds in the natural series is well known.[2] W. S. Johnson and co-workers[3] have prepared and described the properties of several 18-nor-D-homosteroids bearing a carbonyl or hydroxyl group in the 17a-position. As a result of a cooperative effort with Professor Johnson, we became interested in 17a-alkyl-18-nor-D-homotestosterones and several closely related compounds.

Following the directions of Johnson *et al.*,[3c] 1-methoxy-8-keto-10a-methyl-5,6,8,9,10,10a,11,12-octahydrochrysene (I) was converted to the 3-ketal and reduced stepwise to produce *dl*-3-ethylenedioxy-18-nor-D-homoandrost-5-en-17a-one (II) along with a lesser amount of the C:D-*cis* isomer(III) which has not been previously reported. The latter was readily isomerized to the *trans* isomer (II) by treatment with base. In our hands the overall yield of pure II from the aromatic ketal was about 5% compared with 17% reported. In view of the critical nature of the Birch reduction, such variations in yields are not unexpected. Our yield of about 25% in the two step reduction of I to the saturated ketone (IV) compares more favorably with that obtained by Johnson's group.

Treatment of the saturated ketone (IV) with ethylmagnesium bromide afforded a good yield of a single product (VIII) which has been designated as a 17a $\alpha$ alcohol. This configuration assignment is based upon the work of Ruzicka and co-workers,[4] who have shown that the addition of methylmagnesium bromide to D-homoandrosterone gave the 17a$\beta$-methyl isomer exclusively. Examination of molecular models (II and IV) indicates that the absence of an angular methyl group at C-13 favors frontside approach by a bulky molecule such as a

(1) Present address: Aerojet General Corp., Sacramento, California.

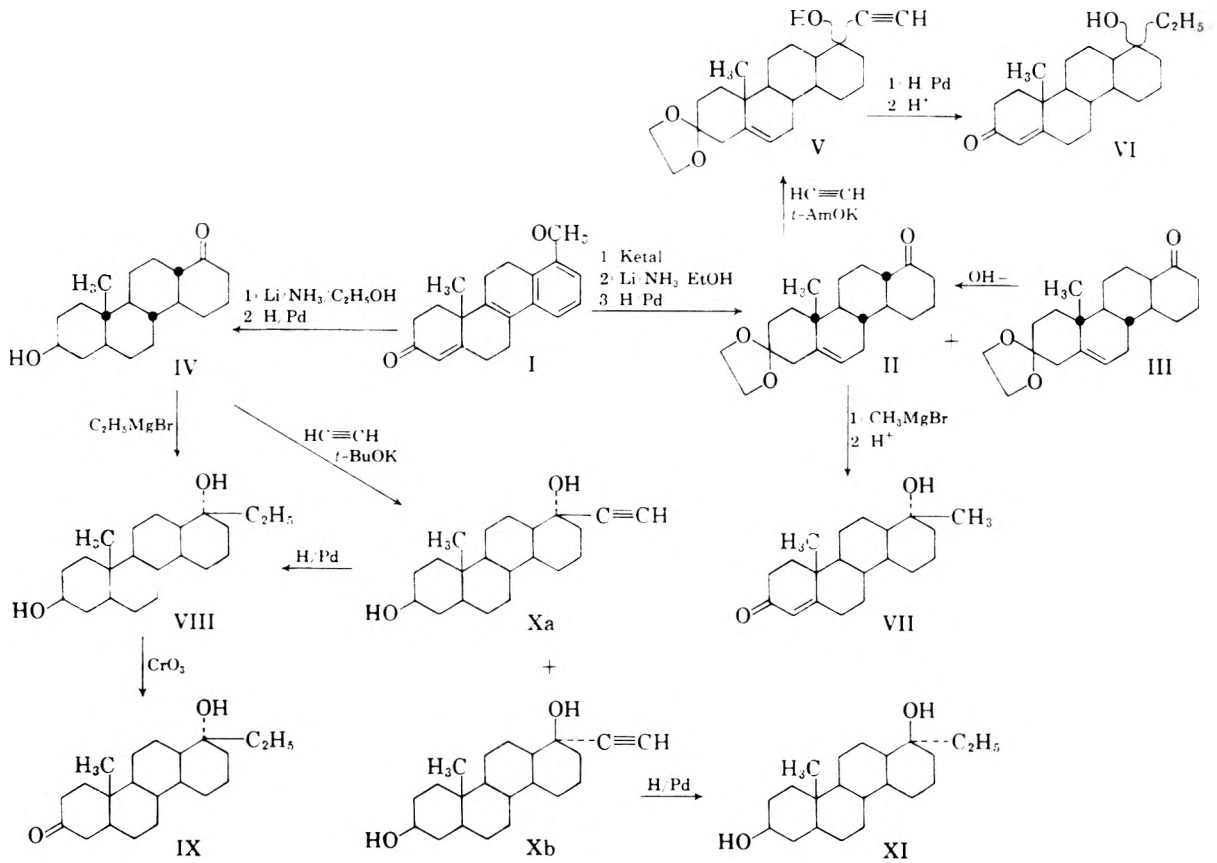
(2) (a) C. Djerassi, L. Miramontes, G. Rosenkrantz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954). (b) F. B. Colton, L. N. Nysted, B. Riegel, and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957).

(3) (a) W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **77**, 817 (1955). (b) W. S. Johnson, B. Bannister and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956). (c) W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **78**, 6354 (1956).

(4) L. Ruzicka, N. Wahba, P. Th. Herzig, and H. Heusser, *Ber.*, **85**, 491 (1952).

Grignard reagent to an even greater extent than that observed by Ruzicka.

Ethynylation of IV by Stavely's[5] method yielded two 17a-epimers (Xa and Xb) whose configurations were established by hydrogenation of X to form the Grignard adduct (VIII). Again referring to the models, we believe that the more compact potassium acetylide molecule can attack the ketone in a random manner, giving rise to both $\alpha$- and $\beta$-isomers.




Similar treatment of the ketone (II) gave a crude product (V), undoubtedly a mixture of 17a-epimers, which upon catalytic hydrogenation and hydrolysis produced the alkyl nortestosterone (VI). The low yield and difficulty in isolation of the latter strongly indicates the formation of a 17a-isomer. Lack of material precluded the study necessary for configuration assignment in this instance.

*Biology.* The biological studies on compounds VI, VII, VIII, IX, Xb and XI were conducted by Dr. Francis Saunders and associates of these laboratories. The Hershberger[6] modification of the levator ani method of Eisenberg and Gordon was employed for the determination of the anabolic activities. The androgenic effects were measured by the increase in weight of the prostate and seminal vesicles. In both tests male rats castrated at thirty days of age were employed as subjects, and testosterone propionate was the reference standard. None of the test compounds exhibited androgenic or anabolic activities greater than 5% of that of the standard.

(5) H. Stavely, *J. Am. Chem. Soc.*, 61, 79 (1939).

(6) L. G. Hershberger, Elva Shipley, and Roland Meyer, *Proc. Soc. Exptl. Biol. Med.*, 83, 175 (1953).

## EXPERIMENTAL

*C:D-cis Isomer of dl-ethylenedioxy-18-nor-D-homoandrost-5-en-16a-one* (III). Twenty-five grams of the ketal of I were reduced with lithium and alcohol in ammonia.[3c] After hydrolysis of the enol ether and rearrangement, the crude unsaturated ketone was hydrogenated over palladium-on-carbon, and the product was chromatographed over Florisil. From the eluates just preceding the saturated ketone (II), there was obtained 400 mg. of a solid which, upon crystallization from isopropyl ether, weighed 260 mg. and melted at 205–207°.

*Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.36; H, 9.15. Found: C, 76.20; H, 9.25.

Isomerization was effected by treating a solution of 93 mg. of the *cis* compound (III) in 20 ml. of alcohol with a solution of 30 mg. of potassium hydroxide in 0.35 ml. of water. After 2.5 hr. at room temperature the solvent was vacuum distilled and the residual oil was taken up in ether. The ether solution was washed with water, dried and evaporated, yielding 94 mg. of product, m.p. 131–144°. Crystallization from isopropyl ether gave 32 mg. of the *trans* epimer (II) which melted at 141–144° and was shown to be identical with an authentic sample of II by infrared spectra and mixed melting point.

The identity of III was further established by hydrolysis with 80% acetic acid to form the known *dl*-18-nor-D-homoandrost-4-ene-3,17a-dione.[3c]

*dl-18-nor-D-homo-17aβ-methyltestosterone* (VII). To a solution of 570 mg. of the ketal (II) in 40 ml. of ether was added

10 ml. of a 4*M* solution of methylmagnesium bromide in ether. The resulting mixture was refluxed for 2.0 hr. and then cautiously hydrolyzed with 35 ml. of 70% acetic acid. After evaporation of the ether, the acidic solution was heated on a steam bath for 0.5 hr. to hydrolyze the ketal group. After the cooled solution was made alkaline with dilute sodium hydroxide, it was extracted well with ether and the extract was washed with water. Drying and removal of the solvent gave 555 mg. of crude product, which, after two crystallizations from isopropyl ether, weighed 226 mg. and melted at 198–200°.

*Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.56; H, 9.98.

Careful workup of the mother liquors yielded an additional 100 mg. of VII, m.p. 194–199°. There was no evidence of an isomeric product.

*dl-18-nor-D-homo-17a-ethyltestosterone* (VI). A solution of 0.5 g. of potassium in 60 ml. of dry *t*-amyl alcohol was saturated with acetylene at 0°. To this cold solution was added 0.5 g. of the ketone (II) in 40 ml. of dry toluene during a 0.3 hr. period, after which the mixture was treated with acetylene for 4.5 hr. at 0° with vigorous stirring. The stoppered flask was then stored in the refrigerator overnight. The mixture was treated with 100 ml. of water, the solvent layer was separated and the aqueous layer was extracted with ether. The combined solutions were washed free of alkali, dried, and evaporated to give 590 mg. of crude product (V), m.p. 145–168°. Infrared spectrum showed the absence of the carbonyl group.

The crude acetylenic alcohol was hydrogenated at atmospheric pressure in 80 ml. of absolute alcohol over 150 mg. of 5% palladium-on-carbon. The partially crystalline product (505 mg.) was dissolved in 15 ml. of 80% acetic acid and heated on a steam bath for 0.5 hr. to hydrolyze the ketal. The cooled solution was diluted with 20 ml. of water, neutralized with sodium bicarbonate, and extracted thoroughly with ether. The extract was washed, dried, and evaporated to yield 421 mg. of a partially crystalline oil which was chromatographed on silica. Crystallization of the solid fractions (170 mg.) afforded 80 mg. of VI as colorless needles, m.p. 160–161°.

*Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.88; H, 10.12.

Re-working the mother liquors gave 30 mg. of less pure product, m.p. 147–155°.

*dl-18-nor-D-homo-17aβ-ethylandrostane-3β,17aα-diol* (VIII). Grignard reagent was prepared in ether from 10.9 g. of ethyl bromide and 2.43 g. of magnesium. One hundred milliliters of dry benzene was added, and then the solvent was distilled until the vapor temperature reached 70°. To this solution was added during 5 min. with good stirring a solution of 1 g. of dl-18-nor-D-homoepiandrosterone (IV) in 50 ml. of dry benzene. The mixture was refluxed for 1 hr. and then stirred overnight at room temperature. After hydrolysis with 600 ml. of ice cold 1*M* hydrochloric acid, the benzene layer was separated, and the aqueous layer was extracted with three 100-ml. portions of chloroform. The combined solvent solutions were washed twice with water, dried, and then evaporated to give 1.08 g. of a pale yellow crystalline solid. Recrystallization from 30 ml. of ethyl acetate produced 700 mg. of tiny white needles, m.p. 188°.

*Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.70; H, 11.47.

*dl-18-nor-D-homo-17aβ-ethylandrostane-17aα-ol-3-one* (IX). A solution of 500 mg. of the diol (VIII) in 5 ml. of pyridine was added with swirling to an ice cooled mixture of 500 mg. of chromic acid in 5 ml. of pyridine. After 0.25 hr. the dark mixture was removed from the ice bath and stored overnight at room temperature. After dilution with 300 ml. of ethyl acetate, the mixture was filtered and the insoluble sludge was rinsed with 50 ml. of ethyl acetate. The filtrate and washings were combined and washed with two 100-ml. portions of 0.2*N* hydrochloric acid. The acid washings were back extracted with ethyl acetate and the combined extracts were washed with brine. Removal of solvent in vacuum gave 458 mg. of crude ketone (IX) which, upon crystallization from 20 ml. of ethyl acetate (Darco), weighed 365 mg. and melted at 197–198°.

*Anal.* Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.02; H, 10.73.

*dl-18-nor-D-homo-17aβ-ethynylandrostane-3β,17aα-diol* (Xa) *and dl-18-nor-D-homo-17aα-ethynylandrostane-3β,17aβ-diol* (Xb). Eight-tenths of a gram of potassium was dissolved in 50 ml. of anhydrous *t*-butyl alcohol under nitrogen atmosphere. After the addition of 10 ml. of dry toluene the solution was chilled in an ice bath and saturated with acetylene. A solution of 0.2 g. of the saturated ketone (IV) in 40 ml. of dry toluene was then added during a 5 min. period while maintaining a moderate stream of acetylene. The resulting pale yellow solution was stirred for 4.5 hr. longer in an ice bath under a slow stream of acetylene and then stored in the refrigerator overnight. Following the addition of 250 ml. of water the solution was extracted with three 50-ml. portions of chloroform. The combined extracts were washed with water and dried over sodium sulfate. Removal of the solvent yielded 0.199 g. of a pale yellow solid which was very insoluble in common solvents and melted at 210–240°. Infrared showed no carbonyl absorption.

Eight-tenths of a gram of the above epimeric mixture was triturated with 8 ml. of ethyl acetate at room temperature. The insoluble portion was collected on a filter (400 mg.) and then extracted with 40 ml. of boiling isopropyl ether. The insoluble fraction was again separated (280 mg.) and crystallized from 16 ml. of absolute alcohol to give 180 mg. of white needles, m.p. 254–256° (Xb). A second crop of 50 mg., m.p. 253–256°, was obtained by concentration of the alcoholic mother liquor.

*Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found C, 79.78; H, 10.22.

The ethyl acetate and isopropyl ether filtrates from the above procedure were combined and evaporated to dryness at room temperature (150 mg.). Successive crystallizations from ethyl acetate and absolute alcohol yielded 50 mg. of needles melting at 220–221° (Xa).

*Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.71; H, 10.42.

*Hydrogenation of dl-18-nor-D-homo-17aβ-ethynylandrostane-3β,17aα-diol* (Xa). A solution of 30 mg. of Xa in 15 ml. of absolute alcohol was hydrogenated at atmospheric pressure over 10 mg. of 5% palladium-on-carbon catalyst. Crystallization of the crude product from 0.9 ml. of ethyl acetate gave 20 mg. of needles, m.p. 184–186°, which was identical (mixed melting point and infrared spectra) with the Grignard adduct (VIII).

*Hydrogenation of dl-18-nor-D-homo-17aα-ethynylandrostane-3β,17aβ-diol* (Xb). A solution of 123 mg. of the acetylenic alcohol (Xb) in 25 ml. of absolute alcohol was hydrogenated at atmospheric pressure over 20 mg. of 5% palladium-on-carbon catalyst. Crystallization of the crude product (m.p. *ca.* 225°) from 10 ml. of butanone yielded 105 mg. of the 17aα-ethyl compound (XI) m.p. 229–231°.

*Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.56; H, 11.26.

CHICAGO 80, ILL.

[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

# Catechol Derivatives of Estrogens[1]

JACK FISHMAN, MARIA TOMASZ, AND ROSEMARIE LEHMAN

*Received September 18, 1959*

The preparation of 2-methoxyestriol (IIa), 2-hydroxyestriol, 3-methyl ether (IIc), 2-hydroxyestradiol, 3-methyl ether (IVc), 2-hydroxyestradiol (IVf), and 2-hydroxyestrone (Vb), with various derivatives and intermediates is described.

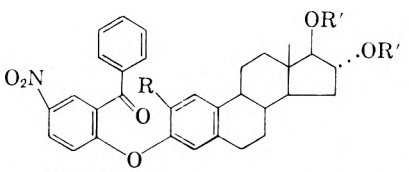
The synthesis of actual or anticipated estrogen metabolites has been a continuing concern of these laboratories and recently emphasis has been given to compounds with an additional oxygen function on ring A.[2,3] This communication deals with the preparation of some catechol derivatives of estrogens together with certain of the mono- and dimethyl ethers of these steroids. The natural occurrence of these products as female hormone metabolites is under active investigation.

Since metabolic transformation of the estrogenic hormone in man yields large amounts of estriol,[4] it was logical to anticipate, in analogy to the presence of 2-methoxyestrone,[5] that the 2-methoxy derivative of estriol would also be present as the end product of a particular biochemical pathway. This indeed proved to be the fact[6] and identification and isolation of the metabolite were enormously facilitated by the availability of that compound through an effective synthesis. Starting with estriol the procedure for introduction of a methoxyl group used for the preparation of 2-methoxyestradiol[2] was clearly applicable. An alternate route starting with 2-methoxyestrone and elaborating the ring-D glycol structure by the method of Leeds *et al.*[7] was also considered, but was abandoned in favor of the direct preparation.

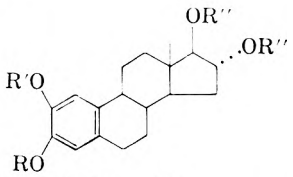
Condensation of estriol with 2-chloro-5-nitrobenzophenone gave the ether Ia, which was acetylated to the diacetate Ib. Cyclization of the latter in a sulfuric-acetic acid mixture and subsequent oxidation with 30% hydrogen peroxide gave the 2-hydroxy compound Ic which, on direct methylation with diazomethane, yielded the 2-methoxy derivative Id. Alkaline hydrolysis of Id removed both the acetate and nitrobenzophenone groups, and after purification by counter current distribution, 2-methoxyestriol (IIa), m.p. 215–218° was obtained. The new compound was, as expected, somewhat less polar than estriol, and exhibited the characteristic ultraviolet absorption maximum at 286 mμ.

Compounds like the 2-hydroxybenzophenone ether Ic readily undergo the Smiles rearrangement in the presence of alkali,[8] and brief treatment of Ic with alkali resulted in a mixture of starting material and rearrangement product. Methylation

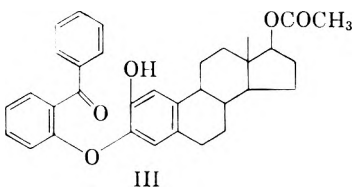
CHART I



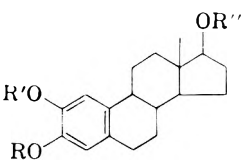
Ia. R = R′ = H
b. R = H, R′ = $CH_3CO$
c. R = OH, R′ = $CH_3CO$
d. R = $CH_3O$, R′ = $CH_3CO$

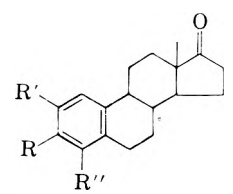


IIa. R = R″ = H, R′ = $CH_3$
b. R = $CH_3$, R′ = H, R″ = $CH_3CO$
c. R = $CH_3$, R′ = R″ = H
d. R = R′ = $CH_3$, R″ = H



III





IVa. R = $CH_3$, R′ = H, R″ = $CH_3CO$
b. R = H, R′ = $CH_3$, R″ = $CH_3CO$
c. R = $CH_3$, R′ = R″ = H
d. R = R′ = $CH_3$, R″ = $CH_3CO$
e. R = R′ = $CH_3$, R″ = H
f. R = R′ = R″ = H
g. R = R′ = H, R″ = $CH_3CO$

Va. R = R′ = $CH_3O$, R″ = H
b. R = R′ = OH, R′ = H
c. R = R′ = $C_6H_5COO$, R″ = H
d. R = $CH_3O$, R′ = H, R″ = OH
e. R = R″ = OH, R′ = H

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

(2) J. Fishman, *J. Am. Chem. Soc.*, **80**, 1213 (1958).

(3) S. Kraychy, *J. Am. Chem. Soc.*, **81**, 1702 (1959).

(4) C. T. Beer and T. F. Gallagher, *J. Biol. Chem.*, **214**, 335, 351 (1954).

(5) S. Kraychy and T. F. Gallagher, *J. Am. Chem. Soc.*, **79**, 1213 (1957); *J. Biol. Chem.*, **229**, 519 (1957).

(6) J. Fishman and T. F. Gallagher, *Arch. Biochem. and Biophys.*, **77**, 511 (1958).

(7) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

(8) J. D. Loudon and J. A. Scott, *J. Chem. Soc.*, 265 (1953).

of the mixture with diazomethane and removal of the benzophenone group with piperidine yielded, after chromatography on alumina, two main products. The unaltered fraction, after hydrolysis yielded 2-methoxyestriol (IIa), while the rearrangement product, IIb, on similar hydrolysis, afforded 2-hydroxyestriol, 3-methyl ether (IIc), m.p. 268–271°. The structure of the latter was indicated by the analytical data, the identity of ultraviolet, and similarity of the infrared spectra with that of 2-methoxyestriol (IIa). Final proof of the structure was provided by further methylation of IIc to give IId, identical in all respects with that obtained from 2-methoxyestriol. The possibility that the high melting isomer IIc was 2-methoxyestriol, while the low melting IIa was the rearranged product can be excluded since only one product, IIa, m.p. 215–218°, was obtained when base was excluded during the handling and methylation of Ic.

The relative ease of the Smiles rearrangement in this sequence prompted its use in the preparation of another estradiol derivative. When the 2-hydroxy ether (III) derived from estradiol[2] was dissolved in Claisen alkali, acidified, and extracted, a rearrangement mixture resulted. Methylation and reacetylation followed by piperidine cleavage gave the two expected isomers, 2-methoxyestradiol, 17-acetate (IVb),[2] and 2-hydroxyestradiol, 17-acetate, 3-methyl ether (IVa). Further methylation of either compound gave the identical dimethoxy derivative, IVd. Hydrolysis of IVd afforded 2,3-dimethoxyestradiol (IVe), which on oxidation with chromic acid gave 2,3-dimethoxyestrone (Va). Alkaline hydrolysis of the monoacetate (IVa) gave 2-hydroxyestradiol, 3-methyl ether (IVc) isomeric with 2-methoxyestradiol. Pyridine hydrochloride fusion of either IVc or 2-methoxyestradiol gave in excellent yield 2-hydroxyestradiol (IVf). This compound was also prepared by an alternate route, via the piperidine cleavage of III, and acid hydrolysis of the resulting 2-hydroxyestradiol, 17-acetate (IVg).

Similar demethylation of the two isomeric methoxyestriols, IIa and IIc, proceeded with concomitant dehydration[9] to give 2-hydroxyestrone (Vb); the same product was also readily obtained by demethylation of 2-methoxyestrone. Yet another route proceeded *via* the dibenzoate Vc obtained from oxidation of the dibenzoate of 2-hydroxyestradiol. For comparison purposes 4-hydroxyestrone (Ve) was prepared by the demethylation of 4-hydroxyestrone, 3-methyl ether (Vd) prepared previously in these laboratories[3] and was found to be different from Vb.

The preparation of 2-hydroxyestrone by a different route has already been recorded in the literature[10] although there is some doubt as to the homogeneity of the nitro compound used in that preparation.[11] Some biological properties of 2-hydroxyestradiol and 2-hydroxyestrone have been described,[12,13] but no chemical details or physical constants have been recorded.

NOTE ADDED IN PROOF: After the submission of this manuscript, the preparation of 2-hydroxyestradiol by a different route has been reported. L. R. Axelrod and P. Narasimha Rao, Chemistry and Industry, 1954 (1959).

## EXPERIMENTAL[14]

*16α,17β-Dihydroxy-Δ$^{1,3,5(10)}$-estratriene, 3-(2-benzoyl-4-nitro)-phenyl ether* (Ia). To a solution of 8.3 g. of estriol in 250 ml. of 95% ethanol containing 1.5 g. of potassium hydroxide, was added 6.5 g. of 2-chloro-5-nitrobenzophenone. The solution was refluxed for 48 hr., acidified with dilute sulfuric acid to *p*H 3, and continuously extracted with ether for 24 hr. The ether extract, after drying and evaporation, was taken up in chloroform and passed through a 300 g. alumina column. All material eluted with chloroform was discarded. Elution with chloroform containing 5% methanol afforded 5.6 g. of product, m.p. 122–130°, while 10% methanol eluted 1.5 g. of estriol. The benzophenone ether was recrystallized from methanol to give the analytical sample of Ia, m.p. 132–144°; $\lambda_{max}^{EtOH}$ 255 mμ (ε 16,000), 297 mμ (ε 11,000), $\lambda_{min}^{EtOH}$ 238 mμ (ε 13,000), 282 mμ (ε 10,500). Further recrystallizations did not change the melting point.

*Anal.* Calcd. for $C_{31}H_{31}O_6N$: C, 72.49; H, 6.08. Found: C, 72.67; H, 6.55.

*16α,17β-Diacetoxy-Δ$^{1,3,5(10)}$-estratriene, 3-(2-benzoyl-4-nitro)-phenyl ether* (Ib). Acetylation of Ia with acetic anhydride in pyridine yielded the 16α,17β-diacetate as a viscous oil; the infrared spectrum in chloroform solution showed no hydroxyl absorption at 3600 cm.$^{-1}$ An analytical sample crystallized from acetic acid, melted 74–76°.

*Anal.* Calcd. for $C_{35}H_{33}O_8N$: C, 70.34; H, 5.87. Found: C, 70.63; H, 6.08.

*2-Hydroxy-16α,17β-diacetoxy-Δ$^{1,3,5(10)}$-estratriene, 3-(2-benzoyl-4-nitro)phenyl ether* (Ic). One g. of the diacetate Ib was dissolved in 2 cc. acetic acid and 2 cc. of ice-cold concentrated sulfuric acid was added with cooling. After standing for 0.5 hr. at room temperature the mixture was diluted with 15 cc. of glacial acetic acid and an excess of 30% hydrogen peroxide was added dropwise. The solution was allowed to stand for an additional 0.5 hr., and was then poured into water. The precipitate was filtered off and washed well with water; the dried tan solid weighed 750 mg. The infrared spectrum in chloroform solution exhibited a strong band at 1655 cm.$^{-1}$ characteristic of the conjugated ketone strongly hydrogen bonded with the new hydroxyl.[2]

*2-Methoxy-16α,17β-diacetoxy-Δ$^{1,3,5(10)}$-estratriene, 3-(2-benzoyl-4-nitro)phenyl ether* (Id). Seven hundred mg. of Ic were dissolved in the minimum amount of an ethanol-ether mixture and allowed to stand for 24 hr. with an excess of distilled ethereal diazomethane. Evaporation of solvents and

(9) J. C. Sheehan, W. F. Erman, and P. A. Cruickshank, *J. Am. Chem. Soc.*, **79**, 147 (1957).

(10) J. B. Niederl and H. J. Vogel, *J. Am. Chem. Soc.*, **71**, 2566 (1949).

(11) H. Werbin and C. Holloway, *J. Biol. Chem.*, **223**, 651 (1956).

(12) G. C. Mueller, *Nature*, **176**, 127 (1955).

(13) C. Huggins and E. P. Jensen, *J. Experimental Med.*, **102**, 335 (1955).

(14) Melting points were determined on a hot-stage apparatus and are corrected. Rotations were determined in a 2-dcm. tube and chloroform was the solvent unless otherwise specified. Analyses were performed by Spang Microanalytical Laboratories.

crystallization of the residue from methanol gave the product, m.p. 151–154°. The infrared spectrum of this compound in chloroform solution showed the normal conjugated band at 1672 cm.$^{-1}$ The analytical sample melted 155–158°.

*Anal.* Calcd. for $C_{36}H_{37}O_9N$: C, 68.88; H, 5.94. Found: C, 69.14; H, 6.36.

*2-Methoxyestriol* (IIa). In a nitrogen atmosphere 600 mg. of Id was refluxed for 1 hr. with 6% ethanolic potassium hydroxide. Acidification with sulfuric acid and extraction with chloroform and ether gave the crude product which was purified by a 99 tube counter current distribution in the system 50% aqueous methanol and 1:1 cyclohexane-ethyl acetate. Crystals contained in tubes 20–35 were combined and recrystallized from dilute acetone to give 180 mg. of IIa, m.p. 211–214°.

The analytical sample was obtained from methanol-benzene and melted at 215–218°; $[\alpha]_D^{26}$ +83° (ethanol), $\lambda_{max}^{EtOH}$ 286 mμ (ε 3500), $\lambda_{min}$ 253 mμ (ε 350).

*Anal.* Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.28; H, 8.21.

*2-Hydroxyestriol, 3-methyl ether, 16,17-diacetate* (IIb). Five g. of the benzophenone ether (Ib) were cyclized and oxidized as described previously. The 2-hydroxy product (Ic) was dissolved in alkali, allowed to stand for 15 min., acidified and the partially rearranged product was re-extracted. The crude material was taken up in ethanol and treated with an excess of ethereal diazomethane. The product obtained, a mixture melting at 160–190°, was then reacetylated. The total material was refluxed in 60 cc. of piperidine for 1.5 hr. under nitrogen. The cooled solution was diluted with 200 cc. of benzene and washed well with cold 5% sulfuric acid. After washing with 5% sodium bicarbonate solution and water, an oily residue was obtained when the solvent was removed. This was taken up in benzene and chromatographed on 220 g. of acid washed alumina. Elution with 20% ether-benzene gave 0.6 g. of crystalline material, m.p. 176–180°. The analytical sample of 2-hydroxyestriol, 3-methyl ether, 16,17-diacetate (IIb) was obtained from benzene-petroleum ether and melted at 178–181° $[\alpha]_D^{27}$ −16.5°.

*Anal.* Calcd. for $C_{33}H_{30}O_6$: C, 68.86; H, 7.51. Found: C, 68.80; H, 7.36.

Preceding chromatographic fractions were oils which on hydrolysis with 5% ethanolic potassium hydroxide gave after purification 1 g. of 2-methyloxyestriol (IIa).

*2-Hydroxyestriol, 3-methyl ether* (IIc). Hydrolysis of 0.5 g. of the diacetate (IIb) in 5% ethanolic potassium hydroxide and crystallization of the product from methanol-benzene gave 230 mg. of material m.p. 260–269°. The analytical sample was obtained as needles m.p. 268–271°, $[\alpha]_D^{25}$ +64° (ethanol). The ultraviolet spectrum was identical with that of 2-methoxyestriol (IIa), the infrared spectrum in potassium bromide showed differences only in the 650–1400 cm.$^{-1}$ region.

*Anal.* Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.69; H, 8.24.

*2-Methoxyestriol, 3-methyl ether* (IId). A small amount of IIc was methylated with diazomethane in ether-ethanol. Purification of the product by alumina chromatography and elution with chloroform gave crystals which melted at 100–110°, resolidified, and then melted at 188–191°. The analytical sample was obtained from acetone–petroleum ether as needles melting at 190–192°, $[\alpha]_D^{27}$ +69°. Despite vacuum drying at 50° the sample retained water.

*Anal.* Calcd. for $C_{20}H_{28}O_4 \cdot H_2O$: C, 68.55; H, 8.57. Found: C, 68.31; H, 8.44.

Similar methylation of 2-methoxyestriol (IIa) gave material m.p. 189–191°, identical with the above by mixed melting point and infrared spectra comparison.

*2-Hydroxyestradiol, 3-methyl ether, 17-acetate* (IVa). Eight g. of III was dissolved in Claisen alkali and was allowed to stand at room temperature for 15 min. Acidification and extraction with chloroform gave a crude mixture which was methylated with diazomethane. The methylated product was reacetylated and was then refluxed in 100 ml. of piperidine for 1 hr. After the usual work-up the product was chromatographed on alumina. Elution with 30% benzene in petroleum ether gave 1 g. of 2-methoxyestradiol, 17-acetate (IVb). With 50% benzene in petroleum ether 3.1 g. of IVa, m.p. 198–208° was obtained. The analytical sample of 2-hydroxyestradiol, 3-methyl ether, 17-acetate (IVa) was recrystallized from benzene petroleum ether and melted 210–212°, with long needles forming at 188°, $[\alpha]_D^{27}$ +43.0°.

*Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.17. Found: C, 73.25; H, 8.24.

*2-Hydroxyestradiol, 3-methyl ether* (IVc). One g. of the acetate IVa was hydrolyzed in the usual manner with 5% ethanolic potassium hydroxide to give 0.85 g. of product. Crystallization from acetone afforded the analytical sample of IVc, m.p. 179–181°, $[\alpha]_D^{28}$ +74°.

*Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 74.98; H, 8.44.

*2-Methoxyestradiol, 3-methyl ether, 17-acetate* (IVd). Methylation of IVa with ethereal diazomethane gave after separation from unchanged material the dimethyl ether IVd, m.p. 178–180° from ethanol. The analytical sample melted at 179–182° with sublimation, $[\alpha]_D^{27}$ +53°.

*Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73.75; H, 8.38. Found: C, 73.75; H, 8.71.

The product obtained from a similar methylation of 2-methoxyestradiol, 17-acetate (IVb) was identical with the above by mixed melting point and infrared spectral comparison.

Hydrolysis of the dimethoxy compound IVd with methanolic potassium hydroxide gave 2-methoxyestradiol, 3-methyl ether (IVe), m.p. 131–133° from methanol-ether. The material retained solvent tenaciously with melting at 100–110° and resolidification. The analytical sample showed similar behavior in melting point, $[\alpha]_D^{27}$ +85°.

*Anal.* Calcd. for $C_{20}H_{26}O_3 \cdot {}^1/_2CH_3OH$: C, 74.59; H, 8.92. Found: C, 74.12; H, 9.02.

*2-Methoxyestrone, 3-methyl ether* (Va). Oxidation of a small amount of the dimethoxyestradiol compound IVc, with chromic acid in acetone gave, on the usual work-up, the 17-keto derivative Va, m.p. 172–175° from methanol. The analytical sample of 2-methoxyestrone, 3-methyl ether (Va), was obtained as needles, m.p. 173–176°.

*Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.43; H, 8.28. Found: C, 76.41; H, 8.21.

The same compound was also obtained by methylation of 2-methoxyestrone.

*2-Hydroxyestradiol* (IVf). One g. of the 3-methyl ether (IVc) was heated with 2 g. of freshly distilled pyridine hydrochloride for 15 min. at 200–220°. Dilution with water and extraction with a chloroform-ethanol mixture gave 700 mg. of product as tan colored crystals from dilute methanol. Recrystallization from the same solvent afforded the analytical sample which melted at 110–113° resolidified and melted again at 155–158°; $[\alpha]_D^{28}$ +90° (ethanol), $\lambda_{max}^{EtOH}$ 289 (ε 3600), $\lambda_{min}$ 251 (ε 650). The material was hydroscopic and despite drying at 65° retained a molecule of water.

*Anal.* Calcd. for $C_{18}H_{24}O_3 \cdot H_2O$: C, 70.56; H, 8.55. Found: C, 70.87; H, 8.56.

This same compound (IVf) was also obtained by an alternate route from III. Piperidine cleavage of III gave 2-hydroxyestradiol, 17-acetate (IVg), which crystallized from benzene-petroleum ether and melted at 100–109°, resolidified, and melted 182–185°. The analytical sample of IVg was dried at 65° for 12 hr. and melted 182–185°, $[\alpha]_D^{26}$ +59°.

*Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.88; H, 7.74.

Acid hydrolysis of the above with 10% ethanolic sulfuric acid afforded 2-hydroxyestradiol (IVf).

*2-Hydroxyestrone* (Vb). One hundred mg. of 2-methoxyestrone was heated with pyridine hydrochloride as previously described. The reaction mixture was diluted with water

and filtered. The precipitate (63 mg.), crystallized from benzene, melted at 192–194°. The analytical sample of Vb melted at 194–196°; $[\alpha]_D^{27}$ +172° (ethanol).

*Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.52; H, 7.69. Found: C, 75.14; H, 7.76.

The same compound was obtained from either IIa or IIc on heating with pyridine hydrochloride for 1 hr. at 200°.

An alternative route led via the Schotten-Bauman benzoylation of 2-hydroxyestradiol (IVf) to give the dibenzoate which on oxidation with chromic acid in acetic acid gave 2-hydroxyestrone, 2,3-dibenzoate (Vc) m.p. 172–174° from ethanol.

*Anal.* Calcd. for $C_{32}H_{30}O_5$: C, 77.71; H, 6.11. Found: C, 77.66; H, 6.10.

Mild alkaline hydrolysis of the above under a nitrogen atmosphere gave 2-hydroxyestrone (Vb).

*4-Hydroxyestrone* (Ve).[15] Pyridine hydrochloride fusion of 200 mg. 4-hydroxyestrone, 3-methyl ether (Vd) gave 138 mg. of product which crystallized from benzene-methanol with a m.p. 260–265° dec. The analytical sample obtained from the same solvent melted at 266–270° dec. with sublimation; $[\alpha]_D^{27}$ +155° (ethanol).

*Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.49: H, 7.74. Found: C, 74.99; H, 7.67.

*Acknowledgment.* The authors wish to thank Dr. T. F. Gallagher for his advice and interest in this work. They wish to thank Mrs. Beatrice S. Gallagher for the infrared spectra.

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(15) The diacetate of this compound has been prepared by oxidation with lead tetracetate, A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **80**, 5683 (1958).

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

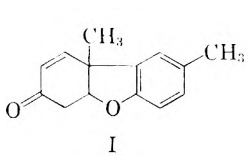
# Compounds Related to a Possible Precursor of Diploicin[1]

C. R. SMITH, JR.[2]

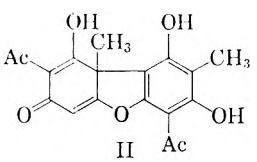
*Received September 23, 1959*

The synthesis of compounds related to a possible biosynthetic precursor of diploicin (IVb) a chlorine-containing lichen substance, is described. The relative ease of decarboxylation of 3,5-dichloro-*o*-orsellinic acid and two of its derivatives is discussed. 2,4-Dichloroörcinol undergoes diacylation preferentially, despite steric factors which should favor monoacylation.

Recent work on oxidative coupling of phenols, involving one-electron-transfer oxidizing agents, has elucidated the true nature of the crystalline dimer obtained by oxidizing *p*-cresol with alkaline ferricyanide (I).[3] Usnic acid (II), a lichen metabolite, has been synthesized by a similar process.[3] Scott has also utilized this coupling process in carrying out the partial synthesis of (±)-dehydrogriseofulvin and (±)-geodin methyl ether from related benzophenone derivatives.[4] Brockmann and coworkers have demonstrated related oxidations of hypericin precursors.[5] Bruice oxidized 3-methoxymesitol with alkaline ferricyanide and obtained only linear coupling and hydroxylation products,[6] in contrast to I and II, which resulted from free radical coupling followed by ionic cyclization. The concept of oxidative coupling of phenols as a biogenetic mechanism has been discussed in detail by Barton and Cohen.[7]



I



II

Diploicin (IVb), a chlorine-containing lichen metabolite,[8] was selected as a prospective further example of a natural product which could be synthesized by oxidative coupling of a phenolic precursor *in vitro*. The structure of diploicin, which is obtained from *Buellia canescens*, was elucidated by Nolan and co-workers.[9,10,11] Our initial objective was preparation of a compound such as IIIb, whose blocking groups could be readily removed. A subsequent conversion IIIa→IVa, effected by oxidative cyclization through electron pairing, was envisioned as follows:

(1) This investigation was supported by Research Grant EF-5415 from the National Institutes of Health.

(2) National Heart Institute Research Fellow, University of Glasgow, 1955–56. Present address, Northern Regional Research Laboratory, Peoria, Illinois.

(3) D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, *J. Chem. Soc.*, 1956, 530.

(4) A. I. Scott, *Proc. Chem. Soc.* (*London*), 1958, 195.

(5) H. Brockmann, *Proc. Chem. Soc.* (*London*), 1957, 304.

(6) T. C. Bruice, *J. Org. Chem.*, **23**, 246 (1958).

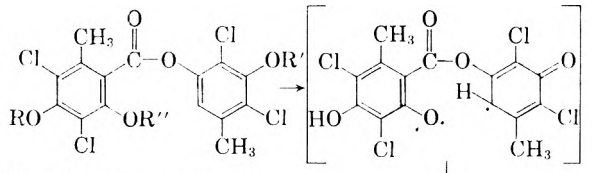
(7) D. H. R. Barton and T. H. Cohen in *Festschrift Arthur Stoll*, Birkhäuser AG, Basel, 1957, p. 117.

(8) For reviews on lichen substances, *cf.* Y. Asahina and S. Shibata, *The Chemistry of Lichen Substances*, Japan Society for Promotion of Science, Tokyo, 1954; S. Shibata in *Encyclopedia of Plant Physiology*, Vol. X, ed. by W. Ruhland, Springer-Verlag, Berlin, 1958, p. 560.

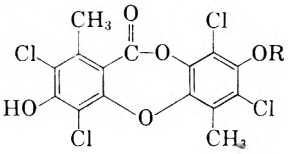
(9) P. A. Spillane, J. Keane and T. J. Nolan, *Sci. Proc. Roy. Dublin Soc.*, **21**, 333 (1936).

(10) T. J. Nolan and D. Murphy, *Sci. Proc. Roy. Dublin Soc.*, **22**, 315 (1940).

(11) T. J. Nolan, J. Algar, E. P. McCann, W. A. Manahan and N. Nolan, *Sci. Proc. Roy. Dublin Soc.*, **24**, 319 (1948).



IIIa. R = R′ = R″ = H
IIIb. R = $CH_2C_6H_5$, R′ = R″ = H
IIIc. R = R″ = $CH_2C_6H_5$, R′ = H
IIId. R = R′ = R″ = $CH_2C_6H_5$



IVa. R = H
IVb. R = $CH_3$

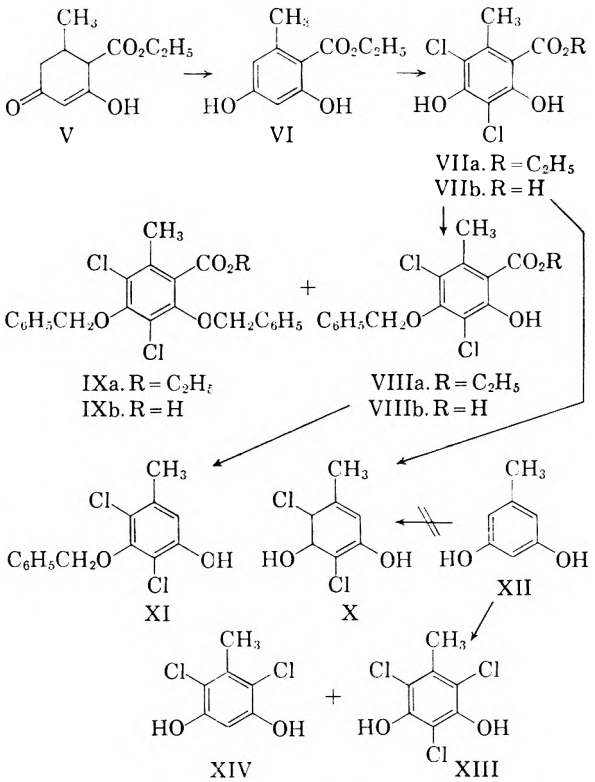
Other modes of cyclization are conceivable, such as formation of a spiro ring as in dehydrogriseofulvin. Expression IIIa is analogous to the class of lichen substances known as *depsides*, while diploicin itself (IVb) is a *depsidone* of the orcinol group.[8] None of these lichen-produced lactones have thus far been synthesized.

The synthesis of the dichloroörsellinic acid moiety of III began with the condensation of acetoacetic ester and ethyl crotonate to form V. The method of von Schilling and Vorländer[12] was used with some modifications found necessary. V was aromatized to yield ethyl *o*-orsellinate (VI) by the method of Pfau.[13] Pfau's procedure employs 20% ferric chloride in acetic acid and gave low yields of impure product in our hands, despite various modifications tried. VI was converted to the dichloro ester VIIa by direct chlorination.[10] VIIa was hydrolyzed to the hitherto unknown acid VIIb by prolonged treatment with either 25% sodium hydroxide at 20° or concentrated sulfuric acid at 0°. Nolan and Murphy had shown previously that conventional hydrolysis with boiling dilute alkali produced concurrent decarboxylation (VIIa → X).[10]

VIIa, when treated with benzyl chloride in ethanolic potassium hydroxide, yielded both monobenzyl and dibenyl ethers (VIIIa and IXa) in a stepwise reaction. It might be anticipated that hydrogen bonding and steric hindrance at the hydroxyl *ortho* to the carbethoxy group would cause the *para*-hydroxyl to be attacked preferentially. Consequently, the monobenzyl ether was considered to be the 4-benzyl derivative (VIIIa). Regeneration of VIIa by hydrogenolysis of VIIIa with palladium–calcium carbonate was demonstrated.

It was hoped that the corresponding monobenzyl acid (VIIIb) would be used to prepared IIIb. However, alkaline hydrolysis of the ester grouping even at room temperature resulted in concurrent decarboxylation and formation of decarboxy derivative XI. Although VIIIb, like VIIb, is a tautomer of a β-keto acid and subject to further activation of its carboxyl by substituent chlorines, it was hardly anticipated that it would be even more susceptible to decarboxylation.

Dibenzyl ether IXa, in marked contrast to VIIa and VIIIa, proved rather resistant to alkaline hydrolysis. It was converted with some difficulty to acid IXb by refluxing with 5% potassium hydroxide in aqueous dioxane. The stability of IXb emphasized the role of the *ortho*-hydroxyl in facilitating the decarboxylation of VIIb and VIIIb, and substantiated the structure assigned to the latter. On treatment with oxalyl chloride, IXb yielded the corresponding acid chloride.

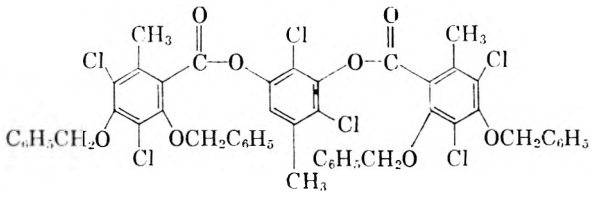


Synthesis of the 2,4-dichloroörcinol moiety (X) required to produce III was attempted by chlorination of orcinol (XII). The only products obtained, however, were 2,4,6-trichloroörcinol (XIII), and the previously unreported 2,6-dichloroörcinol (XIV). Consequently, X had to be prepared by hydrolysis and decarboxylation of difficultly accessible VIIa.

The stage was then set for the attempted preparation of IIIc. It was expected that the 5-hydroxyl of X, being much less hindered sterically than the 3-hydroxyl, could be acylated preferentially, especially with a bulky acyl group like IXb. However, when X was acylated with the acid chloride of IXb, the only product which could be characterized appeared to be a *diacyl* derivative. Though not obtained pure, elementary analyses together with its infrared spectrum and its negative response to

(12) R. von Schilling and D. Vorländer, *Ann.*, **308**, 184 (1899).
(13) A. St. Pfau, *Helv. Chim. Acta*, **16**, 283 (1933).

a ferric chloride test supported the diacyl formulation XV rather than IIIc. This wholly unexpected result was rationalized by assuming that because



XV

of its electron-withdrawing character, an acyl substituent, once attached to the 5-hydroxyl, increased the acidity of the 3-hydroxyl sufficiently that the latter could compete successfully for unreacted acyl chloride molecules, resulting in formation of XV.

Efforts were then directed towards preparation of IIId from intermediates having all interfering hydroxyl groups blocked. Earlier experiments had fortuitously provided an elegant method for preparing XI, which accordingly was acylated with the acid chloride of IXb. The low overall yield at this point, however, so reduced the quantity available for this experiment that the small amount of solid product could not be adequately characterized. Its infrared spectrum was similar to that of XV, as would be expected.

## EXPERIMENTAL[14]

*Preparation of ethyl 1,2-dihydro-o-orsellinate* (V).[12] Twenty-three grams of sodium (1 mole) was added to 300 ml. of absolute ethanol, warming slightly to dissolve the last few grams. Then were added successively 126 g. (1 mole) of ethyl acetoacetate and 102 g. (1 mole) of ethyl crotonate. The mixture was refluxed with continuous stirring for 2 hr. A slurry of sodium enolate appeared 20 to 25 min. after addition of the reagents was complete, and the mixture gradually thickened to a paste. At the end of 2 hr., the mixture was chilled and acidified with 5% sulfuric acid. Considerable sodium sulfate separated out, which was removed by filtration. The filtrate was diluted with 200 ml. of water, then extracted with chloroform. The solvent was removed, yielding 174 g. of oily product, which was chilled until crystallization began, then diluted with 60 ml. of 40–60° petroleum ether and let stand overnight. A yield of 80 g. of product was obtained upon filtration. This material was satisfactory for dehydrogenation after thorough drying, but could be recrystallized from petroleum ether–benzene; m.p. 87–89° (lit.,[12] m.p. 89–90°).

*Dehydrogenation of ethyl 1,2-dihydro-o-orsellinate* (V). The following was typical: 40 g. of V was refluxed 1 hr. with 8.0 g. of anhydrous ferric chloride (or the equivalent amount of ferric chloride hexahydrate) and 400 ml. of 20% aqueous acetic acid. The mixture was then diluted with 200 ml. of water and extracted with ether. The ether extract was, in turn, extracted repeatedly with 50 ml. portions of saturated sodium carbonate, then evaporated, yielding 17.5 g. of VI as a dark amorphous solid. This was recrystallized from benzene—first crop, 7.0 g., m.p. 122–129°; second crop, 2.3 g., m.p. 120–125°. A second recrystallization produced material melting at 131–132° (lit.,[13] m.p. 131–132°). Changes in Pfau's published procedure, such as varying reaction time and concentration of ferric chloride, produced even poorer yields.

*Chlorination of ethyl o-orsellinate* (VI). This preparation was carried out by a procedure similar to that applied to methyl *o*-orsellinate by Nolan and Murphy.[10] A 55 g. portion (0.281 mole) of VI was dissolved in 3 l. of chloroform chilled in an ice bath. There was added slowly and with mechanical stirring 310 ml. of chlorine (2.2 × 0.281 mole) in carbon tetrachloride. After 45 min., 45 ml. of pyridine was added; the mixture was subsequently freed of pyridine by extraction with water. After drying, the solution was evaporated to a small volume; half this volume of carbon tetrachloride was added. A yield of 69 g. of ethyl 3,5-dichloroörsellinate (VIIa) was collected, m.p. 160–163° (lit.,[10] m.p. 159–161°).

*Hydrolysis of ethyl 3,5-dichloro-o-orsellinate* (VIIa). *A. Sulfuric acid method.* A 3.00 g. portion of VIIa was dissolved in ice cold conc. sulfuric acid and let stand 6 days at 0°. The mixture was then poured into ice water and extracted with ether. The ether, upon evaporation, yielded 2.69 g. of acid VIIb, m.p. 195–200°; 0.91 g. of this acid was purified by dissolving it in ether, extracting it with 0.1*N* sodium bicarbonate, liberating it with hydrochloric acid, and extracting with ether. From the ether was obtained 0.53 g., 202–207° dec. After three recrystallizations from benzene-ether, the acid melted at 210–211° dec.

*Anal.* Calcd. for $C_8H_6Cl_2O_4$: C, 40.53; H, 2.55; Cl, 29.92. Found: C, 40.75; H, 2.79; Cl, 29.64.

*B. 25% Sodium hydroxide method.* One gram of VIIa was dissolved in 30 ml. of 25% sodium hydroxide and let stand 7 days at room temperature. The solution was then diluted with water, acidified and extracted with ether. Upon evaporation, 0.91 g. of VIIb was obtained, m.p. 185–195° dec.

*Ethyl 3,5-dichloro-o-orsellinate 4,6-dibenzoate.* VIIa (12.0 g.) was dissolved in 68 ml. of methyl ethyl ketone. Potassium carbonate (6 g.) was added and the mixture was heated to reflux; 13.2 g. of benzoyl chloride dissolved in 12 ml. of methyl ethyl ketone was added dropwise and refluxing continued 3.5 hr. The mixture was then filtered and evaporated, yielding a foamy solid which was extracted with chloroform. The chloroform solution was extracted with 0.1*N* sodium hydroxide, dried, and evaporated to yield 5.9 g. of dibenzoate, which crystallized on trituration with ethanol. This was recrystallized four times from ethanol; 0.39 g., m.p. 109–110°, was obtained.

*Anal.* Calcd. for $C_{24}H_{18}Cl_2O_6$: C, 60.90; H, 3.83. Found: C, 61.28; H, 4.00.

*4,6-Dibenzyl and 4-benzyl ethers of ethyl 3,5-dichloro-o-orsellinate.* VIIa (7.13 g.) was dissolved in 700 ml. of absolute ethanol containing 10.5 g. of potassium hydroxide; 112 ml. of benzyl chloride was added to the mixture. After 24 hr., 4 g. additional potassium hydroxide was added. At the end of 3 days, the reaction mixture was partitioned between water and ether. Upon concentrating the ether layer, additional aqueous liquor separated out and was combined with the original aqueous layer.

The strongly alkaline aqueous layer was acidified and extracted with ether. From the ether was obtained 5.05 g. of dark oily material. This was triturated with and crystallized from ether; 1.45 g. of solid monobenzyl ether (VIIIa) was obtained. This was recrystallized from benzene, yielding 0.83 g., m.p. 179–180°. A 36.6 mg. sample of VIIIa was subjected to hydrogenolysis in ethyl acetate solution with 10% palladium on calcium carbonate; 2.61 cc. were consumed, 5% in excess of theory for one mole. The product (35 mg.) melted at 160–161° and showed no depression of melting point when mixed with VIIa.

*Anal.* Calcd. for $C_{17}H_{16}Cl_2O_4$: C, 57.48; H, 4.54; Cl, 19.96. Found: C, 57.42; H, 5.08; Cl, 20.22.

The ether layer from the above partitioning was dried over sodium sulfate and concentrated. The bulk of the excess benzyl chloride was removed by vacuum distillation leaving

(14) Melting points were determined in capillary tubes in a hot block apparatus, except as noted, and are corrected. Infrared spectra were determined with a Unicam Infrared Spectrophotometer as Nujol mulls.

a dark, partially crystalline residue, 6.47 g. This was chromatographed on 200 g. of activity V alumina; 4.13 g. of dibenzyl ether (IXa) was obtained by elution with 300 ml. of benzene. A 0.85 g. portion of this was recrystallized twice from 60–80° petroleum ether, yielding 0.22 g., m.p. 77–78°.

*Anal.* Calcd. for $C_{24}H_{22}Cl_2O_4$: C, 64.73; H, 4.98; Cl, 15.92. Found: C, 64.44; H, 4.48; Cl, 15.75.

*Hydrolysis of ethyl 3,5-dichloro-o-orsellinate 4,6-dibenzyl ether* (IXa). A 5% potassium hydroxide solution was prepared from 12.5 g. of potassium hydroxide, 112.5 g. of dioxane and 125 ml. of water. A 4.13 g. portion of IXa was refluxed overnight in 200 ml. of this potassium hydroxide solution; the solution tended to separate into two phases, but vigorous reflux maintained satisfactory mixing. After cooling, the mixture was partitioned between water and chloroform. The basic layer was acidified and extracted with chloroform; 1.48 g. of solid acid was obtained on evaporating the extract. This was recrystallized from benzene-petroleum ether; first crop, 0.77 g., m.p. 180–182°; second crop, 0.10 g.

A 13.8-mg. portion of this acid was subjected to hydrogenolysis in ethyl acetate in the presence of 10% palladium-on-calcium carbonate. There was an uptake of 1.79 cc. of hydrogen compared to the theoretical amount of 1.58 cc.

*Anal.* Calcd. for $C_{22}H_{18}Cl_2O_4$: C, 63.32; H, 4.35; Cl, 17.00. Found: C, 63.52; H, 4.35; Cl, 16.90.

*Hydrolysis and decarboxylation of ethyl 3,5-dichloro-o-orsellinate 4-benzyl ether* (VIIIa). A 0.120-g. position of VIIIa was dissolved in 40 ml. of 12% aqueous sodium hydroxide (the most concentrated in which it was soluble), and let stand 3 days at room temperature. The solution was then diluted with water, acidified, and extracted with chloroform. A residue of 0.082 g. was obtained from the chloroform after drying; this was chromatographed on activity V alumina. By benzene elution, 0.050 g. of crystalline material was obtained, m.p. 94–95° (Kofler) after drying *in vacuo* at 45°. This substance was shown by elemental analyses and infrared spectrum (OH peak at 3406 cm.$^{-1}$, no carbonyl peak) to be *2,4-dichloroörcinol 3-benzyl ether* (XI) rather than the desired acid (VIIIb).

*Anal.* Calcd. for $C_{14}H_{12}Cl_2O_2$: C, 59.39; H, 4.27; Cl, 25.04. Found: C, 59.96; H, 4.39; Cl, 25.32.

Experiments were carried out directed towards deliberate hydrolysis and decarboxylation of VIIIa by refluxing with 1% aqueous sodium hydroxide. Some XI could be isolated by chromatographing products obtained on activity V alumina, but a satisfactory reproducible method was not established.

*Acylation of 2,4-dichloroörcinol* (X). The acid chloride of IXb was prepared by refluxing 0.380 g. (0.91 mmole) of the acid with excess oxalyl chloride 2 hr. in a micro reflux assembly with careful exclusion of moisture. Excess oxalyl chloride was removed by vacuum. A 0.178-g. portion (0.92 mmole) of 2,4-dichloroörcinol, prepared according to the procedure of Nolan and Murphy,[10] was dissolved in dry pyridine and added to the acid chloride. The mixture was let stand overnight, then most of the pyridine was removed by vacuum. The residue was partitioned between ether and 0.1*N* sodium bicarbonate. The ether was dried and evaporated, yielding 0.56 g. of XV. This was recrystallized twice from ethanol-ether; 0.105 g. was obtained, m.p. 104–106°. The infrared spectrum had a peak at 1750 cm.$^{-1}$ (carbonyl) but none in the OH region. The ferric chloride test was negative.

*Anal.* Calcd. for $C_{51}H_{38}Cl_6O_8$: C, 61.77; H, 3.86; Cl, 21.46. Found: C, 62.54; H, 3.95; Cl, 21.22.

Calcd. for $C_{29}H_{22}Cl_4O_5$ (monoacyl derivative): C, 58.80; H, 3.75; Cl, 23.95.

This experiment was repeated twice with variations. In the first instance, mechanical stirring was used and the acid chloride was added to X. In the second instance, the latter procedure was used, but with a twofold excess of X. In both cases, the products appeared to be the same diacyl derivative (XV).

*Acylation of 2,4-dichloroörcinol 3-benzyl ether* (XI). This was carried out in a manner similar to that described in the preceding section, except that X was replaced by its 3-benzyl ether (XI). A solid product was isolated by chromatography whose infrared spectrum indicated acylation had taken place (no OH peak) and which was similar to that of XV. The quantity in hand was too small for further characterization.

*Chlorination of orcinol* (XII). Orcinol (10.6 g.) was dissolved in 1.5 l. of chloroform chilled in an ice bath. Two moles of chlorine in carbon tetrachloride, plus 10% excess, was added slowly with mechanical stirring. After addition was completed, the mixture was extracted twice with 250-ml. portions of 0.1*N* sodium bicarbonate. The solution was then dried and concentrated to a small volume. Half this volume of petroleum ether was added and 5.8 g. of solid was collected, m.p. 101–105°. This was recrystallized from chloroform-petroleum ether, then three times from benzene, yielding a substance melting at 165.5–167° after sublimation. The melting point and elementary analyses indicated that this must be *2,6-dichloroörcinol* (XIV) rather than the desired 2,4-dichloroörcinol (lit.,[10] m.p. 121°).

*Anal.* Calcd. for $C_7H_6Cl_2O_2$: C, 43.55; H, 3.14; Cl, 36.74. Found: C, 43.72; H, 3.37; Cl, 37.05.

A second compound was obtained by concentrating the mother liquor from the first crystallization of XIV and recrystallizing the resulting residue from benzene. This proved to be *2,4,6-trichloroörcinol* (XIII), m.p. 123–124° (lit., m.p. 123°[15]; 127°[16]).

*Anal.* Calcd. for $C_7H_5Cl_3O_2$: C, 36.96; H, 2.22; Cl, 46.77. Found: C, 36.79; H, 2.40; Cl, 46.58.

Separation of XIII and XIV was also effected by chromatographing combined residues from recrystallizations on silica gel. Both compounds were eluted by collecting successive fractions with 9:1 benzene-ether. The trichloro compound was eluted first. No 2,4-dichloroörcinol (X) was obtained from the reaction mixture.

*Acknowledgments.* The author wishes to thank Prof. D. H. R. Barton, F.R.S., for valuable discussions and advice in connection with this work, also Dr. G. Eglinton for infrared spectra, and Mr. J. M. L. Cameron and Miss M. W. Christie for microanalyses.

PEORIA, ILL.

(15) J. Stenhouse *Ann.*, **163**, 174 (1872).
(16) Th. Zincke, *Ber.*, **26**, 311 (1893).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NORTHWESTERN UNIVERSITY]

# Organoboron Compounds. XII. Heterocyclic Compounds from Benzeneboronic Acid[1]

R. L. LETSINGER AND STEPHEN B. HAMILTON

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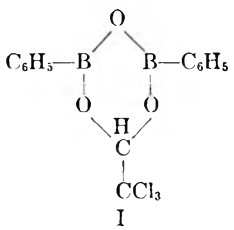
New types of compounds were prepared by condensing benzeneboronic acid with chloral hydrate, benzoin, and a mixture of benzoin and aniline. The product from benzoin, 2,4,5-triphenyl-1,3,2-dioxaborole was very readily oxidized to benzil and was relatively resistant to hydrolysis in neutral or acidic solutions.

In view of the smooth conversion of benzeneboronic acid and *o*-phenylenediamine to 2-phenyl-1,3-dihydro-2,1,3-benzoboradiazole,[2] we examined the behavior of benzeneboronic acid with several other substances which might be expected to yield heterocyclic compounds by condensation reactions. New compounds were isolated in high yields from reactions with chloral hydrate, benzoin, and an equimolar mixture of benzoin and aniline.[3] Formulas I–III, respectively, were assigned to these substances on the basis of the mode of formation, analyses, infrared spectra, and chemical behavior.



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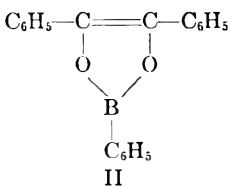

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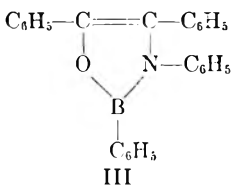


III

Compound I is unusual in that the boron-oxygen heterocycle contains carbon at the aldehyde stage of oxidation. Whereas six-membered ring compounds containing either boron and oxygen (boroxines) or carbon and oxygen (aldehyde trimers) are well known, a mixed compound of this type does not seem previously to have been described. As expected, compound I was relatively unstable, decomposing slowly to give triphenylboroxine at 150°.

Compound II, 2,4,5-triphenyl-1,3,2-dioxaborole, exhibited several interesting properties. Perhaps the most distinctive feature was the ease of oxidation. Cyclohexane and anhydrous dioxane solutions of compound II were stable indefinitely; however, aqueous dioxane or ethanol solutions rapidly acquired a yellow color due to formation of benzil. The rate of oxidation increased in alkaline solutions which were saturated with oxygen. Table I summarizes data on the oxidation of compound II, benzoin, and an equimolar mixture of benzoin and benzeneboronic acid (hydrolytic products of compound II) by molecular oxygen in alkaline aqueous alcoholic solutions. From experiments 1, 2, and 3 it is seen that compound II was very extensively oxidized under conditions for which benzoin was virtually unchanged and the mixture of benzoin and benzeneboronic acid was attacked to only a minor extent. It is also apparent that compound II was oxidized more rapidly than it was hydrolyzed. Finally, experiments 4 and 5 as well as 2 and 3 demonstrate that benzeneboronic acid accelerated the oxidation of benzoin under these conditions.

Weissberger[4] postulated that oxidation of benzoin in alkaline solution involved a slow, rate-determining enolization followed by reaction of the enolate ion with molecular oxygen. An extension of this mechanism to the oxidation of compound II seems plausible. According to this the rate determining step would be generation of an enolate ion (IV) by attack of hydroxide ion on boron, a reaction which could well be much faster than removal of the α-hydrogen in benzoin by hydroxide ion. The activating effect of benzeneboronic acid on the oxidation of benzoic (exp. 5) may depend upon formation in solution of a low concentration of compound II or a related charged complex which can yield IV.

(1) For the previous paper in this series see: R. L. Letsinger and J. R. Nazy, *J. Am. Chem. Soc.*, 81, 3013 (1959).

(2) R. L. Letsinger and S. B. Hamilton, *J. Am. Chem. Soc.*, 80, 5411 (1958).

(3) A sharp melting substance was also obtained from a reaction of benzeneboronic acid with mandelic acid in toluene. It could be sublimed without decomposition and the analysis corresponded to $C_6H_5CHCOOBC_6H_5$; however, the infrared

spectrum contained in addition to a band at 5.57 μ (the ring carbonyl group) bands at 5.82 μ and in the 2.9–4.0 μ region characteristic of the carboxyl group. It appears that some hydrolysis had occurred in the samples used for the spectral determinations. The ease of hydrolysis of acyloxyboron compounds has been noted by W. Gerrard, M. F. Lappert, and R. Shafferman, *J. Chem. Soc.*, 3648 (1958).

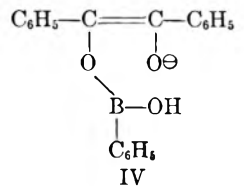
(4) A. Weissberger, *Ber.*, 65, 1815 (1932).

TABLE I[a]

OXIDATION OF COMPOUND II AND BENZOIN IN ALKALINE AQUEOUS ALCOHOLIC SOLUTIONS

| Exp. | Reactants | Time at Reflux, min. | Yields, % | | |
|---|---|---|---|---|---|
| | | | Benzil | Benzoin | Benzeneboronic[b] anhydride |
| 1 | Compound II[c] | 5 | 71 | 8 | 54 |
| 2 | Benzoin[c] | 5 | 0 | 98 | — |
| 3 | Mixture[d] | 5 | 9 | 84 | 98 |
| 4 | Benzoin[c] | 60 | 21 | 71 | — |
| 5 | Mixture[b] | 60 | 84 | 0 | <25 |

[a] For procedure and isolation of products see Experimental section. [b] The recovered boronic acid was converted to the anhydride on drying to constant weight. [c] The quantities were: compound II, 1.50 g., benzoin, 1.068 g. [d] The mixture consisted of 1.068 g. of benzoin and 0.523 g. of benzeneboronic anhydride. The anhydride is very rapidly converted to benzeneboronic acid in solutions containing water.



IV

Two other reactions attest to the susceptibility of compound II to oxidation. (1) Compound II was converted within three minutes to benzil and benzeneboronic acid by a dilute solution of nitric acid in acetic acid; the yields were virtually quantitative. By contrast, benzoin was unchanged by treatment with the nitric acid–acetic acid reagent for an hour. (2) A flocculant, white precipitate formed when dry oxygen was passed through a pentane solution of compound II which was irradiated by ultraviolet light.[5] Neither the catechol nor the *meso*-hydrobenzoin esters of benzeneboronic acid yielded percipitates under these conditions. Furthermore, no reaction occurred when a pentane solution of compound II was irradiated in the absence of oxygen or was treated with oxygen in the absence of light. The photo-oxidation product from compound II very rapidly turned brown and became oily on exposure to the atmosphere. Phenol and benzil were among the products formed.

Another interesting property of compound II is the resistance to hydrolysis. The borole could be recovered in 90% yield or better after dissolution in neutral or acidified hot, aqueous ethanol under a nitrogen atmosphere. The possibility that significant amounts of compound II hydrolyzed and subsequently reformed may be ruled out since similar treatment of solutions containing equimolar amounts of benzoin and benzeneboronic acid did not yield the borole.

In alkaline solutions hydrolysis was more rapid and was accompanied by oxidation even when the solutions were swept with nitrogen gas. An indication of the rate of these reactions was gained by the method of Steinberg and Hunter,[6] which involves determination of the time, termed the half-life, for the indicator to change in a dioxane-water solution containing the boron compound, one half the equivalent amount of sodium hydroxide, excess mannitol and phenophthalein. At 15° both the catechol and *meso*-hydrobenzoin esters of benzeneboronic acid consumed base at a rate too fast to measure; however, the half-life of compound II amounted to twenty-four seconds. Since some oxidation occurred, as evidenced by appearance of the yellow color characteristic of benzil, this time represents a minimum value for the half-life of hydrolysis of compound II.

Borate and boronate esters generally hydrolyze with extreme rapidity in solutions containing water. Exceptions have been noted with esters of amino alcohols (*e.g.*, triethanolamine borate[7]) which are stabilized by chelation and with esters containing bulky groups around the boron.[6,8] The stability of compound II can be attributed to neither chelation nor steric hindrance (steric hindrance is less in compound II than in *meso*-hydrobenzoin benzeneboronate, which hydrolyzes very rapidly). It is probably due to a resonance stabilization associated with the dioxaborole ring system. An analogous explanation has been advanced to account for the unusually slow rate of hydrolysis of the dihydrobenzoboradiazoles.[2,9]

Compound III, 2,3,4,5-tetraphenyl-1,3,2-oxazaborole, was even more sensitive to aerial oxidation than compound II. Indeed, development of a reddish color and the odor of phenol were noticeable after several hours' exposure to air and sunlight. Treatment of a benzene solution of compound III with dilute sodium hydroxide afforded a 75% yield of benzil anil (V). Attempts to re-

(5) Ultraviolet lamp Model M11, 110–125 volts, Black Light Products, Chicago, Ill.

(6) H. Steinberg and D. Hunter, *Ind. Eng. Chem.*, **49**, 174 (1957).

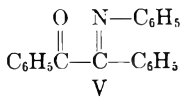
(7) H. C. Brown and E. A. Fletcher, *J. Am. Chem. Soc.*, **73**, 2808 (1951).

(8) In addition, some esters such as mannitol tribenzeneboronate, H. Kuivila and E. Soboczenski, *J. Org. Chem.*, 19, 780 (1954), can be precipitated from aqueous solutions. This fact does not mean, however, that the hydrolytic rate of such substances in solution would be slow.

(9) M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3076 (1958).

TABLE II

| Wt. Cpd. II, g. | Organic Solvent | Solvent Added | Cpd. II Recovered | |
|---|---|---|---|---|
| | | | g. | % |
| 0.50 | 20 Ml. 95% ethanol | 5 Ml. water | 0.481 | 96 |
| 0.50 | 50 Ml. 95% ethanol | 5 Ml. water + 5 ml. of aq. 0.08*M* HCl | 0.45 | 90 |
| 0.65 | 35 Ml. acetic acid | 15 Ml. water | 0.58 | 89 |



V

crystallize compound III from ethanol-water solutions likewise yielded benzil anil.

The synthesis of compound III provides another example of formation of a boron-nitrogen bond at the expense of a boron-oxygen bond.[2] With respect to the reaction path leading to the oxazaborole, two stable substances, benzoin anil and compound II, appeared to be possible intermediates. Evidence that neither is in fact an intermediate was gained by heating toluene solutions of (a) benzoin anil and benzeneboronic anhydride and (b) compound II and aniline. In neither case was compound III formed; the starting materials were isolated in high yield. It is also of interest that compound II failed to react with *o*-phenylene diamine in hot toluene. By contrast, the boronic acids and their esters generally react readily with *o*-phenylenediamine to give dihydrobenzoboradiazoles.[2]

## EXPERIMENTAL

Melting points were taken on a Fisher-Johns melting point block and are uncorrected. Carbon, hydrogen, and nitrogen analyses were performed by Miss Hilda Beck unless other wise indicated. The infrared spectra were determined with a Baird double-beam recording spectrophotomer with the sample in potassium bromide, and the ultraviolet spectra were taken with a Beckman ratio recording spectrophotometer, Model DK-2.

*Reaction with chloral hydrate.* A solution containing 2.0 g. of benzeneboronic acid and 2.71 g. of chloral hydrate in 50 ml. of chloroform was partially distilled below 30° at reduced pressure to remove the water liberated in the reaction. Pentane was added, the solution filtered, and pentane removed at reduced pressure until a crystalline product (I) appeared: 2.44 g. (84%), m.p. 116–117°. The infrared spectrum had neither hydroxyl nor carbonyl bands, but showed absorption at 7.4 $\mu$ (B—O). Strong bands present at 8.8, 11.9, 12.1, 14.9, and 15.1 $\mu$ were absent in the spectrum of benzeneboronic anhydride. Conversely, the anhydride absorbed strongly at 9.15 $\mu$ while compound I did not.

*Anal.* Calcd. for $C_{14}H_{11}O_3Cl_3B$: C, 47.4; H, 3.12; neut. equiv., 177.6; mol. wt., 355.2. Found: C, 47.4; H, 3.21; neut. equiv. (with mannitol) 179; mol. wt. 361.

A sample of compound I (0.5203 g.) was heated at 150–160° for 18 hr. in a nitrogen atmosphere; weight after heating, 0.2744 g. (90% calcd. as the boroxine); m.p. 210–215°. After sublimation at reduced pressure the boroxine melted at 214–216° and did not depress the melting point of an authentic sample of triphenylboroxine (benzeneboronic anhydride).

*2,4,5-Triphenyl-1,3,2-dioxaborole* (III). A toluene solution (50 ml.) containing 2.44 g. of benzeneboronic acid and 4.24 g. of benzoin was heated in a flask fitted with a take-off adapter to remove the water azeotrope. Toluene was then removed *in vacuo* until the product solidified. Recrystallization from pentane yielded 5.43 g. (91%) of purified material, m.p. 112–113°; $\lambda_{max}$ (in cyclohexane), 285 m$\mu$ ($\epsilon$ 16,500), 242 m$\mu$ ($\epsilon$ 12,800), 220 m$\mu$ ($\epsilon$ 25,000). The wave length and intensity of the main band (285) were greater than for closely related substances such as *cis*-stilbene-$\alpha,\beta$-diol diacetate,[10] catechol benzeneboronate ($\lambda_{max}$ 273 m$\mu$, $\epsilon$ 14,720, in cyclohexane), and *meso*-hydrobenzoin benzeneboronate ($\lambda_{max}$ 268 m$\mu$, $\epsilon$ 865, in cyclohexane), in accord with the idea that the dioxaborole system possesses a degree of aromatic character. The infrared spectrum had bands at 6.1 $\mu$ (C=C) and 7.4 $\mu$ (B—O) and no bands in the hydroxyl or carbonyl regions.

*Anal.* Calcd. for $C_{20}H_{15}BO_2$: C, 80.58; H, 5.07; neut. equiv., 298. Found: C,[11] 80.64; H, 5.16; neut. equiv. (titration in the presence of mannitol), 294.

Compound II neither dissolved directly in cold, concd. sulfuric acid nor was it extracted from a pentane solution which was shaken with sulfuric acid. By contrast, benzoin and hydrobenzoin readily dissolved in sulfuric acid to give deeply colored solutions.

Solid samples of compound II which were exposed to sunlight in the presence of air acquired a deep yellow color on the surface after a few days, presumably as a result of conversion to benzil.

*Alkaline oxidation of compound* II *and benzoin.* Data on yields, quantities of reagents, and times of reaction are given in Table I. The conditions were the same in all cases except where noted in the table. As a representative example, the reaction of compound II is described in detail.

Compound II (1.50 g.) was dissolved in 75 ml. of hot 95% ethanol into which oxygen was bubbling. After addition of 20 ml. of 0.074*M* sodium hydroxide (an intense yellow color appeared when the alkali was added) the solution was refluxed for 5 min., diluted with water to precipitate neutral organic products, cooled, concentrated at reduced pressure, and filtered. The precipitate, 0.72 g., m.p. 95.5–96.5°, did not depress the melting point of an authentic sample of benzil. A second crop of crystals, obtained by further concentration of the solution, yielded on fractional crystallization from pentane 0.025 g. of benzil and 0.08 g. of benzoin. Acidification of the aqueous solution and extraction with ether afforded a white solid which on drying gave 0.28 g. of benzeneboronic anhydride, identified by its melting point (214–216°) and infrared spectrum.

*Nitric acid oxidation of compound* II. To 0.50 g. of the dioxaborole suspended in 10 ml. of glacial acetic acid at 30° was added a mixture of 1 ml. of concentrated nitric acid and 4 ml. of acetic acid. The dioxaborole rapidly dissolved and the solution became intensely yellow. After 3 min. benzil was precipitated by dilution with water; 0.34 g., m.p. 94–95°. Partial neutralization (to about *p*H 6) of the filtrate with sodium hydroxide and ether extraction gave 0.17 g. (98%) of benzeneboronic anhydride, m.p. 214–216°.

A sample of benzoin (0.36 g.) in a mixture of 14 ml. of acetic acid and 1 ml. of nitric acid did not produce a yellow

(10) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd Ed., D. C. Heath and Co., (1957), pp. 170–180.

(11) The carbon analysis was performed by the Huffman Microanalytical Laboratory, Wheatridge, Colo., by the "moist oxygen" technique. Conventional combustion analysis for carbon was unsatisfactory.

color within an hour period. Addition of water then reprecipitated benzoin, 0.35 g. (98% recovery).

*meso-Hydrobenzoin benzeneboronate.* This compound was prepared in the same manner as compound II except that 2.13 g. of *meso*-hydrobenzoin and 1.22 g. of benzeneboronic acid were used as reactants; weight, 2.58 g. (90%), m.p. 92–93°.

*Anal.* Calcd. for $C_{20}H_{17}BO_2$: C, 80.2; H, 5.72; neut. equiv., 300. Found: C, 81.0; H, 5.80; neut. equiv. (titration in presence of mannitol), 304.

A sample of ester (0.4085 g.) was dissolved in 50 ml. of ether and shaken with 20 ml. of 1*M* sodium hydroxide. By conventional procedures there were obtained 0.283 g. (98%) of *meso*-hydrobenzoin, m.p. 133.5–135°, from the ether layer and 0.14 g. (99%) of benzeneboronic anhydride, m.p. 218–220°, from the aqueous layer.

*Recrystallization of compound* II *from hydroxylic solvents.* (See Table II.) These recrystallizations were carried out with solvents which had previously been boiled to remove dissolved oxygen. Thereafter a slow stream of nitrogen was bubbled through the solutions and a nitrogen atmosphere maintained until the precipitate had been collected. In each case compound II was dissolved in the hot organic solvent; water or dilute hydrochloric acid was then added and the resulting solution was boiled for a few minutes and allowed to cool. Compound II crystallized and was collected by filtration, m.p. 113–114°.

*Attempted preparation of compound* II *in aqueous ethanol.* A solution containing 0.205 g. of benzeneboronic acid, 0.365 g. of benzoin, 20 ml. of 95% ethanol, and 5 ml. of water was refluxed for 5 min. and then cooled in an ice bath. No crystals formed; if compound II had been present it should have separated at this stage (see previous experiment on recrystallization of compound II). On addition of 40 ml. of distilled water benzoin, 0.350 g. (98%), m.p. 127–131°, separated; it did not depress the melting point of an authentic sample of benzoin.

*Hydrolysis of compound* II. (*a*) *In alkaline solution.* Nitrogen gas was passed through a hot solution consisting of 25 ml. of 95% ethanol, 5 ml. of distilled water, and 5 ml. of 0.074*M* sodium hydroxide. Compound II (0.50 g.) was added and the resulting solution cooled. From the mixture were isolated compound II (28%), benzoin and benzeneboronic anhydride (products from hydrolysis of II) in 42% and 52% yield, respectively, and benzil (product of oxidation) in 11% yield.

(*b*) *Estimation of minimum half-life of hydrolysis.* (Method of Steinberg and Hunter[6]). In each case a solution containing 70 ml. of dioxane, 5 ml. of distilled water, 2.72 ml. of 0.0740*M* solution hydroxide (0.200 mmole), and 2.0 g. of mannitol was heated to the boiling point, saturated with nitrogen gas, and cooled to 15°. Three drops of a phenophthalein indicator solution and 0.400 mmole of the boronic acid derivative were added in succession. The boron compounds dissolved almost immediately. The time lapse between addition of the sample and the disappearance of the indicator color was too short to measure for the catechol and *meso*-hydrobenzoin esters of benzeneboronic acid. For compound II it was 24 sec.

*2,3,4,5-Tetraphenyl-1,3,2-oxazaborole* (III). A toluene solution (50 ml.) containing 1.22 g. of benzeneboronic acid, 2.12 g. of benzoin, and 0.93 g. of aniline was heated to reflux at room temperature, the water azeotrope removed, and the toluene removed at reduced pressure. Recrystallization of the resulting solid from hexane yielded 3.07 g. (77%) of a white crystalline product (III); m.p. in a sealed capillary tube in a nitrogen atmosphere, 183–185°; m.p. on a Fisher-Johns block in air, 134–167° (slow heating), 164–175° (rapid heating). Evaporation of the hexane mother liquors and recrystallization of the resulting solid from ethanol-water afforded 0.53 g. (17%) of compound II, m.p. 112–113°. The infrared spectrum of product III had bands at 6.1 $\mu$ (C=C) and 7.4 $\mu$ (B—O or B—N) and no bands attributable to OH, NH, or C=O; it differed also from the spectrum of compound II. The ultraviolet spectrum resembled that of compound II in having a broad absorption band with $\lambda_{max}$ 284 m$\mu$, $\epsilon$ 24,200 (in cyclohexane) and a minimum about 245 m$\mu$, however it lacked a second maximum in the region of 242 m$\mu$.

*Anal.* Calcd. for $C_{26}H_{20}ONB$: C, 83.7; H, 5.40; N, 3.75. Found: C, 83.4;[12] H, 5.02; N, 3.15.

Compound III (0.50 g.) was dissolved in 20 ml. of benzene and allowed to stand for 4 days in the presence of air. Ether was added and the solution extracted with dilute sodium hydroxide. The organic layer was dried with magnesium sulfate, treated with charcoal to reduce the color, and distilled at reduced pressure until crystallizaton set in. On recrystallization from pentane 0.29 g. (75%) of benzil anil, m.p. 106–107.5° (lit.[12] m.p. 106–108°), was obtained.

*Reaction with mandelic acid.* Equimolar quantities of benzeneboronic acid (1.22 g.) and mandelic acid (1.52 g.) were heated to reflux in 25 ml. of toluene and the water azeotrope removed. The solid obtained on concentrating the solution afforded, after recrystallization from pentane, 1.44 g. (60%) of a compound melting at 124–125° (see footnote 3).

*Anal.* Calcd. for $C_{14}H_{11}O_3B$: C, 70.6; H, 4.66; neut. equiv., 116. Found: C, 70.7; H, 4.82; neut. equiv. (mannitol present), 118.

EVANSTON, ILL.

(12) M. Siegfield, *Ber.*, **25**, 2600 (1892).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# Addition of Silylmetallic Compounds to Olefins

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*Received September 28, 1959*

Triphenylsilylpotassium and triphenylsilyllithium have been found to add to the olefinic linkage of 1,1-diphenylethylene and of triphenylethylene. No addition occurred, under corresponding conditions, to tetraphenylethylene and to a variety of aliphatic and alicyclic olefins. For comparison purposes, triphenyl-(1,1-diphenylethyl)silane and triphenyl-(1,1,2-triphenylethyl)silane were synthesized by metalation of triphenyl(diphenylmethyl)silane with *n*-butyllithium and subsequent treatment with methyl sulfate and benzyl chloride, respectively.

It has been reported recently that triphenylsilylpotassium (I) adds to the carbon-carbon double bond of *trans*-stilbene[1] to give triphenyl-(1,2-diphenylethyl)silane (II). In addition to II, a

$$\underset{\text{I}}{(C_6H_5)_3SiK} + C_6H_5{-}CH{=}CH{-}C_6H_5 \xrightarrow{H_2O} (C_6H_5)_3Si{-}CH(C_6H_5){-}CH_2{-}C_6H_5$$
$$\text{II}$$

variety of other compounds of higher molecular weight was isolated from the reaction of *trans*-stilbene with triphenylsilyllithium[2] (III).

As an extension of these studies, the addition of triphenylsilyl-metallic compounds to other olefins has now been investigated. I and III were found to add to 1,1-diphenylethylene. In correspondence with the addition products of other organoalkalimetal compounds to this olefin,[3] the structure of triphenyl-(2,2-diphenylethyl)silane (IV) is assigned to the product obtained from both reactions in high yields.

$$\underset{\text{III}}{(C_6H_5)_3SiLi} + (C_6H_5)_2C{=}CH_2 \xrightarrow{H_2O} (C_6H_5)_3SiCH_2CH(C_6H_5)_2$$
$$\text{IV}$$

Compound IV was also obtained from the reaction of 1,1-diphenylethyl chloride with triphenylsilylpotassium. 1,1-Diphenylethyl chloride has been reported to dehydrohalogenate quite readily to form 1,1-diphenylethylene.[4] A similar course of reaction might have taken place in its reaction with I, as a result of which IV might have formed from the addition of excess I to the 1,1-diphenylethylene formed in this manner.

As I and III had been found to add to benzophenone in a reverse manner,[5] giving rise to a product in which the silicon atom is bonded to the oxygen, a second possible mode of addition of I and III to 1,1-diphenylethylene has to be considered: namely, the formation of triphenyl-(1,1-diphenylethyl)silane (V) by the addition reaction. In order to throw light on these reactions, it seemed desirable to synthesize IV and V by independent methods.

Organolithium compounds have been reported to add to the olefinic linkage of triphenylvinylsilane.[6] The corresponding reaction of phenyllithium with triphenyl-β-styrylsilane was investigated in the hope of synthesizing compound IV in this manner. However, no addition took place. Instead, tetraphenylsilane was isolated from the reaction mixture, apparently formed by a displacement reaction. An analogous transformation has

$$C_6H_5CH{=}CHSi(C_6H_5)_3 + C_6H_5Li \longrightarrow (C_6H_5)_4Si + C_6H_5CH{=}CHLi$$

been reported in the reaction of *n*-butyllithium with triphenyl(phenylethynyl)silane.[7]

The metalation of benzyltriphenylsilane[7] by *n*-butyllithium had been reported to occur in the side chain. A similar reaction was expected with triphenyl(diphenylmethyl)silane. When the latter compound was metalated with *n*-butyllithium in a mixture of tetrahydrofuran and ether and subsequently treated with methyl sulfate, V was isolated in a 58% yield. The compound was shown to be unlike the addition compound IV.

$$(C_6H_5)_3SiCH(C_6H_5)_2 \xrightarrow{+\ n\text{-}C_4H_9Li} (C_6H_5)_3SiCLi(C_6H_5)_2$$
$$(C_6H_5)_3SiCH(C_6H_5)_2 \xrightarrow{+\ C_6H_5CH_2Cl} (C_6H_5)_3SiC(C_6H_5)_2CH_2(C_6H_5) \quad \text{VI}$$
$$(C_6H_5)_3SiCLi(C_6H_5)_2 \xrightarrow{+\ (CH_3)_2SO_4} (C_6H_5)_3SiC(CH_3)(C_6H_5)_2 \quad \text{V}$$

Molecular rearrangements excluded, I and III might be expected to add to 1,1-diphenylethylene in a 1,2- or a 2,1-manner. As structure V has been excluded, the addition compound very probably has structure IV.

(1) H. Gilman and T. C. Wu, *J. Am. Chem. Soc.*, **75**, 234 (1953).

(2) A. G. Brook, K. M. Tai, and H. Gilman, *J. Am. Chem. Soc.*, **77**, 6219 (1955).

(3) K. Ziegler and K. Bähr, *Ber.*, **61**, 253 (1928).

(4) C. S. Schoepfle and J. D. Ryan, *J. Am. Chem. Soc.*, **52**, 4021 (1930).

(5) H. Gilman and T. C. Wu, *J. Am. Chem. Soc.*, **75**, 2935 (1953); H. Gilman and G. D. Lichtenwalter, *J. Am. Soc.*, **80**, 607 (1958).

(6) L. F. Cason and H. G. Brooks, *J. Org. Chem.*, **19**, 1278 (1954); *J. Am. Chem. Soc.*, **74**, 4582 (1952).

(7) H. Gilman and H. Hartzfeld, *J. Am. Chem. Soc.*, **73**, 5878 (1951). See also, H. Gilman, R. A. Benkeser, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 1689 (1950); L. H. Sommer, L. J. Tyler, and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 2872 (1948).

Triphenylsilyllithium also added smoothly to triphenylethylene. The addition may have taken place in a 1,2- or a 2,1-manner. Triphenyl-(1,1,2-triphenylethyl)silane (VI) was synthesized by metalation of triphenyl(diphenylmethyl)silane with *n*-butyllithium and subsequent treatment with benzyl chloride, and was shown to be unlike the addition compounds. In correspondence with the related addition of 2-phenyl-2-propylpotassium to 9-benzylidenefluorene,[8] the structure of triphenyl-(1,2,2-triphenylethyl)silane (VII) is assigned to the addition product of III to triphenylethylene.

$$\text{III} + (C_6H_5)_2C{=}CHC_6H_5 \longrightarrow (C_6H_5)_3SiCH(C_6H_5)CH(C_6H_5)_2$$

VII

No addition product was isolated from the reaction of I or III, under corresponding conditions, with tetraphenylethylene. Triphenylsilylpotassium also did not add to a variety of aliphatic and alicyclic olefins (see Table I).

TABLE I

REACTION OF TRIPHENYLSILYLPOTASSIUM WITH OLEFINS

| Olefin | Reaction Time, hr. | Yield of Pure Triphenylsilanol, % | Other Products Isolated[a] |
|---|---|---|---|
| *n*-Octene-1 | 96[b] | 63 | |
| *n*-Octene-1 | 48[c] | 25 | $R_4Si$, 24% $(R_3Si)_2O$, 22% |
| *n*-Dodecene-1 | 72[b] | 78 | |
| *n*-Dodecene-1 | 48[c] | 21 | $R_4Si$, 36% $(R_3Si)_2O$, 20% |
| *n*-Hexadecene-1 | 24[b,e] | 86 | |
| *n*-Octadecene-1 | 24[b,e] | 89 | |
| Cyclohexene | 48[d] | 87 | |
| Cyclohexene | 48[b] | 66 | |
| 1-Methylcyclopentene | 48[b] | 72 | |
| 1,1-Diphenylethylene | 2[b] | — | Adduct, 42% |
| Tetraphenylethylene | 48[d] | 74 | $R_2C{=}CR_2$, 70% |
| Tetraphenylethylene | 3[b] | 52 | $R_2C{=}CR_2$, 74% |
| 1,4-Diphenylbutadiene-1,3 | 5[d] | 42 | $R_3SiSiR_3$, 12% |
| $\Delta^{9,9'}$-Bifluorene | 3[b] | — | Tars |

[a] R represents a phenyl group. [b] The excess alloy present after the preparation of triphenylsilylpotassium was removed by the amalgamation procedure. See ref. 10. [c] 1,2-Dimethoxyethane was used as a solvent. [d] Excess alloy was present in the system. [e] Dr. K. M. Tai (unpublished studies) treated $R_3SiK$ with these olefins in a 1,2-dimethoxyethane and obtained 30% of $R_4Si$, 28% of $R_3SiOH$ and 30% of $(R_3Si)_2O$ from *n*-hexadecene-1, while *n*-octadecene-1 gave 32% of $R_4Si$, 17% of $R_3SiOH$ and 42% of $(R_3Si)_2O$ (R is a phenyl group).

(8) K. Ziegler, F. Crössmann, H. Kleiner, and O. Schäfer, *Ann.*, **473**, 1 (1929). 2-Phenyl-2-propylpotassium did not add to triphenylethylene.

## EXPERIMENTAL[9]

*Triphenyl(2,2-diphenylethyl)silane. A. From triphenylsilylpotassium and 1,1-diphenylethylene.* A triphenylsilylpotassium suspension was prepared in ether by cleaving 0.01 mole of hexaphenyldisilane according to a described procedure.[10] The excess alloy was removed by the amalgamation method.[10] The triphenylsilylpotassium suspension so obtained was added to 3.6 g. (0.02 mole) of 1,1-diphenylethylene dissolved in 20 ml. of ether. Some heat was evolved, the reaction mixture became deep red and finally dark brown. After 2 hr. of stirring at room temperature, the mixture was hydrolyzed. The ethereal solution was dried over sodium sulfate and the solvent removed by distillation. The gummy residue gradually solidified on standing. Recrystallization three times from ethanol gave 3.5 g. (42%) of triphenyl(2,2-diphenylethyl)silane as lustrous plates, melting at 106–108°.

*Anal.* Calcd. for $C_{32}H_{28}Si$: Si, 6.37. Found: Si, 6.43, 6.45.

*B. From triphenylsilyllithium and 1,1-diphenylethylene.* A solution of 0.0122 mole of triphenylsilyllithium[11] in tetrahydrofuran was added to 2.2 g. (0.0122 mole) of 1,1-diphenylethylene. A deep red color developed immediately and heat was evolved. After stirring for 30 minutes at room temperature, the mixture was hydrolyzed. From the organic layer, after drying with sodium sulfate and removal of the solvent by distillation, an oily residue was obtained which slowly solidified. Recrystallization from a mixture of ethanol and benzene gave two crops of triphenyl(2,2-diphenylethyl)-silane, 3.5 g., m.p. 105–107°, and 0.8 g., m.p. 103–106°. Recrystallization from the same solvent pair raised the melting point to 107–108°. The yields was 80%.

*C. From triphenylsilylpotassium and 1,1-diphenylethyl chloride.* A solution of 4.3 g. (0.01 mole) of 1,1-diphenylethyl chloride (supplied by the Techniservice Co., New York, N. Y.) in 20 ml of ether was added, within a period of 2 min., to an amalgamated suspension of 0.02 mole of triphenylsilylpotassium.[10] The reaction mixture became brownish-red and some heat was evolved. After 2 hr. of stirring, Color Test I[12] became negative. The reaction mixture was hydrolyzed and filtered to separate 1.1 g. of hexaphenyldisilane, m.p. 365–368°, identified by mixed melting point. The ethereal solution was dried and the solvent removed by distillation. The residue was recrystallized twice from ethanol to give 4.1 g. (47%) of shiny crystals, m.p. 106–107°. A mixed melting point with triphenyl(2,2-diphenylethyl)silane was not depressed. The infrared spectra of these two products were identical.

*D. From triphenyl-β-styrylsilane and phenyllithium. (Attempted).* A solution containing 0.002 mole of phenyllithium in tetrahydrofuran, prepared according to a reported procedure,[13] was added to 0.5 g. (0.00138 mole) of triphenyl-β-styrylsilane. The deep red solution soon turned brown. After stirring for 2 hr. at room temperature, the mixture was hydrolyzed, some ether was added, and the solvent removed from the dried organic layer. The pale yellow residue was chromatographed on alumina. The product eluted with petroleum ether (b.p. 60–70°) was recrystallized

(9) All melting points are uncorrected. Reactions involving organometallic compounds were carried out in an atmosphere of dry, oxygen-free nitrogen. Silicon analyses were carried out according to the procedure of H. Gilman, H. W. Melvin, Jr., and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 5767 (1950).

(10) H. Gilman and T. C. Wu, *J. Org. Chem.*, **18**, 753 (1953).

(11) H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, **80**, 608 (1958).

(12) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(13) H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22**, 1165 (1957).

from a mixture of benzene and ethanol to give 0.18 g. (39%) of tetraphenylsilane, m.p. 230–233°, identified by mixed melting point and infrared spectra. No other product was isolated from the mother liquor.

*Triphenyl(1,1-diphenylethyl)silane.* An ethereal solution of 0.015 mole of *n*-butyllithium[14] was added at once to a solution of 5.0 g. (0.012 mole) of triphenyl(diphenylmethyl)-silane, dissolved in 25 ml. of tetrahydrofuran. Heat was evolved and the solution turned deep red immediately. After stirring for 40 min. at room temperature, an excess of methyl sulfate was added. The color of the solution was discharged immediately. Hydrolysis and the usual work-up of the organic layer gave an oily residue, which gradually solidified. Two recrystallizations from a mixture of benzene and ethanol gave 3.0 g. (58%) of triphenyl(1,1-diphenylethyl)silane, m.p. 193–195°.

*Anal.* Calcd. for $C_{32}H_{28}Si$: Si, 6.37. Found: Si, 6.34, 6.47.

*Triphenyl(1,2,2-triphenylethyl)silane.* A solution of 0.020 mole of triphenylsilyllithium[11] in tetrahydrofuran was added with stirring to 5.12 g. (0.020 mole) of triphenylethylene. A deep red color developed immediately and heat was evolved. After stirring for 1 hr. at room temperature, the mixture was hydrolyzed. Subsequent to the usual work-up of the organic layer, an oily residue was obtained, which partially solidified. Two recrystallizations from a mixture of benzene and ethanol gave 6.4 g. (62%) of triphenyl(1,2,2-triphenylethyl)-silane, m.p. 171–172°.

*Anal.* Calcd. for $C_{38}H_{32}Si$: Si, 5.45. Found: Si, 5.42, 5.59.

*Triphenyl(1,1,2-triphenylethyl)silane.* An ethereal solution of 0.015 mole of *n*-butyllithium[14] was added at once to a solution of 5.0 g. (0.012 mole) of triphenyl(diphenylmethyl)-silane, dissolved in 25 ml. of tetrahydrofuran. After stirring for 40 min. at room temperature, an excess of benzyl chloride was added. The color of the solution was discharged after a few minutes. Hydrolysis and the usual work-up of the organic layer gave a yellow oil, which partially solidified on standing with 10 ml. of petroleum ether (b.p. 60–70°). The crystalline product was recrystallized three times from a mixture of benzene and ethanol to give 1.5 g. (25%) of triphenyl-(1,1,2-triphenylethyl)silane, m.p. 198–200°.

*Anal.* Calcd. for $C_{38}H_{32}Si$: Si, 5.45. Found: Si, 5.58, 5.60.

(14) 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).

*Reaction of triphenylsilyllithium with tetraphenylethylene.* A solution of 0.015 mole of triphenylsilyllithium in tetrahydrofuran was added to 5.0 g. (0.015 mole) of tetraphenylethylene. Apparently no reaction took place. The mixture was stirred for 6 hr. at room temperature, at which time the solution had turned deep brown. After stirring for one additional hour at 50°, the mixture was hydrolyzed with dilute acid. The work-up of the organic layer gave oily crystals, which were washed with 25 ml. of petroleum ether (b.p. 60–70°) and recrystallized from ethyl acetate to give 4.2 g. (84%) of tetraphenylethylene, m.p. 222–224° (mixed melting point). The filtrate was chromatographed on alumina. With petroleum ether as an eluent, 2.2 g. (56%) of triphenylsilane was obtained, m.p. 43–45° (after recrystallization from methanol).

*Attempted reactions of triphenylsilylpotassium with other olefins.* All reactions were carried out in the same manner. The triphenylsilylpotassium suspension was mixed with an equimolar amount of the olefinic compound and the mixture stirred for a certain period of time. Then water was added, the layers separated, the organic layer dried, and the solvent removed. The residue was recrystallized from petroleum ether (b.p. 60–70°) to give triphenylsilanol as the chief product. The results are given in Table I. In two experiments using 1,2-dimethoxyethane as the solvent in place of ether, a mixture of tetraphenylsilane and hexaphenyldisiloxane also was obtained.

In the reaction of $\Delta^{9,9'}$-bifluorene with triphenylsilylpotassium in ether, heat was evolved and the reaction mixture became very dark. The work-up gave a tar-like material, from which no pure product has been isolated.

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AMES, IOWA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SAN JOSE STATE COLLEGE]

# Synthesis and Cleavage of *N*-Trimethylsilylpyrrole[1]

RALPH FESSENDEN AND DAVID F. CROWE

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*N*-Trimethylsilylpyrrole has been synthesized by the reaction of potassium pyrrole and trimethylchlorosilane and by an exchange reaction between hexamethyldisilazane and pyrrole. *N*-Trimethylsilylpyrrole has been found to be stable in ethanol; however, it undergoes cleavage to pyrrole and silicon derivatives (trimethylsilanol, hexamethyldisiloxane, or trimethylethoxysilane, depending upon the conditions of the reaction) in boiling water and in refluxing aqueous ethanol. The cleavage reaction is catalyzed by either acid or base. *N*-Trimethylsilylpyrrole undergoes decomposition when heated in a sealed tube at 225°. No evidence for the formation of 2-trimethylsilylpyrrole in this reaction could be obtained. Infrared spectra are given for *N*-trimethylsilylpyrrole and tetrapyrrylsilane.

Although a number of compounds containing the silazane linkage are known, there appears to be no reported study of the stability of such a linkage in which the nitrogen of the silazane is in an aromatic heterocyclic system. In view of the known susceptibility of the silazane linkage to cleavage by water, alcohols, and other reagents,[2] this investigation has been directed toward preparation of such a compound and a study of its cleavage reactions.

Silazane compounds undergo solvolysis and

(1) This work was supported by a Frederick Gardner Cottrell grant from Research Corporation.

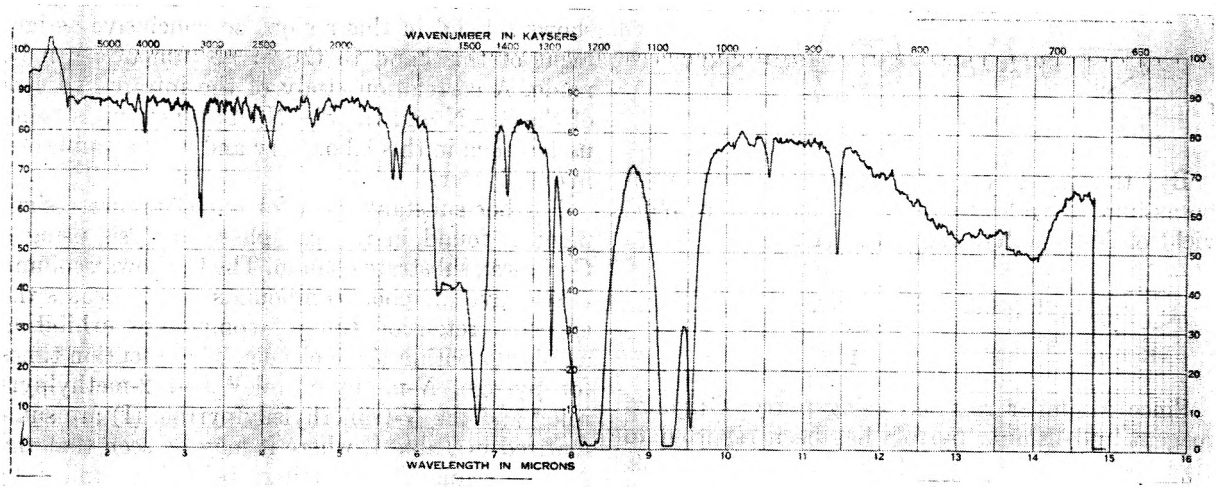



Fig. 1. Infrared spectrum of tetrapyrrylsilane (II). Carbon tetrachloride.

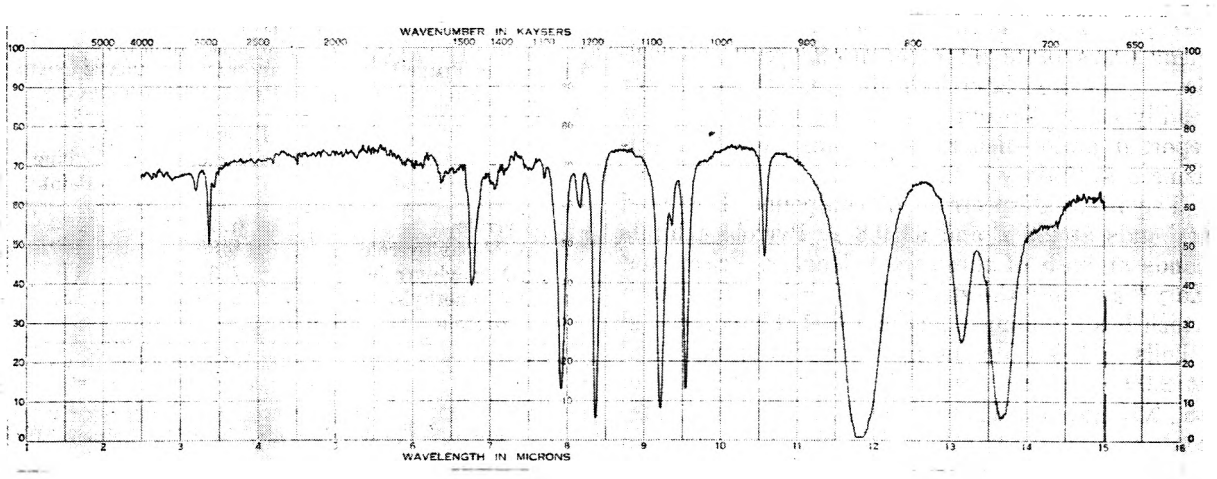



Fig. 2. Infrared spectrum of *N*-trimethylsilylpyrrole (I). Thin film

cleavage in the presence of either acids or bases. Andrianov[3] has reported that ethereal solutions of triethylaminosilane, *N*-methyltriethylaminosilane, and *N*,*N*-dimethyltriethylaminosilane yield triethylsilanol when treated with water for one hour. Under similar conditions, the *N*,*N*-diethyltriethylaminosilane failed to cleave, but when homogeneous conditions (acetone solution) were used, the silanol was obtained. Kraus and Nelson[4] report that triethylsilanol was obtained from the steam distillation of *N*-ethyltriethylaminosilane.

The instability of the silazane and the disilazane bonds have been utilized to synthesize other silicon compounds. Sulfur and phosphorus silicon compounds have been obtained by the cleavage of silazanes and disilazanes by the appropriate reagents.[5] Halosilanes,[6] hydroxysilanes,[7] and alkoxysilanes[8] can be obtained from silazanes or disilazanes.

For our work we have chosen to prepare and study *N*-trimethylsilylpyrrole (I). A few silylpyrroles have been synthesized. Reynolds[9] has prepared tetrapyrrylsilane (II), dichloropyrrylsilane, and tripyrrylsilane from potassium pyrrole and the appropriate chlorosilane. He reports that these compounds decompose in acid, base, water or alcohols.

(2) (a) F. S. Kipping, *Proc. Chem. Soc.*, **23**, 8 (1907); (b) P. A. Di Giorgio, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **71**, 3254 (1949); (c) P. D. George, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **75**, 6308 (1953); (d) von M. Becke-Goehring and G. Wunsch, *Ann.*, **618**, 43 (1958).

(3) K. A. Andrianov, S. A. Golubtsov, and E. A. Semenova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk* (1958) 47; *Chem. Abstr.*, **52**, 11734f (1958).

(4) C. A. Kraus and W. K. Nelson, *J. Am. Chem. Soc.*, **56**, 195 (1934).

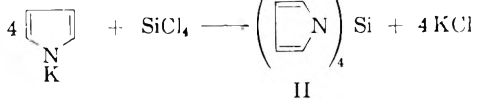
(5) Ref. 2(d).

(6) D. L. Bailey, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 435 (1948).

(7) C. S. Miner, L. A. Bryan, R. P. Holysz, and G. W. Pedlow, *Ind. Eng. Chem.*, **39**, 1368 (1947).

(8) (a) Ref. 7; (b) P. A. Di Giorgio, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **71**, 3254 (1949); (c) A. P. Kreshkov, L. V. Myshlyaeva, and L. M. Khananashvili, *Zhur. Obshchei Khim.*, **28**, 2112 (1958); *Chem. Abstr.*, **53**, 2074g (1959).

(9) (a) J. E. Reynolds, *J. Chem. Soc.*, **95**, 505 (1909); (b) J. E. Reynolds, *J. Chem. Soc.*, **95**, 508 (1909).



II

By treatment of trimethylchlorosilane with potassium pyrrole there was obtained a 38% yield of *N*-trimethylsilylpyrrole (I).

I

Since a similar reaction using pyrryl Grignard reagent and lithium pyrrole has been reported to give 2-trimethylsilylpyrrole,[10] the *N*-silylpyrrole was also prepared by an exchange reaction of pyrrole with hexamethyldisilazane;[11] of the type reported by Speier *et al.*[12] This reaction would not be expected to yield the 2-isomer unless a rearrangement takes place after the initial reaction. Evidence presented later indicates that this does not readily occur. To our knowledge, this is the first reported amine-disilazane exchange reaction utilizing a secondary amine.

The infrared spectrum of compound I is void of bands at 2.9 $\mu$ and at 9.8 $\mu$. Pyrrole exhibits bands at both of these wave lengths. Frisch and Kary[10] assigned the structure of their compound,[13] which has a boiling range of 148–151° (compound I boils at 153°), on the presence of a strong band at 2.99 $\mu$, which would indicate the presence of an NH group. Their published spectrum also contains a band at 9.8 $\mu$. When the spectrum of compound I contained bands at these two wave lengths, the gas chromatogram also showed a large peak corresponding to pyrrole. However, when compound I was purified by use of separation on the gas chromatography unit, both of these bands in the infrared disappeared. This suggests that Frisch and Kary used the spectrum of a mixture of pyrrole and *N*-trimethylsilylpyrrole (I) for their structure assignment. The possibility that the small band at 3.2 $\mu$ in the spectrum of I is the NH band is eliminated by comparison with the spectrum of tetrapyrrylsilane (II), prepared *via* the method of Reynolds.[14] In the spectrum of this compound a band appears at 3.2 $\mu$, indicating that this band is due to the CH on the pyrrole ring rather than an NH group. Of further interest is a strong band at 9.55 $\mu$ which appears in the spectra of both I and II. A number of silazanes prepared in this laboratory show a band in the region between 9.5 $\mu$ and 9.9 $\mu$. However, since pyrrole also shows a band in this region, no conclusive assignment of this band to the Si—N function can be made. A correlation study of the infrared spectra of the Si—N and the Si—N—Si functions is being undertaken in this laboratory and will be published in detail later.

Further substantiation for our structure assignment is found in the gas phase analysis using a Carbowax substrate column. The Carbowax column is selective for polar compounds and increases the expected retention time of compounds exhibiting a polarity within the molecule. The retention times for pyrrole, *N*-methylpyrrole[15] and 2-methylpyrrole[16] and the *N*-trimethylsilylpyrrole (I) are summarized in Table I, where it may be seen that the *N*-silylpyrrole (I) exhibited behavior similar to that of the *N*-methylpyrrole rather than that of the 2-methylpyrrole.

TABLE I

RETENTION TIMES USING A CARBOWAX SUBSTRATE COLUMN AND BOILING POINTS FOR PYRROLE DERIVATIVES[a]

| Compound | Retention Time, Min. | Boiling Point |
|---|---|---|
| Pyrrole | 6.10 | 130 |
| *N*-Methylpyrrole | 1.80 | 114 |
| 2-Methylpyrrole | 7.30 | 149[b] |
| *N*-Trimethylsilylpyrrole | 2.10 | 153 |

[a] Column temperature was 160°. Column length was 10′. The flow rate was 60 ml./min. See Experimental for other details. [b] H. Fischer and H. Orth, *Die Chemie des Pyrroles*, Akademische Verlagsgesellschaft, M.B.H., Leipzig, 1934, p. 40.

Since no higher boiling components could be detected using the Carbowax or the Silicone column at high temperatures, it is indicated that no 2-silylpyrrole was present in the distillation fraction boiling 150–153°.

*N*-Trimethylsilylpyrrole (I) was also obtained by treatment of the Grignard reagent of pyrrole with trimethylchlorosilane; however, the yield of I was very small. Polymerization of pyrrole prevented complete recovery of the *N*-silylpyrrole which had been detected in the gas chromatogram. Again, no peak in the gas chromatogram corresponding to 2-trimethylsilylpyrrole could be detected.

*N*-Trimethylsilylpyrrole is a colorless liquid boiling at 153°. Its ultraviolet spectrum (cyclohexane) is similar to that of pyrrole except that the extinction coefficient is smaller. No $\lambda_{max}$ could be detected between 2250 Å and 2500 Å.

For the investigation of the cleavage of the *N*-trimethylsilylpyrrole, gas chromatography (5′ Sili-

(10) K. C. Frisch and R. M. Kary, *J. Org. Chem.*, 21, 931 (1956).

(11) It should be noted here that the exchange reaction would not occur in the absence of ammonium sulfate.

(12) J. L. Speier, R. Zimmerman, and J. Webster, *J. Am. Chem. Soc.*, 78, 2278 (1956).

(13) 2-Trimethylsilylpyrrole.

(14) Ref. 9(a).

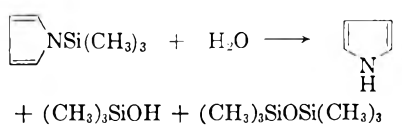
(15) Obtained through the courtesy of the Ansul Corporation.

(16) Prepared by A. J. Castro and M. Hugo of this laboratory.

cone column) was utilized for analysis of the product ratios. The extent of cleavage was judged by the increase in the area under the pyrrole peak and the corresponding decrease in that under the *N*-silylpyrrole peak. The other products detected in the gas chromatograms were trimethylsilanol, trimethylethoxysilane or hexamethyldisiloxane, depending upon the reaction conditions which were employed.

Upon reflux of the *N*-silylpyrrole with water for twelve hours and extraction and distillation of the ether-soluble fraction, complete cleavage was observed. Pyrrole was isolated and identified by gas phase chromatographic comparison with an authentic sample and by its infrared spectrum. Other products observed in the gas chromatogram of the ether-soluble material were hexamethyldisiloxane and, presumably, trimethylsilanol. The disiloxane was identified by gas chromatographic comparison with an authentic sample of this material, and the presence of the trimethylsilanol is suggested by the strong band below 3.0 $\mu$ in the infrared spectrum of the lower-boiling fraction. Gas chromatography indicates that this infrared band is not due to water.

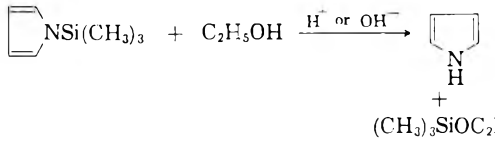
Besides showing the susceptibility of this silazane to cleavage in boiling water, the experiment indicates that the pyrrole moiety had not undergone cleavage or rearrangement during the preceding reactions. This observation lends further support to the assigned structure of I. Such mild conditions would not be expected to cleave a Si—C bond, as would be the case if the compound were 2-trimethylsilylpyrrole.



$$\text{NSi(CH}_3)_3 + \text{H}_2\text{O} \longrightarrow \text{NH} + (\text{CH}_3)_3\text{SiOH} + (\text{CH}_3)_3\text{SiOSi(CH}_3)_3$$

The stability of the *N*-silylpyrrole to cleavage in a homogeneous medium was next investigated. In ethanol, the *N*-silylpyrrole was found to be stable up to three days at room temperature. When the solution was heated under reflux for one hour, only about 0.1% cleavage could be detected. When an aqueous-ethanol (33% water by volume) solution was used, the cleavage was detected proceeding at a reasonable rate. When the solution had been heated under reflux for thirty minutes about 20% cleavage could be detected and, after one hour of reflux, about 30% could be detected by gas phase analysis.

The cleavage of the *N*-silylpyrrole was found to be catalyzed by either acid or base. When a drop of hydrochloric acid was added to an ethanolic solution of the *N*-silylpyrrole at room temperature, quantitative cleavage took place in less than one minute. Pyrrole and trimethylethoxysilane were detected as the cleavage products. No trace of the *N*-silylpyrrole could be detected in the gas chromatogram.



$$\text{NSi(CH}_3)_3 + \text{C}_2\text{H}_5\text{OH} \xrightarrow{\text{H}^+ \text{ or } \text{OH}^-} \text{NH} + (\text{CH}_3)_3\text{SiOC}_2\text{H}_5$$

Similar results were observed when a small amount of potassium hydroxide was added to an ethanol solution of the *N*-silylpyrrole at room temperature. Again the cleavage was quantitative in less than one minute. The major products of the cleavage were pyrrole and trimethylethoxysilane. Again no trace of the *N*-silylpyrrole could be detected in the gas chromatogram.

The cleavage of I by boiling water, acids, and bases is not surprising in light of the known chemistry of the silazanes and the disilazanes.[17] However, the stability of I in ethanolic solution is unusual. Nonsterically-hindered silazanes[18] generally undergo cleavage very rapidly in homogeneous media. *N*-Trimethylsilylpyrrolidine[19] cleaves when exposed to moist air, and great care is necessary to keep the molecule intact. Miner[20] reports that the di-*t*-alkoxydiaminosilanes form tetraalkoxysilanes when warmed with a primary alcohol. This suggests that there is some stabilization of the silazane bond in *N*-trimethylsilylpyrrole, probably due to *d*-orbital participation of the silicon atom in the aromatic system of the pyrrole ring, a type of participation suggested by Rochow, Hurd, and Lewis[21] in trisilylamine [$(H_3Si)_3N$]. Such *d*-orbital participation is also found to a small extent in other silyl aromatic compounds.[22]

No evidence of thermal rearrangement of the silyl group to the 2- or the 3-position of pyrrole could be obtained.[23] When the *N*-silylpyrrole was heated seventeen hours in a sealed tube at 225°, extensive charring resulted. Gas phase analysis of the liquid remaining after the pyrolysis showed only the starting *N*-silylpyrrole. No other isomers could be detected. When *N*-trimethylsilylpyrrole was heated under reflux with diphenyl ether (b.p. 247°)

(17) R. O. Sauer and R. H. Hasek, *J. Am. Chem. Soc.*, **68**, 241 (1946).

(18) Hexaphenyldisilazane [H. H. Reynolds, L. A. Bigelow, and C. A. Kraus, *J. Am. Chem. Soc.*, **51**, 3067 (1929)] and *N*-triphenylsilylhydrazobenzene [D. Wittenberg, M. V. George, T. C. Wu, D. H. Miles, and H. Gilman, *J. Am. Chem. Soc.*, **80**, 4532 (1958)] are purified by crystallization from alcoholic solutions.

(19) Unpublished observations from this laboratory.

(20) See Ref. 7.

(21) E. G. Rochow, D. T. Hurd and R. N. Lewis, *The Chemistry of Organometallic Compounds*, John Wiley and Sons, Inc., New York, 1957, p. 32.

(22) (a) H. Soffer with T. DeVries, *J. Am. Chem. Soc.*, **73**, 5817 (1951); (b) R. A. Benkeser and H. R. Krysiak, *J. Am. Chem. Soc.*, **75**, 2421 (1953).

(23) *N*-Alkylpyrroles are reported to form 2-alkylpyrroles when heated to 200–250° [R. H. Wiley, *Organic Chemistry, An Advanced Treatise*, Vol. IV, H. Gilman, ed., John Wiley and Sons, Inc., New York, 1953, p. 749].

for twelve hours, no decomposition was observed and, again, no other isomers could be detected in the gas chromatogram.

## EXPERIMENTAL[24]

*Technique of gas phase analysis.* For the gas phase analyses, an Aerograph gas phase chromatography unit was employed. Two columns, both obtained from the Wilkens Instrument Co., were used: a 5′ column, Silicone on firebrick, for nonpolar separation, and a 10′ column, Carbowax 20M on firebrick, for separation of polar compounds. The temperature was held constant for a given analysis, and the helium flow was held constant at 100 ml. per minute.

Two injection techniques were used for analysis: (a) injection into the instrument of an undiluted sample and (b) dilution of 50–100 mg. of the sample with 1 ml. of ether or benzene and injection of an aliquot of this solution. In each case, the volume of sample injected was 0.005 ml.

Peak assignments were made by comparison of retention times and, in some cases, by the addition of known material to the unknown mixture. The retention times were measured from the air peak rather than from the actual time of injection and are accurate to 0.05 min. (3 sec.).

The areas under the peaks are reported as percentages of the total area under all the observed peaks, not including that of the solvent. These are not the correct percentages of the components in the mixture, but are reasonable approximations.

*N-Trimethylsilylpyrrole* (I). *A. From potassium pyrrole.* In a 500-ml. round bottom flask, fitted with reflux condenser, mechanical stirrer, and dropping funnel, were placed 50 ml. of sodium-dried ether, 25 ml. of sodium-dried benzene and 13.4 g. (0.20 mole) of pyrrole (obtained Ansul Chemical Company). To this solution was added 7.4 g. (0.19 mole) of diced metallic potassium. The mixture was heated under reflux for 1.5 hr. and then cooled to room temperature, and 16.2 g. (0.15 mole) of trimethylchlorosilane was added over a 5-min. period. After the addition the mixture was allowed to stand at room temperature for 48 hr.

The reaction mixture was then filtered to remove the potassium chloride which had formed, and the filtrate was distilled at atmospheric pressure. The *N*-silylpyrrole was collected in seven fractions, 8.0 g., b.p. 150–152°, $n_D^{26}$ 1.4654–1.4621. A redistilled sample was used for analysis.

*Anal.* Calcd. for $C_7H_{13}NSi$: C, 60.5; H, 9.4; N, 10.1; Si, 20.3. Found: C, 60.9; H, 9.4; N, 9.2; Si, 19.9, 20.4.[25]

Gas phase analysis data, using the Carbowax column is tabulated in Table I.

B. *From pyrrylmagnesium iodide.* To 200 ml. of an ether solution of methylmagnesium iodide, freshly prepared from 42.5 g. (0.25 mole) of methyl iodide and 7.3 g. (0.3 mole) of magnesium, was added 16.7 g. (0.25 mole) of pyrrole. The solution was heated under reflux for 15 min., then cooled to room temperature. To this mixture was then added, dropwise, 27.0 g. (0.25 mole) of trimethylchlorosilane. A moderately exothermic reaction took place. After the addition had been completed, the mixture was heated under reflux for 2 hr., then allowed to stand overnight. The reaction mixture was filtered and the bulk of the ether removed by slow distillation at atmospheric pressure. An attempt to distill fractionally this material resulted in the formation of a solid black cake, which was removed from the flask and extracted with ether overnight using a Soxhlet extractor. The ether soluble material was then distilled and 2.0 g. (6%) of *N*-trimethylsilylpyrrole was obtained, b.p. 150–152°. A considerable amount of semisolid pot residue remained and was investigated using the gas phase chromatography instrument for the possible presence of other trimethylsilylpyrrole isomers. In the gas chromatogram, only one high-boiling component could be detected, its retention time the same as that of an authentic sample of *N*-trimethylsilylpyrrole.

*C. From hexamethyldisilazane.* Hexamethyldisilazane was prepared in 45% yield using the procedure of Sauer[26] from 1.0 mole of trimethylchlorosilane and excess ammonia gas. The disilazane was isolated by distillation, b.p. 122–124°, $n_D^{20}$ 1.4075 (lit.,[27] b.p. 124–126°, $n_D^{20}$ 1.4080).

In a 100-ml. round bottom flask were placed 15.2 g. (0.094 mole) of hexamethyldisilazane, 11.5 g. (0.17 mole) of pyrrole and a few crystals of ammonium sulfate. The mixture was heated for 6 hr. at 110° then fractionally distilled without further work-up. There was obtained 13.5 g. (51%) of the *N*-silylpyrrole, b.p. 150–151°. Gas phase analysis of product using both Carbowax and Silicone columns showed that it was identical with the compound obtained from potassium pyrrole and trimethylchlorosilane. Only starting material and the *N*-silylpyrrole were detected in the gas chromatogram.

Attempts without ammonium sulfate were unsuccessful. No reaction product was obtained when pyrrole and the disilazane were heated 10 hr. in ether solution or when they were heated 12 hr. without solvent. In both these reactions, the starting materials were recovered upon distillation and no *N*-silylpyrrole could be detected in the gas chromatograms of the pot residues.

*Cleavage of N-trimethylsilylpyrrole with water.* In a 50-ml. round bottom flask were placed 13.9 g. (0.10 mole) of *N*-trimethylsilylpyrrole and 20 ml. of water. The mixture was heated under reflux for 12 hr. During the reflux period, no color change was observed. The mixture was then continuously extracted with ether for 3 hr. A second continuous extraction for 12 hr. yielded no additional material. After drying with sodium sulfate, the ether from the first extraction was removed by slow distillation and the resulting material was fractionally distilled. Two main fractions were observed in this distillation: Fraction 1, 5.6 g., b.p. 98–102°, a mixture of trimethylsilanol and hexamethyldisiloxane; Fraction 2, 5.9 g., b.p. 128–130°, pyrrole. The total weight recovered (including the intermediate fractions) was 15.9 g.

Gas phase analysis (Silicone column, T = 148°) of the first main fraction yielded two peaks: peak 1, retention time, 0.32 min. and peak 2, retention time, 0.65 min. The area under peak 1 was *ca.* 60%, and that of peak 2, *ca.* 40%. The retention time of peak 2 was the same as that of an authentic sample of hexamethyldisiloxane. It is believed that peak 1 corresponds to trimethylsilanol, although it was not compared to an authentic sample of that compound. A large band at 2.80 $\mu$ (—OH) in the infrared spectrum of this lower-boiling fraction was observed.

(24) All melting points and boiling points are uncorrected. Fractional distillations were accomplished using a 2-meter modified Podbeilniak column (*cf.* J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, p. 237). Infrared spectra were recorded using thin films or carbon tetrachloride solutions on a Beckman IR-4 instrument. The ultraviolet spectrum was obtained using a Beckman Model DU Spectrophotometer. Carbon, hydrogen, and nitrogen analyses were performed by the Berkeley Microanalytical Laboratory. Silicon analyses were performed in this laboratory.

(25) The silicon analysis was accomplished by slow oxidation with fuming sulfuric acid and ignition to constant weight. When nitric acid was used with sulfuric acid, the analysis was *ca.* 10% low, presumably due to the formation of stable compounds which were lost during the ignition. Fuming sulfuric acid was necessary because I decomposed extremely slowly in concentrated sulfuric acid, even at 150°. In view of the rapid acid-catalyzed cleavage of I to pyrrole, this stability in hot concentrated sulfuric acid is not understood.

(26) R. O. Sauer, *J. Am. Chem. Soc.*, 66, 1707 (1944).

(27) Ref. 26.

The infrared spectrum of the last fraction and that of pyrrole were identical. Gas phase chromatography at 148° and at 130° using a Silicone column showed peaks which had the same retention times as those of an authentic sample of pyrrole.

*Attempted reaction of N-trimethylsilylpyrrole with ethanol.* In a 10-ml. Erlenmeyer flask were placed 116 mg. of *N*-trimethylsilylpyrrole and 2.0 ml. of ethanol (containing less than 1% water), and the mixture was swirled for 1 min. A 0.005-ml. aliquot was removed and injected into the gas phase instrument (Silicone column, T = 110°). Only one peak, which had the same retention time as that of *N*-trimethylsilylpyrrole was observed. The ethanol mixture was then heated under reflux for 1 hr., after which time another 0.005-ml. aliquot was injected into the gas phase instrument. This time two peaks were detected, the major one having the same retention time as the *N*-trimethylsilylpyrrole and the second (shorter retention time) the same as that of pyrrole; however, the area of the pyrrole peak was only 0.12% of the total area of the two peaks. The mixture was allowed to stand 3 days at which time the area under the pyrrole peak was 0.14% of the total area. No other compounds, besides ethanol, were detected in any of the gas chromatograms.

*Reaction with aqueous ethanol.* In a 10-ml. Erlenmeyer flask were placed 56 mg. of *N*-trimethylsilylpyrrole, 1.0 ml. of ethanol, and 0.5 ml. of water. After 15 min. a 0.005-ml. aliquot was removed and injected into the gas phase instrument (Silicone column, T = 110°). The major peak was that of *N*-trimethylsilylpyrrole. A small deflection in the base-line having the same retention time as pyrrole was detected; however, the area was too small for an area comparison. After the solution had been heated under reflux for 30 min., the pyrrole peak had increased to 19.5% of the total, and after 1 hr., 29%.

*Acid-catalyzed reaction.* In a 10-ml. Erlenmeyer flask were placed 110 mg. of *N*-trimethylsilylpyrrole, 2.0 ml. of ethanol and 1 drop of concentrated hydrochloric acid. The solution was swirled and, in less than 1 min. after the initial mixing, a 0.005-ml. aliquot was injected into the gas phase instrument (Silicone column, T = 105°). Three peaks were observed: peak 1, retention time, 0.80 min., area, 22%; peak 2, retention time, 12.0 min., area, 30%; and peak 3, retention time, 1.60 min., area, 48%. Under the same conditions, pyrrole had a retention time of 1.60 min. and *N*-trimethylsilylpyrrole, 5.20 min. No trace of the *N*-trimethylsilylpyrrole could be detected. Peak 2 had the same retention time as a sample of trimethylethoxysilane prepared from trimethylchlorosilane and ethanol.

*Base-catalyzed reaction.* In a 10-ml. Erlenmeyer flask were placed 71 mg. of *N*-trimethylsilylpyrrole and 1.0 ml. of ethanol. To this solution was added 4 mg. of potassium hydroxide (in ethanol) and the mixture was swirled for 1 min., then a 0.005 ml. aliquot was injected into the gas phase instrument (Silicone column, T = 105°). Two major peaks were observed and the trace of a third was detected; peak 1, retention time, 0.04 min., trace; peak 2, retention time, 0.74 min., 51%; peak 3, retention time, 1.56 min., 48%. Under the same conditions, the retention time for pyrrole was 1.57 min. and the time for *N*-trimethylsilylpyrrole was 5.15 min. No deflection in the base line could be detected at 5.15 min., indicating the absence of the *N*-silylpyrrole. Peak 2 had the same retention time as a sample of trimethylethoxysilane prepared from trimethylchlorosilane and ethanol.

*Attempted thermal rearrangement of N-trimethylsilylpyrrole.* One gram of *N*-trimethylsilylpyrrole was sealed in a glass tube and heated at 225° for 17 hr. By the end of the heating period the material had undergone extensive charring. An aliquot of the liquid remaining was analyzed using gas phase chromatography (Silicone column, T = 110°), and only one peak (*N*-silylpyrrole) could be detected.

Another attempt was made, using diphenyl ether as solvent. A mixture of 10 ml. of diphenyl ether (b.p. 259°) and 1.0 g. of *N*-trimethylsilylpyrrole was heated under reflux for 12 hr. No charring was observed. Gas phase analysis of the reaction mixture indicated that the *N*-silylpyrrole had not undergone rearrangement. Only peaks corresponding to the *N*-silylpyrrole and the diphenyl ether were detected. *N*-Trimethylsilylpyrrole was isolated from the reaction mixture using the gas phase instrument; its infrared spectrum was identical with that of the starting *N*-silylpyrrole.

*Tetrapyrrylsilane* (II). To 0.2 mole of potassium pyrrole in 150 ml. of ether and 75 ml. of benzene was added 0.05 mole of silicon tetrachloride over a 30-min. period, and the mixture was heated under reflux for 45 min. The potassium chloride was filtered from the mixture and the solution was allowed to stand overnight. The white, needle-like crystals which formed were filtered and recrystallized from benzene to yield 0.7 g. (4.5%) of tetrapyrrylsilane (II), m.p. 167.5–168.5° (lit.,[28] m.p. 173°).

SAN JOSE, CALIF.

(28) Ref. 9(a).

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[CONTRIBUTION NO. 11 FROM THE EXPLORATORY RESEARCH LABORATORY OF DOW CHEMICAL OF CANADA, LIMITED]

# Organophosphorus Compounds. VII.[1a] Alkyl- and Arylphosphorodihalidothioates Containing Fluorine

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*O*-Alkyl- and *O*-arylphosphorodifluoridothioates were prepared from phosphorus thiohalides with alcohols and phenols. *O*-Arylphosphorochlorofluoridothioates were prepared from phosphorus thiodichlorofluoride and phenols.

The synthesis of *O*-alkylphosphorodihalidothiates were first reported by Pistschimuka[2,3] and involved the reaction of phosphorus thiochloride or bromide with an alcohol:[4,5,6]

$$PSX_3 - ROH \longrightarrow ROPSX_2 + HX \quad (X = Cl, Br)$$

(1a) Part VI, *J. Org. Chem.*, 24, 1443 (1959).

(1b) Present address: Research Department, Imperial Oil Limited, Sarnia, Ontario, Canada.

(2) P. Pistschimuka, *Ber.*, 41, 3854 (1908).

(3) P. Pistschimuka, *J. Russ. Phys. Chem. Soc.*, 44, 1406 (1912).

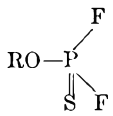
(4) V. M. Plets, *Zhur. Obschei Khim.*, 6, 1198 (1936).

(5) V. M. Plets, *Zhur. Obschei Khim.*, 8, 1296 (1938).

(6) T. W. Martin, G. R. Norman, E. A. Weilmuenster, *J. Am. Chem. Soc.* 70, 2523 (1948).

TABLE I

*O*-ALKYLPHOSPHORODIFLUORIDOTHIOATES AND *O*-ARYLPHOSPHORODIFLUORIDOTHIOATES



| R | Yield (%) | B.P. (C./mm.) | $n_D^{20}$ | Fluorine Calcd. | Fluorine Found |
|---|---|---|---|---|---|
| Ethyl | 63 | 78–78.5/760[a] | 1.3942 | 26.00 | 25.65 |
| Isopropyl | 60 | 88–89/760 | 1.3813 | 23.57 | 23.35 |
| *t*-Butyl | 61 | 47–48/20 | 1.3889 | 22.32 | 22.49 |
| Cyclohexyl | 72 | 42–43/5 | 1.4408 | 18.98 | 19.06 |
| Phenyl | 82 | 52–52.5/14 | 1.4869 | 19.56 | 19.71 |
| *o*-Cresyl | 85 | 59–60/10 | 1.4849 | 18.25 | 18.42 |
| *o*-Nitrophenol | 68 | 118–120/8 | 1.5389 | 15.88 | 15.94 |
| *p*-Chlorophenyl | 84 | 52/4 | 1.5033 | 16.62 | 16.81 |
| *α*-Naphthyl | 81 | 82–83/2 | 1.5704 | 15.55 | 15.27 |

[a] Booth and co-workers[7] reported b.p. 78.4°.

According to another method which has been used to a lesser extent, sulfur was added to alkylphosphorodichloridites[5] to yield alkylphosphorodichloridothiates:

$$ROPCl_2 + S \longrightarrow ROPSCl_2$$

The synthesis of an alkylphosphorodihalidothioate containing fluorine was accomplished first by Booth and his co-workers,[7] who achieved a fluorine exchange in the case of ethylphosphorodichloridothioate by using antimony trifluoride.

$$C_2H_5OPSCl_2 \xrightarrow{SbF_3} C_2H_5OPSClF \xrightarrow{SbF_3} C_2H_5OPSF_2$$

The present authors[8] previously reported the preparation of alkylphosphorochlorofluoridothioates by the reaction of phosphorus thiodichlorofluoride and alcohol.

$$PSCl_2F + ROH \longrightarrow ROPSClF + HCl$$

Of the *O*-arylphosphorodihalidothioates, only the *O*-arylphosphorodichloridothioates were investigated in detail. Methods, including the reaction of phosphorus thiochloride with a basic aqueous solution of a phenol,[9,10] addition of sulfur to *O*-arylphosphorodichloridites at elevated temperatures[11,12,13] and reacting a phenol, phosphorus thiochloride, and pyridine as the acid binding agent[14] were used for their synthesis.

*O*-Phenylphosphorodibromidothioates were also synthetized.

No arylphosphorodihalidothioates containing fluorine were known at the time the present investigation was undertaken.

In this paper, the reaction of various phosphorus thiohalides containing fluorine with alcohols and phenols is described. These reactions yielded alkyl- and arylphosphorodihalidothioates containing fluorine.

At first the reaction of phosphorus thiofluoride, phosphorus thiochlorodifluoride, and phosphorus thiobromodifluoride with equimolar amounts of alcohols and phenols was studied, in the presence of pyridine as an acid binding agent. Alkyl- and arylphosphorodifluoridothioates were obtained according to the following general reaction equations:

$$PSF_3 + ROH + C_6H_5N \longrightarrow ROPSF_2 + C_5H_5N \cdot HF$$

$$PSClF_2 + ROH + C_5H_5N \longrightarrow ROPSF_2 + C_5H_5N \cdot HCl$$

$$PSBrF_2 + ROH + C_5H_5N \longrightarrow ROPSF_2 + C_5H_5N \cdot HBr$$

R = alkyl, aryl

Some characteristic physical and analytical data of the prepared compounds are given in Table I.

The ethyl-, isopropyl-, *t*-butyl-, cyclohexylphosphorodifluoridothioates are colorless liquids. They fumed in air to some extent depending on their vapor pressure and were immiscible with water, although on standing they underwent aqueous hydrolysis.

The phenyl-, *o*-cresyl-, *o*-nitrophenyl-, *p*-chlorophenyl-, and *α*-naphthylphosphorodifluoridothioates are liquids immiscible with water and are colorless with one exception—the yellow *o*-nitrophenylphosphorodifluoridothioate.

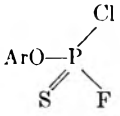
In the presence of oxygen both the alkyl- and the arylphosphorodifluoridothioates are oxidized with the production of sulfur dioxide. The presence of sulfur dioxide leads to the formation of red colored decomposition products.

In the following part of the work *O*-arylphosphorochlorofluoridothioates were prepared starting from phosphorus thiodichlorofluoride and phenols.

(7) H. S. Booth, D. R. Martin, F. E. Kendall, *J. Am. Chem. Soc.*, **70**, 2523 (1948).
(8) G. A. Olah, A. A. Oswald, *Liebigs Ann. Chem.*, **602**, 118 (1957).
(9) W. Autenrieth, O. Hildebrand, *Ber.*, **31**, 1094 (1898).
(10) W. Autenrieth, W. Meyer, *Ber.*, **58**, 840 (1925).
(11) R. Anschutz, W. O. Emery, *Ann.*, **253**, 117 (1889).
(12) W. Strecker, C. Grossman, *Ber.*, **49**, 64 (1916).
(13) F. Ephraim, *Ber.*, **44**, 3414 (1911).
(14) L. R. Drake and co-workers (Dow Chemical Co.) U. S. Patent 2,552,537 and 2,552,541.

TABLE II

*O*-ARYLPHOSPHOROCHLOROFLUORIDOTHIOATES



| Ar | Yield (%) | B.P. (°C/mm.) | $n_D^{20}$ | Cl % Calcd. | Cl % Found | F % Calcd. | F % Found |
|---|---|---|---|---|---|---|---|
| Phenyl | 85 | 60.5–61/5 | 1.5290 | 16.83 | 17.07 | 9.02 | 9.06 |
| *o*-Cresyl | 84.5 | 89–90/8 | 1.5274 | 15.78 | 16.04 | 8.45 | 8.68 |
| *m*-Cresyl | 88 | 103–104/8 | 1.5251 | 15.78 | 15.62 | 8.45 | 8.23 |
| *p*-Cresyl | 87 | 99–100/8 | 1.5260 | 15.78 | 15.49 | 8.45 | 8.36 |
| *m*-Methoxyphenyl | 81 | 110–111/8 | 1.5345 | 14.73 | 14.47 | 7.89 | 7.73 |
| *p*-Chlorophenyl | 85 | 100.5–101/7 | 1.5449 | 28.93 | 28.93 | 7.75 | 7.56 |
| *p*-Nitrophenyl | 70.5 | 119–120/5 | 1.5641 | 13.86 | 13.86 | 7.43 | 7.66 |
| $\alpha$-Naphthyl | 77 | 116–117/4 | 1.6061 | 13.60 | 13.31 | 7.28 | 7.21 |
| $\beta$-Naphthyl | 75 | 118–119/3 | 1.6062 | 13.60 | 13.53 | 7.28 | 6.85 |

Because of the decreased reactivity of phenols as compared to alcohols, pyridine was used to bind the hydrochloric acid formed:

$$PSCl_2F + ArOH + C_5H_5N \longrightarrow ArOPSClF + C_5H_5N \cdot HCl$$

In this manner the phenyl-, *o*-cresyl-, *m*-cresyl-, *p*-cresyl-, *p*-chlorophenyl, *p*-nitrophenyl-, *m*-methoxyphenyl-, $\alpha$-naphthyl-, $\alpha$-naphthylphosphorochlorofluoridothioates were obtained. The yields were almost quantitative. No considerable amounts of diarylphosphorofluoridothioates were formed in in the preparation of any of the above mentioned derivatives. Pyridine could be replaced by other tertiary amines, such as dimethylaniline or triethylamine, which forms ammonium salts with the hydrochloric acid formed in a similar manner. Some characteristic physical and analytical data of the compounds are given in Table II.

The *O*-arylphosphorochlorofluoridothioates are liquids immiscible with water and have a slightly acrid odor. They can be distilled in vacuum without decomposition and are colorless except for *p*-nitrophenylphosphorochlorofluoridothioate which is light yellow.

The reaction of phosphorus thiochloride with basic aqueous phenolates gave in several cases only diarylphosphorochloridothioates, or triarylphosphorothioates.[1] Phosphorus thiodichlorofluoride, however, reacted with an aqueous solution of sodium phenolate to yield 62% phenylphosphorochlorofluoridothioate:

$$PSCl_2F + C_6H_5-ONa \rightarrow C_6H_5-OPSClF + NaCl$$

## EXPERIMENTAL

Absolute solvents and anhydrous reagents were used in all cases except for the reaction with aqueous sodium phenolate. During the course of the experiments the necessary precautions were taken to protect the reagents and the product from moisture.

*O-Alkylphosphorodifluoridothioates.* A mixture of 15 g. (0.11 mole) of phosphorus thiochlorodifluoride (or the equivalent amount of phosphorus thiofluoride or phosphorus thiobromodifluoride) and 100 ml. of ether was stirred and cooled in a Dry Ice-acetone bath to −78°. To the cool solution 20 ml. ether solution of 0.1 mole of alcohol and 8.3 g. (0.105 mole) of pyridine was added dropwise. During the addition the temperature of the reaction mixture did not rise above −60°. Then the reaction mixture was allowed to reach room temperature while the stirring was continued. The pyridine hydrochloride, which had precipitated, was filtered off by suction and washed with 15 ml. ether. On distilling the combined filtrates, the solvent was removed first, then the crude product which remained was fractionated. In the case of the alkylphosphorodifluoridothioates prepared from *t*-butyl and cyclohexyl alcohols, the fractionation was carried out in vacuum. The yields and some physical and analytical data of the pure compounds may be found in Table I.

*O-Arylphosphorodifluoridothioates.* To a solution of 15 g. (0.11 mole) of phosphorus thiochlorodifluoride (or the equivalent amount of phosphorus thiofluoride or phosphorus thiobromodifluoride) and 0.1 mole of the corresponding phenol in 100 ml. of toluene, 8.3 g. (0.105 mole) of pyridine in 30 ml. of toluene was added dropwise while stirring and cooling the mixture with Dry Ice-acetone. The temperature of the reaction mixture did not exceed −50° during the addition. While the stirring was continued, the reaction mixture was allowed to come to room temperature and to stand 2 hr. until completion of the reaction. The work up of the products followed a procedure analogous to that mentioned above for alkylphosphorodifluoridothioates. The yields and physical and analytical data of the compounds obtained are shown in Table I.

*O-Arylphosphorochlorofluoridothioate.* To a solution of 16.7 g. (0.11 mole) of phosphorus thiodichlorofluoride in 20 ml. of benzene a solution of 94 g. (0.1 mole) of the corresponding phenol in 30 ml. benzene was added. Then to the resulting mixture 7.9 g. (0.1 mole) of pyridine diluted with 20 ml. of benzene was added dropwise at room temperature with water cooling and stirring. The reaction mixture was kept for an additional half hour at room temperature and then for another half hour at 40° in order to complete the reaction. The pyridine hydrochloride precipitate was filtered with suction and washed with benzene. The combined filtrates were fractionated *in vacuo* after removal of the benzene at atmospheric pressure. The yields of compounds and their physical and analytical data are given in Table I.

Using dimethylaniline as the acid binding agent a yield of 74%, with triethylamine 81%, of *O*-phenylphosphorochlorofluoridothioate was obtained. In the case of dimethylaniline, the hydrochloride was difficult to filter and was therefore removed by washing with water.

*Preparation of O-phenylphosphorochlorofluoridothioate with aqueous sodium phenolate.* A solution of 9.4 g. (0.1 mole) of

phenol in 82 ml. of 5% aqueous sodium hydroxide was added dropwise to 16.7 g. (0.11 mole) of phosphorus thiodichlorofluoride with shaking and water-cooling. The reaction mixture was stirred for an additional half hour and then allowed to stand at room temperature. The oil which separated was dissolved in 50 ml. of benzene and washed with 1.5% aqueous sodium hydroxide solution until neutral. The benzene phase was dried over sodium sulphate, then the solvent was removed and the residual liquid fractionated in vacuo. Phenylphosphorochlorofluoroidothioate, $n_D^{20} = 1.5298$, was obtained between 60–61°/5 mm. in 62% yield.

*Anal.* Calcd. Cl, 16.83; F, 9.02. Found: Cl, 16.45; F, 9.05.

SARNIA, ONT., CANADA

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE GEORGIA INSTITUTE OF TECHNOLOGY]

# Methylene Derivatives as Intermediates in Polar Reactions. XX. The Reactions of Aqueous and Alcoholic Base with Chlorodifluoromethane and Difluoroiodomethane[1]

JACK HINE AND ARTHUR D. KETLEY

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We have reinvestigated a report that with 15% potassium hydroxide in ethanol for forty-eight hours at 35°, chlorodifluoromethane, chlorodifluoroiodomethane, and difluoroiodomethane gave no reaction, 24% chlorodifluoromethane, and 19% difluoromethane, respectively. It was found that chlorodifluoromethane reacts essentially completely with ethanolic potassium hydroxide within a few minutes and that difluoroiodomethane yields no more than 5%, if any, difluoromethane. Rate constants were determined for the reaction of difluoroiodomethane with hydroxide ion in aqueous solution. From the results obtained it appears that the reaction is initiated by a concerted $\alpha$-dehydroiodination to yield difluoromethylene directly in one step.

Haszeldine has reported that chlorodifluoromethane is stable to the action of 15% potassium hydroxide in 95% ethanol for forty-eight hours at 35°,[2] and that under the same conditions chlorodifluoroiodomethane yields 24% chlorodifluoromethane and that difluoroiodomethane yields 19% difluoromethane. Our observations that chlorodifluoromethane is quite reactive toward aqueous alkali,[3] sodium methoxide[4] and potassium isopropoxide[5] caused us to doubt the first two reports. For the latter two reported reactions the mechanisms

$$CClF_2I \xrightarrow{OH^-} CClF_2^- \xrightarrow{\text{solvent}} CHClF_2$$

and

$$CHF_2I \xrightarrow{OH^-} CHF_2^- \xrightarrow{\text{solvent}} CH_2F_2$$

were suggested.[2] In view of our evidence that attempts to generate the chlorodifluoromethyl anion instead bring about the concerted formation of the intermediate difluoromethylene and thence its reaction products,[3,6] the reaction reported for chlorodifluoroiodomethane seemed improbable, and in view of our observation that $\alpha$-fluorine is the least effective of the $\alpha$-halogen substituents at facilitating carbanion formation[7] we doubted the formation of a methylene halide reported from difluoroiodomethane (but not chlorofluoroiodomethane nor fluorodiiodomethane). We have therefore reinvestigated some of these points and also carried out some related experiments of interest.

## RESULTS AND DISCUSSION

When solutions of chlorodifluoromethane and potassium hydroxide in ethanol are mixed at 35°, a copious precipitate of potassium chloride is formed within minutes. Titrations revealed that the theoretical amount of chloride ion (± 5%) was formed within 5 minutes. This observation makes the report of a 24% yield of chlorodifluoromethane formed (from chlorodifluoroiodomethane) after 48 hours in ethanolic potassium hydroxide[2] difficult to understand.

The volatile products of the reaction of difluoroiodomethane with ethanolic potassium hydroxide were studied in a number of runs. Fluoroform, ethyl difluoromethyl ether, and varying amounts of starting materials were found, but no clear evidence for methylene fluoride formation could be obtained. Experiments with authentic methylene fluoride showed that not more than about 5% could have been formed and remained undetected.

In order to learn more about the mechanism of the reaction of difluoroiodomethane with base the kinetics of the reaction with aqueous sodium hydroxide were studied. This haloform proved to be

(1) This work was supported in part by the U. S. Atomic Energy Commission. For the preceding article in this series see J. Hine, A. D. Ketley, and K. Tanabe, *J. Am. Chem. Soc.*, in press.

(2) R. N. Haszeldine, *J. Chem. Soc.*, 4259 (1952).

(3) J. Hine and P. B. Langford, *J. Am. Chem. Soc.*, **79**, 5497 (1957).

(4) J. Hine and J. J. Porter, *J. Am. Chem. Soc.*, **79**, 4493 (1957).

(5) J. Hine and K. Tanabe, *J. Am. Chem. Soc.*, **80**, 3002 (1958).

(6) J. Hine and D. C. Duffey, *J. Am. Chem. Soc.*, **81**, 1131 (1959).

(7) J. Hine, N. W. Burske, M. Hine, and P. B. Langford, *J. Am. Chem. Soc.*, **79**, 1406 (1957).

the most reactive that has been studied[8] and for this reason and its relatively volatile character the rate constants obtained, particularly at the higher temperatures, are less reliable than most of those reported previously. The second-order rate constants observed are $(0.96 \pm 0.08) \times 10^{-2}$, $(6.0 \pm 0.4) \times 10^{-2}$, and $(51.8 \pm 4) \times 10^{-2}$ (all in l. mole$^{-1}$ sec.$^{-1}$) at 0°, 21.2° and 40°, respectively. Thus difluoroiodomethane is about one thousand times as reactive toward hydroxide ion in aqueous solution as is methyl iodide[9] at the temperatures we have employed. As one $\alpha$-fluoro substituent has been found to *decrease* the $S_N2$ reactivity of methyl halides,[10] the reaction of difluoroiodomethane seems to be much too rapid to be proceeding by the $S_N2$ mechanism, and therefore more probably involves a dihalomethylene intermediate. Although the rate of carbanion formation that would be expected for difluoroiodomethane cannot be predicted very precisely, from the data obtained on related compounds[7,8,11] it does not seem probable that the rate constant in water at 0° would be greater than about $10^{-3}$ l. mole$^{-1}$ sec.$^{-1}$ Thus, as difluoroiodomethane hydrolyzes faster than it would be expected to form carbanions, it hydrolyzes by a concerted mechanism in which there is no carbanion intermediate, but in which difluoromethylene is formed in a single step, as proposed earlier for bromodifluoromethane and chlorodifluoromethane.[3]

## EXPERIMENTAL

*Difluoroiodomethane.* When mercuric fluoride was allowed to react with iodoform in the manner described previously in the preparation of fluorodiiodomethane,[11] about a 30% yield of difluoroiodomethane, b.p. 21–22°, was obtained from liquid collected in a Dry-Ice trap at the end of the system and from the forerun of the fluorodiiodomethane distillation. Ruff reported a boiling point of 21.6° for the compound.[12] Some material was also made by the reaction of mercuric fluoride with fluorodiiodomethane.

*Reactions of chlorodifluoromethane.* Chlorodifluoromethane[13] was bubbled into 95% ethanol at room temperature to prepare a solution. When this solution at 35° was added to an equal volume of 15% ethanolic potassium hydroxide at the same temperature, a copious precipitate of potassium chloride began to form within a minute or two. After 10 min. the chloride formed from 10 ml. of the haloform solution was found to require 10.4 ml. of 0.0579*M* silver nitrate solution for titration. Another 10-ml. sample from the same solution was found to require 10.9 ml. of the silver nitrate solution after 1020 minutes.

*Reaction of difluoroiodomethane.* In a typical reaction with alcoholic potassium hydroxide, 1.0 ml. of difluoroiodomethane was added to 100 ml. of 15% potassium hydroxide in 95% ethanol in an apparatus designed to capture any gaseous products. A vigorous reaction immediately ensued and the infrared spectrum of the gaseous products, including those given off after the reaction solution was heated to boiling, revealed the presence of only fluoroform, ethyl difluoromethyl ether, and a little unchanged difluoroiodomethane. Because of similarities in absorption spectra, a little methylene fluoride could have escaped detection but not enough to account for more than a 5% yield. Separate experiments on methylene fluoride showed that under the reaction condition used it would not have been decomposed and it would have been evolved as a gas from the reaction solution.

*Kinetic runs.* The kinetics of reaction of difluoroiodomethane with hydroxide ion in aqueous solution were studied by a method like that described previously for bromodifluoromethane.[3] In a run at 0.0°, the first and sixth samples of haloform solution taken were found, by reaction with excess alkali, to be 0.04110 and 0.04080*N* in haloform. It was assumed that the haloform concentration in the other samples varied linearly in the order that the samples were taken. The data obtained in this run are listed in Table I. In most of the other runs made the rate constants fell to a greater or smaller extent than those given in Table I. We do not know the reason for this fall, but its existence suggests that the average rate constant may be less reliable than indicated by the average deviation. Because of the speed of the reaction and the volatility of the haloform, the rate constants obtained at higher temperatures may be even less reliable.

TABLE I

REACTION OF DIFLUOROIODOMETHANE WITH AQUEOUS SODIUM HYDROXIDE AT 0.0°

| Time (sec.) | $N^a$ $CHF_2I$ | $[NaOH]_t^b$ | 100 k |
|---|---|---|---|
| 507 | 0.04104 | 0.00785 | 1.130 |
| 801 | 0.04098 | 0.00712 | 1.032 |
| 1127 | 0.04092 | 0.00657 | 0.923 |
| 1500 | 0.04086 | 0.00578 | 0.924 |
| 2000 | 0.04074 | 0.00500 | 0.895 |
| 2880 | 0.04068 | 0.00405 | 0.830 |
| | | Average | 0.956 ± 0.084 |

[a] The normality of haloform is 3 + f times the molarity. [b] $[NaOH]_0 = 0.00987$.

ATLANTA, GA.

(8) J. Hine and S. J. Ehrenson, *J. Am. Chem. Soc.*, **80**, 824 (1958).

(9) E. A. Moelwyn-Hughes, *Proc. Roy. Soc.* (*London*), **A196**, 540 (1949).

(10) J. Hine, C. H. Thomas, and S. J. Ehrenson, *J. Am. Chem. Soc.*, **77**, 3886 (1955); J. Hine, S. J. Ehrenson and W. H. Brader, Jr., *J. Am. Chem. Soc.*, **78**, 2282 (1956).

(11) J. Hine, R. Butterworth, and P. B. Langford, *J. Am. Chem. Soc.*, **80**, 819 (1958).

(12) O. Ruff, *Ber.*, **69**, 299 (1936).

(13) The material used has been described previously.[4]

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

# The Claisen Rearrangement. III. Benzyl 2-Propenyl-4,6-dimethylphenyl Ether[1]

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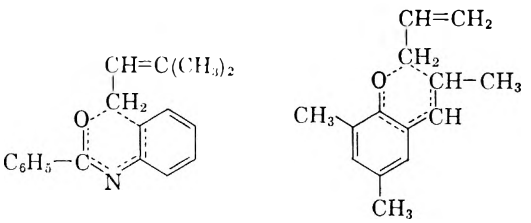
Benzyl 2-propenyl-4,6-dimethylphenyl ether has been synthesized and its behavior at temperatures up to 210° has been studied. At 135–150° the ether starts to polymerize but shows no tendency to form phenolic products. Between 180–210° the formation of phenolic materials is evident. One liquid phenolic compound was isolated and identified as 2-(2-benzylpropyl)-4,6-dimethylphenol. This identification was confirmed by synthesis.

Since Claisen's discovery[2] of the thermally initiated rearrangement of *O*-allyl ethers to C-allyl derivatives a host of investigators have accumulated a large body of knowledge much of which serves to delineate the scope of the reaction. Claisen thus found[3] that allyl 2-propenyl-4,6-dimethylphenyl ether undergoes thermal conversion to a phenolic compound to which he assigned the structure, 1-(2-hydroxy-3,5-dimethylphenyl)-2-methylpenta-1,4-diene. Recently Lauer and Wujciak[4] proved the structure of the product of this rearrangement and showed further that an appropriately substituted allyl group appears in uninverted form in the product. Schmid, Fahrni, and Schmid,[5] using $C^{14}$, showed that a small fraction (*circa* 16%) of the product contained the allyl group in inverted form. As they found the process to be strictly intramolecular, they proposed an eight-membered ring transition state to account for the inverted product.

The bulk of the rearrangment product can be nicely accommodated by the widely-accepted double-cycle mechanism for the *para* rearrangement.[6] However, an alternative mechanism involving only the *alpha* carbon of the allyl group was suggested by Lauer[7] to account for the rearrangement of *O*-($\gamma,\gamma$-dimethylallyl)benzanilide, and reiterated in his discussion of the side chain rearrangement.[4] Although this is indeed a particularly attractive possibility, considering the economy




of atomic motion achieved thereby, it is less attractive geometrically. Thus the bonding of the alpha carbon in the transition state must involve the *p* orbital lobes used by the central carbon in an $S_N2$ substitution, *i.e.* the oxygen atom, *alpha* carbon of the allyl group, and *beta* carbon of the propenyl side chain should preferentially occupy a linear arrangement.

In light of the above discussion it was advisable to submit the possibility of the single cycle mechanism to experimental test. Unfortunately the most useful test of mechanism devised previously, that of inversion of the allyl group or lack of it, is not applicable in this case. Of the several possible tests we were able to devise, the simplest capitalized upon the fact that in a benzyl ether the *alpha* carbon is completely analogous to the *alpha* carbon of the allyl group but the *gamma* carbon is not. Thus the benzyl ether is not able to undergo the conventional Claisen rearrangement.[8] While benzyl ethers do indeed rearrange under a more drastic thermal impetus[9] or under free radical initiation,[10] it was felt that under the usual conditions a benzyl ether should not undergo the double cycle rearrangement. Conversely if the single cycle process were operable, the rearrangement should proceed normally with the benzyl ether.

The benzyl ether was prepared from the known[3] 2-propenyl-4,6-dimethylphenol using the sodium salt of the phenol in methanol and benzyl chloride. Although the resultant ether, a yellow oil, could not be distilled unchanged under normal vacuum distillation at 0.1–1 mm. pressures, it was distilled readily without decomposition *via* molecular distillation. However, the distilled material was

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(2) L. Claisen, *Ber.* **45**, 3157 (1912).

(3) L. Claisen and E. Tietze, *Ann.* **449**, 81 (1926).

(4) W. Lauer and D. Wujciak, *J. Am. Chem. Soc.* **78**, 5601 (1956).

(5) K. Schmid, P. Fahrni, and H. Schmid, *Helv. Chim. Acta*, **39**, 708 (1956).

(6) *Cf.* S. J. Rhoads, and R. L. Crecelius, *J. Am. Chem. Soc.* **77**, 5057 (1955) and W. Haegele and H. Schmid, *Helv. Chim. Acta*, **40**, 13,255 (1957) for a discussion of this mechanism.

(7) W. Lauer and R. Lockwood, *J. Am. Chem. Soc.* **76**, 3974 (1954).

(8) S. G. Powell and R. Adams, *J. Am. Chem. Soc.* **42**, 646 (1920) L. Claisen, F. Kremers, F. Roth, and E. Tietze, *Ann.* **442**, 210 (1925).

(9) O. Behagel and H. Freiensehner, *Ber.* **67**, 1368 (1934).

(10) M. Kharasch, G. Stampa, and W. Nudenberg, *Science*, **116**, 309 (1952).

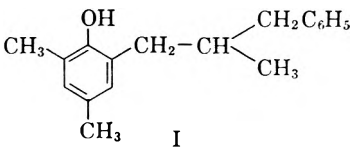
still a light lemon yellow and was therefore carefully chromatographed on alumina. There were obtained thereby two distinct fractions, the first a colorless mobile oil and the second a viscous yellow liquid. The colorless oil was rechromatographed, taken up in petroleum ether and extracted with Claisen's alkali and after removal of the solvent distilled again *via* molecular distillation. This product shows infrared bands at 973 and 1648 cm.$^{-1}$ (disubstituted double bond in *trans* form), 1378 cm.$^{-1}$ (C-$CH_3$), 1218 cm.$^{-1}$ (Ar—O—$CH_2$), 856 cm.$^{-1}$ (tetrasubstituted benzene ring) and 732 and 696 cm.$^{-1}$ (monosubstituted benzene ring.) It absorbed exactly two moles of hydrogen and the phenolic product obtained from the reaction mixture showed an infrared spectrum identical with that of an authentic sample of 2-propyl-4,6-dimethylphenol. We believe the structure of the starting material is thoroughly established by this data. The composition of the yellow liquid is now under investigation.

An attempt made to find the mildest possible condition for rearrangement disclosed that at temperatures as low as 135° the ether formed a thick gel, growing a deep yellow in the process. No hydroxyl absorption was noted even after prolonged heating at this temperature. This presumed polymerization has not been further studied.

Not until the temperature reaches 180° does any reaction productive of phenolic material set in. All runs for study of the phenolic products were made at 200–210° where the formation of these materials was rapid enough to provide sufficient base soluble material before polymerization made the product unmanageable. The benzyl ether was free of peroxide as indicated by starch-iodide test and free radical reactions were minimized by carrying out the reaction in the dark under oxygen-free nitrogen.

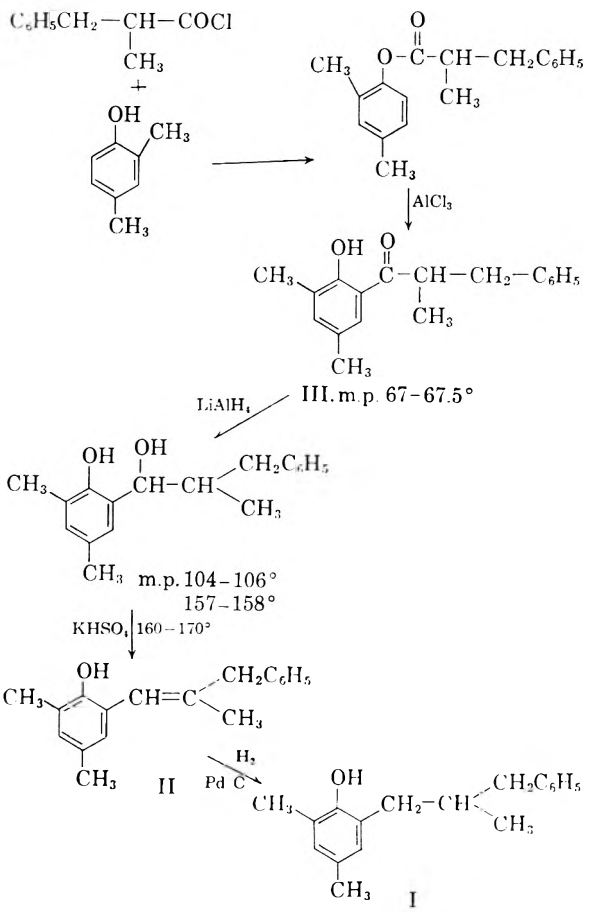
There was obtained by extraction of the heated material with Claisen's alkali about 20% of a phenolic substance, whose hydroxyl group was sufficiently hindered to render it insoluble in 6*N* aqueous alkali. This substance, a viscous clear liquid, b.p. 132–134° (0.15 mm.), $n_D^{20}$ 1.5567, showed a refractive index below that, $n_D^{25}$, 1.5710, of the starting material and did not add bromine. This evidence which suggested loss of the side chain double bond was confirmed by the infrared spectrum. This latter showed bands at 3600 cm.$^{-1}$ (absorption slowly tapering off on the low frequency side) characteristic of a hindered hydroxyl, 1605 and 1490 cm.$^{-1}$ (an aromatic ring), 1375 cm.$^{-1}$ (C-$CH_3$ groups), 859 substituted benzene ring) and 738 and 698 cm.$^{-1}$ (a monosubstituted benzene ring). No absorption appeared in the regions from 810–840 cm.$^{-1}$ or 1640–1660 cm.$^{-1}$—characteristic of trisubstituted double bonds.

As the basic skeleton contains both a tetrasubstituted and a monosubstituted benzene ring, the hydroxyl group is present and more heavily hindered than the hydroxyl in 2-propenyl-4,6-dimethylphenol, and as no double bond is present in the side chain, the compound isolated was assigned the structure 2-(2-benzylpropenyl)-4,6-dimethylphenol (I). The correctness of this proposal



I

was verified by a synthesis of this molecule by the route shown in the attached sequence. Thus 2,4-dimethylphenyl α-methyldihydrocinnamate was prepared from the acid chloride of the known[11] α-methyldihydrocinnamic acid. This ester was submitted to the Fries rearrangement to give a




mediocre yield of a solid ketone assigned the structure III. The migratory group was placed in the six position because the product shows strong evidence of chelation, in that a dilute solution in cetane shows no other carbonyl band than one at 1640 cm.$^{-1}$, which can only be attributed to a strongly hydrogen-bonded conjugated carbonyl.[12] The evidence in favor of this interpretation is

(11) F. S. Kipping and A. E. Hunter, *J. Chem. Soc.* **83**, 1005 (1903).

(12) M. Flett, *J. Chem. Soc.* 1441 (1948).

strengthened by the appearance of the hydroxyl band in the region of C–H stretching, 3000–3100 cm.$^{-1}$, indicative of a strong hydrogen bond.

Reduction of the ketone gave a nearly quantitative yield of alcohol, m.p. 105–154°. After separation of the diastereomers *via* chromatography on silicic acid and repeated crystallization from benzene-hexane there were obtained two isomeric alcohols, m.p. 104–106° (27%) and 157–158° (43%). The infrared spectra showed two hydroxyl bands, one at 3480, the other at 3360 cm.$^{-1}$ for the higher melting isomer and 3600 and 3360 cm.$^{-1}$ for the lower. Neither shows absorption near 1640 cm.$^{-1}$. Either isomer on dehydration gave the same olefin, 2-(2-benzylpropenyl)-4,6-dimethylphenol (II). This substance, the expected product of the single cycle rearrangement process, showed infrared bands at 805 cm.$^{-1}$ and 1645 cm.$^{-1}$, characteristic of conjugated trisubstituted double bonds, as well as more complex C-H bending absorption in the 1480–1440 cm.$^{-1}$ region, and a doublet at 1300, 1320 cm.$^{-1}$ which serve to differentiate it effectively from the product actually isolated.

This olefin absorbs one mole of hydrogen when treated with hydrogen over palladium-on-charcoal at room temperature. The final product and that isolated from the thermal treatment of the benzyl ether show identical physical constants and infrared spectra. This unexpected product does not arise as a result of heating substance II under the rearrangement conditions, for such treatment failed to alter the refractive index of II appreciably and the infrared spectrum also indicated that no serious changes had occurred. It is apparent therefore that this saturated but rearranged material must arise during the thermal treatment of the ether itself.

Of course, this interesting and highly intriguing result negates the possibility of answering the question which prompted this study. Further work is needed before the means by which the benzyl group is transferred from the oxygen to the carbon atom can be made apparent. Published speculation on that process seems unwarranted at present.

## EXPERIMENTAL[13]

*Benzyl 2-propenyl-4,6-dimethylphenyl ether.* A 49% yield of 2-propenyl-4,6-dimethylphenol, m.p. 72–73°, was obtained for the three-step synthesis of Claisen and Tietze[3] from 2,4-dimethylphenol. A freshly prepared solution of sodium methoxide, 7.1 g. (0.31 mole) of sodium in 150 ml. of absolute methanol, was mixed with 50 g. (0.31 mole) of 2-propenyl-4,6-dimethylphenol. To the boiling solution was added 39 g. (0.31 mole) of benzyl chloride over a 20 min. period. The solution was boiled for an additional 3 hr. After being allowed to cool, the solution was mixed with 30–60° petroleum ether and exhaustively extracted with Claisen's alkali. The petroleum ether solution was dried over anhydrous sodium sulfate, the solvent removed initially by distillation at atmospheric pressure, and completed *in vacuo* at 100° for 2 hr. The crude ether, 70.5 g. (78%), was a mobile light yellow liquid, $n_D^{20}$ 1.5711, $d_{23}^{25}$ 1.0395.

The crude ether was distilled in a Hickman molecular still at a bath temperature of 70–80° at $10^{-6}$ mm. pressure. The distillate was a mobile lemon yellow liquid which was chromatographed on activity II–III alumina (Woelm) using petroleum ether as eluant. The first eluate was a colorless liquid which was taken up in petroleum ether, extracted with Claisen's alkali, dried over anhydrous magnesium sulfate and redistilled in the molecular still. This substance had infrared bands at 696, 732, 856, 973, 1217, 1378, and 1648 cm.$^{-1}$. It showed no absorption in the 1650–1800 or 3100–3600 cm.$^{-1}$ regions. It had an $n_D^{25}$ 1.5710 and $\lambda_{max}$ 252 mm. $\epsilon$ = 11,300.

*Anal.* Calcd. for $C_{18}H_{20}O$: C, 85.71; H, 7.93. Found: C, 85.64; H, 7.89. A second eluate, a thick deep yellow oil, was obtained but was not further investigated.

The colorless material was hydrogenated over 10% palladium-on-carbon in glacial acetic acid under atmospheric pressure. Absorption ceased after 2 moles of hydrogen were absorbed. Most of the acetic acid was removed *via* evaporation under reduced pressure after removal of the catalyst. The product was taken up in petroleum ether, washed with water, and the resulting phenolic material removed by extraction with 6*N* NaOH. After acidification of the basic extracts the phenol was isolated as usual and distilled in vacuo b.p. 90–95° (1.5 mm.), $n_D^{25}$ 1.5193. The infrared spectrum of this product was identical with that of an authentic sample of 2-propyl-4,6-dimethylphenol prepared from 2-allyl-4,6-dimethylphenol[3] by hydrogenation as above.

*Rearrangement.* The above ether was heated under reflux (135°) at 0.01 mm. pressure for 8 hr. The very viscous, deep-red resultant material showed no absorption at 3200–3600 cm.$^{-1}$. Another sample (14.59) of the ether was heated in the dark under oxygen-free nitrogen at 200–210° (bath temperature) for 6 hr.

The residual material (12.0 g.) was taken up in petroleum ether and extracted with several portions of 6*N* aqueous sodium hydroxide followed by Claisen's alkali. Each of the combined extracts was acidified and extracted with petroleum ether. Upon evaporation of the solvent, no product was obtained from the 6*N* alkali extract and 2.8 g. (19%) of a clear viscous liquid, b.p. 132–134° (0.15 mm.), $n_D^{22}$ 1.5570 was obtained from the Claisen's alkali extract. This substance showed notable infrared bands at 698 and 738, 859, 1375, 1490, and 1605, and 3600 cm.$^{-1}$.

From the original petroleum ether solution there was recovered, after the base extractions, 9.2 g. (63%) of a neutral polymer. This was not further investigated.

*2,4-Dimethylphenyl α-methyldihydrocinnamate.* α-Methyldihydrocinnamic acid was prepared by conventional alkylation of diethyl methylmalonate with benzyl chloride followed by basic hydrolysis in 80% aqueous ethanol and decarboxylation at 180–200°. The yield of acid, b.p. 150–152° (8 mm.), $n_D^{21}$ 1.5142, $d_4^{22}$ 1.0644, $M_D$ calcd. 46.54, found 46.32 was 62% from methyl malonate. The literature[11] gives b.p. 160° (12 mm.) for this acid.

A 44-g. (0.27 mole) sample of this acid was treated at 40° with 64 g. (0.54 mole) of thionyl chloride. After 14 hr. the mixture was heated to reflux for 2 hr. The acid chloride was isolated by distillation, b.p. 116–117° (10 mm.), $n_D^{22}$ 1.5162, yield 47.2 g. (96%).

To a solution containing 85.5 g. (0.70 mole) of 2,4-dimethylphenol in 1 l. of dry benzene, 118 g. (0.65 mole) of the acid chloride was added dropwise over a period of 1 hr. The mixture was heated under reflux for 3 hr. The reaction mixture was washed with water and dilute sodium bicarbonate and then dried. The ester was isolated by distillation, b.p. 146–147° (0.5 mm.), $n_D^{23}$ 1.5372, $d_{23}^{26}$ 1.0437, 148.5 g. (86%) as a clear oily liquid.

*Anal.* Calcd. for $C_{18}H_{20}O_2$: C, 80.59; H 7.46. Found: C, 80.65; H, 7.44. $M_D$ Calcd. 79.79; found 80.16.

(13) Analyses by Drs. Weiler and Strauss, Oxford, England. The authors are indebted also to Baird Atomic, Inc. and the Shell Oil Company for infrared spectra.

This ester shows strong absorption at 1760 cm.$^{-1}$, the high frequency being characteristic of phenolic esters.[14]

*2-(1-Oxo-2-benzylpropyl)-4,6-dimethylphenol.* A mixture of 107 g. (0.4 mole) of the above ester and 160 g. (1.21 moles) of anhydrous aluminum chloride was allowed to stand 20 hr. at room temperature. It was then heated on a steam bath for 2 hr. with vigorous stirring. After hydrolysis of the complex with cold conc. hydrochloric acid, the desired ketone was isolated by filtration and recrystallized from 90% ethanol, m.p. 67–67.5°, yield 43 g. (40%).

*Anal.* Calcd. for $C_{18}H_{20}O_2$: C, 80.59; H, 7.46. Found: C, 80.37; H, 7.37. An infrared band at 1640 cm.$^{-1}$ characteristic of a strongly hydrogen-bonded conjugated ketone[12] was exhibited by this material in cetane solution.

*2-(1-Hydroxy-2-benzylpropyl)-4,6-dimethylphenol.* The ketone prepared above, 11.0 g. (0.041 mole), was added dropwise to a solution containing 0.9 g. (0.024 mole) of lithium aluminum hydride in 200 ml. of dry ether. After destruction of excess lithium aluminum hydride the mixture was poured on iced 10% sulfuric acid. The ether layer was separated and the aqueous layer was extracted twice with 100-ml. portions of ether. The combined extracts were washed with dilute ammonia, then with water until neutral, and dried. Evaporation of the ether left 10.8 g. (98%) of a crystalline alcohol, m.p. 105–154°. The mixture of diastereomers was separated by crystallization from a 50-50 benzene-hexane mixture. The pure high-melting isomer was obtained from a chloroform eluate from a silicic acid column. It crystallized as fine silky needles, m.p. 157–158°, 4.7 g. (43%).

*Anal.* Calcd. for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15. Found: C, 80.20; H, 8.12.

This isomer showed two partly overlapping bands in the OH stretching region at 3360 and 3480 cm.$^{-1}$. No band in the region around 1640 cm.$^{-1}$ was observed.

The low melting isomer crystallized as compact crystals, m.p. 104–106°, 3.1 g. (28%) after repeated crystallization from benzene. It showed two well resolved bands in the infrared at 3600 and 3360 cm.$^{-1}$.

*Anal.* Calcd. for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15. Found: C, 80.05; H, 8.21.

*2-(2-Benzylpropenyl)-4,6-dimethylphenol.* A mixture of 1.2 g. (0.0044 mole) of 2-(1-hydroxy-2-benzylpropyl)-4,6-dimethylphenol, m.p. 157–158°, and 1.5 g. of freshly fused potassium acid sulfate was heated at 160–170° for 30 min. The product was isolated by ether extraction and purified by distillation, b.p. 124–125° (0.15 mm.), $n_D^{21}$ 1.5795, $d_{23}^{25}$ 1.0267, 0.96 g. (86%).

*Anal.* Calcd. for $C_{18}H_{20}O$: C, 85.71; H, 7.93. Found: C, 86.09; H, 8.12.

$M_D$: Calcd.: 79.18. Found: 80.21.

Similar dehydration of the alcohol, m.p. 104–106°, gave 96% yield of a product with identical physical properties and infrared spectrum. Both samples showed absorption at 805 cm.$^{-1}$ and 1645 cm.$^{-1}$ characteristic of a double bond and lacked the doublet in the O—H stretching region.

*2-(2-Benzylpropyl)-4,6-dimethylphenol.* A solution of olefin in glacial acetic acid was reduced at room temperature and atmospheric pressure over palladium-on-charcoal. One mole of hydrogen was absorbed. The solution was poured into water and the product extracted with petroleum ether. The reduced material was isolated in high yield by distillation under reduced pressure. Both the physical properties and infrared spectra were identical with those of the phenolic product from the reaction of the benzyl ether.

*Anal.* Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.70. Found: C, 85.2; H, 8.84.

CORVALLIS, ORE.

(14) J. F. Grove and H. A. Willis, *J. Chem. Soc.* 877 (1951).

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

# Polarographic Reduction of Some Biaryls and Arylalkenes[1,2]

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Polarographic half-wave reduction potentials of twenty-seven aromatic hydrocarbons (including fifteen conjugated alkenylnaphthalenes, the phenylnaphthalenes, the phenylanthracenes, and the binaphthyls) were obtained under comparable conditions in a solvent-electrolyte mixture of 0.1*M* tetra-*n*-butylammonium iodide in 75% dioxane-water. In general, among isomeric compounds, the facility of reduction is found to increase with lessened steric restriction to the attainment of coplanarity in the molecule. Notable exceptions to this rule are found in the cases of the vinyl- and cyclopentenylnaphthalenes, where the 1-naphthyl isomers are reduced at slightly less negative potentials than the sterically less-hindered 2-isomers. Results are interpreted in terms of angles of twist present in the substrate molecules at the time of electron addition (transition state) and inherent conjugative powers of the alkenyl and aryl moieties. Coulometric data are reported for seven compounds.

The polarographic reducibilities of styrene[4] and biphenyl[5] are considered manifestations of the general phenomenon of conjugation inasmuch as the $\pi$-electronic systems, as present in benzene and ethylene,[6] are not similarly reducible. In general, one might anticipate that the electroreducibility of any biaryl or arylalkene would depend on at least three inherently different (but closely associated) factors, *viz.* (a) the conjugative powers

(1) Abstracted (in part) from the Ph.D. dissertation of C. D. Lind, University of Oregon, June, 1956. This research was supported in part by a grant from The Petroleum Research Fund administered by the AMERICAN CHEMICAL SOCIETY and in part through sponsorship by the Office of Ordnance Research, U. S. Army, contract no. DA-04-200-ORD-176. Grateful acknowledgment is hereby made to these donors.

(2) Presented (in part) at the Northwest Regional Meeting of the AMERICAN CHEMICAL SOCIETY, Spokane, Washington, June, 1957. Paper XI in the series on Chemical Reactivities of Arylcycloalkenes. For paper X see ref. 15.

(3) Research Associate, 1957–1958.

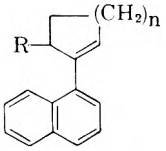
(4) H. A. Laitinen and S. Wawzonek, *J. Am. Chem. Soc.*, 64, 1765 (1942).

(5) S. Wawzonek and H. A. Laitinen, *J. Am. Chem. Soc.*, 64, 2365 (1942).

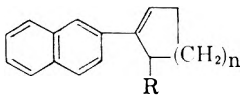
(6) M. v. Stackelberg, *Polarographische Arbeitsmethoden*, W. de Gruyter and Co., Berlin, 1950, pp. 210–211.

of the aryl and alkenyl moieties, (b) the angle of twist in the molecule, and (c) steric hindrance to approach of the substrate to the mercury cathode. This paper reports the results of experiments employing comparable procedures for all compounds used and designed particularly to investigate the influences of factors (a) and (b).

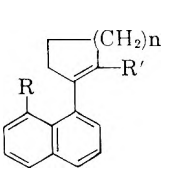
For this study fifteen conjugated naphthylalkenes, the phenylnaphthalenes, the binaphthyls, and the phenylanthracenes (as well as some parent arenes and alkylarenes used for comparison) were reduced polarographically in an electrolyte consisting of 0.1*M* tetra-*n*-butylammonium iodide in 75% dioxane-water. Data for these compounds are recorded in Table I, examination of which shows that some compounds exhibit only one reduction wave while others exhibit two. For each compound the decision on the number of such waves is based on the following criteria (listed in approximate order of priority): (1) visual appearance of the polarogram, especially where two clearly separated waves are observable, (2) numerical values of the diffusion current constants, and (3) coulometry on a semimicro scale. Criterion (2) was sometimes sufficiently definitive to differentiate between a *bona fide* single wave and two overlapping but visually unresolved waves by comparison with similar data from cases treated successfully by means of criterion (1). Coulometry was interpreted on the basis that ideally each wave for a naphthylalkene should involve two electrons. As justification for this latter interpretation it was found that both the single wave for naphthalene and the first wave (of two visually separated waves of equal height) for IV consumed two electrons. The criteria employed for each compound are noted in Table I. The coulometric procedure and results are discussed later in this paper.



IV. R = H, n = 1
VI. R = H, n = 2
VIII. R = H, n = 3
(XIIIa. R = $CH_3$, n = 1)[7]
XV. R = $CH_3$, n = 2



V. R = H, n = 1
VII. R = H, n = 2
IX. R = H, n = 3
XIV. R = $CH_3$, n = 1
XVII. R = $CH_3$, n = 2



XIII.[7] R = H, R′ = $CH_3$, n = 1
XVI. R = H, R′ = $CH_3$, n = 2
XVIII. R = $CH_3$, R′ = H, n = 1
XIX. R = $CH_3$, R′ = H, n = 2

From Table I, it is apparent that the facility of electroreduction increases with decreasing (average) angle of twist, $\theta$, in isomeric biaryls. Thus, one has the orders 2-phenylnaphthalene <1-phenylnaphthalene; 2,2′-binaphthyl <1,2′-binaphthyl <1,1′-binaphthyl; and 2-phenylanthracene < 1-phenylanthracene < 9-phenylanthracene both in $\theta$ and in $-E_{1/2}'$ (for the first or only wave). Such orders could be ascribed to differences in electrical polarizabilities of the substrate molecules and/or to steric hindrance to adsorption of such molecules on the cathode. Steric hindrance ought to be particularly significant if the transition complex for electroreduction involved a coplanar substrate adsorbed flatwise on the mercury surface. On the other hand these orders are inconsistent with expectations based on relative values of the conjugative power, $C_t$,[8] for the isomeric naphthyl and isomeric anthryl groups. Thus Badger, Pearce, and Pettit[9] and Braude and Gore[10] have summarized experimental results which indicate that $C_t$ for the 1-naphthyl group is greater than that for the 2-naphthyl group and the Pullmans[11] have noted that, in general, $C_t$ for any position on an aromatic hydrocarbon should vary directly with the free-valence number of the position. If, then, $C_t$ were a controlling factor in electroreducibility of these biaryls one would expect to find reverse orders (from those observed) in $-E_{1/2}'$ for all three sets of isomers. In this same regard the small differences in $E_{1/2}'$ between the pairs 9,9′-bianthryl–anthracene (XXVIII and XXIII) and rubrene-naphthacene (XXX and XXIX) have been ascribed[12] to a large deviation from coplanarity in the former member of each pair.

That $C_t$ is important, however, as a determinant of electroreducibility seems apparent if one selects

(7) The compound to which we now assign structure XIII is the same one as was previously designated by structure XIIIa. Structure XIIIa was proposed on the basis of chemical degradative studies (*cf.* ref. 21). On the other hand structure XIII (but not structure XIIIa) is consistent with the NMR spectrum of the substance (run in trideuterochloroform at 60 megacycles using tetramethylsilane as an internal standard, determined and interpreted through the courtesy of Mr. LeRoy Johnson of Varian Associates) which shows a very complex multiplet at *ca.* 450 cycles (aromatic hydrogens) and small spin splittings but no large doubling at *ca.* 91 cycles (methyl group attached to a carbon bearing no hydrogen) and lacks a signal at *ca.* 320 cycles (expected for a hydrogen on a doubly bonded carbon). Structure XIII is also preferred on the basis of the behavior of this compound in studies on rates of catalytic hydrogenation (L. H. Klemm and Roger Mann, unpublished).

(8) In a previous paper [L. H. Klemm, H. Ziffer, J. W. Sprague, and W. Hodes, *J. Org. Chem.*, 20, 190 (1955)] $C_t$ was called the "conjugative effect." The present nomenclature is consistent with that used in ref. 11.

(9) G. M. Badger, R. S. Pearce, and R. Pettit, *J. Chem. Soc.*, 1112 (1952).

(10) E. A. Braude and P. H. Gore, *J. Chem. Soc.*, 41 (1959).

(11) B. Pullman and A. Pullman, *Progress in Organic Chemistry*, Vol. 4, J. W. Cook, ed., Butterworths, London, 1958, Chap. 2, especially pp. 64–65. See also C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.*, 195A, 188 (1948).

(12) G. J. Hoijtink, *Rec. trav. chim.*, 74, 1525 (1955).

TABLE I

POLAROGRAPHIC DATA FOR SOME SUBSTITUTED NAPHTHALENES, ANTHRACENES, AND NAPHTHACENES

| Compound No. | Substituent(s) on Parent Substrate Molecule | Half-wave Reduction Potential[a] (in v. *vs.* S.C.E.) First Wave $-E_{1/2}'$ | Second Wave $-E_{1/2}''$ | $\frac{i_d}{cm.^{2/3}t^{1/6}}$ (in $\mu$-amp.-mmole$^{-1}$-l.-mg.$^{-2/3}$-sec.$^{1/2}$) First Wave | Second Wave | Criteria for Number of Waves[b] |
|---|---|---|---|---|---|---|
| | On Naphthalene | | | | | |
| I | None | — | 2.46 | — | 2.6 | V, D, C |
| II | 1-Vinyl | 2.09 | 2.52 | 2.5 | 2.6 | V, D |
| III | 2-Vinyl | 2.12–2.15[c] | 2.54 | 2.7–3.9[c] | 2.7 | V, D |
| IV | 1-(1-Cyclopentenyl) | 2.27 | 2.53 | 2.1 | 2.2 | V, C, D |
| V | 2-(1-Cyclopentenyl) | 2.30 | 2.55 | 2.1 | 3.4 | V |
| VI | 1-(1-Cyclohexenyl) | 2.46 | 2.56 | 1.7 | 1.9 | C[d] |
| VII | 2-(1-Cyclohexenyl) | 2.38 | 2.56 | 2.1 | 3.1 | V |
| VIII | 1-(1-Cycloheptenyl) | 2.41 | 2.52 | 1.9 | 2.0 | C, D[e] |
| IX | 2-(1-Cycloheptenyl) | 2.35 | 2.56 | 1.7 | 1.5 | V |
| X | 1-Cyclopentyl | — | 2.53 | — | 3.4 | V[e] |
| XI | 1-Phenyl | 2.40 | — | 2.5 | — | V,[e] D |
| XII | 2-Phenyl | 2.30 | 2.51 | 2.5 | 2.6 | V, D |
| XIII | 1-(2-Methyl-1-cyclopentenyl) | (2.42) | (2.50) | (1.3) | (1.3) | D[e,f] |
| XIV | 2-(5-Methyl-1-cyclopentenyl) | 2.37 | 2.50 | 1.7 | 1.4 | C[g] |
| XV | 1-(6-Methyl-1-cyclohexenyl) | 2.43 | 2.52 | 1.8 | 1.7 | D[d] |
| XVI | 1-(2-Methyl-1-cyclohexenyl) | (2.46) | (2.55) | (1.4) | (1.4) | D[e,f] |
| XVII | 2-(6-Methyl-1-cyclohexenyl) | 2.42 | 2.50 | 1.2 | 1.1 | C[e] |
| XVIII | 8-Methyl, 1-(1-cyclopentenyl) | 2.36 | 2.51 | 1.8 | 1.8 | V, D |
| XIX | 8-Methyl, 1-(1-cyclohexenyl) | (2.42) | (2.49) | (1.1) | (1.1) | D[e,f] |
| XX | 1-(1-Naphthyl) | 2.33[h] | 2.54 | —[i,j] | —[i,j] | V[k] |
| XXI | 1-(2-Naphthyl) | 2.24 | 2.47 | 1.1 | 2.3 | V |
| XXII | 2-(2-Naphthyl) | 2.17[l] | 2.47[m] | —[j,n] | —[j,n] | V |
| | On Anthracene | | | | | |
| XXIII | None | 1.96 | — | 1.9 | — | V[e] |
| XXIV | 1-Phenyl | 1.89 | ?[o] | 0.8 | — | V |
| XXV | 2-Phenyl | 1.87 | 2.58 | —[n] | —[n,p] | V |
| XXVI | 9-Phenyl | 1.92 | — | 1.8 | — | V[e] |
| XXVII | 9-Methyl | 1.94 | — | 2.1 | — | V[e] |
| XXVIII | 9-(9-Anthryl)[q] | 1.97 | 2.38 | 3.0 | 0.9 | — |
| | On Naphthacene | | | | | |
| XXIX | None[q] | 1.58 | 1.84 | — | — | — |
| XXX | 9,10,11,12-Tetraphenyl[q] | 1.55 | 1.80 | — | — | — |

[a] For a compound showing only one wave, the half-wave potential ($E_{1/2}$) is given under whichever column seems more appropriate. [b] V denotes visual observation of the polarogram; C, coulometry; D, diffusion current constant. [c] The shape of the curve and the high value for the diffusion current constant indicate that this wave may actually consist of two partly superimposed smaller waves—one a minor pre-wave of absolute value <2.09 and the other at −2.15 (diffusion current constant ≦ 2.7). Gas chromatography of III (conducted by Drs. G. H. Beaven and E. A. Johnson at the Medical Research Council Laboratories, London, England) showed the presence of 10–15% of an impurity therein. [d] Some polarograms show the visual semblance of two waves; others do not. [e] No indication of the presence of more than one wave in the polarogram was visually apparent. [f] In this case the value of the diffusion current constant, as well as other observations, is not definitive for the presence of two waves rather than of one. The numerical data listed are therefore parenthesized. [g] The polarogram shows a slight indication of two waves. [h] One calculates a value of 2.35 on the basis of the results of Hoijtink (ref. 12) using 96% dioxane and assuming a change of +0.10 v. in $E_{1/2}'$ (as found for naphthalene) in changing the solvent to 75% dioxane. [i] No diffusion current constant is given inasmuch as the characteristics of the capillary used are unknown. [j] The two waves are approximately equal in height. [k] For coulometric results see Table II. [l] A pre-wave of height 1/4 to 1/3 of the first wave occurs at *ca.* −2.01 v. [m] Measured in 0.175*M* tetra-*n*-butylammonium iodide. [n] The concentration of the solution (nearly saturated) was not known quantitatively. [o] Though a second wave is present, the polarogram did not allow determination of $E_{1/2}''$. [p] The height of this wave is 3–4 times that of the first wave. [q] Data of Hoijtink (ref. 12), corrected for effect of solvent as noted in preceding footnote [h].

series of compounds for which $\theta$-distributions should be equivalent or nearly so and reductions of analogous structural features should ensue (*vide infra*). Thus, one notes that 2,2′-binaphthyl reduces more readily than does 2-phenylnaphthalene. Also, for the 2-alkenylnaphthalenes reducibility is fostered in the order (of alkenyl substituents) vinyl > cyclopentenyl > cycloheptenyl > cyclohexenyl. The relationship vinyl > cyclopentenyl > cyclohexenyl is in accord with the order of $C_r$ as based on ultraviolet absorption spectra[13] and Diels-

(13) See ref. in footnote 8.

Alder reactivity.[14] Although the appropriate relative $C_t$-value for the cycloheptenyl group is not clearly known, it is generally considered to be equal to or less than that of the cyclohexenyl group.[15,16] On the other hand, one would expect the cyclohexenylnaphthalenes to reduce more readily than their cycloheptenyl homologs if bulkiness of the substituent were the sole pertinent structural factor involved.

For arylalkenes and biaryls one would anticipate that $E_{1/2}'$ would be dependent on $\theta_p$, the angle of twist in the molecule at the time of electron addition, rather than on $\theta$, the angle of twist in the unperturbed molecule present in solution. Electrical polarization and/or preferential flatwise adsorption of the substrate should operate to make $\theta_p < \theta$, if possible. As molecular models indicate little or no steric hindrance to the attainment of coplanarity[13] in the 2-substituted arenes III, V, VII, IX, XII, XXII, and XXV, we suggest that these molecules are rotated into virtual coplanarity[17] prior to (or in the process of) electroreduction ($\theta_p \leqq 0°$). Comparison of $E_{1/2}'$-values listed in Table I shows that in only two cases (the vinylnaphthalenes and the cyclopentenylnaphthalenes) does the 1-isomer reduce more readily than the 2-isomer (as expected on the basis of $C_t$). It is proposed, therefore, that of the 1-naphthyl compounds studied, only II and IV (where steric hindrance to rotation of the alkenyl group into coplanarity would be least) have $\theta_p \leqq 0°$. For all of the other biaryls and arylalkenes listed it is believed that $\theta_p > 0°$.

Seven compounds (*cf.* Table II) were studied by coulometry using an electrolysis cell containing a silver anode, a mercury cathode maintained at a potential 0.08 to 0.15 volt more negative than $E_{1/2}$ (*i.e.* either $E_{1/2}'$ or $E_{1/2}''$ as the case may be), and the same solvent-electrolyte as employed in polarography. The cell was designed to meet the requirements of (a) an inert atmosphere, (b) low internal resistance, (c) efficient mixing of components in the cathode chamber, and (d) a mechanical means of preventing the flakes of silver iodide (arising from reaction at the anode) from contacting the cathode (and being reduced there). Requirement (d) proved the most difficult to satisfy without deleterious effects on (b). It was met by using a diaphragm consisting of a piece of filter paper and a plug of glass wool, suspended (by means of a glass support) between large electrodes in close proximity. Even use of a thin, coarse sintered-glass diaphragm raised the internal resistance of the cell so much that successful coulometry could not be achieved. Thus, with the latter diaphragm, onset of electrolysis occurred only at a high potential drop (*ca.* 100 v.) across the cell and was accompanied by excessive heating (even boiling) of the solution as well as by formation of dark suspended particles throughout the cell. Inasmuch as half-wave reduction potentials are known to vary with apparatus and solvent used, our method was standardized against naphthalene which consistently absorbed 2.0 ± 0.2 electrons/molecule when the cathode potential was maintained at −2.60 v. (*vs.* S.C.E.). As noted elsewhere, the first visually observable wave of IV also corresponded to absorption of two electrons per molecule, while the visually singular waves of VI, VIII, XIV, and XVII corresponded to absorption of four. 1,1′-Binaphthyl (XX) absorbed four electrons/molecule when the cathode potential was maintained at a value intermediate between $E_{1/2}'$ and $E_{1/2}''$ or a total of seven electrons/molecule when such potential was held more negative than $E_{1/2}''$ throughout the electrolysis.

TABLE II

COULOMETRY OF SEVEN HYDROCARBONS IN 0.1*M* TETRA-*n*-BUTYLAMMONIUM IODIDE IN 75% DIOXANE-WATER

| Compound No. | Controlled Cathode Potential (v. *vs.* S.C.E.) | No. of Trials | Electrons Absorbed per Molecule of Compound | Permanganate Test on Resultant Solution |
|---|---|---|---|---|
| I | −2.60 | 4 | 2.0 ± 0.2 | + |
| IV | −2.40 | 1 | 2.0 ± 0.2 | − |
| VI | −2.65 | 2 | 4.1 ± 0.3 | + |
| VIII | −2.60 | 3 | 4.1 ± 0.3 | + |
| XIV | −2.65 | 3 | 4.1 ± 0.5 | + |
| XVII | −2.60 | 3 | 4.2 ± 0.2 | + |
| XX | −2.42 | 1 | 4.0 ± 0.2 | + |
| XX | −2.65 | 3 | 6.9 ± 0.5 | + |

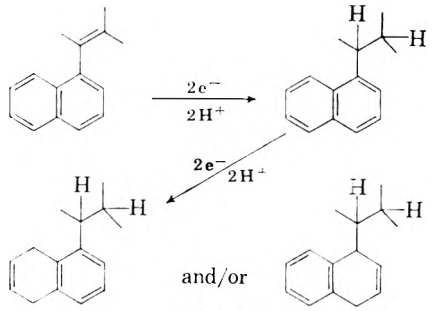
Remembering that only conjugated benzene rings and carbon-carbon double bonds are electroreducible and that naphthalene reduces more readily than biphenyl, one can, in certain instances, assign selected polarographic waves to reduction of particular bonds or systems of bonds in the substrate. Thus, the single wave exhibited by 1-phenylnaphthalene may be ascribed to the transformation of this compound to 1-phenyl-1,4-dihydronaphthalene; the two waves of 2-phenylnaphthalene, to double reduction of the substituted ring of the naphthyl moiety to yield 2-phenyl-1,2,3,4-tetrahydronaphthalene; and the single wave for anthracene and 9-substituted anthracenes, to reduction at the 9,10-positions. For the alkenylnaphthalenes reduction should proceed according to generalized Scheme I, which is in agreement with the coulometric results and permanganate tests recorded for IV, VI, VIII, XIV, and XVII in

(14) L. H. Klemm, W. Hodes, and W. B. Schaap, *J. Org. Chem.*, **19**, 451 (1954).

(15) L. H. Klemm, B. T. Ho, C. D. Lind, B. I. MacGowan, and E. Y. K. Mak, *J. Org. Chem.*, **24**, 949 (1959).

(16) G. Baddeley, *Ann. Repts.*, **LI**, 170–171 (1954); W. M. Schubert and W. A. Sweeney, *J. Am. Chem. Soc.*, **77**, 2297 (1955); O. H. Wheeler, *J. Am. Chem Soc.*, **78**, 3216 (1956).

(17) Any molecule having an angle of twist between $-\alpha°$ and $+\alpha°$ (*cf.* ref. 13) should be experimentally indistinguishable from one where $\theta_p$ is precisely 0°.




Scheme I

Table II and with the observation that $E_{1/2}''$ for IV is numerically equal to $E_{1/2}$ (single wave) for 1-cyclopentylnaphthalene (X). It might also be noted that values of $E_{1/2}''$ (but not of $E_{1/2}'$) for these alkenes are (a) only slightly dependent (maximum deviation from average, 0.03 v.) on the nature of the alkenyl group and its position on the naphthalene ring and (b) more negative than $E_{1/2}$ for naphthalene. Situation (b) may be the result of electron donation by the alkyl group to the naphthyl moiety and/or steric hindrance by such group to preferred orientation of the molecule onto the mercury surface. On the contrary, however, the methyl group (*cf.* our data for the pairs XXIII *vs.* XXVII and IV *vs.* XVIII, as well as those reported for naphthalene *vs.* the monomethylnaphthalenes[18] and benz[*a*]anthracene *vs.* its 7,12-dimethyl derivative[5]) show little, if any, effect on $E_{1/2}$ ($\Delta E_{1/2} \leqslant 0.02$ v.), as compared to hydrogen. Clarification of the reason for this discrepancy between the effects of the methyl group and those of the other alkyl groups must await further experimentation.

## EXPERIMENTAL

Preparations and/or purifications of all substrates (except XXII), the solvent,[19] and the electrolyte have been described previously.[14,15,20-26] XXII, obtained as a by-product from the reaction of 2-naphthylmagnesium bromide with cyclohexanone, was chromatographed on alumina and recrystallized from ethanol, m.p. 186–188°.

*Polarography.* The solvent-electrolyte mixture, 0.1*M* tetra-*n*-butylammonium iodide in 75% (by volume) dioxane in water, was pre-electrolyzed in an H-type cell for 30 min. at an applied potential of 2.8 v. in an atmosphere of purified[27] nitrogen. The resultant solution had a *p*H of *ca.* 9 as measured by a Beckman instrument. Polarography proper was conducted using a Fisher Electropode; an attached potentiometer for measuring E, the applied potential, to an accuracy of ±0.2 mv.; Sargent S-29417 capillary tubing (typical characteristics: $m$ = 0.6–0.9 mg. per sec., $t$ = 8–11 sec. at E = 0), and a thermostated (25.0 ± 0.2°) three-compartmental cell consisting effectively of an H-cell with an intermediate vertical compartment separated from the cathode compartment by means of a sintered glass disk of medium porosity and from the anode compartment by a similar disk plus an agar-potassium chloride plug. The anode compartment constituted a saturated calomel electrode.[28] The intermediate compartment contained saturated aqueous tetra-*n*-butylammonium iodide (renewed for each experiment) to reduce diffusion of potassium ion from anode to cathode and of dioxane in the opposite direction. To the cathode compartment (purified nitrogen atmosphere) were added 5 ml. of pre-electrolyzed solution and 1, 2, or 3 ml. (added in 1-ml. increments to give runs at three different concentrations) of hydrocarbon stock solution, made up by diluting 1 ml. of *ca.* 6 × $10^{-2}M$ hydrocarbon in 75% dioxane to 10 ml. with pre-electrolyzed solution. The current $i$ was obtained from the average of the minimum and maximum deflections of the damped galvanometer. Values of $E_{1/2}$ were corrected for $i$R drop (R = 5000 ohms) across the cell and generally were within 8 mv. of one another for the various runs on any one compound.

In one case (XVIII) where the polarogram showed some irregularities, $i_d$, the diffusion current, was ascertained as a function of the effective head of mercury and was consistent with expectations for a diffusion-controlled reduction process.[29] Unlike the cases reported by Wawzonek and Laitinen[5] anthracene and substituted anthracenes showed no special irregularities in diffusion current constants or shapes of polarograms in our studies. Polarographic data are reported in Table I.

*Coulometry.* The electrolytic cell consisted of a 250-ml. pyrex beaker containing a magnetically stirred lower layer of mercury (cathode), an upper layer of 50 ml. of 75% dioxane containing 0.1*M* tetra-*n*-butylammonium iodide and (when desired) the reducible hydrocarbon, and an anode compartment (suspended in the electrolytic solution just above the cathode and bearing a horizontal circular silver plate anode) partitioned from the cathode compartment by means of a glass sieve holding a filter paper and a plug of glass wool. The glass sieve was prepared from a glass tube bearing a coarse sintered glass disk sealed flush with the lower end. Several holes were drilled completely through the glass disk in order to decrease internal resistance of the cell. The entire cell was sealed from contact with air by means of a tightly fitting closure plate and rubber stoppers bearing the necessary wires and tubes for operation. Purified nitrogen was passed through the apparatus continuously. The outlet tube of an external, saturated calomel electrode was inserted into the cell in close proximity to the upper

(18) R. A. Burdett and B. E. Gordon, *Anal. Chem.*, **19**, 843 (1947).

(19) Attention should be called to the highly toxic nature of even low concentrations of dioxane in the atmosphere when one is exposed thereto over extended periods of time [*cf.* N. I. Sax, *Dangerous Properties of Industrial Materials*, Reinhold Publishing Corp., New York, 1957, p. 636]. In the interests of safety for laboratory personnel it is strongly recommended that *all steps in purification of this solvent or of handling it other than in tightly closed containers should be conducted in a good hood.*

(20) L. H. Klemm and W. Hodes, *J. Am. Chem. Soc.*, **73**, 5181 (1951).

(21) L. H. Klemm and H. Ziffer, *J. Org. Chem.*, **20**, 182 (1955).

(22) L. H. Klemm, J. W. Sprague, and H. Ziffer, *J. Org. Chem.*, **20**, 200 (1955).

(23) L. H. Klemm, J. W. Sprague, and E. Y. K. Mak, *J. Org. Chem.*, **22**, 161 (1957).

(24) W. E. Bachmann and L. H. Klemm, *J. Am. Chem. Soc.*, **72**, 4911 (1950).

(25) L. H. Klemm, D. Reed, and C. D. Lind, *J. Org. Chem.*, **22**, 739 (1957).

(26) L. H. Klemm, D. Reed, L. A. Miller, and B. T. Ho, *J. Org. Chem.*, **24**, 1468 (1959).

(27) We are indebted to Dr. W. B. Schaap of Indiana University for directions on the construction of a self-regenerating vanadous sulfate-perchloric acid column used in this purification.

(28) O. F. Steinbach and C. V. King, *Experiments in Physical Chemistry*, American Book Co., New York 1950, p. 175.

(29) I. M. Kolthoff and J. J. Lingane, *Polarography*, 2nd Ed., Interscience Publishers, New York, 1952, Vol. I, pp. 85–86.

surface of the mercury cathode. The potential difference between the S.C.E. and the cathode was measured by means of a potentiometer. A gas coulometer[30] and a milliammeter were placed in series with the electrolysis cell and a voltmeter was placed in parallel with it. The voltage across the cell was adjusted manually.

In operation the solvent-electrolyte mixture (without hydrocarbon) was pre-electrolyzed by allowing a current of 50 milliamp. to flow through the cell for 15 min. Then a potential difference of 20 v. was maintained across the cell until the cathode had attained the potential desired for the electroreduction. During this time a record of current *vs.* cathode potential was made. When the current had ceased to decrease with time (residual value 2–6 milliamp.), the initial reading of the coulometer was noted, a sample of 1 ml. of standard 0.1–0.2*M* hydrocarbon substrate in 75% dioxane was added to the cathode compartment, and a timer was started. As the cathode potential immediately became more positive, the overall potential was again raised to 20 v. and the previous procedure of adjusting the voltage was repeated. When the current had reached a steady background value again (1–3 hr.) electrolysis was stopped. The total number of coulombs passed during the electrolysis proper (as calculated from the gas coulometric readings) was corrected for background current-flow (as based both on time of electrolysis and intervening cathode potentials). A sample of the electrolytic solution was withdrawn and tested for unsaturation by means of aqueous permanganate. Results are recorded in Table II.

(30) J. J. Lingane, *J. Am. Chem. Soc.*, 67, 1916 (1945).

EUGENE, ORE.

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[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY]

# Catalytic Oxidation of Hydrocarbons. Initiation by Ozone

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The isomeric xylenes are readily oxidized to the respective toluic acids with oxygen in acetic acid solvent at reflux temperature. The reaction is catalyzed by cobalt ion and initiated by ozone. *m*-Toluic acid and *p*-toluic acid are oxidized further at a slower rate to the corresponding dibasic acids. When *o*-toluic acid is oxidized the product, o-phthalic acid, chelates with cobalt ion and interferes with the chain initiation step, ROOH + Co(III) $\longrightarrow$ ROO· + Co(II) + $H^+$, inhibiting the reaction.

Ozone is a powerful oxidant and will oxidize silver (I) ions to silver(II) ions[1] in acid solution. We have found that the characteristic green color of cobalt(III) acetate appears when an ozone-oxygen stream is passed into cobalt(II) acetate solutions in acetic acid. We felt that a more efficient oxidation system might be obtained if the acetaldehyde-oxygen in the Hull oxidation[2] was replaced by ozone-oxygen. An oxidation of *p*-xylene in acetic acid at reflux temperature was effected by introducing oxygen containing *ca.* 2% ozone into the vigorously stirred system. The reaction rapidly attained the characteristic green color described in the Hull oxidation. However, the product of the reaction is principally terephthalic acid. Furthermore, the ozone can be stopped after the green color is attained and the reaction is self-sustaining, *i.e.* it continues without further addition of ozone. Toluene and some substituted toluenes are also oxidized to the corresponding carboxylic acids. If the water formed is removed continuously then phthalide can be oxidized to phthalic anhydride which does not interfere with the oxidation.

We found that *o*-xylene, unlike the other two isomers, cannot readily be oxidized to the dibasic acid. Initially, we felt that the *o*-phthalic acid formed might be degraded further. Subsequent investigation showed that *o*-phthalic acid was stable in the reaction mixture. However, when it was present in the reaction in an amount at least equivalent (moles) to the cobalt(II) ion the characteristic green color of cobalt(III) ion could not be obtained even when ozone-oxygen mixtures were passed through continuously. Furthermore, self-sustaining oxidations of any of the xylenes could not be obtained when it was present in appreciable amounts. As a consequence, an *o*-xylene oxidation can be initiated with ozone and the reaction which essentially proceeds stepwise will stop when most of the *o*-xylene is converted to *o*-toluic acid and an amount of phthalic acid equivalent to the cobalt ion in solution is formed. At this point the reaction mixture is no longer green but is the pink color characteristic of cobalt(II) acetate. If the initiator, ozone, is added continuously, more *o*-phthalic acid can be produced at a much reduced rate. The other xylenes are also oxidized to the corresponding dibasic acids in the presence of *o*-phthalic acid at a reduced rate if ozone is added continuously.

Since the intermediate toluic acids have dissociation constants of the same order of magnitude as the solvent acetic acid, they would be expected to have little effect on the catalyst. Isophthalic and terephthalic acids are relatively insoluble in the reaction mixture and also do not interfere with the catalyst. However, *o*-phthalic acid is not only the strongest acid present in the reaction mixture, but it can also form a chelate with cobalt(II) and co-

(1) A. A. Noyes, S. L. Hoard, and K. S. Pitzer, *J. Am. Chem. Soc.* 57, 1221–9 (1935).

(2) D. C. Hull, U. S. Patent 2,673,217, March 23, 1954.

balt(III) ions[3] and this would change the oxidation potential of the system.[4] Generally it is found that the higher valence state is stabilized to some degree.

Redox catalysts, such as cobalt ion, function in the following manner:[5]

$$Co^{+2} + ROOH \longrightarrow Co^{+3} + RO\cdot + OH^-$$
$$Co^{+3} + ROOH \longrightarrow Co^{+2} + ROO\cdot + H^+$$

Since the catalyst in the Hull oxidation must be at least partly in the trivalent state, we can perhaps assume that the reaction of solvated cobalt(III) ion with hydroperoxide is the principal chain initiation step. It is this step that would be interfered with by any material that stabilizes the cobalt ion in the trivalent state. This is in agreement with the experimental data. In the presence of *o*-phthalic acid the oxidation will continue only when the initiator, ozone, is added continuously to the reaction mixture.

## EXPERIMENTAL

A round bottom flask was equipped with a gas inlet tube, a thermometer, and a condenser which also served as a gas exit tube. Efficient oxygen–liquid mixing was obtained with a vibromixer stirrer. The ozonizer was the conventional concentric tube type with a brine electrolyte. The phthalic acids and intermediate toluic acids produced in all cases were substantially pure as indicated by melting point or neutral equivalent where the material did not melt below 300°.

*Oxidation of m-xylene.* To a 2-l. reaction flask was added 130 g. (1.23 moles) of *m*-xylene, 40 g. (0.16 mole) of cobalt(II) acetate tetrahydrate and 1 l. of glacial acetic acid. An ozone (2 g. per hr.)-oxygen stream was passed into the vigorously stirred solution at reflux temperature (115–120°) at a rate of 70 l. per hr. The ozone was stopped after 75 min., at which time the solution was dark green in color. The reaction was continued for a further 15 hr. during which time the reaction mixture remained dark green in color. After cooling to room temperature, the precipitated isophthalic acid was removed by filtration and washed with a small amount of acetic acid to remove cobalt salts. An aliquot of the combined filtrate and washings was evaporated to dryness, then treated with dilute hydrochloric acid to dissolve cobalt salts. Ether extraction separated the *m*-toluic acid from the isophthalic acid. The total yield of isophthalic acid obtained was 136.3 g. (67%) and *m*-toluic acid 35.2 g. (21%).

Similar results are obtained in the oxidation of *p*-xylene.

*Oxidation of o-xylene.* To a 2-l. reaction flask was added 312 g. of *o*-xylene, 40 g. cobalt(II) acetate tetrahydrate and 750 ml. glacial acetic acid. An ozone (2.2 g. per hr.)-oxygen stream was passed through the vigorously stirred solution at reflux temperature (115–120°) at a rate of 90 l. per hr. The ozone was stopped after 1.5 hr. at which time the solution was dark green in color. At the end of 10 hr., the reaction was pink in color. After cooling, the reaction mixture was flooded with 3.5 l. of water and the precipitated *o*-toluic acid was removed by filtration, washed with water, and air dried to yield 308 g. of *o*-toluic acid (77%). No attempt was made to recover more *o*-toluic acid from the filtrate.

When ozone is passed through the reaction mixture continuously, appreciable amounts of *o*-phthalic acid are formed. The following oxidations were run containing varying amounts of catalyst. An ozone (1 g. per hr.)-oxygen stream (36 l. per hr.) was passed through a vigorously stirred solution containing the catalyst, and 10.6 g. (0.1 mole) of *o*-xylene in 200 ml. of glacial acetic acid at reflux temperature. After 7.5 hr., the acetic acid was removed by distillation and the residue was treated with enough dilute hydrochloric acid to dissolve the cobalt salts. After filtration the *o*-toluic acid was separated from the *o*-phthalic acid by extraction with chloroform.

| | $Co(OAc)_2 \cdot 4H_2O$ (moles) | Yield (moles) | |
|---|---|---|---|
| | | *o*-Toluic acid | *o*-Phthalic acid |
| 1 | 0.1 | 0.049 | 0.025 |
| 2 | 0.02 | 0.061 | 0.019 |
| 3 | 0.004 | 0.061 | 0.008 |

*Oxidations in the presence of o-phthalic acid.* When oxygen containing 1.5% ozone was passed through a glacial acetic acid (250 ml.) solution containing 10 g. of cobalt(II) acetate tetrahydrate (0.04 mole) and 20 g. of *o*-phthalic acid (0.12 mole) at 115° for 2 hr., the solution darkened slightly but did not attain the dark green color characteristic of cobalt(III) acetate that is attained in the absence of *o*-phthalic acid. The oxidation of the xylenes to phthalic acids will proceed in the presence of *o*-phthalic acid only if ozone is passed through the reaction continuously.

*Oxidation of p-xylene in the presence of o-phthalic acid.* To a solution of 5 g. (0.02 mole) of cobalt(II) acetate tetrahydrate in 200 ml. of glacial acetic acid was added 8.6 g. (0.08 mole) of *p*-xylene and 3.3 g. (0.02 mole) of *o*-phthalic acid. An ozone (2 g. per hr.)-oxygen stream (60 l. per hr.) was passed through the vigorously stirred solution at reflux temperature. After 2.5 hr., the reaction mixture was cooled, filtered, and washed with a small amount of acetic acid to yield 10.2 g. (76%) of terephthalic acid.

In a similar experiment 10 g. (0.06 mole) of *o*-phthalic acid was added to the reaction mixture. After 5 hr., there was obtained 9.8 g. (73%) of terephthalic acid. No attempt was made to isolate the *p*-toluic acid from the filtrates.

*Oxidation of p-methoxytoluene.* To a solution of 6 g. (0.024 mole) of cobalt(II) acetate tetrahydrate in 200 ml. of glacial acetic acid, was added 12 g. (0.1 mole) of *p*-methoxytoluene. An ozone (1.0 g. per hr.)-oxygen stream (30 l. per hr.) was passed through the vigorously stirred solution at reflux temperature. After 1.9 hr., the ozone was stopped and the reaction was continued for 2.1 hr. further. The reaction mixture was flooded with water and the copious pale yellow precipitate separated by filtration and dried in a vacuum desiccator. There was obtained 12.2 g. (82%) of *p*-anisic acid, which begins to soften at 178°, m.p. 184–187°; neutral equivalent 150, 152 (theory 152).

*Oxidation of phthalide.* To a solution of 5 g. (0.02 mole) of cobalt(II) acetate in 300 ml. of glacial acetic acid was added 15 g. (0.11 mole) of phthalide. A stream of ozone (1.7 g. per hr.)-oxygen was passed through the vigorously stirred solution at the temperature of reflux. Acetic acid was removed continuously from the reaction mixture through an 8-inch Vigreux column. During a 5-hr. period, a total of 400 ml. of acetic acid was removed from the reaction mixture and a total of 200 ml. of acetic acid was gradually added to the reaction mixture. The ozone was stopped after 4 hr. and after 1 hr. further, the reaction mixture was cooled. There was deposited 13.4 g. (81%) colorless needles, m.p. 132°. There was no depression in a mixed melting point with an authentic sample of phthalic anhydride.

SCHENECTADY, N. Y.

(3) M. Bobtelsky and I. Bar-Gadda, *Bull. soc. chim. France*, 20, 687 (1953).

(4) A. E. Martell and M. Calvin, *Chemistry of the Metal Chelate Compounds*, Prentice Hall, Inc., New York (1953) p. 58–9.

(5) For a discussion of metal-catalyzed autooxidation see C. Walling, *Free Radicals in Solution*, John Wiley & Sons, Inc. (New York) 1957, pp. 427–30.

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

# The Ozonization of Methyl Oleate[2]

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The effect of solvent on the ozonization of methyl oleate and on the reductive decomposition of the ozonolysis products has been studied. The use of a reactive solvent such as methanol or acetic acid resulted in isolated product yields of 87%. Carbonyl yields before isolation of product were on the order of 90–92%. The use of a nonreactive solvent such as ethyl acetate or heptane resulted in low yield and impure products. The results are explained on the basis of the Criegee zwitterion mechanism for ozonization.

The ozonide of oleic acid and the cleavage products obtained by treatment with water azelaic semialdehyde, azelaic acid, pelargonaldehyde, and pelargonic acid were first described by Harries and Thieme.[3] This original work was carried out without the use of solvent. Subsequently, hexane,[4] chloroform,[5] carbon tetrachloride,[6] glacial acetic acid,[7,8] ethyl chloride,[9] ethyl acetate,[10] and ethyl alcohol[11] have been used as solvents. The highest yields of isolated product (60% of pure or 75% of crude methyl azelaaldehydate) were obtained by ozonization in glacial acetic acid followed by reduction with zinc.[8] Azelaic semialdehyde has been isolated in 80% yield as the semicarbazone by ozonization in ethyl chloride followed by catalytic hydrogenation in methanol.[9] Sodium oleate has also been ozonized in aqueous solution, but the apparent yield of product, isolated as the oxime, was only 53%.[12]

Recent studies on the ozonization of various unsaturated compounds have shown not only methanol[13–16] but also ethanol[17] to be a superior reaction medium. Methanol reacts to a considerable extent with ozone at −15°,[18] but in the presence of an unsaturated compound little reaction occurs between the ozone and methanol, and the products of such a reaction do not interfere in the analysis or isolation of carbonyl compounds.[16]

Application of methanol to the ozonization of methyl oleate in the present work resulted in a significant improvement in the yield of isolated carbonyl compounds. Thus, when chemical reduction with zinc and acetic acid was used, the total carbonyl yield as determined by the hydroxylamine hydrochloride method was 92%. The isolated yield of methyl azelaaldehydate with a two degree boiling range and purity of 92% was 88%. Redistillation gave a product of 96% purity. The hydroxylamine analyses were confirmed by gas chromatography.

Because methanol is not a satisfactory solvent for glycerides at ozonization temperatures, other solvents and solvent combinations were investigated. Furthermore, a solvent system was sought which would obviate the washing step required to remove the dissolved zinc salts. Methylene chloride and propionic acid were tried (Table I). Methylene chloride precipitated the zinc salts as they were formed, but an unsatisfactory yield was obtained. Reduction in propionic acid could not be carried out with zinc in the absence of water.

Catalytic hydrogenation was then investigated. Hydrogenation with 5% palladium on calcium carbonate to give an 80% yield of azelaic semialdehyde isolated as the semicarbazone has been reported.[9] Hydrogenation was carried out in methanol after removal of the ethyl chloride used for the ozonolysis. Ethyl oleate ozonized and hydrogenated in ethyl acetate gave a 57% yield of the desired aldehydic products.[10] A British patent describes the use of ethanol in the ozonization of oleic acid with subsequent hydrogenation in the same solvent, the product being isolated as the aldoxime.[11] No yield is stated.

The use of methanol as a common solvent for both ozonization and hydrogenation has been described in the preparation of adipaldehyde from

(1) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) Presented in part before the Division of Organic Chemistry at the 136th meeting of the American Chemical Society at Atlantic City, N. J., September 16, 1959.

(3) C. Harries and C. Thieme, *Ann.*, **343**, 318 (1905).

(4) E. Molinari and E. Soncini, *Ber.*, **39**, 2735 (1906).

(5) C. Harries and C. Thieme, *Ber.*, **38**, 2844 (1906).

(6) C. Harries, *Ber.*, **39**, 3728 (1906).

(7) B. Helferich and W. Schäfer, *Ber.*, **57B**, 1911 (1924).

(8) C. R. Noller and R. Adams, *J. Am. Chem. Soc.*, **48**, 1074 (1926).

(9) F. G. Fischer, H. Düll, and L. Ertel, *Ber.*, **65B**, 1467 (1932).

(10) M. Stoll and A. Rouvé, *Helv. Chim. Acta*, **27**, 950 (1944).

(11) A. S. Carpenter and F. Reeder, Brit. Patent **743,491** (to Courtaulds, Ltd.) Jan. 18, 1956.

(12) H. Ohtsuki and H. Funahashi, Japan Patent **8417**, Dec. 21, 1954; U. S. Patent **2,862,940**, Dec. 2, 1958.

(13) P. S. Bailey, *J. Org. Chem.*, **22**, 1548 (1957).

(14) P. S. Bailey and B. M. Shashikant, *J. Org. Chem.*, **23**, 1089 (1958).

(15) E. Briner and D. Frank, *Helv. Chim. Acta*, **21**, 1297 (1938).

(16) N. A. Milas, J. T. Nolan, Jr., and P. Ph. H. L. Otto, *J. Org. Chem.*, **23**, 624 (1958).

(17) J. L. Warnell and R. L. Shriner, *J. Am. Chem. Soc.*, **79**, 3165 (1957).

(18) F. L. Greenwood, *J. Org. Chem.*, **10**, 414 (1945).

TABLE I

OZONIZATION OF METHYL OLEATE

| Solvent (Volume, %) | Ozone, % of Theory | | Temperature of Reduction | Yield, % | | | Methyl Azelaaldehydate Purity[a] |
|---|---|---|---|---|---|---|---|
| | Consumed | Not Consumed | | Total Carbonyl | Pelargonaldehyde | Methylazelaaldehydate | |
| A. Chemical Reduction (Zinc + Acetic Acid) | | | | | | | |
| Methanol | 101 | 1.6 | 30 to 35 | 92 | 77 | 88 | 92 |
| Methylene chloride | 105 | 1.7 | 30 to 35 | 72 | 75 | 76 | 87 |
| Methylene chloride | 132 | 1.0 | 30 to 35 | — | 72 | 66[b] | — |
| Propionic acid | 124 | 2.1 | — | (No reduction occurred in absence of water) | | | |
| B. Catalytic Hydrogenation (10% Palladium on Charcoal) | | | | | | | |
| Methanol[c] | 115 | 3 | −10 to 0 | 78 | 83[d] | 85[d] | 84 |
| *n*-Butanol | 98 | 4.8 | <0 | 63 | — | — | — |
| Propionic acid | 113 | 4.7 | <8 | 81 | — | 44[b] | — |
| Ethyl acetate | 107 | 3.0 | 25 | — | 70 | 87 | 75 |
| Ethyl acetate | 118 | 5.0 | 25 | — | — | 81[b] | — |
| Ethyl acetate + 20% methanol | 110 | 4.4 | <13 | — | 69[e] | 76[e] | — |
| Ethyl acetate + 20% acetic acid | 114 | 4.0 | 25 | — | 76 | 83[f] | 87 |
| Methyl acetate + 20% methanol | 105 | 2.7 | 20 | — | 82[d] | 87[d] | — |
| *n*-Heptane + 50% ethanol | 120 | 2.2 | >20 | 68 | — | 60[e] | — |
| *n*-Heptane + 20% *t*-butanol | 141 | 4.4 | 50 | — | 60 | 67[b] | — |

[a] Purity determined by the hydroxylamine hydrochloride method. [b] An impure product was obtained, as indicated by the refractive index. [c] Average of seven runs. [d] Product was isolated as the dimethyl acetal. [e] Product was isolated as the diethyl acetal. [f] On basis of methyl oleate consumed in ozonization, calculated from methyl stearate recovered, yield was 93%.

cyclohexene.[19,20] A yield of about 50% of the aldehyde was reported in this patented work.

When methanol was used as the common solvent for the ozonization and subsequent hydrogenation of methyl oleate, fair yields (78%) of carbonyl compounds were obtained (Table I). Hydrogenation was carried out at atmospheric pressure with 10% palladium on charcoal. Direct distillation of the reaction product, however, resulted in an apparent mixture of aldehyde and acetal compounds. Conversion of the carbonyl products to the dimethyl acetals resulted in the isolation by distillation of the acetal of pelargonaldehyde in 83% yield and of the acetal of methyl azelaaldehydate in 85% yield. Conversion to the acetal was accomplished by treatment with 2,2-dimethoxypropane in the presence of ammonium chloride. The purity of the product was 84%, as determined by the hydroxylamine method, although the refractive index ($n_D^{30}$ = 1.4301) was close to that of a sample analyzing over 95% ($n_D^{30}$ = 1.4297).

The use of catalytic hydrogenation in a number of other solvents was then investigated. The best results were obtained when methanol or acetic acid was used in combination with methyl or ethyl acetate. Here again, the use of an alcohol resulted in the formation of a mixture of aldehydes and acetals. However, conversion of the product to the acetals gave 82% yield of pelargonaldehyde dimethyl acetal and 87% yield of methyl azelaaldehydate dimethyl acetal. Conversion to the acetals could be obviated by using acetic acid, which made possible the isolation of methyl azelaaldehydate in 83% yield by direct distillation. The purity of the product obtained by this method was 87% and redistillation was not effective in improving the purity. The refractive index of the product was not a criterion for purity, as was true for the acetal.

The following single solvents were tried but found to be unsatisfactory: *n*-butanol, propionic acid, and ethyl acetate. The solvent combinations 50% ethanol in heptane and 20% *t*-butanol in heptane were also found to be unsatisfactory. Note that the temperature at which hydrogenation could be carried out depended upon the solvent used (Table I). Hydrogenation in the alcohols or the acids, or combinations of these in ethyl acetate, readily occurred below room temperature. On the other hand, hydrogenation in ethyl acetate alone or in *n*-heptane with either ethanol or *t*-butanol present took place only above room temperature. The presence of peroxidic oxygen in the latter solvents could be detected only with potassium iodide in glacial acetic acid, whereas it could be readily detected in the other solvents by means of aqueous potassium iodide.

These differences in behavior are explained by the Criegee mechanism for ozonization.[21,22] It is

(19) E. I. du Pont de Nemours and Co., Inc., Brit. Patent 709,450, May 26, 1954.

(20) E. E. Fisher, U. S. Patent 2,733,270 (to Du Pont), Jan. 31, 1956.

(21) P. S. Bailey, *Chem. Revs.*, 58, 925 (1958).

(22) R. Criegee, G. Blust, and H. Zinke, *Ber.*, 87, 766–768 (1954).

postulated that the addition of ozone to a double bond results in a primary ozonide which breaks down to a zwitterion and a carbonyl compound. The zwitterion may react in any one of several different ways: with itself to form a dimeric or polymeric peroxide, with a carbonyl compound to form an ozonide with the classical five-membered cyclic structure, with a compound having an active hydrogen; or it may undergo rearrangement. The zwitterion reacts with methanol to form a methoxy hydroperoxide,[23] and with glacial acetic acid to give a mixture of acetoxy hydroperoxides and polymeric peroxides.[14]

It is apparent that polymeric peroxides were formed in the solvents in which hydrogenation occurred only above room temperature, and that these entered into a number of side reactions which resulted in impure products and low yields. On the other hand, the alkoxy or acetoxy peroxides formed in the solvents in which hydrogenation occurred below room temperature resulted in high yields of pure products. The presence of ethanol or *t*-butanol apparently was not sufficient to prevent polymeric peroxide formation in heptane.

Since methoxy hydroperoxide compounds described in the literature appear to be unusually stable, the mixture of those which would be formed from methyl oleate according to the following equation was isolated:

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH_3 \xrightarrow[CH_3OH]{O_3}$$

$$CH_3(CH_2)_7\begin{cases}\text{—CHO or}\\ \text{—CHOOH}\\ \quad|\\ \quad OCH_3\end{cases}$$

I

$$+\ CH_3OOC(CH_2)_7\begin{cases}\text{—CHO or}\\ \text{—CHOOH}\\ \quad|\\ \quad OCH_3\end{cases}$$

II

Analyses for carbon, hydrogen, and methoxyl showed the resultant product to be a mixture of the methoxy hydroperoxides and the hemiacetals formed by reaction with an additional molecular amount of methanol. This material, when ignited, burned gently for several seconds before more vigorous oxidation occurred.

## EXPERIMENTAL

*Ozonization procedure.* The reactor vessel consisted of a cylindrical flask with a ₹ 55/50 outer joint, which was attached to a reactor head containing fittings for a stirrer, a thermometer, a condenser, a dropping funnel, and a gas inlet, all passing through a ₹ 55/50 inner joint. Pure oxygen was passed through a 1 in. × 3 ft. column packed with indicating Drierite[24] to remove traces of moisture, then into a Welsbach Model T-23 laboratory ozonator.[24] The oxygen, containing 2–3% ozone, was passed through a gas dispersing bulb into the bottom of the reaction medium at a rate of from 1 to 2 l. of oxygen per min. The exit gases from the reactor were passed through a potassium iodide absorber, then a wet test meter. During the course of the reaction a small side-stream of the ozonized oxygen was also passed through a potassium iodide absorber, then through a wet test meter. Titration of the iodine liberated made it possible to calculate the rate of ozone produced in mmoles per liter of oxygen. By this means the total amount of ozone introduced to the system and also the amount absorbed by the system were calculated. Less than 1% of the ozone was not absorbed by the system until near the end point of the reaction.

Examples of the preferred procedures for both chemical reduction and catalytic hydrogenation follow.

*Chemical reduction.* Methyl oleate having an iodine value of 84.3 and a refractive index of 1.4481 (30.2°) was obtained from Applied Science Laboratories, State College, Pa.[24] No polyunsaturated compounds were detected by alkali isomerization, and no impurities were detected by gas chromatography. The methyl oleate (120.4 g., 0.40 g. mole of unsaturation) was dissolved in 1800 ml. of reagent grade methanol in a 2-l. round bottom reactor and cooled to −20°. Oxygen containing 1.092 mmoles of ozone per liter was passed through the solution at the rate of 1.94 l. per minute. At the end of 195 min., the potassium iodide solution at the exit of the reactor became strongly colored indicating that ozone was no longer being absorbed. The total amount of ozone consumed was 101% of theory, and 1.6% of theory was not absorbed in the reactor but was absorbed by the potassium iodide solution. Glacial acetic acid (150 ml.) was added, and the solution was warmed to 30°. Zinc dust was added, a small pinch at a time, until a total of 60 g. had been added, while maintaining the temperature at 30–35° with cooling. The mixture was filtered and distilled on a steam bath until about one half of the methanol had been removed. Methylene chloride (500 ml.) and water (500 ml.) were added, and the layers separated. The methylene chloride layer was washed with water (each wash was back-washed with a small amount of methylene chloride) until free of acid. It was then dried over anhydrous calcium sulfate. Analysis of this solution by the hydroxylamine hydrochloride method showed that a 92% yield of carbonyl products was obtained. It should be noted that the washing step should be carried out as soon as possible and as thoroughly as possible, otherwise varying amounts of the dimethyl acetal will form.

Methylene chloride was removed from the solution by distillation on the steam bath. The residue was distilled under vacuum through a small Vigreux column using a nitrogen capillary ebullator. There was obtained 43.9 g. of pelargonaldehyde boiling at 37–47° (0.35 mm.), $n_D^{30.2}$ 1.4193 (lit., $n_D$ 1.4245). An additional 2.27 g. was recovered from the solid carbon dioxide trap for a total yield of 81%. Methyl azelaaldehydate (65.3 g.) was obtained as a fraction boiling 94–96° (0.75 mm.) $n_D^{30.2}$ 1.4348 (lit., $n_D^{20}$ 1.4384) and purity of 92%. Redistillation of this fraction gave a product purity of 96%. Another fraction (4.87 g.) was obtained boiling at 96–120° (0.30 mm.) $n_D^{30.2}$ 1.4349, and having a purity of 74.7%. The total yield of crude methyl azelaaldehydate was 94% or 85.4% of pure methyl azelaaldehydate.

The use of methylene chloride for the ozonization and reduction solvent (Table I) resulted in precipitation of the zinc salts. However, poor carbonyl yields and impure products were obtained, even with consumption of ozone at nearly the theoretical level. Reduction in propionic acid did not proceed until water was added. Since an extraction step would then be necessary, the experiment was not carried to completion.

Methyl azelaaldehydate has been reported to have a tendency to polymerize.[8] However, it was found that after storage under nitrogen at 0° for 4 weeks, methyl azelaalde-

(23) G. Lohaus, *Ann.*, **583**, 6 (1953).

(24) The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

hydate could be recovered quantitatively with no evidence of polymer formation.

*Catalytic hydrogenation.* Methyl oleate (15.0 g., 0.05 g. mole) having an iodine value of 84.8 and $n_D$ 1.4481 (30.2°) was dissolved in 210 ml. of methyl acetate and 40 ml. of methanol. The ozonization was carried out as before. The amount of ozone consumed was 118% of the theoretical, and 2.9% of theory was found to have been absorbed by the potassium iodide solution. At the end of the ozonization the solution was purged with nitrogen, then hydrogen. The catalyst (0.1 g. of 10% palladium on charcoal) was dispersed in a small amount of methyl acetate and added to the solution through a dropping funnel. The solution was allowed to warm to 22° gradually as hydrogen was passed through the solution, and at the end of 1.5 hr. a negative test for peroxide (carried out with potassium iodide in glacial acetic acid) was obtained. Analysis of this solution by the hydroxylamine hydrochloride method gave misleading results because of hydrolysis of the ester to acetic acid. Distillation of this solution gave a product of indefinite composition.

In a similar experiment the product was converted to the dimethyl acetal. To the product solution was added 25 ml. of 2,2-dimethoxypropane and 0.1 g. of ammonium chloride. The mixture was distilled at atmospheric pressure to a pot temperature of 95° to remove the methyl acetate. An additional 50 ml. of methanol and 15 ml. of 2,2-dimethoxypropane were added and the distillation continued to a pot temperature of 105°, at which point the vapor temperature was 64.5°. The total heating period was about 6 hr. The residue was cooled, filtered, transferred to a similar distillation flask equipped with a nitrogen capillary ebullator, and distilled under reduced pressure through a 1 in. × 6 in. glass helices packed column. There was recovered from 15.0 g. of methyl oleate, 7.69 g. (82%) of a fraction boiling 56.5–70° (0.35 mm.) $n_D^{30.2}$ 1.4166, and a fraction (10.13 g., 87%) boiling 95–103° (0.35 mm.) $n_D^{30.2}$ 1.4302. Since the latter value did not agree with that recorded in the literature[7] ($n_D^{18.8}$ 1.4312) for the dimethyl acetal of methyl azelaaldehydate, elemental analyses were carried out on a redistilled fraction having a boiling point of 88° (0.25 mm.), $n_D^{30.2}$ 1.4301.

*Anal.* Calcd. for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41; sapon. equiv. 232.3. Found: C, 61.89; H, 10.29; sapon. equiv. 231.

A more convenient procedure involved ozonization in the ethyl acetate–acetic acid solvent mixture followed by catalytic hydrogenation. Direct distillation of the product solution resulted in the isolation of methyl azelaaldehydate, $n_D^{30.2}$ 1.4347, in 83% yield. Analysis by the hydroxylamine hydrochloride method indicated a purity of 87%. Apparently, a relatively low proportion polymeric peroxides, which are reported to be found as well as the acetoxy peroxides,[14] were present.

The other solvents which were tried (Table I) resulted in low yields of impure products.

*Isolation of the methoxy hydroperoxides.* Methyl oleate (6.0 g., 0.020 g. mole) was ozonized in 150 ml. of methanol in the manner described. The amount of ozone consumed was 107% of theory and the amount absorbed in the potassium iodide trap was 6.0% theory. The solution was filtered, and methanol was removed in a rotary evaporator at a temperature of 21° first under vacuum from a water aspirator and then finally at a pressure of 0.2 mm. for a total time of about 18 hr. under vacuum. The colorless oil which remained weighed 7.8 g.

*Anal.* Calcd. for $C_{20}H_{40}O_6$: (an equimolar mixture of I and II) C, 63.80; H, 10.71; methoxyl, 16.48. Found: C, 63.3; H, 10.8; methoxyl, 19.5.

*Acknowledgment.* The authors wish to express their appreciation to Mrs. Clara McGrew and to Mrs. Bonita Heaton for the microanalyses.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND BACTERIOLOGY, STATE UNIVERSITY OF IOWA]

# Preparation of Long Chain Alkyl Hydroperoxides[1]

S. WAWZONEK, P. D. KLIMSTRA,[2,3] AND R. E. KALLIO

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Dodecyl, tetradecyl, hexadecyl, and octadecyl hydroperoxides have been prepared for testing as intermediates in the biological oxidation of saturated hydrocarbons. The hydroperoxides were prepared in a state of purity varying from 92–100 per cent by the alkylation of hydrogen peroxide in basic medium with the corresponding alkyl methanesulfonate.

In the study of the oxidation of saturated hydrocarbons by certain microorganisms, recent data indicate that biological oxidation of paraffins occurred at one terminal carbon and did not involve the formation of an olefin, epoxide, or 1,2-glycol.[4]

In this work a series of hydroperoxides containing twelve, fourteen, sixteen, and eighteen carbon atoms have been synthesized for testing as possible intermediates in this oxidation.

Of the methods available the reaction of a Grignard reagent with oxygen[5] and the alkylation of hydrogen peroxide with alkyl methanesulfonates[6] were studied as possible sources of these compounds.

Treatment of dodecylmagnesium bromide with oxygen at −75° gave a peroxidic product which could not be separated by distillation under reduced pressure from the tetracosane formed. In contrast to the stability reported for decyl hydroperoxide towards distillation,[6] dodecyl hydroper-

(1) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donor of said fund.

(2) Abstracted in part from the Ph.D. Thesis of P. D. Klimstra, June 1959.

(3) American Chemical Society–Petroleum Research Fund Predoctoral Fellow.

(4) J. E. Stewart, R. E. Kallio, D. P. Stevenson, A. C. Jones, and B. O. Schissler, *J. Bacteriol.*, **78**, 441 (1959).

(5) C. Walling and S. A. Buckler, *J. Am. Chem. Soc.*, **75**, 4372 (1953); **77**, 6032 (1955).

(6) H. R. Williams and H. S. Mosher, *J. Am. Chem. Soc.*, **76**, 2984 (1954).

TABLE I

ALKYL METHANESULFONATES

| Methanesulfonate | Reaction Temp. | Yield, % | M.P. | Formula | Analyses: Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| Dodecyl | 5–10° | 70.2 | 33° | $C_{13}H_{28}SO_3$ | 59.10 | 59.36 | 10.67 | 10.30 |
| Tetradecyl | 45–50° | 72.5 | 44–45° | $C_{15}H_{32}SO_3$ | 61.60 | 61.27 | 10.92 | 10.38 |
| Hexadecyl | 55–60° | 72.6 | 54.5–56° | $C_{17}H_{36}SO_3$ | 63.71 | 63.79 | 11.32 | 11.43 |
| Octadecyl | 50–60° | 69.7 | 61–62° | $C_{19}H_{40}SO_3$ | 65.51 | 65.44 | 11.50 | 11.22 |

oxide undergoes decomposition since fractions containing dodecanal-1 and dodecanol-1 were obtained. Separation of the acidic hydroperoxide from the neutral materials by means of alkali, which was used successfully in the methanesulfonate method, was not investigated.

The method of Williams and Mosher[6] with suitable modifications gave the desired hydroperoxides in a state of purity varying from 92–100 per cent. Due to the insolubility of the sulfonates, the alkylation of the hydrogen peroxide had to be carried out in a large volume of methanol. The only water introduced into the reaction mixture was that present in the 30 per cent hydrogen peroxide used. The yields and physical properties of the hydroperoxides are given in Table II. The low yield of octadecyl hydroperoxide obtained is caused by the poor solubility of octadecyl methanesulfonate in methanol.

By-products obtained in the preparation of dodecyl, tetradecyl, and hexadecyl hydroperoxides were the corresponding alkyl peroxides. Only tetradecyl and hexadecyl peroxides were isolated in a pure condition.

The only indication of a hydroperoxide group by infrared analysis was a shift in the hydroxyl peak for the corresponding alcohol from 2.94 to 2.84$\mu$. Williams and Mosher[7] have reported a similar shift in the peak of the hydroxyl group for the lower members of the alkyl hydroperoxide series. In addition they found a band at about 11.8 $\mu$ for the oxygen-oxygen group which became smaller as the alkyl group became larger. This band was not observed for the hydroperoxides prepared in this work. Bands for carbonyl and water impurities were also reported by Williams and Mosher and were likewise found in this study. The carbonyl peak found for dodecyl hydroperoxide could be duplicated in optical density by using an amount of dodecanal-1 calculated equivalent to the amount of impurity present in the dodecyl hydroperoxide. The aldehydes and water probably result from the attack of the base on the hydroperoxide according to the scheme proposed by Kornblum,[8] and were difficult to remove from the lower members.

(7) H. R. Williams and H. S. Mosher, *Anal. Chem.*, **27**, 517 (1955).

(8) N. Kornblum and H. E. DeLamare, *J. Am. Chem. Soc.*, **73**, 880 (1951).

## EXPERIMENTAL[9]

*Reaction of dodecylmagnesium bromide with oxygen.* Dodecylmagnesium bromide was prepared in a flask fitted with a stopcock in the bottom by the addition of dodecyl bromide (25 g.) over a period of 2 hr. to magnesium (2.4 g.) in 125 ml. of dry ether. Dry nitrogen was passed through the system before and during the reaction and a crystal of iodine was necessary to initiate the reaction. All the magnesium disappeared after 2.5 hr.

The resulting Grignard solution was added to an ether solution (100 ml.) saturated with oxygen at −75° in the course of 4 hr. After the addition was completed, oxygen was bubbled through the reaction mixture for an additional 3 hr. The reaction mixture was decomposed with 6*N* hydrochloric acid and extracted with ether. Removal of the ether gave a residue which distilled under reduced pressure (0.02–0.45 mm.) with decomposition. Fractions obtained were further purified by crystallization. The first fraction boiling at 78° (0.045 mm.) was recrystallized from methanol and melted at 26–27°. A positive peroxide test and elemental analysis indicated that this compound was probably dodecyl peroxide.

*Anal.* Calcd. for $C_{24}H_{50}O_2$: C, 77.76; H, 13.56. Found: C, 77.30; H, 12.47.

Fraction two distilled at 96–98° (0.3 mm.) and had the odor of dodecanal-1. Elemental analysis, infrared spectra, and a refractive index of 1.4500 at 20° indicated that this fraction was mainly lauryl alcohol.

Fraction three boiling at 150–170° (0.025–0.030 mm.) was recrystallized from methylene chloride and melted at 46–47°. Infrared analysis and carbon-hydrogen values pointed to an impure sample of tetracosane.

*Alkyl methanesulfonates.* A mixture of methanesulfonyl chloride (0.02 mole) and alcohol (0.20 mole) was stirred at the temperature indicated in Table I while dry pyridine (0.40 mole) was added over a period of 3 hr. The reaction mixture was stirred for an additional 30 min. and poured into 130 ml. of 10 per cent hydrochloric acid. The solution was extracted with two 85-ml. portions of ether and the ether layer was washed with water and a sodium bicarbonate solution. Removal of the ether gave an oily residue which was recrystallized from petroleum ether (b.p. 30–60°). The yields, melting points, and analyses are given in Table I.

*Alkyl hydroperoxides.* The alkyl methanesulfonate (0.008 mole) dissolved in methanol (for the amount see Table II) was treated at room temperature with 30 per cent hydrogen peroxide (100 g.) and powdered potassium hydroxide (20.0 g.) and the mixture was stirred: dodecyl, 600 ml. methanol, 59 hrs.; tetradecyl, 800 ml. methanol, 65 hr.; hexadecyl, 1.2 l. methanol, 72 hr.; octadecyl, 1.8 l. methanol, 99 hrs. The resulting mixture was cooled in ice and treated with 20 g. of powdered potassium hydroxide in 100 ml. of absolute methanol. The resulting precipitate was filtered, redissolved in methanol, acidified with concentrated hydrochloric acid and extracted with hexane. Evaporation of the hexane after washing with water gave tetradecyl peroxide (3.5 g.),

(9) Boiling points and melting points are not corrected.

TABLE II

YIELDS AND PROPERTIES OF ALKYL HYDROPEROXIDES

| Alkyl Group | Yield, % | M.P. ° | (OOH)[10,11] Analysis, % | Formula | Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|
| *n*-Dodecyl | 55.8 | 12–13 | 95 | $C_{12}H_{26}O_2$ | 71.28 | 71.26 | 12.87 | 12.42 |
| *n*-Tetradecyl | 42.4 | 29–30.5 | 92 | $C_{14}H_{30}O_2$ | 73.05 | 73.58 | 13.05 | 12.56 |
| *n*-Hexadecyl | 31 | 42–44 | 98.8 | $C_{16}H_{34}O_2$ | 74.42 | 74.24 | 13.18 | 13.17 |
| *n*-Octadecyl | 8.9 | 49–50 | 100 | $C_{18}H_{38}O_2$ | 75.39 | 74.81 | 13.25 | 13.00 |

hexadecyl peroxide (2.5 g.), and octadecyl methanesulfonate (17 g.), respectively.

Tetradecyl peroxide melted at 36.5° and gave an infrared spectra which had only carbon-hydrogen and carbon-oxygen peaks.

*Anal.* Calcd. for $C_{28}H_{58}O_2$: C, 78.87; H, 13.61. Found: C, 78.58; H, 13.61.

Hexadecyl peroxide melted at 44–46° and gave a similar spectra to tetradecyl peroxide.

*Anal.* Calcd. for $C_{32}H_{66}O_2$: C, 79.67; H, 13.69. Found: C, 79.00; H, 13.43.

The alkaline filtrate from the original precipitate was diluted with water (100 ml.) and extracted twice with 125-ml. portions of hexane. Concentration of the hexane extract gave impure dodecyl peroxide (4 g.) and unreacted tetradecyl methanesulfonate (3 g.) and hexadecyl methanesulfonate (4 g.) respectively.

The dodecyl peroxide was difficult to purify. The principal contaminations based on the infrared spectra were the corresponding methanesulfonate and aldehyde.

The basic solution was cooled to 0° and made slightly acid with concentrated hydrochloric acid. Extraction with three 125-ml. portions of hexane followed by removal of the solvent under reduced pressure gave an oil which, in the case of tetradecyl, hexadecyl, and octadecyl hydroperoxides, solidified at room temperature. Further purification was accomplished by dissolving the oil (10 g.) in absolute methanol (100 ml.) containing potassium hydroxide (20 g.), cooling the resulting solution, and then adding water (25 ml.). Extraction with two 30-ml. portions of hexane was followed by acidification of the methanol solution. Three extractions with 30-ml. portions of hexane followed by removal of the solvent gave the hydroperoxide. The properties of these compounds and yields are listed in Table II.

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(10) C. D. Wagner, R. H. Smith, and E. D. Peters, *Anal. Chem.*, 19, 976 (1947).

(11) A. I. Vogel, *Elementary Practical Organic Chemistry, Part III, Quant. Org. Anal.*, Spottiswoode, Ballantyne and Co. Ltd., London, 1958, p. 836.

[CONTRIBUTION FROM THE NAVAL STORES RESEARCH STATION[1]]

# Preparation of Some Vinyl Alkyl Pinates[2]

J. B. LEWIS AND G. W. HEDRICK

*Received September 8, 1959*

Some monoalkyl pinates, 2,2-dimethyl-3-(alkoxycarbonyl)cyclobutaneacetic acids and alkyl 2,2-dimethyl-3-(carboxy)-cyclobutaneacetates, were vinylated by the vinyl interchange method of Adelman. Vinyloxycarbonyl forms of the ethyl, *n*-butyl, 2-ethylhexyl, and hydronopyl mono esters, and vinyl acetate forms of the ethyl, *n*-butyl, and 2-ethylhexyl mono esters were prepared and characterized. Divinyl pinate and vinyl 2-ethylhexyl phthalate are reported also. The preparation of these esters by vinyl interchange is more satisfactory than by the Reppe procedure.

A study concerned with the internal plasticization of polyvinyl chloride led to the preparation of a number of vinyl alkyl pinates.[3]

Schildknecht[4] stated that dibasic acid monovinyl and divinyl esters are generally difficult to prepare. Adelman[5] reported the preparation of vinyl octyl phthalate and vinyl adipate, presumably monovinyl, by vinyl interchange reaction with vinyl acetate.

Adelman presented evidence to show that esters do not undergo vinyl interchange, *e.g.* only the free carboxyl group of monooctyl phthalate reacted with vinyl acetate.

The synthesis of a number of monoalkyl pinates, the alkyl acetate and the alkyloxycarbonyl forms, is reported in another paper.[6] Both types of monoethyl, -*n*-butyl, -2-ethylhexyl, and -hydronopyl[7] pinates were prepared. The preparation of the vinyl esters of these half esters are reported in this paper, excepting vinyl 2,2-dimethyl-3-(hydronopyloxycarbonyl)cyclobutane acetate.

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) Presented at the 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 13–18, 1959.

(3) In cooperation with Dr. C. S. Marvel, University of Illinois, under contract with the U. S. Department of Agriculture.

(4) C. E. Schildknecht, *Vinyl and Related Polymers*, John Wiley & Sons, Inc., New York, 1952, p. 382.

(5) R. L. Adelman, *J. Org. Chem.*, 14, 1057 (1949)

(6) J. B. Lewis and G. W. Hedrick, *J. Org. Chem.*, 24, 1870 (1959).

(7) J. P. Bain, *J. Am. Chem. Soc.*, 68, 638 (1946).

The method of Reppe[8] proved unsatisfactory for the preparation of these mixed esters with the conditions employed. However, vinylation of the monoesters was accomplished in good yields by use of vinyl acetate and the vinyl interchange procedure of Adelman[5] with a slight modification which consisted of washing the vinyl acetate free esterification mass to remove the mercury catalyst and acidic components. This additional step decreased the still residue.

A small amount of divinyl ester was always formed during the reaction of monoalkyl pinates with vinyl acetate. This is in contrast to Adelman's hypothesis that esters do not react with vinyl acetate under the conditions employed. However, in a vinyl interchange reaction as the reaction proceeds the acetic acid concentration builds up. When this occurs transesterification can take place, thereby liberating some free acid which then is available for vinylation. This was demonstrated by mixing vinyl acetate, diethyl pinate, and acetic acid using the conditions of the vinyl interchange reaction. One to two per cent of the diester was vinylated in this reaction.

Divinyl pinate was prepared for characterization and comparison with material obtained from the other vinylations. The esters and physical properties are given in Table I. Samples of the vinyl esters were reduced and the properties of the saturated esters were determined. Vinyl 2-ethylhexyl phthalate was prepared for polymerization and comparison with the vinyl pinates. The results are included in this paper since the physical properties are somewhat different from those reported previously.

## EXPERIMENTAL

*Vinyl 2,2-dimethyl-3-(ethoxycarbonyl)cyclobutane acetate. Reppe process.* 2,2-Dimethyl-3-(ethoxycarbonyl)cyclobutaneacetic acid,[9] 214 g. (1 mole), and zinc oxide, 15.7 g. (0.19 mole), were added to 250 ml. toluene and heated to reflux to remove water by trapping in a decanter. The solution was almost clear, although some of the zinc salts remained undissolved. Glacial acetic acid, 13.8 g., was added to clarify completely the solution.

Vinylation was accomplished with acetylene by the Reppe procedure.[8] The product was isolated by washing the toluene solution with dilute sulfuric acid, water and dilute carbonate solution. The solvent was stripped under water aspirator vacuum and the residue distilled using a 24-inch Vigreux column. The following fractions were obtained: (1) 5 ml., 20° to 87.5° (0.4 mm.); (2) 50.1 g., 87.5° to 96° (0.4 mm.); (3) 52 g., 97° (0.5 mm.) to 99° (0.55 mm.). Five ml. of the 2nd and 3rd fractions polymerized violently when 0.3% benzoyl peroxide was added. Both polymers were insoluble in acetone, benzene and methanol indicating cross linking presumably because of the presence of divinyl pinate.

*Vinyl interchange reaction.* Monoethyl pinate, above, neut. equiv. 214, 455 g. (2.13 moles) was dissolved in 1193 g. (13.9 moles) freshly distilled vinyl acetate (Eastman Organic Chemicals) containing 1.22 g. copper resinate. Mercuric acetate, 9.4 g. (0.029 mole), was dissolved therein while stirring at room temperature and 2.33 g. (0.023 mole) concentrated sulfuric acid was added slowly. The final solution was clear and bright green in color. After standing 72 hr., 10 g. sodium acetate (0.12 mole) was added. The excess vinyl acetate was stripped by water aspirator vacuum maintaining the still residue at 20° to 30°. The crude ester was dissolved in 500 ml. ether. This solution was washed with dilute aqueous sulfuric acid, then two 500-ml. portions of a dilute solution of alkali maintained at *p*H 8 to 9 with sodium hydroxide and soda ash and finally with water. Acidification of the alkaline extract gave 50 g. recovered starting material. Removal of the solvent as above and distillation, bulb-to-bulb, gave 431 grams, b.p. 100°, 1.9 mm. to 1.5 mm., with 30 g., residue. Redistillation at 2 mm. using a 24-inch Vigreux column gave the following fractions: (1) 10 g. up to 106°, (2) 72 g., 106° to 111°, (3) 28 g., 111° to 112°, and (4) 300 g., 112°.

The last three fractions were combined for removal of divinyl pinate by distillation through a 45-cm. column packed with extruded nickel. The results are tabulated as follows, Table I:

TABLE I

DISTILLATION OF CRUDE VINYL 2,2-DIMETHYL-3-(ETHOXYCARBONYL)CYCLOBUTANEACETIC ACID

| Fractions | B.P., 2 mm. | Wt. (g.) | Composition,[a] % A | Composition,[a] % B | Hydrogenation[b] Equivalent |
|---|---|---|---|---|---|
| 1a | 104–108 | 16 | 95.1 | 4.9 | 1.97 |
| 2a | 108–111 | 17 | 95.1 | 4.9 | 1.97 |
| 3a | 111 | 11 | 11.1 | 88.9 | 1.11 |
| 4a | 111–113 | 40 | 1.8 | 98.2 | 1.02 |
| 5a | 113 | 21 | 1.4 | 98.6 | 1.01 |
| 6a | 113 | 210 | 1.4 | 98.6 | 1.016 |

Residue 55 g. [a] Calcd., as (A) divinyl pinate, as (B) monovinyl ester. [b] Determined by hydrogenation in acetic acid solution with 5% palladium on carbon catalyst. Platinum oxide gave erroneously high results.

Fractions 4a through 6a were combined and the divinyl ester removed by distillation, using the nickel-packed column at a high reflux ratio. The remainder was distilled at a more rapid rate. A sample of fraction 4a and samples of the final distillate with and without 2% added divinyl pinate were polymerized in bulk with benzoyl peroxide as the initiator. The polymers from 4a and the sample with added divinyl pinate were not soluble in benzene, thus indicating cross linking. It is apparent that divinyl pinate is produced by this vinyl interchange reaction.

*Divinyl pinate.* In preparation of zinc pinate by reacting zinc oxide and pinic acid in toluene for use as a catalyst in the Reppe process the reaction mass was thick with insoluble zinc pinate. Furthermore, addition of acetic acid did not dissolve the salt. In another experiment the zinc salt from 42.8 g. (0.2 mole) of monoethyl pinate, alkyloxycarbonyl form was prepared and 184 g. (1 mole) of pinic acid added. After vinylation by addition of acetylene as with the half ester above and working up the product 76 g. crude ester was obtained, b.p. 90 to 150°, 1.0 mm. Since the bulk of the material distilled at 130°, it was concluded the product was chiefly monovinyl pinate.

Because of the difficulties obtained by the Reppe process divinyl pinate was prepared by the vinyl interchange method of Adelman. The product was isolated without washing to remove the catalyst and acidic components. From 82 g. pinic acid (0.44 mole) 30 g. (0.126 mole) of good divinyl pinate was obtained by a bulb-to-bulb distillation and finally distillation using an 18-inch column packed with 1/8-

(8) J. W. Copenhaver and M. H. Bigelow, *Acetylene and Carbon Monoxide Chemistry*, Reinhold Publishing Corp., New York, p. 59.

(9) Pinic acid esters used in this work consisted of mixtures of *cis-d-* and *cis-dl*-isomers.[6]

inch glass helices; diethyl ester from reduction, $n_D^{20}$ 1.4457.

*Vinyl interchange with vinyl acetate and diethyl pinate.* In order to show that an interchange reaction can occur between an ester and vinyl acetate, 121 g. (0.5 mole) of diethyl pinate was treated at room temperature with vinyl acetate using a mercury catalyst as above. In addition 21 ml. glacial acetic acid was added to simulate conditions toward the end of a normal vinyl interchange reaction. The first portion of the distillate, about 10 g., b.p. 100 to 113°, 2 mm., contained vinyl ester which on hydrogenation absorbed 0.008 mole hydrogen. Subsequent fractions combined, 48 g., b.p. 113° to 114°, 2 mm., decolorized bromine in carbon tetrachloride. The last fraction, 4 g., contained no unsaturated compounds.

*Vinyl 2,2-dimethyl-3-(n-butoxycarbonyl)- and -3-(2-ethylhexyloxycarbonyl)cyclobutane acetates.* Vinylation of 2,2-dimethyl-3-(*n*-butoxycarbonyl)- and -3-(2-ethylhexyloxycarbonyl)cyclobutaneacetic acid was accomplished by the vinyl interchange procedure used for the 3-ethoxycarbonyl derivative. With the higher molecular weight esters the volume of vinyl acetate charged was increased. With the butyl ester 644 g. (7.48 moles) and with the 2-ethylhexyl ester 793 g. (9.22 moles) vinyl acetate were used per mole pinate ester. Because of the higher boiling point of these higher molecular weight esters, isolation to free them of divinyl pinate was easier than with the ethyl ester.

*Ethyl, n-butyl, 2-ethylhexyl and hydronopyl 2,2-dimethyl-3-(vinyloxycarbonyl)cyclobutane acetates.* Vinylation of ethyl, *n*-butyl, 2-ethylhexyl and hydronopyl 2,2-dimethyl-3-(carboxy)cyclobutane acetates resulted in 70 to 80% yields by reacting the monoesters with vinyl acetate as above. The vinyl acetate was increased for the higher molecular weight esters.

The vinylation of 454 g., (2.12 moles) of monoethyl pinate gave 413 g. crude ester. The results of fractionation using the nickel packed column mentioned before are tabulated in Table II.

In this instance the presence of divinyl pinate was indicated from hydrogenation data. Redistillation gave 355 g. almost pure vinyl ester. The presence of divinyl pinate was observed in all the vinylations made.

*Vinyl 2-ethylhexyl phthalate.* Because of the instability of mono-2-ethylhexyl phthalate toward distillation the crude mixture containing principally anhydride, mono and diester was vinylated by the vinyl interchange method. Since the physical constants obtained for vinyl 2-ethylhexyl ester differs from the data given by Adelman[5] it is presumed that he used *n*-octyl alcohol in his synthesis.

The results of the characterization of the vinyl esters are tabulated in Table III. Divinyl pinate and vinyl alkyl pinates were reduced and the resulting diethyl esters identified by refractive index and density.[6]

TABLE II

DISTILLATION OF ETHYL 2,2-DIMETHYL-3-(VINYLOXYCARBONYL)CYCLOBUTANE ACETATE

| Fractions | B.P., 2 mm. | Wt., g. | Composition,[a] % A | % B | Hydrogenation Equivalent |
|---|---|---|---|---|---|
| 1 | 68 to 104 | 25 | — | — | — |
| 2 | 105 to 112 | 48 | 7.6 | 92.4 | 1.078 |
| 3 | 112 to 113 | 45 | 1.2 | 98.8 | 1.012 |
| 4 | 113 | 270 | 0.8 | 99.2 | 1.009 |

[a] Calcd. as (A) divinyl pinate, as (B) monovinyl ester.

TABLE III

VINYL ALKYL PINATES

| Vinyl Alkyl Esters | Hydrogenation Equivalent[a] | B.P. Mm./Hg | | $n_D^{20}$ | $d^{20}$ | Formula | Analyses Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|---|
| Vinyl Acetates ROC(=O)<cyclobutane>CH$_2$COCH=CH$_2$ | | | | | | | | | | |
| Ethyl | 0.99 | 113 | 2.0 | 1.4558 | 1.0220 | $C_{13}H_{20}O_4$ | 64.98 | 8.39 | 64.81 | 8.39 |
| *n*-Butyl | 0.99 | 135–136 | 2.0 | 1.4569 | 0.9992 | $C_{15}H_{24}O_4$ | 67.13 | 9.01 | 66.82 | 8.96 |
| 2-Ethylhexyl | 0.98 | 142 | 0.4 | 1.4594 | 0.9691 | $C_{19}H_{32}O_4$ | 70.33 | 9.94 | 70.52 | 9.75 |
| Alkyl Acetates CH$_2$=CH$_2$OC(=O)<cyclobutane>CH$_2$COR | | | | | | | | | | |
| Ethyl | 1.009 | 113 | 2.0 | 1.4556 | 1.0200 | $C_{13}H_{20}O_4$ | 64.98 | 8.39 | 64.86 | 8.47 |
| *n*-Butyl | 0.99 | 130–134 | 2.0 | 1.4560 | 0.9980 | $C_{15}H_{24}O_4$ | 67.13 | 9.01 | 66.82 | 8.96 |
| 2-Ethylhexyl | 1.007 | 138 | 0.1 | 1.4592 | 0.9686 | $C_{19}H_{32}O_4$ | 70.33 | 9.94 | 70.26 | 9.83 |
| Hydronopyl | 1.004 | 170 | 0.1 | 1.4872 | 1.0287 | $C_{22}H_{34}O_4$ | 72.89 | 9.45 | 72.83 | 9.54 |
| Others | | | | | | | | | | |
| Divinyl pinate | 1.99 | 110–112 | 2.0 | 1.4667 | 1.0343 | $C_{13}H_{18}O_4$ | 65.53 | 7.61 | 65.46 | 7.69 |
| Vinyl 2-ethylhexyl phthalate | 1.00 | 144 | 0.1 | 1.5008 | 1.0364 | $C_{18}H_{24}O_4$ | 71.03 | 7.95 | 71.25 | 8.20 |

[a] Equivalents hydrogen per mole.

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OLUSTEE, FLA.

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

# New Organic Compounds for Use in Insect Control

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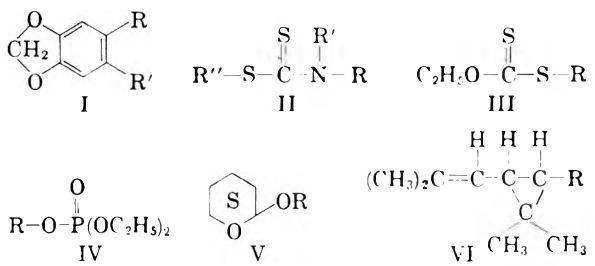
The preparation and physical constants of some new 3,4-methylenedioxyphenyl compounds, dithiocarbanilates, ethyl xanthates, diethyl phosphates, 2-substituted tetrahydropyrans, and chrysanthemumyl and chrysanthemumoyl derivatives for use in insect control are described.

In addition to the use of insecticides, other approaches that may help in the control of insect pests are explored in this Division. For example, insect attractants,[1,2] repellents,[2] and insecticide potentiating materials (synergists)[3] are being investigated. As part of these studies a variety of new compounds (sixty-six in all), including 3,4-methylenedioxyphenyl derivatives (I), dithiocarbanilates (II), ethyl xanthates (III), diethyl phosphates (IV), 2-substituted tetrahydropyrans (V), and chrysanthemumyl and chrysanthemumoyl derivatives (VI) were synthesized. Their preparation and physical constants are reported here.



Although 3,4-methylenedioxybenzyl esters (I R = H, halogen or alkyl, R′ = $CH_2OCR''$, with O) have been extensively investigated, compounds with α-substituted side chains (I R = halogen or alkyl, R′ = $CHR'''OCR''$, with O) have not. Two such compounds, 6-chloro-α-ethylpiperonyl chrysanthemumate and the α-methyl analog, were synthesized because of their similarity to the insecticide barthrin (6-chloropiperonyl chrysanthemumate).[4] The obvious preparative route to the intermediate α-alkyl-6-chloropiperonyl alcohol needed for the synthesis of the α-alkyl esters is *via* the reaction of 6-chloropiperonal with the appropriate Grignard reagent. This starting material, 6-chloropiperonal, was prepared initially by treating piperonal with chlorine gas,[5] but instead of the reported yield of 60%, less than 35% of the pure product was obtained consistently. In a simpler procedure the 6-chloropiperonal was obtained in 50% yield by allowing a mixture of piperonal, benzoyl peroxide, glacial acetic acid, and sulfuryl chloride to stand at room temperature for ten days.

For small-scale preparations of the α-alkyl-6-halopiperonyl alcohol intermediates, the appropriate Grignard reagent was added to a suspension of 6-chloropiperonal in a large volume of ether. Attempts to prepare the pure intermediate alcohols on a large scale by this procedure were unsuccessful because of the insolubility of 6-chloropiperonal in ether.

The chlorination of 3,4-methylenedioxyphenyl acetate (sesamyl acetate) with sulfuryl chloride proceeded in good yield without the benzoyl peroxide catalyst. This result was not anticipated, since it is reported that phenyl acetate does not react with sulfuryl chloride under mild conditions in the absence of catalyst.[6]

The investigation resulted also in a synthesis in pure form and in reasonable yield of new compounds of the type I in which R = halogen and R′ = $OC_2H_4R''$. In the sequence of reactions hydroxyethylation of sesamol[3,7] with ethylene carbonate was followed by acetylation of the free hydroxyl group, chlorination with sulfuryl chloride, and finally deacetylation which produced I (R = Cl, R′ = $OC_2H_4OH$) in good yield. Treatment of the alcohol with phosphorus tribromide gave β-bromo-2-chloro-4,5-methylenedioxyphenetole (Table I, No. 13) in 83% yield. Of interest was the finding that sesamol and 6-chlorosesamol were

(1) S. I. Gertler, L. F. Steiner, W. C. Mitchell, and W. F. Barthel, *J. Agr. Food Chem.*, **6**, 592 (1958).

(2) S. A. Hall, N. Green, and M. Beroza, *J. Agr. Food Chem.*, **5**, 663 (1957).

(3) M. Beroza and W. F. Barthel, *J. Agr. Food Chem.*, **5**, 855 (1957); M. Beroza, *J. Agr. Food Chem.*, **4**, 49 (1956).

(4) W. F. Barthel, B. H. Alexander, J. B. Gahan, and P. G. Piquett, U. S. Patent 2,886,485, May 12, 1959; W. F. Barthel and B. H. Alexander, *J. Org. Chem.*, **23**, 1012 (1958); W. A. Gersdorff and P. G. Piquett, *J. Econ. Entomol.*, **52**, 85 (1959).

(5) A. Parys, *Rec. Trav. Chim.*, **49**, 17 (1930).

(6) A. Peratoner, *Gazz. Chim. Ital.*, **28**, I, 197 (1898); H. C. Brown, *Ind. Eng. Chem.*, **36**, 785 (1944).

(7) J. Boesecken, W. D. Cohen, C. J. Kip, *Rec. Trav. Chim.*, **55**, 815 (1936); B. H. Alexander, T. A. Oda, R. T. Brown, and S. I. Gertler, *J. Org. Chem.*, **23**, 1969 (1958); S. I. Gertler, B. H. Alexander, and M. Beroza, *J. Org. Chem.*, **24**, 327 (1959); B. H. Alexander, S. I. Gertler, R. T. Brown, T. A. Oda, and M. Beroza, *J. Org. Chem.*, **24**, 1504 (1959).

readily hydroxyethylated with ethylene carbonate, whereas attempts to hydroxyethylate 2-(2-methylallyl)-4,5-methylenedioxyphenol or the methyl ester of 3-hydroxy-2-naphthoic acid in the same manner were unsuccessful. Molecular models indicated that steric hindrance might be responsible for the lack of reactivity.

The methyl carbanilates (Table IV, Nos. 65 and 66) were made by the procedure of Losanitsch[8] from the intermediate ammonium butyldithiocarbanilate and ammonium *p*-chlorodithiocarbanilate, which are yellow to off-white solids. The ammonium salts are new compounds similar to those described by Miller,[9] which are unstable at room temperature and decompose, liberating ammonium thiocyanate, hydrogen sulfide, and free sulfur; consequently no attempt was made to analyze them for the elements. However, the esters prepared from the salts are stable and gave good elemental analyses.

Kenner and Williams[10] describe the synthesis of diethyl phosphates from phenols and diethyl phosphite. We have found their procedure applicable to other hydroxy compounds.

The preparation of other compounds is described in the experimental section and the physical constants are given in the Tables.

The yields obtained in this study can probably be improved since purity of compounds rather than yield was emphasized.

## EXPERIMENTAL

*3,4-Methylenedioxyphenyl compounds* (Table I) All compounds except Numbers 3–7, 12, 13, and 15 were prepared by the general procedures reported previously from this laboratory.[4,7]

*2-(3,4-Methylenedioxyphenoxy)ethanol* (*No. 3*). This compound was prepared from sesamol[7] and ethylene carbonate by the procedure of Carlson and Cretcher.[11]

*2-(3,4-Methylenedioxyphenoxy)ethyl acetate* (*No. 4*). Acetyl chloride (0.61 mole) was added dropwise to a stirred solution of 2-(3,4-methylenedioxyphenoxy)ethanol (0.61 mole), pyridine (0.61 mole) and benzene (500 ml.) at 25°. After standing overnight at room temperature, the mixture was transferred to a separatory funnel, where it was washed successively with water, 5% aqueous hydrochloric acid, water, saturated sodium bicarbonate, and saturated sodium chloride. The benzene layer was dried, and after removal of the benzene the residue was distilled. The first fraction boiled at 163–168°/23 mm. and was obtained in 33% yield; $n_D^{25}$ 1.5269. The second fraction, which contained the desired product (No. 4) boiled at 122–135°/1 mm. and solidified in the receiving flask. The solid melted at 56–58° after recrystallization from aqueous ethanol. A mixed melting point with the starting material, 2-(3,4-methylenedioxyphenoxy)ethanol, which melted at 57–58°, was depressed to 38–48°.

The aforementioned first fraction was identified as sesamyl acetate by comparing it with the sesamyl acetate previously reported by Beroza;[3] its isolation from the reaction mixture in 33% yield indicates that 2-(3,4-methylenedioxyphenoxy)-ethanol was partly cleaved, probably because of the hydrogen chloride liberated during the formation of the ester from the acid chloride.

*2-(2-Chloro-4,5-methylenedioxyphenoxy)ethyl acetate* (*No. 15*). Sulfuryl chloride (0.5 mole) was added dropwise to a stirred solution of 2-(3,4-methylenedioxyphenoxy)ethyl acetate (0.4 mole) in glacial acetic acid (200 ml.) while maintaining a temperature below 50°. After addition of the sulfuryl chloride, the mixture was stirred at room temperature for 0.5 hr., then poured into ice and water with stirring. Crystallization occurred on standing. The crystals were filtered off, washed with water, dried, and recrystallized from ethanol.

*β-Bromo-2-chloro-4,5-methylenedioxyphenetole* (*No. 13*). A mixture of 2-(2-chloro-4,5-methylenedioxyphenoxy)ethyl acetate (0.2 mole) and 2*N* sodium methylate (110 ml.) was allowed to stand at 25° overnight, and then poured into ice and water with stirring, whereupon crystallization occurred. The crystals were washed with water, dried, and recrystallized from ethanol, giving practically pure 2-(2-chloro-4,5-methylenedioxyphenoxy)ethanol, which melted at 82–83°. Treatment of this compound (0.6 mole) with phosphorus tribromide (0.19 mole)[12] at 75–80°, with stirring for 2 hr. produced a residue which when poured into ice and water gave the crystalline β-bromo-2-chloro-4,5-methylenedioxyphenetole.

*2-Bromo-4,5-methylenedioxy-α-toluenethiol* (*No. 6*). 6-Bromopiperonyl bromide[4] was treated with thiourea according to the procedures described by Urquhart and co-workers.[13]

*6-Bromopiperonyl thioacetate* (*No. 7*). Prepared from 2-bromo-4,5-methylenedioxy-α-toluenethiol, benzene, acetyl chloride, and pyridine in the usual way.

*2-Chloro-4,5-methylenedioxyphenyl acetate* (*No. 12*). Sulfuryl chloride (0.26 mole) was added dropwise to a stirred solution of sesamyl acetate[3] (0.25 mole) and glacial acetic acid (90 ml.) at 25°. The solution turned blue initially, but later became yellow as the temperature rose to 40°. After stirring for 0.25 hr. at 35–40° to remove sulfur dioxide and hydrogen chloride, the solution was poured into ice and water, where precipitation of the crystalline product occurred.

*6-Chloropiperonal.* A solution of piperonal (0.25 mole), glacial acetic acid (200 ml.), benzoyl peroxide (10 g.), and sulfuryl chloride (0.75 mole) was allowed to stand at room temperature for 10 days. It was then poured into a well stirred ice and water mixture, where crystallization occurred. The crystals, after being washed with cold water and dried, were recrystallized from aqueous ethanol and obtained in 50% yield; a mixed melting point with an authentic sample melting at 114–115° was not depressed.[14]

*Ethers of tetrahydropyran* (Table II). The ethers were prepared in diethyl ether from the alcohol, 2,3-dihydropyran, and a catalytic amount of concentrated hydrochloric acid, according to procedure described by Ott.[15]

*Xanthates* (Table II). The compounds were made in the usual way from the alkyl or aryl halide, potassium xanthogenate, and ethanol.[16]

*Diethyl phosphates* (Table II). The phosphates were made from the phenol or alcohol and diethyl hydrogen phosphite, according to a minor modification of the procedure of Kenner and Williams.[10] It seemed preferable to stir rather than

(8) S. M. Losanitsch, *Ber.*, **24**, 3021 (1891).

(9) L. P. Miller, *Contrib, Boyce Thompson Inst.*, **5**, 31 (1933).

(10) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).

(11) W. W. Carlson and L. H. Cretcher, *J. Am. Chem. Soc.*, **69**, 1955 (1947); W. W. Carlson, U. S. Patent **2,448,-767**, Sept. 7, 1948.

(12) G. C. Harrison and H. Diehl, *Org. Syntheses*, **Coll. Vol. III**, 370 (1955).

(13) G. G. Urquhart, J. W. Gates, Jr., and R. Connor, *Org. Syntheses*, **21**, 36 (1941).

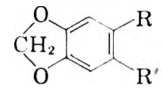
(14) K. Weisze, *Ber.*, **43**, 2605 (1910).

(15) A. C. Ott, M. F. Murray, and R. L. Pederson, *J. Am. Chem. Soc.*, **74**, 1239 (1952).

(16) A. I. Vogel, *Practical Chemistry*, p. 484, Longmans, Green and Co., New York, 1951.

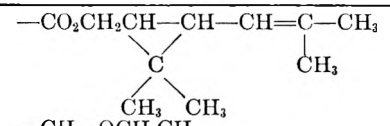
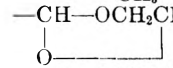
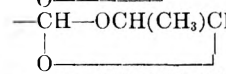
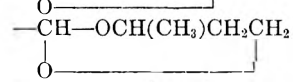
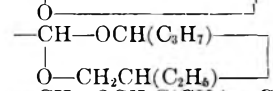
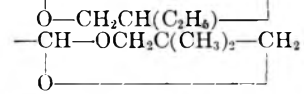
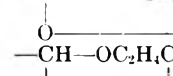
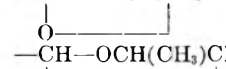
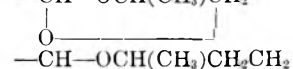
TABLE I

3,4-METHYLENEDIOXYPHENYL COMPOUNDS



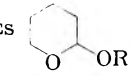
| No. | R | R′ | Yield, % | B.P., °C./Mm. | $n_D^{25}$ or M.P. | Molecular Formula | Analyses: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | $-O_2C-(CH_2)_6CH_3$ | 75 | 156–160/0.7 | 1.4967 | $C_{15}H_{20}O_4$ | 68.16 | 68.89 | 7.63 | 7.77 |
| 2 | H | $-O_2C-CH_2C_6H_5$ | 78 | 152–162/0.15 | 1.5712 | $C_{15}H_{12}O_4$ | 70.30 | 70.08 | 4.72 | 4.66 |
| 3 | H | $-OC_2H_4OH$ | 59 | — | 57–58 (toluene) | $C_9H_{10}O_4$ | 59.33 | 59.82 | 5.53 | 5.23 |
| 4 | H | $-OC_2H_4O_2C-CH_3$ | 38[a] | — | 56–58 (alcohol and water) | $C_{11}H_{12}O_5$ | 58.92 | 58.82 | 5.40 | 5.64 |
| 5 | H | $-O_2C-CH_3$ | 33[a] | 163/24 | — | $C_9H_8O_4$ | 60.00 | 59.79 | 4.47 | 4.48 |
| 6 | Br | $-CH_2SH$ | 99 | 112–128/0.2 | 70–71[b] (alcohol) | $C_8H_7BrO_2S$ | 38.88 | 37.81 | 2.86 | 3.14 |
| 7 | Br | $-CH_2SC(=O)-CH_3$ | 47 | — | 108–109 (benzene and petroleum ether) | $C_{10}H_9BrO_3S$ | 41.54 | 41.42 | 3.11 | 3.15 |
| 8 | Br | $-CH_2OCH_2-C(CH_3)_2-CH=CH-CH=C(CH_3)_2$ | 55 | 165–173/0.5 | 1.5410 | $C_{18}H_{23}BrO_3$ | 58.86 | 59.16 | 6.31 | 6.50 |
| 9 | Br | $-CH_2OC_2H_4OC_4H_9$ | 61 | 148–157/0.5 | 1.5260 | $C_{14}H_{19}BrO_4$ | 50.77 | 51.00 | 5.78 | 5.73 |
| 10 | Br | $-CH_2OCH(CH_3)CH_2OCH_3$ | 52 | 124–131/0.3 | 1.5410 | $C_{12}H_{15}BrO_4$ | 47.54 | 47.42 | 4.99 | 4.89 |
| 11 | Br | $-CH_2OC_2H_4OC_2H_4OC_4H_9$ | 59 | 161–173/0.2 | 1.5221 | $C_{16}H_{23}BrO_5$ | 51.27 | 51.08 | 6.18 | 6.32 |
| 12 | Cl | $-O_2C-CH_3$ | 64 | — | 86–87 (alcohol) | $C_9H_7ClO_4$ | 50.37 | 50.52 | 3.29 | 3.49 |
| 13 | Cl | $-OC_2H_4Br$ | 83 | — | 73–74 (propanol) | $C_9H_8BrClO_3$ | 38.67 | 38.49 | 2.88 | 2.80 |
| 14 | Cl | $-OC_2H_4OC(=O)-CH-CH-CH=C(CH_3)-CH_3$ with $C(CH_3)_2$ | 58 | 197–198/1.0 | 1.5335 | $C_{19}H_{23}ClO_5$ | 62.21 | 62.23 | 6.32 | 6.12 |
| 15 | Cl | $-OC_2H_4OC(=O)-CH_3$ | 77 | — | 64–65 (alcohol) | $C_{11}H_{11}ClO_5$ | 51.07 | 50.73 | 4.29 | 4.24 |
| 16 | Cl | $-CH(C_2H_5)OC(=O)-CH-CH-CH=C(CH_3)-CH_3$ with $C(CH_3)_2$ | 73[c] | 160–177/0.3 | 1.5281 | $C_{20}H_{25}ClO_4$ | 65.83 | 65.93 | 6.91 | 6.99 |
| 17 | Cl | $-CH_2OC_2H_4OCH_3$ | 65 | 172–189/26 | 1.5307 | $C_{11}H_{13}ClO_4$ | 54.00 | 53.76 | 5.35 | 5.46 |
| 18 | Cl | $-CH_2OCH_2-CH-CH-CH=C(CH_3)-CH_3$ with $C(CH_3)_2$ | 50 | 146–149/0.2 | 1.5296 | $C_{18}H_{23}ClO_3$ | 66.97 | 66.78 | 7.18 | 7.36 |

TABLE I *Continued*

| No. | R | R′ | Yield, % | B.P., °C./Mm. | $n_D^{25}$ or M.P. | Molecular Formula | Analyses | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Carbon | | Hydrogen | |
| | | | | | | | Calcd. | Found | Calcd. | Found |
| 19 | Cl |  | 33 | — | 70–71 (alcohol) | $C_{13}H_{21}ClO_4$ | 64.18 | 64.37 | 6.28 | 6.26 |
| 20 | Br |  | 83 | — | 72–73 (alcohol) | $C_{10}H_9BrO_4$ | 43.97 | 43.94 | 3.30 | 3.42 |
| 21 | Br |  | 87 | 130–131/0.3 | 1.5638 | $C_{11}H_{11}BrO_4$ | 45.99 | 46.56 | 3.83 | 3.99 |
| 22 | Br |  | 47 | — | 112–113 (alcohol) | $C_{12}H_{13}BrO_4$ | 47.85 | 48.14 | 4.32 | 4.56 |
| 23 | Br |  | 48 | — | 67–68 (alcohol) | $C_{16}H_{21}BrO_4$ | 53.79 | 54.52 | 5.88 | 6.03 |
| 24 | Br |  | 96 | — | 114–115 (alcohol) | $C_{13}H_{15}BrO_4$ | 49.53 | 49.07 | 4.76 | 4.69 |
| 25 | Br |  | 84 | — | 93–95 (alcohol) | $C_{11}H_{11}BrO_4$ | 46.01 | 45.85 | 3.76 | 3.71 |
| 26 | Cl |  | 85 | 111–112/0.1 | 1.5442 | $C_{11}H_{11}ClO_4$ | 54.43 | 54.61 | 4.53 | 4.73 |
| 27 | Cl |  | 79 | — | 115–116 (alcohol) | $C_{12}H_{13}ClO_4$ | 56.14 | 55.82 | 5.07 | 5.21 |

[a] See preparation of this compound in Experimental section. [b] This product contains an impurity that we could not remove. [c] The α-methyl analog was also prepared, but we were unable to purify the product; the boiling range was 168–183°/0.8 mm., $n_D^{25°}$ 1.5304.

TABLE II

XANTHATES $\left(C_2H_5OC(=S)-SR\right)$, DIETHYL PHOSPHATES $\left(R-OP(=O)-(OC_2H_5)_2\right)$, AND TETRAHYDROPYRAN DERIVATIVES 

| No. | R | Yield, % | B.P./Mm. | $n_D^{25}$ | Molecular Formula | Analyses: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Other Calcd. | Other Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Xanthates | | | | | | | |
| 28 | i-$C_3H_7$ | 77 | 86–90/14 | 1.5231 | $C_6H_{12}OS_2$ | 43.86 | 44.16 | 7.37 | 7.18 | — | — |
| 29 | —$CH_2C{\equiv}CH$ | 44 | 112–119/15 | 1.5409 | $C_6H_8OS_2$ | 44.97 | 44.87 | 5.03 | 5.56 | — | — |
| 30 | —CH(—$CH_2$—$CH_2$—)$CH_2$ | 76 | 123–136/17 | 1.5497 | $C_8H_{14}OS_2$ | 50.48 | 50.52 | 7.41 | 7.36 | — | — |
| 31 | —$C_2H_4C_6H_5$ | 77 | 116–117/0.6 | 1.5869 | $C_{11}H_{14}OS_2$ | 58.37 | 58.73 | 6.23 | 6.42 | — | |
| | | | | Diethyl phosphates | | | | | | | |
| 32 | 3,4-$CH_2O_2$—$C_6H_3$— | 70 | 133–142/0.15 | 1.4926 | $C_{11}H_{15}O_6P$ | — | — | — | — | (P) 11.30 | 11.52 |
| 33 | 2-Br-4,5-$CH_2O_2$—$C_6H_2$— | 58 | 170–172/0.6 | 1.5228 | $C_{11}H_{14}BrO_6P$ | — | — | — | — | (Br) 22.63 | 22.61 |
| 34 | 3-$CH_3$—$C_6H_4$—$CH_2$— | 37 | 123–126/0.4 | 1.4816 | $C_{12}H_{19}O_4P$ | 55.81 | 55.38 | 7.42 | 7.36 | — | — |
| 35 | 3,4-$(CH_3)_2$—$C_6H_3$—$CH_2$— | 41 | 133–135/0.4 | 1.4865 | $C_{13}H_{21}O_4P$ | 57.34 | 56.42 | 7.78 | 7.50 | — | — |
| 36 | 2,4-$(CH_3)_2$—$C_6H_3$—$CH_2$— | 30 | 128–130/0.3 | 1.4849 | $C_{13}H_{21}O_4P$ | 57.34 | 56.57 | 7.78 | 7.52 | — | — |
| 37 | —$CH_2C{\equiv}CH$ | 55 | 136–141/25 | 1.4274 | $C_7H_{13}O_4P$ | 43.75 | 43.44 | 6.82 | 6.71 | — | — |
| 38 | —$CH_2C(CH_3){=}CH_2$ | 51 | 127–133/21 | 1.4239 | $C_8H_{17}O_4P$ | 46.15 | 46.28 | 8.23 | 8.53 | — | — |
| | | | | Tetrahydropyrans | | | | | | | |
| 39 | —$C_2H_4OC_2H_4OC_4H_9$ | 71 | 162–176/18 | 1.4447 | $C_{13}H_{26}O_4$ | 63.38 | 63.35 | 10.64 | 10.56 | — | — |
| 40 | —$CH_2$—CH(—C($CH_3$)($CH_3$)—)—CH—C($CH_3$) | 62 | 140–147/17 | 1.4719 | $C_{15}H_{26}O_2$ | 75.58 | 75.45 | 11.00 | 10.94 | — | — |
| 41 | —$CH_2$—$C_6H_2$—2Br—4,5-$CH_2O_2$ | 48 | 147–149/0.2 | 1.5565 | $C_{13}H_{15}BrO_4$ | 49.54 | 48.65 | 4.80 | 4.73 | — | — |
| 42 | —$C_2H_4OC_2H_4OCH_3$ | 48 | 131–146/20 | 1.4458 | $C_{10}H_{20}O_4$ | 58.80 | 59.06 | 9.87 | 9.82 | — | — |

TABLE III. CHRYSANTHEMUMYL AND CHRYSANTHEMUMOYL DERIVATIVES

$(CH_3)_2C{=}CH{-}CH{-}CH{-}R$ (C bonded to $CH_3$ and $CH_3$)

| No. | R | Yield, % | B.P./Mm. | $n_D^{25°}$ | Molecular Formula | Analyses: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|---|
| 43 | $-CH_2OH$ | 92 | 107–108/14 | 1.4707 | $C_{10}H_{18}O$[a] | 77.92 | 76.92 | 11.76 | 11.74 |
| 44 | $-CH_2O_2C-CH_3$ | 81 | 112–113/14 | 1.4557 | $C_{12}H_{20}O_2$ | 73.47 | 73.55 | 10.20 | 10.18 |
| 45 | $-CH_2O_2C-C_2H_5$ | 62 | 121–122/13 | 1.4548 | $C_{13}H_{22}O_2$ | 74.29 | 74.49 | 10.48 | 10.62 |
| 46 | $-CH_2O_2C-C_6H_4$-*o*-$CH_3$ | 87 | 123–124/0.3 | 1.5152 | $C_{18}H_{24}O_2$ | 79.41 | 79.14 | 8.82 | 8.55 |
| 47 | $-CH_2O_2C-C_6H_4$-*p*-$OCH_3$ | 83 | 146–148/0.3 | 1.5253 | $C_{18}H_{24}O_3$ | 75.00 | 74.85 | 8.33 | 8.34 |
| 48 | $-CO_2CH_2CH{=}CH_2$ | 94 | 119–120/12 | 1.4693 | $C_{13}H_{20}O_2$ | 74.95 | 74.55 | 9.67 | 9.45 |
| 49 | $-CO_2CH_2CH(CH_3)_2$ | 91 | 124–125/12 | 1.4569 | $C_{14}H_{24}O_2$ | 74.75 | 74.24 | 10.78 | 10.94 |
| 50 | $-CO_2CH(CH_3)C_2H_5$ | 89 | 121–122/12 | 1.4554 | $C_{14}H_{24}O_2$ | 74.75 | 74.48 | 10.78 | 10.70 |
| 51 | $-CO_2C_2H_4Br$ | 80 | 87–88/0.3 | 1.4908 | $C_{12}H_{19}BrO_2$[b] | 52.37 | 53.46 | 6.95 | 7.12 |
| 52 | $-CO_2CH(CH_3)_2$ | 84 | 110–111/12 | 1.4538 | $C_{13}H_{22}O_2$ | 74.23 | 73.56 | 10.54 | 10.25 |
| 53 | $-CO_2C_4H_9$ | 89 | 132/12 | 1.4594 | $C_{14}H_{24}O_2$ | 74.75 | 74.85 | 10.78 | 11.02 |
| 54 | $-CO_2-CH_2-$  | 38 | 167–170/0.2 | 1.5694 | $C_{21}H_{24}O_2$ | 81.78 | 81.52 | 7.84 | 7.54 |
| 55 | $-CO_2-$  | 53 | | 82–83 (alcohol) | $C_{20}H_{22}O_2$[c] | 81.60 | 81.22 | 7.53 | 7.37 |
| 56 | $-CO_2-C_6H_4-Cl$  | 53 | 169–171/0.2 | 1.5600 | $C_{16}H_{15}ClO_2$ | 46.13 | 45.89 | 3.63 | 3.64 |
| 57 | $-CO_2C_2H_4SC_2H_5$ | 76 | 110–127/0.8 | 1.4890 | $C_{14}H_{24}O_2S$[a] | 65.58 | 65.71 | 9.43 | 9.29 |

[a] Crude product prepared earlier by W. F. Barthel (unpublished data). [b] Slowly decomposes on standing. [c] Crude product prepared earlier by N. Mitlin, N. Green, W. A. Gersdorff, and M. S. Schechter, U. S. Dept. Agr., **ARA E-865**, 5 pp. (1953).

TABLE IV. OTHER COMPOUNDS

| No. | Name | Yield, % | B.P./Mm. | $n_D^{25}$ or M.P. | Molecular Formula | Analyses: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 58 | Isopentyl 1-naphthoate | 72 | 148–151/0.4 | 1.5638 | $C_{16}H_{18}O_2$ | 79.31 | 79.50 | 7.49 | 7.25 | — | — |
| 59 | *N*-(*p*-Phenylazophenyl)-1-naphthamide | 53 | — | 212–214 (alcohol) | $C_{23}H_{17}N_3O$ | — | — | — | — | 11.96 | 12.04 |
| 60 | *N*,*N*-Dipropyl-1-naphthamide | 78 | 146–149/0.2 | 1.5745 | $C_{17}H_{21}NO$ | 79.96 | 80.34 | 8.29 | 8.17 | — | — |
| 61 | *N*,*N*-Diethyl-1-naphthamide | 77 | 145–148/0.3 | 1.5910 | $C_{15}H_{17}NO$ | 79.28 | 79.06 | 7.52 | 7.33 | — | — |
| 62 | *N*-(1-Naphthoyl)piperidine | 47 | 160–185/0.3 | 97° (alcohol) | $C_{16}H_{17}NO$ | — | — | — | — | 5.85 | 5.99 |
| 63 | α-Ethylbenzyl trichloroacetate | 66 | 80–84/0.2 | 1.5134 | $C_{11}H_{11}Cl_3O_2$ | 46.92 | 47.45 | 3.94 | 4.32 | — | — |
| 64 | 2-(Ethylthio)ethyl butyrate | 80 | 106–110/12 | 1.4543 | $C_8H_{16}O_2S$ | 54.50 | 55.15 | 9.15 | 8.95 | — | — |
| 65 | Methyl butyldithiocarbanilate | 30 | — | 68–70 (alcohol) | $C_{12}H_{17}NS_2$ | — | — | — | — | 5.85 | 5.68 |
| 66 | Methyl *p*-chlorodithiocarbanilate | 46 | — | 108–110 (methanol) | $C_8H_8ClNS_2$ | — | — | — | — | 6.43 | 6.47 |

shake the reaction mixture, and also to wash any aliphatic organic layers containing the crude unsaturated phosphate esters with a saturated salt solution rather than with dilute hydrochloric acid.

*Chrysanthemumyl and chrysanthemumoyl derivatives* (Table III). The chrysanthemumyl derivatives were made from chrysanthemumyl alcohol, prepared by reducing synthetic ethyl chrysanthemumate with lithium aluminum hydride in the usual way. The double bond was not affected by this reduction. The esters of the alcohol were made *via* the acid chloride route with pyridine as an acid acceptor. Similarly the esters of synthetic chrysanthemumic acid were made from chrysanthemumoyl chloride.[17]

*Preparation of other compounds* (Table IV). The esters and amides were obtained in the usual manner from a mixture of the alcohol, phenol, or amine with the proper acid chloride, pyridine, and benzene. The methyl and ammonium dithiocarbanilates were made by the general procedure of Miller[9] and Losanitsch.[8]

BELTSVILLE, MD.

(17) Y. L. Chen and W. F. Barthel, *J. Am. Chem. Soc.*, 75, 4287 (1953).

# Notes

A department for short papers of immediate interest.

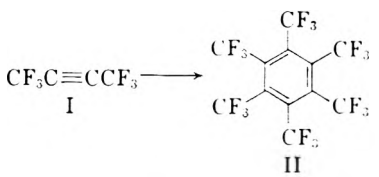
## The Trimerization of Hexafluoro-2-butyne

J. F. Harris, Jr., R. J. Harder, and G. N. Sausen

*Received October 12, 1959*

The trimerization of alkyl and aryl substituted acetylenes to give substituted benzenes is well known,[1] but there appear to be no reports of trimerization of a fluoroalkyl acetylene.[2]

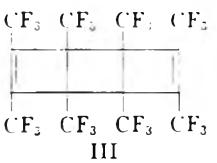
We have found that the novel hexakis(trifluoromethyl)benzene (II) can be obtained in yields of 70 to 75% by heating hexafluoro-2-butyne (I) with trifluoromethyl iodide or iodine at 260° under pressure. Smaller yields have also been obtained by heating the butyne alone at 275°.



I II

Hexakis(trifluoromethyl)benzene (II) is a colorless, crystalline, readily sublimable compound melting at 210–212° (sealed capillary). The fluorine nuclear magnetic resonance spectrum in acetone consists of a single, unsplit resonance line, indicating that the fluorine atoms are all equivalent. The results of cryoscopic molecular weight measurements in benzene were about 4 to 7% higher than the value calculated for the trimer, while the molecular weight determined by the x-ray method was 3% low. However, mass spectrometric analysis showed the parent ion of mass 486 and a series of ions logically derived from it.

The infrared spectrum of the trimer is characterized by many of the bands reported by Brown[3] for a compound, m.p. 208–209°, which was obtained by heating I at 320°, and to which the tetrameric structure III was assigned on the basis of an ebullioscopic molecular weight determination.[4] The

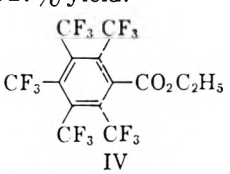


III

ultraviolet spectrum of the trimer is also strikingly similar ($\lambda_{max}$ 287 mμ, log ε 2.22) to that reported by Ekström[5] for Brown's compound ($\lambda_{max}$ 287 mμ, log ε 2.24). The similarities in reaction conditions, melting point, and, NMR infrared and ultraviolet spectra lead us to suggest that Brown's compound is actually the trimer (II).

Because of the bulkiness of trifluoromethyl groups, it was not possible to construct a model (Stuart-Briegleb) of the trimer without distorting the benzene ring from its normal planar configuration. It was, in fact, not possible to place more than three trifluoromethyl groups in adjacent positions without ring distortion. The resulting model had the trifluoromethyl groups locked in a highly crowded conformation. The unusual behavior of the trimer toward basic hydrolysis (see below) might be attributed to its highly crowded structure.

The trimer was found to be resistant to hydrolysis by sulfuric acid or by a chlorosulfonic acid–sulfuric acid mixture, in contrast to the ready hydrolysis reported for *m*- and *p*-bis(trifluoromethyl)benzene under these conditions.[6] However, hydrolysis by bases occurs readily; treatment of the trimer with two moles of potassium hydroxide in ethanol led to the formation of ethyl pentakis(trifluoromethyl)-benzoate (IV) in 27% yield.



IV

### EXPERIMENTAL

*Hexakis(trifluoromethyl)benzene* (II). *a. Catalytic.* A mixture of 11.1 g. (0.068 mole) of hexafluoro-2-butyne, 1.8 g. (0.009 mole) of trifluoromethyl iodide, and 0.3 ml. of perfluorodimethylcyclohexane was sealed in a platinum tube under a nitrogen atmosphere, and the tube pressured externally with nitrogen. The tube was heated at 260° under 1000 atm. pressure for 15 hr. The reaction mixture was cooled below 0°, filtered, and the solid residue was air-dried. There was thus obtained 7.89 g. (71.1%) of hexakis(trifluoromethyl)benzene (II), melting at 209–210° (sealed capillary). The melting point was unchanged by recrystallization from acetone, benzene, or methanol.

*Anal.* Calcd. for $C_{12}F_{18}$: C, 29.65; F, 70.35; mol. wt., 486. Found: C, 29.78; F, 70.45; mol. wt., 505, 522 (cryoscopic in benzene).

Replacement of the trifluoromethyl iodide catalyst with

(1) (a) A. W. Reppe and W. J. Schweckendick, *Ann.*, **560**, 104 (1948); (b) D. C. McKinley, *Ind. Eng. Chem.*, **44**, 995 (1952).

(2) Monofluoroacetylene has been reported to trimerize spontaneously; W. J. Middleton and W. H. Sharkey, *J. Am. Chem. Soc.*, **81**, 803 (1959).

(3) H. C. Brown, *J. Org. Chem.*, **22**, 1256 (1957).

(4) Ebullioscopic molecular weight determinations (benzene) on the trimer carried out in our laboratory resulted in very high values (825, 850). This may be due to the volatility of the compound, resulting in the loss of material during the determination.

(5) B. Ekström, *Chem. Ber.*, **92**, 749 (1959).

(6) P. G. Scheurer and G. M. le Fabe, *J. Am. Chem. Soc.*, **72**, 3308 (1950).

iodine (0.1 mole per mole of hexafluoro-2-butyne) gave a 70.5% yield of nearly pure II as a pale yellow solid, m.p. 209–211° (with previous softening).

The infrared spectrum (carbon tetrachloride) has strong absorption at 8.1–8.3, 8.51, and 9.51 $\mu$, with much weaker bands at 7.12, 7.43, 7.61, and 7.73 $\mu$. Additional bands for II at 8.63m, 8.75m, 12.41s, 13.35s and 13.79s $\mu$ are detected by use of a potassium bromide wafer. The trimer crystals are monoclinic. X-ray diffraction data were determined from a single crystal grown from acetone. There are four formula weights per unit cell with a space group of $C^5_{2h}P2_1/c$, $a_0$ = 9.42, $b_0$ = 16.54, $c_0$ = 8.98. The $\beta$ angle is 99.5°. Assuming a molecular weight of 486.24, the x-ray density is 2.33.[7] The density at 25° ("Ultracene") is 2.2603, corresponding to a molecular weight of 470.

The trimer (50% in acetone) has an $F^{19}$ resonance at −945 c.p.s. at 40 mc./sec., relative to trifluoroacetic acid = 0.[8]

*b. Thermal.* An 80-cc. stainless steel bomb containing 25 g. (0.155 mole) of I was heated for 7 hr. at 275° and 7 hr. at 285°. A pressure drop from 905 p.s.i. at 275° to 390 p.s.i. at 285° occurred during this time. After cooling and venting the bomb, there was obtained 15.1 g. of fluffy solid. Sublimation of 14 g. of this material at 100°, 1 mm. for 2 hr. yielded 5.47 g. of wet crystals. Pentane extraction of this material left 3.53 g. of II, m.p. 210–212° (sealed capillary).

*Hydrolysis of* II. Approximately one half of 11.0 g. (0.023 mole) of II was dissolved in 1 l. of hot absolute ethanol. Then one third of a solution of 3.4 g. (0.052 mole) of potassium hydroxide in 35 ml. of ethanol and 2 ml. of water was added during 20 min. The rest of the trimer was dissolved in the mixture, and the remainder of the base was added slowly. After standing overnight at room temperature, the volume was reduced to 150 ml., and the hot solution was decanted from precipitated potassium fluoride. Upon cooling the solution in an ice-salt bath, there was obtained 4.22 g. of colorless leaflets, m.p. 72–76°. Recrystallization from pentane gave 3.0 g. (27%) of ethyl pentakis(trifluoromethyl)-benzoate (IV), m.p. 89–90°.

*Anal.* Calcd. for $C_{14}H_5F_{15}O_2$: C, 34.30; H, 1.03; F, 58.14. Found: C, 34.51; H, 1.40; F, 58.24.

Carbonyl absorption in the infrared was at 5.67 $\mu$ (potassium bromide disk) and the proton NMR spectrum indicated the presence of an ethyl group. The fluorine NMR spectrum had complex absorption in the $CF_3$ region which is consistent with the unsymmetrical, highly crowded structure IV.

Attempts to isolate other hydrolysis products from this reaction were unsuccessful.

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(7) E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press Inc., N. Y., 1955, p. 468.

(8) The convention employed here is that resonances occurring at high field relative to the reference are assigned positive values.

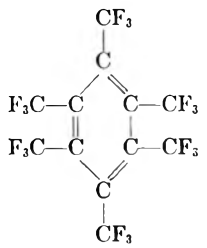
## Hexa(trifluoromethyl)benzene[1]

H. C. BROWN, H. L. GEWANTER, D. M. WHITE, AND W. G. WOODS[2]

*Received October 16, 1959*

The thermal reaction of perfluorobutyne-2 under autogenous pressure has been reported previously[3] as producing a white, crystalline compound believed to be the polycyclic tetramer. Further examination of this compound by Ekstrom[4] led to the incorrect assignment of the structure as octa(perfluoromethyl)cyclooctatetraene.

A redetermination of the molecular weight of the product, both by ebullioscopic method in benzene and by isothermal distillation in benzene, gave a value of 472, which is reasonably close to the value of 486 expected for the trimer of perfluorobutyne. Further consideration has therefore been given to the structure and additional data obtained which shows conclusively that this compound is actually the previously unreported hexa(trifluoromethyl)benzene (I).



I

The fluorine nuclear magnetic resonance in dilute tetrahydrofuran of two samples of the trimer was determined at 40 megacycles/sec. and about 10,000 gauss and only one, single unsplit peak was found. This peak is found displaced 433 c.p.s. to lower magnetic fields than the fluorine resonance of benzotrifluoride and some 2,320 c.p.s. to higher fields from the fluorine peak of tribromofluoromethane, the latter being used as an internal standard. It was shown conclusively that this one peak contained all the fluorine atoms in the fluorocarbon, as no detectable resonance could be found at ± 5,000 c.p.s. from the observed peak. Furthermore, known solutions of the perfluorobutyne trimer and benzotrifluoride were prepared in which the ratios of the number of fluorine atoms due to the trimer to those due to benzotrifluoride were 0.988 : 1.010. The spectra were run and the integrated areas of the two peaks determined with a planimeter which gave values of 0.99 ± 0.09 and 1.11 ± 0.12 for the ratios. Coupled with the observation that only one peak can be detected, this result shows clearly that the trimer contains only one type of fluorine atom.

The ultraviolet absorption spectrum (max 285 m$\mu$, log $\epsilon$ = 2.20) of the perfluorobutyne trimer tends to confirm the presence of an aromatic ring. The ultraviolet extinction coefficient of this com-

(1) This work was supported in part by the Office of Naval Research under Contract N-onr 580(03); NR 356-333 with the University of Florida. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) Present address: U. S. Borax Research Corporation, Anaheim, California.

(3) H. C. Brown, *J. Org. Chem.*, 22, 1256 (1957).

(4) B. Ekstrom, *Ber.*, 92, 749 (1959).

pound, when compared with the extinction coefficients for trifluoromethyl benzene and *bis*(trifluoromethyl)benzene, is in the expected range. The ultraviolet curve showed a smoothing out effect with an electron donating solvent such as ether when compared with the spectrum determined in chloroform. The inductive effect of the eighteen fluorine atoms would be expected to make the ring very electron deficient and could account for this phenomenon.

The solubility characteristics of the trimer are appropriate to an electron deficient structure, as it has a low solubility in benzene but is soluble in electron rich solvents. A solubility in tetrahydrofuran greater than that in ethyl ether is consistent with the greater basicity of the former.

The melting point of the perfluorobutyne trimer is in the range expected for hexa (trifluoromethyl)-benzene. A plot of the melting points of the methylbenzenes *vs.* the melting points of the known trifluoromethylbenzenes is linear.

All the evidence shown above is based on the physical properties of the trimer and substantiates the proposed aromatic ring structure. We would like to report, in addition, that unequivocal chemical confirmation of the ring structure was obtained by vapor phase chlorination of the trimer under ultraviolet irradiation to produce chlorotrifluoromethane and hexachlorobenzene.

Preparation of hexa(trifluoromethyl)benzene has been modified to include a relatively cold reservoir in the pyrolysis tube for condensation of the product as formed. Yields of 68% of the resublimed or recrystallized product have been obtained.

Further work on reactions of hexa(trifluoromethyl)benzene promoted by free radical attack and also by the attack of nucleophilic reagents is in progress.

## EXPERIMENTAL

*Hexa(trifluoromethyl)benzene.* Hexafluorobutyne-2 (20 g., 0.123 mol.) was condensed into a previously evacuated heavy wall Pyrex tube 55 cm. × 2.4 cm. designed to project from a vertical tube furnace approximately 6 in. The tube was then sealed and heated at 375° for 60 hr. The autogenous pressure in the 250 ml. tube was calculated to be about 25 atm. As the reaction proceeded, the solid product condensed in the exposed, relatively cool portion of the tube. The tube was cooled, opened, and the condensed solid removed and resublimed. Recrystallization from carbon tetrachloride gave 13.7 g. (68.5%) of pure hexa(trifluoromethyl)benzene, m.p. 209° (sealed tube).

*Chlorination of hexa(trifluoromethyl)benzene.* Hexa(trifluoromethyl)benzene (4.86 g., 0.01 mol.) was placed in a 500 cc. Vycor flask. Dry chlorine gas, 4.4 g. (0.062 mol.), was condensed into the flask, and the flask was sealed and heated to 260° under ultraviolet radiation supplied by a Hanovia utility lamp for 44 hr. The vessel was cooled and opened into a vacuum system to remove the volatile material which was subsequently bubbled through a 10% solution of sodium hydroxide to remove any unreacted chlorine. The remaining gas was identified by molecular weight determination (Dumas-104) and infrared spectra as chlorotrifluoromethane. The solid product was recrystallized from benzene to give pure hexachlorobenzene, m.p. 229–230°, mixed melting point with authentic samples 229–231°. The infrared spectra of this solid material also corresponded to that of an authentic sample of hexachlorobenzene.

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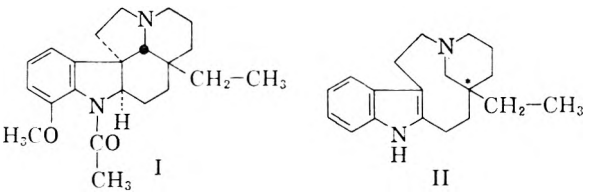
## Quebrachamine. II

Hermann Kny and Bernhard Witkop

*Received October 1, 1959*

The establishment by x-ray analysis of the structure I for aspidospermine[1–3] makes II an attractive



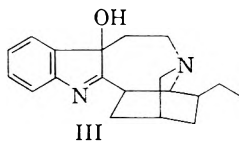

formulation for quebrachamine.[4] This note reports two further experiments designed to clarify the nature of the substituent, H or R, at the α-indole position, and identifies the "*N*(*a*)-acetyldihydroindole base" previously reported,[4] as I.

The positive Ehrlich and Hopkins-Cole reactions of quebrachamine suggested an α-unsubstituted indole ring. Such α-unsubstituted indoles may be characterized or diagnosed by their α,α′-disulfides. Quebrachamine trichloroacetate reacted in benzene with disulfur dichloride to yield a crystalline disulfide, whose ultraviolet absorption peak showed the expected shift to longer wave lengths.[5] Reductive hydrolysis, however, gave back quebrachamine. It must be concluded that quebrachamine disulfide is an abnormal disulfide in which two molecules of quebrachamine are linked together by an S-S bridge attached to an unknown position of the indole part. Tetrahydrocarbazole did not yield a disulfide.

Another reaction characteristic of α-unsubstituted indoles is their oxidation to (di)oxindole derivatives with *N*-bromosuccinimide.[6] Quebrachamine under such conditions gave a tribromo com-

(1) S. C. Nyburg and J. F. D. Mills, *Tetrahedron Letters*, **11**, 1 (1959).
(2) G. F. Smith and J. T. Wrobel, *J. Chem. Soc.*, in press.
(3) H. Conroy, P. R. Brook, and Y. Amiel, *Tetrahedron Letters*, **11**, 4 (1959).
(4) *Cf.* B. Witkop, *J. Am. Chem. Soc.*, **79**, 3193 (1957).
(5) *Cf.* K. Freter, J. Axelrod, and B. Witkop, *J. Am. Chem. Soc.*, **79**, 319 (1957).
(6) A. Patchornik, W. B. Lawson, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 4747 (1958).

pound $C_{19}H_{23}N_2Br_3$, m.p. 290°, whose ultraviolet spectrum (Table I) was similar to that of the hydroxy base $C_{19}H_{26}N_2O$, m.p. 188°. Both these compounds have peaks similar to, but extinctions higher than, the β-hydroxyindolenine III derived from ibogamine (Table I).[7] This type of spectrum, intermediate between indole and indolenine, may




III

point to transannular interaction with $N_b$. No definite structures are assigned to these products at this time. The failure of *N*-bromosuccinimide to convert quebrachamine to an oxindole derivative is proof for an α-substituted indole nucleus. This is in agreement with the results of recent studies of the nuclear magnetic resonance spectrum of quebrachamine[8] which clearly shows the absence of the peak characteristic of the proton in the α-position of the indole ring.

TABLE I

ULTRAVIOLET SPECTRA IN 95% ETHANOL

| Compound | $\lambda_{max}$ | $\epsilon$ |
|---|---|---|
| Hydroxy base $C_{19}H_{26}N_2O$, m.p. 188°, from quebrachamine | 295 | 7,080 |
| | 286 | 7,590 |
| | 227 | 28,200 |
| Tribromo compound $C_{19}H_{23}N_2Br_3$, m.p. 290°, from quebrachamine | 293 | 7,470 |
| | 285 | 7,440 |
| | 231 | 44,000 |
| Hydroxyindolenine III from ibogamine | 292 | 3,020 |
| | 281 | 3,200 |
| | 253-254 | 3,910 |
| | 228 | 13,700 |
| | 222 | 19,800 |

The same study led to the conclusion that the NMR peaks of possible indolenine tautomers of cycloheptenoindole, cyclooctenoindole and of II, a cyclononenoindole, would be masked by the multiplicity of saturated methylene protons.

The so-called "*N*(*a*)-acetyldihydroindole base," m.p. 213°,[4] and the "isomeric hydroxy base," m.p. 103°,[4] turned out to be aspidospermine and deacetylaspidospermine.[9] Apparently the latter is admixed with samples of "pure" quebrachamine, m.p. 144°, which give a single spot on chromatograms in three different solvent systems. Repeated recrystallization gave a sample, m.p. 145–146°, $[\alpha]_D^{20}$ −116.5°, which with hydrogen peroxide in acetic acid gave solely the hydroxy base, m.p. 188°.

(7) D. F. Dickel, C. L. Holden, R. C. Maxfield, L. E. Paszek, and W. I. Taylor, *J. Org. Chem.*, **80**, 123 (1958).

(8) L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, in press.

(9) We are greatly indebted to Prof. H. Conroy for pointing out first these possibilities.

## EXPERIMENTAL[10]

*Fractional recrystallization of quebrachamine.* A sample of quebrachamine (5 g.) obtained through the courtesy of E. Merck, Darmstadt,[11] was recrystallized twice from methanol and showed then m.p. 143–145°, $[\alpha]_D^{20}$ −117.3° (*c*, 1.0 in 95% $C_2H_5$). Further recrystallizations from cyclohexane furnished 5 fractions of increasing solubility which had the following melting points: 145–146°; 145–146°; 146–147°; 145–146°; 144–145°. The rotations of the first four fractions were all $[\alpha]_D^{20}$ −116.5 ± 2°. The last fraction and mother liquors had $[\alpha]_D^{20}$ −118.8 ± 2° which slowly increased on standing in solution, since the hydroxy base $C_{19}N_{26}N_2O$, $[\alpha]_D^{20}$ −504°, is formed.

*Chromatographic analysis.* In three solvent systems (a) 2-butanol–formic acid–water (75:15:10), (b) 99% of a mixture of 2 parts of methanol, 1 part of benzene, 1 part of 1-butanol and 1 part of water, and 1% of a 15% aq. ammonia solution, (c) phenol–formic acid–water (120 g.:1.6 cc.:40 cc.) quebrachamine traveled close to the solvent front (Whatman No. 1 filter paper) showing $R_f$ values >0.9. Deacetylaspidospermine was indistinguishable in these systems. In amyl alcohol–water (90:6) there was a slight separation of quebrachamine ($R_f$ 0.92) and deacetylaspidospermine (0.83) which however was insufficient to detect 10% deacetylaspidospermine in a mixture made up with quebrachamine. The use of filter paper impregnated with borate buffer of *p*H 7.4, 9.3, and 10.4 did not improve the separation.

*Electropherograms*[12] of mother liquors of quebrachamine in acidic buffer systems showed the presence of small amounts of oxy base $C_{19}H_{26}N_2O$, m.p. 188°, which moved slightly faster than quebrachamine. Deacetylaspidospermine moved (after 50 min.) approximately twice as fast as quebrachamine and was detectable by its coloration on spraying with 1% ethanolic cinnamaldehyde solution and subsequent exposure to hydrogen chloride gas. In mixtures made up of 50% quebrachamine and 50% deacetylaspidospermine separation and detection were still possible, but 10% deacetylaspidospermine admixed to quebrachamine could not be detected in this way.

*Identification of "base $C_{21}H_{28}N_2O_2$, m.p. 213°" with aspidospermine.* By the action of 6 cc. of acetic acid–30% hydrogen peroxide (1:1) on 0.5 g. of commercial "pure" quebrachamine 40 mg. of the base considered to be an $N^a$-acetylhydroxy- derivative $C_{21}H_{28}N_2O_2$ of quebrachamine was obtained.[4] The mixed melting point of this base with aspidospermine ($C_{22}H_{30}N_2O_2$) was 213°. The ultraviolet and infrared spectra of the two bases were identical. No aspidospermine was found when the purest sample of quebrachamine obtained by repeated recrystallizations first from methanol and then from cyclohexane was oxidized with peracetic acid. This led only to the formation of the base $C_{19}H_{26}N_2O$, m.p. 188°.

*Quebrachamine disulfide.* To a cooled solution of 29.2 mg. of quebrachamine in 10 ml. of anhydrous benzene was added 100 mg. of anhydrous trichloroacetic acid and 1 ml. of a solution of 6.8 mg. of disulfur dichloride ($S_2Cl_2$) in benzene. After 2 hr. the reaction mixture was poured into an excess (*ca.* 100 ml.) of petroleum ether (b.p. 30–40°). The precipitate was removed by centrifugation, washed with ether and petroleum ether, and recrystallized from petroleum ether to colorless crystals (20 mg., 60%), m.p. 166°; $R_f$ 0.25, compared with quebrachamine 0.8 (2,4-lutidine-*t*-amyl alcohol, 1:1, saturated with water). The reactions according to Ehrlich, Hopkins-Cole and with cinnamic aldehyde were

(10) All melting points are corrected. The analyses were performed by the Analytical Services Unit of this laboratory, under the direction of Dr. W. C. Alford.

(11) We are greatly indebted to Dr. Jan Thesing for his assistance and cooperation.

(12) Approximately 50 volts/cm., using the Wieland-Pfleiderer Pherograph [*cf. Angew. Chem.*, **67**, 257 (1955)].

all negative. The Keller reaction, concd. sulfuric acid containing a trace of ferric ion, was positive.

*Anal.* Calcd. for $C_{38}H_{50}N_4S_2$: C, 72.79; H, 7.99; N, 8.94; S, 10.23. Found: C, 72.50; H, 8.04; N, 9.06; S, 10.33.

*Ultraviolet spectrum:* $\lambda_{max}$ (log $\epsilon$) 300 (3.56); 212 (4.30).

*Infrared spectrum* (potassium bromide): 2.95–2.98 (broad); 3.43; 3.58; 6.05vw; 6.20vw; 6.44s; 6.86vs; 7.25m; 7.39s; 7.52w; 7.86m; 8.10m; 8.28m; 8.39s; 8.56w; 8.74m; 8.86m; 9.08w; 9.37w; 9.74m; 9.88m; 10.0vw; 10.11vw; 10.36m; 10.69w; 11.51m $\mu$.

On reductive hydrolysis of the disulfide (10 mg.) with zinc in acetic acid the ether solution of the crude reaction product showed (in chloroform) a band at 5.81 $\mu$ of medium intensity, and 6.20vs, both bands typical of oxindole derivatives. However, on purification of the material *via* the picrate only a small amount of quebrachamine picrate, m.p. 193°, identified by mixed melting point and infrared spectrum, was obtained. The same result was given by the reduction of the disulfide with Raney nickel.

*Quebrachamine "tribromide."* *N*-Bromosuccinimide (0.222 g.) was added slowly with mechanical stirring to 0.141 g. of quebrachamine in 3 ml. of glacial acetic acid and 2 ml. of water. Stirring was continued for 1 hr. at room temperature and then 4*N* sodium hydroxide was added in the cold until the solution was at *p*H 6. Extraction with dichloromethane and *n*-propyl alcohol yielded a yellow oil which was crystallized from chloroform and benzene to yield 0.08 g. of cotton-like needles, m.p. 287–289°. The analytical sample was prepared by a recrystallization from the same solvents. It displayed m.p. 290°, ultraviolet spectrum $\lambda_{max}$ 231 ($\epsilon$ 44,000), 285 ($\epsilon$ 7,440), 293 ($\epsilon$ 7,470) and had no carbonyl absorption in the infrared.

*Anal.* Calcd. for $C_{19}H_{23}N_2Br_3$: C, 43.96; H, 4.47; Br, 46.18. Found: C, 43.99; H, 4.59; Br, 45.99. The formula $C_{19}H_{25}N_2Br_3$ (C, 43.79; H, 4.84; Br, 46.00) is not excluded.

*Acknowledgment.* We are greatly indebted to Drs. K. Freter and A. A. Patchett for experimental assistance, to Dr. H. Conroy for helpful discussions and to Dr. G. F. Smith for an advance copy of his manuscript prior to publication.

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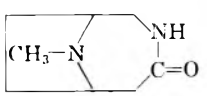
## Synthesis of 9-Methyl-3,9-diazabicyclo[4.2.1]-nonane

R. J. MICHAELS AND H. E. ZAUGG

*Received September 29, 1959*

This note reports the preparation of the title compound, II, by treatment of tropinone with hydrazoic acid to give the bicyclic lactam I which was reduced with lithium aluminum hydride. The overall yield of II was 61%.

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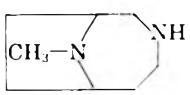


II

This scheme provides access to a bicyclic homopiperazine system of potential value as an intermediate for compounds of pharmacological interest.

### EXPERIMENTAL

*9-Methyl-3,9-diazabicyclo[4.2.1]nonan-4-one* (I). A solution of 11.1 g. (0.08 mole) of tropinone in 100 ml. of chloroform cooled to −5° in an ice-salt bath was treated dropwise with stirring with 25 ml. of concentrated sulfuric acid, keeping the temperature below 15°. After cooling to 5° the stirred reaction mixture was treated with 10.4 g. (0.16 mole) of sodium azide in approximately 0.5–1 g. portions at such a rate that the temperature did not exceed 35°. Addition of the azide required about 2 hr. after which the reaction mixture was stirred at 50° for another 2 hr. It was then poured into a 600 ml. beaker one third filled with ice. Solid potassium carbonate was added portionwise until the mixture was strongly alkaline. This was followed by 50 ml. of a 60% potassium hydroxide solution; the inorganic salts were removed by filtration and washed well with chloroform. The alkaline filtrate was extracted with three portions of chloroform and the combined chloroform washings and extracts were dried over anhydrous sodium sulfate. Filtration of the drying agent followed by removal of the chloroform by distillation gave 11.1 g. (90%) of crude I, m.p. 79–83°. For analysis, a sample was converted to the hydrochloride, m.p. 258–259° dec. (from ethanol).

*Anal.* Calcd. for $C_8H_{15}ClN_2O$: C, 50.39; H, 7.93; N, 14.69. Found: C, 50.42; H, 7.96; N, 14.59.

*9-Methyl-3,9-diazabicyclo[4.2.1]nonane* (II). To a solution of 11.0 g. (0.071 mole) of I in 400 ml. of dry ether was added dropwise with stirring under an atmosphere of dry nitrogen, a solution of 6.8 g. (0.18 mole) of lithium aluminum hydride in 200 ml. of dry ether. Addition was complete in 0.5 hr., and the mixture was stirred and refluxed for 46 hr.

Water (25 ml.) was added dropwise to the cooled reaction mixture which was then filtered by suction. The filter cake was washed well with ether and the combined filtrate and washings were dried over anhydrous sodium sulfate. Filtration and removal of the ether by distillation followed by vacuum distillation of the residual oil gave 6.8 g. (68%) of II, b.p. 111–113° (38 mm.), $n_D^{24}$ 1.4992.

*Anal.* Calcd. for $C_8H_{16}N_2$: C, 68.52; H, 11.50; N, 19.98. Found: C, 68.71; H, 11.91; N, 20.26.

*II.Dihydrochloride*, m.p. 290–291° dec. (from dry ethanol).

*Anal.* Calcd. for $C_8H_{18}Cl_2N_2$: C, 45.08; H, 8.51. Found: C, 45.46; H, 8.61.

*Acknowledgment.* The authors are indebted to Mr. E. F. Shelberg and his associates for the microanalyses.

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## Preparation of *m*- and *p*-Diethynylbenzenes

ALLAN S. HAY

*Received September 30, 1959*

We wished to prepare reasonably large quantities of *m*- and *p*-diethynylbenzenes. Deluchat[1]

(1) R. Deluchat, *Ann. chim.*, 1 [11] 181–255 (1934).

had prepared these compounds by a laborious seven step synthesis starting from the corresponding xylene isomer. This route was obviously not satisfactory for relatively large scale preparation of these materials.

When the commercially available divinylbenzene mixture[2] (40% *m*- and *p*-divinylbenzenes) is brominated in chloroform solution, 1,4-bis(1,2-dibromoethyl)benzene separates on cooling. Recrystallization from chloroform yields the pure material. The bromination residue now contains 1,3-bis-(1,2-dibromoethyl)benzene along with considerable quantities of the dibromodiethylbenzenes from the ethylstyrenes in the starting material. A molecular distillation readily separates the dibromodiethylbenzenes from the tetrabromodiethylbenzene. The latter fraction on crystallization from ethanol yields pure 1,3-bis(1,2-dibromoethyl)benzene. Treatment with four moles of potassium *t*-butoxide in *t*-butanol readily converts the tetrabromodiethylbenzenes to the respective diethynylbenzenes.

## EXPERIMENTAL

*Bromination of mixed divinylbenzenes.* Bromine (1300 g., 8.13 moles) was added over 2 hr. with stirring to a cooled solution of 750 g. mixed divinylbenzene (40% = 2.3 moles *m*- and *p*-divinylbenzene) in 1200 ml. of chloroform. The reaction mixture was then cooled to 5° and a voluminous precipitate settled out which was separated by filtration. Recrystallization from chloroform yielded 264 g. (0.59 mole) of 1,4-bis(1,2-dibromoethyl)benzene, m.p. 155–157° (lit.[1] m.p. 157°). The two filtrates were combined and the chloroform removed on a rotating evaporator at 100° (3 mm.). The residue was then fractionated in a molecular still. Distillation at 50° (40–70 $\mu$) and then at 80° (20–50 $\mu$) separated most of the dibromodiethylbenzenes. The residue which was a viscous sirup was distilled at 150° (12–30 $\mu$). The distillate crystallized when triturated with cold alcohol and after recrystallization from alcohol yielded 420 g. (0.93 mole, combined yield of 66%), 1,3-bis(1,2-dibromoethyl)benzene, m.p. 65–66.5° (lit.[1] m.p. 64°).

*p-Diethynylbenzene.* To a solution of 18 g. (0.46 mole) of potassium in 1 l. of *t*-butanol at the temperature of reflux was added 50 g. (0.11 mole) of 1,4-bis(1,2-dibromoethyl)-benzene. After 1 hr. the reaction mixture was made up to 4 l. with ice water and the pale yellow solid was removed by filtration. There was isolated 9.8 g. (0.078 mole, 71% yield) of *p*-diethynylbenzene, m.p. 95° (lit.[1] m.p. 95°). Sublimation at 90–100° (2 mm.) gave a colorless solid m.p. 96.5°.

*m-Diethynylbenzene* was prepared in an identical fashion and in comparable yield from 1,3-bis(1,2-dibromoethyl)-benzene. After flooding with water the product was isolated by ether extraction and distillation to yield *m*-diethynylbenzene, b.p. 78° (14 mm.), $n_D^{20}$ 1.5825 (lit.[1] b.p. 78° (15 mm.) $n_D^{18}$ 1.5841).

*Acknowledgment.* The distillations were performed by Mr. E. M. Hadsell. It is a pleasure to acknowledge the very capable assistance of Mr. R. J. Flatley.

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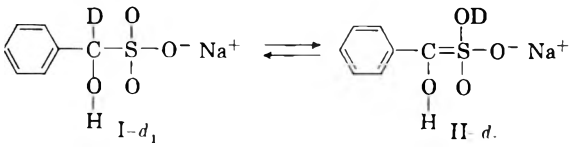
(2) Purchased from Monomer-Polymer Laboratories, 5000 Landgon Street, P.O. Box 9522, Philadelphia 24, Pa.

## Absence of Exchange by the "Aldehydic" Hydrogen of Benzaldehyde Sodium Bisulfite

JOHN A. SOUSA AND J. DAVID MARGERUM

*Received October 19, 1959*

In 1939 Thompson and Cromwell reported that in contrast to the lack of hydrogen-deuterium exchange by aldehydes, benzaldehyde-$d_1$ sodium bisulfite (I-$d_1$) exchanged up to 76% with conductivity water in a period of seventeen days.[1] They suggested that this could be evidence for the enolization of the bisulfite complex. Such an enol form (II-$d_1$) would be of particular interest since it postulates an expanded valence shell of ten electrons for the sulfur atom in the complex.




We desired to prepare some deuterated benzaldehydes by utilizing the reverse of this reported exchange reaction. We first attempted to prepare benzaldehyde-$d_1$ by placing benzaldehyde sodium bisulfite (I) in excess deuterium oxide for a long period of time, as indicated in experiment 1, Table I. The infrared spectrum of the aldehyde showed that no exchange had occurred.[2] Similar experiments (2, 4, and 5 through 9) were made using different methods of separating the products, and of determining the extent of exchange by infrared analysis. These experiments were conducted under various conditions such as exposure to near ultraviolet light or in the presence of added substances which might somehow have acted as catalysts in the original work. Experiment 3 is essentially a duplication of one experiment of the reported exchange reaction, using benzaldehyde prepared from lithium aluminum deuteride.[2] In every experiment no hydrogen-deuterium exchange was found on the "carbonyl" carbon of I or I-$d_1$. Thus, there is no evidence for the existence of an enol form, such as II-$d_1$.

The attempted exchange experiments are summarized in Table I. The infrared spectra of I and I-$d_1$ are shown in Fig. 1. The deuterated complex is readily distinguished from I by the absence of bands at 1411 and 845 cm.$^{-1}$ and the presence of bands at 1347, 969, 945, and 766 cm.$^{-1}$ [3].

(1) A. F. Thompson, Jr., and N. H. Cromwell, *J. Am. Chem. Soc.*, **61**, 1374 (1939).

(2) K. B. Wiberg, *J. Am. Chem. Soc.*, **76**, 5371 (1954).

(3) Deutero-benzaldehyde is easily distinguished from benzaldehyde by the large shift in the C—H stretching frequency (*cf.* ref. 2), and also shows the absence of bands at approximately 1387, 826, and 714 cm.$^{-1}$ and the presence of bands at approximately 1222, 791, and 733 cm.$^{-1}$.

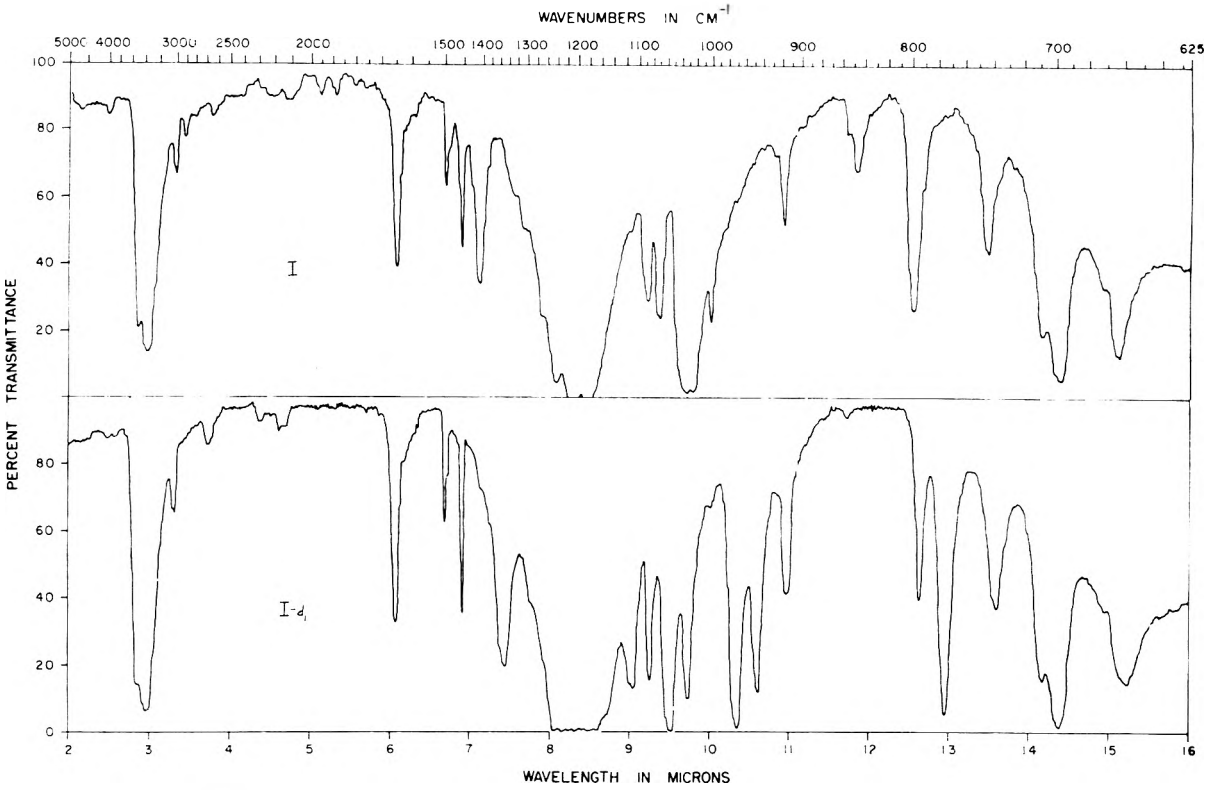



Fig. 1. Infrared spectra of benzaldehyde sodium bisulfite (I) and benzaldehyde-$d_1$ sodium bisulfite (I-$d_1$) in potassium bromide disks

TABLE I

ATTEMPTED PROTIUM EXCHANGE IN BENZALDEHYDE SODIUM BISULFITE ADDITION COMPOUND (I)

| Expt. | Reactants | Mole Ratio of Reactants | Period, Days | Light | Method of Separation | Products Analyzed |
|---|---|---|---|---|---|---|
| [a] | I-$d_1$/$H_2O$ | 1/11.1 | 17 | — | Vac. distln. | $H_2O$ |
| 1 | I/$D_2O$ | 1/31.5 | 28 | Dark | $Na_2CO_3$ rxn. | BzH |
| 2 | I/$D_2O$ | 1/35 | 26 | Dark | Vac. distln. | BzH |
| 3 | I-$d_1$/$H_2O$ | 1/11.7 | 34 | Dark | Vac. distln. | $H_2O$ |
| | | | | | $Na_2CO_3$ rxn. | BzD |
| 4 | I-$d_1$/$H_2O$ | 1/11.1 | 2 | Near UV | Evaporation | I |
| 5 | I/$D_2O$ | 1/31.5 | 45 | Rm. light | Evaporation | I |
| 6 | (Same as 5; 1 drop 6*N* HCl added to 2 ml. of solution) | | | | | |
| 7 | (Same as 5; 1 drop 6*N* NaOH added to 2 ml. of solution) | | | | | |
| 8 | (Same as 5; *ca.* 100 mg. 5% Pd-$BaSO_4$ added to 2 ml. of solution) | | | | | |
| 9 | (Same as 5; *ca.* 50 mg. quinoline-sulfur added to 2 ml. of solution) | | | | | |

[a] Ref. 1.

The increases in the density of water observed in the work of Thompson and Cromwell[1] could not have been due to an exchange reaction. A possible explanation of their results may be found in our observation that benzaldehyde and sulfur dioxide vapors appear to exist in equilibrium with the benzaldehyde sodium bisulfite complex. In the vacuum distillation of water from a water-complex mixture at room temperature, small but significant amounts of benzaldehyde and sulfur dioxide are carried over into the water, which would increase its density.

## EXPERIMENTAL

Benzaldehyde sodium bisulfite (I) was prepared by mixing 40% aqueous sodium bisulfite with a slight excess of freshly distilled benzaldehyde, allowing the complex to separate on standing, filtering it, washing it three times with ether and drying over phosphorus pentoxide at 1 $\mu$ for 1.5 hr. Benzaldehyde-$d_1$ sodium bisulfite (I-$d_1$) was prepared by Weiberg's method.[2] The 5% palladium-barium sulfate and the quinoline-sulfur were prepared as described in *Organic Reactions*.[4]

*Reaction conditions and separation of products.* All experiments were carried out in evacuated, out-gassed, sealed-off tubes.[1] These were allowed to stand at room temperature, in the dark or in room light as indicated in Table I, except for experiment 5 in which exposure was made with a water cooled AH-6 mercury arc (glass envelope) for 29 hr. using Corning glass filter No. 5840 followed by 20 hr. without a filter. Separation by vacuum distillation was made at 25° for water and between 60° and 115° for benzaldehyde. In experiments 1 and 3 the complex was treated with an excess

(4) E. Mosettig and R. Mozingo, *Org. Reactions*, IV, 386–9 (1948).

of 3% sodium carbonate followed by ether extraction, drying over magnesium sulfate, and distillation of the benzaldehyde at reduced pressure under nitrogen.

*Analysis.* In all of the experiments infrared absorption spectra were used to analyze for the presence of deuterated and undeuterated products. Most of the spectra were taken with a calcium fluoride prism in a Perkin-Elmer model 112 Spectrometer. The benzaldehyde and benzaldehyde-$d_1$ were run between sodium chloride plates or in carbon tetrachloride solution; water and deuterium oxide were run in thin calcium fluoride cells[5]; crystals of I and I-$d_1$ were run using the model 85 microscope attachment to the 112. Spectra of I and I-$d_1$ (recrystallized from water and dried under vacuum) were also run in potassium bromide disks on a Baird Model A and are shown in Fig. 1.

*Instability of the complex under vacuum.* At 60° large amounts of benzaldehyde, sulfur dioxide, and water were vacuum distilled from I in a period of several days. These were identified by mass spectral analysis with a Consolidated Electrodynamics model 21-103C mass spectrometer. Similarly, at 25° more than 7% of the benzaldehyde was vacuum distilled from a dry sample of I in 5 days, and was analyzed by its ultraviolet spectrum with a Cary model 11 spectrophotometer. A mixture of 1.86471 g. of I (freshly washed with ether and dried) and 1.48630 g. of water was placed in one arm of a U-tube, which was outgassed and evacuated. The water was vacuum distilled for 2 hr. into the other arm from a maximum temperature of 25°. After dilution to 5.0 ml. the water had a *p*H of 3.1 compared to an initial *p*H of 6.0 and the ultraviolet spectrum (measured in a 0.0107 cm. calcium fluoride cell) showed a total of 0.0016 g. of free benzaldehyde. When diluted again by 1/50 (measured in a 1.00 cm. cell) it showed a total of 0.0021 g. of free benzaldehyde. The difference in free aldehyde with concentration can probably be attributed to some benzaldehyde-sulfurous acid complex formation. Thompson and Cromwell, using comparable amounts of water and complex, found that after vacuum distillation the water had increased in total weight between 0.00213 and 0.00756 g. and attributed this to an exchange reaction.

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(5) R. C. Gore, R. B. Barnes, and E. Petersen, *Anal. Chem.*, 21, 382 (1949).

## Unsaturated Four-Membered Ring Compounds. III. The Reactivity of Benzocyclobutene Toward Electrophilic Substitution

FREDERICK R. JENSEN AND GARY MACIEL

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In view of the possible effects of compression of the bond angles in benzene on the rate of substitution, it was of interest to determine the absolute reactivity of benzocyclobutene towards electrophilic substitution. Although the bond angles and interatomic distances have not been determined for benzocyclobutene, it is to be expected that the bond angles to the cycloalkane ring are appreciably smaller than the normal bond angle of 120°.

The electrophilic reaction selected was the aluminum chloride–catalyzed benzoylation reaction using ethylene chloride as solvent. Since substitution of a methyl group in benzene increases the rate of reaction by a factor of 132 (Table I), the benzoylation reaction is very sensitive to substitution effects. Any net effect of the fused ring should give a marked change in the rate of benzoylation. The aromatic compounds selected as standards for reference purposes were *o*-xylene, indane, and tetralin.

For this reaction, individual experiments follow second order kinetics according to expression 1.

$$\text{rate} = k_2(C_6H_5COCl{\cdot}AlCl_3)(ArH) \qquad (1)$$

However, the value of $k_2$ depends on the initial concentration of the complex.[1] With benzocyclobutene, the reactions apparently followed second-order kinetics to about 50% reaction and then the rates of reaction fell off rapidly. After ten to fifteen minutes, the reaction mixtures began to darken and turned progressively darker with time. The cause of this behavior was not investigated. The reactions of the other compounds followed second-order kinetics to at least 90% reaction, and the reaction mixtures stayed colorless for at least twenty-four hours.

The results are summarized in Table I.[2] The three compounds with the fused cycloalkane rings react two to three times faster than *o*-xylene. However, benzocyclobutene reacts only slightly faster than indane and tetralin. Since there is no rate acceleration, any decreased stability of benzocyclobutene by the bond compressions must be countered by an equal degree of instability of the transition state.

TABLE I

RATES OF THE ALUMINUM CHLORIDE–CATALYZED BENZOYLATION OF SELECTED BENZENE DERIVATIVES IN ETHYLENE CHLORIDE SOLUTION AT 25°[a]

| Aromatic | $k_2 \times 10^3$ (l.m.$^{-1}$ sec.$^{-1}$) | Relative Rate[b] |
|---|---|---|
| Benzene | 0.00855 | 1/1700 |
| Toluene | 1.13 | 1/13 |
| *o*-Xylene | 15.1 | 1 |
| Benzocyclobutene | 41[c] | 2.8 |
| Indane | 28.6 | 1.9 |
| Tetralin | 33.6 | 2.3 |

[a] For benzene and toluene, initial concentrations 0.222*M*; for the other compounds, 0.200*M*. [b] The small effect of initial concentration on rate is ignored in calculating the relative rates. [c] Less than 50% reaction. The calculated rate constants for benzocyclobutene decrease sharply after 50% reaction.

There are at least two explanations which could account for the "normal" reactivity of benzocyclo-

(1) F. R. Jensen, *J. Am. Chem. Soc.*, 79, 1226 (1957).

(2) When no unusual reactivities were observed, the decision was made not to determine the manner in which the benzoyl chloride is consumed. The reported rate constants probably represent the upper limit for aromatic substitution.

butene. One possible explanation is that the bond compressions have no effect on the resonance stabilization of the molecule. The second possibility is that the resonance stabilization of benzocyclobutene is decreased by the bond compressions, but that the stabilization of the transition state by the cycloalkane ring is less for benzoyclobutene than for tetralin and indane.

It is of interest to note that indane and tetralin are both more reactive than *o*-xylene. There is probably very little difference in the steric hindrance to attack in the *ortho*- positions of these molecules. Nor can, the effect be attributed to the substitution of hydrogen by an alkyl group, since ethylbenzene is less reactive than toluene in the benzoylation reaction.[3] The increased reactivity may be due to the presence of more favorable configurations for hyperconjugation[4] with the alkyl groups in the transition states for substitution of indane and tetralin than for *o*-xylene.

### EXPERIMENTAL

The benzocyclobutene was prepared by the catalytic hydrogenolysis of 1,2-dibromobenzocyclobutene using the method given by Cava and Napier for the hydrogenolysis of 1,2-diiodobenzocyclobutene.[5] Whereas yields of 20–55% were reported using the diiodo- compound, yields of 80–85% were obtained using the dibromo- compound. The hydrocarbon sample by mass spectral analysis[6] contained 99.6% of material with mass number 104, and the infrared spectrum corresponded to that reported for benzocyclobutene.[4] The benzocyclobutane had b.p. 150.5°/754 mm. (lit.,[4] b.p. 150°/748 mm.). The other hydrocarbons had purities of at least 99.5% as shown by cooling curve determinations. The other reactants and the solvent were purified as described previously.[1] The reactions were followed by determining the rate of disappearance of benzoyl chloride.[3]

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(3) H. C. Brown, B. A. Bolto, and F. R. Jensen, *J. Org. Chem.*, **23**, 414 (1958).

(4) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2326 (1958).

(5) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2255 (1958).

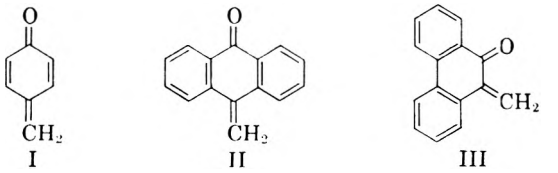
(6) We are indebted to Mr. Seymour Meyerson of the Standard Oil Company (Ind.) for the mass spectra analysis.

## Dimer of 10-Methylene-9-phenanthrone

PETE D. GARDNER AND HOSSEIN SARRAFIZADEH R.

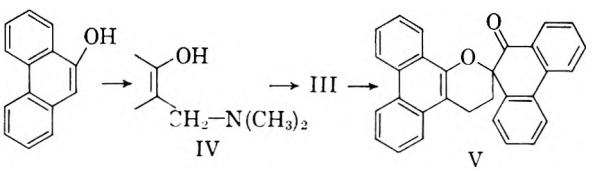
*Received September 18, 1959*

Although several highly substituted homologs of quinone methide (I) are known only one has been reported which contains its double bond terminally II.[1] In an attempt to obtain a compound having the *ortho*-functionality of I for purposes of studying its chemistry, we have directed our efforts toward the synthesis of 10-methylene-9-phenanthrone (III). It might be expected to be stable both by analogy with II and by consideration of the relatively small energy difference between it and the fully aromatic phenanthrene system (10-methyl-9-phenanthrol). Naively, perhaps, one might expect it to have properties similar to those of a hyper-reactive aryl vinyl ketone. Molecular orbital calculations are not helpful in making predictions in cases of this sort because of the oxygen atom; a new parameter is required, the uncertainty in which would permit one to have but little faith in the result. At any rate, one would expect the molecule to have a large delocalization energy and a large free valence value at the terminal carbon atom.[2]




I II III

The condensation of 9-phenanthrol with formaldehyde and dimethylamine under very mild conditions afforded the expected Mannich base IV which proved to be very unstable. Loss of nitrogen occurred during attempts to purify it and the majority of such experiments gave, directly, a high-melting, nitrogen-free substance V. Treatment of a crude sample of IV with methyl iodide gave the methiodide which was also unstable and afforded, as before, the yellow compound. The reaction of 9-phenanthrol with formaldehyde afforded V directly indicating similar instability of the 10-methylol compound.



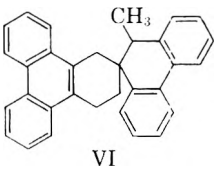

IV V

The dimeric quinone methide V absorbs at 5.94 $\mu$ in the infrared. Its ultraviolet spectrum exhibits high intensity maxima at 250, 275, 295, and 306 m$\mu$ with $\epsilon$ values ($\times 10^4$) 5.65, 2.74, 1.07, and 0.950, respectively. Low intensity absorption is at 340 and 360 m$\mu$ with $\epsilon$ ($\times 10^3$) 3.82 and 2.65, respectively. Reduction of V with lithium aluminum hydride afforded the corresponding carbinol. The latter substance absorbs in the infrared at 2.90 $\mu$ but the 5.94 band found in the spectrum of V is not present. The ultraviolet spectrum exhibits high intensity absorption at 256, 276, and 297

(1) E. Clar, *Ber.*, **69**, 1686 (1936) and references cited therein.

(2) Compare, for example, with *p*-quinodimethane, predicted by calculations[3] to be nearly as stable as benzene (stable as reflected by delocalization energy) but highly reactive. Experimental evidence bearing only on its reactivity is available.

mμ with ε (× $10^4$) 6.35, 3.32, and 1.44 respectively. Low intensity absorption at 343 and 362 mμ has ε 1.92 × $10^3$. This spectrum is almost identical with that of the dihydro dimer of 9,10-phenanthraquinodimethane (VI).[4] Extinction coefficients of low intensity absorption make it clear that only one of the phenanthrene nuclei retains the 9,10-double bond. On the basis of these data, and in consistency with characterized quinone methide dimers in other series,[5] the substance is formulated as V.




VI

## EXPERIMENTAL[6]

*9-Phenanthrol.* This substance was prepared by the procedure of Bachman[7] (22–40% yields) and also by application of the method developed by Hawthorne[8] for another phenol (26% yield).

*10-Dimethylaminomethyl-9-phenanthrol* (IV) *and its methiodide.* A solution of 5.9 g. of 9-phenanthrol in 20 ml. of ethanol was treated with 6.0 ml. of 25% aqueous dimethylamine and 2.3 ml. of 36% aqueous formaldehyde. After standing for 8 hr. at room temperature, the mixture was freed of solvent, without heating, at an aspirator. The solid residue (crude IV) could not be purified without decomposition and so was dissolved in ether and converted to the methiodide using 5.0 g. of methyl iodide. After 12 hr. at room temperature the salt was collected by filtration and washed with ether. The methiodide in this crude state (4.0 g. 35%) melted with decomposition at 225°. Attempts to purify it resulted in the formation of V.

*Anal.* Calcd. for $C_{18}H_{20}NI$: N, 3.55. Found: N, 3.92.

*Dimer of 10-methylene-9-phenanthrone* (V). A solution of 7.0 g. of 9-phenanthrol, 3.2 ml. of 38% aqueous formaldehyde and 6.2 ml. of 25% aqueous dimethylamine in 60 ml. of ethanol was heated under reflux for 2 hr. The mixture, containing suspended yellow solid, was filtered and the filtrate was concentrated to a small volume whereupon additional solid crystallized. The combined solids were recrystallized from benzene to give 3.2 g. (43%) of well formed yellow prisms of V, m.p. 251–252°.

*Anal.* Calcd. for $C_{30}H_{20}O_2$: C, 87.35; H, 4.89. Found: C, 87.13; H, 4.82.

Spectral data are described in the discussion section.

A similar experiment in which the dimethylamine was replaced by a catalytic quantity of pyridine gave the same substance in 40% yield. Reactions conducted in the absence of base of any kind afforded the dimer in 36% yield.

*Lithium aluminum hydride reduction of* V. One gram of the dimer (V) was heated for 10 hr. under reflux in a suspension of a very large excess of lithium aluminum hydride in 50 ml. of tetrahydrofuran. Excess hydride was destroyed by the cautious addition of water followed by dilute hydrochloric acid. Isolation of the product by ether extraction and the usual processing of the extract afforded 0.90 g. (90%) of the expected carbinol, m.p. 249–250°. This substance appeared as colorless prisms after several recrystallizations from ethyl acetate and had the same melting point. The carbonyl absorption found at 5.94 μ in V was lacking in the spectrum of the carbinol. Hydroxyl absorption appeared at 2.9 μ. The ultraviolet spectrum is described in the discussion.

*Anal.* Calcd. for $C_{30}H_{22}O_2$: C, 86.93; H, 5.35; mol. wt. 414. Found: C, 86.64; H, 5.15; mol. wt. 480 (cryoscopic in benzil).

*Acknowledgment.* The authors are indebted to the Robert A. Welch Foundation for the financial support of this work.

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(3) C. A. Coulson, D. P. Craig, A. Maccoll, and A. Pullman, *Discussions Faraday Soc.*, **2**, 46 (1947).

(4) P. D. Gardner and H. Sarrafizadeh R., *J. Am. Chem. Soc.*, in press.

(5) See for example K. Hultzsch, *J. prakt. Chem.*, **159**, 180 (1941).

(6) Melting points are corrected. Infrared spectra were obtained in potassium bromide wafers. Ultraviolet spectra were of 95% ethanol solutions.

(7) W. E. Bachman, *J. Am. Chem. Soc.*, **56**, 1363 (1934).

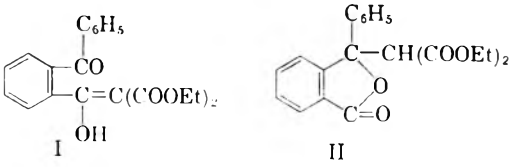
(8) M. F. Hawthorne, *J. Org. Chem.*, **22**, 1001 (1957).

## Condensation of *o*-Benzoylbenzoyl Chloride with Ethyl Malonate

C. F. KOELSCH

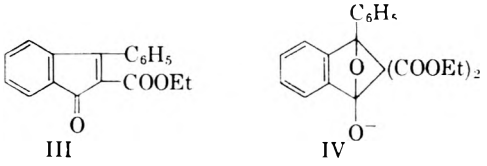
*Received September 23, 1959*

The compound formed by action of *o*-benzoylbenzoyl chloride on ethoxymagnesiomalonic ester, formerly represented as ethyl 3-phenylphthalidylmalonate (II),[1] is actually the enol form of ethyl *o*-benzoylbenzoylmalonate (I).




I II

Structure I allows simple formulation of the conversion of the substance into ethyl 3-phenylindone-2-carboxylate (III) by aqueous base, whereas with structure II this change requires assumption of a strained intermediate (IV).



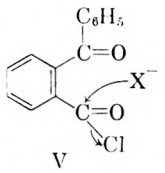

III IV

Spectral and chemical properties of the compound are in agreement with I. In chloroform the compound has a sharp absorption band at 3500 cm.$^{-1}$ (enolic OH), a broad band with maxima at 1600, 1650, 1725 and 1770 cm.$^{-1}$ (C=O and C=C—O), and a broad band at 1260–1300 cm.$^{-1}$ (ester). It gives a deep red-brown color with ferric chloride, and it is soluble in cold 1% sodium hydroxide. Acidification of this solution, if it has not been

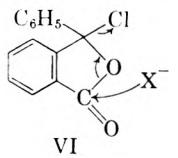
(1) W. L. Yost and A. Burger, *J. Org. Chem.*, **15**, 1113 (1950).

heated or kept too long, precipitates the compound unchanged.

Formation of I has no bearing on the true structure of *o*-benzoylbenzoyl chloride, as illustrated by V and VI.



V



VI

Authentic ethyl 3-phenylphthalidylmalonate (II) can be obtained in good yield from ethyl *o*-benzoylbenzoate and ethyl sodiomalonate in alcohol. The properties of this substance are quite different from those of its isomer. Its infrared spectrum shows absorption at 1720 and 1770 cm.$^{-1}$, corresponding to lactone and ester carbonyl groups. It gives no ferric chloride color and it is insoluble in cold dilute sodium hydroxide. When it is heated with the latter reagent, it dissolves, and acidification then precipitates 3-phenylphthalidyl malonic acid. Heating this acid yields the known[2] 3-phenylphthalidylacetic acid, also obtained directly from the malonic ester by acid hydrolysis.

By analogy with the present results, it is probable that the compound obtained from ethyl benzoylbenzoate and benzyl cyanide is not $C_6H_5COC_6H_4COCHCN$,[3] but rather $HOOCC_6H_4C(C_6H_5)=C(C_6H_5)CN$ or the corresponding lactone. The reported stability to hydrolysis then is easily understandable, and the methylation product is a methyl ester.

## EXPERIMENTAL

*Ethyl o-benzoylbenzoylmalonate* (I). Slight modification of the original preparation[1] enables one to obtain yields of 90–95%. It was not necessary to avoid heating benzoylbenzoyl chloride, and the material was freed of thionyl chloride at 100° under reduced pressure, two portions of dry benzene being added to insure complete volatilization. As I is soluble in and rapidly altered by aqueous sodium carbonate, an excess must be avoided in final washing of the crude product; furthermore, the compound is quite soluble in ether and it is well to use 2:1 ether-ligroin (30–60°) for the first crystallization. The crude product obtained in the present research melted at 80–85°; recrystallization from ethyl acetate–ligroin gave clear prisms, m.p. 86–88° (lit.,[1] 77–79°).

*Anal.* Calcd. for $C_{21}H_{20}O_6$: C, 68.5; H, 5.5. Found[4]: C, 68.4; H, 5.4.

*Ethyl 3-phenylphthalidylmalonate* (II). A solution of 10 g. of sodium in 100 ml. of absolute alcohol was treated with 70 g. of ethyl malonate and then 100 g. of ethyl benzoylbenzoate. The mixture was boiled for 1.5 hr. and then distilled to a sirup under reduced pressure. Addition of 400 ml. of water gave a cloudy solution from which ether extraction (2 × 100 ml.) removed 9.1 g. of ethyl malonate and 20 g. of ethyl benzoylbenzoate. The product was precipitated by acidification as an oil which soon solidified; recrystallization from alcohol and then from ethyl acetate–ligroin gave 95 g. of colorless needles m.p. 100–102°.

*Anal.* Calcd. for $C_{21}H_{20}O_6$: C, 68.5; H, 5.5. Found: C, 68.5; H, 5.6.

When II was boiled with 10% sodium carbonate for about 5 min., it gave a colorless solution. Acidification gave an oil which solidified when it was dried and rubbed with ether. Crystallization from ethyl acetate–ligroin gave an *acid-ester*, colorless needles, m.p. 97–98° that frothed at about 145°.

*Anal.* Calcd. for $C_{19}H_{16}O_6$: C, 67.0; H, 4.7. Found: C, 66.7; H, 4.5.

When 1 g. of II was boiled for 1 hr. with 4 ml. of acetic acid and 4 ml. of 48% hydrobromic acid, it gave 3-phenylphthalide-3-acetic acid, needles from toluene, m.p. 177–178° with previous sintering (lit.,[2] m.p. 179–181°); boiling the acid with methanol-sulfuric acid gave *methyl 3-phenylphthalid-3-acetate*, needles from methanol, m.p. 86–87°; b.p. 230–232° at 10 mm.

*Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.3; H, 5.0. Found: C, 72.0; H, 5.0.

When 6.7 g. of II was boiled 15 min. with 4 g. of sodium hydroxide in 25 ml. of water and the resulting solution was then cooled and acidified, there was obtained 5.3 g. crude *3-phenylphthalidylmalonic acid*, a white powder nearly insoluble in hot acetic acid, ethyl acetate, benzene, or chloroform. Acetone dissolved it easily, however, and crystallization from acetone-ligroin gave 4.1 g. of colorless needles, m.p. 160–164° with gas evolution; the melt resolidified and then melted again at 176–178°.

*Anal.* Calcd. for $C_{17}H_{12}O_6$: C, 65.4; H, 3.9. Found: C, 65.2; H, 3.9.

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(2) W. S. Johnson, A. L. McCloskey, and D. A. Dunnigan, *J. Am. Chem. Soc.*, **72**, 514 (1950).

(3) W. Wislicenus, H. Eichert, and M. Marquardt, *Ann.*, **436**, 95 (1923).

(4) The author thanks Mrs. O. Hamerston for analytical work.

## Condensation Reactions of Phthalaldehydic Acid. I

VAUGHN W. FLOUTZ

*Received September 28, 1959*

On the basis of certain reactions of phthalaldehydic acid several early investigators[1,2] postulated a tautomeric closed-ring form for this compound. This view is substantiated in a recent paper by Wheeler, Young, and Erley,[3] who have examined the infrared absorption of phthalaldehydic acid. These investigators also give data for a considerable number of substituted phthalides prepared by syntheses involving the very reactive 3-position in the 3-hydroxyphthalide form. However, in none of the phthalides which they describe is the carbon atom at the 3-position linked directly to carbon in the substituent.

The solubility and stability of phthalaldehydic

(1) S. Racine, *Ber.*, **19**, 778 (1886).

(2) Bistrzycki and Yessel de Schepper, *Ber.*, **31**, 2790 (1898).

(3) D. D. Wheeler, D. C. Young, and D. S. Erley, *J. Org. Chem.*, **22**, 556 (1957).

acid in concentrated sulfuric acid, and even in mixtures of concentrated sulfuric acid and 20% fuming sulfuric, suggested that condensations might be carried out between phthalaldehydic acid and aromatic hydrocarbons, aryl halides, etc., not unlike the condensation occurring in the production of DDT. A search of the literature revealed that this approach to the synthesis of 3-substituted phthalides from phthalaldehydic acid has been examined only in condensations using certain phenols and phenolic ethers.[2,4,5]

The experiments reported here show that sulfuric acid, which on occasion is bolstered with 20% fuming sulfuric acid, can be employed successfully as the medium for condensing phthalaldehydic acid with a number of aromatic hydrocarbons and aryl halides. Two of the phthalides synthesized and described, namely 3-(2,5-dichlorophenyl)phthalide and 3 - (2,5 - dibromophenyl)phthalide, are apparently unreported in the literature; the others have been prepared by more circuitous methods. Thus the preferred preparation for 3-phenylphthalide, possibly the most important of the phthalides described in this paper, has been the method of Ullman[6,7] which involves the reduction of *o*-benzoylbenzoic acid. 3-Phenylphthalide has also been synthesized by the reaction of phthalaldehydic acid with phenylmagnesium bromide.[8]

The present study is being extended to determine the possibility of similar condensations of phthalaldehydic acid with other aromatics.

## EXPERIMENTAL

The phthalaldehydic acid used in these experiments was purified by a single recrystallization from water. This afforded a white crystalline solid, m.p. 99–100°. The fuming sulfuric acid was Merck 20–23%, reagent grade.

*3-Phenylphthalide.* Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 30 ml. of conc. sulfuric acid, 95–98%. To this solution was added 2.6 g. (0.033 mole) of benzene, and the mixture mechanically stirred at room temperature to disperse the benzene. After about 0.5 hr. the benzene disappeared, giving a homogeneous solution. Stirring was then continued for 0.5 hr.

The reaction mixture, light amber in color, was slowly poured with stirring into about ten times its volume of cold water. The product separated as a thick gum and quickly hardened to a granular solid. After standing until cool the solid was removed, crushed, and thoroughly washed with cold water. The crude product, m.p. 112–114°, weighed 6.9 g. (98%) and was nearly white in color. A single crystallization from ethanol gave 6.0 g. (86%) of white crystals, m.p. 116–117°; lit.,[7] m.p. 115–116°.

*Anal.* Calcd. for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 80.12; H, 4.94.

To verify the product as 3-phenylphthalide 0.5 g. was oxidized with alkaline permanganate solution according to accepted procedure.[9] This gave 0.45 g. of anhydrous *o*-benzoylbenzoic acid, m.p. 127°; lit.,[10] m.p. 127°.

*3-Tolylphthalide.* Three grams (0.02 mole) of phthalaldehydic acid was dissolved in 30 ml. of 5:1 conc. sulfuric acid–water. To this was added 1.84 g. (0.02 mole) of toluene, and the mixture was mechanically stirred to disperse the insoluble toluene. After approximately 2 hr. the toluene disappeared, giving a clear green solution. This was permitted to stand for 1 hr., then poured into a large volume of cold water. The product separated as a yellow gum, soon hardening to a crumbly solid. When cold the solid was removed, pulverized, and washed with cold water. After air-drying the crude product, ivory in color, weighed 4.5 g. (100%). Crystallization from ethanol yielded 3.8 g. (85%) of a white powdery solid which showed no sharp melting point, but softened at 85° and became a clear liquid at *ca.* 115°. This behavior is not unexpected, as the synthesis permits formation of a mixture of the 3-tolylphthalides, particularly the *o*- and *p*-isomers. Reported melting points[11] for the isomers are as follows: 3-(*p*-tolyl)-phthalide, 130°; *o*-, 111°; *m*-, 86.6°.

*Anal.* Calcd. for $C_{15}H_{12}O_2$: C, 80.35; H, 5.39. Found: C, 79.86; H, 5.47.

*3-(p-Xylyl)-phthalide.* Three grams (0.02 mole) of phthalaldehydic acid was dissolved in 20 ml. of 9:1 conc. sulfuric acid-water. To this solution at room temperature was added 2.12 g. (0.02 mole) of *p*-xylene and the mixture was stirred to disperse the insoluble hydrocarbon. After about 30 min. the mixture became orange in color and homogeneous. The reaction product was then isolated in the same manner as described previously for 3-phenylphthalide. After air drying the crude product, ivory in color, weighed 4.5 g. (94%) and melted at 104–111°. Crystallization from ethanol yielded a white powder-like solid, m.p. 111–112°; lit.,[12] m.p. 112°.

*Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.84; H, 5.68.

To verify the product as 3-(*p*-xylyl)phthalide 0.5 g. was subjected to alkaline permanganate oxidation.[9] This gave 0.48 g. of 2-(*o*-carboxybenzoyl)terephthalic acid (commonly called benzophenone-2,2′,5′-tricarboxylic acid) m.p. 282° dec. Neut. equiv. Calcd.: 105; found: 108.

*3-(Chlorophenyl)phthalide.* Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 30 ml. of 2:1 conc. sulfuric acid-20% fuming sulfuric acid. To this was added 3.75 g. (0.033 mole) of chlorobenzene, and the mixture was stirred to disperse the insoluble halide. As a slight temperature rise occurs, the reaction vessel was kept in a water bath at room temperature during the initial stages of the reaction. After some 45 min. the dispersed phase disappeared, leaving a homogeneous solution. The reaction product was then separated and dried as previously described for 3-phenylphthalide. The crude material weighed 8.2 g. (100%) and was nearly white in color. Crystallization from ethanol gave a white, microcrystalline solid. The purified product failed to melt sharply, softening at 85° and becoming completely liquid at 95°. This is to be expected, as the reaction for preparation permits formation of isomeric 3-(chlorophenyl)-phthalides, the *o*- and *p*- in particular. Successive recrystallizations of first crops of crystals from ethanol gave a gradual rise of softening temperature. The melting point of 3-(*p*-chlorophenyl)phthalide reported[13] is 124°. The product melting at 85–95° was used for the analysis.

(4) Bistrzycki and Oehlert, *Ber.*, **27**, 2632 (1894).

(5) M. M. Brubaker and R. Adams, *J. Am. Chem. Soc.*, **49**, 2279 (1927).

(6) F. Ullmann, *Ann.*, **291**, 23 (1896).

(7) C. R. Hauser, M. T. Tetenbaum, and D. S. Hoffenberg, *J. Org. Chem.*, **23**, 861 (1958).

(8) Mermod and Simonis, *Ber.*, **41**, 982 (1908).

(9) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd ed. D. C. Heath and Co., Boston, Mass., 1955, p. 203, No. 3.

(10) W. Hemilian, *Ber.*, **11**, 838 (1878).

(11) Dimeter Ivanov Dalev, *Annuaire univ. Sofia, Fac. phys.-math.*, Livre II, **41**, 37–68 (1944–45); *Chem. Abstr.*, **49**, 4595b (1955).

(12) E. Clar, Fr. John, and B. Howran, *Ber.*, **62**, 940 (1929).

(13) J. O'Brochta and A. Lowy, *J. Am. Chem. Soc.*, **61**, 2765 (1939).

*Anal.* Calcd. for $C_{14}H_9O_2Cl$: C, 68.72; H, 3.71; Cl, 14.49. Found: C, 68.74; H, 3.90; Cl, 14.67.

*3-(Bromophenyl)phthalide.* Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 30 ml. of 2:1 conc. sulfuric acid-20% fuming sulfuric acid. To this was added 5.23 g. (0.033 mole) of bromobenzene. Following essentially the same procedure outlined for the preparation of 3-(chlorophenyl)phthalide there was obtained 9.25 g. (96%) of crude product. Crystallization from ethanol yielded a white crystalline solid which did not show a sharp melting point but softened at 92° and finally became completely liquid *ca.* 105°, indicating a mixture of isomers. The reported[14] melting point for 3-(*p*-bromophenyl)phthalide is 139–140°.

*Anal.* Calcd. for $C_{14}H_9O_2Br$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.32; H, 3.07; Br, 27.47.

*3-(2,5-Dichlorophenyl)phthalide.* Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 36 ml. of 1:1 concentrated sulfuric acid-20% fuming sulfuric acid. To this was added 4.9 g. (0.033 mole) of *p*-dichlorobenzene. In order to keep the insoluble *p*-dichlorobenzene in melted condition the reaction vessel was placed in a water bath maintained at 65–70°. The mixture was mechanically stirred, and after about 2 hr. the dispersed *p*-dichlorobenzene disappeared, yielding a homogeneous reddish-brown solution. The mixture was allowed to stand in the hot water bath for an additional hour, then cooled and poured slowly with stirring into about ten times its volume of cold water. The product separated as a gum which gradually hardened. When cold the solid was removed and the lumps crushed and washed several times with cold water. The crude product, light tan in color, weighed 8.4 g. (90%) and melted at 128–130°. Recrystallization from ethanol, with added Norit, gave colorless needles, m.p. 130–131°.

*Anal.* Calcd. for $C_{14}H_8O_2Cl_2$: C, 60.24; H, 2.89; Cl, 25.41. Found: C, 59.90; H, 2.80; Cl, 25.54.

*3-(2,5-Dibromophenyl)phthalide.* Five grams (0.033 mole) phthalaldehydic acid was dissolved in 45 ml. of 2:1 conc. sulfuric acid-20% fuming sulfuric acid. To this solution was added 7.86 g. (0.033 mole) of *p*-dibromobenzene, and the reaction vessel was then placed in an oil-bath at a bath temperature of 90–95° in order to maintain the insoluble *p*-dibromobenzene in a melted state for better dispersion. Following essentially the same procedure used in the preparation of 3-(2,5-dichlorophenyl)phthalide, there was obtained 12.2 g. (99%) of crude product, light ivory in color, m.p. 121–124°. Crystallization from ethanol, with added Norit, afforded colorless crystals, m.p. 124–125°.

*Anal.* Calcd. for $C_{14}H_8O_2Br_2$: C, 45.69; H, 2.19; Br, 43.43. Found: C, 45.49; H, 2.37; Br, 43.59.

*Acknowledgment.* The author is indebted to the Dow Chemical Company for supplying the phthalaldehydic acid. Appreciation is expressed to Professor Walter A. Cook who provided some of the microanalytical data.

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(14) E. D. Bergmann and E. Loewenthal, *Bull. soc. chim. France*, **1952**, 66–72.

## Dicyclopropylglycolic Acid

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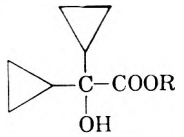
The interesting physiological activity of certain basic esters of benzilic acid is well known.[1] The availability of dicyclopropyl ketone through the convenient procedure of Hart and Curtis[2] has now made possible the preparation of the analog of benzilic acid, dicyclopropylglycolic acid (I).



I. R = H
II. R = $CH_3$
III. R = $—CH_2CH_2N(C_2H_5)_2 \cdot HCl$

Although Hart and Curtis showed that dicyclopropyl ketone reacts with the usual carbonyl reagents, we have been unable to prepare its cyanohydrin. Nor does it appear to form a chloroform addition product[3] from which the hydroxyacid could be derived. In these respects dicyclopropyl ketone resembles benzophenone.

The desired acid I was finally secured through permanganate oxidation of 1,1-dicyclopropyl-2-propyn-1-ol, derived from dicyclopropyl ketone by addition of sodium acetylide.[4] The yield of the oxidation step was only fair (40–45%).

Direct acid-catalyzed esterification of I could not be accomplished. Use of an ion exchange resin as the acid catalyst was no better. Likewise the action of either methyl iodide or dimethyl sulfate on the sodium salt of I produced no ester. Finally, however, II was obtained in 71% yield using diazomethane. The basic ester III was formed by treating the acid I with diethylaminoethyl chloride in isopropanol according to the method of Horenstein and Pählicke.[5]

### EXPERIMENTAL

*Dicyclopropylglycolic acid* (I). To a stirred suspension of 40.8 g. (0.3 mole) of 1,1-dicyclopropyl-2-propyn-1-ol in 800 ml. of water held at 3–5° by means of an ice bath was added dropwise, over a period of 2.5 hr., a solution of 118.5 g. (0.75 mole) of potassium permanganate in 850 ml. of water. After stirring in the ice bath for another 1.5 hr., a large quantity of a filter aid (filtercel) was added and stirring was continued overnight in a refrigerated room.

The manganese dioxide and filter aid were collected at the filter and washed well with water. The combined filtrate and washings were decolorized with charcoal and extracted with ether from which, after drying and removal of ether by distillation, 6.0 g. (15%) of the acetylenic carbinol was recovered.

The ice-cold alkaline solution was acidified by the dropwise addition of cold concentrated sulfuric acid, and then extracted with five 200-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave

(1) Alfred Burger, *Medicinal Chemistry*, Interscience Publishers, Inc., New York, 1951, Vol. I, p. 423.

(2) H. Hart and O. Curtis, Jr., *J. Am. Chem. Soc.*, **78**, 112 (1956).

(3) C. Weizmann, E. Bergmann, and M. Sulzbacher, *J. Am. Chem. Soc.*, **70**, 1153, 1189 (1948).

(4) F. E. Fischer and K. E. Hamlin, in press.

(5) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

an oily semisolid product (33 g.) which was collected at the vacuum filter. Recrystallization from hexane (Skellysolve B) gave 12.3 g. of first crop, m.p. 83–85° and 6.1 g. of second, m.p. 82–84° (18.4 g. = 46% of theory, based on unrecovered carbinol). Several more recrystallizations for analysis raised the melting point to 84–86°.

*Anal.* Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75; O, 30.73. Found: C, 61.68; H, 7.97; O, 30.80.

The infrared spectrum was consistent with the assigned structure.

*Methyl dicyclopropylglycolate* (II). To a solution of 6 g. of diazomethane in 100 ml. of ether was added a solution of 8 g. (0.051 mole) of dicyclopropylglycolic acid (I) in 50 ml. of ether. After standing at room temperature in the dark for 24 hr., the ether was removed by distillation and the residual oil was distilled under reduced pressure. After a forerun, 2.1 g., b.p. 30–124° (60 mm.), the methyl ester II distilled at 124° (60 mm.); yield, 6.2 g. (71%), $n_D^{23}$ 1.4535.

*Anal.* Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.18; H, 8.51.

The infrared spectrum, including a band at 1.63 $\mu$ in the near infrared, characteristic of the cyclopropane ring,[6] was consistent with the assigned structure.

*β-Diethylaminoethyl dicyclopropylglycolate hydrochloride* (III). A solution of 7.8 g. (0.05 mole) of dicyclopropylglycolic acid (I) and 7.5 g. (0.055 mole) of β-diethylaminoethyl chloride in 60 ml. of isopropanol was refluxed with stirring for 18 hr. On cooling, the product crystallized. It was collected by vacuum filtration and dissolved in 50 ml. of cold water. Addition of excess cold 40% sodium hydroxide solution precipitated an oil (free ester base) which was taken up in ether, washed with water and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, a slight excess of ethereal hydrogen chloride solution was added and the precipitated hydrochloride was collected. Three recrystallizations from ethanol gave 6.5 g. (45%) of the ester hydrochloride III, m.p. 152–154°

*Anal.* Calcd. for $C_{14}H_{26}ClNO_3$: C, 57.62; H, 8.98; N, 4.80; Cl, 12.15. Found: C, 57.77; H, 8.98; N, 4.82; Cl, 12.17.

(6) W. H. Washburn and M. J. Mahoney, *J. Am. Chem. Soc.*, **80**, 504 (1958).

*Acknowledgments.* The authors are indebted to Mr. E. F. Shelberg and Mr. W. H. Washburn and their associates for the microanalyses and infrared spectra, respectively.

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## Synthesis of 3-Hydroxypyridines. I. Condensation of Aromatic Aldehydes with Ethyl Cyanoacetate

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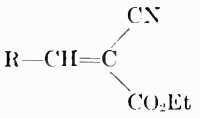
In the course of investigations of methods of syntheses of 3-hydroxypyridines in progress in this laboratory, it was necessary to prepare a series of compounds of type I.



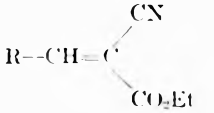
The α,β-unsaturated cyanoesters, I, in which R is an aromatic group, were prepared by condensation of the appropriate aromatic aldehyde with ethyl cyanoacetate by the general Knoevenagel[1] reaction using piperidine as a catalyst.[2] In this

(1) J. Scheiber and F. Meisel, *Ber.*, **48**, 257 (1915).

(2) See for example P. D. Gardner and R. I. Brandon, *J. Org. Chem.*, **22**, 1704 (1957).

TABLE I

CONDENSATION OF ALDEHYDES WITH ETHYL CYANOACETATE



| R | Yield, % | M.P.[a] | Calcd. Carbon | Calcd. Hydrogen | Calcd. Nitrogen | Found[b] Carbon | Found[b] Hydrogen | Found[b] Nitrogen |
|---|---|---|---|---|---|---|---|---|
| *o*-$ClC_6H_4$— | 61 | 54–55[c,d] | 61.16 | 4.28 | 5.95 | 61.11 | 4.03 | 5.97 |
| 3,4-$(C_2H_5O)_2C_6H_3$— | 86 | 126–127[e] | 66.42 | 6.62 | 4.84 | 66.40 | 6.64 | 4.95 |
| *p*-$(ClCH_2CH_2)_2NC_6H_4$— | 89 | 174–175[e] | 56.31 | 5.32 | 8.21 | 56.38 | 5.54 | 7.93 |
| 3,4-$(CH_2O_2)C_6H_3$— | 77 | 106–107[e,f] | 63.67 | 4.52 | 5.71 | 63.70 | 4.63 | 5.47 |
| *o*-$O_2NC_6H_4$— | 68 | 101–103[e,g] | 58.53 | 4.09 | 11.38 | 58.82 | 4.16 | 11.60 |
| 3-$CH_3O$-4-$HOC_6H_3$— | 92 | 108–109[e,h] | 63.15 | 5.30 | 5.67 | 63.13 | 5.39 | 5.90 |
| *p*-$HOC_6H_4$— | 58 | 173–174[e,i] | 66.35 | 5.11 | 6.45 | 66.69 | 5.05 | 6.23 |
| *p*-$(CH_3CH_2)_2NC_6H_4$— | 81 | 95–96[e] | 70.56 | 7.40 | 10.29 | 70.42 | 7.49 | 10.09 |
| *o*-$O_2NC_6H_4CH{=}CH$— | 83 | 141–142[e] | 61.76 | 4.44 | 10.29 | 62.21 | 4.42 | 10.42 |

[a] All melting points are uncorrected. [b] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Straus, Oxford, Eng. [c] Recrystallized from 95% ethanol. [d] Reported m.p. 53° (from esterification of acid), J. A. McRae and C. Y. Hopkins, *Can. J. Res.*, **7**, 248 (1932). [e] Recrystallized from chloroform. [f] Reported m.p. 104° (from esterification of acid), C. H. Clarke and F. Francis, *Ber.*, **44**, 273 (1911). [g] Reported m.p. 96° (from condensation reaction), F. Reidel, *J. prakt. Chem.*, (2), **54**, 533 (1896). [h] Reported m.p. 111° (from esterification of acid), reference as footnote f. [i] Reported m.p. 162–163° (from condensation reaction), reference as footnote g.

manner, the compounds shown in Table I were prepared.

All of the compounds reported had infrared spectra which exhibited a nitrile band at 2195 ± 10 cm.$^{-1}$ and an ester band at 1700 ± 10 cm.$^{-1}$

## EXPERIMENTAL

*Reagents.* The author thanks Kay-Fries Chemicals, Inc. for a generous gift of ethyl cyanoacetate. The aldehydes used were obtained from commercial sources and used without further purification or were prepared by standard literature methods. Thanks go to the Antara Chemicals Division of General Aniline and Film Corp. for a sample of *p*-diethylaminobenzaldehyde.

*Typical condensation.* To a mixture of 22.6 g. (0.2 mole) of ethyl cyanoacetate and 0.2 mole of aldehyde in about 60 ml. of dry dioxane at 0° was added dropwise 0.8 ml. of piperidine. After standing overnight at room temperature, crystals had formed (in a few cases cooling was needed to promote crystallization). The solids were filtered, washed, dried, and recrystallized several times from an appropriate solvent.

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# Preparation of Various Substituted Pyrimidines[1]

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During the last decade, numerous pyrimidines and purines have been investigated which might be useful in human cancer chemotherapy, and several have been found to possess tumor-inhibiting properties.[3,4] The pharmacological activity of these compounds has prompted the preparation of various substituted pyrimidines.

The substituted pyrimidines synthesized during the course of this investigation have incorporated the physiologically active ring systems of pyridine and thiophene and were prepared in hopes that some of them would exhibit physiological activity of some type, since they are related to a number of the biological and medicinal agents, such as nucleic acids, several vitamins and enzymes, uric acid, and sulfadiazine.

Pharmacological tests of these substituted pyrimidines are being made.

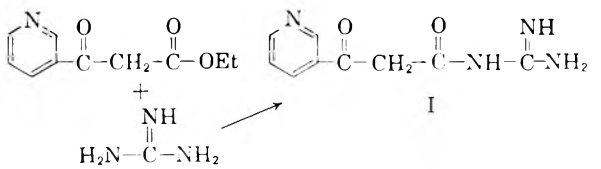
The substituted pyrimidines synthesized are listed in Table I and Table II and were prepared by condensing the appropriate β-diketone or β-keto ester with guanidine carbonate. The general procedure is given in the experimental section.

The 2-amino-4-alkyl-6-(α-thienyl)pyrimidines were prepared by condensing the appropriate acyl-2-thenoylmethane with guanidine carbonate.

The 2-amino-4-alkyl-6-(β-pyridyl)pyrimidines were prepared by the same method, but the appropriate nicotinylacylmethane was employed.

In the case of 2-amino-4-hydroxy-6-(α-thienyl)-pyrimidines, ethyl β-keto-(α-thienyl)propionate was condensed with guanidine carbonate.

In the attempted preparation of 2-amino-4-hydroxy-6-(β-pyridyl)pyrimidine, ethyl nicotinoylacetate was treated with guanidine carbonate, but ring closure did not occur as the intermediate product (I) was obtained instead.



I

The infrared spectra of these pyrimidines have been recorded and showed prominent peaks near 3200–3100 cm.$^{-1}$ due to CH stretching vibrations. In addition, strong peaks were noted in the region near 1665 cm.$^{-1}$, 1600–1565 cm.$^{-1}$ and 1555–1540 cm.$^{-1}$ which are due to C=C and C=N vibrations, respectively, in this aromatic system. There is some belief that the higher frequency bands are due to $NH_2$ deformations modes rather than C=C and C=N vibrations themselves.[5] There is also a strong band near 3320 cm.$^{-1}$ and this is assigned to the $NH_2$ group.

## EXPERIMENTAL

*Preparation of substituted pyrimidines.* The substituted pyrimidines were prepared by heating 3.5 g. of the appropriate β-diketone or β-keto ester with 1.5 g. of guanidine carbonate at 130–140° for 3–4 hr. according to the method of Evans.[6] The molten mass was allowed to cool and then dissolved in hydrochloric acid. The substituted pyrimidine was then precipitated upon the addition of dilute ammonium hydroxide.

The substituted pyrimidine was recrystallized three times from absolute alcohol, and white crystals were obtained. The average yield was 20%.

The respective picrates were prepared by dissolving 0.1 g. of the pyrimidine in 5 ml. of absolute alcohol and adding a saturated solution of picric acid dissolved in absolute alcohol. Upon standing, the picrate settled out and was recrystallized from absolute alcohol.

In the case of the 2-amino-4-hydroxy-6-(α-thienyl)pyrimidine, the acid-base technique was not employed, but the pyrimidine was recrystallized from 80% alcohol.

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(1) This work is based on a thesis submitted by James J. Zelko in partial fulfillment for the degree of Master of Science at Loyola University, Chicago, Ill.

(2) Cooperative National Science Foundation Fellow, Summer 1959.

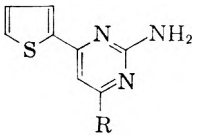
(3) C. Heidelberger, N. C. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, and J. Scheiner, *Nature*, **179**, 663 (1957).

(4) R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Amer. Chem. Soc.*, **79**, 4559 (1957)

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Second Edition, John Wiley and Sons, (New York, 1956), p. 282.

(6) P. N. Evans, *J. prakt. Chem.* [2] **48**, 513 (1893).

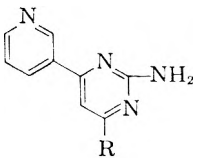
TABLE I

PYRIMIDINES OF TYPE 

| R | Molecular Formula | M.P. | % Nitrogen Calcd. | % Nitrogen Found[a] | Molecular Formula | M.P.[b] | % Nitrogen Calcd. | % Nitrogen Found[a] |
|---|---|---|---|---|---|---|---|---|
| —$CH_3$ | $C_9H_9N_3S$ | 172° | 21.97 | 21.50 | $C_{15}H_{12}N_6O_7S$ | 243–248° | 19.93 | 19.94 |
| —$C_2H_6$ | $C_{10}H_{11}N_3S$ | 139° | 20.47 | 20.32 | $C_{16}H_{14}N_6O_7S$ | 233–237° | 19.34 | 19.25 |
| —*n*-$C_3H_7$ | $C_{11}H_{13}N_3S$ | 116° | 19.16 | 19.13 | $C_{17}H_{16}N_6O_7S$ | 213–214° | 18.74 | 18.81 |
| —*i*-$C_3H_7$ | $C_{11}H_{13}N_3S$ | 115° | 19.16 | 19.03 | $C_{17}H_{16}N_6O_7S$ | 220–222° | 18.74 | 18.65 |
| *n*-$C_4H_9$ | $C_{12}H_{15}N_3S$ | 79° | 18.01 | 18.27 | $C_{18}H_{18}N_6O_7S$ | 196–199° | 18.17 | 18.00– |
| *i*-$C_4H_9$ | $C_{12}H_{15}N_3S$ | 110° | 18.01 | 18.17 | $C_{18}H_{18}N_6O_7S$ | 175–176° | 18.17 | 17.92 |
| *n*-$C_5H_{11}$ | $C_{13}H_{17}N_3S$ | 82° | 16.99 | 16.88 | $C_{19}H_{20}N_6O_7S$ | 163–164° | 17.64 | 17.60 |
| —OH | $C_8H_7N_3OS$ | 306° dec. | 21.74 | 21.95 | $C_8H_7N_3O_8S$ | 241–248° | 19.90 | 19.72 |

[a] Nitrogen analyses by Micro-Tech Laboratories, Skokie, Ill. [b] Melting points of the picrates were taken in a sealed evacuated capillary tube, are uncorrected, and all melt with decomposition.

TABLE II

PYRIMIDINES OF TYPE 

| R | Molecular Formula | M.P. | % Nitrogen Calcd. | % Nitrogen Found[a] | Molecular Formula | M.P.[b] | % Nitrogen Calcd. | % Nitrogen Found[a] |
|---|---|---|---|---|---|---|---|---|
| —$CH_3$ | $C_{10}H_{10}N_4$ | 205° | 30.09 | 29.83 | $C_{16}H_{13}N_7O_7$ | 245–249° | 23.60 | 23.75 |
| *t*-Butyl | $C_{13}H_{16}N_4$ | 138° | 24.43 | 24.43 | $C_{19}H_{19}N_7O_7$ | 210–212° | 21.43 | 21.34 |
| *i*-Butyl | $C_{13}H_{16}N_4$ | 149° | 24.66 | 24.66 | $C_{19}H_{19}N_7O_7$ | 206–207° | 21.43 | 21.38 |
| Phenyl | $C_{15}H_{12}N_4$ | 166° | 22.57 | 22.57 | $C_{21}H_{15}N_7O_7$ | 223–225° | 20.53 | 20.78 |

[a] Nitrogen analyses by Micro-Tech Laboratories, Skokie, Ill. [b] Melting points of the picrates were taken in a sealed evacuated capillary tube, are uncorrected, and all melt with decomposition.

*Preparation of* I. A 3.5-g. sample of ethylnicotinoylacetate and 5 g. of guanidine carbonate was heated at 140° for 1 hr. The molten mass was allowed to cool and recrystallized from 80% alcohol, and light colored crystals were obtained melting at 283–288° dec.

*Anal.* Calcd. for $C_9H_{10}O_2N_4$: N, 27.37. Found: N, 27.17.

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## Quaternary Ammonium Salts. IV. Synthesis and Decomposition of *N*-Methyl-*N*,*N*-di-*n*-propylanilinium Salts

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In continuation of the research done by Fahim and Galaby,[1] Fahim and Fleifel,[2] and Fahim *et al.*,[3] we now have studied the synthesis and decomposition of some *N*-methyl-*N*,*N*-di-*n*-propylanilinium salts. The tertiary bases, used as starting materials in this investigation, were prepared by propylation of the corresponding primary aromatic amines with tri-*n*-propyl phosphate as recommended by Bilman *et al.*[4] for the preparation of dipropylaniline. The dipropylanilines obtained were identified through the picrate. The boiling points and the yields of the tertiary bases are recorded in Table I.

TABLE I
TERTIARY BASES

| Primary aromatic amine | Boiling point of the dipropylaniline | Yield, % |
|---|---|---|
| *p*-Anisidine | 158–160/15 mm. | 70 |
| *o*-Anisidine | 142–145/15 mm. | 45 |
| *p*-Phenetidine | 166–168/60 mm. | 44 |
| *o*-Phenetidine | 173–175/60 mm. | 45 |
| *p*-Toluidine | 165–168/65 mm. | 51 |
| *m*-Toluidine | 170–173/60 mm. | 51 |
| *o*-Toluidine | 144–146/55 mm. | 58 |

(1) H. A. Fahim and M. Galaby, *J. Chem. Soc.*, 3529 (1950).

(2) H. A. Fahim and A. M. Fleifel, *J. Chem. Soc.*, 2761 (1951).

(3) H. A. Fahim, F. G. Baddar, and M. Galaby, *J. Chem. Soc.*, 317 (1955).

(4) J. H. Bilman, A. Radike, and A. W. Mundy, *J. Am. Chem. Soc.*, **64**, 2977 (1942).

TABLE II

QUATERNARY IODIDES, QUATERNARY PICRATES, PICRATES OF STARTING MATERIALS AND PRODUCTS

| Starting Material | Compound | Solvent[c] | M.P. | Yield, % | Formula | Carbon, % Calcd. (Found) | Hydrogen, % Calcd. (Found) | Iodine, % Calcd. (Found) |
|---|---|---|---|---|---|---|---|---|
| Ia | *N*-Methyl-*N*,*N*-di-*n*-propyl-*p*-anisidinium iodide | A | 142–143 | 100[a] | $C_{14}H_{24}ONI$ | | | 36.39 (36.3) |
| | *N*-Methyl-*N*,*N*-di-*n*-propyl-*p*-anisidinium picrate | B | 103–104 | | $C_{20}H_{26}O_8N_4$ | 53.33 (53.40) | 5.77 (5.80) | |
| | *N*,*N*-di-*n*-propyl-*p*-anisidine picrate | B | 93–94 | | $C_{19}H_{24}O_8N_4$ | 52.3 (52.40) | 5.50 (5.70) | |
| | *N*-Methyl-*N*-propyl-*p*-anisidine picrate | B | 102 | | $C_{17}H_{20}O_8N_4$ | 50.0 (49.80) | 4.90 (4.95) | |
| Ib | *N*-Methyl-*N*,*N*-di-*n*-propyl-*o*-anisidinium iodide | A | 238–239 | 45 | $C_{14}H_{24}ONI$ | | | 36.39 (36.9) |
| | *N*-Methyl-*N*,*N*-di-*n*-propyl-*o*-anisidinium picrate | B | 143–144 | | $C_{20}H_{26}O_8N_4$ | 53.33 (53.75) | 5.77 (5.90) | |
| | *N*,*N*-di-*n*-propyl-*o*-anisidine picrate | B | 110 | | $C_{19}H_{24}O_8N_4$ | 52.3 (52.14) | 5.50 (5.70) | |
| | *N*-Methyl-*N*-propyl-*o*-anisidine picrate | B | 139–140 | | $C_{17}H_{20}O_8N_4$ | 50.0 (49.50) | 4.90 (5.0) | |
| Ic | *N*-Methyl-*N*,*N*-di-*n*-propyl-*p*-phenetidinium iodide | A | 241–242 | 100 | $C_{15}H_{26}ONI$ | | | 35.59 (36.2) |
| | *N*-Methyl-*N*,*N*-di-*n*-propyl-*p*-phenetidinium picrate | B | 117 | | $C_{21}H_{28}O_8N_4$ | 54.31 (53.90) | 6.03 (5.90) | |
| | *N*,*N*-di-*n*-propyl-*p*-phenetidine picrate | B | 105–106 | | $C_{20}H_{26}O_8N_4$ | 53.33 (53.98) | 5.77 (6.05) | |
| | *N*-Methyl-*N*-propyl-*p*-phenetidine picrate | B | 137–138 | | $C_{18}H_{22}O_8N_4$ | 51.18 (51.65) | 5.21 (5.10) | |
| Id | *N*-Methyl-*N*,*N*-di-*n*-propyl-*o*-phenetidinium iodide | A | 233–234 | 53 | $C_{15}H_{26}ONI$ | | | 35.59 (36.2) |
| | *N*-Methyl-*N*,*N*-di-*n*-propyl-*o*-phenetidinium picrate | B | 139–140 | | $C_{21}H_{28}O_8N_4$ | 54.31 (53.80) | 6.03 (5.90) | |
| | *N*,*N*-di-*n*-propyl-*o*-phenetidine picrate | B | 96 | | $C_{20}H_{26}O_8N_4$ | 53.33 (53.01) | 5.77 (5.79) | |
| | *N*-Methyl-*N*-propyl-*o*-phenetidine picrate | B | 184–185 | | $C_{18}H_{22}O_8N_4$ | 51.18 (51.75) | 5.21 (5.30) | |
| Ie | *N*-Methyl-*N*,*N*-di-*n*-propyl-*p*-toluidinium iodide | A | 133–134 | 80 | $C_{14}H_{24}NI$ | | | 38.02 (38.76) |
| | *N*-Methyl-*N*,*N*-di-*n*-propyl-*p*-toluidinium picrate[b] | B | 140–141 | | $C_{20}H_{26}O_7N_4$ | 55.27 (55.26) | 6.0 (6.09) | |
| | *N*,*N*-di-*n*-propyl-*p*-toluidine picrate | B | 109 | | $C_{19}H_{24}O_7N_4$ | 54.28 (53.97) | 5.71 (5.67) | |
| | *N*-Methyl-*N*-propyl-*p*-toluidine picrate | B | 284–285 | | $C_{17}H_{20}O_7N_4$ | 51.0 (50.86) | 5.0 (4.85) | |
| If | *N*-Methyl-*N*,*N*-di-*n*-propyl-*m*-toluidinium iodide | A | 148–149 | 37 | $C_{14}H_{24}NI$ | | | 38.02 (38.6) |
| | *N*,*N*-di-*n*-propyl-*m*-toluidine picrate | B | 128–129[d] | | $C_{19}H_{24}O_7N_4$ | 54.28 (54.27) | 5.71 (5.74) | |
| | *N*-Methyl-*N*-propyl-*m*-toluidine picrate | B | 89–90 | | $C_{17}H_{20}O_7N_4$ | 51.0 (50.59) | 5.0 (5.12) | |
| Ig | *N*,*N*-di-*n*-propyl-*o*-toluidine picrate | B | 140–141 | | $C_{19}H_{24}O_7N_4$ | 54.28 (54.29) | 5.71 (5.90) | |

[a] The yields of *N*-methyl-*N*,*N*-di-*n*-propylanilinium salts were calculated on the basis of the iodide. [b] *N*-Methyl-*N*,*N*-di-*n*-propyl-*m*-toluidinium picrate was obtained as a yellow oil which could not be solidified. [c] A = methanol-ether; B = ethanol. [d] F. J. Wobb, W. S. Cook, H. E. Albert, and G. E. P. Smith, *Ind. Eng. Chem.*, **46**, 1711 (1954) (*Chem. Abstr.*, 14282 (1954)), gave the same m.p. for the picrate, when they prepared the tertiary base (If) by the action of *n*-propyl bromide in aqueous potassium carbonate.

*N*-Methyl-*N*,*N*-di-*n*-propylanilinium salts of the tertiary bases (Ia–g) were prepared by the action of methyl iodide on the corresponding *N*,*N*-di-*n*-propylanilines.

$$\underset{\text{I}}{ArN(C_3H_7)_2} + CH_3I \longrightarrow \underset{\text{II}}{[ArN(C_3H_7)_2CH_3]^+I^-}$$

| | |
|---|---|
| Ia. Ar = *p*-$CH_3OC_6H_4$— | IIa. Ar = *p*-$CH_3OC_6H_4$— |
| b. Ar = *o*-$CH_3OC_6H_4$— | b. Ar = *o*-$CH_3OC_6H_4$— |
| c. Ar = *p*-$C_2H_5OC_6H_4$— | c. Ar = *p*-$C_2H_5OC_6H_4$— |
| d. Ar = *o*-$C_2H_5OC_6H_4$— | d. Ar = *o*-$C_2H_5OC_6H_4$— |
| e. Ar = *p*-$CH_3C_6H_4$— | e. Ar = *p*-$CH_3C_6H_4$— |
| f. Ar = *m*-$CH_3C_6H_4$— | f. Ar = *m*-$CH_3C_6H_4$— |
| g. Ar = *o*-$CH_3C_6H_4$— | |

Only in the case of *N*,*N*-di-*n*-propyl-*o*-toluidine, could the formation of the quaternary ammonium salt not be achieved under normal conditions, when the tertiary base was treated with methyl iodide or methyl sulfate, due probably to steric effect.[1,2]

The thermal decomposition of the quaternary ammonium iodides was affected by heating above their melting points. The remaining tertiary bases, left after decomposition, were identified as the corresponding picrates. Mixed melting-point determination of the picrates of the starting materials (Ia–f) and the picrates obtained on thermal decomposition, showed depression in each case. This fact, together with the analytical figures obtained from decomposition picrates, indicated that thermal decomposition led to the formation of the mixed dialkylaniline, i.e., *n*-propyl iodide was always eliminated and *N*-methyl-*N*-propyl aromatic base was left. A similar result has been reported previously.[1–3]

Decomposition of the iodides IIa–f with ethanolic sodium ethoxide followed the same route observed in the thermal decomposition. Mixed melting-point determination of the picrates obtained on thermal decomposition and those from alkaline decomposition showed no depression, indicating that they are identical. The quaternary iodides, the quaternary picrates, the picrates of the starting materials, and the picrates of the products of decomposition are listed in Table II.

## EXPERIMENTAL

*Preparation of the dipropylanilines* (Ia–g). Tri-*n*-propyl phosphate was prepared according to the general procedure described for the synthesis of *n*-alkyl phosphates.[5]

The method used for the preparation of Ia–g was that adopted by Bilman *et al.*[4] The corresponding picrates were prepared by mixing an ethanolic solution of the freshly distilled tertiary base with saturated ethanolic solution of picric acid. The products were filtered and crystallized.

*Preparation of the quaternary ammonium iodides.* Equimolecular proportions of the tertiary base Ia–g and methyl iodide were mixed in a sealed tube and left for some days at room temperature (20°) (in case of Ia, Ic, and Ie), or heated at 100° for 5–10 hr. (Ib, Id, and If), (40 hr. in case of Ig). The solid products were washed with ether and crystallized.

*Preparation of the quaternary ammonium picrates.* The quaternary ammonium picrates were obtained when an aqueous solution of the corresponding iodide was added to an excess of a saturated aqueous solution of picric acid. The precipitate was collected, dried, and crystallized.

*Decomposition of the quaternary ammonium iodides.* (a) *By heat.* The thermal decomposition of the iodides IIa–f was effected by heating 0.5 g. of the pure substance in a Pyrex tube above its melting point until bubbles ceased to evolve. The oily residue was extracted with ether, filtered to remove any undecomposed iodide and the ether removed. A few drops of ethanol were added, followed by a saturated ethanolic solution of picric acid. The picrate was filtered off and crystallized.

(b) *By ethanolic sodium ethoxide.* The decomposition of the iodides IIa–f was carried out by heating (1.5 g.) with ethanolic sodium ethoxide [from metallic sodium (0.3 g.) and absolute ethanol (20 ml.)] for 5 hr. on the steam bath. Sodium iodide, formed as a result of decomposition, was filtered, the ethanol was concentrated and a few ml. of water added. The oil that separated was taken up in ether, dried, and the ether removed. The oily residue was converted into the picrate, which was then filtered and crystallized.

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(5) G. R. Dutton and C. R. Noller, *Org. Synthesis*, **Vol. XVI**, p. 9.

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## Thiophosgenation of Dimethylammonium Chloride[1]

EUGENE LIEBER[2] AND J. P. TRIVEDI

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In continuation of studies[3] on the preparation and properties of the thiatriazole ring system a supply of dimethylthiocarbamyl chloride (II) was required. Billiter and Rivier[4,5] report a convenient procedure using dimethylammonium chloride (I) and thiophosgene in the presence of aqueous sodium hydroxide. The thiophosgene (in alcohol-free chloroform) is added to an aqueous solution of I followed by slow addition of sodium hydroxide, the temperature being maintained at 25° by addition of ice. Yields of 65 to 95% of II were reported. Two moles of alkali are used per mole of I and at the end of the reaction the aqueous phase was reported[4] to be alkaline. At this point the chloroform layer changes from red to yellow in color. In our hands the repetition of this procedure failed to confirm any of these observations; only a 7%

(1) The authors gratefully acknowledge the support of these studies by the Air Force Office of Scientific Research.

(2) Present address: Department of Chemistry, Roosevelt University, Chicago 5, Illinois, to whom all correspondence should be addressed.

(3) E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.*, **37**, 563 (1959).

(4) O. Billiter and H. Rivier, *Ber.*, **37**, 4319 (1904).

(5) Houben-Weyl, *Methoden der Organischen Chemie*, Georg Thieme Verlog, Stuttgart, Germany, volume IX, page 830 (1955).

yield of II was obtained, the aqueous layer was acidic and the chloroform layer remained red in color. In addition, a nicely crystalline product melting at 104° consistently appeared by fractional recrystallization of the crude II. This was identified as tetramethylthiuram monosulfide (III) and in one experiment (Table I) it became the major product. Tetramethylthiourea was also isolated in this instance. Billiter and Rivier[4] fail to mention the formation of any by-products in their reaction.

TABLE I

THIOPHOSGENATION OF DIMETHYLAMMONIUM CHLORIDE[a]

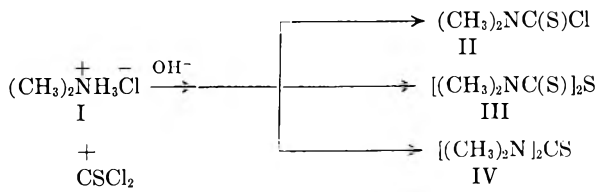
| Temp. ° | Ratio NaOH/ $Me_2\overset{+}{N}H_3\overset{-}{Cl}$ | % Yield of Dimethylthiocarbamyl Chloride |
|---|---|---|
| 28 | 1 | 2 |
| 28 | 2 | 7 |
| 28 | 2.5 | None[b] |
| 20 | 2.7 | 25[c] |
| 10 | 2 | 15 |
| −5[d] | 2 | 38 |
| −20[e] | 2 | 46–50 |

[a] In all experiments a one to one molar ratio of thiophosgene to dimethylammonium chloride was maintained. [b] Tetramethylthiuram monosulfide was isolated in 1.6% yield, the major product being an unworkable oil. [c] The major product (47%) was III; 5% of IV was also obtained. [d] The temperature varied from 0° to −5°. [e] The temperature varied from −10° to −20°.

An investigation of this reaction was conducted. The results are summarized in Table I. Increasing the quantity of sodium hydroxide until the aqueous layer became alkaline was without effect, in fact no yield of II was obtained and only 1.6% of III and an intractable oil were the major products. The most important variable was the temperature of the reaction regardless of whether the aqueous phase ended up in an acidic or alkaline condition. The lowest practical temperature with the set of reagents used was found to be −10 to −20° in which case consistent yields of II of 46 to 50% were obtained. At lower temperatures increase in sodium hydroxide reduces the yield of II while favoring the formation of III. This suggests that the formation of III can be accounted for by a nucleophilic displacement of chloride ion by sulfide ion: the sulfide ion arising from the alkaline

$$2\ \mathrm{II} + S^{=} \longrightarrow \mathrm{III} + 2\ Cl^{-}$$

hydrolysis of the thiophosgene.




EXPERIMENTAL[6,7]

*Dimethylthiocarbamyl chloride* (II). Into a three necked round-bottom flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel and surrounded by acetone-Dry Ice bath was placed 8.3 g. (0.1 mole) of dimethylammonium chloride dissolved in 10 ml. of water. The temperature was adjusted to −10°. Thiophosgene (12 g., 0.1 mole) dissolved in 30 ml. of alcohol-free chloroform was added to the reaction flask with stirring over a period of 30 min. An aqueous solution of sodium hydroxide (100 ml. of a 2*M* solution) was then added over a period of 1 hr., not allowing the temperature to rise above −10°. The mixture was finally stirred for an additional 30 min., the chloroform layer separated and immediately dried over calcium chloride. The chloroform was then removed at reduced pressure at steam bath temperature. The residue (which is semisolid when cooled in an ice bath) was recrystallized from petroleum ether yielding a product melting at 41° in agreement with that reported.[4] The yield varied from about 5 to 5.5 g. (45 to 50% based on I).

*Tetramethylthiuram monosulfide* (III). This arises (Table I) from the fraction-crystallization of crude II. It was identified by mixture melting point with an authentic specimen of tetramethylthiuram monosulfide prepared according to the procedure of von Braun and Stechele.[8] When using anhydrous ether (as solvent for the thiophosgene) II is recovered as the ether soluble fraction, while recrystallization of the ether-insoluble residue yields III.

*Tetramethylthiourea* (IV). This was found in several instances as a by-product of the fractional crystallization of II. It was identified by its melting point[9] of 75–76°.

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(6) Melting points are uncorrected.

(7) The thiophosgene was supplied by the Rapter Chemical Company, Chicago, Illinois. Vapor phase chromatography showed this to be 99% plus in thiophosgene content.

(8) J. von Braun and F. Stechele, *Ber.*, **36**, 2274 (1903).

(9) O. Billiter, *Ber.*, **43**, 1856 (1910).

## Cyclic Sulfites and the Bissinger Rearrangement

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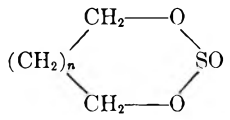
The "Bissinger rearrangement" is a convenient name for the reaction first described by Bissinger, Kung, and Hamilton,[1] in which a dialkyl sulfite gives an alkyl alkanesulfonate on heating with a tertiary base. Dimethyl sulfite gave a 49–56% yield of methyl methanesulfonate after 24 hr. with 1 mol. per cent of tributylamine; the yield decreased with increasing size of alkyl groups. The rearrangement of dimethyl sulfite gave dimethyl ether as by-product, and a mechanism was suggested which accounted for both the rearrangement and the ether formation. We have found triethylamine is also a

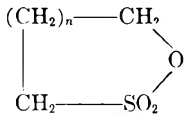
(1) W. E. Bissinger, F. E. Kung, and C. W. Hamilton, *J. Am. Chem. Soc.*, **70**, 3940 (1948).

satisfactory catalyst, but not quinoline or dimethylaniline.

If the Bissinger rearrangement of trimethylene sulfite (Ia) were successful, it would provide a convenient route to



Ia. $n = 1$
Ib. $n = 2$



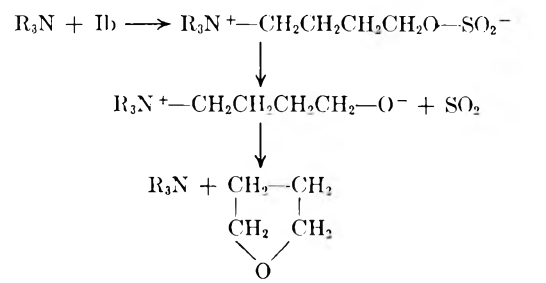
IIa. $n = 1$
IIb. $n = 2$

3-hydroxy-1-propanesulfonic acid sultone (IIa) whose preparation from allyl alcohol has been described.[2] Similarly, a successful rearrangement of tetramethylene sulfite (Ib) would provide a route to 4-hydroxy-1-butanesulfonic acid sultone (IIb) which has been prepared from 4-chlorobutyl acetate.[3]

In an attempt to prepare Ia, Majima and Simanuki[4] obtained mainly trimethylene chloride. Myles and Prichard[5] state that 1,4-butanediol and longer chain glycols give only chain polymers when treated with thionyl chloride and pyridine below 35°. However, successful preparations have been reported by de la Mare and co-workers,[6] and also by Szmant and Emerson.[7] We have prepared both Ia and Ib in reasonable yield from the corresponding glycol and thionyl chloride by the method of Kyrides.[8]

The attempted rearrangement of Ib gave only tetrahydrofuran as an identifiable organic product in 76% yield. It was substantially pure; in one experiment traces of two carbonyl containing impurities were detected by paper chromatography. The attempted rearrangement of Ia gave a mixture of six organic products including acrolein and propionaldehyde, together with water and sulfur dioxide. The same reaction of ethylene sulfite gave seven organic products including acetaldehyde.

The formation of tetrahydrofuran from tetramethylene sulfite is compatible with the mechanism advanced by Bissinger *et al.* for the formation of dimethyl ether as a by-product from dimethyl sulfite. The reaction may be formulated as shown:



The formation of a five-membered ring is favored for steric reasons; trimethylene and ethylene sulfites would lead to four- and three-membered rings, and the decomposition of the zwitterionic intermediate to aldehyde products is understandable.

## EXPERIMENTAL[9]

*Preparation of cyclic sulfites. Tetramethylene sulfite* was prepared from tetramethylene glycol and thionyl chloride by the method of Kyrides[8] in 45% yield. The product had b.p. 119° at 15 mm., $n_D^{20}$ 1.4650; $d_4^{20}$ 1.2537; $R_D$. Calcd.: 29.90. Found: 30.02 (lit.,[7] $n_D^{25}$ 1.4631).

*Trimethylene sulfite* was prepared from trimethylene glycol and thionyl chloride by the same method in 42% yield. The product had b.p. 76° at 15 mm., $n_D^{20}$ 1.4567; $d_D^{20}$ 1.3225; $R_D$. Calcd. 25.25. Found 25.14 (lit., $n_D^{25}$ 1.4509,[6] $n_D^{20}$ 1.4530[7]).

*Ethylene sulfite* was prepared similarly in 79% yield and had b.p. 70° at 20 mm., $n_D^{20}$ 1.4461 (lit.,[6] $n_D^{25}$ 1.4450).

*Analytical methods.* Gas chromatography of the products was carried out using a McWilliam-Dewar detector[10] and dioctyl phthalate as stationary phase supported on 30–50 mesh crushed "Insulox"[11]; nitrogen was the carrier gas and the column temperature was 100°. The retention times, $q$, are given relative to benzene (1.00) under the same conditions.[12] Peak heights relative to the largest peak are shown in parentheses. The organic products were also treated with dinitrophenylhydrazine in methanol, and the mixed dinitrophenylhydrazones were separated by descending paper chromatography in a heptane-methanol system.[13–15] Finally, the products were examined by infrared spectroscopy in a Perkin Elmer Model 12C instrument using sodium chloride optics.

*Rearrangement products.* The rearrangement was attempted by heating the sulfite (0.2 mol.) with triethylamine (0.01 mol.) at a pot temperature of 180° for 9 hr. The reaction mixture was distilled and the distillate examined. In each case the residue was an intractable tar.

*Tetramethylene sulfite* gave tetrahydrofuran in 76% yield. The distillate had b.p. 64–70°; $n_D^{20}$ 1.4030 (lit.,[16] b.p. 64–66°; $n_D^{20}$ 1.4070). Gas chromatography showed no trace of contaminants, and the product had retention time identical with an authentic specimen. In one experiment, the paper chromatograph showed very faint traces of two carbonyl components which ran slower than crotonaldehyde; in a second experiment, not even these trace impurities were found. Tetrahydrofuran was characterized as tetramethylene

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(3) W. E. Truce and F. D. Hoerger, *J. Am. Chem. Soc.*, **76**, 5357 (1954).
(4) R. Majima and H. Simanuki, *Proc. Imp. Acad. Japan*, **2**, 544 (1926); *Chem. Abstr.*, **21**, 1796 (1927).
(5) W. J. Myles and J. H. Prichard, U. S. Patent **2,465,-915**; *Chem. Abstr.*, **43**, 4835 (1949).
(6) C. A. Bunton, P. B. D. de la Mare, P. M. Greaseley, D. R. Llewellyn, N. H. Pratt, and J. G. Tillett, *J. Chem. Soc.*, 4751 (1958).
(7) H. H. Szmant and W. Emerson, *J. Am. Chem. Soc.*, **78**, 454 (1956).
(8) L. Kyrides, *J. Am. Chem. Soc.*, **66**, 1006 (1944).
(9) Melting points and boiling points are uncorrected.
(10) I. G. Williams and R. A. Dewar, "*Second Symposium on Gas Chromatography*," (ed. D. H. Desty), Butterworths Scientific Publications, London, 1958, p. 174.
(11) "Insulox" is the registered trade name for an insulating firebrick manufactured by Nonporite Pty. Ltd., Hawthorn, Victoria.
(12) R. J. Cvetanovic and K. O. Kutschke, "*Vapor Phase Chromatography*" (ed. D. H. Desty), Butterworths Scientific Publications, London, 1957, p. 87.
(13) F. E. Huelin, *Australian J. Sci. Res.*, **5B**, 328 (1952).
(14) D. F. Meigh, *Nature (London)*, **170**, 579 (1952).
(15) D. A. Forss, E. A. Dunstone, and W. Stark, *Chem. & Ind.*, **42**, 1292 (1954); **45**, 521 (1957).
(16) T. H. Durrans, "*Solvents*," Chapman & Hall Ltd., London, 7th ed., 1957, p. 185.

bis(2-thiopseudourea)dipicrate, prepared from 1,4-diiodobutane made by a modification of the method of Stone and Schechter.[17] To 5 g. of potassium iodide was added 5 ml. of sirupy phosphoric acid (85%) and 1 ml. of rearrangement product. The mixture was refluxed gently for 1.5 hr., then 10 ml. of water was added, and the whole was extracted with 15 ml. of ether. The ether solution was washed with water, sodium thiosulfate solution and again with water; then the ether was removed and replaced by 10 ml. of ethanol. A 1-g. sample of thiourea was added, and after 10 min. refluxing, 0.5 g. of picric acid. The precipitated tetramethylene bis(2-thiopseudourea)dipicrate was filtered, washed with ethanol, and dried, m.p. 240° dec. (lit.[18] 240–242° dec.). A specimen prepared in the same way from authentic tetrahydrofuran also had m.p. 240° dec., and the mixed melting point of the two was the same.

*Trimethylene sulfite* gave a product which showed five peaks on the gas chromatograph, at $q$ = 0.17 (26), 0.32 (100), 0.42 (48), 0.86 (48), 2.22 (7). The second peak was an unresolved mixture of acrolein ($q$ = 0.29) and propionaldehyde ($q$ = 0.32). In check experiments, these were not resolved on a squalane column at 100° or 64°. Three aldehydes were detected by paper chromatography, acrolein ($R_f$ = 0.21), propionaldehyde ($R_f$ = 0.26) and a third ($R_f$ = 0.35) which is thought to be an aldol condensation product. Infrared spectroscopy of the mixture confirmed the presence of acrolein and propionaldehyde by the C=C and C=O stretching bands in the 6$\mu$ region. There were no indications at any time of the presence of acetone.

*Ethylene sulfite* gave a product which showed seven peaks on the gas chromatograph at $q$ = 0.14 (100), 0.54 (6), 0.60 (6), 0.90 (35), 1.14 (12), 1.64 (94), and 3.18 (6). Two of these were identified as acetaldehyde ($q$ = 0.16) and paraldehyde ($q$ = 0.56). Paper chromatography of the dinitrophenylhydrazone from the product showed only one spot due to acetaldehyde ($R_f$ = 0.12), and the 6$\mu$ region of the infrared spectrum confirmed this.

*Acknowledgments.* The author is indebted to Mr. G. J. Long for experimental assistance and to the Chief Scientist, Australian Defence Scientific Service, Department of Supply, Melbourne, Australia, for permission to publish.

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(17) H. Stone and H. Schechter, *Org. Syntheses*, **30**, 33 (1950).

(18) A. W. Nineham, *J. Chem. Soc.*, 2601 (1953).

## Synthesis of Certain Sulfonium Analogs of Meperidine and of the Methadone Class of Analgesics

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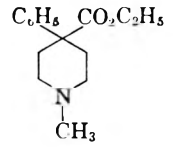
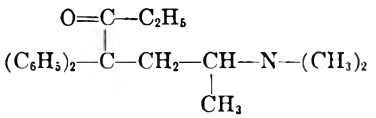
*Received October 12, 1959*

In continuation of our investigations[1] dealing with the preparation of sulfonium analogs of pharmacologically active tertiary and quaternary amines, we wish to report the synthesis of sulfonium analogs of meperidine[3] and also of the methadone class. Both meperidine and methadone are important analgesic agents.



Meperidine



Methadone

The meperidine sulfonium analog VI was prepared from the known 4-cyano-4-phenyltetrahydrothiapyran (III).[7] This nitrile (III) was converted to the 4-carbethoxy intermediate (V) by direct ethanolysis in the presence of sulfuric acid or, more satisfactorily, in two steps by hydrolysis with 70% aqueous sulfuric acid to the corresponding acid[7] (IV) followed by esterification with ethanolic hydrogen chloride. Treatment of V with excess methyl iodide then gave the desired analog (VI); reaction of V with excess ethyl iodide afforded the corresponding ethiodide.

The intermediate nitrile (III) was obtained directly by the sodium amide-catalyzed condensation of phenylacetonitrile (I) with bis(2-chloroethyl) sulfide, a synthesis originally described by Eisleb[7] and which in our hands afforded a 40% yield of III. This nitrile (III) was also prepared from 1,5-dichloro-3-cyano-3-phenylpentane (II)[8] on treatment with sodium sulfide. Although the latter procedure avoids the use of the dangerous mustard gas, the preparation of the 1,5-dichloride (II) requires three steps, and in our experience proceeded in relatively poor over-all yield (11%).[9] It was also possible to prepare the more advanced intermediate, 4-carbethoxy-4-phenyltetrahydrothiapyran (V), by direct condensation of bis(2-chloro-

(1) M. J. Weiss and M. B. O'Donoghue, *J. Am. Chem. Soc.*, **79**, 4771 (1957). This paper contains a review of sulfonium analog work in the pharmaceutical field. The preparation of sulfonium derivatives in the phenazine series has been reported recently.[2]

(2) S. O. Winthrop and M. A. Davis, *J. Am. Chem. Soc.*, **80**, 4331 (1958).

(3) There are two reports in the literature concerning unsuccessful attempts to prepare sulfonium analogs of the 1-methyl-4-acyloxy-4-phenylpiperidine class.[4,5] These piperidines are closely related to meperidine and are active analgesics.[6]

(4) H. M. E. Cardwell, *J. Chem. Soc.*, 1059 (1950).

(5) V. Mychajlyszn and J. O. Jilek, *Chem. Listy*, **50**, 1479 (1956); *Chem. Abstr.*, **51**, 2666 (1957).

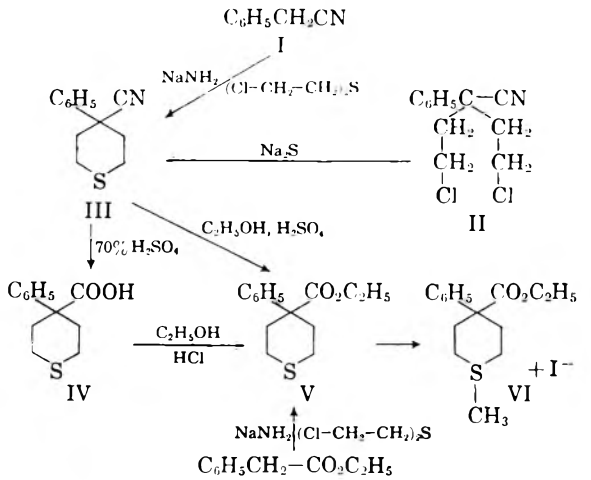
(6) A. Ziering, L. Berger, S. D. Heineman and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

(7) O. Eisleb, *Ber.*, **74B**, 1433 (1941).

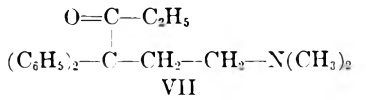
(8) F. Bergel, A. L. Morrison, and H. Rinderknecht, *J. Chem. Soc.*, 265 (1944).

(9) Dichloride II was obtained by condensation (sodium amide) of phenylacetonitrile (I) with 2-vinyloxyethyl chloride, acid hydrolysis of the vinyloxy groups and treatment of the resulting 1,5-diol with thionyl chloride.[8]

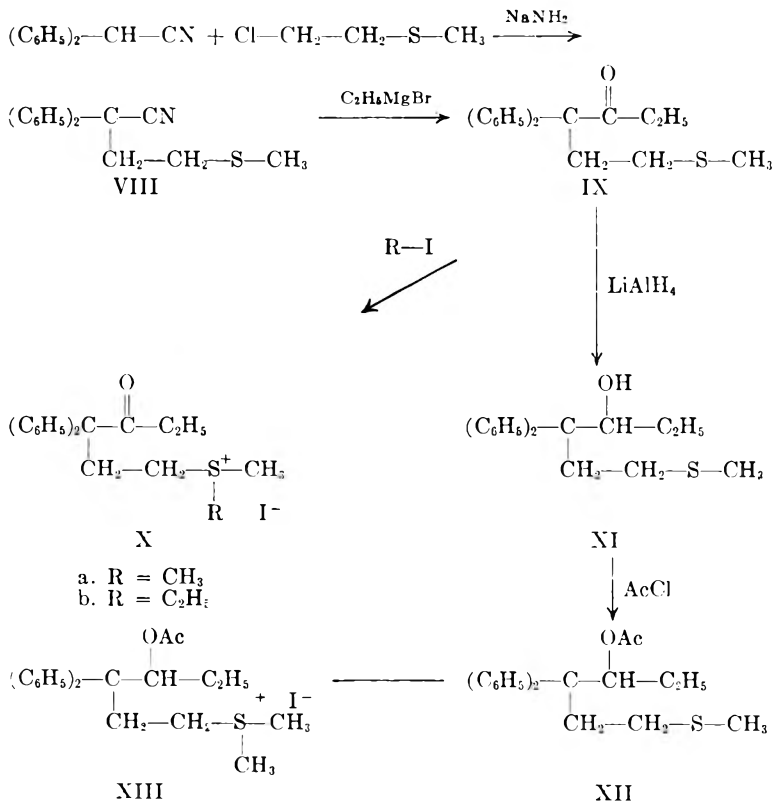
ethyl) sulfide with ethyl phenylacetate in the presence of sodium amide. However, the yield for this reaction was very poor (12% crude).




A sulfonium analog of methadone itself was not prepared because of the potential synthetic difficulties involved in the development of the isopropyl side chain.[10] Instead, analogs of the closely related VII were prepared. This compound has a β-dimethylaminoethyl side-chain instead of the β-dimethylaminoisopropyl side-chain found in methadone, and it is reported to be an effective analgesic agent in experimental animals and man although it is not as active as methadone.[11] Since the completion of our work, the synthesis of one sulfonium analog of VII has been reported.[5] We have also prepared this compound (Xa) although by a somewhat different route, and have in addition prepared several other methadone-type sulfonium analogs.




Condensation of diphenylacetonitrile with (2-chloroethyl)methyl sulfide in the presence of sodium amide afforded the alkylated diphenylacetonitrile-(VIII) in 42% yield. This compound was prepared by the Czechoslovak workers[5] from 3,3-diphenyl-3-cyanopropyl bromide and sodium methyl mercaptide. Conversion of VIII to the dimethyl sulfonium analog (Xa) was carried out in the same manner as reported by these workers;[5] that is, by methyl iodide treatment of the sulfide (IX), prepared by reaction of ethyl magnesium bromide with nitrile (VIII). Reaction of IX with ethyl iodide afforded the ethyl sulfonium analog (Xb).




Although reduction of the carbonyl group in methadone to give methadol generally causes a decrease in analgesic activity, acetylation of meth-

(10) A. Berger, *Medicinal Chemistry*, Interscience Publishers, Inc., New York, N. Y., 1951, p. 182.

(11) C. C. Scott, E. B. Robbins, and K. K. Chen, *Science*, **104**, 587 (1946); E. C. Kleiderer, J. B. Rice, V. Conquest, and J. H. Williams, Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D. C.

adol results in a restoration of this activity.[12] Therefore, it was of interest to prepare a sulfonium analog of the acetyl methadol type structure. Lithium aluminum hydride reduction of ketone IX gave the corresponding carbinol (XI) in 65% yield. Treatment of this carbinol with acetyl chloride produced a 59% yield of the acetate (XII), which on reaction with methyl iodide afforded the desired sulfonium analog (XIII).

None of the sulfonium analogs reported in this paper showed significant analgesic activity.

## EXPERIMENTAL[13]

*1,5-Dichloro-3-cyano-3-phenylpentane* (II). This compound was prepared by the three-step synthesis described by Bergel and coworkers[8] in an over-all yield of 11.4%, m.p. 51–52°.

*4-Cyano-4-phenyltetrahydrothiapyran* (III). To a solution of 25.3 g. (0.105 mole) of 1,5-dichloro-3-cyano-3-phenylpentane (II) in 125 ml. of ethanol was added a solution of 25.2 g. (0.105 mole) of sodium sulfide nonahydrate in 75 ml. of water. A clear solution did not form. The mixture was refluxed on a steam bath for 27 hr., then cooled and poured into ice water. The milky solution was extracted several times with ether. The combined ether extracts were dried, filtered, and evaporated. The residue consisted of two oily layers. The lower layer was distilled; the main fraction, 7.8 g. (37%), boiled at 137–142° at 1 mm., $n_D^{26}$ 1.5729. Eisleb[7] reports a boiling point of 175° at 6 mm.

*4-Carbethoxy-4-phenyltetrahydrothiapyran* (V). (A) *By ethanolysis of nitrile* III. A mixture of 20.3 g. (0.1 mole) of 4-cyano-4-phenyltetrahydrothiapyran (III), 30 g. of 98% sulfuric acid, 0.26 g. of water, 46 g. of ethanol, and 5.36 g. of ammonium chloride was heated in a glass-lined autoclave at 160° for 7 hr. The contents of the autoclave were treated with ice water and the mixture was extracted with ether. The ether extracts were dried, filtered, and evaporated to give 5.5 g. (22%) of the ester as an oil.

(B) *By esterification of acid* IV. A mixture of 5.5 g. (0.025 mole) of 4-carboxy-4-phenyltetrahydrothiapyran (IV)[7] and 35 ml. of ethanol, which had been saturated with hydrogen chloride, was placed in a pressure bottle, and warmed on a steam bath for about 14 hr. After cooling, the solvent was removed and the residue was dissolved in ether. The ether solution was washed with a dilute sodium carbonate solution, dried, and evaporated. This gave the ester V as a light brown oil, which was used as such for the preparation of the sulfonium salts VI.

(C) *From ethyl phenylacetate and bis(2-chloroethyl)sulfide.* To a solution of sodium amide,[14] prepared from 16.6 g. (0.72 mole) of sodium and 500 ml. of liquid ammonia, was added 59 g. (0.36 mole) of ethyl phenylacetate in 100 ml. of dry ether. The mixture was stirred and warmed gently to remove the ammonia which was replaced with 300 ml. of ether. A solution of 30 ml. (0.284 mole) of bis(2-chloroethyl)sulfide was then added dropwise during 5 min. The mixture was refluxed on a steam bath for 1 hr., 200 ml. of toluene was added and refluxing was continued for 90 min. (reflux temperature was 95–100°).

After cooling to 10°, water was added cautiously to decompose any unreacted sodium amide, and when the reaction was no longer exothermic, a large amount of ice water was added. The toluene layer was dried over calcium sulfate (Drierite), filtered and distilled. A 10-g. forerun boiling at 82–83° at 1 mm. was followed by the product (8.4 g., 29%) boiling at 160–162° at 1 mm. A small amount of solid which codistilled with the product proved to be phenylacetamide, m.p. 155.5–156.5°, admixture of which with an authentic sample showed no depression in melting point.

*4-Carbethoxy-1-methyl-4-phenylhexahydrothiapyrylium iodide* (VI). A solution of 4-carbethoxy-4-phenyltetrahydrothiapyran (V), obtained *via* procedure B from 5.5 g. of IV, in 45 ml. of methyl iodide, was allowed to stand at room temperature for 24 hr. The sulfonium salt separated as a crystalline solid (3.5 g., 36%), m.p. 139–140° dec.

In a pilot run, the product was recrystallized from ethanol to give white crystals melting at 135–136° dec.

*Anal.* Calcd. for $C_{15}H_{21}IO_2S$: C, 45.9; H, 5.40; I, 32.4; S, 8.17. Found: C, 45.9; H, 5.65; I, 32.4; S, 8.00.

*4-Carbethoxy-1-ethyl-4-phenylhexahydrothiapyrylium iodide.* This compound was prepared in a manner similar to that described above for the methiodide salt except that the ester was dissolved in acetone and then treated with a large excess of ethyl iodide. The ethiodide salt was obtained after drowning the reaction solution in ether. The product melted at 117.5–118°.

*Anal.* Calcd. for $C_{16}H_{23}IO_2S$: C, 47.3; H, 5.70; I, 31.2; S, 7.89. Found: C, 47.1; H, 5.68; I, 30.5; S, 8.23.

*2,2-Diphenyl-4-methylthiobutyronitrile* (VIII). A solution of 386.5 g. (2 moles) of diphenylacetonitrile in 1530 ml. of dry benzene was added dropwise with stirring, over a period of 1 hr., to a mixture of 100 g. (2.5 moles) of sodium amide[14] in 1000 ml. of dry benzene. The reaction was not exothermic. The mixture was stirred at 40° for 1 hr., then 221 g. (2 moles) of 2-chloroethyl methyl sulfide[15] was added dropwise at 32–34° during 2.5 hr. The mixture was then stirred at 50–70° for 15 hr. The liquid was decanted from the precipitated solids into a separatory funnel and water was added. The benzene layer was separated and washed three times with small portions of water. The solvent was removed and the residual oil was distilled. After an initial fraction (b.p. 124–170° at 2 mm.) which consisted largely of diphenylacetonitrile (187 g., 49% recovery) and a small intermediate fraction, the product VIII was obtained boiling at 182–185° at 2 mm. (227 g., 42%; $n_D^{26}$ 1.5880).

*Anal.* Calcd. for $C_{17}H_{17}NS$: C, 76.4; H, 6.41; N, 5.24; S, 12.0. Found: C, 76.3; H, 6.38; N, 5.33; S, 11.2.

Mychajlyszn and Jilek[5] prepared this compound in 71% yield, b.p. 160–165° at 1 mm., by the reaction of sodium methylmercaptide with 2,2-diphenyl-4-bromobutyronitrile.

*4,4-Diphenyl-6-methylthiohexanone-3* (IX). Ethyl magnesium bromide was prepared from 36 g. (0.33 mole) of ethyl bromide, 8 g. (0.33 mole) of magnesium and 160 ml. of ether. A solution of 53.5 g. (0.2 mole) of 2,2-diphenyl-4-methylthiobutyronitrile (VIII) in 120 ml. of toluene was added. The solvent was distilled until the internal temperature rose to 102°. The mixture was stirred, warmed at 102–110° for 4.5 hr., and then allowed to stand at room temperature overnight. Ice was cautiously added to decompose the Grignard complex. The reaction was exothermic and the temperature rose to 50–60°. When the heat evolution had subsided, 100 ml. of dilute hydrochloric acid was added and the mixture was warmed on the steam bath for 2 hr. The two layers were separated, and the aqueous layer was extracted three times with small portions of benzene. The benzene extracts were combined with the toluene layer and distilled at reduced pressure. After a small forerun (8.8 g.), the product (IX) boiled at 165–178° at 1 mm., and weighed 39.9 g. (67%), $n_D^{30}$ 1.5823. Mychajlyszn and Jilek[5] report a b.p. of 170–173° at 0.5 mm.

A sample of material boiling at 176–177° at 1 mm., $n_D^{29}$ 1.5828, was analyzed.

*Anal.* Calcd. for $C_{19}H_{22}OS$: C, 76.5; H, 7.43; S, 10.7. Found: C, 76.5; H, 7.43; S, 10.8.

(12) Ref. 10, p. 184.

(13) Melting points are uncorrected.

(14) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 122 (1954).

(15) *Org. Syntheses*, Coll. Vol. II, p. 136, John Wiley and Sons, New York, N. Y., 1943.

*Dimethyl-(3,3-diphenyl-4-oxohexyl)sulfonium iodide* (Xa). A solution of 5.8 g. of 4,4-diphenyl-6-methylthiohexanone-3 (IX) in 20 ml. of methyl iodide was allowed to stand for 4 days. The product (Xa) separated as a white crystalline material, which after 2 recrystallizations from 95% ethanol, weighed 5.3 g., m.p. 125.5° (gas evolution). Mychajlyszn and Jilek[5] report a m.p. of 122°.

*(3,3-Diphenyl-4-oxohexyl)-ethylmethylsulfonium iodide* (Xb). A solution of 25.3 g. (0.085 mole) of 4,4-diphenyl-6-methylthiohexanone-3 (IX) in 75 ml. acetone was treated with 46.8 g. (0.3 mole) of ethyl iodide. The solution was allowed to stand at room temperature for several days. The sulfonium salt separated out during this time as a crystalline solid. The mixture was filtered and the light yellow solid weighed 5.4 g., m.p. 114–115.5°. After recrystallization from 15 ml. of 95% ethanol there was obtained 4.3 g. of a white solid, m.p. 118.5–119°.

*Anal.* Calcd. for $C_{21}H_{27}IOS$: C, 55.5; H, 5.99; I, 27.9; S, 7.06. Found: C, 55.4; H, 5.61; I, 27.8; S, 7.47.

*4,4-Diphenyl-6-methylthiohexanol-3* (XI). A mixture of 4.6 g. (0.12 mole) of lithium aluminum hydride in 200 ml. of ether was refluxed on a steam bath in an atmosphere of nitrogen for 4.5 hr. A solution of 119.3 g. (0.4 mole) of 4,4-diphenyl-6-methylthiohexanone-3 (IX) in 200 ml. of ether then was added dropwise over a period of 40 min. The mixture was refluxed for 2.5 hr. Wet ethyl acetate (40 ml.) was added cautiously to decompose the complex and any unreacted lithium aluminum hydride. After the decomposition was complete, 300 ml. of ice water was added. This gave a milky solution, which separated into 2 layers after standing overnight. The aqueous layer was acidified with dilute sulfuric acid, and then extracted several times with ether. The ether extracts were combined, dried over sodium sulfate, filtered, and evaporated. The residue, a thick viscous oil, was distilled at reduced pressure. The product boiled at 182–184° at 1–2 mm. and weighed 77.4 g. (64.5%). This oil solidified to a white solid, m.p. 66–69°. Recrystallization from a mixture of hexane and petroleum ether gave 75.2 g. of the product XI, m.p. 70–71.5°.

*Anal.* Calcd. for $C_{19}H_{24}OS$: C, 75.9; H, 8.05; S, 10.7. Found: C, 76.1; H, 8.22; S, 10.6.

*4,4-Diphenyl-6-methylthio-3-hexyl acetate* (XII). A mixture of 90 g. (0.3 mole) of 4,4-diphenyl-6-methylthiohexanol-3 (XI) in 400 ml. of dry pyridine was stirred and cooled in an ice bath while 27 g. (0.35 mole) of acetyl chloride was added over a period of 30 min. at 10–12°. The ice bath was removed and the temperature raised slowly until a clear solution formed (about 2 hr.). The solution was stirred at room temperature for 3 hr., and then poured onto ice water which had been made slightly acid with dilute hydrochloric acid. The mixture was extracted three times with portions of ether, and the ether extracts were combined, dried, filtered, and evaporated. The residue, a thick viscous amber oil, was distilled at reduced pressure. The product (XII) boiled at 180–188° at 1 mm. and weighed 60.5 g. (59%).

*(4-Acetoxy-3,3-diphenylhexyl)-dimethylsulfonium iodide* (XIII). This compound was prepared from XII and methyl iodide by the procedure described above for the preparation of Xa. It was obtained in 38% yield after crystallization from 95% ethanol, m.p. 121.5–122.5°.

*Anal.* Calcd. for $C_{22}H_{29}IO_2S$: C, 54.5; H, 6.03; I, 26.2; S, 6.62. Found: C, 54.2; H, 6.44; I, 26.2; S, 6.21

*Acknowledgment.* We wish to thank Mr. O. Sundberg and staff for microanalyses. We are indebted to Dr. A. Osterberg and staff of the Experimental Therapeutics Section of these laboratories for the pharmacological evaluation of these compounds.

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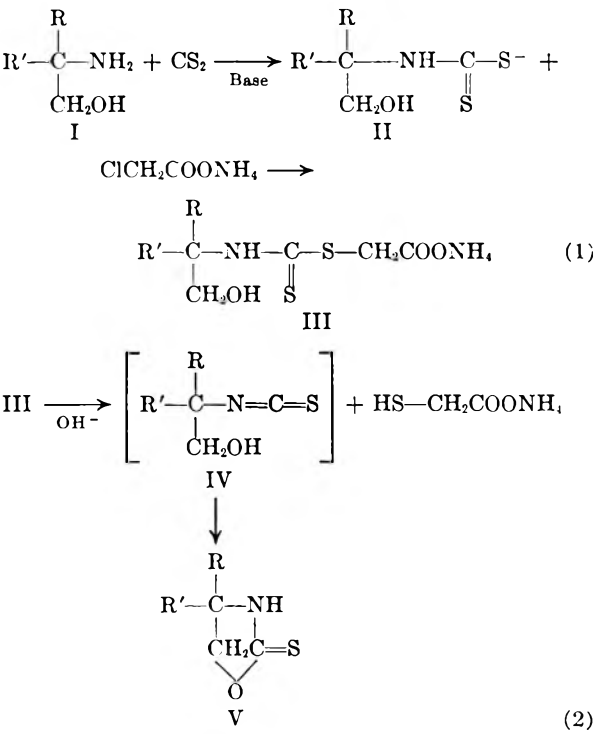
## Preparation of 2-Thioöxazolidones from Substituted Dithiocarbamylacetic Acids

WILLARD T. SOMERVILLE AND CARL N. ANDERSEN

*Received September 17, 1959*

2-Thioöxazolidones[1] substituted in the 4- and 5- positions have been prepared from aminoalcohols by reaction with carbon disulfide and potassium hydroxide[2,3] and by the decomposition of thiuram disulfides derived from 2-aminoalcohols.[3]

We have now found that *N*-substituted dithiocarbamylacetic acid derivatives produced from 2-aminoalcohols, carbon disulfide, and monochloracetic acid (Equation 1) may be decomposed by alkali to form a substituted 2-thioöxazolidone and thioglycolic acid (Equation 2).



(1)



(2)

The expected product of the scission of the substituted dithiocarbamylacetic acid would be a hydroxyalkyl isothiocyanate (IV), but this apparently cyclizes to the corresponding 2-thioöxazolidone (V).[4]

In the above manner, 2-methyl-2-aminopropanol-1, I R=R′=$CH_3$, yields 4,4-dimethyl-2-

(1) We have confirmed the work of M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4792 (1950), who has shown by infrared spectra that these materials are thioketones and do not contain SH groups. Therefore, they are more properly termed 2-thioöxazolidones rather than oxazoline-2-thiols.

(2) H. A. Bruson and J. W. Eastes, *J. Am. Chem. Soc.*, **59**, 2011 (1937).

(3) A. A. Rosen, *J. Am. Chem. Soc.*, **74**, 2994 (1952).

(4) B. Holmberg, *J. Prakt. Chem.*, **79**, 263 (1909) observed that dithiocarbamylacetic acid in alkali solution produced thioglycolic acid and thiocyanic acid.

thioöxazolidone whereas the carbon disulfide and alkali process of Bruson[2] produces a mixture of the 2-thioöxazolidone and thiazoline compounds. Similarly 2-aminobutanol-1, (I).R = H, R′ = $C_2H_5$, produces a thioöxazolidone derivative instead of a substituted thiazoline. The reaction products are thus similar to those obtained by the thiuram procedure.[3]

## EXPERIMENTAL[5]

*Preparation of substituted 2-thioöxazolidone from 2-amino alcohols.* A mixture of 1 mole (89.1 g.) 2-aminobutanol-1, or 2-methyl-2-aminopropanol-1, and 90 g. of ammonium hydroxide was cooled in an ice bath at 10° and 76 g. of carbon disulfide were added over a 15-min. period, and then stirred for 1 hr. or until it became a clear uniform solution. A solution prepared by dissolving 94.5 g. (1 mole) of monochloracetic acid in 70 ml. of water and neutralizing with 70 ml of ammonium hydroxide solution was added to the above dithiocarbamate solution. This reaction was somewhat exothermic and the temperature rose to 20 to 25°. Stirring was continued for an hour after addition was complete and the mixture was then allowed to stand overnight. The white crystals of the substituted 2-thioöxazolidone which formed, were filtered by suction on a Büchner funnel and washed with a small amount of cold water. The yield was 45 to 55 g. of air dried crystals (35–42% of theory).

*4-Ethyl-2-thioöxazolidone*, (V), R = H; R′ = $C_2H_5$. The white crystals prepared above from 2-aminobutanol-1 melted at 72.8 to 73.2° after recrystallization from alcohol (lit.,[6] m.p. 74–75°). These crystals were soluble in alcohol, ethyl acetate, benzene, and acetone.

*Anal.* Calcd. for $C_5H_9NOS$: C, 45.77; H, 6.91; N, 10.68; S, 24.44. Found: C, 46.06; H, 6.88; N, 10.35; S, 24.56.

*4,4-Dimethyl-2-thioöxazolidone*, (V), R = R′ = $CH_3$. When recrystallized from alcohol, the melting point was 124.6 to 125.8° (lit.,[6] m.p. 123–125°). The compound was soluble in alcohol, benzene, and ethyl acetate.

*Anal.* Calcd. for $C_5H_9NOS$: C, 45.77; H, 6.91; N, 10.68; S, 24.44. Found: C, 45.96; H, 6.78; N, 9.90; S, 25.04.

RESEARCH DEPARTMENT
VAN AMERINGEN-HAEBLER (A DIVISION OF
INTERNATIONAL FLAVORS & FRAGRANCES INC.)
UNION BEACH, N. J.

(5) Microanalysis by the Clark Microanalytical Laboratory, Urbana, Ill.

(6) C. Y. Hopkins, *Can. J. Research*, B20, 268 (1942).

## Studies on Hydroxybenzotriazoles

H. SINGH AND R. S. KAPIL[1]

*Received October 8, 1959*

Several compounds containing the grouping >NOH have been reported[2] to be useful as organic precipitating agents. 1-Hydroxy-1,2,3-benzotriazoles also contain a similar grouping. In view of the fact that they can be prepared readily by the action of sodium hydroxide[3,4j] or hydrazine hydrate on *o*-nitrophenylhydrazines[4] or even from *o*-dinitrobenzenes,[4a,j] it was considered worthwhile to synthesize some additional derivatives and study their analytical behavior.

1-Hydroxy-1,2,3-benzotriazoles have been prepared by the action of hydrazine hydrate on *o*-nitrophenylhydrazines and also on *o*-dinitrobenzenes. They are suitable for the estimation of silver ion with which they give a quantitative precipitate.

Details of their analytical behavior shall be published elsewhere.

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(2) (a) F. Ephriam, *Ber.*, **63**, 1928 (1930). (b) G. Denigs, *Bull. soc. pharm. Bordeaux*, **70**, 101 (1932). (c) D. C. Sen, *J. Indian Chem. Soc.*, **15**, 473 (1938). (d) J. F. Flagg and N. H. Furman, *Ind. Eng. Chem., Anal. Ed.*, **12**, 529 (1940). (e) K. J. Keuning and J. V. Dubsky, *Rec. trav. chim.*, **59**, 978 (1940). (f) P. Wenger, R. Duckert, and M. Busset, *Helv. Chim. Acta*, **24**, 889 (1941).

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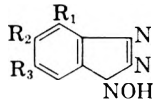
TABLE I

1-HYDROXY-1,2,3-BENZOTRIAZOLES




| No. | $R_1$ | $R_2$ | $R_3$ | Formula | Color | M.P. °C | Analysis Calcd. | Analysis Found |
|---|---|---|---|---|---|---|---|---|
| 1 | H | Cl | H | $C_6H_4N_3OCl$ | Colorless plates | 210d[a,b] | Cl: 20.93 | 20.8 |
| 2 | H | Br | H | $C_6H_4N_3OBr$ | Colorless plates | 220d[a] | Br: 37.39 | 37.2 |
| 3 | H | I | H | $C_6H_4N_3OI$ | Colorless plates | 200d[a] | I: 48.66 | 48.4 |
| 4 | H | Cl | $CH_3$ | $C_7H_6N_3OCl$ | Colorless needles | 203d[a] | Cl: 19.34 | 19.2 |
| 5 | H | I | $CH_3$ | $C_7H_6N_3OI$ | Colorless needles | 182[a] | I: 46.18 | 46.0 |
| 6 | H | Cl | Cl | $C_6H_3N_3OCl_2$ | Colorless needles | 215[a,c] | Cl: 34.81 | 34.5 |
| 7 | Br | H | Br | $C_6H_3N_3OBr_2$ | Colorless needles | 218d[a] | Br: 54.61 | 54.4 |

[a] Recrystallized from ethanol. [b] Lit.,[4h] m.p. 204–205°. [c] Lit.,[4g] m.p. 194–196°.

EXPERIMENTAL[5]

*5-Bromo-1-hydroxy-1,2,3-benzotriazole.* To a solution of 2-nitro-5-bromophenylhydrazine (0.5 g.) in ethanol (20 ml.) was added hydrazine hydrate (2 ml. 50%). It was heated on a water bath for 0.5 hr., concentrated to a small volume, diluted with water and filtered. The filtrate on acidification with dilute hydrochloric acid gave 5-bromo-1-hydroxy-1,2,3-benzotriazole (0.3 g.) as colorless plates from ethanol, m.p. 220° dec. By adopting a similar procedure other hydroxybenzotriazoles were prepared. The data concerning the new compounds are listed in Table I. All of them explode above their melting points.

*Acknowledgment* The authors wish to express their gratitude to Dr. S. S. Joshi, D.Sc., for his kind interest in this work.

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(5) All melting points are uncorrected.

## Identification of Caffeic Acid in Cigarette Smoke

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*Received July 13, 1959*

No previous report has been made of the presence of caffeic acid (3,4-dihydroxycinnamic acid) in cigarette smoke. Several groups of workers[1-3] however, have reported finding free caffeic acid in various cured tobaccos, but Roberts and Wood,[4] using fresh cigar tobacco, and Weaving,[5] using flue-cured tobaccos, could find none in their samples. Dieterman *et al.*[6] have recently pointed out that esculetin (6,7-dihydroxycoumarin) in tobacco may often be confused on paper chromatograms with caffeic acid. In the present study on tobacco in eight brands of cigarettes commonly smoked in the U. S., every sample tested was found to contain free caffeic acid. Also, in every case, the main stream smoke from the cigarette contained free caffeic acid.

In the purification of scopoletin (6-methoxy, 7-hydroxycoumarin) from cigarette smoke and from various tobacco extracts,[7,8] two or more interfering blue fluorescing compounds persisted with the scopoletin through several developments of paper chromatograms. Dieterman *et al.*[6] identified one of these interfering compounds as esculetin. The present identification establishes free caffeic acid as the other blue fluorescing compound.

During paper chromatography in certain acid solvent systems, such as 15% acetic acid–water, caffeic acid appears as two distinct zones. These have been shown to be *cis*- and *trans*- caffeic acid.

EXPERIMENTAL

*Caffeic acid from cigarette tobacco.* The tobacco obtained from one hundred and twenty cigarettes (three each from forty packs of the same brand) was mixed and ground to a powder. Six 5.5-g. samples of this powder were thoroughly extracted with 85% isopropyl alcohol, as previously described by Yang *et al.*[7] The combined extracts were concentrated under reduced pressure, and the concentrate was then subjected to separation by mass paper chromatography.[7] After the initial chromatography with Whatman 3MM paper, using the solvent system *n*-butyl alcohol–acetic acid–water (6:1:2 v./v.), each zone containing caffeic acid, still mixed with some esculetin and scopoletin, was cut off and then eluted with methanol. The eluates were combined and streaked on S & S No. 589, Red Ribbon, chromatography paper, and developed in the system chloroform–acetic acid–water (2:1:1 v./v., bottom layer). This solvent system proved to be superior to the nitromethane-benzene-water system (2:3:5 v./v., upper layer) used in our previous studies on scopoletin and esculetin. In the chloroform system, the scopoletin ($R_f$ = 0.75) moves in a narrow zone quite removed from those of esculetin ($R_f$ = 0.39) and of caffeic acid ($R_f$ = 0.35). This was also the case with the benzene–propionic acid–water system (2:2:1 v./v., top layer) with $R_f$ values: scopoletin (0.66); caffeic acid (0.32); and esculetin (0.26). The two top zones resulting from paper chromatography with the chloroform system contained primarily caffeic acid and esculetin. They were cut off from each chromatogram together; sewn onto a new sheet of paper; and then developed in ethyl acetate–formic acid–water (10:2:3 v./v.). Each zone containing caffeic acid, with a trace of esculetin still present, was cut off and eluted with the ethyl acetate solvent system. The eluates were combined and again streaked on S & S No. 589 paper and developed in 15% acetic acid–water. Although separation of caffeic acid from esculetin was completed by this chromatography with acetic acid, an isomer of caffeic acid now appeared as a separate, third zone.

The two zones of isomeric caffeic acid were cut from each chromatogram as a unit and sewn onto a new sheet of chromatography paper. Each such sheet was then developed in the ethyl acetate system to obtain one narrow blue zone for identification studies.

*Identification of caffeic acid.* The combined eluates containing the purified caffeic acid from each single zone obtained in the ethyl acetate system were then co-chromatographed with authentic caffeic acid purchased from California Foundation for Biochemical Research, using the *n*-butyl alcohol–acetic acid–water, chloroform–acetic acid–water, ethyl acetate–formic acid–water, benzene–propionic acid–water, and nitromethane-benzene-water systems already described, and *n*-butyl alcohol–benzene–pyridine–water (5:1:3:3 v./v., upper layer), isopropyl alcohol–pyridine–acetic acid–water (8:8:1:2 v./v.), and 15% acetic

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(8) C. H. Yang, Y. Nakagawa, and S. H. Wender, *Anal. Chem.*, **30**, 2041 (1958).

acid–water. Both the reference and isolated caffeic acid solutions gave the same $R_f$ values in every test. In the 15% acetic acid system, both the reference and unknown caffeic acid samples gave two zones each, with corresponding $R_f$ values.

The isolated and reference caffeic acids behaved similarly towards the chromogenic agents previously reported.[6] In addition, both gave the same color reaction with the Höfner reagent[4] (pink, changing to yellowish-brown) and with 2% alcoholic ferric chloride solution (green changing to gray).

The absorption spectra exhibited by the isolated caffeic acid in ethanol, and in buffer solutions at *p*H 3.5 and 6.8, checked in each case with the corresponding spectrum exhibited by the reference caffeic acid in ethanol and in buffer solutions at *p*H 3.5 and 6.8 in our laboratory and with those reported for these preparations by Sutherland.[9]

*Caffeic acid in the mainstream smoke of cigarettes.* The smoking of eight brands of cigarettes for caffeic acid analysis was performed by a procedure similar to the one already described for scopoletin in smoke by Yang *et al.*[8] Because caffeic acid, however, was present only in a trace amount in the smoke, samples representing smoke from forty packs of cigarettes were combined and concentrated to obtain sufficient caffeic acid for unambiguous studies by paper chromatography. The separation, purification, and identification of caffeic acid from the cigarette smoke condensates were carried out by mass paper chromatography in the same manner as already described above for determination of caffeic acid in tobacco. Cigarettes analyzed included Camel, Lucky Strike, Philip Morris, Old Gold Straights, Pall Mall, Winston, Viceroy, and Oasis.

*Isomerization of caffeic acid.* On paper chromatography with 15% acetic acid–water, the reference caffeic acid gave two distinct zones. The farther moving zone ($R_f$ = 0.50) was called "CA-1," and the slower moving zone ($R_f$ = 0.42) was called "CA-2." Each blue fluorescing zone was cut out separately; sewn onto separate new sheets of paper; and again developed in the 15% acetic acid. It was observed that from the slower moving zone (CA-2), the faster moving zone (CA-1) was produced every time that a separated CA-2 zone was rechromatographed in this acid system. If this procedure, involving separation by paper chromatography, cutting, sewing, and rechromatography of the CA-2 was repeated even five or more times, the slower moving zone of caffeic acid, would in every case, continue to change to give both isomers. The fluorescence of this slower moving zone would be weaker on each subsequent chromatogram. The CA-1 zone likewise gave both isomers on rechromatography of the faster moving zones, but produced only a relatively small amount of the CA-2 each time that the CA-1 was developed in the 15% acetic acid–water.

Both CA-1 and CA-2 co-chromatographed with the reference caffeic acid to give only one spot in all the solvent systems mentioned in this paper, except in the 15% acetic acid–water. In this latter system, the major spot from the reference caffeic acid on the first chromatograms was identical with CA-2, and the minor spot was the same as CA-1. Both CA-1 and CA-2 gave the same color reactions when tested with all the chromogenic agents described in this report.

Williams[10] has reported that cinnamic acid derivatives give two spots on paper chromatography with 2% acetic acid–water. He suggested that this was a case of *cis-trans* isomerization on paper. He did not, however, point out which spot corresponded to which isomer. Recently, Butler and Siegelman[11] have reported that the faster moving zone of caffeic acid during paper chromatography with 5% acetic acid–water is *cis-*, and the slower moving zone is *trans-*caffeic acid, on the basis that ultraviolet light converted a part of the slower moving zone into the faster moving one. Our slower moving zone behaved similarly, and based on their conclusions, it would appear that our CA-1 is *cis-* and our CA-2 is *trans-*caffeic acid. For further confirmation of these *cis* and *trans* configuration assignments to CA-1 and CA-2, we undertook ultraviolet and infrared spectral studies as described in following paragraphs.

*Ultraviolet absorption spectra of the caffeic acids.* Although the isomeric caffeic acids CA-1 and CA-2 could be readily obtained as completely separated zones on paper chromatograms, much difficulty was experienced in getting solutions of either isomer completely free of the other. During the preparation of such solutions by extraction or elution of the individual zones from the paper, and application of heat, isomerization was usually found to occur, and an equilibrium mixture was set up according to the temperature, solvent, etc. used. During such handling, except for the paper chromatography step itself, the CA-1 (*cis*) shifted more readily into the CA-2 (*trans*) than did CA-2 to CA-1. For the ultraviolet spectrophotometry, a solution consisting mainly of isomer CA-1 (but not entirely free of the other isomer) and another preparation consisting mainly of CA-2 were prepared as described in the next paragraph.

Each isomeric zone was cut from the chromatogram separately and eluted with 95% ethanol in an elution chamber. Each eluate was then evaporated to dryness, *in vacuo*, without application of heat. The residue, containing the caffeic acid isomer plus a filter paper impurity, was then dissolved by 1 ml. of hot distilled water, added drop by drop, while the container was kept rotating. A blank solution containing the filter paper impurity, but no caffeic acid, was prepared in exactly the same manner as just described, except that no caffeic acid was present on the sheet of chromatography paper. The aqueous solution of each isomer was then added to cold distilled water in separate cuvettes, drop by drop, with a capillary tube. To the cuvette used as a blank, approximately an equal amount of the blank solution containing the filter paper impurity, but no caffeic acid, was added. The absorption spectra of these CA-1 and CA-2 solutions were then measured with the Beckman spectrophotometer, Model DU. Results are shown in Fig. 1. The CA-1 preparation exhibited its high maximum

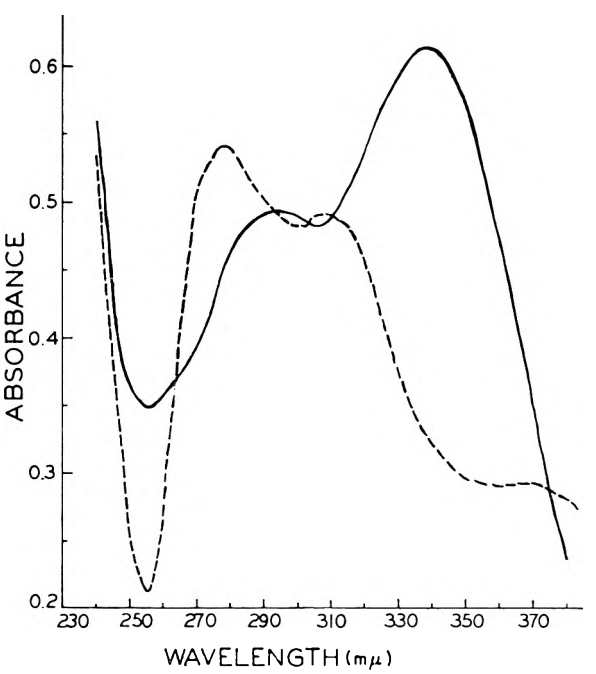


Fig. 1. Absorption spectra of aqueous solutions of caffeic acid prepared from zones CA-1 (- - - -) and CA-2 (———).

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(10) A. H. Williams, *Chem. & Ind. (London)*, 120 (1955).

(11) W. L. Butler and H. W. Siegelman, *Nature*, **183**, 1813 (1959).

at 278 mμ, whereas the CA-2 preparation had an even higher maximum at 340 mμ. Mixing of various amounts of CA-1 and CA-2 shifted the 340 mμ maximum of CA-2 to various corresponding lower wave lengths.

To interpret these results, one uses the working rule which states that when the absorption properties of the *cis-trans* isomers of a substance differ, "the more elongated isomer absorbs at somewhat longer wave lengths and more intensely."[12]

Haskins and Gorz[13] recently have found that such absorption data apply in their studies on *cis-* and *trans-o*-cinnamic acid. If this rule should also hold with caffeic acid, CA-1 would then appear to be the *cis* isomer and CA-2 the *trans* isomer of caffeic acid. These assignments of *cis* and *trans* to the caffeic acid isomers check with the designations in above paragraphs.

*Infrared absorption spectra of the caffeic acids.* To prepare samples of CA-1 and CA-2 for infrared studies, caffeic acid solution was streaked onto S & S No. 589 paper and developed in 15% acetic acid–water. The CA-1 and CA-2 zones were cut out and separately eluted with methyl alcohol. The eluate containing CA-1 was extracted with *n*-hexane, which is supposed to favor solution of the *cis* isomer.[14] The hexane was removed *in vacuo* at room temperature in the dark, and crystals of CA-1 were obtained. The methyl alcohol eluate CA-2 was concentrated *in vacuo* almost to dryness, in the dark at room temperature, and the residue was extracted several times with ethyl ether. Crystals of CA-2 were obtained after evaporation of the ether. Two milligrams of each of the crystalline CA-1 and CA-2 were mixed with 400 mg. of potassium bromide and made into pellets. These were studied with the Perkin-Elmer recording infrared spectrophotometer, Model 21.

At 814 cm.$^{-1}$, the absorption of the compound from CA-2 (*trans*) showed stronger intensity than did the absorption from compound CA-1 (*cis*). Bellamy[15] states that conjugation of the double bond with carbonyl groups has a very marked effect, and that the group —CH=CHCOOR (*cis*) absorbs near 820 cm.$^{-1}$ with sufficient regularity for this to be a useful assignment. He continues by stating that this absorption from the *cis* form is usually much weaker in intensity than that from the *trans* series. Also, at 1640 cm.$^{-1}$, CA-2 showed stronger absorption than did CA-1. Thus, the infrared data confirmed the previous indications that the CA-2 fraction was primarily the *trans* isomer, and the CA-1 fraction was mainly the *cis* isomer of caffeic acid.

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(15) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co. Ltd., London, 1954, p. 48.

## Halogenation of Glycoluril and Diureidopentane

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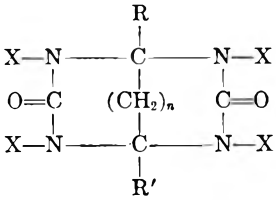
The literature reveals the preparation of 1,3,4,6-tetrachloro-3a,6a-diphenylglycoluril (I),[1,2] 1,3,4,6-tetrachloro-3a,6a-dimethylglycoluril (II),[2,3] and of 1,3,4,6-tetrachloro-3a-methyl-6a-phenylglycoluril (III)[2] but does not disclose 1,3,4,6-tetrachloroglycoluril (IV). This paper deals with the preparation of IV and some related compounds.



| | R | R′ | X | *n* |
|---|---|---|---|---|
| I | $C_6H_5$ | $C_6H_5$ | Cl | 0 |
| II | $CH_3$ | $CH_3$ | Cl | 0 |
| III | $CH_3$ | $C_6H_5$ | Cl | 0 |
| IV | H | H | Cl | 0 |
| V | H | H | Br | 0 |
| VI | H | H | I | 0 |
| VII | H | H | H | 0 |
| IX | $CH_3$ | $CH_3$ | H | 1 |
| X | $CH_3$ | $CH_3$ | Cl | 1 |

We found that chlorination of aqueous suspensions of glycoluril (VII),[4–6] under a variety of conditions, gave IV. Excellent yields were obtained when the chlorination mixture was kept neutral or slightly alkaline (*p*H 7–8) by the addition of various basic materials either as solids or as solutions. Although a wide variety of alkaline materials was successfully used, a 1 to 6*N* sodium hydroxide solution was the most convenient alkali to add.

Bromination of glycoluril to 1,3,4,6-tetrabromoglycoluril (V) required somewhat more alkaline conditions (*p*H 8–11). The use of analogous techniques failed to give tetraiodoglycoluril (VI).

A clear solution resulted on treatment of an aqueous suspension of VII with half the theoretical amount of chlorine required for the preparation of IV. Further chlorination of this solution caused the precipitation of IV. Concentration of the clear solution resulted in the isolation of a dichloroglycoluril (VIII). No attempt was made to separate or characterize the possible isomers.

No material corresponding to a mono- or a trichloroglycoluril was found. Chlorination of VII to a theoretical trichloroglycoluril stage gave a solid which was readily separated into IV and VIII by extraction with water. The water solubility, at

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(5) R. A. Pingree and M. A. Dahlen, Textile Finishing Treatments, P.B. Report 1576, Appendix III, Hobart Publishing Company, Washington, D. C.

(6) W. Baird, C. B. Brown, and G. R. Perdue, Textile Auxiliary Products of I. G. Farbenindustrie, P.B. Report 32565, Page 12, Hobart Publishing Company, Washington, D. C.

room temperature, of IV was found to be 0.01 g./100 ml. while that of VIII was 0.27 g./100 ml.

This is the first instance that we are aware of in which a dihaloglycoluril has been isolated. Because VII was converted almost entirely into VIII before any significant amount of IV was observed, we are led to believe that other glycolurils could be similarly chlorinated. However, because of different solubility characteristics, the partial chlorination of other glycolurils might not be as easy to follow visually as was our example.

Chlorination of the related diureidopentane (IX), prepared by the method of de Haan,[7] gave tetrachlorodiureidopentane (X) but, because of the great insolubility of the materials involved, the chlorination proceeded with greater difficulty.

The products described are relatively stable. Pure, dry samples of IV and VIII have been kept in stoppered clear-glass vials at room temperature for as long as two years with only a 5–10% loss of available chlorine. However, mixtures with wet, strongly alkaline materials (sodium metasilicate and sodium metasilicate pentahydrate) resulted in rapid decomposition of IV and VIII, which, on occasion, became violent.

### EXPERIMENTAL[8]

*Glycoluril* (VII). A stirred solution of 30% aqueous glyoxal (2250 g., 11.6 mole) and urea (1900 g., 31.7 mole) in 4 l. of water was heated to 85–95° and maintained at this temperature for 20–30 min. while concentrated hydrochloric acid (25–45 ml.) was added as needed to maintain the solution at *p*H 1.5–2.0. Cooling, filtering, and recrystallizing from water with the aid of decolorizing carbon gave 850–900 g. (52–55%) of white crystalline VII, decomposing at 300°.

*Tetrachloroglycoluril* (IV). A stirred suspension of VII (71 g., 0.5 mole) in 3200 ml. of water was treated with chlorine (150 g., 2.1 mole) at the rate of 20–40 g./hr. while 6*N* sodium hydroxide solution was added at such a rate as to maintain the mixture at *p*H 7–8, as measured with a *p*H meter. The resulting white solid was filtered, washed twice with 1-l. portions of water, and dried to give 136 g. (97%) of IV, decomposing slowly above 280°.

*Anal.* Calcd. for $C_4H_2Cl_4N_4O_2$: C, 17.2; H, 0.7; Cl, 50.7; N, 20.0. Found: C, 17.5; H, 0.8; Cl, 50.5; N, 20.2. Infrared examination did not show the NH band (3170 cm.$^{-1}$) present in VII.

*Dichloroglycoluril* (VIII). This was carried out as in the preparation of IV except that 78 g. (1.1 mole) of chlorine was used. The solution was filtered to remove traces of IV and concentrated under vacuum at 50° to a volume of about 200 ml. The resulting solid was filtered, washed with two 100-ml. portions of water, and dried to give 90 g. (85%) of VIII, melting with rapid decomposition at 180°.

*Anal.* Calcd. for $C_4H_4Cl_2N_4O_2$: C, 22.8; H, 1.9; Cl, 33.6; N, 26.5. Found: C, 22.5; H, 1.6; Cl, 33.0; N, 26.0.

*Tetrabromoglycoluril* (V). A stirred suspension of VII (7.1 g., 0.05 mole) in 2200 ml. of water was treated with bromine (80.0 g., 0.5 mole) over a 3-hr. period while the mixture was maintained at *p*H 9–10. The resulting solid after filtering, washing with two 500-ml. portions of water, and drying gave 17.2 g. (75%) of V melting at 292–295° with decomposition.

*Anal.* Calcd. for $C_4H_2Br_4N_4O_2$: C, 9.8; H, 0.4; Br, 69.6. Found: C, 10.5; H, 0.8; Br, 65.5.

*Tetrachlorodiureidopentane* (X). A stirred suspension of IX (56 g., 0.3 mole) in 3 l. of water was treated with chlorine (110 g., 1.55 mole) over a 4-hr. period while the mixture was maintained at *p*H 5–8. The white solid was filtered, washed with several portions of water and dried to give 87 g. (90%) of X melting at 210° with decomposition.

*Anal.* Calcd. for $C_7H_8Cl_4N_4O_2$: Cl, 44. Found: Cl, 41.5.

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(7) T. de Haan, *Rec. trav. chim.*, **27**, 162 (1908).

(8) All melting points are uncorrected. Elemental and infrared analysis by the Diamond Alkali Company Research Analytical Laboratory.

## C-73: A Metabolic Product of *Streptomyces albulus*

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C-73 is a crystalline compound which accompanies cycloheximide and E-73 in the broths of *Streptomyces albulus*. The three compounds have identical carbon skeletons. C-73 has an aromatic ring in place of the cyclohexanone ring which is common to cycloheximide and E-73. The structure of C-73 is shown (I.)

The isolation of the five fractions designated as A-73 (fungicidin), B-73, C-73, D-73 (cycloheximide), and E-73 from the culture filtrates of *Streptomyces albulus* has been described earlier.[1] Among these, E-73 showed pronounced antitumor activity in experimental animals and its structure has been elucidated.[2] The present paper deals with the chemical nature of C-73.

C-73 (I) is a pale yellow crystalline solid sparingly soluble in common organic solvents. Elementary analysis corresponds to the empirical formula $C_{15}H_{17}O_4N$. Its occurrence with cycloheximide in the culture broths and the close similarity between their empirical formulae $C_{15}H_{17}O_4N$ and $C_{15}H_{23}O_4N$ suggested a possible structural relationship between the two.

The ultraviolet spectrum of C-73 has maxima at 262 and 345 mμ ($\epsilon$ = 10,870 and 4,550 respectively). The infrared spectrum shows bands at 5.80, 5.90, 6.10, and 6.26 μ among others. The substance shows bright yellow fluorescence under ultraviolet light. It gives a dark green color with alcoholic ferric chloride, indicating the presence of a phenolic group. C-73 is soluble in aqueous alkali to give bright yellow solutions.

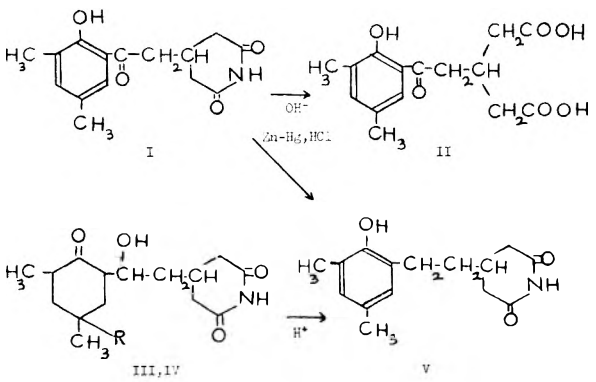
(1) K. V. Rao and W. P. Cullen, *J. Am. Chem. Soc.*, in press.

(2) K. V. Rao, *J. Am. Chem. Soc.*, in press.

Acetylation of C-73 yields a colorless mono acetate, $C_{17}H_{19}O_5N$. C-73 forms an orange red 2,4-dinitrophenylhydrazone as evidence for the presence of the carbonyl group. The color reaction with ferric chloride, the ultraviolet spectrum and the diminished hydroxyl band in the infrared spectrum suggest that the carbonyl group is *ortho* to the phenolic hydroxyl. Boiling C-73 with aqueous alkali produces one molar equivalent of ammonia and an acidic compound (II). This acid, which is dibasic (N = 147) has the molecular formula $C_{15}H_{18}O_6$. It has ultraviolet absorption maxima at 262 and 345 m$\mu$ ($\epsilon$ = 11,000 and 4600 respectively, similar to the original compound). It also retains the fluorescence and the ferric chloride reaction typical of C-73.

Methylation of C-73 yields a colorless methylation product $C_{17}H_{21}O_4N$ which contains one methoxyl and one methylimide group.

The properties described thus far indicate the presence of a phenolic group, a keto group and an imide group in C-73. It may be recalled that both cycloheximide (III) and E-73 (IV) contain an imide group. As C-73 differs from cycloheximide only by the lack of six hydrogen atoms, the possibility appeared that the former is an aromatized analogue of cycloheximide. Among the alternatives considered, structure I appeared most probable. During the course of the work on the structure of E-73, some of the phenolic transformation products of the latter became available and it appeared that C-73 could be related to one of them. Accordingly C-73 was reduced by the Clemmensen procedure whereby a colorless crystalline product (V) was obtained. This was shown to be identical in all respects to desacetyl dehydro E-73 described earlier.[2] The formation of this common intermediate is considered as a proof for structure I for C-73. The reactions are described in Fig. 1. Unlike cycloheximide or E-73, C-73 has little or no antitumor activity in experimental animals.




III. R = H
IV. R = O Ac

Fig. 1. Comparaison of C-73 with cycloheximide and E-73

## EXPERIMENTAL

*C-73 was purified* by crystallization from a mixture of methanol and chloroform. The product separated out as pale yellow needles, m.p. 198–199°.

*Anal.* Calcd. for $C_{16}H_{17}O_4N$: C, 65.44; H, 6.22, N, 5.09. Found: C, 65.57; H, 6.33; N, 5.10.

*For acetylation*, C-73 (0.2 g.) was left at room temperature with acetic anhydride (2 ml.) and pyridine (0.5 ml.) for 24 hr. The reagents were removed by a current of air and the residue crystallized from a mixture of methylene chloride and ether. The acetyl derivative separated as colorless needles, m.p. 149–150°.

*Anal.* Calcd. for $C_{17}H_{19}O_5N$: C, 64.34; H, 6.04; N, 4.41. Found: C, 63.34; H, 6.52; N, 4.42.

*The 2,4-dinitrophenylhydrazone* of C-73 was prepared by the action of 2,4-dinitrophenylhydrazine in 2*N* methanolic hydrochloric acid. The derivative separated as orange red rectangular plates which did not melt below 280°.

*Anal.* Calcd. for $C_{21}H_{21}O_7N_5$: C, 55.38; H, 4.65; N, 15.38. Found: C, 55.84; H, 4.84; N, 15.00.

*Alkaline hydrolysis of C-73.* A solution of C-73 (0.5 g.) in aqueous sodium hydroxide (25 ml.) was refluxed for 2 hr. A current of nitrogen was passed through the solution during the hydrolysis and the exit gases trapped in 1*N* hydrochloric acid. The distillate was concentrated to dryness and the residue crystallized from methanol-acetone.

*Anal.* Calcd. for $NH_4Cl$: N, 26.17; Cl, 66.28. Found: N, 26.85; Cl, 66.10.

The alkaline hydrolysis mixture was acidified and the precipitated solid crystallized from aqueous methanol. The product separated as long, colorless needles, m.p. 126–127°.

*Anal.* Calcd. for $C_{15}H_{18}O_6$: C, 61.23; H, 6.16. Found: C, 61.16; H, 6.20.

*Methylation of C-73.* A mixture of C-73 (0.5 g.), acetone (50 ml.), dimethyl sulfate (2 ml.), and anhydrous potassium carbonate (8 g.) was refluxed for 12 hr., the solvent was distilled, the residue treated with water and the mixture extracted twice with methylene chloride. Concentration of the solvent extract gave a colorless crystalline solid which was recrystallized from a mixture of ether-isopropyl ether. The methyl ether separated as colorless rectangular prisms, m.p. 100–101°.

*Anal.* Calcd. for $C_{17}H_{21}O_4N$: C, 67.32; H, 6.97; N, 4.61; OMe,[1] 10.21; NMe,[1] 9.56. Found: C, 67.46; H, 7.10; N, 4.77; OMe, 10.48; NMe, 8.0.

*Reduction of C-73.* Zinc amalgam was prepared from zinc dust (5 g.) and a 0.5% solution of mercuric chloride. The supernatant liquid was decanted and a solution of C-73 (0.3 g.) in a mixture of ethanol (20 ml.) and 6*N* hydrochloric acid (20 ml.) was added and the whole refluxed for 4 hr. After 2 hr., an additional quantity (5 ml.) of the acid was added. At the end of the reaction, the mixture was filtered, the residue washed with ethanol, and the filtrate concentrated to remove the ethanol. Extraction of the aqueous concentrate with ether followed by evaporation of the extract gave a colorless crystalline solid. When recrystallized from aqueous methanol, V separated as colorless glistening rectangular plates, m.p. 147–148°. A mixed melting point with desacetyl dehydro E-73[2] (V) (obtained by heating E-73 (IV) with 6*N* hydrochloric acid) was undepressed. The ultraviolet spectra ($\lambda_{max}$ at 280 m$\mu$, $\epsilon$ = 2000) and the infrared spectra were identical.

*Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.43; H, 7.52; N, 5.67.

*Acknowledgment.* The author is grateful to Dr. R. L. Wagner for analyses.

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## Ethanolysis of 2-Substituted-4-arylidene-5-oxazolones. Effect of Trifluoromethyl Substitution on the Arylidene Ring

ROBERT FILLER AND HERMAN NOVAR

*Received September 17, 1959*

The ultraviolet absorption spectra of azlactones are usually measured in 95% ethanol, chloroform, ether, or acetic acid as solvents. A hypsochromic shift of the principal maximum of unsaturated azlactones has been observed[1] when dilute ethanolic solutions were allowed to stand at room temperature for several days. This shift is due to the noncatalyzed solvolysis of the oxazolone to form the open chain ester and this change offers a convenient means for following the course of the reaction spectrophotometrically.

Thus, 2-phenyl-4-benzylidene-5-oxazolone (Ia), $\lambda_{max}^{EtOH}$ 360 m$\mu$[2] was gradually converted into ethyl $\alpha$-benzamidocinnamate (IIa), $\lambda_{max}^{EtOH}$ 282 m$\mu$. After three to four days, about 50% conversion had occurred and the reaction was complete within twenty-one days.[1] We have confirmed these results and have further observed that 2-methyl-4-benzylidene-5-oxazolone (Ib), $\lambda_{max}$ 328 m$\mu$, was much more readily solvolyzed to IIb, $\lambda_{max}$ 281 m$\mu$, with conversion almost complete after twenty-eight hours. This increased rate of alcoholysis of 2-methyl analogs has been observed previously with another oxazolone[1] and is consistent with the facile hydrolysis of Ib with boiling water-acetone to give the $\alpha$-acetamido acid.[3] Ia is stable under the latter conditions.

In the course of our studies on trifluoromethyl-substituted aromatic amino acids, we have prepared and similarly examined several analogs of Ia and Ib (see Table I), possessing trifluoromethyl groups in the *ortho* and *meta* positions of the arylidene ring. The preparation of these compounds will be discussed in a forthcoming paper.[4]

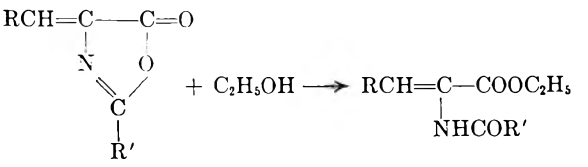
Ic ($\lambda_{max}$ 359 m$\mu$) was largely converted to the open-chain, $\alpha,\beta$-unsaturated ester after twenty-four hours and had reacted completely within seventy-two hours, while the *meta* trifluoromethyl compound, Id ($\lambda_{max}$ 358 m$\mu$), and the 2-methyl counterparts, Ie ($\lambda_{max}$ 324 m$\mu$) and If ($\lambda_{max}$ 322 m$\mu$), showed no evidence of unchanged oxazolone after twenty four hours.

These results reflect the enhancement of solvolysis due to the electronic influence of the trifluoromethyl group in labilizing the oxazolone ring. The site of attack is the lactone carbonyl moiety and it is difficult, as the results are not quantitative, to evaluate, particularly in the case of the *o*-trifluoromethyl compound, the relative importance of the *inductive* and *field* effects in the total electrical effect. Such an evaluation has been made by Roberts[5] for *o*-substituted phenylpropiolic acids and esters.

It is also of interest to note that the spectra of the 2-phenyl-4-trifluoromethylbenzylidene-5-oxazolones (Ic and Id) did not reveal any sign of *trans*-acylation during their preparation by the Erlenmeyer-Plöchl reaction, in contrast to the observations of Bennett and Niemann in the preparation of the 4-(*p*-fluorobenzylidene) analog.[6]

Concentrations of solutions were about 5 $\mu$g oxazolone/cc. Measurements were made with a Beckman DK-2 spectrophotometer.

TABLE I




I II

| Compound | Substituents R | Substituents R' |
|---|---|---|
| a | $C_6H_5$ | $C_6H_5$ |
| b | $C_6H_5$ | $CH_3$ |
| c | *o*-$C_6H_4CF_3$ | $C_6H_5$ |
| d | *m*-$C_6H_4CF_3$ | $C_6H_5$ |
| e | *o*-$C_6H_4CF_3$ | $CH_3$ |
| f | *m*-$C_6H_4CF_3$ | $CH_3$ |

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CHICAGO 16, ILL.

(1) E. L. Bennett and E. Hoerger, *J. Am. Chem. Soc.*, **74**, 5975 (1952).

(2) D. A. Bassi, V. Deulofeu, and F. A. F. Ortega, *J. Am. Chem. Soc.*, **75**, 171 (1953).

(3) *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1.

(4) R. Filler and H. Novar, in press.

(5) J. D. Roberts and R. A. Carboni, *J. Am. Chem. Soc.*, **77**, 5554 (1955).

(6) E. L. Bennett and C. Niemann, *J. Am. Chem. Soc.*, **72**, 1803 (1950)

## The Synthesis of a Novel Ester of Phosphorus and of Arsenic

J. G. VERKADE[1a] AND L. T. REYNOLDS[1b]

*Received September 28, 1959*

Stetter and Steinacker[2] report the synthesis of 1-phospha-2,8,9-trioxa-adamantane (II) and the corresponding 1-oxide and 1-sulfide. Using a modification of their synthetic method, we have pre-

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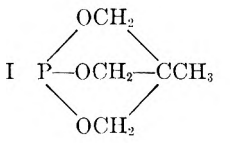
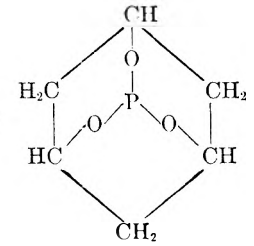
(2) H. Stetter and K. Steinacker, *Ber.*, **85**, 451 (1952).

pared the heretofore unknown 1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane (I) in which the phosphorus-oxygen bond angles are even more restricted and the organic group less bulky.



I



II

Compounds I and II function as excellent donors. This is the consequence of the minimal steric hindrance, increased availability of the phosphorus lone-pair electrons, and the high symmetry of the ligands. By contrast, the trialkoxyphosphorus compounds of comparable molecular weight are relatively poor donors.[3] It has been found[4] that I and II form stable complexes with various metal ions and addition compounds with Group III Lewis acids. The arsenic analogues of I and II are also presently being investigated in this respect.

Despite the opportunity for polymer formation in the preparation, it is possible to obtain I in 40% yield. The preparation is effected by allowing phosphorus trichloride to react with 2-hydroxymethyl-2-methyl-1,3-propanediol at high dilution in tetrahydrofuran in the presence of a base (pyridine). Because of its volatility, I is separated from the reaction products by sublimation *in vacuo*. Contrary to expectation, I is very stable to air oxidation over a period of months, although it is quite hygroscopic. On the other hand, II is quite unstable in air.[2]

The slightly soluble 1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane - 4 - sulfide is obtained in nearly quantitative yield when sulfur is allowed to react with I at 140° in a sealed tube. The solid product remains after any unreacted starting materials have been extracted with carbon disulfide.

The previously unknown -4-arsa- analogue of I is obtained in 38% yield by using arsenic trichloride instead of phosphorus trichloride in the preparation of the bicyclic arsenic compound. The volatile product is separated from the polymeric reaction mixture by sublimation *in vacuo*. The colorless crystalline sublimate is quite unstable to moisture and hydrolyzes readily.

Attempts to synthesize the 4-oxide and the 4-sulfide of the -4-arsa- compound have thus far been unsuccessful.

The infrared spectra of these compounds are commensurate with the assigned structures. The P=O stretching frequency appears as a strong band at 1325 $cm^{-1}$. It is interesting to note that this frequency lies somewhat above the range generally assigned to this band.[5] The P=S stretching frequency occurs as a band of medium intensity at 800 $cm.^{-1}$ which lies within the range generally assigned to such compounds.[6]

(3) A. Arbuzov and V. Zoroastrova, *Doklady Akad. Nauk S.S.S.R.*, **84**, 503 (1952).

(4) To be published elsewhere.

## EXPERIMENTAL[7,8]

*1-Methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane.* Tetrahydrofuran was distilled after refluxing over lithium aluminum hydride for 3 hr.; the portion boiling from 65–66° was taken. Pyridine was distilled after refluxing over barium oxide for 3 days: the portion boiling at 115° was taken. Two solutions were prepared: (1) a solution of 8.8 ml. (0.1 mole) freshly distilled phosphorus trichloride diluted to 75 ml. with tetrahydrofuran and (2) a solution of 12 g. (0.1 mole) 2-hydroxymethyl-2-methyl-1,3-propanediol in 24.2 ml. (0.3 mole) pyridine. The latter solution was also diluted to 75 ml. with tetrahydrofuran. These two solutions were simultaneously added dropwise over a period of 45 min. to 100 ml. of vigorously stirred tetrahydrofuran under dry nitrogen. The white reaction mixture was then stirred for 30 min., after which the pyridinium hydrochloride was allowed to settle. The clear supernatant liquid was filtered and the residue washed with two 30-ml. portions of tetrahydrofuran. Tetrahydrofuran was then distilled from the solution *in vacuo* until the residue became a white syrupy mass. The product was sublimed at 1 mm. pressure and room temperature on to a water-cooled finger until sublimation ceased. The temperature was then gradually raised by means of an oil bath to 80° and held constant within 2° of this temperature until no more product sublimed. To effect purification, the crude product was sublimed three times at 50° and 1 mm. pressure, yield, 5.9 g. (40%), m.p. of the colorless prismatic crystals 97–98°.

Instead of further sublimation, the product may be recrystallized from hot *n*-heptane.

*Anal.* Calcd.: C, 40.60; H, 6.08. Found: C, 40.55; H, 6.07. Mol. wt. Calcd.: 148. Found: 157.

*1-Methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane-4-oxide.* To a solution of 1.48 g. (0.01 mole) 1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane in 5 ml. absolute ethanol was added dropwise 1.13 ml. (0.01 mole) of 100 volume hydrogen peroxide. The crystals formed on cooling the solution were filtered, washed with 4 ml. cold absolute ethanol, dried, and sublimed three times at 155° and 1 mm. pressure, yield, 1.5 g. (92%), m.p. of the colorless acicular crystals 249–250°.

*Anal.* Calcd.: C, 36.60; H, 5.48. Found: C, 36.90; H, 5.48.

*Mol. wt.* Calcd.: 164. Found: 171.

The residue may also be recrystallized from absolute ethanol instead of subliming to effect purification.

*1-Methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane-4-sulfide.* A glass tube containing a mixture of 1.48 g. (0.01 mole) of I and 0.32 g. (0.01 mole) sulfur was evacuated, sealed, and heated to 140° in an oil bath for 5 min. After the vigorous reaction subsided, the tube was allowed to cool and the contents ground to a fine powder. The yellow powder was allowed to stand under 30 ml. of carbon disulfide for 24 hr. in order to dissolve any unchanged starting materials. The

(5) L. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, Ed. 2, 1958, p. 312.

(6) L. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, Ed. 2, 1958, p. 321.

(7) Melting points are uncorrected.

(8) Molecular weights were obtained by cryoscopic determination in nitrobenzene.

white powder was further extracted with three 20-ml. portions of carbon disulfide, dried and sublimed three times at 140° and 1 mm. pressure, yield, 1.6 g. (89%), m.p. of the colorless acicular crystals 224–225°.

*Anal.* Calcd.: C, 33.40; H, 5.00. Found: C, 33.56; H, 5.18.

*Mol. wt.* Calcd.: 180. Found: 174.

*1-Methyl-4-arsa-3,5,8-trioxabicyclo[2.2.2]octane.* The preparation of this compound involved arsenic trichloride and was analogous to that of the -4-phospha- compound. The first sublimation of the crude syrup, however, was carried out at room temperature. The solid sublimate, contaminated with a small amount of oily material, was dissolved in ether, in which the oily substance was insoluble. The ether solution was decanted and evaporated to dryness. The residual white solid was sublimed three times at room temperature and 1 mm. pressure, yield, 38%, m.p. of the colorless prismatic crystals 41–42°.

*Anal.* Calcd.: C, 31.25; H, 4.68. Found: C, 31.15; H, 4.68.

*Mol. wt.* Calcd.: 192. Found: 185.

*Infrared Spectra.* Spectra were taken in chloroform and carbon disulfide solutions as well as in nujol mulls on a Perkin-Elmer Model 21 Spectrophotometer.

*Acknowledgment.* The authors gratefully acknowledge the help of Prof. E. G. Rochow in making possible the execution of this work.

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## Phosphonic Acid and Esters. II. Formation of Telomers in Olefin/Phosphorous Acid Reactions

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*Received August 31, 1959*

In Part I it was shown that alkylphosphonic acids (I) could be formed by the addition of phosphorous acid to olefins in the presence of peroxides or ultraviolet irradiation (steps 1–2).[1] The low

$$RCH{=}CH_2 + \cdot P(O)(OH)_2 \longrightarrow \underset{\text{III}}{RCHCH_2P(O)(OH)_2} \quad (1)$$
$$\text{II}$$

$$III + HP(O)(OH)_2 \longrightarrow \underset{\text{I}}{RCH_2CH_2P(O)(OH)_2} + II \quad (2)$$

yields of products obtained were attributed to the occurrence of polymerization, inhibition by allylic abstraction and telomerization (steps 3–4). Specific evidence for the occurrence of telomerization was provided by the isolation of a telomeric 2:1 adduct,

$$III + RCH{=}CH_2 \longrightarrow \underset{\text{IV}}{RCHCH_2CHRCH_2P(O)(OH)_2} \quad (3)$$

$$IV + HP(O)(OH)_2 \longrightarrow \underset{\text{V}}{RCH_2CH_2CHRCH_2P(O)(OH)_2} + II \quad (4)$$

2-hexyldecylphosphonic acid (VI; V, R = *n*-hexyl), as well as the primary reaction product (*n*-octylphosphonic acid) from the reaction of 1-octene and phosphorous acid. Similar telomers have been shown to arise in the peroxide initiated addition of dialkyl phosphonates to olefins.[2] In order to determine the extent of telomer formation, the previous investigation[1] has now been extended to a study of the reactions of 1-hexene, 1-decene, and cyclohexene.

1-Hexene was treated with phosphorous acid in the presence of dibenzoyl peroxide at reflux temperature; fractionation of the products led to the isolation of *n*-hexylphosphonic acid (23%) and the 2:1 adduct, 2-butyloctylphosphonic acid (VII; V, R = *n*-butyl). Reaction with 1-decene gave *n*-decylphosphonic acid (18%) and 2-octyldodecylphosphonic acid (VIII; V, R = *n*-octyl). A reinvestigation of the cyclohexene/phosphorous acid reaction led to the isolation of 2-cyclohexylcyclohexylphosphonic acid (IX) and the primary reaction product, cyclohexylphosphonic acid. Thus, telomerization appears to be generally characteristic of the olefin/phosphorous acid reactions and additional evidence for the low transfer constant of phosphorous acid is provided.

The structures proposed for the telomeric acids (V) are those which would arise from telomerization of conventional (head to tail) orientation, i.e., attack of the radical (III) at the terminal olefinic carbon.[3] The identity of the acids (V) was confirmed by comparison with samples prepared by an independent route: peroxide initiated addition of diethyl phosphonate to the appropriate olefin and acidic hydrolysis of the resulting diethyl alkylphosphonate. The requisite olefins, including

$$RCH_2CH_2CR{=}CH_2 + HP(O)(OC_2H_5)_2 \longrightarrow V$$

the previously unreported 2-hexyl-1-decene, were conveniently prepared from the corresponding ketones by means of the Wittig reaction. In each case the acid prepared independently was identical with the 2:1 adduct isolated from the olefin/phosphorous acid reactions.

The independent route employed above is, however, capable of yielding two produts: V by attack of the phosphonate radical at the terminal olefinic carbon and the isomeric 2-methyl alkylphosphonic acid $RCH_2CH_2CR(CH_3)P(O)(OH)_2$ by attack at carbon two. On the basis of the known chemistry and orientation of this and similar free radical addition reactions, terminal attack is most probable.[2,4,5] A conclusive demonstration was

(1) C. E. Griffin and H. J. Wells, *J. Org. Chem.*, 24, 2049 (1959).

(2) A. R. Stiles, W. E. Vaughan, and F. F. Rust, *J. Am. Chem. Soc.*, 80, 714 (1958).

(3) Alternatively, the attack of III at carbon two of the olefin would yield a primary radical (less stable than the secondary radical IV) and, ultimately, the isomeric acid $RCH(CH_3)CHRCH_2P(O)(OH)_2$.

(4) P. C. Crofts, *Quarterly Revs.*, 12, 363 (1958).

(5) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, 1957, pp. 239–89.

provided by the synthesis of VII by an unequivocal route: Arbuzov reaction between 1-bromo-2-butyloctane and triethyl phosphite followed by hydrolysis. A sample of the acid prepared in this manner was identical with VII prepared by the addition of diethyl phosphonate to 2-butyl-1-octene. By analogy structure V is proposed for the acids VI, VIII, and IX.

## EXPERIMENTAL

The olefin/phosphorous acid reactions were conducted according to the method previously reported[1]; a 1:1 molar ratio of olefin to phosphorous acid was employed. The 1:1 adducts were isolated by direct crystallization, while the 2:1 adducts were most conveniently isolated by anion exchange chromatography of reaction residues. Reactants and products are listed.

*1-Hexene: n-hexylphosphonic acid* (23%), m.p. 105–106° (from ligroin) (reported[6] m.p. 104.5–106°); *2-butyloctylphosphonic acid* (VII) (8%), m.p. 99–100° (from 50% ethanol).

*1-Decene: n-decylphosphonic acid* (18%), m.p. 101.5–103° (from ligroin) (reported[6] m.p. 102–102.5°); *2-octyldodecylphosphonic acid* (VIII) (6%), m.p. 94–95° (from $H_2O$).

*Cyclohexene: cyclohexylphosphonic acid* (20%)[1]; *2-cyclohexylcyclohexylphosphonic acid* (IX) (9%), m.p. 98–99.5° (from 50% ethanol).

*1-Octene* experiments are reported in Part I.

*2-Alkyl-1-alkenes* were prepared from the appropriate ketones[7] and triphenylphosphine methylene by the modification of a method described in the literature.[8] Products were isolated directly by distillation after removal of triphenylphosphine oxide by filtration.

*2-Butyl-1-octene* (from undecanone-5)[9] b.p. 83–84°/12 mm. (reported[9] b.p. 88–89°/14 mm.).

*2-Octyl-1-dodecene* (from nonadecanone-9)[7] b.p. 184–186°/10 mm. (reported[10] b.p. 193–195°/12 mm.).

*2-Hexyl-1-decene* (from pentadecanone-7)[11] b.p. 165–166°/9 mm.

*Anal.* Calcd. for $C_{16}H_{32}$: C, 85.63; H, 14.37; mol. wt., 224.4. Found: C, 85.60; H, 14.49; mol. wt. (Rast), 225.9.

*1-Cyclohexylcyclohexene* was prepared according to the method of Truffault.[12]

*Alkylphosphonic acids* were prepared from the corresponding olefins and diethyl phosphonate (1:4 molar ratio) in the presence of di-*t*-butyl peroxide according to established procedure.[2] Upon completion of reaction, unchanged diethyl phosphonate was removed by distillation under reduced pressure; the residue was hydrolyzed with coned. hydrochloric acid. Filtration and recrystallization gave the phosphonic acid.

*2-Hexyldecylphosphonic acid* (VI) m.p. 100.5–101.5° (from ligroin) (reported[1] m.p. 100.5–101.5°).

*Anal.* Calcd. for $C_{16}H_{35}O_3P$: C, 62.71; H, 11.51; neut. equiv., 153.2. Found: C, 62.84; H, 11.38; neut. equiv., 153.6.

*2-Butyloctylphosphonic acid* (VII) m.p. 99–100° (from 50% ethanol).

*Anal.* Calcd. for $C_{12}H_{27}O_3P$: C, 57.57; H, 10.87; neut. equiv., 125.2. Found: C, 57.59; H, 11.01; neut. equiv., 125.9.

*2-Octyldodecylphosphonic acid* (VIII) m.p. 94–95° (from $H_2O$).

*Anal.* Calcd. for $C_{20}H_{43}O_3P$: C, 66.26; H, 11.96; neut. equiv., 181.3. Found: C, 66.30; H, 11.76; neut. equiv., 182.9.

*2-Cyclohexylcyclohexylphosphonic acid* (IX) m.p. 98–99.5° (from 50% ethanol).

*Anal.* Calcd. for $C_{12}H_{23}O_3P$: C, 58.50; H, 9.41; neut. equiv., 123.1. Found: C, 58.61; H, 9.43; neut. equiv., 124.2.

In each case the alkylphosphonic acid prepared in this manner was identical with the 2:1 adduct isolated from the olefin/phosphorous acid reactions. Mixture melting points and infrared spectra were employed as criteria of identity.

*2-Butyloctylphosphonic acid* (VII) was prepared independently by a conventional Arbuzov reaction. 1-Bromo-2-butyloctane was prepared by the action of phosphorus tribromide on the corresponding alcohol in pyridine; after removal of solvent under reduced pressure, the reaction mixture was filtered and dissolved in ether. The ethereal extract was washed with water, dilute hydrochloric acid, and dilute ammonium hydroxide and dried over anhydrous sodium sulfate; removal of ether under reduced pressure gave the crude alkyl bromide. A mixture of the alkyl bromide and a three fold excess of triethyl phosphite was heated at 150° for 30 hr. The reaction mixture was treated as above to isolate the acid. A sample of acid from this preparation was identical with the product of the 2-butyl-1-octene/diethyl phosphonate reaction.

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(6) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **67**, 1180 (1945).

(7) Prepared according to the method of F. L. Breusch and F. Baykut, *Chem. Ber.*, **86**, 684 (1953).

(8) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

(9) J. v. Braun and H. Kroper, *Ber.*, **62B**, 2880 (1929).

(10) J. v. Braun and G. Manz, *Ber.*, **67B**, 1696 (1934).

(11) M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).

(12) R. Truffault, *Bull. soc. chim. France*, (5), **3**, 442 (1936).

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## Potential Anticancer Agents.[1] XXX. Analogs of *N,N',P*-Triphenylphosphonothioic Diamide

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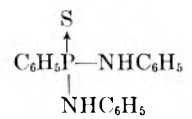
*Received September 21, 1959*

One of the compounds found in the mass screening program of the Cancer Chemotherapy National Service Center to have slight antitumor activity is *N,N',P*-triphenylphosphonothioic diamide (I). This compound showed borderline activity against adenocarcinoma 755. The synthesis of a number of

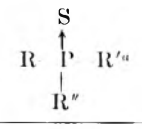


I

analogs of I for test evaluation was undertaken in this laboratory. The compounds were selected to give the widest possible diversity of structural types (Table I). These compounds were made by interaction of the appropriate phosphorus chloride and amine by one of several methods described in the Experimental.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, in press.

TABLE I



| No. | R | R′ | R″ | M.P., °C. | Procedure | Yield,[b] % | Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Carbon, % | | Hydrogen, % | | Nitrogen, % | |
| | | | | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| II | $C_6H_5$— | *p*-$ClC_6H_4NH$—[f] | *p*-$ClC_6H_4NH$— | 181–182 | A | 62[c] | 55.0 | 54.7 | 3.85 | 4.30 | 7.13 | 7.33 |
| III | $C_6H_5$— | *o*-$ClC_6H_4NH$—[f] | *o*-$ClC_6H_4NH$— | 113–114 | B[g] | 52[c] | 55.0 | 54.8 | 3.85 | 4.00 | 7.13 | 7.15 |
| IV | $C_6H_5$— | 3,4-$Cl_2C_6H_3NH$— | 3,4-$Cl_2C_6H_3NH$— | 145 | B[g] | 47[c] | 46.8 | 46.4 | 2.83 | 3.03 | 6.06 | 6.08 |
| V | $C_6H_5$— | 3,4-$(CH_3)_2C_6H_3NH$— | 3,4-$(CH_3)_2C_6H_3NH$— | 132–133 | A | 70[c] | 69.2 | 69.4 | 6.62 | 6.66 | 7.37 | 7.22 |
| VI | $C_6H_5$— | *p*-$CH_3OC_6H_4NH$— | *p*-$CH_3OC_6H_4NH$— | 112–114 | A | 32[c] | 62.5 | 62.6 | 5.51 | 5.66 | 7.29 | 7.34 |
| VII | $C_6H_5$— | *p*-$O_2NC_6H_4NH$— | *p*-$O_2NC_6H_4NH$— | 198–200 | C[h] | 30[e] | 52.2 | 52.3 | 3.65 | 3.98 | 13.5 | 13.3 |
| VIII | $C_6H_5$— | *p*-$(C_2H_5O_2C)C_6H_4NH$— | *p*-$(C_2H_5O_2C)C_6H_4NH$— | Amorph. | B[g] | 87 | 61.5 | 61.8 | 5.38 | 5.64 | 5.98 | 6.11 |
| IX | $C_6H_5$— | —$NH_2$ | —$NH_2$ | 38–40 | D | 50[c] | 41.8 | 42.2 | 5.27 | 5.40 | 16.3 | 16.3 |
| X | $C_6H_5$— | $C_2H_5NH$— | $C_2H_5NH$— | 80–81[i] | A | 79[c] | 52.6 | 52.7 | 7.50 | 7.40 | 12.3 | 12.2 |
| XI | $C_6H_5$— |  |  | 111–112 | A | 62[c] | 53.8 | 53.9 | 6.78 | 6.92 | 8.97 | 8.90 |
| XII | $C_6H_5$— | $C_6H_5O$— | $C_6H_5NH$— | 93–96[j] | E | 53[c] | 66.4 | 66.6 | 4.96 | 5.12 | 4.31 | 4.67 |
| XIII | $C_6H_5NH$— | $C_6H_5NH$— | $C_6H_5NH$— | 150–151 | A | 43[d] | 63.7 | 64.0 | 5.35 | 5.44 | 12.7 | 12.7 |
| XIV | $C_6H_5O$— | $C_6H_5NH$— | $C_6H_5NH$— | 122–123 | E | 74[c] | 63.5 | 63.3 | 5.04 | 5.15 | 8.23 | 8.42 |
| XV | $C_6H_5PO(NHC_6H_5)_2$ | | | 207–210[k] | A | 61[c] | | | | | | |

[a] All the compounds contained the proper infrared bands for the type of phenyl substituent as well as P—N bands at 11.0–13.3 μ. Compounds with a P → S bond showed a band at 13.5–14.5 μ. [b] Yields are after at least one recrystallization. [c] Recrystallized from absolute ethanol. [d] Recrystallized from 95% ethanol. [e] Recrystallized from aqueous acetone. [f] The *m*-chloro analog failed to crystallize and the crude product could not be obtained in an analytically pure condition. [g] Procedure A failed to give a crystallizable product or gave a much lower yield. [h] Procedures A and B failed to give any appreciable reaction. [i] Reported[4] m.p. 85.7–86°. [j] Reported[5] m.p. 103°. [k] Reported[6] m.p. 211°.

Although compound I showed activity against adenocarcinoma 755 when tested in these laboratories, none of the analogs showed any appreciable activity against this tumor, sarcoma 180, or leukemia L-1210.[2]

## EXPERIMENTAL[3]

*Procedure A.* To a solution of 1.12 g. (9.2 mmoles) of 3,4-xylidene in 20 ml. of anhydrous ether was added 0.50 g. (2.4 mmoles) of phenylphosphonothioic dichloride dropwise with stirring. The reaction mixture was allowed to stand overnight at room temperature protected from moisture, then the precipitated 3,4-xylidine hydrochloride was removed by filtration. Evaporation of the filtrate to dryness *in vacuo* gave a solid, which was recrystallized from absolute ethanol to give 0.70 g. (77%) of white crystals of V, m.p. 128–130°. Further recrystallizations raised the melting point to 132–133°. The analytical data are recorded in Table I.

*Procedure B.* A flask containing a mixture of 26.4 g. (0.207 mole) of *o*-chloroaniline and 10.0 g. (0.048 mole) of phenylphosphonothioic dichloride was placed in an oil bath at room temperature and the temperature raised to 165° over 15–20 min., then held at that temperature for 1 hr. The mixture was cooled, then dissolved in 150 ml. of chloroform. Treatment of the chloroform solution with 100 ml. of 1*N* hydrochloric acid caused the precipitation of *o*-chloroaniline hydrochloride. After the removal of the hydrochloride by filtration, the layers were separated and the chloroform layer was washed with two 60-ml. portions of 2*M* aqueous ammonia and 100 ml. of water. The chloroform layer was dried over magnesium sulfate, then concentrated to dryness *in vacuo* to yield 14.8 g. of a white solid. Recrystallization from absolute ethanol gave 9.6 g. (52%) of III as white crystals, m.p. 112–114°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 113–114°. The analytical data are recorded in Table I.

*Procedure C.* To a mixture of 12.98 g. (0.094 mole) of *p*-nitroaniline and 7.44 g. (0.094 mole) of pyridine in 400 ml. of dry benzene was added 10.0 g. (0.047 mole) of phenylphosphonothioic dichloride dropwise with stirring over a period of about 10 min. After the addition was complete, the reaction was heated at reflux for 7 hr., then cooled and concentrated to dryness *in vacuo*. The residue was dissolved in 200 ml. of ethyl acetate and washed with two 100-ml. portions of 1*N* hydrochloric acid, 150 ml. of 2*M* aqueous ammonia, and finally with two 100-ml. portions of water. The ethyl acetate solution was dried over magnesium sulfate, then evaporated to dryness *in vacuo*. The solid residue was dissolved in 200 ml. of acetone, then water (approximately 50 ml.) was added until the solution became slightly turbid. The solution was cooled to 0° overnight, then filtered to yield 5.95 g. (30%) of pale yellow crystals of VII, m.p. 196–200°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 198–200°. The analytical data are recorded in Table I.

*Procedure D.* To 40 ml. of concentrated ammonium hydroxide was added 2.0 g. (9.5 mmoles) of phenylphosphonothioic dichloride dropwise with stirring. An oily layer separated which slowly crystallized on standing. The reaction was heated on a steam bath for 0.5 hr., then concentrated to dryness *in vacuo* and the residue was taken up in 20 ml. of water. The aqueous layer was extracted with two 10-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, then evaporated to dryness *in vacuo* to yield 0.91 g. (57%) of an oil. Crystallization from absolute ethanol gave 0.80 g. (50%) of IX as white crystals, m.p. 30–35°. Recrystallization from absolute ethanol raised the melting point to 38–40°. The analytical data are recorded in Table I.

*Procedure E.* A solution of 7.3 g. (0.078 mole) of phenol and 6.2 g. (0.078 mole) of pyridine in 20 ml. of anhydrous ether was added dropwise with stirring to a solution of 13.2 g. (0.078 mole) of thiophosphoryl chloride in 20 ml. of anhydrous ether over a period of about 10 min. The reaction mixture was heated at reflux for 1 hr., then cooled to 0° and the precipitated pyridine hydrochloride was removed by filtration. The filtrate was concentrated to dryness *in vacuo* to yield 15.6 g. (88%) of crude *o*-phenylphosphorothioic dichloride as an oil.

To a cold (5–10°) solution of 15.6 g. of this dichloride in 10 ml. of dry benzene was added 28.1 g. (0.30 mole) of aniline in 30 ml. of benzene dropwise with stirring. The reaction mixture was stirred for 2 hr. in an ice bath, then filtered to remove aniline hydrochloride. The filtrate was concentrated to dryness *in vacuo* to yield a solid, which was recrystallized from absolute ethanol to give 17.4 g. (74%) of XIV as white crystals, m.p. 118–120°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 122–123°. The analytical data are recorded in Table I.

*Acknowledgment.* The authors are indebted to Dr. Peter Lim for interpretation of the infrared spectra.

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(2) These tests were performed at Stanford Research Institute by Dr. Joseph Greenberg and staff under a contract with the Cancer Chemotherapy National Service Center.

(3) Melting points were taken on a Fisher-Johns block and are uncorrected.

(4) E. J. Kohn, U. E. Hanninen, and R. B. Fox, Naval Research Laboratory *Rept.* C-3180, 1947.

(5) M. F. Hersman and L. F. Audrieth, *J. Org. Chem.*, **23**, 1889 (1958).

(6) A. Michaelis, *Ann.*, **293**, 215 (1896).

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## Selective Oxidation of Alkyl Groups

Lloyd N. Ferguson and Andrew I. Wims[1]

*Received October 1, 1959*

Previous workers[2] have shown that the oxidation of *p*-dialkylbenzenes with nitric acid will yield alkylbenzoic acids, but no generalization has been expressed concerning the relative ease of oxidation of the alkyl groups. Cullis[3] reported the relative rates of oxidation of some monoalkylbenzenes by permanganate. However, other than with *t*-butyl groups, the literature reveals that permanganate oxidizes dialkylbenzenes to benzene dicarboxylic acids. It would be useful sometimes in organic synthesis to be able to oxidize selectively only one alkyl group of dialkylbenzenes. For this reason,

(1) Taken from the M.S. Thesis of Andrew I. Wims, Howard University, 1959. Present position: Teaching Assistant, Pennsylvania State University.

(2) *Cf.* W. F. Tuley and C. S. Marvel, *Org. Syntheses*, **Coll. Vol. III.** Wiley and Sons, N. Y., 1955, p. 822; G. F. Hennion, A. J. Driesch, and P. L. Dee, *J. Org. Chem.*, **12**, 1102 (1952).

(3) C. F. Cullis and J. W. Ladbury, *J. Chem. Soc.*, 555 4186 (1955).

and to seek some principle for predicting the relative ease of oxidizing alkyl groups, a study was made of the selective oxidation of dialkylbenzenes with nitric acid. The identity and purity of the products were verified by mixed melting points and infrared spectra.

## EXPERIMENTAL

*Preparation of compounds.* Those dialkylbenzenes not readily available commercially were prepared by the Wurtz-Fittig reaction.[4] Of the required substituted benzoic acids, only *p*-ethylbenzoic acid had to be synthesized, which was prepared by carbonating *p*-ethylphenylmagnesium bromide.[5]

The melting or boiling points of the compounds used in this study are listed in Table I. All liquids were distilled at reduced pressures and a constant boiling fraction taken. The boiling point of a small sample was then determined at atmospheric pressure. All solids were recrystallized from ethanol to constant melting points.

*Oxidations with nitric acid.* A typical oxidation with nitric acid can be described for *p*-cymene. A mixture of 15 g. of *p*-cymene, 70 ml. of water, and 20 ml. of concentrated nitric acid was placed in a flask. The mixture was allowed to reflux gently for 8 hr. After cooling, the solid was collected and dissolved in 60 ml. of 1*N* sodium hydroxide. The alkaline solution was distilled over zinc dust until the distillate ran clear, in order to reduce any nitrated products. The solution was then acidified with dilute hydrochloric acid. The precipitate was recrystallized from ethanol to a constant melting point of 180°. The literature value for *p*-toluic acid is 181°. A mixed melting point with an authentic sample of *p*-toluic acid was 180–180.5°. Its infrared spectrum in spectro grade dimethylformamide had the characteristic band of *p*-toluic acid at 13.14 $\mu$, while the characteristic band of cumic acid at 12.88 $\mu$ was absent.

Other dialkylbenzenes were oxidized similarly. Little attention was given to per cent yields, although the yields were sufficiently large to make the reactions suitable for a preparation. In all cases, only one of the two potential acids was recovered, and it was identified by mixed melting point with an authentic sample and infrared spectra.

*Permanganate oxidations.* A few attempts were made to use potassium permanganate for oxidizing one alkyl group of a given dialkylbenzene, but except when a *t*-butyl group was one of the alkyl groups, only the respective dicarboxylic acid was obtained. For example, *p*-*t*-butyltoluene yielded *p*-*t*-butylbenzoic acid, whereas *p*-cymene gave terephthalic acid. Experiments were made using a 10:1 molar ratio of hydrocarbon to permanganate at temperatures of 60–70°.

*Infrared spectra.* Spectra of the substituted benzoic acids were measured in spectro grade *N*,*N*-dimethylformamide in a Perkin Elmer spectrophotometer 12C using a rock salt optical system. Characteristic bands for the acids were found as follows: *p*-Toluic acid 13.14 $\mu$; *p*-ethylbenzoic acid 13.04 $\mu$; *p*-cumic acid 12.88 $\mu$; *p*-*t*-butylbenzoic acid 12.80 $\mu$.

TABLE I

PHYSICAL PROPERTIES OF COMPOUNDS USED IN THIS STUDY

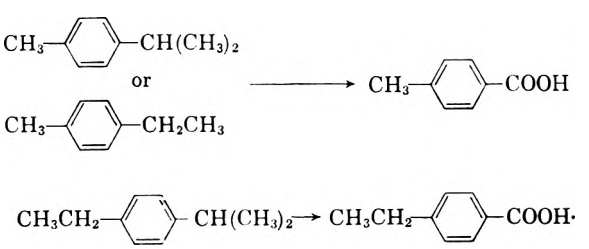
| Compound | Observed | Literature |
|---|---|---|
| | B.P. | |
| *p*-Ethylcumene | 194–194.5 | 194[a] |
| *p*-*t*-Butylethylbenzene | 206–206.5 | 205.4[b] |
| *p*-*t*-Butylcumene | 222–222.5 | 220[c] |
| *p*-*n*-Propylethylbenzene | 204 | 202–206[d] |
| *p*-Isobutylethylbenzene | 211 | 210[e] |
| *p*-Ethyltoluene[f] | 162.5 | 161–162[g] |
| *p*-Cymene[h] | 176 | 177[i] |
| *p*-*t*-Butyltoluene[h] | 191.5 | 192–193[j] |
| *p*-Bromoethylbenzene[f] | 187–188 | 188–189[k] |
| Isopropyl bromide[h] | 60 | 59.4[l] |
| *t*-Butylbromide[h] | 74 | 73.3[m] |
| *p*-Bromocumene[f] | 218 | 216[n] |
| *n*-Propylbromide[h] | 70 | 71[l] |
| Isobutyl bromide[h] | 92 | 91[p] |
| *o*-Ethyltoluene[f] | 164–165 | 164.8–165[q] |
| | M.P. | |
| *p*-Toluic acid[h] | 180.5 | 181[r] |
| Cumic acid[h] | 118–119 | 117–118[s] |
| *p*-*t*-Butylbenzoic acid[h] | 165.5 | 164[j] |
| *p*-Ethylbenzoic acid | 111–112 | 110–111[t] |
| *o*-Toluic acid[h] | 104–105 | 102–103[u] |
| | $n_D$ | |
| *p*-Methylbenzyl methyl ether | 1.4991 | 1.4990[v] |

[a] D. Todd, *J. Am. Chem. Soc.*, **71**, 1356 (1949). [b] G. F. Hennion, A. J. Driesch, and P. L. Dee, *J. Org. Chem.*, **12**, 1102 (1952). [c] V. N. Ipatev, N. A. Orlov, and A. D. Petrov, *Chem. Zentr.*, I, 2081 (1930). [d] Ng. Ph. Bun-Hou, Ng. Hoan, and Ng. D. Xuong, *Rec. trav. chim.*, **71**, 285 (1952). [e] O. Wallach, *Ann.*, **414**, 210 (1917). [f] Purchased from Aldrich Chemical Co. [g] F. Richter and W. Wolff, *Ber.*, **63**, 1723 (1930). [h] Purchased from Eastman Kodak Co. [i] K. T. Serijan, H. F. Hipsher, and L. C. Gibbons, *J. Am. Chem. Soc.*, **71**, 873 (1949). [j] P. S. Varma, *J. Indian Chem. Soc.*, **14**, 157 (1937). [k] E. L. Skaw and R. MacCullogh, *J. Am. Chem. Soc.*, **57**, 2439 (1935). [l] R. S. Schwartz, B. Post, and I. Fankuchen, *J. Am. Chem. Soc.*, **73**, 4490 (1951). [m] J. W. Copenhauer, M. F. Roy, and C. F. Marvel, *J. Am. Chem. Soc.*, **57**, 1311 (1935). [n] A. L. Soloman and H. C. Thomas, *J. Am. Chem. Soc.*, **72**, 2028 (1950). [p] K. Auwers, *Ann.*, **419**, 109 (1919). [q] O. Herb, *Ann.*, **258**, 10 (1890). [r] L. Bert, *Bull. soc. chim.*, **37**, 1400 (1925). [s] Org. Synthesis, **Coll. Vol. III**, 822 (1955). [t] M. J. Schlatter and R. D. Clark, *J. Am. Chem. Soc.*, **75**, 361 (1953). [u] R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, p. 250 (1957). [v] C. D. Gutsche and H. E. Johnson, *J. Am. Chem. Soc.*, **77**, 109 (1955).

## DISCUSSION

Nitric acid oxidation of *p*-methyl-, *p*-ethyl, and *p*-isopropyl-*t*-butylbenzenes always gave *p*-*t*-butylbenzoic acid as the only isolated product. This inertness of the *t*-butyl group to oxidation has been observed previously. For example, Ligge[6] attempted to oxidize *p*-di-*t*-butylbenzene with chromic oxide, aqueous potassium permanganate, and several concentrations of nitric acid. Only 50% nitric acid at 180° brought about a significant oxidation of the *p*-di-*t*-butylbenzene.

Initial experiments on the oxidation of diethylbenzenes with 15% nitric acid gave the following results:




(4) *Cf.* E. Wertheim, *A Laboratory Guide for Organic Chemistry*, 3rd ed., McGraw-Hill, N. Y., 1948, p. 128.

(5) *Cf.* H. Gilman, N. B. St. John, and F. Schulze, *Org. Syntheses*, **Coll. Vol. II**, Wiley and Sons, N. Y., 1943, p. 425.

(6) D. I. Ligge, *J. Am. Chem. Soc.*, 69, 2088 (1947).

It can be seen that, exclusive of the *t*-butyl groups, the preferential oxidation of these respective alkyl groups decreases in the order, isopropyl, ethyl, methyl. This is the order of increasing electronegativity of the groups and also of the increasing number of *alpha* hydrogens. Hence, to explore further the selectivity shown, groups were chosen which have the same number of *alpha* hydrogens but a third group of varying electronegativity. For example, *p*-isobutylethylbenzene, has a methyl group and an isopropyl group, attached to the *alpha* carbons. In this case, oxidation produced *p*-ethylbenzoic acid. Thus, it appears that the relative ease of oxidation of the alkyl groups, provided there is at least one $\alpha$-hydrogen atom, is determined by the relative electronegativity of the alkyl groups attached to the *alpha* carbon atoms. To test this idea, *p*-*n*-propylethylbenzene, was oxidized. *p*-Ethylbenzoic acid was obtained, again supporting the idea expressed above. In all cases, mixed melting points and infrared spectra of the oxidation products showed no sign of other *p*-alkylbenzoic acids being present.

The nitric acid oxidations in this study can be summarized as follows:

$$p\text{-}CH_3C_6H_4CH_2CH_3 \longrightarrow p\text{-}CH_3C_6H_4COOH$$

$$p\text{-}CH_3C_6H_4CH(CH_3)_2 \nearrow$$

$$o\text{-}CH_3C_6H_4CH_2CH_3 \longrightarrow o\text{-}CH_3C_6H_4COOH$$

$$p\text{-}R_1\text{—}C_6H_4\text{—}R_2 \longrightarrow p\text{-}R_1\text{—}C_6H_4COOH$$

$R_1$ = ethyl; $R_2$ = *n*-propyl, isopropyl, and isobutyl

$R_1$ = *t*-butyl; $R_2$ = methyl, ethyl, isopropyl

This generalization about the relative ease of oxidation of carbon-attached side chains only applies to hydrocarbon groups. Once a carbon-oxygen, carbon-nitrogen, or carbon halogen bond is formed, the carbon is easily oxidized. For example, the $CH_2OH$, CH=O, and $CH_2Cl$ groups are probably much more easily oxidized than alkyl groups in spite of the fact that there are highly electronegative atoms attached to the $\alpha$-carbon. To test this idea, *p*-methylbenzyl methyl ether was prepared and oxidized with 15% nitric acid. As expected, the product was *p*-toluic acid.

In summary, it can be generalized that 15% nitric acid will oxidize dialkylbenzenes to alkylbenzoic acids, and with groups containing at least one $\alpha$-hydrogen atom, the relative ease of oxidation increases with decreasing electronegativity of the groups attached to the $\alpha$-carbon.

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## Oxidation of a Secondary Alkyl Tosylate by Dimethyl Sulfoxide

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*Received October 29, 1959*

In the course of a study of the thermal decomposition of tosylates of secondary alcohols as a route to olefins, we had occasion in one instance to examine the modification reported by Nace.[1] In his procedure dimethyl sulfoxide is used as a medium and sodium hydrogen carbonate is optionally used to protect the olefin formed from the action of the liberated sulfonic acid.

When the tosylate (I) of 1,3-diphenoxy-2-propanol (II) was heated with dimethyl sulfoxide and sodium bicarbonate for six hours at a maximum temperature of 103°, the only product recovered was unchanged starting material. When the reaction temperature was allowed to rise to 150°, 10% of the input of I was recovered as its saponification product II; the remainder was converted to a yellow oil which, after distillation followed by crystallization of the distillate, was found to be 1,3-diphenoxy-2-propanone (III). III showed carbonyl absorption in the infrared; its melting point and that of its 2,4-dinitrophenylhydrazone agreed with the values reported in the literature.[2]

While the oxidation by dimethyl sulfoxide of phenacyl[3] and benzyl halides[4] and of tosylates of benzyl alcohols[5] to aldehydes has been reported,[6] the oxidation of a secondary alkyl tosylate to the corresponding ketone seems not to have been noted before.

Attempts to oxidize II directly by dimethyl sulfoxide were unsuccessful.

### EXPERIMENTAL[7]

*Dimethyl sulfoxide* was obtained from the Stepan Chemical Co. and used without purification.

*1,3-Diphenoxy-2-propyl p-toluenesulfonate* (I) was prepared from the alcohol and *p*-toluenesulfonyl chloride in pyridine according to the usual procedure. The crude yield was 95%, m.p. 117–119°. After recrystallization from 2-propanol the product melted at 121°.

*Anal.* Calcd. for $C_{22}H_{22}O_5S$: C, 66.32; H, 5.57. Found: C, 66.08; H, 6.08.

(1) H. R. Nace, *Chemistry & Industry (London)*, 1629 (1958).

(2) J. Munch-Petersen, *Acta Chem. Scand.*, **5**, 519 (1951).

(3) N. Kornblum, *et al.*, *J. Am. Chem. Soc.*, **79**, 6562 (1957).

(4) H. R. Nace, U. S. Patent **2,888,488**, May 26, 1959.

(5) N. Kornblum, *et al.*, *J. Am. Chem. Soc.*, **81**, 4113 (1959).

(6) I. M. Hunsberger and J. M. Tien, *Chemistry & Industry (London)*, 88 (1959) also report the oxidation of ethyl bromoacetate to ethyl glyoxylate and propose a mechanism for the reaction.

(7) Melting points were taken on a Fisher-Johns block and are uncorrected.

*Attempted preparation of 1,3-diphenoxy-2-propene.* A suspension of 19.9 g. (0.05 mole) I and 4.2 g. (0.05 mole) sodium bicarbonate in 75 ml. dimethyl sulfoxide was stirred vigorously and warmed slowly, so that it reached 90° in 63 min. and 100° in 140 min. Carbon dioxide evolution was fairly brisk beginning at the former temperature. After 4 hr. at 100° the reaction mixture was poured onto ice. The gummy solid was broken up, washed thoroughly with water and dried *in vacuo*, wt. 17.3 g. Recrystallization from 2-propanol yielded unchanged I, melting point and mixture m.p. 121–122°.

*Oxidation of* I *by dimethyl sulfoxide.* The reaction mixture was prepared as in the experiment above and heated more strongly so that it remained in the range 138–150° for 2 hr. It was then poured onto ice. The precipitated tar was dissolved in benzene and the solution washed several times with water, dried over sodium sulfate and filtered. Evaporation of the benzene at room temperature left 11.6 g. of a brown semisolid residue. Trituration with 2-propanol at room temperature followed by filtration removed 1.2 g. of solid which, after purification, was found to be identical with II. After removal of the propanol from the filtrate, the residual liquid was distilled, b.p. 158–163°/0.30–0.36 mm. Trituration of the distillate with Skellysolve F induced crystallization. The solid after two recrystallizations from 50% 2-propanol melted at 57° (reported[2] 59–60°). The infrared spectrum showed strong absorption at 5.90 $\mu$.

The *2,4-dinitrophenylhydrazone* after recrystallization from ethanol containing a little ethyl acetate melted at 128° (reported[2] 125–126°).

*Anal.* Calcd. for $C_{21}H_{17}N_4O_6$: N, 13.30. Found: N, 13.96.

RESEARCH AND ENGINEERING DIVISION
MONSANTO CHEMICAL COMPANY
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## Crystalline Racemic Bornyl Acetate

WILLIAM J. CONSIDINE

*Received August 14, 1959*

Although optically pure bornyl acetate has long been known to be a low melting solid with a tendency to supercool, nothing is known about the melting behavior of mixtures of the two optical antipodes. A search of the literature uncovered only a statement by Haller[1] that racemic bornyl acetate did not crystallize, even at −17°. Having samples of pure *d*-bornyl acetate and *l*-bornyl acetate available, the melting point behavior of mixtures of the two was investigated.

When a mixture of equal parts of the dextro and laevo isomers was stored in a freezing chest for a week, crystallization occurred to give a solid mass which had a melting point of 7.0°. With this assurance, a series of mixtures was prepared and the melting points taken: % levo isomer (m.p.); 100%, m.p. 27°; 75%, 18.5°; 62.5%, m.p. 12°; 50%, m.p. 7°; 37.5%, m.p. 12°; 25%, m.p. 17.5°, 0% (i.e. 100% dextro isomer), m.p. 26.5°.

A plot of these melting point data gives a symmetrical fusion curve with a single eutectic point demonstrating[2] the formation of a simple conglomerate or racemic mixture. This behavior is to be contrasted with the much more common occurrence of a racemic compound, or, rarely, a solid solution.

### EXPERIMENTAL[3]

The *d*-bornyl acetate, [α] + 41.2°, used in this study had a melting point of 26.5° (lit.[1] [α] + 44.38°; m.p. 24°). The *l*-bornyl acetate, [α] − 42.0°, had a melting point of 27.0° (lit.[1] [α] − 44.45°; m.p. 24°). Each sample, and mixture, was originally crystallized by storage in a freezing chest (−10°) for periods up to one week. Thereafter recourse was had to seeding when necessary.

FELTON CHEMICAL COMPANY, INC.
BROOKLYN 37, N. Y.

(1) M. A. Haller, *Comp. rend.*, **109**, 29 (1889).

(2) A. Findlay (ed. Campbell and Smith), *The Phase Rule and Its Applications*, 9th Ed., Dover, New York, 1951, p. 190.

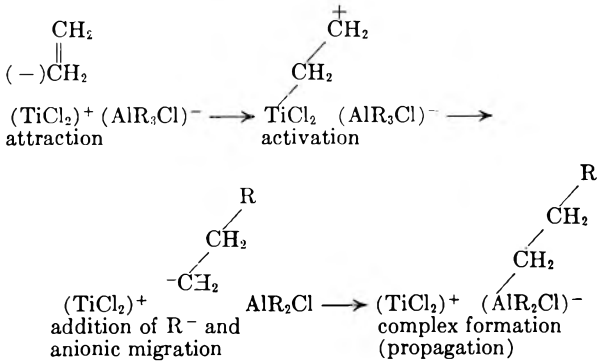
(3) All melting points are uncorrected and rotations (D line) are determined on the supercooled liquid at ambient temperatures. The temperature at which the last crystal disappeared was recorded as the melting point.

## Interpretation of Some Reactions on Complex Ionic Bonds[1a]

HEINZ UELZMANN

*Received July 16, 1959*

The mechanism of olefin polymerization with Ziegler catalysts has been considered to occur on complex ions, such as $(TiCl_2)^+(AlR_3Cl)^-$ from $TiCl_3/AlR_3$, with the direct participation of the cation metal and anion metal.[1b] The initiating step of the polymerization is the activation of the monomer on a cation of a transition element. The second step is the migration of the activated monomer to the anion metal (aluminum for instance, or titanium) which occurs at the moment when the propagation starter ($R^-$, $H^-$) neutralizes the cationic transition state of the monomer. The migration can be compared with the addition of a metal alkyl to a Lewis type metal alkyl with the formation of more stable complex ions. The polymerization mechanism of ethylene on $(TiCl_2)^+(AlR_3Cl)^-$ complex is formulated below.



The addition of the propagation starter and the migration of the monomer are concerted reactions.

The principal reasons why this mechanism proceeds are the following:

1. Special activity of transition metal cations for the activation of the monomer (low temperature initiation) can be based on the fact that inner orbitals (3*d*) participate in resonance stabilization of the electrons accepted from the monomer.
2. Migration of the monomer from titanium to aluminum is explained by the formation of a more stable aluminum carbon bond.
3. The addition of the carbanion chain end of the polymer to the cationically activated monomer (propagation) occurs continuously because it is still activated (excited) from the previous migration.
4. Very high molecular weight polymers are obtained because the growing chain end is resonance-stabilized in the complex anion, thus diminishing termination reactions.

The cation can be blocked by electron donors (ethers, amines, etc.) which form more stable coordination complexes with the cation than the monomer does.

The formation of a four valent titanium cation can be expected when titanium tetrachloride and aluminum triisobutyl are allowed to react at −78°. The ionic structure below has been proposed for the red, soluble complex formed under these conditions.[1b,2]

$$TiCl_4 + AlR_3 \xrightarrow[-78°]{} (TiCl_3)^+(AlR_3Cl)^-$$

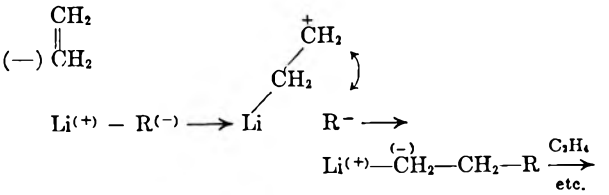
R = isobutyl

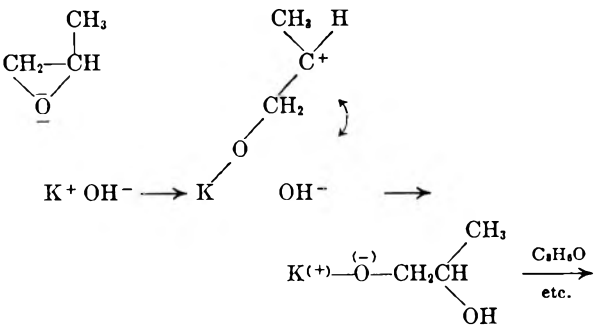
This complex decomposes above −30° yielding $TiCl_3R$ and $AlR_2Cl$ which can form another complex. The driving force for the decomposition in this direction is the formation of a more stable aluminum-chlorine bond.[2]

The ionic nature of the complex solution at −78° has been proven by A. Malatesta[3] in conductivity measurements.

*Polymerization on simple and complex ionic bonds.* The catalytic site in ionic polymerizations can be a simple or a complex ionic bond.

When a simple ionic bond is involved the polymerization takes place on one metal atom only. Catalysts with simple ionic bonds are. for instance, $Li^{(+)}—R^{(-)}$ or $R_2Al^{(+)}—R^{(-)}$ for ethylene polymerization or $K^+OH^-$, $Zn(C_2H_5)_2/H_2O$,[4] and strontium carbonate[5] for epoxides




No migration of the monomer, therefore, is likely to occur in a simple ionic mechanism and it can be expected that both activation and propagation proceed on the same metal-oxygen bond (K—O, Zn—O, Sr—O, etc.).

The active site can also be a complex ionic bond which can be represented by a complex acid, such as $H^+(AlBr_4)^-$ for α-olefins (cationic propagation), $H^+(FeCl_2OR)^-$, $H^+(BF_4)^-$ for cyclic ethers, or a complex salt, such as a Ziegler catalyst from $TiCl_3/AlR_3$ for olefins or Price's catalyst $ZnCl_2/Al(OR)_3$ for epoxides.[6] The increase in reactivity by complex formation is generally known[7] and is due to a strong ionic or polarized complex bond on which monomers or other reactive molecules are activated according to their polarization.

In olefin polymerization reactions complex ionic bonds generally offer better control of propagation than simple ionic bonds. The growing chain is more effectively resonance-stabilized as a member of a complex ion than as a simple ion. Therefore, complex catalysts allow the chain to grow longer yield-

(1a) This treatise is based on a paper presented at the Symposium on Stereoregulated Polymerizations at the Polytechnic Institute of Brooklyn, Brooklyn, N. Y., Nov. 22, 1958.

(1b) H. Uelzmann, *J. Polymer Sci.* **32**, 457 (1958).

(2) H. Uelzmann, *J. Polymer Sci.* **37**, 561 (1959). The heat of formation for the aluminum-chlorine bond (based on aluminum chloride) is 55.6 kcal., and for the titanium chlorine bond 44.8 kcal. (based on titanium tetrachloride). However, the heat of formation of titanium-chlorine in titanium trichloride is 55 kcal. and in titanium dichloride 57 kcal. which is close to the aluminum-chlorine value. Weak addition complexes can be expected to be formed, and an equilibrium according to

$$TiCl_2 + AlR_3 \rightleftarrows (TiCl)^+(AlR_3Cl)^-$$
$$TiCl_3 + AlR_3 \rightleftarrows (TiCl_2)^+(AlR_3Cl)^-$$
$$RTiCl_3 + AlR_2Cl \rightleftarrows (RTiCl_2)^+(AlR_2Cl_2)^-$$
$$RTiCl_2 + AlR_2Cl \rightleftarrows (RTiCl)^+(AlR_2Cl_2)^-$$

is possible. The nature of the R group, its stability, polarity, and steric factor is not accounted for in these formulations and will influence the complex formations.

(3) A. Malatesta, paper presented at the Ninth Canadian Polymer Forum, Oct. 26–28, 1959, Toronto, Ontario, Canada.

(4) Junji Furukawa *et al.*, *J. Polymer Sci.*, **36**, 541 (1959).

(5) F. N. Hill, F. E. Bailey, Jr., and J. T. Fitzpatrick, *Ind. Eng. Chem.*, **50**, 5 (1958). Belgian Patent No. 557,766.

(6) C. C. Price and Maseh Osgan, *J. Polymer Sci.*, **34**, 153 (1959). Belgian Patent No. 566,583.

(7) G. Wittig, *Angew. Chem.*, **70**, 65 (1958).

ing high degrees of polymerization. This is particularly true in anionic propagations where the cation or the anion portion of the catalytic bond can be efficiently complexed and where termination reactions by hydride ion abstraction require higher activation energies. In cationic propagations low temperatures are usually required for the formation of long chains in order to avoid proton eliminations or hydride shifts.

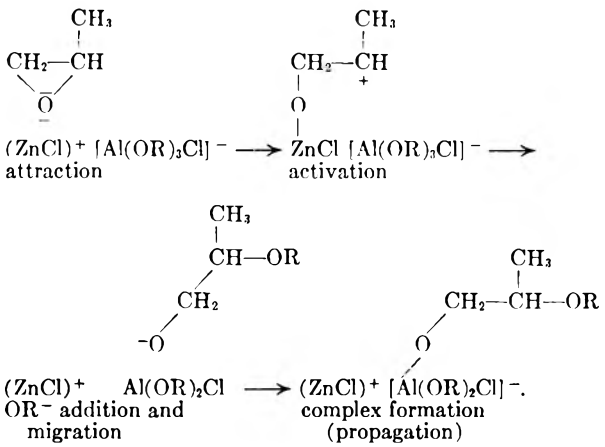
K. Ziegler and co-workers[8] obtained only low molecular weight polyethylenes with aluminum alkyls, but polymers of high molecular weight resulted when these metal alkyls were complexed with compounds of transition elements.

A similarity in structure can be expected between Ziegler catalysts, such as $TiCl_3/AlR_3$, and Price's catalyst $ZnCl_2/Al(OR)_3$. In both cases an electron donor reacts with a Lewis acid to form complex ions with two metal atoms:

$$\underset{\text{donor}}{TiCl_3} + \underset{\text{acceptor}}{AlR_3} \longrightarrow (TiCl_2)^+ (AlR_3Cl)^-$$

$$\underset{\text{donor}}{ZnCl_2} + \underset{\text{acceptor}}{Al(OR)_3} \longrightarrow (ZnCl)^+ (Al(OR)_3Cl)^-$$

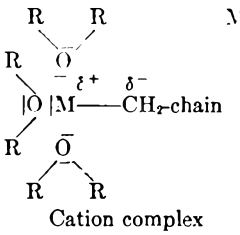
Therefore, it is likely that propylene oxide polymerizes similarly to ethylene when Price's catalyst is used:



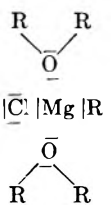

The migration of the monomer is comparable to the addition of an alcoholate anion to a Lewis type alcoholate. Other epoxides would polymerize similarly.

The ionic bond on which the polymerization proceeds offers two possibilities for complexing: the cationic or the anionic part. The mechanism of polymerization and consequently the properties of the resulting polymers can be strongly influenced by either kind of complexing.

*Cation complexes.* Electron donors, such as ethers or tertiary amines, will react with the cation to form association complexes. The complexing could go so far that the cation completes its outer electron shell to form an octet:




Similar complexes are generally known to be formed by the interaction of Grignard compounds and ethers:




Cation complexes are also formed from lithium or sodium cations and ethers [Szwarc catalysts,[9] Dainton catalysts], or alcoholate and chlorine anions [Alfin catalysts[10]]. The differences in the polymerization of butadiene (or styrene) in the presence or absence of these cation complexes (ether solvents) are generally known. Propagation on an ether-complexed or salt-complexed sodium cation gives usually high molecular weight polymers and promotes stereo-preserving polymerizations [formation of *trans*-1,4-polybutadiene from *trans* conformational monomeric butadiene[1b]]. However, when the energy level of the complexed cation is lower than the energy level required for the activation of the monomer no polymerization will occur. This is possibly the reason why conjugated dienes or styrene but not ethylene or $\alpha$-olefins can be polymerized with Szwarc-type or Alfin-type catalysts. Since less energy is required for the activation of a conjugated system the complexed cations can activate dienes but not mono-olefins. The same seems to be true for lithium alkyls which normally polymerize ethylene to a certain degree. In the presence of ethers no polymerization of ethylene is observed.

*Anion complexes.* If the propagation starter ($R^-$, $H^-$, $OR^-$, $OH^-$) is a member of a Lewis acid it can become a member of a complex anion by adding a negative ion.

$$TiCl_3 + AlR_3 \longrightarrow (TiCl_2)^+ (AlR_3Cl)^- \text{ (olefins)}$$

$$TiCl_3 + TiCl_3R \longrightarrow (TiCl_2)^+ (TiCl_4R)^- \text{ (olefins)}$$

$$ZnCl_2 + Al(OR)_3 \longrightarrow (ZnCl)^+ (Al(OR)_3Cl)^- \text{ (epoxides)}$$

$$R—OH + FeCl_3 \longrightarrow H^+ (FeCl_3OR)^- \text{ (epoxides)}$$

The activation would be cationic, followed by a migration and anionic propagation of the monomer.

Prerequisites for this type of anionic propagation are:

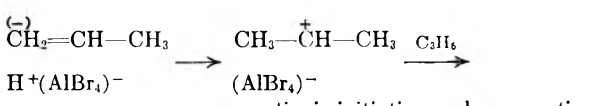
(8) K. Ziegler *et al.*, *Angew. Chem.*, **68**, 721 (1956).

(9) M. Szwarc *et al.*, *J. Am. Chem. Soc.*, **78**, 2656 (1956).

(10) A. A. Morton, *Ind. Eng. Chem.* **42**, 1488 (1950).

1. The cation must always be reformed for the activation of new monomers.
2. The complex anion must contain a propagation starter which neutralizes the cationically activated monomer.
3. The bond of the polymer chain to the metal of the complex anion must be more stable than the bond to the activating cation to assure migration and propagation.

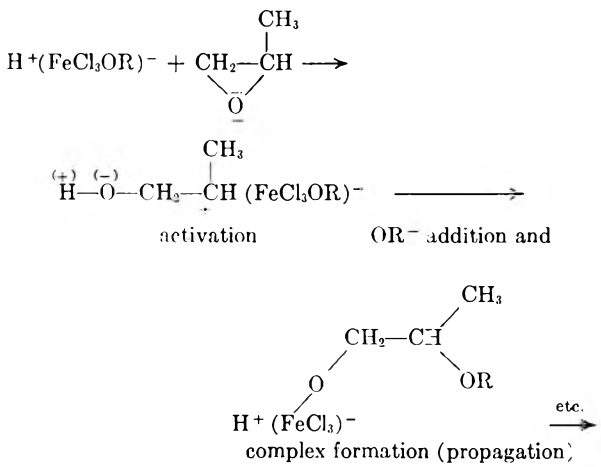
If the afore mentioned prerequisites are not fulfilled the following course of reactions for $\alpha$-olefins could be concluded. The cation can not be reformed when a complex acid such as $H^+(AlBr_4)^-$ is used because of the elimination of the proton with the formation of a stable methyl group and a rather homopolar bond.




cationic initiation and propagation

The carbonium ion formed allows cationic propagation only. If activated on a metal cation the bond of propylene to the cation is still ionic and allows migration, propagation, and reformation of the metal cation.

Contrary to olefins the anionic polymerization of epoxides by complex acids seems to be possible. The activating proton of the complex acid is not destroyed after the initiation of the monomer because of the formation of an ionizable hydroxyl group.



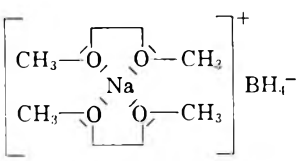

complex formation (propagation)

A cationic propagation would occur if the negative complex ion does not contain a propagation starter which would neutralize the cationically activated monomer. Such a complex acid could be $H^+BF_4^-$. On the other hand $H^+(BF_3OR)^-$ or $H^+(BF_3OH)^-$ could propagate anionically.

Cationic mechanisms with $H^+BF_4^-$ as a catalyst for the polymerization of cyclic ethers are generally known.

*Reductions with complex metal hydrides.* It can be deduced from the mechanisms discussed in the foregoing section that a similar migration of ionized groups or molecules from one metal to another is much more common in organic chemistry than hitherto expected.

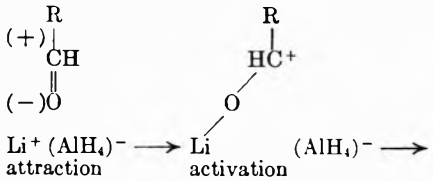
In reduction mechanisms of organic compounds with complex hydrides (lithium aluminum hydride, sodium aluminum hydride, sodium borohydrides, etc.) a direct participation of both the cation metal and anion metal would explain why there can be differences in reactivities when the cation metals are changed. H. C. Brown and co-workers[11] found that lithium borohydride reduces ester groups but sodium borohydride does not. Since different cations also differ in energy levels or steric factors their participation in the reduction mechanism as the initiating or activating site (attracting negatively polarized atoms, such as oxygen, nitrogen) explains their deviating behavior and selectivity in the above-mentioned complex ions. A reaction mechanism which proceeds solely on the complex anion allows no interpretation of this phenomenon. As already discussed the energy level of the cation can be modified additionally by the formation of coordination complexes with solvents which act as electron donors (ethers, amines). H. C. Brown *et al.*[11] have found that sodium borohydride in ethyleneglycol dimethylether reduces aldehydes but not ketones. It can be assumed that the sodium cation forms a coordination complex (octet formation) with the ether:

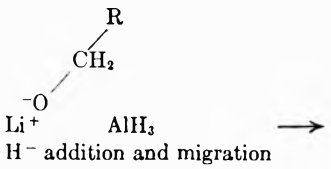


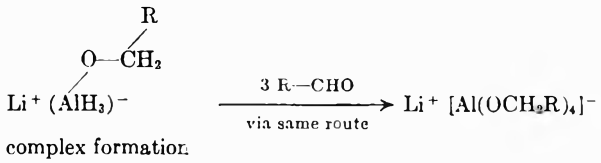

The activity of the sodium cation is decreased to such an extent that it can still activate aldehydes but not ketones. The latter apparently require higher activation energies than aldehydes and are more sterically hindered. The complete mechanism of the reduction of an aldehyde by lithium aluminum hydride is explained by the sequence of reactions shown below.

The negatively polarized oxygen atom, as the most exposed reactive atom of the aldehyde, is attracted and activated by the cation with the formation of a lithium-oxygen bond and a carbonium ion (cationic transition state). A hydride ion adds to the carbonium ion and the resulting alcoholate ion migrates and adds to the aluminum. The driving force is the reformation of stable complex ions. Here the migration compares with a simple addition of lithium alcoholate to $AlH_3$:

(11) H. C. Brown, Lecture series "Frontiers in Chemistry," April 24, 1959, Western Reserve University, Cleveland, Ohio.




It can be expected that many other reactions of complex ionic bonds follow a similar mechanism, particularly in those cases where exposed reactive atoms are negatively polarized and, therefore, are subject to a cationic activation.

CENTRAL RESEARCH LABORATORIES
THE GENERAL TIRE AND RUBBER COMPANY
AKRON, OHIO

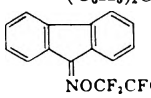
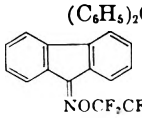
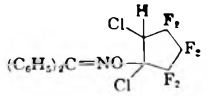
# Communications TO THE EDITOR

## Fluorinated *O*-Alkyl Oximes. Solid Derivatives of Fluorinated Olefins

*Sir:*

We wish to report the reaction between oximes and fluorinated olefins giving addition compounds, *O*-alkyl oximes, which are either solids or liquids depending on the oxime used in the reaction. The reaction is brought about in pyridine, or pyridine and benzene, in the presence of sodium hydroxide or potassium hydroxide and at 5° to 25° depending on the olefin. Most fluorinated ethylenes and other similarly substituted olefins undergo this reaction. Yields are usually high, ranging from 60 to 95%, most often closer to the latter value. The solids are easily recrystallized from ethanol. High molecular weight oximes such as benzophenone oxime and fluorenone oxime always gave solid products in the reactions studied so far; lower molecular weight oximes such as acetone oxime give liquid products.

Examples of these oximino ethers are the following: (satisfactory analytical data have been obtained on all of the compounds reported).

| Compounds | M.P.° |
|---|---|
| $(C_6H_5)_2C{=}NOCF_2CFClH$ | 33.5 |
|  | 56.0 |
| $(CH_3)_2C{=}NOCF_2CFClH$ | b.p. 75.5/50 |
| $(C_6H_5)_2C{=}NOCF_2CCl_2H$ | 63 |
| $(CH_3)_2C{=}NOCF_2CCl_2H$ | b.p. 66/18 |
| $(C_6H_5)_2C{=}NOCF_2CFHCF_3$ | 39.5 |
|  | 52 |
| $(C_6H_5)_2C{=}NOCF_2CBr_2H$ | 72.5–73 |
| $(C_6H_5)_2C{=}NOCF_2Cl_2H$ | 118 |
| $(C_6H_5)_2C{=}NOCF_2CH_2Cl$ | 66.5 |
| $(C_6H_5)_2C{=}NOCF_2CH_2Br$ | 71 |
|  | 73 |

Under the same conditions 1,1-difluoroethylene, 1,2-dichloro-1,2-difluoroethylene, bromoethylene, and tetrachloroethylene did not react.

An attempt to obtain hydrolytic scission at the double bond of these ethers by means of dilute hydrochloric acid resulted in an attack at a carbon-bearing fluorine, giving off hydrogen fluoride with a subsequent attack on the glass apparatus. This hydrolysis is believed to be analogous to the hydrolysis of fluorinated ethers having the structure $-CH_2-O-CF_2-$ which hydrolyze to esters $-CH_2-O-\overset{\overset{O}{\|}}{C}-$ when treated with strong acid.

More work in this respect is in progress and will be reported in detail in the near future.[1]

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF COLORADO
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J. R. LACHER
J. D. PARK

Received February 12, 1960

(1) These studies are being supported in part by the Quartermaster Corp. U.S. Army and by a fellowship grant from the Continental Oil Co., Ponca City, Okla.

## Stereochemistry of the Claisen Rearrangement[1]

*Sir:*

Aside from the interesting interpretive arguments of Hart[2] based on the experimental findings of Alexander and Kluiber,[3] the stereochemistry of the Claisen rearrangement has not received any attention. Since the retention of configuration suggested by Hart is not in accord with the results of work on the closely related $S_Ni'$ reaction,[4] we should like to report that we cannot confirm the suggestions made by Hart.

Assuming that the point of bond severance and the point of attachment of the migratory allyl group must lie on the same side of the benzene ring it may be seen that inversion of configuration requires the formation of a *trans* double bond between the $\alpha$ and $\beta$ carbon atoms of Fig. 1. This correspondence between the stereochemistry at the double bond and the asymmetric atoms holds for the 32 possible transition states (all combinations of initial *cis* or *trans* and final *cis* or *trans* double bonds, boat or chair conformation and R. or S configuration) providing only that the initial assumption is valid. The relation between double bond geometry and configurational changes for all cases is given in

(1) This research was supported in part by the National Science Foundation as grant NSF-G7432. Paper number four on the Claisen Rearrangement.

(2) H. Hart, *J. Am. Chem. Soc.*, **76**, 4033 (1954).

(3) E. R. Alexander and R. W. Kluiber, *J. Am. Chem. Soc.*, **73**, 4304 (1951).

(4) H. L. Goering and R. W. Greiner, *J. Am. Chem. Soc.*, **79**, 3464 (1957); H. L. Goering and R. R. Jacobson, *J. Am. Chem. Soc.*, **80**, 3277 (1958). F. Caserio, G. E. Dennis, R. H. deWolfe, and W. G. Young, *J. Am. Chem. Soc.*, **77**, 4182 (1955).

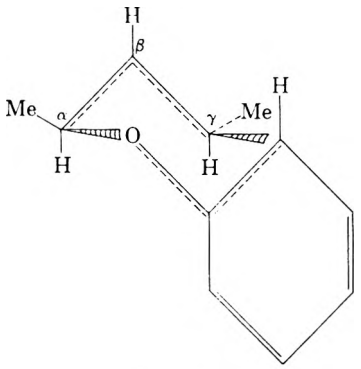


Figure 1

Table I. It is clear then that the stereochemistry of Claisen rearrangement may be studied equally readily by optical methods[3] or by a study of the geometric isomerism about the double bond. Utilizing the latter method we have prepared a sample of *cis*-4-phenoxypent-2-ene, b.p. 43–45° (0.6 mm.), $n_D^{20}$ 1.5097 (*Anal.* Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.55; H, 8.58), infrared band at 718 cm.$^{-1}$, by semihydrogenation of 4-phenoxypent-2-yne, b.p. 59.5–60° (0.65 mm.) $n_D^{20}$ 1.5254 (*Anal.* Calcd. for $C_{11}H_{12}O$: C, 82.48; H, 7.55. Found C, 82.56; H, 7.56) over the Lindlar[5] catalyst. A sample of *trans*-4-phenoxypent-2-ene, b.p. 48–48.5° (0.4 mm.), $n_D^{20}$ 1.5101 (lit.[3] $n_D$ 1.5110), infrared band at 965 cm.$^{-1}$, was also prepared by standard methods. Each isomer was free of the other geometric form as indicated by infrared spectroscopy.

TABLE I

| Geometry | | |
|---|---|---|
| Initial double bond | Final double bond | Config. Relation |
| *trans* | *trans* | Invert. |
| *trans* | *cis* | Reten. |
| *cis* | *trans* | Reten. |
| *cis* | *cis* | Invert. |

Each ether was rearranged in a 1*M* solution in boiling mesitylene (b.p. 163°) and the unchanged ether as well as the rearrangement product recovered in each case. In each case the rearrangement product consisted of mainly (*ca.* 90%) *o*-(1-methyl-*trans*-but-2-enyl)phenol, b.p. 64–65° (0.2 mm.). $n_D^{20}$ 1.5325. However in each case a small but significant amount of *cis* product was obtained and the amount was notably greater in the product from the *trans* ether. These results were reproduced in three separate runs, the analysis being by infrared spectroscopy. It is interesting that the *trans* ether was recovered as pure *trans* ether after partial reaction whereas the *cis* ether was slowly converted to the *trans* form. However, prolonged heating of the product from the rearrangement of either the *cis* or *trans* ether under the conditions of the rearrangement produced no change as indicated by infrared spectra.

These results can be consistently interpreted by assuming a cyclic transition state whose geometry resembles that of the chair form of cyclohexane (Fig. 1) and applying the principles of conformational analysis. This brings the stereochemistry of the Claisen rearrangement into accord with that of the $S_Ni'$ process and shows that it occurs with high stereospecificity.

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(5) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

## New Synthesis of 4-Hydroxycoumarins[1]

*Sir:*

The principal known methods for the synthesis of 4-hydroxycoumarins are: (a) condensation of acetyl salicyloyl chlorides with acetoacetic, cyanoacetic, or malonic ester and conversion of the resulting 3-substituted 4-hydroxycoumarins to the corresponding 4-hydroxycoumarins;[2] (*b*) cyclization of acetyl methyl salicylates in the presence of an alkali metal;[3] (c) condensation of *o*-hydroxyacetophenones with diethyl carbonate in the presence of an alkali metal[4] and (d) cyclization of diaryl malonates in the presence of anhydrous aluminum chloride at about 180°.[5]

We have evolved a new and simple process for the synthesis of 4-hydroxycoumarins in which a phenol is treated with an equimolecular proportion of a malonic acid in the presence of a mixture of 2–3 moles each of anhydrous zinc chloride and phosphorus oxychloride as the condensing agent at temperatures preferably between 60–75°. The success of this reaction is dependent upon the specific condensing action of the mixture of anhydrous zinc chloride and phosphorus oxychloride[6] which are individually almost ineffective. Other condensing agents such as anhydrous aluminum chloride, stannic chloride, and ferric chloride and mixtures with phosphorus oxychloride are also ineffective. Lower alkyl esters of malonic acid or substituted malonic acid may also be used in the reaction, but usually

(1) V. R. Shah, J. L. Bose, and R. C. Shah (to Council of Scientific & Industrial Research, India), Indian Patent 62890, Jan. 20, 1958. Patents filed in U.S.A., U.K., Switzerland, and Germany.

(2) R. Anschütz, *Ber.*, **36**, 465 (1903).

(3) H. Pauly and K. Lockemann, *Ber.*, **48**, 28 (1915).

(4) J. Boyd, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 174 (1948).

(5) E. Ziegler and H. Junek, *Monatsh.*, **86**, 29 (1955).

(6) P. K. Grover, G. D. Shah, and R. C. Shah, *J. Chem. Soc.*, 3982 (1955).

poor yields of 4-hydroxycoumarins are then obtained.

The new method would appear to be of industrial significance for the production of 4-hydroxycoumarin which is a key intermediate for the synthesis of a number of leading anticoagulant drugs, like dicoumarol and tromexan, and also for the synthesis of modern anticoagulant rodenticides, warfarin and fumarin.

Small quantities of diaryl malonates were often isolated from the reaction product. The possibility of formation of diaryl malonates *in situ* and their further cyclization under the conditions of our method was, however, unlikely since no appreciable quantity of 4-hydroxycoumarins could be obtained when diaryl malonates such as diphenyl malonate were heated with a mixture of anhydrous zinc chloride and phosphorus oxychloride under the usual conditions of the new method.

We have condensed successfully by our method phenols such as phenol, thiophenol, *o*-, *m*-, and *p*-cresols, 2,5-xylene-1-ol, $\alpha$- and $\beta$-naphthols, and resorcinol, with malonic acid to give, in most cases, good yields of the corresponding known 4-hydroxycoumarins. Thymol and *p,p'*-dihydroxydiphenyl with malonic acid yielded respectively 5-methyl-8-isopropyl-4-hydroxycoumarin, m.p. 223–224°, (*Anal.* Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.45; H, 6.19) and 4,4'-dihydroxy-6,6'-dicoumarin m.p. > 360°, difficult to combust and characterized through the diacetyl derivative, m.p. 229–230° (*Anal.* Calcd. for $C_{22}H_{14}O_8$: C, 65.03; H, 3.47. Found: C, 65.50; H, 3.77). We have also successfully condensed substituted malonic acids, such as *n*-propyl-, *n*-butyl-, *n*-hexyl-, and phenylmalonic acid with phenol to give good yields of the corresponding known 3-substituted 4-hydroxycoumarins. *n*-Octylmalonic acid with phenol yielded 3-*n*-octyl-4-hydroxycoumarin, m.p. 143–144° (*Anal.* Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.76; H, 8.21).

The following preparation of 4-hydroxycoumarin is typical: A mixture of phenol (225 g.), malonic acid (247.5 g.), anhydrous zinc chloride (979 g.), and phosphorus oxychloride (657 ml.) was heated with stirring at 60–65° for 35 hr., cooled and decomposed with ice and water and allowed to stand. The resulting crude 4-hydroxycoumarin was collected, dissolved in 10% sodium carbonate and acidified. At about the neutral point some oily by-product separated out and was removed. Acidification of the remaining solution gave 4-hydroxycoumarin of m.p. 201–203° in 64% yield. On recrystallization from water or dilute alcohol pure 4-hydroxycoumarin of m.p. 209–210° was obtained.

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## Convenient Method for Splitting Diethyl Ether

*Sir:*

During the course of investigation of methods for the preparation of lanthanon iodides in which we were attempting to use diethyl ether as a solvent we discovered an unusual reaction. Anhydrous hydrogen iodide reacts immediately with diethyl ether at room temperature to produce ethyl alcohol and ethyl iodide.

$$C_2H_5OC_2H_5 + HI \rightleftharpoons C_2H_5I + C_2H_5OH$$

A two layer system is obtained which can be separated by means of a separatory funnel. Undoubtedly hydrogen iodide reacts further with some of the ethyl alcohol to produce more ethyl iodide and some water.

Though we have not conducted a detailed investigation of this reaction it appears that it may be quite superior to the usual method of refluxing ethers with aqueous solutions of hydrogen iodide to split them. We have suggested that a student at another university study the general application of this reaction as a method for splitting ethers.

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