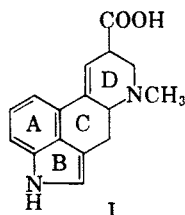


Communications TO THE EDITOR

New Synthetic Approach to Benzo[f]quinolines and Dihydrolysergic Acid

Sir:

The elegant total synthesis¹ of lysergic acid (I) and syntheses of the corresponding dihydro compound² and unsaturated ergolines³⁻⁵ have been accomplished by various schemes which, with one recent exception,⁶ were based upon the general concept of ring D closure after construction of a suitable ABC tricyclic compound¹⁻⁴ or substituted AC (naphthalene) system.^{4,5}



We wish to report now a series of reactions, differing in principle from these methods, in which ring C and then finally ring B of a dihydrolysergic acid precursor are formed after establishing rings A and D. The present approach involves some methods which although not unprecedented, are novel inasmuch as they have not been applied until now to elaboration of this or any other type of complex polycyclic compound. These methods include: (1) preparation of 5-phenyl-6-methyl-2-pyridones, (2) means for conversion of the methyl group in such pyridones (II) to the pyruvic acid side chain (III) required for cyclization to a benzo[f]quinoline (IV), and (3) reduction of α -chlorobenzoquinolines (IV. X = Cl) to 1,4-dihydro compounds (VI) which may be rearomatized to the dechlorinated compounds (IV. X = H).

(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).

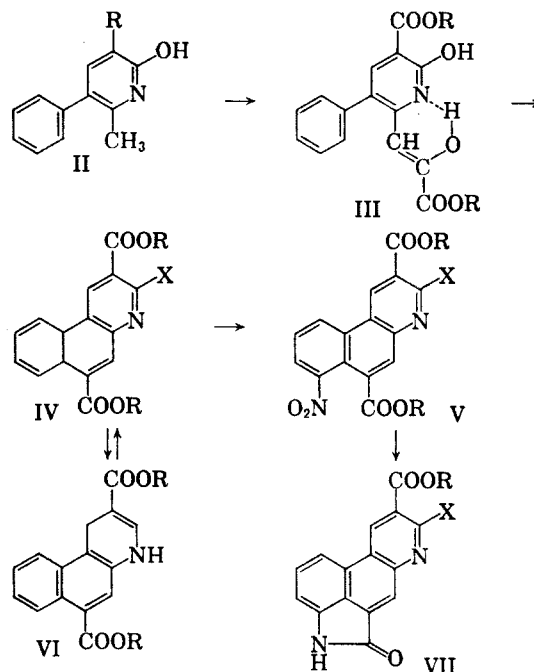
(2) F. C. Uhle and W. A. Jacobs, *J. Org. Chem.*, **10**, 76 (1945).

(3) A. Stoll and T. Petrzilka, *Helv. Chim. Acta*, **36**, 1125 (1953).

(4) F. R. Atherton, F. Bergel, A. Cohen, B. Heath-Brown, and A. H. Rees, *Chem. & Ind. (London)*, 1151 (1953).

(5) W. A. Jacobs and R. G. Gould, *J. Biol. Chem.*, **126**, 67 (1938); **130**, 399 (1939).

(6) H. Plieninger, M. Schach von Wittenau, and B. Kiefer, *Ber.* **91**, 2095 (1958), have prepared a compound of this type by Pschorr ring closure between rings A and D.



Compound II (R = CN) (m.p. 296° dec. *Anal.* Found: C, 74.25; H, 4.93; N, 12.9) was obtained by condensation of 1-hydroxymethylene-1-phenylpropanone⁷ with cyanoacetamide, and was hydrolyzed to the acid II (R = COOH) (m.p. 265° dec. *Anal.* Found: C, 68.17; H, 4.89; N, 6.3). Treatment of this acid with oxalyl chloride in the presence of phosphorus oxychloride gave, after treatment with water, a partly-complexed product consisting essentially of the chelated enolic acid III (R = H) (dec. from 190°; green ferric chloride test), which was identified by the corresponding ethyl ester, III (R = C₂H₅) (m.p. 170°. *Anal.* Found: C, 63.88; H, 5.44; N, 4.05; deep green ferric chloride test; infrared in Nujol, 5.79, 5.94, 6.12, and 6.21 μ). Cyclization of III (R = H) with concd. sulfuric acid gave IV (R = H; X = OH) (m.p. > 360°. *Anal.* Found: N, 5.04), again better characterized as the ethyl ester, IV (R = C₂H₅; X = OH) (m.p. 211°; *Anal.* Found: C, 67.03; H, 5.04; N, 4.17; infrared in Nujol: 5.80, 5.88, 6.01, and 6.16 μ). The tricyclic structure for IV was confirmed by absence of both the ferric chloride test and the infrared mono-substituted benzene peak (700 cm.⁻¹) shown by III, and by the enhanced ultraviolet absorption at long wave lengths. Compound IV (R = H; X = OH) was converted to the corresponding chloro-acid chloride (X = Cl) with phosphorus pentachloride in phosphorus oxychloride, and thence by treatment with methanol to IV (R = CH₃; X = Cl) (m.p.

(7) G. N. Walker, *J. Org. Chem.*, **23**, 34 (1958).

188°; *Anal.* Found: C, 61.99; H, 3.69; N, 4.44; Cl, 1.09; $\lambda_{\text{max}}^{\text{Nujol}}$ 5.79 μ). Although nitration of this chloroester gave V (R = CH₃; X = Cl) (m.p. 231° dec. *Anal.* Found: C, 54.9; H, 3.2; N, 7.4; Cl, 9.6) which could be converted *via* palladium-catalyzed reduction to VII (R = CH₃; X = Cl) (m.p. 306° dec. *Anal.* Found: C, 61.47; H, 3.03; N, 9.15; Cl, 11.6), dechlorination of these compounds was impracticable and it was therefore necessary to proceed as follows. Reduction of IV (R = CH₃; X = Cl) with sodium borohydride removed the chlorine and reduced the benzo[f]-quinoline to corresponding 1,4-dihydroderivate, VI (R = CH₃) (m.p. 218° dec. *Anal.* Found: 68.9; H, 5.08; N, 4.74; infrared in Nujol, 3.05, 5.83 and 6.03 μ) which was aromatized with palladium-charcoal in xylene to IV (R = CH₃; X = H) (m.p. 150°. *Anal.* Found: C, 69.17; H, 4.50; N, 4.89; infrared, 5.75 and 5.80 μ). Nitration of the latter compound in analogy with Jacobs' experiments⁵ on similarly constituted compounds, led almost exclusively to V (R = CH₃; X = H) (m.p. 204°. *Anal.* Found: C, 59.86; H, 3.66; N, 8.5), and subsequent reduction and lactam ring closure, using palladium-charcoal in acetic acid,⁸ afforded compound VII (R = CH₃; X = H) (*Anal.* Found: C, 69.04; H, 3.68; N, 10.06), identical, in respect to melting point (302°), mixed melting point (undepressed), infrared spectrum (identical, with ester and lactam peaks at 5.80 and 5.84 μ , respectively), and ultraviolet spectrum with an authentic specimen^{2,9} of that compound. Hydrolysis gave the corresponding acid,² VII (R = X = H) (m.p. > 360°. *Anal.* Found: C, 68.0; H, 3.2; N, 10.6) which has been converted² to dihydrolysergic acid.

A full account of this work and related studies will appear in the future. We wish to express our sincere appreciation to Mr. Louis Dorfmann and his entire staff for microanalytical and spectral data, and to Dr. E. Schlittler for unfailing encouragement.

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(8) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955).

(9) We are greatly indebted to Dr. Frederick C. Uhle of Harvard Medical School for a generous sample of this compound. The ultraviolet spectrum has been published (*cf.* ref. 6).

Substitution Reactions of Derivatives of 2-Anthrol at the 1- and 3-Positions¹

Sir:

Discrepancies contained in recent work^{2,3} on the Fries rearrangement of 2-anthryl acetate (I)

(1) This study was supported, in part, by Grant G-7640 from the National Science Foundation and by a grant from the Research Corp.

prompt us to publish briefly the preliminary results obtained in our independent study⁴ of this reaction and of the formylation of 2-methoxyanthracene (II). Thus, both the hydroxyketone (III), m.p. 218–219° dec., obtained³ in 83% yield from the high-temperature rearrangement of I, and the hydroxyketone (IV), m.p. 112–113°, obtained² in unspecified low yield from rearrangement in nitrobenzene at room temperature, are reported to be methyl 2-hydroxy-1-anthryl ketone, an apparently rigorous proof of structure having been offered in each case.

Both III and IV have been obtained independently in this Laboratory⁴ under roughly similar conditions but in greatly different yields. Thus, the Fries rearrangement of I in nitrobenzene (0.5 hr. at room temperature) produced IV, m.p. 115–116.5°, in yields of about 60%, whereas the high temperature reaction (1.5 hr. at 140°, no solvent) produced III, m.p. 226–227° dec., in yields of 3–13%. Mixture melting points of the methyl ethers and acetates of III and IV have shown that they are different isomers, and repeated attempts to obtain III in higher yield have failed.

The proof of structure described by Shah and Sethna² was independently employed by us,⁴ and their assignment of the 2,1 orientation to IV is confirmed. The 2,3 orientation is assigned to III, since infrared spectra⁵ revealed strong intramolecular hydrogen bonding. The Dakin oxidation of III to 1,2-anthradiol, which Jain and Seshadri³ advanced as proof of structure, conceivably could be explained by contamination with IV, which also is formed in low yield from the high-temperature Fries rearrangement.

Formylation of II with *N*-methylformanilide and phosphorus oxychloride has afforded a mixture (about 70% yield) of approximately equal amounts of two difficultly separable methoxyaldehydes, m.p. 192–194.5° and 116–117°. Separate demethylations produced, respectively, the known 2-hydroxy-1-anthraldehyde³ (V), m.p. and mixed m.p. 166.5–167°, and a new hydroxyaldehyde (VI), m.p. 228–231° dec., most probably the 3,2 isomer since infrared spectra⁵ revealed strong intramolecular hydrogen bonding. The 1,2 orientation of both IV and V was confirmed by proton magnetic resonance spectra.⁶

The above work apparently represents the first two examples of the formation of comparable

(2) N. H. Shah and S. Sethna, *J. Org. Chem.*, **24**, 1783 (1959).

(3) A. C. Jain and T. R. Seshadri, *J. Sci. Industr. Res.*, **15B**, 61 (1956).

(4) J. L. Ferrari and I. M. Hunsberger, Abstracts of Papers, 136th Meeting of the American Chemical Society, Sept. 1959, p. 21 P.

(5) Determined at the University of Illinois through the courtesy of Dr. H. S. Gutowsky.

(6) Determined at the University of Illinois through the courtesy of Dr. H. S. Gutowsky and Dr. A. L. Porte.