and gave analytical data: C, 38.25; H, 6.22; N, 11.31; Cl, 12.52 (Calcd. for $C_{27}H_{49}O_7O_{17}\cdot 3HCl$: C, 38.01; H, 6.14; N, 11.49; Cl, 12.47).

When assayed with *K. pneumoniae* in a broth dilution test,[5] the anhydrous mannosidostreptomycin had a potency of *circa* 210 units/mg.[6]

Additional information on the properties and activities of these crystalline hydrochlorides will be published at a later date.

We wish to express our appreciation to Dr. R. Donovick, Mr. R. Blue, and Mr. D. Lapedes for the bio-assays, Mr. F. Russo-Alesi for the countercurrent distributions, and Mr. J. Alicino for the micro-analysis.

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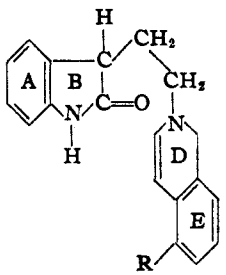
THE SYNTHESIS OF KETOYOBYRINE

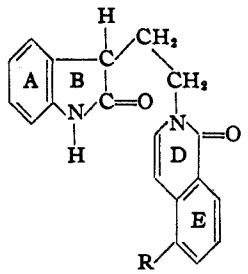
Sir:

For several years we have been investigating the possibility of synthesizing the basic ring structure of yohimbine by ring closure of isoquinolylethyl oxindoles of the type represented by formula (I).[1] The introduction of the double bond in ring D presented numerous difficulties because of the ease with which compounds of the type (I) (as well as the yohimbine molecule itself) suffer cleavage at the nitrogen atom of ring D. Moreover, we have pointed out[1] that 1,2-dihydroisoquinolines like (I) are virtually unknown.

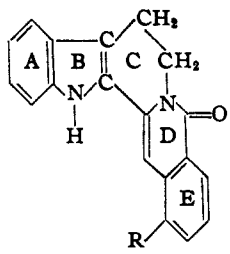
Accordingly, our efforts were later directed toward the preparation and ring closure of compounds of the type represented by formula (II)



(I) (R = CH_3 or H)



(II) (R = CH_3 or H)



(III) Ketoyobyrine (R = CH_3)

where the appropriate double bond of ring D could be introduced without difficulty. Ring closure of such a compound would lead to compounds of the structure (III), which type of structure has recently been proposed for ketoyobyrine, on the basis of an exhaustive study of its chemistry[2a] and likewise on the basis of a comparison of its absorption spectrum with that of rutaecarpine.[2b]

Pending more complete presentation of our various syntheses of the type of structure represented by (III), we wish to record our synthetic confirmation of this proposed structure for ketoyobyrine.

6-Methylhomophthalic acid, m. p. 196°, was prepared from *o*-tolylacetic acid[3] by conversion *via* the Arndt–Eistert reaction into *o*-tolylpropionic acid, which was then treated according to the method of Mercer and Robertson.[4] Condensation with tryptamine yielded N-(β-indolylethyl)-6-methylhomophthalimide, m. p. 228°. Conversion of the latter into the corresponding homophthalamic acid,[5] m. p. of picrate 147°, methylation of the acid with diazomethane, m. p. of methyl ester 222°, dec., followed by ring closure with phosphorus oxychloride, yielded ketoyobyrine, m. p. 316–318°, dec.

Anal. Calcd. for $C_{20}H_{16}ON_2$: C, 79.98; H, 5.37; N, 9.32. Found: C, 79.43; H, 5.55; N, 9.24. Comparisons of the ultraviolet absorption spectrum of synthetic ketoyobyrine with that of the product of natural origin showed the two to be identical. Absorption maxima for synthetic material: at 385, 366 and 340 mμ, log ε 4.40, 4.51 and 4.52, respectively.

(1) Julian, Magnani, Pikl and Karpel, THIS JOURNAL, **70**, 174 (1948).

(2) (a) Woodward and Witkop, THIS JOURNAL, **70**, 2409 (1948); (b) Raymond-Hamet, *Compt. rend.*, **226**, 137 (1948).

(3) Julian, Karpel, Magnani and Meyer, THIS JOURNAL, **70**, 180 (1948).

(4) Mercer and Robertson, *J. Chem. Soc.*, 288 (1936).

(5) *Cf.* Haworth, Perkin and Pink, *J. Chem. Soc.*, 1709 (1925).

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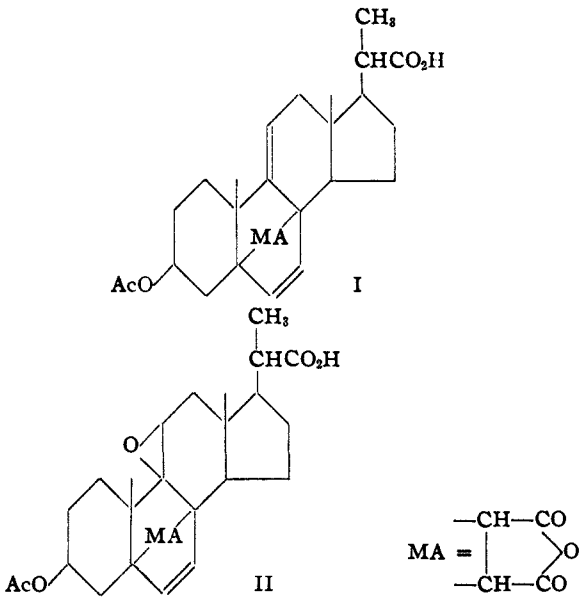
THE OZONIZATION OF THE MALEIC ANHYDRIDE ADDUCT OF DEHYDROERGOSTERYL ACETATE

Sir:

A recent publication of Bergmann and Stevens[1] describes the preparation of the maleic anhydride adduct of 3(β)-acetoxy-9,11-oxidobisnor-5,7-choladienic acid (II) by the ozonization of 9,11-oxidoergosteryl acetate–maleic anhydride adduct. For some time previous a study of analogous reactions has been under way in our laboratories and we now wish to report the preparation of the maleic anhydride adduct of 3(β)-acetoxybisnor-5,7,9-cholatrienic acid (I) by the selective ozonization of 9,11-dehydroergosteryl acetate–maleic anhydride adduct (III).

A solution of the dehydroadduct (III) in methylene chloride was treated with two equiva-

(1) Bergmann and Stevens, *J. Org. Chem.*, **13**, 10 (1948).



lents of ozone at −30°. The methylene chloride was replaced with glacial acetic acid and the ozonide decomposed with zinc dust. After separation of the zinc, the acetic acid solution was treated with chromic acid in acetic acid at 20° for three hours and the excess chromic acid was decomposed with sodium bisulfite solution. The reaction mixture was poured into water and the precipitate of the bisnor acid (I), m.p. 226–237°, was separated by filtration. For analysis, the acid (I) was crystallized from ether–hexane, m.p. 240–243°. The yield of pure acid (I) was 55% of the theoretical.

Anal. Calcd, for $C_{28}H_{34}O_7$: C, 69.69; H, 7.10; Found: C, 69.73; H, 7.10.

Treatment of the acid (I) with diazomethane in methylene chloride gave the maleic anhydride adduct of methyl 3(β)-acetoxybisnor-5,7,9-cholatrienate (IV), m.p. 246–248°. *Anal.* Calcd. for $C_{29}H_{36}O_7$: C, 70.14; H, 7.31. Found: C, 69.98; H, 7.48. After saponification, methylation with diazomethane, and acetylation with acetic anhydride, the trimethyl ester of the maleic acid adduct of 3(β)-acetoxybisnor-5,7,9-cholatrienic acid (V) was obtained, m.p. 193–195°. *Anal.* Calcd. for $C_{31}H_{42}O_8$: C, 68.61; H, 7.80. Found: C, 68.66; H, 7.65. The trimethyl ester of the maleic acid adduct of 3(β)-acetoxy-9,11-oxidobisnor-5,7-choladienic acid (VI) was prepared by treating the acetoxytrimethyl ester (V) with monoperphthalic acid. It was crystallized from ether, m.p. 208–209.5°. *Anal.* Calcd. for $C_{31}H_{42}O_9$: C, 66.64; H, 7.58. Found: C, 66.76; H, 7.64.

The 9,11-oxido compound was also prepared from the methyl ester of I by perphthalic acid treatment and had a melting point of 263–265° (block), which is in fair agreement with that reported for the methyl ester of II by Bergmann and Stevens.[1]

Details of this work, together with further conversions of compound I, will be published at a later date.

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RECEIVED JUNE 18, 1948

DEGRADATIVE STUDIES ON STREPTOMYCIN

Sir:

Degradation of dihydrostreptomycin with barium hydroxide under conditions which convert streptidine to streptamine[1] yielded an amorphous, antibiotically inactive product containing barium chloride. This substance was acetylated with pyridine and acetic anhydride to a crystalline compound (I), m. p. 261.5–262.5°, $[\alpha]^{23}D$ −84° (*c* 1, water).

Anal. Calcd. for $C_{16}H_{24}O_{12}N_3(CH_3C)(COCH_3)_{10}$: C, 50.92; H, 6.25; N, 4.57; O-acetyl, 7.61 cc. of 0.1 *N* NaOH per 100 mg. CH_3-C, 32.3: mol. wt., 919.9. Found: C, 50.64; H, 6.17; N, 4.47; O-acetyl,[2] 7.37 cc.; CH_3-C,[3] 32.3; mol. wt., 920 (Rast).

Methanolysis of I with subsequent reacetylation yielded hexaacetylstreptamine,[1,4] transition point[1] 250°, m. p. 341–345°, N, 6.61% (calcd. 6.50), and methyl pentaacetyldihydro-α-L-streptobiosamide,[5–8] m. p. 194–195°, unchanged on admixture with a specimen prepared from dihydrostreptomycin trihydrochloride, $[\alpha]^{23}D$ −120° (*c* 0.5, chloroform). I is designated decaacetyldideguanyldihydrostreptomycin. It was found to be readily soluble in methanol, water and hot ethanol, sparingly so in chloroform, ethyl acetate and ethanol, and insoluble in benzene and ethyl ether.

Aqueous solutions of N,N,N-tetraacetyldideguanyldihydrostreptomycin (II), N^1,N^3-diacetylstreptamine (III) and N-acetyldihydro-α-L-streptobiosaminide (IV) were prepared by partial deacetylation of the aforementioned acetyl derivatives with 0.05 *N* sodium hydroxide in water–dioxane. These N-acetates were subjected to oxidation with a large excess of buffered periodate at *p*H 4.9 and 20.0° and showed the following

(1) R. L. Peck, C. E. Hoffhine, Jr., Elizabeth W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **68**, 776 (1946).

(2) M. L. Wolfrom, M. Konigsberg and S. Soltzberg, *ibid.*, **58**, 490 (1936).

(3) R. U. Lemieux and C. B. Purves, *Can. J. Research*, **B25**, 485 (1947).

(4) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, J. S. Meek, P. S. Skell, W. A. Strong, J. T. Alberi, Q. R. Bartz, S. B. Binkley, H. M. Crooks, I. R. Hooper and Mildred C. Rebstock, *Science*, **103**, 53 (1946).

(5) Q. R. Bartz, J. Controulis, H. M. Crooks, Jr., and Mildred C. Rebstock, *ibid.*, 2163 (1946).

(6) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn and K. Folkers, THIS JOURNAL, **68**, 2557 (1946).

(7) I. R. Hooper, L. H. Klemm, W. J. Polglase and M. L. Wolfrom, *ibid.*, **68**, 2120 (1946); **69**, 1052 (1947).

(8) J. Fried and O. Wintersteiner, *ibid.*, **69**, 79 (1947).