

*Anal.* Found: C, 63.25; H, 7.34; Cl, 8.44, prepared from the corresponding 21-mesylate with lithium chloride in acetic acid was inactive in the liver glycogen assay at 10 times the minimum effective dose of cortisone acetate.

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### A CONTRIBUTION TO THE CHEMISTRY OF STEROID 17,21-OXIDES

Sir:

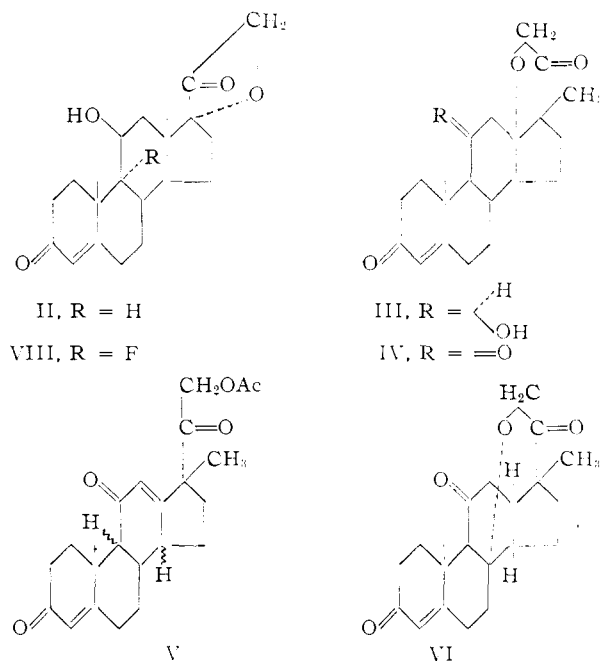
Treatment of 11 $\beta$ ,17 $\alpha$ -dihydroxy-21-iodo-4-pregnene-3,20-dione<sup>1</sup> (I) with silver dihydrogen phosphate afforded, in addition to the steroid 21-phosphate, a water-insoluble by-product, m.p. 237–243° (dec.),  $[\alpha]_D^{25} +246^\circ$ ;  $\lambda_{max}^{MeOH}$  240.5  $\mu$  ( $\epsilon = 16,300$ );  $\lambda_{max}^{Chf}$  2.72  $\mu$ , 2.8–2.88  $\mu$  (OH), 5.54  $\mu$  (20-ketone), 6.0  $\mu$  (3-ketone), 6.15  $\mu$  ( $\Delta^4$ -double bond);  $\lambda_{max}^{Ni}$  2.95  $\mu$ , 5.55  $\mu$ , 6.0–6.05  $\mu$ , sh 6.12  $\mu$ ; Found: C, 73.49; H, 8.15. The mobility of the compound by paper strip chromatography is nearly identical with that of 11 $\beta$ -hydroxyprogesterone. The product was formulated as 17 $\alpha$ ,21-epoxy-11 $\beta$ -hydroxy- $\Delta^4$ -pregnene-3,20-dione (II). The same structure has been assigned<sup>2</sup> to a different product VII (m.p. 198.5–201°;  $[\alpha]_D^{25} +69^\circ$ ;  $\lambda_{max}^{Chf}$  5.72  $\mu$ , 6.02  $\mu$ , 6.16  $\mu$ ) which Allen, *et al.*, obtained by treating 17,21-epoxy-11 $\beta$ -hydroxy- $\Delta^4$ -pregnene-3,20-dione 3,20-bisethylene ketal with aqueous methanolic sulfuric acid. However, the infrared spectrum of VII is inconsistent with structure II, since 3-oxetanones generally absorb at 5.55  $\mu$ .<sup>3</sup> The properties of VII are, however, in fair agreement with a substance III (m.p. 201–206°;  $[\alpha]_D^{25} +52^\circ$ ;  $\lambda_{max}^{MeOH}$  240  $m\mu$  ( $\epsilon = 16,400$ );  $\lambda_{max}^{Ni}$  2.79  $\mu$ , 2.95  $\mu$ , 5.72  $\mu$ , 6.03  $\mu$ , 6.17  $\mu$ ; Found: C, 73.37; H, 7.96) which resulted from treating II with methanolic sulfuric acid. III was shown to be 13 $\alpha$ ,21-epoxy-11 $\beta$ -hydroxy-17 $\beta$ -methyl-18-nor-17 $\alpha$ - $\Delta^4$ -pregnene-3,20-dione by relating the position of the oxide-bridge to the hydroxyl function at C-11. Oxidation of III with chromium trioxide-pyridine<sup>4</sup> gave the 11-ketone IV (m.p. 157–158°;  $\lambda_{max}^{MeOH}$  236  $m\mu$  ( $\epsilon = 15,200$ );  $\lambda_{max}^{Ni}$  5.70  $\mu$ , 5.83  $\mu$ , 5.97  $\mu$ , 6.16  $\mu$  (no OH);  $\lambda_{max}^{Chf}$  5.70  $\mu$ , 5.82  $\mu$ , 5.99  $\mu$ , 6.16  $\mu$ ; Found: C, 73.49; H, 7.56). When the latter was refluxed with pyridine and acetic anhydride, a large increment in the extinction at 238  $m\mu$  occurred, demonstrating the formation of a second  $\alpha,\beta$ -unsaturated ketone group. Since the product (V) (m.p. 185–186°;  $\lambda_{max}^{CH_3OH}$  238  $m\mu$  ( $\epsilon = 26,200$ );  $\lambda_{max}^{Ni}$  5.72  $\mu$  and 5.83  $\mu$  (21-acetate, 20-ketone), 6.02  $\mu$  and 6.18  $\mu$  (3-

keto- $\Delta^4$  and 11-keto- $\Delta^{12}$ -systems), 8.08  $\mu$  (acetate); Found: C, 71.69; H, 7.17) in contrast to III, gave a positive tetrazolium test, it is formulated as 21-acetoxy-17 $\beta$ -methyl-18-nor-9 $\zeta$ ,14 $\zeta$ -17 $\alpha$ - $\Delta^4$ ,12-pregnadiene-3,11,20-trione.

Structure VI, an unlikely alternative for the methanol-sulfuric acid product on mechanistic grounds, is ruled out further by the u.v. spectrum of V, and because the reaction sequel I  $\rightarrow$  V can be paralleled in the 9 $\alpha$ -fluorohydrocortisone series.

The conversion of II to III resembles the conversion of 3 $\beta$ -acetoxy-16 $\alpha$ ,17 $\alpha$ -epoxy- $\Delta^5$ -pregnene-20-one to 3 $\beta$ -acetoxy-16 $\beta$ -formyloxy-17 $\beta$ -methyl-18-nor-17 $\alpha$ - $\Delta^5$ ,13-pregnadiene-20-one with formic acid in the presence of sulfuric acid.<sup>5</sup> The stabilization of the intermediate carbonium ion at C-13 by ring closure rather than by formation of an olefin had, however, not been previously described.

We have also prepared 17 $\alpha$ ,21-epoxy-9 $\alpha$ -fluoro-11 $\beta$ -hydroxy- $\Delta^4$ -pregnene-3,20-dione (VIII), m.p. 236° (dec.),  $[\alpha]_D^{25} +192^\circ$ ;  $\lambda_{max}^{MeOH}$  237  $m\mu$  ( $\epsilon = 16,900$ );  $\lambda_{max}^{Ni}$  3.0  $\mu$ , 5.5  $\mu$ , 6.07  $\mu$ , sh 6.17  $\mu$ ; Found: C, 69.18; H, 7.47.<sup>6</sup> It is of considerable interest that whereas compounds II–V are essentially inactive<sup>7</sup> in the systemic granuloma inhibition and liver glycogen tests, VIII exhibited anti-inflammatory activity of the same order of magnitude as hydrocortisone in these tests.<sup>7</sup>



CONTRIBUTION OF THE  
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(1) C. T. Bergstrom, U. S. Patent 2,684,908, July 27, 1954.

(2) W. S. Allen, S. Bernstein, M. Heller and R. Littell, *THIS JOURNAL*, **77**, 4784 (1955). Dr. Bernstein, whom we advised of our results, informed us that he, too, has come to question the correctness of his structural assignment and that he is pursuing the matter himself.

(3) G. B. Hoey, D. O. Dean and C. T. Lester, *ibid.*, **77**, 391 (1955); B. L. Murr, G. B. Hoey and C. T. Lester, *ibid.*, **77**, 4430 (1955).

(4) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(5) K. Heusler and A. Wetstein, *Ber.*, **87**, 1301 (1954).

(6) The 11-keto-analog of II was first isolated by Dr. R. E. Beyler and Miss F. Hoffman in another connection and independently assigned a 17,21-oxide structure.

(7) We are very much indebted to Dr. C. A. Winter and Dr. C. C. Porter for the animal assays.