SYNTHESIS OF 11-KETO STEROIDS

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epinochrome; however, adrenochrome under non-reductive conditions as described above remains unchanged.

5,6-Dihydroxy-N-methylindole was first obtained by Duliere and Raper[5] by intramolecular oxidation-reduction in the presence of sulfur dioxide of the red solution of enzymatically oxidized N-methyltyrosine (or from a red solution resulting from oxidation of epinine with silver oxide). They isolated it as the dimethyl ether which was subsequently identified by Burton[6] who had observed the same rearrangement in the presence of alkali and who also prepared the diacetate. 5,6-Dihydroxy-N-methylindole itself was first isolated by partial reduction of adrenochrome,[3] after Bergel and Morrison[7] had demonstrated its formation by reduction of iodoadrenochrome, but isolated its diacetate only.

In a communication that has just come to our attention, Harley-Mason and Bu'Lock[8] report that zinc ion catalyses the decolorization of the red solution from the oxidation of epinine or of its carboxy derivative. Our observations on the spontaneous rearrangement of pure epinochrome in the solid state and on the catalytic rearrangement of its solutions over palladium emphasize the facility with which this oxidation–reduction occurs under a variety of conditions.

(5) Duliere and Raper, *Biochem. J.*, **24**, 239 (1930).
(6) Burton, *J. Chem. Soc.*, 546 (1932).
(7) Bergel and Morrison, *ibid.*, 48 (1943).
(8) Harley-Mason and Bu'Lock, *Nature*, **166**, 1036 (1950).

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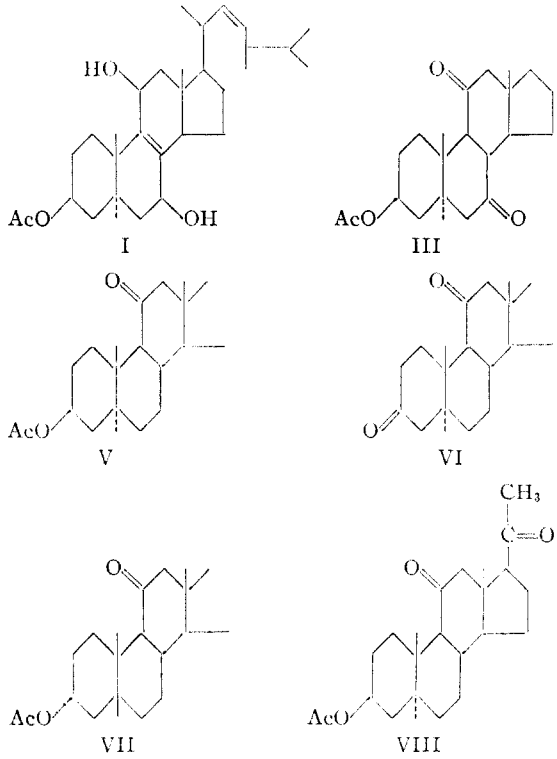
SYNTHESIS OF 11-KETO STEROIDS

Sir:

We wish to report a practical and general scheme for the synthesis of 11-keto steroids from $\Delta^{5,6}$ steroids, devoid of functional groups in ring C, which has been successfully applied to ergosterol, stigmasterol, diosgenin and to certain of their degradation products.

Starting with ergosterol acetate, the derived known $\Delta^{7,9(11),22}$ ergostatrien-3β-ol acetate (ergosteryl-D-acetate)[1] is treated with one equivalent of perbenzoic acid to give a crystalline epoxide; m.p. 202–205°; α_D −35° ($CHCl_3$); found: C, 79.01; H, 10.50. Hydrolytic rearrangement of the epoxide yielded $\Delta^{8,22}$-ergostadien-3β,7,11-triol 3-acetate (I) m.p. 248–252°; α_D +85° ($CHCl_3$); found: C, 76.04; H, 10.24; active hydrogens (Zerewitinoff determination) 2.1. Chromic acid oxidation of the triol monoacetate afforded $\Delta^{8,22}$-ergostadien-3β-ol-7,11-dione acetate, II; m.p. 135–136°; α_D +18.5° ($CHCl_3$); $\lambda_{max.}$ 266 mμ, E_m 9360 (isoöctane); $\lambda_{max.}$ 270 mμ, E_m 8700 (alcohol); found: C, 76.91; H, 9.58. The dienedione on reduction with zinc and acetic acid was converted into Δ^{22}-ergostene-3β-ol-7,11-dione (III); m.p. 197–200°; α_D −30° ($CHCl_3$); found: C, 76.68; H, 7.59. Modified Wolff–Kishner reduction[2] of the latter provided a monoketone, Δ^{22}-ergostene-3β-ol-11-one (IV); m.p. 173–174°; α_D +26.6° ($CHCl_3$); found: C, 81.72; H, 11.29. Ozonolysis of the acetylated ketoergostene, and esterification of the acidic side chain degradation product yielded an ester which proved to be methyl 3β-hydroxy-11-keto-bisnor*allo*cholanate acetate (V); m.p. 191–194°; α_D +24° ($CHCl_3$); found: 71.89; H, 9.15. The structure of the degradation product was unequivocally established by relating it to methyl 3,11-diketo-bisnor*allo*cholanate (VI) (m.p. 201–204°; α_D +63°; found: C, 74.18; H, 9.20) prepared by an independent synthesis from the known methyl 3-acetoxy-11-keto-bisnorcholanate (VII).[3]



Methyl Δ^5-3-hydroxy-bisnorcholenate acetate, obtained from either stigmasterol or cholesterol, was converted into methyl $\Delta^{5,7}$-3-hydroxybisnorcholadienate acetate[4] which was transformed into methyl 3-hydroxy-7,11-diketo-bisnor*allo*cholanate acetate (m.p. 228,–230°; α_D − 16° ($CHCl_3$); found: C, 69.30; H, 8.46) in the manner described for the ergosterol series. Wolff–Kishner reduction of the latter and subsequent esterification of the reduction product afforded V identical with that prepared from ergosterol.

Diosgenin acetate was converted to the Δ^7-dehydrodiosgenin acetate[5] which by the same sequence

(1) Windaus and Brunken, *Ann.*, **460**, 225 (1928); Heilbron and Sexton, *J. Chem. Soc.*, 921 (1929); Windaus and Luttringhaus, *Ann.*, **481**, 119 (1930); Heilbron, Johnstone and Spring, *J. Chem. Soc.*, 2248 (1929).
(2) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).
(3) Sarett, *J. Biol. Chem.*, **162**, 601 (1946).
(4) Prepared previously by Bergmann and Stevens, *J. Org. Chem.*, **13**, 10 (1948).
(5) Since completion of this work, the preparation of this compound was reported by Rosenkranz, Romo and Berlin, *J. Org. Chem.*, **16**, 290 (1951). The physical constants of the two products are essentially the same.

of reactions yielded spirostan-3β-ol-11-one acetate (11-ketotigogenin acetate), m.p. 224–229°; α_D −39.4° ($CHCl_3$); found: C, 73.60; H, 9.08. Pyrolysis of the keto genin, oxidation of the pseudogenin and alkaline treatment of the latter provided Δ^{16}-*allo*pregnene-3β-ol-11,20-dione acetate, m.p. 183–185°; α_D +64.5° ($CHCl_3$); $\lambda_{max.}$ 234.5 mμ, E_m 9050 (alcohol); found: C, 73.93; H, 8.83. By hydrogenation of the latter, *allo*pregnane-3β-ol-11,20-dione acetate (m.p. 141–143° (VIII); α_D +88° ($CHCl_3$); found: C, 73.79; H, 8.90) was obtained which was identical with the product obtained by the Barbier-Wieland degradation of VII.

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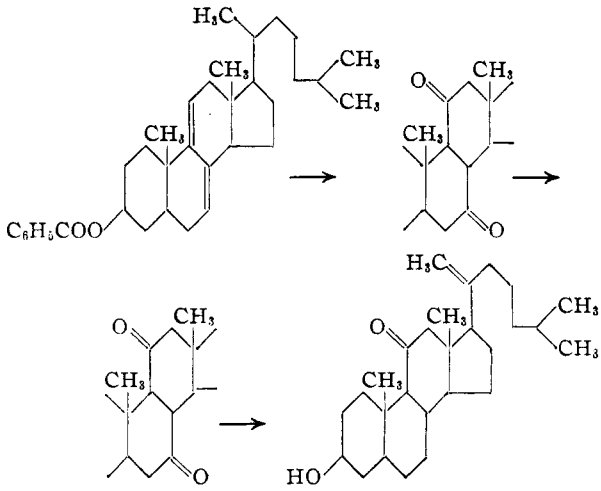
11-KETOLITHOCHOLIC ACID AND 11-KETOCHOLESTANOL FROM THE $\Delta^{7,9(11)}$-DIENES

Sir:

A practical route from cholic acid to methyl 3α,7α-diacetoxy-12-keto-$\Delta^{9(11)}$-cholenate and methyl 12-keto-$\Delta^{7,9(11)}$-lithocholadienate has been reported.[1] Dr. S. Rajagopalan found that both esters are converted in good yield by Wolff–Kishner reduction into $\Delta^{7,9(11)}$-lithocholadienic acid (m.p. 201°, dec., $[\alpha]_D$ +121° Di; methyl ester, m.p. 120°, $[\alpha]_D^{22}$ +119° Di, $\lambda_{max.}^{EtOH}$ 244.5 mμ (log ϵ 4.2)), which forms a methyl ester acetate m.p. 149–150°, $[\alpha]_D$ +123° Di, $\lambda_{max.}^{EtOH}$ 244.5 (log ϵ 4.2) ($C_{27}H_{40}O_4$: C, 75.67; H, 9.64; found: C, 75.56; H, 9.63). We have now found that oxidation of this ester acetate with sodium dichromate dihydrate in acetic acid yields methyl 3α-acetoxy-7,8-oxido-$\Delta^{9(11)}$-cholenate (m.p. 185°, $[\alpha]_D$ +22° Di; $C_{27}H_{40}O_5$: C, 72.94; H, 9.07; found, C, 73.24; H, 9.29) and methyl 3α-acetoxy-7,11-diketo-Δ^8-cholenate (m.p. 115°, $[\alpha]_D$ +36° Di, $\lambda_{max.}^{EtOH}$ 271 mμ, log ϵ 3.85; $C_{27}H_{38}O_6$: C, 70.72; H, 8.35; found: C, 70.65; H, 8.38). The unsaturated oxide, formed also by perbenzoic acid oxidation, was isomerized by zinc and acetic acid, aqueous dioxane at 160°, or methanolic potassium hydroxide (re-esterification) to methyl 3α-acetoxy-7-keto-Δ^8-cholenate (m.p. 182.5° $[\alpha]_D$ −15° Di, $\lambda_{max.}^{EtOH}$ 254 mμ, log ϵ 4.04; found: C, 72.88; H, 9.13). Reduction of the unsaturated diketone with zinc and acetic acid afforded methyl 3α-acetoxy-7,11-diketocholenate (m.p. 162°, $[\alpha]_D$ +25° Di, $C_{27}H_{40}O_6$: C, 70.40; H, 8.75; found: C, 70.28; H, 8.94), which on Wolff–Kishner reduction followed by esterification, acetylation, and chromatography gave both methyl lithocholate acetate (m.p. 134°, $[\alpha]_D$ +44° An, no depression with authentic sample[2]) and methyl 3α-acetoxy-11-ketocholanate[3] (m.p. 131°, $[\alpha]_D$ +67° An, $C_{27}H_{42}O_5$: C, 72.61; H 9.48; found: C, 72.60, H, 9.69, no depression with authentic sample.

Δ^7-Cholestenol (m.p. 123–125°), available from cholesterol by Raney-nickel hydrogenation of the 7-dehydro derivative, was converted by dehydrogenation with mercuric acetate and benzoylation into $\Delta^{7,(911)}$-cholestadienyl benzoate, m.p. 134°, $[\alpha]_D$ +32° Di, $\lambda_{max.}^{EtOH}$ 243 mμ (log ϵ 4.0) (free alcohol), $C_{34}H_{48}O_2$: C, 83.55; H, 9.90; found: C, 83.81; H, 10.05). Oxidation of this diene with sodium dichromate in acetic acid-benzene at 25° yielded, after chromatography, Δ^8-cholestene-3β-ol-7,11-dione-3-benzoate (m.p. 150°, $[\alpha]_D$ about +6° Di, $\lambda_{max.}^{EtOH}$ 268 mμ, log ϵ 3.8, $\lambda_{max.}^{Chf}$ 5.95 μ, $C_{34}H_{46}O_4$: C, 78.72; H, 8.94; found: C, 78.77; H, 9.19); a second oxidation product is formed but



has not been fully characterized. Reduction of the enedione with zinc dust and acetic acid gave cholestane-3β-ol-7,11-dione-3-benzoate, m.p. 200°, $[\alpha]_D$ +3° Di, $C_{34}H_{48}O_4$: C, 78.42; H, 9.29; found: C, 78.37; H, 9.71. Alternately, the total product from oxidation of the diene benzoate (8 g.) was reduced with zinc dust and acetic acid. Chromatography of the mixture yielded the saturated diketone benzoate (m.p. 200°), some of the stenyl benzoate (m.p. 142°, $[\alpha]_D$ −10° Di), and 7-keto-Δ^8-cholestenyl benzoate (m.p. 150°, $[\alpha]_D$ −13° Di, $\lambda_{max.}^{EtOH}$ 252 mμ, log ϵ 3.8, $C_{34}H_{48}O_3$: C, 80.90; H, 9.58; $\lambda_{max.}^{CHCl_3}$ 5.95μ; found: C, 81.02; H, 9.87). Wolff–Kishner reduction of the saturated diketone gave a cholestanolone, m.p. 151°, $[\alpha]_D$ +49° Di, $\lambda_{max.}^{Chf}$ 5.89 μ; $C_{27}H_{46}O_2$: C, 80.54; H, 11.52; found: C, 80.66; H, 11.49. That cholesterol has been converted into the 11-keto stanol is evidenced by analogy to the synthesis in the bile acid series, by the presence of a carbonyl group (infrared) resistant to Wolff–Kishner reduction, and the M_D increment of +96° for the carbonyl group, as compared with known values (+79°, mean of 5 examples, +60 to +96°.[4]

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(1) L. F. Fieser, S. Rajagopalan, M. Tishler and E. Wilson, THIS JOURNAL, in press.

(2) Comparison sample: L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **72**, 5530 (1950).

(3) Comparison sample: R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946).

(4) D. H. R. Barton and W. Klyne, *Chemistry and Industry*, **26**, 757 (1948).