

Studies in the Steroid Group. Part LXVI. Formation of Ergost-14-ene-3 β :5 α -diol and Related Compounds.*

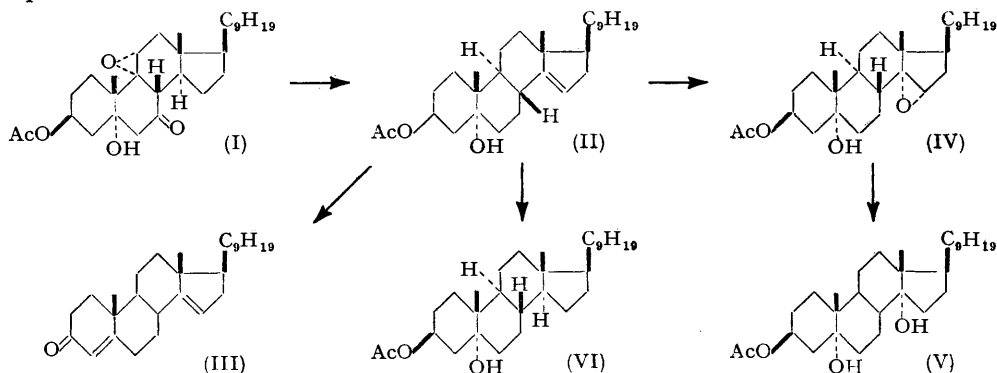
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Treatment of a 9 α :11 α -epoxy-7-oxo-steroid with ethanedithiol and then Raney nickel led to the formation of a Δ^{14} -compound. This yielded an α -epoxide, reducible to a 14 α -hydroxy-steroid.

In an attempt to reduce the 9:11-epoxy-7-ketone (I) (Bladon, Henbest, Jones, Wood, Eaton, and Wagland, *J.*, 1953, 2916) to the corresponding 7-methylene compound, the ketone was treated first with ethanedithiol in the presence of perchloric acid (Hauptmann, *J. Amer. Chem. Soc.*, 1947, **69**, 562; Barton and Rosenfelder, *J.*, 1951, 1048). An uncrystallisable sulphur-containing product was obtained which, on treatment with Raney nickel, afforded a crystalline unsaturated compound in over 50% yield.

This new product has been shown to be 3 β -acetoxyergost-14-en-5 α -ol (II). The presence of the original 5 α -hydroxyl group was indicated by acetylation (acetyl chloride) to a 3 β :5 α -diacetate, and by hydrolysis followed by Oppenauer oxidation to give the unsaturated ketone (III). Infra-red and ultra-violet absorption measurements (Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402; Bladon, Henbest, and Wood, *J.*, 1952, 2737) showed that the olefinic linkage was trisubstituted, and most probably situated at 9(11) or 14(15). A third, less likely possibility, 3 β -acetoxyergost-7-en-5 α -ol (Clayton, Henbest, and Jones, *J.*, 1953, 2015), could be ruled out in view of the difference in properties.



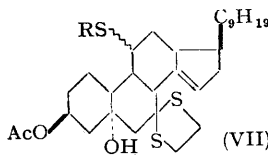
The molecular rotation of the new 5-hydroxy-compound was in better agreement with the 5 α -hydroxy- Δ^{14} - than with the alternative $\Delta^{9(11)}$ -structure (preceding paper; Barton and Klyne, *Chem. and Ind.*, 1948, 755), assuming little vicinal action between the double bond and the hydroxyl group. Monoperphthalic acid afforded an epoxide in good yield, the rotation change on formation of this epoxide being a small positive value ($M_D + 53^\circ$) in contrast to the larger negative change ($M_D - 130^\circ$) recorded for the formation of a 9 α :11 α -epoxide (preceding paper). (These rotation differences are given in more detail below.) Furthermore, the new epoxide was reduced on treatment with lithium aluminium hydride in warm tetrahydrofuran, whereas 3 β -acetoxy-9 α :11 α -epoxyergostane was recovered unchanged (after reacylation) when subjected to the same conditions (see also Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1951, **73**, 118; Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278). The original olefin is therefore the Δ^{14} -compound (II), and the epoxide is formulated as the 14 α :15 α -compound (IV), and its lithium aluminium hydride reduction product as the 3 β :5 α :14 α -triol, mild acetylation of which gives the 3 β -monoacetate (V).

Hydrogenation of (II) readily afforded the saturated diol formulated as (VI), since Δ^{14} -compounds with 17 β -side-chains give 14 α -steroids on reduction (Ruzicka, Plattner,

* Part LXV, preceding paper.

Heusser, and Meier, *Helv. Chim. Acta*, 1947, **30**, 1342). The rotation of (VI) was in excellent agreement with the expected value (3β -acetoxyergostane + 3β -acetoxycholestan-5 α -ol - 3β -acetoxycholestane).

In the absence of crystalline intermediates it is not easy to arrive at a detailed explanation for the formation of the Δ^{14} -compound from (I). However, it is likely that normal thioketal formation takes place at C₍₇₎, and that the 9:11-epoxide ring is opened affording a product with a thio-group at C₍₁₁₎ and a hydroxyl group at C₍₉₎. The latter group may be eliminated and the $\Delta^{8(9)}$ -olefin isomerised to a Δ^{14} -olefin by the perchloric acid present. Products of structure (VII; R = CH₂·CH₂·SH) may thus be present in the non-crystalline thioketal, although sulphur analysis of this material indicated that other compounds containing less sulphur must also be present.



Molecular rotation contributions of $\Delta^{9(11)}$ - and Δ^{14} -bonds.

Average value for Δ^{14} -bond given by Barton and Klyne (<i>loc. cit.</i>)	+28
3β -Acetoxyergost-14-en-5 α -ol (II) - 3β -acetoxyergostan-5 α -ol (VI)	+32
3β -Acetoxyergost-9(11)-ene - 3β -acetoxyergostane	+58

Molecular rotation increments on formation of 9 α :11 α - and 14 α :15 α -epoxides.

Olefin	M_D , olefin	M_D , oxide	Δ	Ref.
3β -Acetoxyergost-14-en-5 α -ol (II)	+ 37°	+ 90°	+ 53°	—
Methyl 3β -acetoxyalloeti-14-enate	+113	+124	+ 11	1
Methyl 3 α :12 α -diacetoxychol-14-enate	+500	+515	+ 15	2
3β -Acetoxyergost-9(11)ene	+ 75	- 55	-130	3
3β -Acetoxy-22 α -spirost-9(11)-ene	-246	-307	- 61	4
Methyl 3 α -acetoxychol-9(11)-enate	+260	+188	- 72	5

References: 1, Plattner, Ruzicka, Heusser, Pataki, and Meier, *Helv. Chim. Acta*, 1946, **29**, 942, 2033. 2, Plattner, Ruzicka, and Holtermann, *ibid.*, 1945, **28**, 1660. 3, Preceding paper. 4, Djerassi, Martinez, and Rosenkranz, *loc. cit.* 5, Fieser and Rajagopalan, *loc. cit.*

EXPERIMENTAL

General experimental directions are as given in Part LXI, *J.*, 1953, 2916.

Reaction of 3β -Acetoxy-9 α :11 α -epoxy-7-oxoergostan-5 α -ol with Ethanedithiol.—A solution of the steroid (1.4 g.) in dioxan (5 c.c.) and ethanedithiol (2.15 g.; Owen and Smith, *J.*, 1951, 2973) containing 60% perchloric acid (0.3 c.c.) was kept at 20° for 2 days. Crystals which separated at first were redissolved by gentle warming. The mixture was diluted with ether and washed thrice with aqueous potassium hydroxide (2%) and twice with water, dried, and evaporated to a glassy residue (1.51 g.). This could not be crystallised (Found: S, 13.6%).

3β -Acetoxyergost-14-en-5 α -ol (II).—The crude thioketal (1.3 g.) was heated under reflux for 9 hr. with Raney nickel (15 c.c. of sludge) and dioxan (80 c.c.). The nickel was filtered off and washed with chloroform, and the filtrates evaporated to a solid residue (1.1 g.). This was acetylated overnight at 20° in the usual way, and the product (in benzene) was chromatographed on alumina (70 g.). Benzene-ether (4:1) (750 c.c.) eluted a solid fraction (780 mg.), which when crystallised from methanol gave material (620 mg.), m. p. 152—156°. Another crystallisation afforded 3β -acetoxyergost-14-en-5 α -ol as plates, m. p. 158—161°, [α]_D + 8° (*c.*, 1.07) (Found: C, 78.5; H, 10.95. C₃₀H₅₀O₃ requires C, 78.55; H, 11.0%). Infra-red spectrum: peaks at 3500 (OH), 1730, 1700, 1250 (acetate), 818 cm.⁻¹ (Δ^{14}); (in CHCl₃) acetate bands at 1715 and 1250 cm.⁻¹.

Alkaline hydrolysis of this acetate gave *ergost-14-ene-3 β :5 α -diol* (plates from methanol), m. p. 215—225°, [α]_D + 10° (*c.*, 0.38) (Found: C, 79.4; H, 11.6. C₂₈H₄₈O₂, $\frac{1}{2}$ CH₃·OH requires C, 79.1; H, 11.6%). 3β :5 α -Diacetoxyergost-14-ene was obtained by heating a mixture of the 3-acetate (100 mg.), chloroform (5 c.c.), acetyl chloride (4 c.c.), and dimethylaniline (6 c.c.) for 18 hr. Isolation with ether gave a gum (140 mg.), which even after chromatography failed to crystallise. It was therefore distilled, b. p. 170—180° (bath)/10⁻⁵ mm., [α]_D + 41° (*c.*, 0.62) (Found: C, 77.1; H, 10.4. C₃₂H₅₂O₄ requires C, 76.75; H, 10.5%). Infra-red spectrum: peaks at 1737 and 1250 cm.⁻¹ (acetate). This partly solidified but the crystals (m. p. 85—90°) could not be recrystallised from a solvent.

Ergosta-4:14-dien-3-one (III).—The above 3:5-diol (120 mg.), dry acetone (3 c.c.), aluminium *tert.*-butoxide (0.75 g.), and toluene (5 c.c.) were heated under reflux for 3 hr., the product then being isolated with ether. The oily material (135 mg.) obtained was distilled

twice, b. p. 190—205° (bath)/10⁻⁵ mm., yielding a pale yellow oil (λ_{\max} . 2400 Å; ϵ 12,500) which solidified. Three crystallisations from methanol gave the *ketone* (12 mg.), m. p. 118—120° (Found: C, 83.5; H, 10.95. C₂₈H₄₄O₁· $\frac{1}{2}$ CH₃·OH requires C, 83.0; H, 11.2%); λ_{\max} . (in EtOH) 2400 Å; ϵ 16,000. The 2:4-dinitrophenylhydrazone (crystallised from ethyl acetate) had m. p. 237—240° (Found: C, 70.45; H, 8.4; N, 10.35. C₃₄H₄₈O₄N₄ requires C, 70.8; H, 8.4; N, 9.7%); λ_{\max} . (in CHCl₃) 2610, 2930, 3930 Å; ϵ 19,000, 11,700, and 31,200 respectively.

3 β -Acetoxyergostan-5 α -ol (VI).—3 β -Acetoxyergost-14-en-5 α -ol (118 mg.) was shaken with pre-reduced Adams catalyst (50 mg.) in glacial acetic acid (12.5 c.c.) in hydrogen until absorption ceased (7.4 c.c. at 22°/761 mm.; calc., 6.5 c.c.). After removal of the catalyst and evaporation, 3 β -acetoxyergostan-5 α -ol crystallised from ethyl acetate as plates, m. p. 204—207° (change of form at 200°), $[\alpha]_D +1^\circ$ (*c*, 0.87) (Found: C, 78.2; H, 11.6. C₃₀H₅₂O₃ requires C, 78.2; H, 11.4%). Infra-red spectrum: peaks at 3450 (OH); 1734, 1702, 1260 cm.⁻¹ (acetate). Hydrolysis yielded *ergostane-3 β :5 α -diol*, m. p. 237—244° (anisotropic liquid > 200°), $[\alpha]_D +8^\circ$ (*c*, 0.46) (Found, in material sublimed at 200°/10⁻⁶ mm.: C, 80.7; H, 11.95. C₂₈H₅₀O₂ requires C, 80.3; H, 12.05%).

3 β -Acetoxy-14 α :15 α -epoxyergostan-5 α -ol (IV).—The Δ^{14} -compound (250 mg.) in dioxan (3 c.c.) was treated with monoperphthalic acid (4 c.c. of 0.65*N*-solution in ether), and the solution kept at 20° overnight. Isolation with ether followed by 2 crystallisations from methanol yielded the *epoxide* (97 mg.) as plates, m. p. 161—163° $[\alpha]_D +19^\circ$ (*c*, 1.17) (Found: C, 76.05; H, 10.55. C₃₀H₅₀O₄ requires C, 75.9; H, 10.6%). A second crop (120 mg.), m. p. 158—161°, was also obtained. The compound was transparent in the 2000—2200-Å region and gave no colour with tetranitromethane.

3 β -Acetoxyergostane-5 α :14 α -diol (V).—The epoxide (70 mg.), lithium aluminium hydride (250 mg.), and purified tetrahydrofuran (12.5 c.c.) were heated under reflux for 8 hr. After addition of ethyl acetate and dilute hydrochloric acid, the product was isolated with ether-chloroform and acetylated overnight in the usual way. Crystallisation from ethanol-methanol gave the 5 α :14 α -diol as fine needles, m. p. 239—241° (change of form near 200°), $[\alpha]_D -5^\circ$ (*c*, 0.7) (Found, on material sublimed at 200°/10⁻⁶ mm.: C, 75.4; H, 10.9. C₃₀H₅₂O₄ requires C, 75.6; H, 11.0%). Infra-red spectrum: peaks at 3210 (OH), 1735 and 1265 cm.⁻¹ (acetate). Lithium aluminium hydride in boiling ether for 1 hr. did not reduce the epoxide.

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