950. *Steroids. Part V.* Oxidation of Ergosteryl-D Acetate 22 : 23-Dibromide.*

By Richard Budziarek, Robert Stevenson, and F. S. Spring.

The paper describes modified routes from ergosteryl-D acetate 22 : 23-dibromide to 11-oxygenated steroids. 3β-Acetoxy-22 : 23-dibromo-9α : 11α-epoxyergostan-7-one (III; $R = C_9H_{17}Br_2$) is converted by alkali into 22 : 23-dibromo-3β : 11α-dihydroxyergost-8-en-7-one (VII; $R' = R'' = H, R = C_9H_{17}Br_2$) and is isomerised by filtration of its benzene solution through alumina into 3β-acetoxy-22 : 23-dibromo-11α-hydroxyergost-8-en-7-one (VII; $R' = Ac, R'' = H, R = C_9H_{17}Br_2$). The last compound is smoothly oxidised by chromic acid to 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (VIII).

Treatment of 3β : 11α-diacetoxy-22 : 23-dibromoergost-8-en-7-one (VII; $R' = R'' = Ac, R = C_9H_{17}Br_2$) with mineral acid gives, after acetylation, a compound provisionally designated as 3β-acetoxy-22 : 23-dibromoergosta-8 : 11-dien-7-one (IX). Catalytic reduction of the diacetate (VII; $R' = R'' = Ac, R = C_9H_{17}Br_2$) in the presence of alkali is accompanied by debromination to 3β : 11α-dihydroxyergost-22-en-7-one (X; R = H).

Budziarek, Newbold, Stevenson, and Spring (*J.*, 1952, 2892) reported that ergosteryl-D acetate (I; $R = C_9H_{17}$) with one mol. of performic acid gives 3β-acetoxyergosta-9(11) : 22-dien-7-one, m. p. 194—197°, $[\alpha]_D$ +20° (II), and that two mols. of performic acid lead to 3β-acetoxy-9α : 11α-epoxyergost-22-en-7-one (III; $R = C_9H_{17}$). The structure (II) was assigned because the compound does not show selective ultra-violet absorption of high intensity and is readily isomerised by alkali or acid to 3β-acetoxyergosta-8 : 22-dien-7-one (IV). The value of this evidence is doubtful since the isomeric 7 : 8-oxides of ergosta-7 : 9(11) : 22-trien-3β-yl acetates are not known, and it is possible that one or both of these may readily rearrange to (IV). In our view it was unlikely that the oxidation product was a 7 : 8-epoxide since it has been converted into (III ; $R = C_9H_{17}$) by partial bromination, followed by oxidation with perbenzoic acid and debromination (Budziarek *et al.*, *loc. cit.*). Although this relation was used as part of the proof of the structure of (III; $R = C_9H_{17}$), the latter is now well established by independent considerations (see below). The structure (II) has now been confirmed by the infra-red absorption spectrum which shows two well-resolved bands: one at 1740 cm.$^{-1}$ ascribed to the 3β-acetate group, and the other at 1715 cm.$^{-1}$ ascribed to the 7-carbonyl group. Recently, Heusser, Anliker, Eichenberger, and Jeger (*Helv. Chim. Acta*, 1952, **35**, 936) described a compound, m. p. 176—177°, $[\alpha]_D$ −58°, obtained by treatment of 7ξ : 11α-dihydroxyergosta-8 : 22-dien-3β-yl acetate (V; $R = C_9H_{17}$) with hydrogen peroxide in acetic acid, as 3β-acetoxyergosta-9(11) : 22-dien-7-one (II). This is probably the same as a compound (m. p. 176—177°, $[\alpha]_D$ −43·5°) obtained by Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler (*J. Amer. Chem. Soc.*, 1952, **74**, 2696) by controlled acid-isomerisation of 9α : 11α-epoxy-

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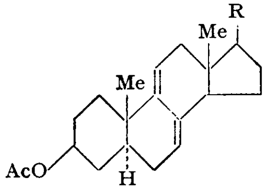
* Part IV, *J.*, 1952, 3646.

ergosta-7 : 22-dien-3β-yl acetate (VI). The proof of structure employed by Heusser *et al.* (*loc. cit.*) for their ketone is the same as that employed by us for the compound, m. p. 194—197°. We conclude that the two βγ-unsaturated ketones probably differ in orientation around $C_{(8)}$.

3β-Acetoxy-9α : 11α-epoxyergost-22-en-7-one (III; $R = C_9H_{17}$) has been prepared directly from ergosteryl-D acetate by oxidation with performic acid (Budziarek *et al.*, *loc. cit.*) and also by oxidation of ergosteryl-D acetate 22 : 23-dibromide followed by debromination of the intermediate 3β-acetoxy-22 : 23-dibromo-9α : 11α-epoxyergostan-7-one (III; $R = C_9H_{17}Br_2$) (Anderson, Stevenson, and Spring, *J.*, 1952, 1901). A further investigation of the second route is now reported.

3β-Acetoxy-22 : 23-dibromo-9α : 11α-epoxyergostan-7-one (III; $R = C_9H_{17}Br_2$), as obtained by oxidation of the dibromide (I; $R = C_9H_{17}Br_2$) with peracetic acid, exists in dimorphous, interconvertible forms. It has been further characterised as semicarbazone and 2 : 4-dinitrophenylhydrazone. Oxidation of (I ; $R = C_9H_{17}Br_2$) with performic acid in ethyl acetate also gives 3β-acetoxy-22 : 23-dibromo-9α : 11α-epoxyergostan-7-one. Treatment of (III; $R = C_9H_{17}Br_2$) with alkali gives 22 : 23-dibromo-3β : 11α-dihydroxyergost-8-en-7-one (VII; $R' = R'' = H$, $R = C_9H_{17}Br_2$) characterised as the 3β : 11α-diacetate and by debromination to (VII; $R' = R'' = H$, $R = C_9H_{17}$) (Budziarek *et al.*, and Heusser *et al.*, *locc. cit.*). Similar debromination of (VII; $R' = R'' = Ac$, $R = C_9H_{17}Br_2$) gave the known 3β : 11α-diacetoxyergosta-8 : 22-dien-7-one (VII; $R' = R'' = Ac$, $R = C_9H_{17}$).

Filtration of a benzene solution of the 9α : 11α-epoxide (III; $R = C_9H_{17}Br_2$) through a column of alumina gives 3β-acetoxy-22 : 23-dibromo-11α-hydroxyergost-8-en-7-one (VII; $R' = Ac$, $R'' = H$, $R = C_9H_{17}Br_2$) characterised by ultra-violet absorption spectra and as the 3β : 11α-diacetate. 3β-Acetoxy-22 : 23-dibromo-11α-hydroxyergost-8-en-7-one and chromic acid give 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (VIII), oxidation proceeding smoothly and in good yield in contrast to that of 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl (V; $R = C_9H_{17}Br_2$) acetate which gives a mixture including 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate and 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (VIII) (Budziarek, Johnson, and Spring, *J.*, 1952, 3410).



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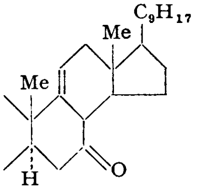

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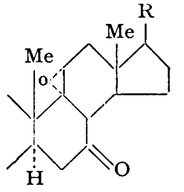

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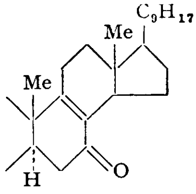

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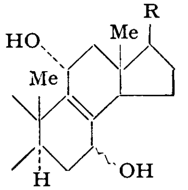

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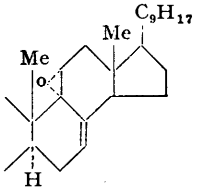

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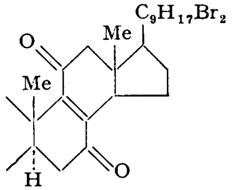

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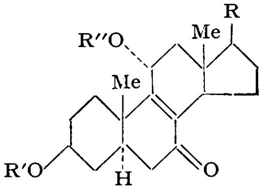

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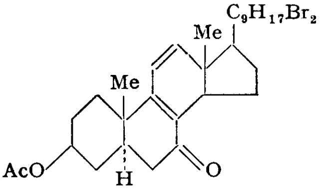

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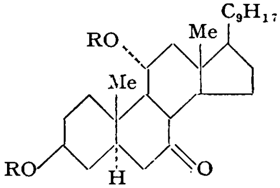

(X)

In an attempt to convert 3β : 11α-diacetoxy-22 : 23-dibromoergost-8-en-7-one into 22 : 23-dibromo-7 : 11-diketoergostan-3β-ol (cf. the similar conversion of 6β-hydroxycholest-4-en-3-one into cholestane-3 : 6-dione; Ellis and Petrow, *J.*, 1939, 1078) the former compound was treated with methanolic hydrogen chloride. The product obtained after acetylation, however, had the molecular formula $C_{30}H_{44}O_3Br_2$ indicating that dehydration had occurred, and showed maxima at 2240 and 2960 Å; it is provisionally formulated as 3β-acetoxy-22 : 23-dibromoergosta-8 : 11-dien-7-one (IX). Similar dehydration of an 11α-hydroxy-7-keto-Δ^8-unsaturated steroid has been observed in the sapogenin series by Stork, Rosenkranz, and Djerassi (*J. Amer. Chem. Soc.*, 1952, **74**, 2918).

Hydrogenation of 3β : 11α-diacetoxy-22 : 23-dibromoergost-8-en-7-one in ethanolic potassium hydroxide over platinum (for conditions see the Experimental section) led to reduction of the 8 : 9-ethylenic linkage accompanied by hydrolysis and side-chain debromination, with formation of 3β : 11α-dihydroxyergost-22-en-7-one (X; R = H) previously described by Heusser *et al.* (*loc. cit.*) and characterised as its diacetate (X; R = Ac).

EXPERIMENTAL

Specific rotations were determined in chloroform solution in a 1-dm. tube at approx. 15°. Ultra-violet absorption spectra were measured in ethanol solution (unless otherwise stated) with a Unicam SP. 500 spectrophotometer. Grade II alumina was used for chromatography.

3β-Acetoxy-22 : 23-dibromo-9α : 11α-epoxyergostan-7-one.—(*a*) Oxidation of 22 : 23-dibromoergosta-7 : 9(11)-dien-3β-yl acetate with peracetic acid (Anderson *et al.*, *loc. cit.*) gave 3β-acetoxy-22 : 23-dibromo-9α : 11α-epoxyergostan-7-one as plates (from chloroform–methanol), m. p. 235°. $[\alpha]_D$ −47°, not altered by recrystallisation from the same solvent. Recrystallisation from acetone gave a second modification as well-defined needles, m. p. 215—220°, raised to 220—221°, $[\alpha]_D$ −48° (*c*, 0·9), by recrystallisation from the same solvent.

The dibromo-keto-oxide (plates, m. p. 235°) in dioxan with Brady's reagent gave the 2 : 4-*dinitrophenylhydrazone* as yellow felted needles (from chloroform–ethanol), m. p. 217—219° (decomp.) (Found: C, 53·0, 53·5; H, 5·95, 6·6. $C_{36}H_{50}O_7N_4Br_2$ requires C, 53·3; H, 6·2%). The ultra-violet absorption spectrum (principal maximum, in chloroform, at 3660 Å, ε = 23,600) is in good agreement with that expected for the 2 : 4-dinitrophenylhydrazone of a saturated ketone (Braude and Jones, *J.*, 1945, 498; Djerassi and Ryan, *J. Amer. Chem. Soc.*, 1949, **71**, 1000). The ketone (plates, m. p. 235°) in water–ethanol–dioxan gave the *semicarbazone* as prisms, m. p. 236—237° (from methanol–chloroform) (Found: C, 54·2; H, 7·3. $C_{30}H_{49}O_4N_3Br_2$ requires C, 54·1; H, 7·2%). Light absorption: Max. at 2280 Å, ε = 14,600.

(*b*) A solution of ergosteryl-D acetate 22 : 23-dibromide (2·32 g.) in warm ethyl acetate (100 c.c.) was treated with formic acid (98—100%; 40 c.c.) and hydrogen peroxide solution (30%; 1·73 c.c.). The suspension was shaken at room temperature for 44 hours, whereafter dissolution was complete. Water was added, the ethyl acetate layer separated, and the aqueous layer extracted with ethyl acetate. The combined ethyl acetate extracts were washed with sodium hydrogen carbonate solution and dried (Na_2SO_4). Removal of the solvent and crystallisation of the residue first from ethanol and then from acetone gave 3β-acetoxy-22 : 23-dibromo-9α : 11α-epoxyergostan-7-one (650 mg.) as needles, m. p. 220—221° (unchanged by drying in a high vacuum at 100°), $[\alpha]_D$ −48° (*c*, 1·0) (Found: C, 57·2; H, 7·5. Calc. for $C_{30}H_{46}O_4Br_2$: C, 57·1; H, 7·35%). It does not give a colour with tetranitromethane in chloroform, or exhibit high-intensity light absorption above 2100 Å. The 2 : 4-dinitrophenylhydrazone separated from chloroform–methanol as needles, m. p. 219—221° undepressed when mixed with the specimen described above. Debromination of an ethanol solution of the substance with zinc dust gave 3β-acetoxy-9α : 11α-epoxyergost-22-en-7-one as needles (from methanol) (initial gel formation), m. p. 221°, $[\alpha]_D$ −82° (*c*, 1·5). Recrystallisation of the lower-melting form of the dibromo-keto-oxide from chloroform–methanol gave the higher-melting modification, m. p. 234—235° (unchanged after drying in a high vacuum at 100°), $[\alpha]_D$ −47° (*c*, 1·6), as plates.

22 : 23-Dibromo-3β : 11α-dihydroxyergost-8-en-7-one.—(*a*) 3β-Acetoxy-22 : 23-dibromo-9α : 11α-epoxyergostan-7-one (either form, 400 mg.) was heated in methanolic potassium hydroxide solution (3%; 40 c.c.) under reflux for 70 minutes. The product, isolated by ether, gave 22 : 23-*dibromo*-3β : 11α-*dihydroxyergost*-8-*en*-7-*one* as plates (from methanol), m. p. 231—232°, $[\alpha]_D$ +4°, +4° (*c*, 0·9, 2·0) (Found: C, 57·0; H, 7·65. $C_{28}H_{44}O_3Br_2$ requires C, 57·1; H, 7·5%). Light absorption: Max. at 2520 Å, ε = 8300.

(*b*) A solution of 3β : 11α-diacetoxy-22 : 23-dibromoergost-8-en-7-one (600 mg.) in benzene (10 c.c.) and methanolic potassium hydroxide (3%; 40 c.c.) was refluxed for 3 hours. 22 : 23-

Dibromo-3β : 11α-dihydroxyergost-8-en-7-one, isolated by ether, crystallised from methanol as plates, m. p. 232°, $[\alpha]_D$ +4° (*c*, 1·3), undepressed in m. p. when mixed with the specimen described above. Light absorption : Max. at 2510 Å, ε = 8000.

3β : 11α-*Diacetoxy*-22 : 23-*dibromoergost*-8-*en*-7-*one*.—Acetylation of the diol (pyridine–acetic anhydride at 100°) gave the 3β : 11α-*diacetate*, needles, m. p. 161—163° (air-dried), from chloroform–methanol, m. p. 201—202° after prolonged drying at 100° in a high vacuum, $[\alpha]_D$ +18° (*c*, 0·6) (Found : C, 57·2; H, 7·4. $C_{32}H_{48}O_5Br_2$ requires C, 57·1; H, 7·2%). Light absorption : Max. at 2520 Å, ε = 10,000.

3β : 11α-*Diacetoxyergosta*-8 : 22-*dien*-7-*one*.—A solution of 3β : 11α-diacetoxy-22 : 23-dibromoergost-8-en-7-one (124 mg.) in ether–ethanol (1 : 1; 30 c.c.) was heated under reflux with zinc dust for 3 hours. The product, isolated by ether, was crystallised from aqueous methanol to give 3β : 11α-diacetoxyergosta-8 : 22-dien-7-one as needles, m. p. 172—174°, $[\alpha]_D$ +11° (Found : C, 75·4; H, 9·6. Calc. for $C_{32}H_{48}O_5$: C, 75·0; H, 9·4%). The m. p. was undepressed when the product was mixed with the specimen described by Budziarek *et al.* (*loc. cit.*) who give m. p. 175—177°, $[\alpha]_D$ +13°.

3β : 11α-*Dihydroxyergosta*-8 : 22-*dien*-7-*one*.—22 : 23-Dibromo-3β : 11α-dihydroxyergost-8-en-7-one (160 mg.) in boiling methanol (50 c.c.) was treated under reflux with zinc dust (1 g.) portionwise (3 hours). 3β : 11α-Dihydroxyergosta-8 : 22-dien-7-one, isolated by ether, crystallised from acetone as prismatic needles, m. p. 214—215°, $[\alpha]_D$ −7° (*c*, 1·0) (Found : C, 78·5; H, 10·5. Calc. for $C_{28}H_{44}O_3$: C, 78·45; H, 10·35%). Light absorption : Max. at 2540 Å, ε = 8600. It is undepressed in m. p. when mixed with the specimen (m. p. 215°, $[\alpha]_D$ −6°) obtained by alkaline hydrolysis of 3β-acetoxy-9α : 11α-epoxyergost-22-en-7-one (Budziarek, Newbold *et al.*, *loc. cit.*). The constants (m. p. 183—185°, $[\alpha]_D$ −17°) given by Anderson, Budziarek, Newbold, Stevenson, and Spring in a preliminary note (*Chem. and Ind.*, 1951, 1035) are incorrect. Heusser *et al.* (*loc. cit.*) give m. p. 207—208° $[\alpha]_D$ −2°.

3β-*Acetoxy*-22 : 23-*dibromo*-11α-*hydroxyergost*-8-*en*-7-*one*.—A solution of 3β-acetoxy-22 : 23-dibromo-9α : 11α-epoxyergostan-7-one (needles, m. p. 220°) (152 mg.) in dry benzene (20 c.c.) was filtered through alumina (2 × 12 cm.). After elution with benzene (400 c.c.) (no eluate), benzene–ether (1 : 1; 500 c.c.) (eluate : solid, 20 mg.), and ether (400 c.c.) (eluate : trace), elution with ether–methanol (1 : 1; 150 c.c.) gave a solid (110 mg.) which, thrice crystallised from methanol, yielded 3β-*acetoxy*-22 : 23-*dibromo*-11α-*hydroxyergost*-8-*en*-7-*one* as needles, m. p. 206—207°, $[\alpha]_D$ −13° (*c*, 1·5) (Found : C, 56·9; H, 7·6. $C_{30}H_{46}O_4Br_2$ requires C, 57·1; H, 7·35%). Light absorption : Max. at 2520 Å, ε = 8000. Acetylation of this compound (pyridine–acetic anhydride) gave the 3β : 11α-diacetate as prismatic needles (from chloroform–methanol), m. p. 162—163° (air-dried) and m. p. 202—203° after prolonged vacuum-drying at 100°. It is undepressed in m. p. when mixed with the specimen described above.

22 : 23-*Dibromo*-7 : 11-*diketoergost*-8-*en*-3β-*yl Acetate*.—3β-Acetoxy-22 : 23-dibromo-11α-hydroxyergost-8-en-7-one (177 mg.) in acetic acid (25 c.c.) was treated with chromic anhydride (21 mg.) in acetic acid (0·63 c.c.) and then with sulphuric acid (2N; 2 drops). The mixture was shaken for 5 minutes, kept at room temperature overnight, and then filtered from a fine flocculent precipitate (20 mg,; m. p. 245°). The solution was diluted with water and the neutral product (140 mg.) isolated by means of ether and crystallised from chloroform–methanol, yielding 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate, plates, m. p. 248—250°, $[\alpha]_D$ +29°. Light absorption : Max. at 2700 Å, ε = 8100. The m. p. was undepressed when mixed with the specimen, m. p. 250—251°, $[\alpha]_D$ +27°, described by Budziarek, Johnson, and Spring (*loc. cit.*).

3β-*Acetoxy*-22 : 23-*dibromoergosta*-8 : 11-*dien*-7-*one*.—A solution of 3β : 11α-diacetoxy-22 : 23-dibromoergost-8-en-7-one (300 mg.) in methanolic hydrogen chloride (5%; 60 c.c.) was refluxed for 4 hours. The product was isolated by means of ether and acetylated with pyridine–acetic anhydride at 100°. Crystallisation then gave plates (200 mg.), m. p. 260—262°, which were purified by chromatography in benzene (20 c.c.) on alumina (2 × 10 cm.). The solid eluted with benzene (300 c.c.) was crystallised from methanol–chloroform to give 3β-*acetoxy*-22 : 23-*dibromoergosta*-8 : 11-*dien*-7-*one* as plates, m. p. 263—264°, $[\alpha]_D$ −13° (*c*, 1·0) (Found : C, 59·0; H, 7·5. $C_{30}H_{44}O_3Br_2$ requires C, 58·7; H, 7·2%). Light absorption : Max. at 2240 (ε = 18,000) and 2960 Å (ε = 6000).

3β : 11α-*Dihydroxyergost*-22-*en*-7-*one*.—3β : 11α-Diacetoxy-22 : 23-dibromoergost-8-en-7-one (250 mg.) in ethanolic potassium hydroxide (0·1N; 100 c.c.) was shaken with hydrogen and platinum (from 50 mg. of PtO_2) at room temperature for 2 hours. The filtered solution was concentrated and then diluted with water, and the product isolated by means of ether. Crystallisation from aqueous methanol gave 3β : 11α-dihydroxyergost-22-en-7-one as needles, m. p.

206—207°, $[\alpha]_D$ −76° (*c*, 0·8) (Found: C, 75·3; H, 11·0. Calc. for $C_{28}H_{46}O_3$,MeOH: C, 75·3; H, 10·9%). It gives a faint yellow colour with tetranitromethane in chloroform and does not exhibit high-intensity absorption above 2200 Å. Heusser *et al.* (*loc. cit.*) give m. p. 204—205° and $[\alpha]_D$ −74° for this compound. 3β : 11α-*Diacetoxyergost*-22-*en*-7-*one*, obtained from the diol by using acetic anhydride and pyridine at 100°, separates from methanol as plates, m. p. 141—142°, $[\alpha]_D$ −67°, −68° (*c*, 0·7, 0·6) (Found: C, 74·8; H, 10·0. $C_{32}H_{50}O_5$ requires C, 74·7, H, 9·8%). Heusser *et al.* (*loc. cit.*, p. **949**, footnote) give m. p. 123—124°, $[\alpha]_D$ −60°.

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