*Steroids. Part IX.** 22 : 23-*Dichloroergosta*-7 : 9(11)-*dien*-3β-*yl Acetate* (*Ergosteryl-D Acetate* 22 : 23-*Dichloride*).

By JOHN PATERSON and F. S. SPRING.

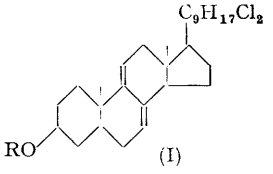
[Reprint Order No. 4677.]

The conversion of ergosteryl-D acetate 22 : 23-dichloride into 11-oxygenated derivatives is described.

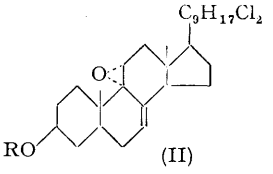
TREATMENT of 5α : 6-dihydroergosteryl acetate † with bromine gives an unstable tetrabromoergostenyl acetate, treatment of which with sodium iodide yields ergosteryl-D acetate 22 : 23-dibromide. Treatment of 5α : 6-dihydroergosteryl acetate with chlorine gives in low yield a mixture of tetrachloroergostenyl acetates I and II of which the former is converted by sodium iodide into ergosteryl-D acetate 22 : 23-dichloride (I; R = Ac) (Anderson, Stevenson, and Spring, *J.*, 1952, 2901). The present paper is mainly concerned with an examination of the reactions of ergosteryl-D acetate 22 : 23-dichloride.

Partial dehalogenation of tetrachloroergostenyl acetate II by zinc dust in ether–ethanol gives 22 : 23-dichloroergosta-7 : 14-dien-3β-yl acetate (ergosteryl-B_3 acetate 22 : 23-dichloride), further dehalogenation of which by zinc dust and acetic acid gives ergosteryl-B_3 acetate.

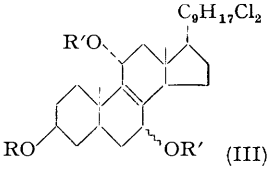
Dehalogenation of ergosteryl-D acetate 22 : 23-dichloride by zinc dust and acetic acid gives ergosteryl-D acetate. The elimination of chlorine from the dichloride is more difficult than the removal of bromine from the dibromide. In the latter case conversion into ergosteryl-D acetate is complete after short treatment with zinc dust in ether–ethanol, conditions which do not effect ergosteryl-D acetate 22 : 23-dichloride. Alkaline hydrolysis of the dichloride merely removes the acetyl group, giving (I; R = H).



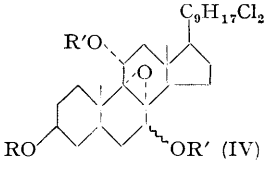
(I)



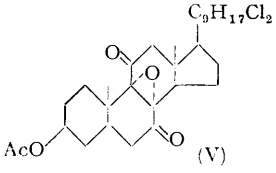
(II)



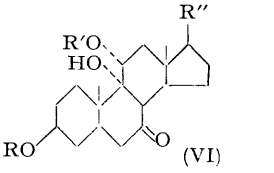
(III)



(IV)



(V)



(VI)

Oxidation of ergosteryl-D acetate 22 : 23-dichloride (I) with 1 mol. of perbenzoic acid gives 22 : 23-dichloro-9α : 11α-epoxyergost-7-en-3β-yl acetate (II; R = Ac), characterised by alkaline hydrolysis to the alcohol (II; R = H). The structure allocated to the epoxide is based on analogy, including a consideration of molecular-rotation differences. Rearrangement of (II; R = Ac) by mineral acid yields 22 : 23-dichloro-7ξ : 11α-dihydroxyergost-8-en-β-yl acetate (III; R = Ac, R' = H), characterised as the triacetate (III; R = R' = Ac) and by alkaline hydrolysis to the triol (III; R = R' = H). Perbenzoic acid oxidises 22 : 23-dichloro-7ξ : 11α-dihydroxyergost-8-ene-3β-yl acetate to 22 : 23-dichloro-8α : 9α-epoxy-7ξ : 11α-dihydroxyergostan-3β-yl acetate (IV; R = Ac, R' = H), which affords normally the triol (IV; R = R' = H) and the triacetate (IV; R = R' = Ac).

Oxidation of the monoacetate (IV; R = Ac, R' = H) with chromic acid yields 22 : 23-dichloro-8α : 9α-epoxy-7 : 11-dioxoergostan-3β-yl acetate (V), the structure of which was confirmed by its conversion into 7 : 11-dioxoergost-22-en-3β-yl acetate (Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892) by zinc dust and acetic acid.

On treatment with mineral acid, 22 : 23-dichloro-8α : 9α-epoxy-7ξ : 11α-dihydroxyergostan-3β-yl acetate (IV; R = Ac, R' = H) undergoes the arrangement

* Part VIII, *J.*, 1953, 956. † Frequently termed " 5-dihydroergosteryl acetate."

observed for 8α : 9α-epoxy-7ξ : 11α-dihydroxyergost-22-en-3β-yl acetate (Heusser, Anliker, Eichenberger, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 936) and 22 : 23-dibromo-8α : 9α-epoxy-7ξ : 11α-dihydroxyergostan-3β-yl acetate (Budziarek, Hamlet, and Spring, *J.*, 1953, 778). The product, 3β-acetoxy-22 : 23-dichloro-9α : 11α-dihydroxyergostan-7-one (VI; R = Ac, R′ = H, R″ = $C_9H_{17}Cl_2$), was identified by its smooth transformation into the known 3β-acetoxy-9α : 11α-dihydroxyergost-22-en-7-one on dechlorination with zinc dust.

The α-orientation of the $C_{(9)}$-hydroxyl group in this and related compounds has been established by Maclean and Spring (see following paper).

Experimental

M. p.s are corrected; specific rotations were measured in chloroform solution (unless otherwise specified) in a 1-dm. tube at 16—18°, and ultra-violet absorption spectra in absolute ethanol.

22 : 23-*Dichloroergosta*-7 : 14-*dien*-3β-*yl Acetate*.—A solution of tetrachloroergostenyl acetate II (385 mg.; $[\alpha]_D$ −257°) in ether (40 c.c.) and ethanol (60 c.c.) was heated under reflux with zinc dust (2 g.) for 2 hr. The product was isolated by means of ether. Crystallisation from chloroform–methanol gave in low yield 22 : 23-*dichloroergosta*-7 : 14-*dien*-3β-*yl acetate*, m. p. 206—209°, $[\alpha]_D$ −173°, −169° (*c*, 1·8, 1·4) (Found: C, 70·5; H, 9·2; Cl, 14·2. $C_{30}H_{46}O_2Cl_2$ requires C, 70·7; H, 9·1; Cl, 13·9%). Light absorption: Max. at 2420 Å (ε 10,000).

Ergosta-7 : 14 : 22-*trien*-3β-*yl Acetate* (*Ergosteryl-B*$_3$ *Acetate*).—A solution of 22 : 23-dichloroergosta-7 : 14-dien-3β-yl acetate (35 mg.) in glacial acetic acid was heated with zinc dust (200 mg.) on the steam-bath for 1 hr. The product, isolated in the usual manner, after many crystallisations from aqueous methanol, gave ergosteryl-B_3 acetate as fine needles, m. p. 132—134°, $[\alpha]_D$ −218° (*c*, 0·3), undepressed in m. p. when mixed with a specimen, m. p. 138—140°, prepared as described by Barton and Brooks (*J.*, 1951, 277). Light absorption: Max. at 2420 Å (ε 8800).

22 : 23-*Dichloroergosta*-7 : 9(11)-*dien*-3β-*ol*.—A solution of ergosteryl-D acetate 22 : 23-dichloride (430 mg.; m. p. 235—237°, $[\alpha]_D$ −44°) in benzene (5 c.c.) and aqueous-methanolic potassium hydroxide (3%; 85 c.c.) was refluxed for 6 hr. The product was isolated by means of ether and crystallised from aqueous acetone, to give 22 : 23-*dichloroergosta*-7 : 9(11)-*dien*-3β-*ol* as needles, m. p. 215—216°, $[\alpha]_D$ +33·5° (*c*, 1·4) (Found: C, 69·5; H, 9·8; Cl, 14·0. $C_{28}H_{44}OCl_2,H_2O$ requires C, 69·3; H, 9·55; Cl, 14·6%). Light absorption: Max. at 2370 (ε 16,200), 2440 (ε 17,700), and 2520 Å (ε 12,500).

22 : 23-*Dichloro*-9α : 11α-*epoxyergost*-7-*en*-3β-*yl Acetate*.—22 : 23-Dichloroergosta-7 : 9(11)-dien-3β-yl acetate (1 g.) in dry chloroform (22·5 c.c.) was treated at 0° with perbenzoic acid (1·3 mols.) in chloroform (6 c.c.) with stirring during 2½ hr. and kept at 0° for 4 hr. The product (1 g.), isolated in the usual manner, was repeatedly crystallised from acetone, to give 22 : 23-*dichloro*-9α : 11α-*epoxyergost*-7-*en*-3β-*yl acetate* as prismatic needles, m. p. 220—221° (decomp.), $[\alpha]_D$ −34°, −34·3° (*c*, 1·1) (Found: C, 68·7; H, 9·1. $C_{30}H_{46}O_3Cl_2$ requires C, 68·55; H, 8·8%). Light absorption: ε_{2080} 3150, ε_{2150} 1600, ε_{2200} 300. The compound gives a light yellow colour with tetranitromethane in chloroform.

Hydrolysis of the acetate for 2½ hr. by boiling 3% ethanolic potassium hydroxide gave 22 : 23-*dichloro*-9α : 11α-*epoxyergost*-7-*en*-3β-*ol* which separates from acetone as prismatic needles, m. p. 221—223°, $[\alpha]_D$ −37° (*c*, 0·6) (Found: C, 69·8; H, 9·3. $C_{28}H_{44}O_2Cl_2$ requires C, 69·6; H, 9·2%). Light absorption: ε_{2060} 5800, ε_{2140} 2100, ε_{2200} 300.

22 : 23-*Dichloro*-7ξ : 11α-*dihydroxyergost*-8-*en*-3β-*yl Acetate*.—22 : 23-Dichloro-9α : 11α-epoxyergost-7-en-3β-yl acetate (3·85 g.) in tetrahydrofuran (40 c.c.) was treated with aqueous sulphuric acid (2N; 1·5 c.c.). The mixture was kept at 16° for 4 hr. and the solid (1·6 g.) collected and washed with chloroform. From the mother-liquor a further crop (0·17 g.) separated after 1 hr. The combined crops were crystallised from pyridine, to give 22 : 23-*dichloro*-7ξ : 11α-*dihydroxyergost*-8-*en*-3β-*yl acetate* as fine needles, m. p. 237—239° (decomp.), $[\alpha]_D$ +74°, +70° (*c*, 0·27, 0·28 in pyridine) (Found: C, 66·3; H, 9·1. $C_{30}H_{48}O_4Cl_2$ requires C, 66·3; H, 8·9%). Light absorption: ε_{2120} 7300, ε_{2150} 6900, ε_{2200} 4600.

22 : 23-*Dichloroergost*-8-*ene*-3β : 7ξ : 11α-*triol* was obtained by refluxing the monoacetate with 3% ethanolic potassium hydroxide for 6½ hr. It separates from aqueous pyridine as rectangular plates, m. p. 225—226° (decomp.), $[\alpha]_D$ +135°, +128° (*c*, 0·2 in pyridine) (Found: C, 67·1; H, 9·4. $C_{28}H_{46}O_3Cl_2$ requires C, 67·05; H, 9·2%). Light absorption: ε_{2120} 6400, ε_{2150} 6000, ε_{2200} 3800.

Acetylation of the monoacetate with pyridine and acetic anhydride gave the *triacetate* which separates from aqueous acetone as needles, m. p. 151—153°, $[\alpha]_D$ +102°, +101° (*c*, 0·77, 0·62) (Found: C, 65·0; H, 8·3. $C_{34}H_{52}O_6Cl_2$ requires C, 65·05; H, 8·4%). Light absorption: ε_{2100} 11,300, ε_{2150} 9650, ε_{2200} 6700.

22 : 23-*Dichloro*-8α : 9α-*epoxy*-7ξ : 11α-*dihydroxyergostan*-3β-*yl Acetate*.—Perbenzoic acid (1·2 mols.) in chloroform (10 c.c.) was added to a suspension of 22 : 23-dichloro-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (1·34 g.) in chloroform (35 c.c.) and the mixture kept at 16° for 4 hr.; dissolution was then complete. The product, isolated in the usual manner and crystallised from acetone, gave 22 : 23-*dichloro*-8α : 9α-*epoxy*-7ξ : 11α-*dihydroxyergostan*-3β-*yl acetate* as prisms, m. p. 277—279° (decomp.), $[\alpha]_D$ +21°, +20° (*c*, 0·87, 1·0) (Found: C, 64·6; H, 8·7. $C_{30}H_{48}O_5Cl_2$ requires C, 64·4; H, 8·6%).

22 : 23-*Dichloro*-8α : 9α-*epoxyergostane*-3β : 7ξ : 11α-*triol* was obtained by refluxing the monoacetate with 3% ethanolic potassium hydroxide containing a little benzene for 3 hr. It separates from aqueous methanol as needles, m. p. 271—273° (decomp.), $[\alpha]_D$ +30°, +28° (*c*, 0·7, 0·5) (Found: C, 65·3; H, 9·0. $C_{28}H_{46}O_4Cl_2$ requires C, 65·0; H, 8·95%).

22 : 23-*Dichloro*-8α : 9α-*epoxy*-3β : 7ξ : 11α-*triacetoxyergostane*, obtained by treatment of the monoacetate with pyridine and acetic anhydride, separates from aqueous acetone as needles, m. p. 212—214°, $[\alpha]_D$ +7°, +5° (*c*, 0·6, 1·1) (Found: C, 63·5; H, 8·4. $C_{34}H_{52}O_7Cl_2$ requires C, 63·4; H, 8·1%).

22 : 23-*Dichloro*-8α : 9α-*epoxy*-7 : 11-*dioxoergostan*-3β-*yl Acetate*.—22 : 23-Dichloro-8α : 9α-epoxy-7ξ : 11α-dihydroxyergostan-3β-yl acetate (230 mg.) in glacial acetic acid (25 c.c.) was treated with a solution of chromic anhydride in acetic acid (N; 2·1 ml.) during 1½ hr. The solution was stirred for 1 hr., and kept overnight at room temperature and then at 45—50° for 30 min. The product (230 mg.) was isolated by means of ether and crystallised from methanol–chloroform, to give 22 : 23-*dichloro*-8α : 9α-*epoxy*-7 : 11-*dioxoergostan*-3β-*yl acetate* as needles, m. p. 223—224° (decomp.), $[\alpha]_D$ −53·4°, −53° (*c*, 0·7, 0·7) (Found: C, 64·7; H, 8·1. $C_{30}H_{44}O_5Cl_2$ requires C, 64·85; H, 8·0%).

7 : 11-*Dioxoergost*-22-*en*-3β-*yl Acetate*.—A solution of 22 : 23-dichloro-8α : 9α-epoxy-7 : 11-dioxoergostan-3β-yl acetate (110 mg.) in glacial acetic acid (15 c.c.) was heated on the steam-bath with zinc dust (1 g.), added portionwise during 3 hr. The product was isolated by means of ether and crystallised from methanol, to give 7 : 11-dioxoergost-22-en-3β-yl acetate as needles, m. p. 196—198°, $[\alpha]_D$ −29° (*c*, 0·6) (Found: C, 76·4; H, 9·4. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%). A mixture with a specimen prepared as described by Budziarek *et al.* (*loc. cit.*) was undepressed in m. p.

3β-*Acetoxy*-22 : 23-*dichloro*-9α : 11α-*dihydroxyergostan*-7-*one*.—A solution of 22 : 23-dichloro-8α : 9α-epoxy-7ξ : 11α-dihydroxyergostan-3β-yl acetate (350 mg.) in acetic acid (5·5 c.c.) was treated with hydrobromic acid (48%; 0·5 ml.). The crystalline solid (225 mg.) separating from the blue solution was collected after 30 min., washed, and crystallised from acetone, to give 3β-*acetoxy*-22 : 23-*dichloro*-9α : 11α-*dihydroxyergostan*-7-*one* as prisms, m. p. 285—286° (decomp.), $[\alpha]_D$ −42° (*c*, 0·85) (Found: C, 64·6; H, 8·7. $C_{30}H_{48}O_5Cl_2$ requires C, 64·4; H, 8·6%).

3β-*Acetoxy*-9α : 11α-*dihydroxyergost*-22-*en*-7-*one*.—A solution of 3β-acetoxy-22 : 23-dichloro-9α : 11α-dihydroxyergostan-7-one (150 mg.) in glacial acetic acid (50 c.c.) was heated for 4 hr. on the steam-bath with zinc dust (2 g.). Isolation of the product with ether gave 3β-acetoxy-9α : 11α-dihydroxyergost-22-en-7-one as rectangular plates (140 mg.) (from methanol), m. p. 267—269°, $[\alpha]_D$ −67° (*c*, 0·7) (Found: C, 73·7; H, 10·0. Calc. for $C_{30}H_{48}O_5$: C, 73·7; H, 9·9%). A mixture with the specimen prepared as described by Budziarek, Hamlet, and Spring (*loc. cit.*) was undepressed in m. p.

22 : 23-*Dichloro*-3β : 9α : 11α-*trihydroxyergostan*-7-*one* was obtained from the monoacetate by refluxing its solution in aqueous-ethanolic potassium hydroxide (1%) containing a little benzene for 1½ hr. It separates from chloroform–methanol as plates, m. p. 286—287° (decomp.), $[\alpha]_D$ −49°, −50° (*c*, 0·3 in pyridine) (Found: C, 63·3; H, 9·2. $C_{28}H_{46}O_4Cl_2$,MeOH requires C, 63·4; H, 9·2%).

Acetylation of the monoacetate by acetic anhydride and pyridine on the steam-bath for 3 hr. gave 3β : 11α-*diacetoxy*-22 : 23-*dichloro*-9α-*hydroxyergostan*-7-*one* which separates from methanol–chloroform as needles, m. p. 292—293° (decomp.), $[\alpha]_D$ −36°, −34° (*c*, 0·6) (Found: C, 64·1; H, 8·6. $C_{32}H_{50}O_6Cl_2$ requires C, 63·9; H, 8·4%).

We are glad to acknowledge our indebtedness to Glaxo Laboratories Ltd. for grants in aid of this work, and to Dr. R. C. Anderson for assistance with some of the experiments described.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, September 25th*, 1953.]