199. *Steroids. Part VIII.* 22 : 23-Dibromo-9ξ : 11α-dihydroxyergostan-3β-yl Acetate and Related Compounds.*

By Richard Budziarek and F. S. Spring.

Oxidation of 22 : 23-dibromo-9ξ : 11α-dihydroxyergostan-3β-yl acetate (I) with chromium trioxide gives 22 : 23-dibromo-9ξ-hydroxy-7 : 11-diketoergostan-3β-yl acetate (III), vigorous treatment of which with alkali followed by acetylation gives the known 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (VII). Whereas treatment of (VII) with zinc dust and acetic acid gives 7 : 11-diketoergost-22-en-3β-yl acetate (XII) with zinc dust in ether–methanol it gives 7 : 11-diketo-8α-ergost-22-en-3β-yl acetate (XI), readily isomerised to (XII) on being heated with acetic acid.

In Parts III and VII (Budziarek, Johnson, and Spring, *J.*, 1952, 3410; Budziarek, Hamlet, and Spring, *J.*, 1953, 778) it was shown that ergosteryl-D acetate 22 : 23-dibromide can be converted into 22 : 23-dibromo-9ξ : 11α-dihydroxy-7-ketoergostan-3β-yl acetate (I) in four stages each of which proceeds in high yield. Oxidation of (I) with chromium trioxide gives 22 : 23-dibromo-9ξ-hydroxy-7 : 11-diketoergostan-3β-yl acetate (III), debromination of which, with zinc, yields 9ξ-hydroxy-7 : 11-diketoergost-22-en-3β-yl acetate (V), also obtained by chromium trioxide oxidation of 9ξ : 11α-dihydroxy-7-ketoergost-22-en-3β-yl acetate (II) (Budziarek, Hamlet, and Spring, *loc. cit.*). Controlled alkaline hydrolysis of (V) gives 3β : 9ξ-dihydroxyergost-22-ene-7 : 11-dione (VI) which is also obtained by zinc dust debromination of the corresponding dibromide (IV).

Although treatment of 22 : 23-dibromo-9ξ-hydroxy-7 : 11-diketoergostan-3β-yl acetate (III) with dilute alkali gives (IV), vigorous treatment of (III) with alkali followed by acetylation of the reaction product, yields, as major product, 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (VII), identical with a specimen prepared by a different route by Budziarek, Johnson, and Spring (*loc. cit.*) who showed that treatment of (VII) with zinc dust and acetic acid gives the well-known 7 : 11-diketoergost-22-en-3β-yl acetate (XII). An attempt was made to limit this last reaction to simple debromination by treatment of (VII) with zinc dust in ether–methanol. Surprisingly, the reaction gave a compound, $C_{30}H_{46}O_4$, $[\alpha]_D$ +30°, which does not show intense absorption above 2200 Å. Simple warming of an acetic acid solution of this compound gives 7 : 11-diketoergost-22-en-3β-yl acetate (XII), $[\alpha]_D$ −28°. The compound, $C_{30}H_{46}O_4$, $[\alpha]_D$ +30°, is also obtained by treatment of 7 : 11-diketoergosta-8 : 22-dien-3β-yl acetate (VIII), 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate (IX), or 8α : 9α-epoxy-7 : 11-diketoergost-22-en-3β-yl acetate (X) in ether–methanol with zinc dust; the conversion of each of these compounds into 7 : 11-diketoergost-22-en-3β-yl acetate by treatment with zinc dust and acetic acid has previously been reported (Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Budziarek, Johnson, and Spring, *loc. cit.*).

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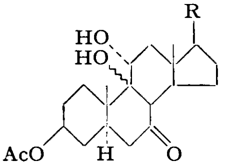
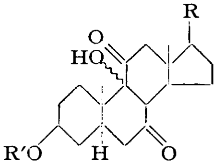
* Part VII, *J.*, 1953, 778.

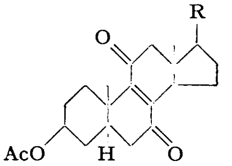
The compound, $C_{30}H_{46}O_4$, $[\alpha]_D$ +30°, is therefore an isomer of 7 : 11-diketoergost-22-en-3β-yl acetate and it must differ from the latter in configuration at $C_{(8)}$ and/or $C_{(9)}$. We suggest that the new isomer is 7 : 11-diketo-8α-ergost-22-en-3β-yl acetate (XI), a *cis*-addition of hydrogen to the 8 : 9-double bond having occurred (cf. Barton, Holness, Overton, and Rosenfelder, *J.*, 1952, 3751, who describe a similar *cis*-addition of hydrogen to a 1 : 4-diketo-2 : 3-ene by treatment with zinc and acetic acid). This view is based on the probability that addition of hydrogen at $C_{(9)}$ occurs from the rear of the molecule to give a 9α-hydrogen, from which it follows that the new isomer must differ from the normal isomer in the configuration at $C_{(8)}$.



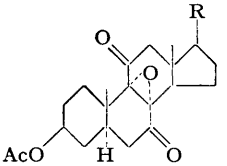
(I) R = $C_9H_{17}Br_2$
(II) R = C_9H_{17}



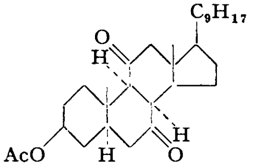
(III) R = $C_9H_{17}Br_2$, R′ = Ac
(IV) R = $C_9H_{17}Br_2$, R′ = H
(V) R = C_9H_{17}, R′ = Ac
(VI) R = C_9H_{17}, R′ = H



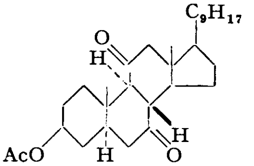
(VII) R = $C_9H_{17}Br_2$
(VIII) R = C_9H_{17}



(IX) R = $C_9H_{17}Br_2$
(X) R = C_9H_{17}



(XI)



(XII)

EXPERIMENTAL

Melting points are corrected. Specific rotations were determined in chloroform solution in a 1-dm. tube at 16—18°. Ultra-violet absorption spectra were measured in absolute ethanol solution, a Unicam SP.500 spectrophotometer being used.

22 : 23-*Dibromo*-9ξ-*hydroxy*-7 : 11-*diketoergostan*-3β-*yl Acetate*.—A solution of 22 : 23-dibromo-9ξ : 11α-dihydroxy-7-ketoergostan-3β-yl acetate (4·0 g.) in glacial acetic acid (1000 c.c.) was treated with one of chromium trioxide in glacial acetic acid (1N; 25 c.c.) added dropwise during 30 minutes at 35—40° with stirring. The solution was kept at room temperature overnight, treated with a little methanol, and concentrated under reduced pressure. After dilution of the solution with water, the product was isolated by means of ether and crystallised from methanol–chloroform, giving 22 : 23-*dibromo*-9ξ-*hydroxy*-7 : 11-*diketoergostan*-3β-*yl acetate* (1·6 g.) as blades, m. p. 256—258°, $[\alpha]_D$ +1·5° (*c*, 4·5) (Found: C, 55·7; H, 7·3. $C_{30}H_{46}O_5Br_2$ requires C, 55·7; H, 7·2%). It does not exhibit light absorption of high intensity above 2000 Å.

22 : 23-Dibromo-9ξ-hydroxy-7 : 11-diketoergostan-3β-yl acetate was recovered unchanged (a) after its solution in acetic anhydride had been heated under reflux for 24 hours, and (b) after its solution in acetic anhydride containing concentrated hydrochloric acid (3 drops) had been heated under reflux for 12 hours.

22 : 23-*Dibromo*-3β : 9ξ-*dihydroxyergostane*-7 : 11-*dione*.—A solution of 22 : 23-dibromo-9ξ-hydroxy-7 : 11-diketoergostan-3β-yl acetate (150 mg.) in methanolic potassium hydroxide (1%; 200 c.c.) was refluxed for 30 minutes. The product, isolated in the usual manner, crystallised from acetone or methanol to give 22 : 23-*dibromo*-3β : 9ξ-*dihydroxyergostane*-7 : 11-*dione* (120 mg.) as needles, m. p. 234—235°, $[\alpha]_D$ +16° (*c*, 1·7) (Found: C, 56·0; H, 7·5. $C_{28}H_{44}O_4Br_2$ requires C, 55·6; H, 7·3%).

Reacetylation of the alcohol (50 mg.), with pyridine (0·5 c.c.) and acetic anhydride (1 c.c.) at 100°, gave the acetate (40 mg.) which separates from methanol–chloroform as blades, m. p. 256—258°, $[\alpha]_D$ +2° (*c*, 1·6), undepressed in m. p. when mixed with the specimen described above.

9ξ-*Hydroxy*-7 : 11-*diketoergost*-22-*en*-3β-*yl Acetate*.—(*a*) A solution of 22 : 23-dibromo-9ξhydroxy-7 : 11-diketoergostan-3β-yl acetate (160 mg.) in ether–methanol (1 : 1; 120 c.c.) was heated under reflux with zinc dust (2 g.) added portionwise during 3½ hours. The product was isolated by means of ether and crystallised from aqueous methanol, giving 9ξ-*hydroxy*-7 : 11-*diketoergost*-22-*en*-3β-*yl acetate* (110 mg.) as felted needles, m. p. 183—185°, $[\alpha]_D$ −23° (*c*, 1·6) (Found: C, 73·85; H, 9·75. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%). It does not exhibit light absorption of high intensity over 2200 Å (ε_{2050} = 3000; ε_{2150} = 1100). The same product was obtained by using zinc and acetic acid at 100°.

(*b*) A solution of 9ξ : 11α-dihydroxy-7-ketoergost-22-en-3β-yl acetate (70 mg.) in glacial acetic acid (30 c.c.) was treated with a solution of chromium trioxide in glacial acetic acid (1N; 0·4 c.c.) added in one portion with shaking at room temperature. The solution was kept at room temperature overnight. A little methanol was added, the solution concentrated under reduced pressure and diluted with water, and the oily product isolated by means of ether. After 2 days with methanol the solid was collected and crystallised from aqueous methanol, giving 9ξ-hydroxy-7 : 11-diketoergost-22-en-3β-yl acetate as felted needles, m. p. 177—180°, $[\alpha]_D$ −25° (*c*, 1·4), undepressed in m. p. when mixed with the specimen described above.

3β : 9ξ-*Dihydroxyergost*-22-*ene*-7 : 11-*dione*.—(*a*) 9ξ-Hydroxy-7 :11-diketoergost-22-en-3β-yl acetate (150 mg.) in methanolic potassium hydroxide (3%; 8 c.c.) was heated gently on the steam-bath for 10 seconds; solution was then complete whereafter a crystalline solid separated immediately. The solid was collected, washed with methanol, and dried (120 mg., needles, m. p. 244—246°). Three recrystallisations from methanol gave 3β : 9ξ-*dihydroxyergost*-22-*ene*-7 : 11-*dione* as needles, m. p. 255—256°, $[\alpha]_D$ −8° (*c*, 0·4 in chloroform–methanol, 20 : 1) (Found: C, 75·5; H, 10·1. $C_{28}H_{44}O_4$ requires C, 75·6; H, 10·0%). It does not exhibit light absorption of high intensity above 2200 Å.

Reacetylation of the diol (30 mg.), with pyridine (0·5 c.c.) and acetic anhydride (1 c.c.) at 100°, gave the acetate (25 mg.) which crystallised from methanol in felted needles, m. p. 183—185°, $[\alpha]_D$ −23° (*c*, 1·5), undepressed in m. p. when mixed with the specimen described above.

(*b*) A solution of 22 : 23-dibromo-3β : 9ξ-dihydroxyergostan-7 : 11-dione (50 mg.) in ether–methanol (1 : 1; 30 c.c.) was heated under reflux with zinc dust (0·5 g.) added portionwise during 3 hours. The product, isolated by means of ether, was crystallised from methanol to yield 3β : 9ξ-dihydroxyergost-22-ene-7 : 11-dione as needles, m. p. 254—256°, $[\alpha]_D$ −7° (*c*, 0·4 in chloroform–methanol, 20 : 1), undepressed in m. p. when mixed with the specimen described above.

22 : 23-*Dibromo*-7 : 11-*diketoergost*-8-*en*-3β-*yl Acetate*.—A solution of 22 : 23-dibromo-9ξ-hydroxy-7 : 11-diketoergostan-3β-yl acetate (400 mg.) in methanolic potassium hydroxide (3%; 120 c.c.) was refluxed for 3 hours. The product was isolated by means of ether and acetylated with acetic anhydride and pyridine. A solution of the acetylated product in benzene (40 c.c.) was filtered through alumina (Grade I/II; 1·5 × 12 cm.). Evaporation of the first two benzene fractions (250 c.c.) gave a solid (250 mg.) which crystallised from methanol–chloroform to yield 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate as hexagonal plates, m. p. 257—259°, $[\alpha]_D$ +30° (*c*, 1·8) (Found: C, 57·6; H, 7·2. Calc. for $C_{30}H_{44}O_4Br_2$: C, 57·3; H, 7·05%); it is undepressed in m. p. when mixed with the material described by Budziarek, Johnson, and Spring (*loc. cit.*). Light absorption: Max. at 2700 Å, ε = 9600.

Evaporation of later benzene fractions gave a yellow solid (100 mg.) which crystallised from methanol–chloroform in yellow elongated plates, m. p. 253—255°, $[\alpha]_D$ +66° (*c*, 1·2) (Found: C, 57·8; H, 7·2%). Light absorption: Max. at 2100 Å (ε = 8000), 2660 Å (ε = 6300), and 3300 Å (ε = 2600).

7 : 11-*Diketo*-8α-*ergost*-22-*en*-3β-*yl Acetate*.—(*a*) A solution of 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (150 mg.) in ether–methanol (1 : 1; 200 c.c.) was heated under reflux with zinc dust (2 g.) added portionwise during 3 hours. The mixture was filtered and the solution slightly concentrated, whereupon small hexagonal plates separated. The solution was cooled and the solid collected, washed with methanol, and dried (100 mg.); it had m. p. 200—204°. Two recrystallisations from acetone gave 7 : 11-*diketo*-8α-*ergost*-22-*en*-3β-*yl acetate* as hexagonal plates, m. p. 204—206°, $[\alpha]_D$ +30°, +28° (*c*, 0·6, 0·5) (Found: C, 76·7; H, 10·1. $C_{30}H_{46}O_4$ requires C, 76·5; H, 9·85%). It does not show light absorption of high intensity above 2200 Å. A mixture with 7 : 11-diketoergost-22-en-3β-yl acetate (m. p. 197—198°, $[\alpha]_D$ −28°) had m. p. 178—198°.

(*b*) Treatment of 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate (60 mg.) in refluxing ether–methanol (1 : 1; 80 c.c.) with zinc dust (1 g.) for 3 hours gave 7 : 11-diketo-8α-ergost-22-en-3β-yl acetate (35 mg.) as hexagonal plates (from acetone), m. p. 203—206°, $[\alpha]_D$ +27° (*c*, 0·5), undepressed in m. p. when mixed with the specimen described under (*a*).

(*c*) Similar treatment of 7 : 11-diketoergosta-8 : 22-dien-3β-yl acetate (200 mg.) gave 7 : 11-diketo-8α-ergost-22-en-3β-yl acetate (150 mg.) as hexagonal plates (from acetone), m. p. 203—205°, $[\alpha]_D$ +27° (*c*, 0·4), undepressed in m. p. when mixed with the specimen described under (*a*).

(*d*) Similar treatment of 8α : 9α-epoxy-7 : 11-diketoergost-22-en-3β-yl acetate (300 mg.) gave 7 : 11-diketo-8α-ergost-22-en-3β-yl acetate (200 mg.) as hexagonal plates (from acetone), m. p. 202—204°, $[\alpha]_D$ +24° (*c*, 0·5), undepressed in m. p. when mixed with the specimen described under (*a*).

7 : 11-*Diketoergost*-22-*en*-3β-*yl Acetate*.—7 : 11-Diketo-8α-ergost-22-en-3β-yl acetate (80 mg., $[\alpha]_D$ +30°) in glacial acetic acid (3 c.c.) was heated on the steam-bath for 45 minutes. The solution was diluted with water and extracted with ether. Removal of ether gave a solid, which was crystallised from methanol to yield 7 : 11-diketoergost-22-en-3β-yl acetate (70 mg.) as small, prismatic needles, m. p. 196—198°, $[\alpha]_D$ −28° (*c*, 1·2) (Found : C, 76·7; H, 10·0. Calc. for $C_{30}H_{46}O_4$: C, 76·5; H, 9·85%). The diketone does not show high intensity light absorption above 2200 Å. It is undepressed in m. p. when mixed with a specimen prepared as described by Budziarek, Johnson, and Spring (*loc. cit.*).

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