Studies in the Steroid Group. Part LXIV. Some Reactions starting from 3β-Acetoxy-9α : 11α-epoxyergosta-7 : 22-diene.*

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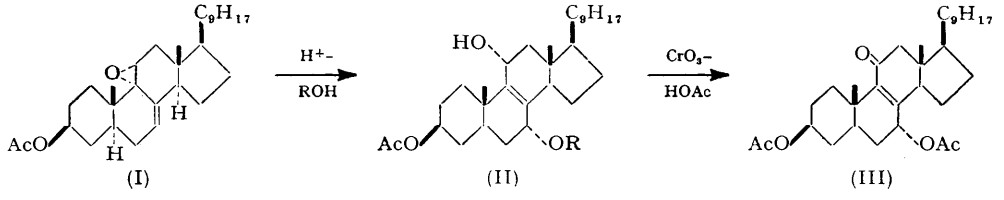
The above Δ^{7}-9 : 11-epoxide (I), when treated successively with the boron trifluoride–ether complex, monoperphthalic acid, and alkali, yields the 7β-hydroxy-$\Delta^{8(9)}$-11-ketone (VIII). The 7 : 11α-diol produced on acid-catalysed hydration of the 9 : 11-epoxide (I) is shown to contain a 7α-hydroxyl group, for acetolysis of the epoxide followed by oxidation affords the isomeric 7α-hydroxy-$\Delta^{8(9)}$-11-ketone (III).

RECENT work has shown that treatment of the 9α : 11α-epoxide (I) with dilute mineral acids yields a 7 : 11-dihydroxy-$\Delta^{8(9)}$-steroid as the primary product (Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Budziarek, Johnson, and Spring, *J.*, 1952, 3410). The 11-hydroxyl group in this compound has been assigned an α-configuration in view of the ready formation of a 3 : 7 : 11-triacetate, but the stereochemistry of the entering 7-hydroxyl group has not been established.

In order to gain further information about this 7 : 11-diol and its mode of formation, the reaction between (I) and acetic acid was studied. The formation of the 7 : 11-diol can be envisaged as (nucleophilic) solvent attack at $C_{(7)}$ on the conjugate acid of (I)—accordingly, substitution of acetic acid for water should give a 7-acetoxy-11-hydroxy-compound (*e.g.*, II; R = Ac). Suitable conditions for the acetolysis of (I) were found with acetic acid–dioxan solutions at 50°, the rotation changing smoothly from the initially negative value to a finally constant positive value. Analysis of the reaction product, isolated in



(I) (II) (III)

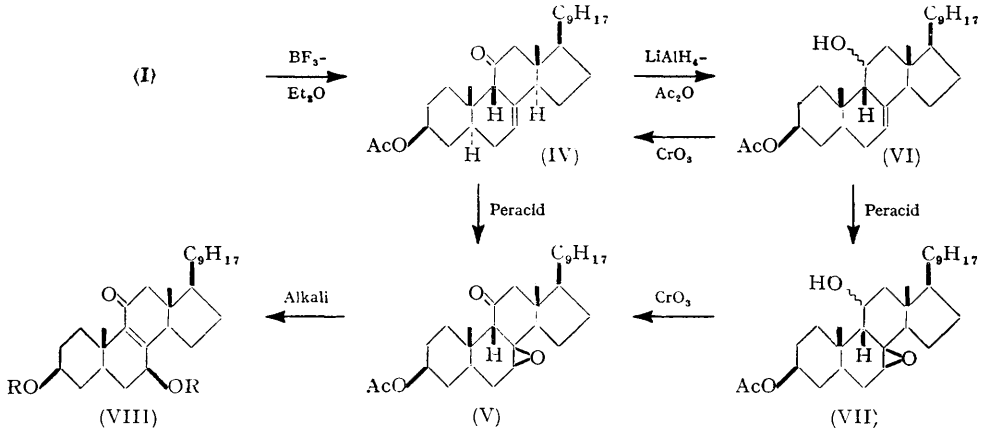
50—60% yield, indicated addition of acetic acid to (I), and the structure (II; R = Ac; 7α-configuration for reasons discussed later) was further indicated by the very ready oxidation (chromic acid in acetic acid rapidly oxidises allylic secondary alcohols; cf.

* Part LXIII, *J.*, 1954, 125.

Henbest and Jones, *J.*, 1948, 1792) to a conjugated ketone (III) (unreactive carbonyl group), and by acetylation to the triacetate obtained previously by acetylation of the known 7 : 11-diol.

The formation of the 7-acetate (II; R = Ac) confirms the mechanism discussed above, but the configuration of the 7-acetate group remained to be decided. This was shown to be α-orientated* by preparing the isomeric 7β-acetoxy-$\Delta^{(8)9}$-11-ketone (VIII; R = Ac) by another route. The boron trifluoride–ether complex isomerises (I) to an 11-oxo-Δ^{7}-9β-steroid (IV) (Heusler and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 398; Part LXII of this series, *J.*, 1953, 2921). The Δ^{7}-bond in (IV), in marked contrast to those in 9α-compounds, is readily hydrogenated, to yield a saturated 11-ketone (cf. Part LXII). This hydrogenation is stereospecific, proceeding by frontal attack of catalyst to yield an 8β : 9β-steroid exclusively.

The Δ^{7}-bond in (IV) reacts preferentially with monoperphthalic acid, to yield the epoxide (V) (Heusler and Wettstein, *loc. cit.*, also prepared this oxide but did not consider its configuration). A β-configuration is assigned to the 7 : 8-epoxy-group in view of the similar stereochemical courses taken by hydrogenation and peracid reactions with other trisubstituted olefinic bonds in the steroid series. It was just possible that epimerisation at $C_{(9)}$ had occurred during the peracid reaction with (IV), for Δ^{7}-9β-11-ketones isomerise very easily to 9α-compounds (Part LXII). However, the 9β-structure for (V) was confirmed by its preparation by an alternative route. Lithium aluminium hydride reduction (and reacetylation) converted (IV) into (VI), which still retained the β-$C_{(9)}$-configuration, for oxidation yielded the original ketone (IV) [the $C_{(11)}$-stereochemistry of (VI) will be discussed in a later paper]. Peracid oxidation of (VI) afforded the 7β : 8β-epoxide (VII) [hydrogenation of (VI) also proceeds by frontal attack, unpublished work], which on oxidation gave the 7β : 8β-epoxy-9β-11-ketone (V), identical with that prepared previously.



Alkaline rearrangement of (V) was followed spectroscopically, the maximum intensity (ε) reached under the conditions chosen being 5800 (the isolated pure diol had ε = 9000). Plotting the concentration of unsaturated ketone against time gave a smooth curve, which indicated that no appreciable amount of the 9α-epimer of (V) was being formed as an intermediate : alkali-assisted removal of the 9β-proton is therefore probably accompanied directly by movement of the negative charge on to the $C_{(7)}$-oxygen. Acetylation of the reaction product yielded (VIII; R = Ac), different from the conjugated ketone (III)

* Two possible reasons may be suggested for the acetate group's entering in the α-configuration at $C_{(7)}$. First, the reaction may simply be another example of "rear attack" which often takes place with steroids of natural configuration, but, secondly, the fact that the original epoxide group and the entering group have the same configuration may be significant, *i.e.*, for electrostatic reasons the acetate (anion) may approach from the same side as the (protonated) epoxide group. Both factors may operate in this instance. The possible importance of the second factor is supported by earlier suggestions of Winstein and Young for which Stork and White (*J. Amer. Chem. Soc.*, 1953, **75**, 4119) have recently provided further experimental support.

obtained previously *via* the acetolysis reaction, which must therefore contain a 7α-acetoxyl group.

It has been noted previously (Henbest, Jones, Wood, and Woods, *J.*, 1952, 4894) that γ-oxygenated αβ-unsaturated ketones often absorb at shorter wave-lengths in the ultra-violet than the corresponding unsubstituted compounds. The 7α- and the 7β-acetate (III and VIII; R = Ac) provide further examples of this effect, $\lambda_{max.}$ being at 2490 Å in each case, compared with 2540 Å observed with 3β-acetoxyergosta-8 : 22-dien-11-one.

Experimental

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

3β : 7α-*Diacetoxyergosta*-8 : 22-*dien*-11α-*ol* (II; R = Ac).—A solution of 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-diene (1 g.) in dioxan (40 c.c.) and acetic acid (40 c.c.) was kept at 50° for 2 days. The product was isolated with ether and chromatographed on deactivated alumina (100 g.). Light petroleum–benzene (3 : 1) eluted starting material (25 mg.), but light petroleum–benzene (1 : 3) yielded material which crystallised from aqueous acetone as needles (600 mg.), m. p. 140—147°. Further crystallisation gave the pure *compound*, m. p. 158—162°, $[\alpha]_D$ +83° (*c*, 2·1) (Found: C, 74·7; H, 9·8. $C_{32}H_{50}O_5$ requires C, 74·75; H, 9·8%). Acetylation gave the 3β : 7α : 11α-triacetate, m. p. 169—171° (undepressed on admixture with an authentic sample), $[\alpha]_D$ +93° (*c*, 1·1).

3β : 7α-*Diacetoxyergosta*-8 : 22-*dien*-11-*one* (III).—Solutions of the above 11-alcohol (2 g.) in acetone (20 c.c.) and chromic acid (290 mg.) in acetic acid (58 c.c.) were mixed and kept at 20° for 2 hr. The green solution was concentrated to a small bulk under reduced pressure and the steroid isolated with ether. The product in benzene was filtered through deactivated alumina (50 g.), to give material (1·8 g.) which when crystallised from methanol afforded *ketone*, m. p. 102—105°, $[\alpha]_D$ +109° (*c*, 0·8) (Found: C, 74·8; H, 9·4. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). In the first preparations of this compound a (subsequently unstable) modification was obtained, m. p. 68—70°; the rotation and light absorption of the two forms were identical. Light absorption: $\lambda_{max.}$ 2490 Å; ε = 8500. Infra-red spectrum (on supercooled melt): peaks at 1735, 1250 (acetate), 1670 (11-ketone), 1595 (Δ^8), and 980 cm.$^{-1}$ (Δ^{22}).

Hydrolysis with 5% potassium hydroxide solution in methanol at 20° overnight afforded the 3β : 7β-*diol* (crystallised from acetone), m. p. 202—205°, $[\alpha]_D$ +149° (*c*, 0·5) (Found, in sublimed sample: C, 78·55; H, 10·5. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%). Light absorption, $\lambda_{max.}$ 2510 Å; ε = 9400.

3β-*Acetoxy*-7β : 8β-*epoxy*-9β-*ergost*-22-*en*-11-*ol* (VII).—A solution of 3β-acetoxy-9β-ergosta-7 : 22-dien-11ξ-ol (200 mg.; m. p. 165—168°) and monoperphthalic acid (1·1 mols.) was kept at 20° for 7 days. Isolation with ether followed by crystallisation from methanol afforded the *epoxide* (90 mg.) as needles, m. p. 190—210°, $[\alpha]_D$ +61° (*c*, 0·83) (Found: C, 76·25; H, 10·3. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%).

3β-*Acetoxy*-7β : 8β-*epoxy*-9β-*ergost*-22-*en*-11-*one* (V).—(*a*) A solution of the Δ^7-steroid (IV) (1 g.) and monoperphthalic acid (1·1 mols.) in dry ether (40 c.c.) was kept at 20° for 3 weeks (alternatively, 10 mols. of peracid were used with a 7 hour reaction time—the reaction was followed polarimetrically). Crystallisation of the product from acetone yielded the epoxide (750 mg.) as needles, m. p. 175—177°, $[\alpha]_D$ −63° (*c*, 0·82) (Found: C, 76·45; H, 9·8. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%) (Heusler and Wettstein, *loc. cit.*, record m. p. 170·5—171·5°, $[\alpha]_D$ −74°).

(*b*) Solutions of (VII) (450 mg.) in acetone (25 c.c.) and chromic acid (8N; cf. *J.*, 1951, 2402) were mixed and kept at 20° for 5 min. Isolation with ether and crystallisation gave a good yield of the epoxy-ketone, m. p. 173—175°, $[\alpha]_D$ −63° (*c*, 0·46). Infra-red spectrum (in CS_2): peaks at 1730, 1250 (acetate), 1715 (shoulder, 11-ketone), and 970 cm.$^{-1}$ (Δ^{22}).

3β : 7β-*Diacetoxyergosta*-8 : 22-*dien*-11-*one* (VIII; R = Ac).—A solution of the foregoing 7β : 8β-epoxide (2 g.) and potassium hydroxide (4 g.) in methanol (400 c.c.) was kept at 20°. The concentration of conjugated ketone (estimated spectroscopically) reached a maximum after 5½ hr., thereafter slowly declining. The product was isolated (after 5½ hr.) with ether, acetylated in the usual way overnight, and then crystallised from methanol, to yield the 3β : 7β-*diacetate* (1·3 g.), m. p. 149—152°, $[\alpha]_D$ +83° (*c*, 0·95) (Found: C, 75·15; H, 9·65. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Light absorption: λ_{max} 2490 Å; ε = 8700. Infra-red spectrum (in Nujol): peaks at 1730, 1240 (acetate), 1658 (11-ketone), and 1593 cm.$^{-1}$ (Δ^8). In another experiment, the reacetylation stage was omitted and the 3β : 7β-*diol* (VIII; R = H) was isolated; it crystallised from acetone as needles, m. p. 213—217°, $[\alpha]_D$ +149° (Found: C, 75·4;

H, 10·35. $C_{28}H_{44}O_3,H_2O$ requires C, 75·3; H, 10·4%). Light absorption: $\lambda_{max.}$ 2530 Å; $\varepsilon = 9000$.

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