955. *Studies in the Steroid Group. Part LVIII.* Oxidation of 5α : 8α-Epidioxy-Δ$^{9(11)}$-steroids.*

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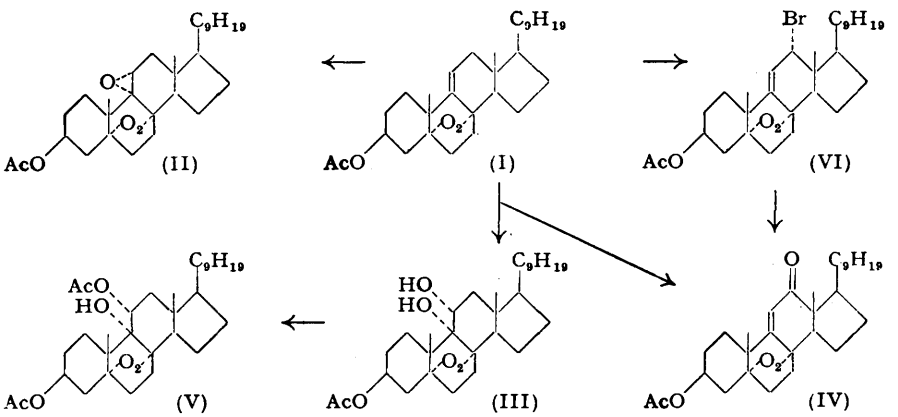
The 9 : 11-ethylenic linkage in 3β-acetoxy-5α : 8α-epidioxyergost-9(11)-ene (I) is shown to be rather unreactive towards oxidizing agents. However, a 9 : 11-epoxide and a 9 : 11-diol have been prepared, albeit in moderate yields. Oxidation with chromic acid results in attack at the 12-position, affording a 12-keto-5α : 8α-epidioxy-Δ$^{9(11)}$-compound; its somewhat unusual light absorption is discussed.

Isolated 9 : 11-ethylenic linkages are moderately reactive, being converted, for instance, into 9α : 11α-epoxides by perbenzoic acid (*inter al.*, Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278). As part of a study of the reactions of this bond in steroids containing also a 5α : 8α-epidioxide bridge, the oxidation of 3β-acetoxy-5α : 8α-epidioxyergost-9(11)-ene (I) (cf. *J.*, 1952, 4883) has been investigated.

Reaction between (I) and perbenzoic acid was very slow; chromatography of the product afforded a 9α : 11α-epoxide (II) (the configuration being assumed by analogy with previous work on the oxidation of Δ$^{9(11)}$-steroids, and also from consideration of molecular models), together with much starting material. Peracetic acid also reacted slowly, to give a low yield of the same product, but permonophthalic acid gave very little of the 9 : 11-epoxide.



Hydroxylation of the 9 : 11-bond in (I) was next studied. No reaction took place between (I) and osmium tetroxide in ether–pyridine even after several weeks at 20°. Likewise potassium permanganate in acetone effected little reaction, but potassium permanganate in acetic acid gave a mixture from which were isolated the 9 : 11-diol (III) (probably 9α : 11α-dihydroxy), and the 12-keto compound (IV), the latter also being

* Part LVII, preceding paper.

produced by chromic acid in acetic acid. The 9 : 11-diol afforded a 3 : 11-diacetate (V), its ready formation indicating the 11α-configuration of the hydroxyl group.

Attempted addition of hypobromous acid to the 9 : 11-bond in (I) with *N*-bromoacetamide and dilute mineral acid gave a good yield of the 12-bromo-compound (VI). The configuration of the bromine substituent is probably α, since attack is likely to take place from the (less hindered) rear [cf. formation of 7α-bromo-Δ^5-steroids (Greenhalgh, Henbest, and Jones, *J.*, 1952, 2380)], and there will be less steric interference between the $C_{(18)}$ methyl group and a 12α-bromine atom. The structure of the bromo-compound was proved by conversion into a 12-formoxy-compound, readily oxidized to the 12-keto-compound (IV). The allylic character of the bromine atom was confirmed by the ready formation of silver halide on treatment with alcoholic silver nitrate, but it was obvious from its reaction with formate ion that the bromine atom in (VI) is markedly less reactive than those in the structurally related 7α-bromo-Δ^5-compounds (Henbest and Jones, *J.*, 1948, 1792, 1798).

The main ultra-violet absorption band exhibited by the 12-keto-compound (IV) was at 2320 Å, *i.e.*, at an appreciably shorter wave-length than those (2400 Å) recorded previously for 12-keto-$\Delta^{9(11)}$-steroids (*inter al.*, Fieser, Rajagopalan, Wilson, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 4133; Mueller, Stobaugh, and Winniford, *ibid.*, p. 2400). This displacement must be connected with the presence of the oxygen substituent at $C_{(8)}$ and there is some evidence that γ-oxygen substituents in αβ-unsaturated ketones cause displacements of $\lambda_{max.}$ to shorter wave-lengths. Thus Ehrenstein and Stevens (*J. Org. Chem.*, 1940, **5**, 318) report that a 6-acetoxy-3-keto-Δ^4-steroid shows $\lambda_{max.}$ 2320 Å, in contrast to 3-keto-Δ^4-steroids with $\lambda_{max.}$ 2410 Å (both in ethanol solution). As further examples the conjugated dienones 3-hydroxy-β-ionone ($\lambda_{max.}$ 2870 Å) and β-ionone ($\lambda_{max.}$ 2960 Å) may be quoted (Henbest, *J.*, 1951, 1074). However, both 11-hydroxy-7-keto-$\Delta^{8(9)}$-steroids and 7-keto-$\Delta^{8(9)}$-steroids absorb maximally at the same wave-length, 2540 Å (cf. Fieser, Herz, and Huang, *J. Amer. Chem. Soc.*, 1951, **73**, 2397; Stork, Romo, Rosenkranz, and Djerassi, *ibid.*, p. 3546; Djerassi, Mancera, Stork, and Rosenkranz, *ibid.*, p. 4499), and further work is obviously required to establish relations between the structures and spectra of such pairs of compounds.

It is believed that the unreactivity of the double bond in (I) is due mainly to the hindrance imposed by the 5α : 8α-epidioxide bridge towards reagents attacking from the rear of the molecule. Examination of models shows that the epidioxide group projects from ring B (which is in the boat form), thus partly covering the approach to the 9 : 11-bond.

Experimental

General experimental directions are given in Part LVI.

3β-*Acetoxy*-5α : 8α-*epidioxy*-9α : 11α-*epoxyergostane* (II).—3β-Acetoxy-5α : 8α-epidioxyergost-9-ene (300 mg.) and perbenzoic acid (1·2 mols.) in chloroform (15 c.c.) were kept at 0° for 4 days. After being washed with dilute sodium carbonate solution the mixture was evaporated under reduced pressure and the residue (315 mg.) was chromatographed on deactivated alumina (60 g.). Elution with light petroleum–benzene (3 : 2) gave starting material (220 mg.), but elution with light petroleum–benzene (1 : 3) gave, after recrystallization from aqueous acetone, the 9 : 11-*epoxide* (35 mg.) as needles, m. p. 206—210°, $[\alpha]_D$ −73° (*c*, 0·67) (Found : C, 73·65; H, 9·75. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%). Peracetic acid at 50° affords this 9 : 11-oxide in similar yield.

3β-*Acetoxy*-5α : 8α-*epidioxy*-12-*ketoergost*-9-*ene* (IV).—Chromic acid (0·45 g.) in acetic acid (7 c.c.) was added to 3β-acetoxy-5α : 8α-epidioxyergost-9-ene (0·3 g.) dissolved in warm acetic acid (7 c.c.). The mixture was heated on a steam-bath for 30 minutes and the product, isolated with ether, was chromatographed in light petroleum on deactivated alumina (60 g.). Elution with light petroleum–benzene (4 : 1) gave gum; elution with light petroleum–benzene (1 : 1) gave a gelatinous solid. Recrystallization of this from methanol afforded a gel, which after being kept at 0° overnight had crystallized to give the 12-*keto*-compound (75 mg.) as small rhombs, m. p. 185—192°, $[\alpha]_D$ +12° (*c*, 0·60) (Found : C, 73·85; H, 9·6. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%). Light absorption : Max., 2320 and 3150 Å; ε = 12,450 and 100 respectively.

Alkaline hydrolysis gave 5α : 8α-*epidioxy*-3β-*hydroxy*-12-*keto*-*ergost*-9-*ene*, platelets (from methanol), m. p. 184—188·5°, $[\alpha]_D$ −5° (*c*, 0·79) (Found : C, 75·3; H, 10·0. $C_{28}H_{44}O_4$ requires

C, 75·6; H, 10·0%). Light absorption: Max. 2325 and 3180 Å; ε = 13,800 and 85 respectively. Infra-red spectrum (in Nujol): 1678 cm.$^{-1}$ (C=O stretching); 1640 cm.$^{-1}$ (C=C stretching).

Oxidation of 3β-*Acetoxy*-5α : 8α-*epidioxyergost*-9-*ene with Permanganate.*—Potassium permanganate (6 g.) in water (40 c.c.) and acetic acid (350 c.c.) was added during 10 minutes to a solution of 3β-acetoxy-5α : 8α-epidioxyergost-9-ene (10·5 g.) in acetic acid (200 c.c.), decolorization being almost immediate. After 45 minutes at 20°, the mixture was poured into water, and the steroid isolated with ether. The total product was chromatographed on alumina (1 kg.) from benzene, development with benzene giving unchanged starting material (*ca.* 2·5 g.), followed by 3β-acetoxy-5α : 8α-epidioxy-12-ketoergost-9-ene (3·5 g.) (IV), m. p. and mixed m. p. 186—192°, $[\alpha]_D$ +13° (*c*, 1·15), after recrystallization from methanol. Elution with ether–methanol (3 : 1) gave a pasty solid, which after further chromatography on deactivated alumina gave almost pure 9 : 11-diol (1·45 g.), m. p. 212—214°. Recrystallization from *iso*propyl ether–dioxan (2 : 1) gave 3β-*acetoxy*-5α : 8α-*epidioxy*-9α : 11α-*dihydroxyergostane* (III) as needles, m. p. 213—215°, $[\alpha]_D$ −58° (*c*, 0·70) (Found: C, 71·0; H, 9·8. $C_{30}H_{50}O_6$ requires C, 71·1; H, 9·95%). With acetic anhydride and pyridine at 20° overnight the diol gave 3β : 11α-*diacetoxy*-5α : 8α-*epidioxy*-9α-*hydroxyergostane* (V) as needles (from methanol), m. p. 216—223°, $[\alpha]_D$ −4° (*c*, 0·24) (Found: C, 70·0; H, 9·5. $C_{32}H_{52}O_7$ requires C, 70·2; H, 9·2%).

3β-*Acetoxy*-12α-*bromo*-5α : 8α-*epidioxyergost*-9-*ene* (VI).—3β-Acetoxy-5α : 8α-epidioxyergost-9-ene (1 g.) was dissolved in *tert.*-butanol (40 c.c.), 0·4N-sulphuric acid (10 c.c.), and the minimum quantity of ether. *N*-Bromoacetamide (700 mg.) was added with stirring. The resulting yellow solution was kept at 20° for 24 hours, during which the bromo-compound (700 mg.) had separated as needles, m. p. 170—171° [a further quantity (200 mg.) of less pure material was obtained from the mother-liquor by ether]. Recrystallization from ethyl acetate–methanol gave the *bromo*-compound as needles, m. p. 178—179° (decomp.), $[\alpha]_D$ +104° (*c*, 1·14) (Found: C, 65·75; H, 8·4; Br, 14·5. $C_{30}H_{47}O_4Br$ requires C, 65·3; H, 8·6; Br, 14·5%). The same compound was obtained by employing *N*-bromosuccinimide with or without the presence of sulphuric acid.

3β-*Acetoxy*-5α : 8α-*epidioxy*-12α-*formoxyergost*-9-*ene.*—Solutions of the foregoing bromo-compound (500 mg.) in dioxan (10 c.c.) and of anhydrous sodium formate (500 mg.) in formic acid (5 c.c.) were mixed, and heated at 80° for 4 hours, after which the solution was kept at 20° overnight. The steroid was isolated with ether; recrystallization from ethyl acetate–methanol yielded laths (340 mg.), m. p. 165—168°. Further recrystallization from the same solvent mixture gave the pure *formoxy*-compound, m. p. 169—170°, $[\alpha]_D$ +123° (*c*, 1·88) (Found: C, 71·85; H, 9·5. $C_{31}H_{48}O_6$ requires C, 72·05; H, 9·35%).

3β-*Acetoxy*-5α : 8α-*epidioxy*-12-*ketoergost*-9-*ene.*—The formoxy-compound (220 mg.) in acetic acid (4 c.c.) was treated with a solution of chromic acid (65 mg.) in acetic acid (10 c.c.). The solution was warmed at 50° for 4 hours and then kept at 20° overnight. Isolation with ether yielded a solid, which was passed in benzene through a short column of alumina (10 g.) (elution with benzene). Recrystallization from ethanol afforded the 12-keto-compound m. p. 174—185 undepressed with a sample prepared as described above, $[\alpha]_D$ +20° (*c*, 1·20). Light absorption: Max., 2310 Å; ε = 10,100.

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