848. *Some* 5α : 6α-*Epoxy*-3-*oxo*-*steroids*.

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Some 5α : 6α-epoxy-3-oxo-steroids have been prepared by oxidation of the corresponding 3β-hydroxy-derivatives with chromic acid–pyridine. The method could not be extended to 5β : 6β-epoxy-3β-hydroxy-steroids as the two compounds studied were converted into 6-oxygenated 3-oxo-Δ^4-steroids.

CERTAIN 5 : 6-epoxy-3-oxo-steroids of the (*allo*)pregnane series were required for biological study. Their direct preparation by epoxidation of the corresponding 3-oxo-Δ^5-steroids seemed unattractive from earlier studies in the cholesterol series. Thus Ruzicka and Bosshard [1] in 1937 oxidised cholest-5-en-3-one with perbenzoic acid, obtaining two isomeric products regarded as the corresponding 5 : 6-epoxides and arbitrarily assigned the designations " α " and " β." Certain fission reactions of the so-called " β-"epoxide, however, led Urushibara and Chuman [2] in 1949 to reformulate this compound as 5α : 6α-epoxycholestan-3-one. Mori and Mukawa [3] subsequently concluded that the previously designated " α-"epoxide was best represented as an unsaturated lactone. In seeking a more convenient route to the required compounds we studied the oxidation of 3β-hydroxy-5 : 6-epoxides with chromium trioxide–pyridine.[4]

From cholesterol α-epoxide we readily obtained 5α : 6α-epoxycholestan-3-one in moderate yield.* Similar oxidation of 5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one [5] furnished 5α : 6α-epoxy*allo*pregnane-3 : 20-dione, the constitution of which followed from its conversion by hydrogen bromide into 6β-bromo-5α-hydroxy*allo*pregnane-3 : 20-dione, which was dehydrated by thionyl chloride in pyridine to the known 6β-bromoprogesterone.[6] 21-Acetoxy-5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one,[7] obtained in improved yield by oxidation of 21-acetoxy-3β-hydroxypregn-5-en-20-one with monoperphthalic acid, was similarly converted into 21-acetoxy-5α : 6α-epoxy*allo*pregnane-3 : 20-dione.

Oxidation of 5β : 6β-epoxy-3β-hydroxy-steroids with chromium trioxide–pyridine followed a less consistent pattern. Cholesterol 5β : 6β-epoxide gave a product from which only 6β-hydroxycholest-4-en-3-one could be isolated. The hitherto unknown 5β : 6β-epoxy-3β-hydroxypregnan-20-one was obtained together with a smaller quantity of the easily separated 5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one, by treating with methanolic potassium hydroxide the material formed by reacting 3β-hydroxypregn-5-en-20-one with hypobromous acid. Its oxidation gave a complex product which yielded only pregn-4-ene-3 : 6 : 20-trione on chromatography.

Addition of hypobromous acid to the ethylenic linkage of 21-acetoxy-3β-hydroxypregn-5-en-20-one, followed by elimination of hydrogen bromide by heating the material with ethanolic potassium acetate, led to the formation of an apparently homogeneous compound,

* Since completion of this work, our attention has been drawn to a similar preparation of 5α : 6α-epoxycholestan-3-one (Mori and Mukawa, *Proc. Japan Acad.*, 1955, **31**, 532).

[1] Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 244.
[2] Urushibara and Chuman, *Bull. Chem. Soc. Japan*, 1949, **22**, 273.
[3] Mori and Mukawa, *ibid.*, 1954, **27**, 479.
[4] Poos, Arth, Beyler, and Sarett. *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[5] Ehrenstein and Stevens, *J. Org. Chem.*, 1941, **6**, 908; Davis and Petrow, *J.*, 1950, 1185.
[6] Sondheimer, Kaufmann, Romo, Martinez, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 4712.
[7] Ehrenstein, *J. Org. Chem.*, 1941, **6**, 626.

$C_{22}H_{34}O_5$, m. p. 192°, initially regarded as 21-acetoxy-5β : 6β-epoxy-3β-hydroxypregnan-20-one. This material was, however, oxidised by chromium trioxide–pyridine to a mixture from which 21-acetoxy-5α : 6α-epoxy*allo*pregnan-20-one was readily isolated, albeit in low yield. The ultraviolet absorption spectra of various mother-liquor fractions showed maxima at 240 and 249 mμ, but the compounds responsible for these absorptions were not obtained pure. These results, together with considerations of molecular-rotation data, led us to suspect the homogeneity of the epoxide, m. p. 192°. Its constitution as the 1 : 1 molecular compound of 21-acetoxy-5β : 6β-epoxy-3β-hydroxypregnan-20-one and the corresponding 5α : 6α-epoxide followed from chromatographic resolution of its diacetate into 3β : 21-diacetoxy-5β : 6β-epoxypregnan-20-one and 3β : 21-diacetoxy-5α : 6α-epoxy-*allo*pregnan-20-one which passed on equimolar admixture into the fully acetylated derivative of the product, m. p. 192°.

Experimental

Optical rotations were measured in chloroform solution in a 1-dm. tube. The ultraviolet absorption spectrum (in *iso*propyl alcohol) was kindly determined by Mr. M. T. Davies, B.Sc.

5α : 6α-*Epoxycholestan*-3-*one*.—Cholesterol 5α : 6α-epoxide (3 g.) in pyridine (30 ml.) was added to chromium trioxide (3 g.) in pyridine (30 ml.). The mixture was kept overnight and then poured into ether (200 ml.), the solution washed with dilute acetic acid, aqueous sodium carbonate, water, and dried, and the solvent removed. Crystallisation of the residue from aqueous ethanol gave 5α : 6α-epoxycholestan-3-one (1·8 g.), needles, m. p. 122—123°, $[\alpha]_D^{20}$ −39° (*c*, 1·0) (Found : C, 81·0; H, 10·8. Calc. for $C_{27}H_{44}O_2$: C, 81·0; H, 11·1%). No depression in m. p. was obtained on admixture with an authentic specimen prepared from cholest-5-en-3-one.

5α : 6α-*Epoxy*allo*pregnane*-3 : 20-*dione*.—5α : 6α-Epoxy-3β-hydroxy*allo*pregnan-20-one (2 g.) in pyridine (20 ml.) was oxidised with chromium trioxide (2 g.) in pyridine (20 ml.) for 18 hr. and the product isolated as described above. The *epoxide* (1·3 g.) formed prisms (from methylene dichloride–methanol), m. p. 194°, $[\alpha]_D^{21}$ +25° (*c*, 1·03) (Found : C, 76·7; H, 9·1. $C_{21}H_{30}O_3$ requires C, 76·4; H, 9·15%).

6β-*Bromo*-5α-*hydroxy*allo*pregnane*-3 : 20-*dione*.—The foregoing compound (300 mg.) in acetone (15 ml.) was treated with hydrogen bromide–acetic acid (0·2 ml. of 50% w/w) in acetone (5 ml.). The pure *bromohydrin* (270 mg.) was collected after 10 min.; the crystals had m. p. 165° (decomp.) (Found : C, 61·7; H, 7·8; Br, 19·4. $C_{21}H_{31}O_3Br$ requires C, 61·3; H, 7·6; Br, 19·4%).

6β-*Bromoprogesterone*.—The foregoing compound (400 mg.) in pyridine (7 ml.) at 0° was treated with thionyl chloride (0·2 ml.) added dropwise during 5 min. After a further 10 min. at 0°, the mixture was poured into ice-water and the solid collected and air-dried giving material (350 mg.), m. p. 140° (decomp.). Purified from acetone–hexane, 6β-bromoprogesterone formed prisms, m. p. 145° (decomp.) (Found : C, 63·9; H, 8·0. Calc. for $C_{21}H_{29}O_2Br$: C, 64·1; H, 7·4%), not depressed on admixture with an authentic specimen.[6]

21-*Acetoxy*-5α : 6α-*epoxy*-3β-*hydroxy*allo*pregnan*-20-*one*.—21-Acetoxy-3β-hydroxypregn-5-en-20-one (5 g.) in methylene dichloride (30 ml.) was treated with monoperphthalic acid (3·6 g.) in ether (60 ml.) for 3 hr. at room temperature. Thereafter the mixture was diluted with methylene dichloride, washed with dilute alkali and water, and dried, and the solvent removed. The residue was crystallised from acetone, giving 21-acetoxy-5α : 6α-epoxy-3β-hydroxy*allo*-pregnan-20-one (4·1 g.) in needles, m. p. 200—201°, $[\alpha]_D^{22}$ +26° (*c*, 0·97) [Ehrenstein [7] gives m. p. 195—197°, $[\alpha]_D$ +15·6° (in acetone)]. A further quantity (600 mg.) of 5α : 6α-epoxide with m. p. 195—197° was obtained by concentration of the mother-liquor.

3β : 21-*Diacetoxy*-5α : 6α-*epoxy*allo*pregnan*-20-*one*, prepared by acetylating the foregoing compound, crystallised from methanol in needles, m. p. 178°, $[\alpha]_D^{21}$ +20° (*c*, 0·93) (Found : C, 69·5; H, 8·4. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%).

21-*Acetoxy*-5α : 6α-*epoxy*allo*pregnane*-3 : 20-*dione*.—21-Acetoxy-5α : 6α-epoxy-3β-hydroxy-*allo*pregnan-20-one (2 g.) was oxidised overnight with chromium trioxide (2 g.) in pyridine (40 ml.) and the product (1·2 g.; m. p. 190—200°) isolated with ether. Purified from aqueous ethanol, the *epoxide* formed needles, m. p. 202—203°, $[\alpha]_D^{22}$ +34° (*c*, 0·78) (Found : C, 71·2; H, 8·6. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

Oxidation of Cholesterol 5β : 6β-*Epoxide*.—Cholesterol β-epoxide (2 g.) was oxidised as in the foregoing preparation and the product, isolated with ether, triturated with cold light petroleum (10 ml.). The insoluble fraction (700 mg.; m. p. *ca.* 160°) was purified from aqueous methanol to give 6β-hydroxycholest-4-en-3-one, flat needles, m. p. 190—191°, alone or on admixture

with an authentic specimen.[8] Acetylation gave 6β-acetoxycholest-4-en-3-one, m. p. and mixed m. p. 102°.

Crystalline material could not be isolated from the fraction soluble in light petroleum.

5β : 6β-*Epoxy*-3β-*hydroxypregnan*-20-*one*.—3β-Hydroxypregn-5-en-20-one (10 g.), suspended in a mixture of dioxan (200 ml.) and water (50 ml.), was treated with *N*-bromoacetamide (7 g.) followed by perchloric acid (2 ml. of 72%) in water (10 ml.). The mixture was stirred for 6 min.; a clear yellow solution was obtained. After addition of a little aqueous sodium sulphite, the mixture was poured into a large volume of water and extracted twice with ether. The combined extracts were well washed, dried, and concentrated to small bulk to give a sparingly soluble solid [6·5 g.; m. p. *ca.* 140° (decomp.)], which could not be recrystallised satisfactorily. It was heated under reflux for 5 min. with potassium hydroxide (3 g.) in methanol (60 ml.), and the solid obtained on pouring the mixture into water crystallised once from aqueous methanol to give needles (4·2 g.), m. p. 172—176°, $[\alpha]_D^{20}$ +52°. Further crystallisation from ethyl acetate gave 5β : 6β-*epoxy*-3β-*hydroxypregnan*-20-*one* (2·4 g.), needles, m. p. 188—189°, $[\alpha]_D^{22}$ +71° (*c*, 1·04) (Found: C, 75·7; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%). The 3β-*acetate* crystallised from aqueous methanol in blades, m. p. 133—134°, $[\alpha]_D^{20}$ +52° (*c*, 1·06) (Found: C, 73·9; H, 9·0. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%).

The ethyl acetate mother-liquor when cooled to below 0° deposited material (0·9 g.; m. p. 170—178°) which, on purification from aqueous ethanol, gave 5α : 6α-epoxy-3β-hydroxy*allo*pregnan-20-one [5] in plates, m. p. 190—191°, $[\alpha]_D^{20}$ +1° (*c*, 1·01) (Found: C, 75·6; H, 9·5%), identified by conversion into the 3β-acetate,[5] m. p. 167—168°, $[\alpha]_D^{20}$ +7° (*c*, 1·3).

Oxidation of 5β : 6β-*Epoxy*-3β-*hydroxypregnan*-20-*one*.—The epoxide (1·9 g.) was treated overnight with chromium trioxide (2 g.) in pyridine (40 ml.), and the product isolated with ether. Purification by direct crystallisation could not be achieved. The material was therefore acetylated in pyridine at room temperature and chromatographed on alumina (50 g.; B.D.H.). The solid fractions (600 mg.) obtained on elution with benzene–ethanol (98 : 2) were purified from methanol to give needles of pregn-4-ene-3 : 6 : 20-trione, m. p. 193—195°, $[\alpha]_D^{20}$ +29° (*c*, 1·2), $\lambda_{max.}$ 251 mμ (ε 10,100) (Found: C, 76·4; H, 8·8. Calc. for $C_{21}H_{28}O_3$: C, 76·8; H, 8·6%) [Amendolla *et al.*[9] give m. p. 193—194°, $[\alpha]_D$ +30°, $\lambda_{max.}$ 250 mμ (ε 10,600)]. Further elution of the column failed to give crystalline fractions.

(α + β)-*Epoxide derived from* 21-*Acetoxy*-3β-*hydroxypregn*-5-*en*-20-*one*.—A solution of 21-acetoxy-3β-hydroxypregn-5-en-20-one (5 g.) in a mixture of dioxan (90 ml.) and water (20 ml.) was treated with *N*-bromoacetamide (3·5 g.), followed by perchloric acid (1 ml. of 72%) in water (5 ml.). After 5 min., a few ml. of aqueous sodium sulphite were added, the mixture was poured into water, and the product was extracted with ether. Concentration of the washed and dried extract gave a solid [4·1 g.; m. p. *ca.* 145° (decomp.)] which failed to crystallise satisfactorily. It was heated under reflux for 20 min. with anhydrous potassium acetate (5 g.) in ethanol (50 ml.), and the solid (3·1 g.; m. p. 177—180°) obtained on pouring the mixture into water was crystallised from aqueous ethanol. The (α + β)-*epoxide* formed needles, m. p. 191—192°, $[\alpha]_D^{22}$ +47° (*c*, 0·78) (Found: C, 70·6; H, 8·4. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%). Attempts to resolve the 1 : 1 molecular compound by chromatography were unsuccessful.

The 3β-*acetoxy-derivative* formed plates (from ethanol), m. p. 155—156°, $[\alpha]_D^{20}$ +55° (*c*, 0·84) (Found: C, 69·1; H, 8·5. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). It (1 g.) was chromatographed on alumina (25 g.; B.D.H.) in benzene. Elution with the same solvent gave a solid (450 mg.) which was crystallised from methanol. 3β : 21-*Diacetoxy*-5β : 6β-*epoxypregnan*-20-*one* separated in needles, m. p. 161—162°, $[\alpha]_D^{22}$ +87° (*c*, 0·76) (Found: C, 69·8; H, 8·7%). Further elution of the column with methylene dichloride gave material crystallising from aqueous ethanol in needles, m. p. 176—178°, $[\alpha]_D^{20}$ +24°. This material gave no depression on admixture with an authentic specimen of 3β : 21-diacetoxy-5α : 6α-epoxy*allo*pregnan-20-one.

A mixture of the foregoing β-epoxide (100 mg.), m. p. 161—162°, and α-epoxide (100 mg.), m. p. 178°, was dissolved in hot ethanol (5 ml.). The plates which separated had m. p. 155°, $[\alpha]_D^{20}$ +56°, and consisted of the 1 : 1 molecular compound.

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[8] Ellis and Petrow, *J.*, 1939, 1078.
[9] Amendolla, Rosenkranz, and Sondheimer, *J.*, 1954, 1226.