133. 6β-*Hydroxy*-3 : 5-cyclo*pregnan*-20-*one and Some Related Compounds.*

By D. K. Patel, V. Petrow, and (Mrs.) I. A. Stuart-Webb.

A number of *cyclo*-steroids has been prepared by standard methods which however failed in two cases.

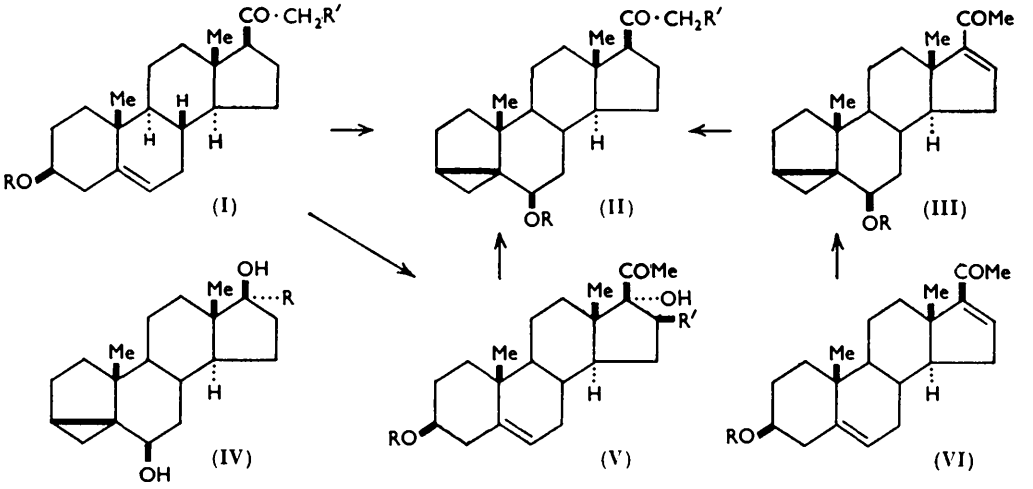
Our interest in 6β-hydroxy-3 : 5-*cyclo*pregnan-20-one (II; R = R′ = H) arose from the observation by Dingemanse and Huis in 'T Veld [1] that administration of 6β-hydroxy-3 : 5-*cyclo*androstan-17-one to a healthy male led to greater excretion of 11β-hydroxylated metabolites in the urine than did that of a comparable quantity of 3β-hydroxyandrost-5-en-17-one. Conversion of pregnenolone (I; R = R′ = H), a biogenetic precursor of the corticosteroids,[2] into the 6β-hydroxy-3 : 5-*cyclo*pregnane derivative (II; R = R′ = H) was therefore expected to yield a structure potentially susceptible to 11β-hydroxylation *in vivo* and thus worthy of biological study. The work was extended to the other 3 : 5-*cyclo*-steroids described below.

6β-Hydroxy-3 : 5-*cyclo*pregnan-20-one (II; R = R′ = H) (see Shoppee and Summers [3] for the stereochemistry and mechanism of the 3 : 5-*cyclo*-steroid rearrangement) was prepared as follows. (*a*) Pregnenolone (I; R = R′ = H) was converted into the benzenesulphonate (I; R = SO_2Ph, R′ = H) and toluene-*p*-sulphonate (I; R = $SO_2{\cdot}C_6H_4Me$, R′ = H),[4,5] which both passed into the required compound when heated with potassium acetate in aqueous acetone.[6] (*b*) Pregnenolone was treated with pyridine–sulphur trioxide (cf. ref. 7) to give pregnenolone pyridinium sulphate (I; R = $SO_3^-C_5H_5NH^+$). Reaction with potassium chloride gave the potassium salt which was transformed into the *cyclo*-steroid when heated with water and benzene under reflux.[8] (*c*) Pregnenolone toluene-*p*-sulphonate was treated with fused potassium acetate suspended in acetic anhydride at

[1] Dingemanse and Huis in 'T Veld, *Acta Physiol. Pharmacol. Neerl.*, 1951/2, **2**, 229.
[2] Saba, Hechter, and Stone, *J. Amer. Chem. Soc.*, 1954, **76**, 3862.
[3] Shoppee and Summers, *J.*, 1952, 3361.
[4] Butenandt and Grosse, *Ber.*, 1937, **70**, 1446.
[5] Karrer, Asmis, Sareen, and Schwyzer, *Helv. Chim. Acta*, 1951, **34**, 1022.
[6] Cf. Beynon, Heilbron, and Spring, *J.*, 1937, 1459.
[7] Sobel and Spoerri, *J. Amer. Chem. Soc.*, 1941, **63**, 1259.
[8] Teich, Rogers, Lieberman, Engel, and Davies, *ibid.*, 1953, **75**, 2523.

100°.[9] After removal of a small quantity of pregnenolone acetate, the residues gave on chromatography a low yield of 6β-acetoxy-3 : 5-*cyclo*pregnan-20-one (II; R = Ac, R′ = H). Hydrolysis of the last compound with methanolic potassium hydroxide gave an oil from which the parent *cyclo*-steroid was obtained after chromatography.

An alternative route to 6β-hydroxy-3 : 5-*cyclo*pregnan-20-one utilised 3β-hydroxypregna-5 : 16-dien-20-one (VI; R = H). This was converted into 6β-hydroxy-3 : 5-*cyclo*pregn-16-en-20-one (III; R = H) by heating its benzenesulphonate or toluene-*p*-sulphonate with



potassium acetate in aqueous acetone. Catalytic hydrogenation of the 16 : 17-unsaturated steroid gave the saturated alcohol (II; R = R′ = H), also obtained in less satisfactory yield by catalytic hydrogenation of the acetate (III; R = Ac), followed by alkaline hydrolysis of the product.

Extension of the 3 : 5-*cyclo*-steroid rearrangement to the 21-acetoxy-derivative (I; R = H, R′ = OAc) of pregnenolone offered no difficulty. The starting material, prepared by Ruschig's method,[10] was converted into the toluene-*p*-sulphonate (I; R = $SO_2 \cdot C_6H_4Me$, R′ = OAc) which passed readily into 21-acetoxy-6β-hydroxy-3 : 5-*cyclo*pregnan-20-one (II; R = H, R′ = OAc) on treatment with potassium acetate in hot aqueous acetone. 3β : 17α-Dihydroxypregn-5-en-20-one, in contrast, resisted rearrangement. For its preparation 16α : 17α-epoxy-3β-hydroxypregn-5-en-20-one [11] was treated with hydrobromic acid to give 16β-bromo-3β : 17α-dihydroxypregn-5-en-20-one (V; R = H, R′ = Br), which passed into 3β : 17α-dihydroxypregn-5-en-20-one on reduction with Raney nickel.[12,13] The toluene-*p*-sulphonate of this compound regenerated the parent alcohol on treatment with potassium acetate, and was recovered unchanged after being heated in slightly alkaline water–benzene mixtures. Similarly, attempts to rearrange 17α-methyl-3β-toluene-*p*-sulphonyloxyandrost-5-en-17β-ol were unsuccessful. 3β-Toluene-*p*-sulphonyloxy-17α-vinyl- and -17α-ethynyl-3β-toluene-*p*-sulphonyloxy-androst-5-en-17β-ol, however, behaved as expected, yielding the *cyclo*-steroids (IV; R = ·CH:CH_2 and ·C:CH).

Experimental

Optical rotations refer to $CHCl_3$ solution in a 1 dm. tube unless otherwise stated.

Pregnenolone benzenesulphonate (I; R = SO_2Ph, R′ = H), prisms, m. p. 144—145° (from

[9] Wallis, Fernholz, and Gephart, *J. Amer. Chem. Soc.*, 1937, **59**, 137.
[10] Ruschig, U.S.P. 2,554,472, 2,554,473, 2,609,379.
[11] Julian, Meyer, and Ryden, *J. Amer. Chem. Soc.*, 1950, **72**, 367; Julian, Meyer, Karpel, and Ryden Waller, *ibid.*, p. 5145; Ringold, Löken, Rosenkranz, and Sondheimer, *ibid.*, 1956, **78**, 816.
[12] Cf. Adams, Patel, Petrow, and Stuart-Webb, *J.*, 1954, 1825.
[13] Adkins, " Reactions of Hydrogen," Univ. Wisconsin Press, Wisconsin, 1937.

acetone–hexane), $[\alpha]_D^{28}$ +14° (*c* 0·537) (Found: C, 70·9; H, 7·6; S, 7·3. $C_{27}H_{36}O_4S$ requires C, 71·0; H, 7·9; S, 7·0%), was prepared by treating pregnenolone (5 g.) in pyridine (50 ml.) with redistilled benzenesulphonyl chloride (5 ml.) overnight at room temperature.

6β-*Hydroxy*-3 : 5-cyclo*pregnan*-20-*one* (II; R = R′ = H).—(*a*) Pregnenolone toluene-*p*-sulphonate (5 g.) (I; R = $SO_3 \cdot C_6H_4Me$, R′ = H) was heated with potassium acetate (5·5 g.) in 50% aqueous acetone (140 ml.) under reflux for 8—18 hr. The mixture was poured into water and the product isolated with chloroform–ether. Crystallisation from acetone gave 6β-*hydroxy*-3 : 5-cyclo*pregnan*-20-*one*, needles, m. p. 180—181°, $[\alpha]_D^{24}$ +123° (*c* 0·663) (Found: C, 80·1; H, 10·1. $C_{21}H_{32}O_2$ requires C, 79·8; H, 10·1%). (*b*) Pregnenolone benzenesulphonate likewise gave the *cyclo*-steroid, m. p. 180—181°, not depressed on admixture with a sample prepared as under (*a*).

Pregnenolone Pyridinium Sulphate (I; R = $SO_3^-C_5H_5NH^+$, R′ = H).—Pregnenolone (5 g.), dry benzene (60 ml.), pyridine (6 ml.), and pyridine–sulphur trioxide (5 g.) were stirred and warmed to 60° for 20 min. under anhydrous conditions. The mixture was cooled to room temperature and hexane (200 ml.) added. After being kept at 0° the precipitated solids were collected, washed with hexane–benzene (5 : 1), and dried in a desiccator. For purification, a sample (1 g.) was dissolved in chloroform (12 ml.) and chilled for a short time, and a small precipitate of pyridine–sulphur trioxide removed. Hexane (48 ml.) was added to the filtrate and, after storage at room temperature, the *pregnenolone pyridinium sulphate* collected and washed with a little hexane; it had m. p. 185—186°, $[\alpha]_D^{21}$ +16° (*c* 0·412) (Found: N, 3·3; S, 6·9. $C_{26}H_{37}O_5NS$ requires N, 3·0; S, 6·7%).

The foregoing compound (3 g.), suspended in water (60 ml.), was added with stirring to a solution of potassium chloride (6 g.) in water (60 ml.). The precipitated pregnenolone potassium sulphate was collected and washed with a little chloroform. It had m. p. 226—228°. A solution of this salt (500 mg.) in water (450 ml.) was made faintly alkaline with a few drops of 2N-sodium carbonate. Benzene (150 ml.) was added and the mixture heated under reflux for 5 hr. The benzene layer was removed, washed with water, dried, and evaporated. The residue was crystallised from acetone, to give 6β-hydroxy-3 : 5-*cyclo*pregnan-20-one, m. p. and mixed m. p. 180—181°.

6β-*Phenylacetoxy*-3 : 5-cyclo*pregnan*-20-*one* (II; R = $CO \cdot CH_2Ph$, R′ = H).—The alcohol (1 g.) in dry benzene (4 ml.) and pyridine (1 ml.) was treated at 0° under nitrogen with phenylacetyl chloride (0·7 ml.). After 19 hr. at room temperature the oily product was isolated with chloroform. It was chromatographed in benzene–hexane (1 : 1) on alumina (30 g.; B.D.H. chromatography grade used throughout). The benzene–hexane (1 : 1) ⟶ pure benzene eluates yielded the *phenylacetate*, needles (from acetone–hexane), m. p. 136—137°, $[\alpha]_D^{23}$ +102° (*c* 0·554) (Found: C, 79·7; H, 8·9. $C_{29}H_{38}O_3$ requires C, 80·2; H, 8·8%).

6β-*Acetoxy*-3 : 5-cyclo*pregnan*-20-*one* (II; R = Ac, R′ = H).—(*a*) This *compound*, prisms, m. p. 144—145° (from ether–hexane), $[\alpha]_D^{24}$ +111° (*c* 0·478) (Found: C, 77·0; H, 9·7. $C_{23}H_{34}O_3$ requires C, 77·1; H, 9·5%), was prepared by heating the alcohol (4·6 g.) with pyridine–acetic anhydride (10 ml. of each) for 1 hr. on the steam-bath. (*b*) Fused potassium acetate (10 g.) was dissolved in boiling acetic anhydride (150 ml.), and the solution cooled to 50°. Pregnenolone toluene-*p*-sulphonate (3·5 g.) was added and the mixture heated with stirring on the steam-bath for 36 hr. The solution was concentrated under reduced pressure and the product isolated with ether (charcoal). Crystallisation from acetone–hexane gave pregnenolone acetate. The residue, in benzene, was chromatographed on alumina (100 g.). The benzene ⟶ benzene–ether eluates yielded 6β-acetoxy-3 : 5-*cyclo*pregnan-20-one, identified by m. p. and mixed m. p.

The foregoing compound (360 mg.) in methanol (18 ml.) was heated with potassium hydroxide (400 mg.) in water (4 ml.) under reflux for 2 hr. The product, in benzene, was passed through a short column of alumina and thereafter crystallised from acetone to give the free alcohol, identified by m. p. and mixed m. p.

3β-*Benzenesulphonyloxypregna*-5 : 16-*dien*-20-*one* (VI; R = SO_2Ph) separated from acetone in needles or plates, m. p. 152—153°, $[\alpha]_D^{24}$ −31° (*c* 0·3244) (Found: C, 71·3; H, 7·3; S, 7·2. $C_{27}H_{34}O_4S$ requires C, 71·4; H, 7·5; S, 7·05%).

6β-*Hydroxy*-3 : 5-cyclo*pregn*-16-*en*-20-*one* (III; R = H) formed prisms, m. p. 136—137°, $[\alpha]_D^{27}$ +90° (*c* 0·44) (Found: C, 79·4; H, 9·3. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%), after crystallisation from acetone–hexane (with Mr. D. N. Kirk, B.Sc.).

6β-*Acetoxy*-3 : 5-cyclo*pregn*-16-*en*-20-*one* separated from ether–hexane in prisms, m. p. 143—145°, $[\alpha]_D^{21}$ + 80° (*c* 1·02) (Found: C, 77·2; H, 8·6. $C_{23}H_{32}O_3$ requires C, 77·5; H, 8·9%).

The free alcohol (III; R = H) (800 mg.) in 90% aqueous methanol (80 ml.) was hydrogenated over 2% palladium–calcium carbonate at atmospheric pressure, and the product crystallised from acetone, to give the *cyclo*-steroid (II; R = R′ = H), m. p. and mixed m. p. 180—181°.

The acetate (III; R = Ac) (2·5 g.) in methanol (100 ml.) was similarly hydrogenated over Raney nickel, to give the acetate (II; R = Ac, R′ = H), m. p. and mixed m. p. 144—145° (Found : C, 77·6; H, 9·8%).

21-*Acetoxy*-3β-*toluene*-p-*sulphonyloxypregn*-5-*en*-20-*one* (I; R = SO_2·C_6H_4Me, R′ = OAc) had m. p. 105°, $[\alpha]_D^{23}$ +25° (*c* 0·412) (Found : C, 67·4; H, 7·8; S, 5·7. $C_{30}H_{40}O_6S$ requires C, 68·2; H, 7·6; S, 6·1%), after crystallisation from acetone–hexane.

21-*Acetoxy*-6β-*hydroxy*-3 : 5-cyclo*pregnan*-20-*one* (II; R = H, R′ = OAc) separated from acetone–hexane in needles, m. p. 122—123°, $[\alpha]_D^{27}$ +114° (*c* 0·464) (Found : C, 73·9; H, 9·3. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1%).

16β-*Bromo*-3β : 17α-*dihydroxypregn*-5-*en*-20-*one* (V; R = H, R′ = Br), m. p. 193—194° (from methylene chloride–hexane), $[\alpha]_D^{18}$ +7° (*c* 0·527 in dioxan) (Found : C, 61·2; H, 7·6; Br, 19·6. $C_{21}H_{31}O_3Br$ requires C, 61·3; H, 7·5; Br, 19·5%), was prepared by treating 16α : 17α-epoxy-3β-hydroxypregn-5-en-20-one (10 g.) in acetic acid (100 ml.) with 30% hydrobromic acid in acetic acid (1 ml.) at room temperature for 30 min.

3β-*Acetoxy*-16β-*bromo*-17α-*hydroxypregn*-5-*en*-20-*one* (V; R = Ac, R′ = Br), m. p. 159—160° (from aqueous methanol), $[\alpha]_D^{22}$ −30° (*c* 0·422) (Found : C, 61·5; H, 7·4; Br, 17·2. $C_{23}H_{33}O_4Br$ requires C, 60·9; H, 7·3; Br, 17·7%), was similarly prepared from 3β-acetoxy-16α : 17α-epoxypregn-5-en-20-one.

17α-*Hydroxy*-3β-*toluene*-p-*sulphonyloxypregn*-5-*en*-20-*one* (V; R = SO_2·C_6H_4Me, R′ = H) had m. p. 153—154° (Found : C, 69·4; H, 7·5. $C_{28}H_{38}O_5S$ requires C, 69·1; H, 7·8%) after crystallisation from acetone–hexane.

17α-*Methyl*-3β-*toluene*-p-*sulphonyloxyandrost*-5-*en*-17β-*ol*, needles (from acetone), had m. p. 122—123°, $[\alpha]_D^{24}$ −62° (*c* 0·97) (Found : C, 70·1; H, 8·0; S, 7·2. $C_{27}H_{38}O_4S$ requires C, 70·7; H, 8·3; S, 7·0%).

3β-*Toluene*-p-*sulphonyloxy*-17α-*vinylandrost*-5-*en*-17β-*ol* separated from acetone–hexane in needles, m. p. 105° (Found : S, 7·0. $C_{28}H_{38}O_4S$ requires S, 6·8%).

17α-*Vinyl*-3 : 5-cyclo*androstane*-6β : 17β-*diol* (IV; R = ·CH:CH_2).—The foregoing compound (2·3 g.) was heated with potassium acetate in 50% aqueous acetone under reflux for 6½ hr. The product, in benzene, was chromatographed on alumina (60 g.). The ether ⟶ ether–acetone eluates yielded the cyclo-*steroid*, m. p. 154—155°, $[\alpha]_D^{21}$ +28° (*c* 0·35) (Found : C, 79·3; H, 10·4. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·1%), after crystallisation from acetone–hexane.

17α-*Ethynyl*-3β-*toluene*-p-*sulphonyloxyandrost*-5-*en*-17β-*ol* formed needles, m. p. 140—141°, $[\alpha]_D^{22}$ −74° (*c* 0·960) (Found : C, 72·1; H, 8·2; S, 6·5. $C_{28}H_{36}O_4S$ requires C, 71·8; H, 7·7; S, 6·84%), on crystallisation from acetone–hexane.

17α-*Ethynyl*-3 : 5-cyclo*androstane*-6β : 17β-*diol* (IV; R = ·C:CH).—The product from 7 g. of the preceding ester was chromatographed in benzene on alumina (200 g.). The ether ⟶ ether–acetone (9 : 1) eluates yielded the cyclo-*steroid*, m. p. 153—154°, $[\alpha]_D^{21}$ −8° (*c* 0·711) (Found : C, 79·6; H, 9·7. $C_{21}H_{30}O_2$ requires C, 80·3; H, 9·6%).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

Chemical Research Laboratories,
The British Drug Houses Ltd. London, N.1.

[*Received, October 1st,* 1956.]