697. *Aza-steroids. Part I.* 3-*Aza*-A-*homo*-5α- *and* -5β-*cholestane.**

By C. W. Shoppee and J. C. P. Sly.

5α-Cholestan-3-one oxime undergoes the Beckmann change to give a single ε-lactam, reduced by lithium aluminium hydride to the parent base 3-aza-A-homo-5α-cholestane. The structures of the ε-lactam and the base are proved by conversion of the former into the known related ε-lactone.

5β-Cholestan-3-one oxime similarly yields a single ε-lactam, reduced by lithium aluminium hydride to the parent base 3-aza-A-homo-5β-cholestane. The structures of this ε-lactam and this base are proved by transformation of the former into the ε-lactone and reduction of this with lithium aluminium hydride to 2 : 3-*seco*-5β-cholestane-2 : 3-diol, which we have prepared from 2 : 3-*seco*-5β-cholestane-2 : 3-dioic acid.

The infrared absorption spectra of the ε-lactams suggest that the seven-membered heterocyclic ring A is strainless.

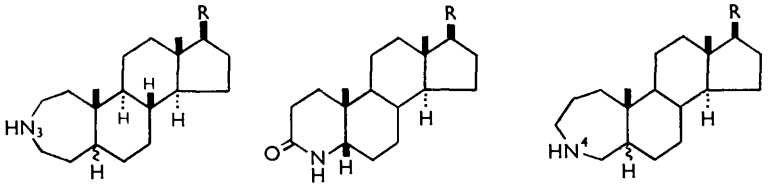
The interesting physiological properties of steroid alkaloids have directed attention to amino-steroids, and numerous papers on the preparation and properties of these compounds have been published.[1] In 1954 we commenced a general study of aza-steroids, with the nitrogen incorporated into ring A, B, C, or D, and embracing the eight series of compounds derived from cholestane, cholane, pregnane, and androstane. We now record

* In this paper acceptance of recent I.U.P.A.C. recommendations is anticipated: the names 5α-cholestane, 5β-cholestane, and 5β-cholane are used in place of cholestane, coprostane, and cholane, respectively (*J.*, 1951, 3527).

[1] *E.g.*, Barnett, Ryman, and Smith, *J.*, 1946, 524, 526, 528; Uhle, *J. Amer. Chem. Soc.*, 1951, **73**, 883; Howarth, McKenna, and Powell, *J.*, 1952, 1110; Šorm, Labler, and Czerny, *Coll. Czech. Chem. Comm.*, 1953, **12**, 842; Fieser and Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 6306; Gould, Shapiro, and Hershberg, *ibid.*, 1954, **76**, 5567; Micheli and Bradsher, *ibid.*, 1955, **77**, 4788.

the preparation of two of the parent bases, 3-aza-A-homo-5α- and -5β-cholestane (as I; R = C_8H_{17}).

Barnett and Reichstein [2] prepared a compound which they regarded as the 24→12-lactam of a methyl 12-amino-11-hydroxy-5β-cholanate, but before our work few communications dealing with aza-steroids have appeared. W. E. Bachmann and Ramirez [3]



(I) (II) (III)

have described the 16-aza-17-oxosteroids derived from (±)-3-deoxyequilenin and (±)-3-deoxy-14-*iso*equilenin; Kaufmann [4] prepared single 17-oxo-17*a*-aza-D-homosteroids from the oximes of dehydro*epi*androsterone, of androst-4-ene-3 : 17-dione, and of (±)-œstrone-*b* benzoate by Beckmann rearrangement; Woodward *et al.*[5] obtained the 4-phenyl and the 4-benzyl derivative of 4-azacholest-5-en-3-one as by-products of their total synthesis of cholesterol; and Clemo and Mishra [6] synthesised 4-aza-1 : 2-*cyclo*pentenophenanthrene from α-naphthylamine and ethyl 2-oxo*cyclo*pentanecarboxylate.

Since our work, Hara [7] has prepared, by essentially the method we used, methyl 4-oxo-3-aza- and 3-oxo-4-aza-5β-cholanate (II; R = $C_4H_8{\cdot}CO_2Me$) and methyl 3-oxo-4-aza- and 4-oxo-3-aza-A-homo-5β-cholanate; by reduction of the latter pair of esters with lithium aluminium hydride, he obtained 3-aza-A-homo-5β-cholan-24-ol (I; R = $C_4H_8{\cdot}CH_2{\cdot}OH$) and 4-aza-A-homo-5β-cholan-24-ol (III; R = $C_4H_8{\cdot}CH_2{\cdot}OH$). The structure of the 4-aza-steroid was established by conversion into 1-azachrysene,[8] whilst that of the 4-aza-A-homosteroid was proved by acid hydrolysis, Hofmann degradation, and ozonolysis to the known 5-oxo-3 : 4-*seco*-A-norcholanic acid; the structures of the corresponding 3-aza-steroids, which were obtained only in traces (1%, 3%), follow by exclusion. By similar reactions Regan and Hayes [9] recently prepared single 17-oxo-17*a*-D-homosteroids from the oximes of dehydro*epi*androsterone acetate and of (+)-œstrone-*b* and its methyl ether by Beckmann rearrangement, and, by reduction with lithium aluminium hydride, the corresponding 17*a*-aza-steroids; structures were assigned on the basis of the ease of esterification of the amino-acids derived by alkaline hydrolysis of the 17-oxo-17*a*-aza-D-homosteroids.

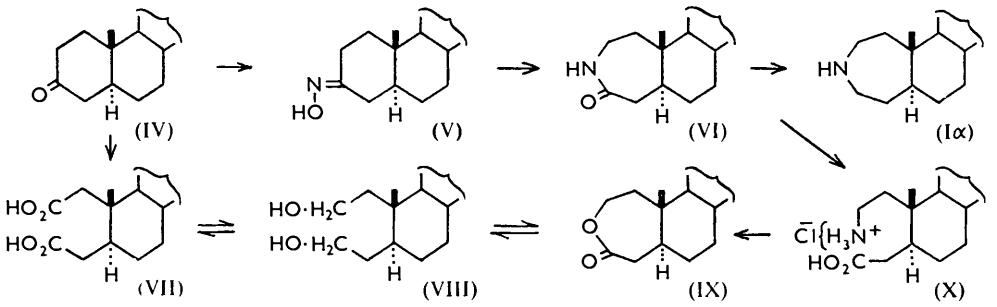
5α-Cholestane-3-one (IV) gives a single oxime (V), which by treatment with thionyl chloride in dioxan undergoes the Beckmann change to yield the ε-lactam (VI); this, by reduction with lithium aluminium hydride, gives 3-aza-A-homo-5α-cholestane (Iα; R = C_8H_{17}), which was characterised by preparation of the *N*-acetyl derivative, the nitrosamine, and the *N*-methyl methiodide.

The structures of the ε-lactam (VI) and the base (Iα) have been proved in the following way. The ε-lactam by hydrolysis with hydrochloric–acetic acid furnishes the amino-acid hydrochloride (X), deaminated by nitrous acid to the analogous hydroxy-acid, which immediately forms the ε-lactone (IX), m. p. 185°, $[\alpha]_D$ +46°. This ε-lactone is identical with that obtained by Nes and Lettré [10] by chromium trioxide oxidation of the diol (VIII),

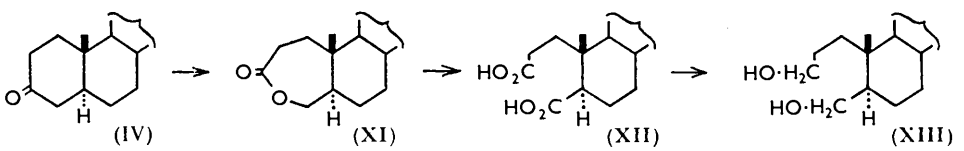
[2] Barnett and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 926.
[3] W. E. Bachmann and Ramirez, *J. Amer. Chem. Soc.*, 1950, **72**, 2527.
[4] Kaufmann, *ibid.*, 1951, **73**, 1779.
[5] Woodward, Sondheimer, Taub, Heusler, and McLamore, *ibid.*, 1952, **74**, 4230.
[6] Clemo and Mishra, *J.*, 1953, 192.
[7] Hara, *Pharm. Bull.* (*Japan*), 1955, **3**, 209, 297.
[8] Mosettig and Krueger, *J. Org. Chem.*, 1938, **3**, 325.
[9] Regan and Hayes, *J. Amer. Chem. Soc.*, 1956, **78**, 639; cf. ref. 4.
[10] Nes and Lettré, *Annalen*, 1956, **598**, 65.

m. p. 156°, which they prepared by reduction with lithium aluminium hydride of the anhydride or the dimethyl ester of the Windaus–Uibrig acid [11] (VII).

The ε-lactone (IX) is different from the isomeride (XI), m. p. 186°, $[\alpha]_D$ +1°, +4°, prepared by Burckhardt and Reichstein [12] and by us from 5α-cholestan-3-one (IV) by oxidation with perbenzoic acid in chloroform at 20°, whose structure is proved by alkaline



hydrolysis to the corresponding hydroxy-acid and oxidation of this as the methyl ester with chromium trioxide in acetic acid at 20° to give, after alkaline hydrolysis, dihydro-Diels's acid [11] (XII). Finally, the ε-lactone (XI), by reduction with lithium aluminium hydride, gives the diol (XIII), m. p. 121°, $[\alpha]_D$ +10°, which is different from the isomeride (VIII).

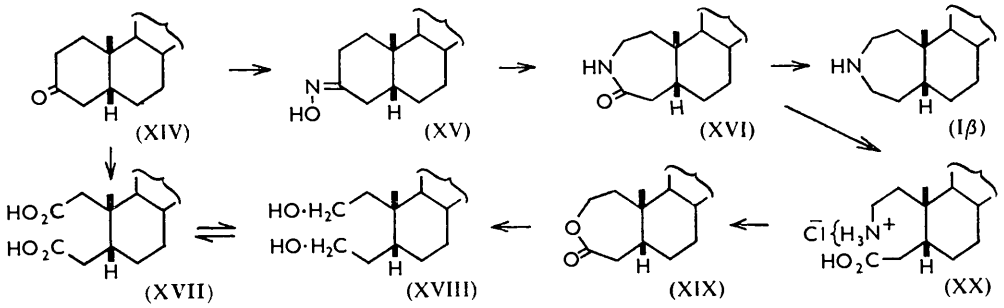


Gardner and Ellis,[13] on protracted oxidation of 5α-cholestan-3-one (IV) with ammonium persulphate in acetic acid at 80°, isolated three lactones, $C_{27}H_{46}O_2$, m. p. 159°, 201°, and 184°. The nature of the second compound is obscure; the first is probably identical with the lactone, m. p. 154—155°, $[\alpha]_D$ +28°, prepared by Nes [14] by oxidation of 2 : 3-*seco*-5α-cholestane-2 : 3-diol (VIII) with chromium trioxide in acetic acid—whereby oxidation of the primary 2-alcohol group, as opposed to the primary 3-alcohol group, has occurred. The third compound, for which no specific rotation is recorded, could be identical with either of the lactones (IX) and (XI).

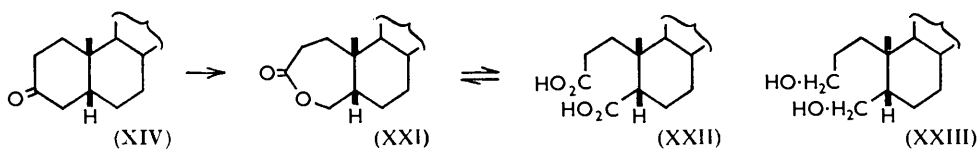
5β-Cholestan-3-one (XIV) affords a single oxime (XV) which, by Beckmann rearrangement with thionyl chloride, gives the ε-lactam (XVI), reduced by lithium aluminium hydride to 3-aza-A-homo-5β-cholestane (Iβ; R = C_8H_{17}), which was characterised as the *N*-acetyl derivative and the *N*-methyl methiodide. The structures (XVI) and (Iβ) rest on the following evidence. The ε-lactam (XVI) by acid hydrolysis yields the amino-acid hydrochloride (XX), deaminated by nitrous acid to the hydroxy-acid which passes into the ε-lactone (XIX), m. p. 183°, $[\alpha]_D$ +50°, reduced by lithium aluminium hydride to the diol (XVIII). The ε-lactone (XIX) was originally obtained by Gardner and Godden [15] from 5β-cholestan-3-one (XVII) as the main product of protracted oxidation with ammonium persulphate in acetic acid at 80°. The diol (XVIII) has also been prepared by us from

[11] Windaus and Uibrig, *Ber.*, 1914, **47**, 2387; Windaus and Dalmer, *Ber.*, 1919, **52**, 162.
[12] Burckhardt and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 1434.
[13] Gardner and Ellis, *Biochem. J.*, 1918, **12**, 72.
[14] Nes, personal communication.
[15] Gardner and Godden, *Biochem. J.*, 1913, **7**, 588.

5β-cholestan-3-one (XIV), by conversion into the 2β-sulphonic methyl ester,[16] and oxidation with chromium trioxide in acetic acid at 70° to 2 : 3-*seco*-5β-cholestane-2 : 3-dioic acid [16,17] (XVII), and reduction of this with lithium aluminium hydride.



The ε-lactone (XIX) differs from the isomeride (XXI), m. p. 157°, $[\alpha]_D$ +49°, first obtained by Gardner and Godden [15] from 5β-cholestan-3-one (XIV) by protracted oxidation with ammonium persulphate in acetic acid at 80°; the isomer (XXI) was also prepared by Burckhardt and Reichstein [12] and by us from 5β-cholestan-3-one (XIV) by oxidation with perbenzoic acid in chloroform at 20°, as well as by Lederer *et al.*[18] The structure (XXI) is proved by alkaline hydrolysis to the hydroxy-acid and oxidation of this as the methyl ester with chromium trioxide in acetic acid at 20° to give, after alkaline hydrolysis, Gardner's acid [15,16] (XXII). The ε-lactone (XXI) by reduction with lithium aluminium hydride affords the diol (XXIII), m. p. 124°, $[\alpha]_D$ +35°.



The principal frequencies in the infrared absorption spectra of the ε-lactams (VI, XVI) are here tabulated, together with those for the isomeric ε-lactam esters (as I or III; R = $C_4H_8{\cdot}CO_2Me$) reported by Hara [7] (who does not specify the conditions of observation).

ε-Lactam		Frequencies (cm.$^{-1}$) NH	[NH]–C=O
(VI)	5α	3420	1655
(XVI)	5β	3420	1658
(Cf. I) 4-Oxo-3-aza-	5β	3115, 3224	1645, 1681
(Cf. III) 3-Oxo-4-aza-	5β	3135, 3236	1664, 1669

The NH stretching frequency observed for (VI) and (XVI) at 3420 cm.$^{-1}$ corresponds with the single band shown by simple secondary amides and lactams in dilute solution. The double peaks observed for the isomeric ε-lactams (as I or III; R = $C_4H_8{\cdot}CO_2Me$) suggest that the measurements were made on the compounds in the solid state.

The carbonyl absorption frequencies are similar to those of normal secondary amides (dilute solution, 1670—1700 cm.$^{-1}$; solid, 1630—1680 cm.$^{-1}$) and comparable with the value 1667 cm.$^{-1}$ for a nine-membered ring lactam reported by Witkop *et al.*[19] This suggests that the seven-membered rings are unstrained.* Accurate models indicate that,

* The ε-lactone (IX) and its isomeride,[14] m. p. 155°, $[\alpha]_D$ +28°, are also strainless, exhibiting $\nu_{max.}$ 1742—1746 cm.$^{-1}$ in CS_2.

[16] Windaus and Kuhr, *Annalen*, 1937, **532**, 52; Windaus and Mielke, *ibid.*, 1938, **536**, 116.
[17] Marker, Wittle, Plambeck, Rohrmann, Krueger, and Ulshafer, *J. Amer. Chem. Soc.*, 1939, **61**, 3317.
[18] Lederer, Marx, Mercier, and Perot, *Helv. Chim. Acta*, 1946, **29**, 1354.
[19] Witkop, Patrick, and Rosenblum, *J. Amer. Chem. Soc.*, 1951, **73**, 2641.

in the A/B-*trans*-compound (VI), ring A is strainless and can exist in various conformations capable of strainless interconversion; in one of these the mutual repulsion of 1α- and 5α-H is minimised at the expense of approach by 2β- and 4*a*β-H, whilst in another 2β- and 4*a*β-H are virtually parallel and almost axial, although rotation of $C_{(1)}$ causes a slight increase in the 1α-, 5α-H interaction. A similar situation holds for the A/B-cis-compounds (XVI: as I or III), with one possible conformation in which 2β- and 5β-H, and 1α- and 4*a*α-H, respectively, are staggered.

Experimental

M. p.s were determined thermoelectrically on a Kofler block (error ±2°). Solvents were rigorously purified and dried and, for chromatography, unless stated otherwise, alumina (Spence type H, activity ~ II) was used. The " usual working up " implies extraction with ether, washing the ethereal extract successvely with 2N-sodium carbonate and water, brief drying (Na_2SO_4), and evaporation. $[\alpha]_D$ are for $CHCl_3$ solutions unless otherwise stated. Ultraviolet absorption spectra were determined for EtOH solutions in a Hilger Uvispek spectrophotometer, whilst infrared absorption spectra were measured for CCl_4 solutions on a Perkin-Elmer Model 21 double-beam instrument, unless otherwise specified.

Beckmann Rearrangement of 5α-*Cholestan*-3-*one Oxime*.—5α-Cholestan-3-one oxime (4·8 g.) in dry dioxan (150 c.c.) was warmed to 40° and thionyl chloride (4·5 c.c.) added with stirring during 5 min. The mixture was kept at 40° for a further 10 min., then made alkaline by saturated sodium hydrogen carbonate solution. The mixture was further diluted with water and extracted with much ether. Working up in the usual manner furnished a solid (4·5 g.), which was chromatographed on aluminium oxide (130 g.) prepared in benzene. Elution with benzene (3 × 450 c.c.) and ether–benzene (1 : 4; 3 × 450 c.c.) furnished a sticky solid; elution with ether–benzene (1 : 1; 5 × 450 c.c.) and ether (5 × 450 c.c.) gave unchanged oxime (930 mg.); elution with ether–chloroform (1 : 1; 2 × 450 c.c.) and chloroform (3 × 450 c.c.) gave 3-*aza*-A-*homo*-5α-*cholestan*-4-*one* (VI) (3·0 g.), which after sublimation at 200—220°/0·02 mm. had m. p. 268—271°, $[\alpha]_D$ +16° (*c* 0·7) (Found: C, 80·8; H, 11·8; N, 3·5. $C_{27}H_{47}ON$ requires C, 80·7; H, 11·8; N, 3·5%).

Lithium Aluminium Hydride Reduction of 4-*Oxo*-3-*aza*-A-*homo*-5α-*cholestane* (VI).—The lactam (1 g.) in dioxan (150 c.c.) was refluxed for 48 hr. with lithium aluminium hydride (1 g.). Excess of hydride was destroyed with water. Repeated extraction of the precipitated aluminium hydroxide with chloroform, followed by evaporation of solvent, gave an oil (950 mg.) which, by treatment with dry hydrogen chloride in ether, gave the insoluble 3-*aza*-A-*homo*-5α-*cholestane hydrochloride*, which crystallised from methanol–ethyl acetate, m. p. 275—280° [Found (after drying at 120°/0·5 mm. for 4 hr.): C, 76·25; H, 11·8. $C_{27}H_{50}NCl$ requires C, 76·4; H, 11·9%]. The hydrochloride with 4N-methanolic potassium hydroxide gave 3-*aza*-A-*homo*-5α-*cholestane* (Iα), b. p. 230—235°/0·7 mm., $[\alpha]_D$ +52° (*c* 0·8), which could not be satisfactorily crystallised (Found: C, 83·3; H, 12·8. $C_{27}H_{49}N$ requires C, 83·6; H, 12·75%). With acetic anhydride–pyridine at 100° for 6 hr. it gave, after crystallisation from aqueous acetone, N-*acetyl*-3-*aza*-A-*homo*-5α-*cholestane*, m. p. 109—111°, $[\alpha]_D$ +50° (*c* 0·8) [Found (after distillation at 235—240°/0·4 mm.): C, 80·5; H, 12·3. $C_{29}H_{51}ON$ requires C, 81·0; H, 11·8%].

N-*Nitroso*-3-*aza*-A-*homo*-5α-*cholestane*.—The aza-steroid, on treatment with sodium nitrite solution in boiling acidic aqueous dioxan, gave N-*nitroso*-3-*aza*-A-*homo*-5α-*cholestane*, m. p. 107—109°, after crystallisation from acetone [Found (after drying at 25°/0·4 mm. for 10 hr.): C, 77·5; H, 11·5. $C_{27}H_{48}ON_2$ requires C, 77·8; H, 11·6%].

N-*Methyl*-3-*aza*-A-*homo*-5α-*cholestane Methiodide*.—The aza-steroid (100 mg.) was heated at 100° for 3 hr. with 99% formic acid (1 c.c.) and 40% formaldehyde (1 c.c.). The mixture was poured into water, basified with ammonia, and extracted with ether. The ethereal solution was washed with water, dried, and evaporated to an oil; this was dissolved in acetone (3 c.c.), methyl iodide (0·3 c.c.) added, and the mixture refluxed for 0·5 hr. Evaporation and trituration of the residual solid with ether gave N-*methyl*-3-*aza*-A-*homo*-5α-*cholestane methiodide*, m. p. 275—277° after crystallisation from methanol–ethyl acetate [Found (after drying at 95°/0·4 mm. for 5 hr.): C, 63·7; H, 9·8; N, 2·7. $C_{29}H_{54}NI$ requires C, 64·0; H, 10·0; N, 2·6%].

Acid Hydrolysis of 3-*Aza*-A-*homo*-5α-*cholestan*-4-*one* (VI).—The lactam (1·5 g.) was refluxed

with acetic acid (300 c.c.) and concentrated hydrochloric acid (75 c.c.) for 40 hr., during which a slow stream of hydrogen chloride was passed through the solution. The solution was evaporated to dryness under reduced pressure. The residual solid was triturated with methanol–water (5 : 1), and the insoluble starting material (0·4 g.) removed. The aqueous methanol solution was evaporated almost to dryness; then a further quantity of unchanged lactam (0·1 g.) was removed. Evaporation of the methanol solution to dryness and crystallisation of the solid product from methanol–ethyl acetate gave 2-*amino*-2 : 3-seco-5α-*cholestan*-3-*oic acid hydrochloride* (X) (1·2 g.), m. p. 220—225° [Found (after drying at 70°/0·5 mm. for 4 hr.): C, 67·8; H, 10·7; N, 2·9. $C_{27}H_{50}O_2NCl,CH_3{\cdot}CO_2Et$ requires C, 68·3; H, 10·7; N, 2·9%].

Deamination of 2-*Amino*-2 : 3-seco-5α-*cholestan*-3-*oic Acid Hydrochloride* (X): 2-*Hydroxy*-2 : 3-seco-5α-*cholestan*-3-*oic* 3 ⟶ 2-*Lactone* (IX).—The hydrochloride (550 mg.) in 55% acetic acid (130 c.c.) was treated with an ice-cold solution of sodium nitrite (1·1 g.) in 55% acetic acid (20 c.c.), shaken intermittently for 1 hr., and left at 15° for a further 40 hr. It was diluted with water, shaken with ether, and filtered, to remove unchanged hydrochloride (220 mg.). The ethereal solution was washed repeatedly with water, dried, and evaporated to a solid (270 mg.), m. p. 175—183°, which was chromatographed on neutral aluminium oxide [20] (8 g.) prepared in benzene–pentane (1 : 1). Elution with benzene (4 × 30 c.c.) gave, after crystallisation from ether–methanol, the lactone (IX) (130 mg.), m. p. 181—183°, $[\alpha]_D$ +46° (*c* 0·7), $\nu_{max.}$ (in CS_2) 1746 cm.$^{-1}$ (CO) (absence of OH band) [Found (after drying at 20°/0·02 mm. for 4 hr.): C, 80·3; H, 11·4. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·4%], which gave no m. p. depression with an authentic specimen of m. p. 184—185°, $[\alpha]_D$ +47°, $\nu_{max.}$ (in CS_2) 1742, 1744 cm.$^{-1}$, prepared by Nes and Lettre.[10, 14]

3-*Hydroxy*-2 : 3-seco-5α-*cholestan*-2-*oic* 2 ⟶ 3-*Lactone* [*by* Dr. W. R. Nes].—Modification of the procedure of Nes and Lettré [10] for oxidation of the diol (VIII), by use of chromium trioxide in acetic acid, affords 3-*hydroxy*-2 : 3-seco-5α-*cholestan*-2-*oic* 2 ⟶ 3-*lactone*, m. p. 154—155°, $[\alpha]_D$ +28°, $\nu_{max.}$ (in CS_2) 1742 cm.$^{-1}$ [absence of OH band, differences from (IX) in the finger-print region] (Found: C, 80·5; H, 11·4. $C_{27}H_{46}O_2$ requires C, 80·6; H, 11·4%).

4-*Hydroxy*-3 : 4-seco-5α-*cholestan*-3-*oic* 3 ⟶ 4-*Lactone* (XI).—5α-Cholestan-3-one (1·2 g.) was treated with a chloroform solution of perbenzoic acid (23 c.c.; 1 c.c. = 52·5 mg. of perbenzoic acid) at 15°, and the solution kept in the dark for 16 hr. Excess of perbenzoic acid was destroyed with potassium iodide solution, and free iodine destroyed with sodium thiosulphate solution. The usual isolation procedure, with washing with sodium hydrogen carbonate solution gave, after crystallisation from ether–methanol, 4-hydroxy-3 : 4-*seco*-5α-cholestan-3-oic 3 ⟶ 4-lactone (XI), m. p. 186°, $[\alpha]_D$ +4° (*c* 1·2) {lit.,[12] m. p. 186—187°, $[\alpha]_D$ +1° (in acetone)}.

3 : 4-seco-5α-*Cholestane*-3 : 4-*diol* (XIII).—4-Hydroxy-3 : 4-*seco*-5α-cholestan-3-oic 3 ⟶ 4-lactone (XI) (150 mg.) in ether (35 c.c.) was refluxed with lithium aluminium hydride (50 mg.) for 1 hr. Excess of hydride was destroyed with ethyl acetate, and the mixture worked up in the usual way to give, after crystallisation from acetone, 3 : 4-seco-5α-*cholestane*-3 : 4-*diol* (110 mg.), m. p. 121—122°, $[\alpha]_D$ +10° (*c* 1·0) [Found (after drying at 20°/0·02 mm. for 6 hr.): C, 79·5; H, 12·2. $C_{27}H_{50}O_2$ requires C, 79·7; H, 12·3%].

Beckmann Rearrangement of 5β-*Cholestan*-3-*one Oxime*.—5β-Cholestan-3-one oxime (m. p. 65—67°; 4·5 g.) in dry dioxan (200 c.c.) was warmed to 40° and thionyl chloride (10 c.c.) added, with stirring, during 5 min. The mixture was kept at 40° for a further 20 min., cautiously neutralised with saturated sodium hydrogen carbonate solution, and extracted with a large volume of ether. The product, a dark brown oil (4·3 g.), was chromatographed on aluminium oxide (130 g.) prepared in benzene–pentane (1 : 1). Elution with benzene–pentane (1 : 1), benzene, and ether furnished uncrystallisable oils (1·3 g.); elution with chloroform–ether (1 : 4, 3 × 200 c.c.; and 3 : 7, 4 × 200 c.c.) gave 3-*aza*-A-*homo*-5β-*cholestan*-4-*one* (XVI) (1·62 g.) which, after sublimation at 190—200°/0·02 mm., had m. p. 166—174° clearing to a homogeneous liquid at 195°, $[\alpha]_D$ +42° (*c* 0·8). Repeated sublimation and crystallisation from methylene chloride failed to alter the m. p. (Found: C, 80·5; H, 11·7; N, 3·45. $C_{27}H_{47}ON$ requires C, 80·7; H, 11·8; N, 3·5%).

Lithium Aluminium Hydride Reduction of 3-*Aza*-A-*homo*-5β-*cholestan*-4-*one* (XVI).—The ε-lactam (XVI) (1 g.) in dry dioxan (125 c.c.) was refluxed with lithium aluminium hydride (1 g.) for 48 hr. Working up as for the 5α-epimeride (VI) gave (*a*) 3-*aza*-A-*homo*-5β-*cholestane*

[20] Reichstein and Shoppee, *Trans. Faraday Soc.*, 1949, **7**, 205.

hydrochloride, m. p. 267—271°, after recrystallisation from methanol–ethyl acetate [Found (after drying at 120°/0·5 mm. for 4 hr.): C, 76·1; H, 11·9. $C_{27}H_{50}NCl$ requires C, 76·4; H, 11·9%], (*b*) 3-*aza*-A-*homo*-5β-*cholestane* (Iβ), b. p. 200—210°/0·5 mm., $[\alpha]_D$ +27° (*c* 2·0) (Found: C, 83·4; H, 12·75; N, 3·8. $C_{27}H_{49}N$ requires C, 83·6; H, 12·75; N, 3·6%), and (*c*) N-*acetyl*-3-*aza*-A-*homo*-5β-*cholestane*, m. p. 105—107°, $[\alpha]_D$ +33° (*c* 0·9), after crystallisation from 90% aqueous acetone [Found (after distillation at 250°/0·5 mm.): C, 80·6; H, 11·95. $C_{29}H_{51}ON$ requires C, 81·0; H, 11·95%].

N-*Methyl*-3-*aza*-A-*homo*-5β-*cholestane Methiodide*.—The aza-steroid (Iβ) (100 mg.), 90% formic acid (1 c.c.), and 40% formaldehyde (1 c.c.) were heated together at 100° for 3 hr. The mixture was poured into water, basified with ammonia, and extracted with ether. The ethereal solution was washed with water, dried, and evaporated. The residual oil was dissolved in acetone (5 c.c.), methyl iodide (0·5 c.c.) added, and the mixture refluxed for 0·5 hr.; evaporation of the solvent and washing of the residual solid with ether gave N-*methyl*-3-*aza*-A-*homo*-5β-*cholestane methiodide*, m. p. 280—282°, after crystallisation from methanol–ethyl acetate [Found (after drying at 100°/0·5 mm. for 2 hr.): C, 64·1; H, 9·8; N, 2·5. $C_{29}H_{45}NI$ requires C, 64·1; H, 10·0; N, 2·6%].

Hydrolysis of 3-*Aza*-A-*homo*-5β-*cholestan*-4-*one* (XVI).—A solution of the ε-lactam (1·05 g.) in acetic acid (200 c.c.) and concentrated hydrochloric acid (55 c.c.) was refluxed for 45 hr. The solution was evaporated to dryness under reduced pressure, and the residual solid (1·1 g.) recrystallised from methanol–ether to give 2-*amino*-2 : 3-seco-5β-*cholestan*-3-*oic acid hydrochloride* (XX) (900 mg.), m. p. 223—229° [Found (after drying at 125°/0·03 mm. for 6 hr.): C, 69·85; H, 10·9; N, 3·0. $C_{27}H_{50}O_2NCl$ requires C, 70·1; H, 11·05; N, 3·1%].

Deamination of 2-*Amino*-2 : 3-seco-5β-*cholestan*-3-*oic Acid Hydrochloride* (XX).—The hydrochloride (500 mg.) in 55% acetic acid (100 c.c.) was treated with a cold solution of sodium nitrite (1 g.) in 55% acetic acid (10 c.c.), and the mixture was set aside overnight at 20°. The mixture was diluted with water, extracted with ether, and filtered to remove unchanged hydrochloride. The ethereal extract was repeatedly washed with water until all the unchanged hydrochloride had been removed, dried, and evaporated to give a solid (220 mg.), which was chromatographed on neutralised aluminium oxide [20] (7 g.) prepared in benzene–pentane (1 : 4). Elution with benzene–pentane (1 : 1) afforded, after crystallisation from ether–methanol, 2-*hydroxy*-2 : 3-seco-5β-*cholestan*-3-*oic* 3 ⟶ 2-*lactone* (XIX), m. p. 182—183°, $[\alpha]_D$ +50° (*c* 1·0) [Found (after drying at 20°/0·03 mm. for 4 hr.): C, 80·6; H, 11·4. $C_{27}H_{46}O_2$ requires C, 80·55; H, 11·4%].

Lithium Aluminium Hydride Reduction of 2-*Hydroxy*-2 : 3-seco-5β-*cholestan*-3-*oic* 3 ⟶ 2-*Lactone* (XIX).—(*a*) The ε-lactone (200 mg.) in ether was refluxed with lithium aluminium hydride for 4 hr. The usual working up gave an oil (190 mg.), which was chromatographed on aluminium oxide (6 g.). Elution with methanol (20 c.c. × 4) gave 2 : 3-seco-5β-*cholestane*-2 : 3-*diol* (XVIII) (140 mg.) as a glass, b. p. 160—165°/0·02 mm., $[\alpha]_D$ +26° (*c* 1·4) (Found: C, 79·5; H, 12·2. $C_{27}H_{50}O_2$ requires C, 79·7; H, 12·3%).

(*b*) 2 : 3-*seco*-5β-Cholestane-2 : 3-dioic acid [16] (300 mg.) in ether was refluxed with lithium aluminium hydride for 5 hr. Working up in the usual way gave an oil (280 mg.), which was chromatographed on aluminium oxide (9 g.). Elution with methanol furnished a glass (220 mg.), b. p. 158—164°/0·02 mm., $[\alpha]_D$ +27° (*c*, 1·6), which did not crystallise (Found: C, 79·4; H, 12·3%).

4-*Hydroxy*-3 : 4-seco-5β-*cholestan*-3-*oic* 3 ⟶ 4-*Lactone* (XXI).—5β-Cholestan-3-one (m. p. 60—61°; 1·3 g.) was treated with a chloroform solution of perbenzoic acid (30 c.c.; 1 c.c. ≡ 30 mg. perbenzoic acid), and the solution kept in the dark at 20° for 22 hr. Excess of perbenzoic acid was destroyed with potassium iodide solution, and the resulting iodine removed with sodium thiosulphate solution. Extraction with ether, followed by washing with sodium hydrogen carbonate solution and water, drying, and evaporation, gave 4-hydroxy-3 : 4-*seco*-5β-cholestan-3-oic 3 ⟶ 4-lactone (1 g.), m. p. 158°, $[\alpha]_D$ +49° (*c* 1·2), after crystallisation from methanol.

3 : 4-seco-5β-*Cholestane*-3 : 4-*diol* (XXIII).—4-Hydroxy-3 : 4-*seco*-5β-cholestan-3-oic 3 ⟶ 4-lactone (XXI) (500 mg.) in ether (120 c.c.) was refluxed with lithium aluminium hydride (200 mg.) for 1 hr. Working up in the usual way gave an oil (450 mg.), which crystallised from ether–pentane to give 3 : 4-seco-5β-*cholestane*-3 : 4-*diol*, m. p. 124—126°, $[\alpha]_D$ +35° (*c* 1·0) [Found (after drying at 20°/0·03 mm. for 18 hr.): C, 79·3; H, 12·0. $C_{27}H_{50}O_2$ requires C, 79·7; H, 12·4%].

One of us (J. C. P. S.) acknowledges the financial support of the Department of Scientific and Industrial Research and of the Commonwealth Scientific and Industrial Research Organisation. We are grateful to Glaxo Laboratories Ltd. and Nicholas (Pharmaceuticals) Pty., Ltd., Melbourne, for gifts of cholesterol, and to Dr. W. R. Nes, National Institute of Health, Bethesda, Maryland, for his collaboration.

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