217. *Steroids and Walden Inversion. Part XXVII.* 3α-Cholesterylamine and Coprostan-3α-ylamine.*

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Cholest-5-ene-3α-carboxylic acid, as its azide, undergoes the Curtius rearrangement to give the 3α-*iso*cyanate, which by acid hydrolysis yields 3α-cholesterylamine. Reduction of the 3α-*iso*cyanate with lithium aluminium hydride affords *N*-methyl-3α-cholesterylamine, methylated to *NN*-dimethyl-3α-cholesterylamine, which is also obtained by Emde degradation of benzyldimethyl-3α-cholesterylammonium iodide.

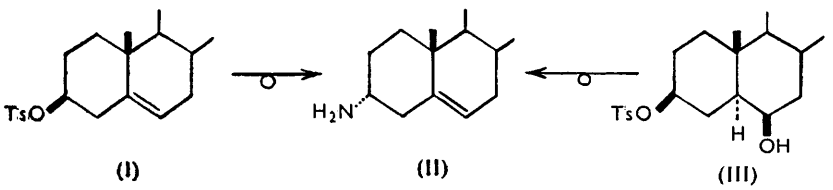
Catalytic hydrogenation of cholest-5-ene-3α-carboxylic acid gives coprostane-3α-carboxylic acid, converted by Curtuis rearrangement of its azide into 3α-acetamidocoprostane, also obtained by hydrogenation of 3α-acetamidocholest-5-ene.

In a re-investigation of the reaction of cholesteryl toluene-*p*-sulphonate (I) with liquid ammonia, Haworth, McKenna, and Powell [1] and Haworth, Lunts, and McKenna [2] isolated three isomeric bases, namely, 3β-cholesterylamine, m. p. 96°, $[\alpha]_D$ −26°, −34°, 3 : 5-*cyclo*-cholestan-6β-ylamine,[3] m. p. 84°, $[\alpha]_D$ +34°, +36°, and 3α-cholesterylamine (II) [which Pierce *et al.*[4] prepared by degradation of *N*-benzyl-3α-cholesterylamine by the procedure of Vavasour, Bolker, and McKay,[5] and by ammonolysis and subsequent dehydration of 6β-hydroxycholestan-3α-yl toluene-*p*-sulphonate (III)].

3α-Cholesterylamine (II) has recently been isolated through its *iso*propylidene derivative by Haworth, Lunts, and McKenna,[2] and we have now prepared it in the following way. Cholest-5-ene-3α-carboxylic acid (V; R = H), in which the configuration of the carboxyl group has been established by Roberts, Shoppee, and Stephenson,[6] was converted by thionyl chloride into the chloride, which with dry sodium azide in anhydrous acetone–dioxan gave the azide (IV). This by the Curtius rearrangement, in which configuration in the migrating group is known to be preserved, furnished the 3α-*iso*cyanate (VIII), which

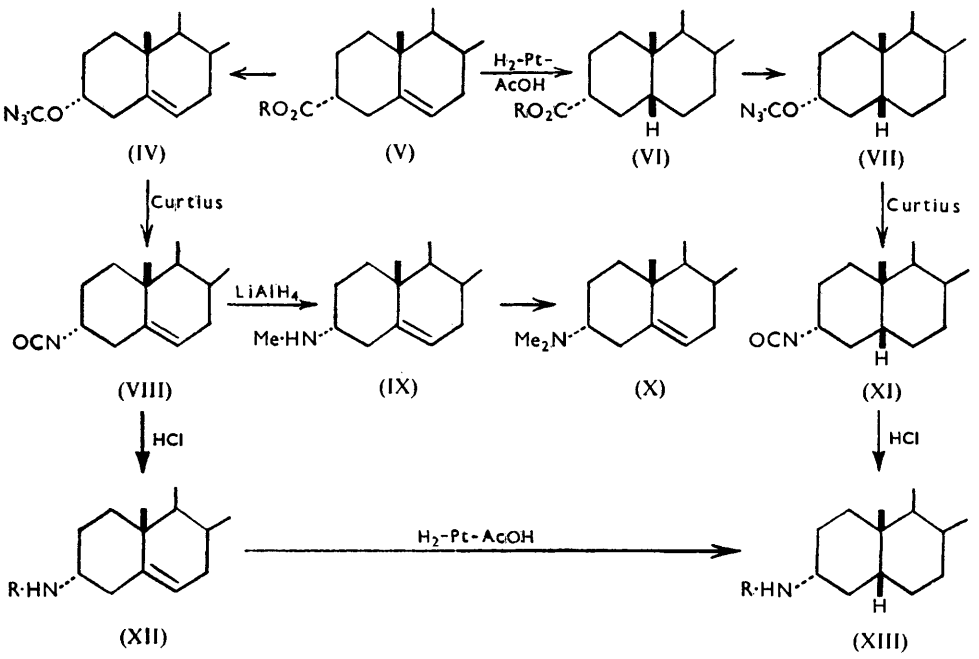
* Part XXVI, *J.*, 1955, 2876.

[1] Haworth, McKenna, and Powell, *J.*, 1953, 1110.
[2] Haworth, Lunts, and McKenna, *J.*, 1955, 986.
[3] Julian, Magnani, Cole, and Meyer, *J. Amer. Chem. Soc.*, 1948, **70**, 1834.
[4] Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694.
[5] Vavasour, Bolker, and McKay, *Canad. J. Chem.*, 1952, **30**, 933.
[6] Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705.



(I) (II) (III)

(II): m. p. 100°, $[\alpha]_D$ −40°, −44° (ref. 1, 2).



Formula	M. p.	[α]	Ref.
(V): R = H	155°	−40°	4
R = Me	114	−40	4
(IX)	85—86	−31	*a*
	86		1
	88	−28	7
(XII): R = H	100	−44	2
	100	−40	4
R = Ac	188	−32	*a*
	182		2
	189		5
	189	−30	4

Formula	M. p.	[α]	Ref.
(VI): R = H	179°	+31°	*a*
R = Me	72	+30	*a*
(X)	69	−31	*a*
	71		1
	69		2
	70	−31	8
(XIII): R = Ac	217	+48	*a*
	180		2

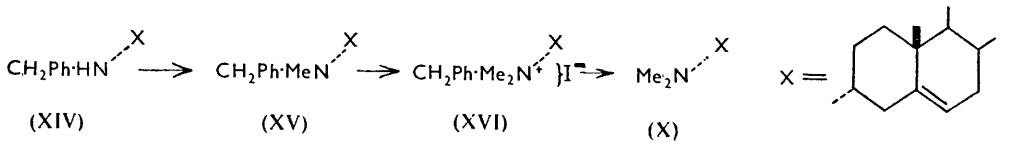
Ref. (*a*) = This work.

could not satisfactorily be purified. The crude 3α-*iso*cyanate, on hydrolysis with hydrochloric acid in benzene–acetic acid, gave 3α-cholesterylamine (XII; R = H) as a colourless oil, which crystallised only with great difficulty and was converted into 3α-acetamidocholest-5-ene (XII; R = Ac).

Reduction of the crude 3α-*iso*cyanate (VIII) with lithium aluminium hydride gave *N*-methyl-3α-cholesterylamine (IX), corresponding with the product prepared from cholesteryl toluene-*p*-sulphonate and monomethylamine by Haworth, McKenna, and Powell [1] and Pierce, Shoppee, and Summers.[7] Methylation gave *NN*-dimethyl-3α-cholesterylamine [8] (X), which was also obtained by the following route: *N*-Benzyl-3α-cholesterylamine [5] (XIV) was methylated with formaldehyde–formic acid, and the

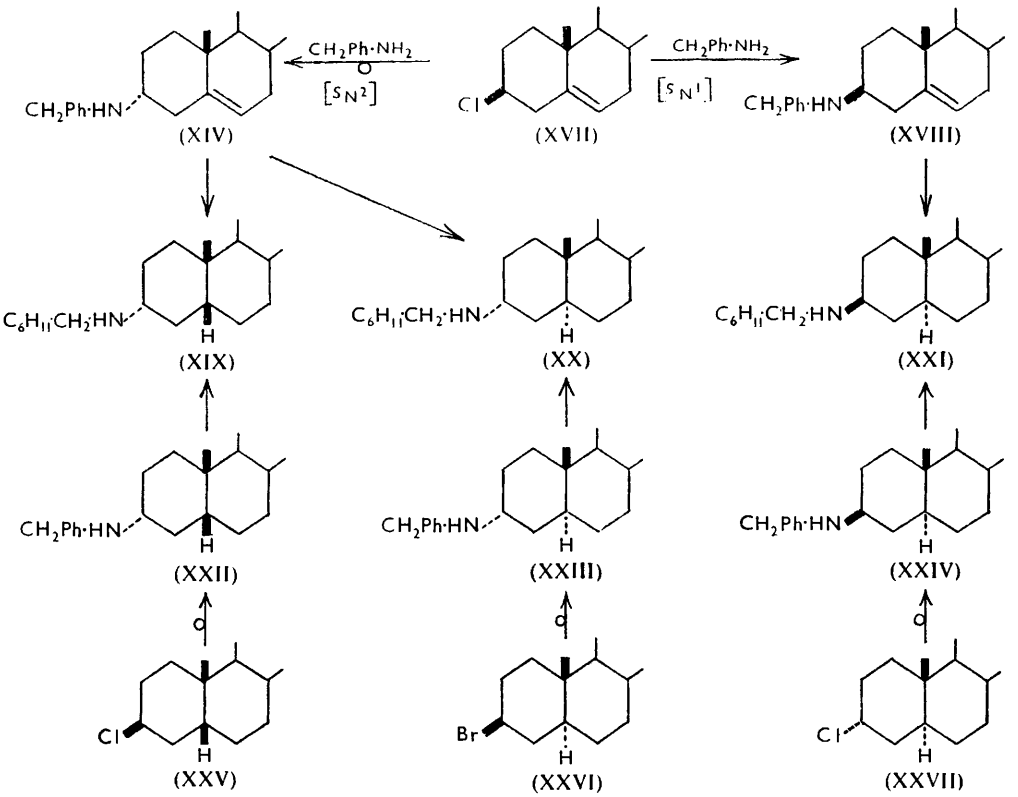
[7] Pierce, Shoppee, and Summers, *J.*, 1955, 690.
[8] Labler, Czerny, and Sorm, *Chem. Listy*, 1954, **48**, 1058.

tertiary base (XV) converted into the methiodide (XVI), which by Emde degradation furnished *NN*-dimethyl-3α-cholesterylamine (X).



(XIV) (XV) (XVI) (X)

It has been shown by Lewis and Shoppee [9] for a variety of substituents that hydrogenation of 3α-substituted cholest-5-enes leads to 3α-substituted coprostanes. Hydrogenation of cholest-5-ene-3α-carboxylic acid (V; R = H) with platinum–acetic acid, in accordance with expectation, gave coprostane-3α-carboxylic acid (VI; R = H), purified through the methyl ester. As in the previous case, the acid yielded the 3α-*iso*cyanate (XI), which was not isolated but was hydrolysed to the oily base (XIII; R = H), which was acetylated to yield 3α-acetamidocoprostane (XIII; R = Ac), identical with specimens prepared (*a*) by hydrogenation of 3α-acetamidocholest-5-ene (XII; R = Ac) with platinum–acetic acid, and (*b*) by ammonolysis of coprostan-3β-yl toluene-*p*-sulphonate.[10] After this work was completed, Haworth, Lunts, and McKenna [2] described the hydrogenation of 3α-acetamidocholest-5-ene (XII; R = Ac) with 15% palladised charcoal in acetic acid to yield 35% of 3α-acetamidocholestane, m. p. 215—216°, $[\alpha]_D$ +33°, accompanied by 46% of an isomeride, m. p. 180°, which is probably an incompletely purified specimen of 3α-acetamidocoprostane (XIII; R = Ac).



(XIV) (XVII) (XVIII)
(XIX) (XX) (XXI)
(XXII) (XXIII) (XXIV)
(XXV) (XXVI) (XXVII)

Some years ago we examined the hydrogenation with platinum oxide in acetic acid of the epimeric *N*-benzyl-3α- (XIV) and -3β-cholesterylamine (XVIII) derived from cholesteryl

[9] Lewis and Shoppee, *J.*, 1955, 1365.
[10] Evans, Shoppee, and Summers, unpublished work.

chloride (XVII) and benzylamine at 180°; the expected products were *N*-benzylcoprostan-3α-ylamine (XXII) and, possibly, some *N*-benzylcholestan-3α-ylamine (XXIII). When these substances were prepared by treatment of coprostan-3β-yl chloride [9,11] (XXV) and cholestan-3β-yl bromide [6] (XXVI) respectively with benzylamine at 180°, they did not correspond with the hydrogenation products. These have now been shown to be *N*-(*cyclo*hexylmethyl)-coprostan-3α-ylamine (XIX) and -cholestan-3α-ylamine (XX) by hydrogenation of the *N*-benzyl bases (XXII, XXIII) with Adams catalyst in acetic acid.

In a similar way, *N*-benzyl-3β-cholesterylamine (XVIII) by hydrogenation with platinum oxide–acetic acid yields *N*-(*cyclo*hexylmethyl)cholestan-3β-ylamine (XXI), also produced by hydrogenation of *N*-benzylcholestan-3β-ylamine (XXIV), which was obtained by treatment of cholestan-3α-yl chloride [12] (XXVII) with benzylamine at 180° and by Wolff–Kishner reduction of *N*-benzyl-6-oxocholestan-3β-ylamine.

Experimental

For general experimental directions see *J.*, 1955, 2876. $[\alpha]_D$ are in $CHCl_3$. Alumina was Spence type H, 200 mesh, activity ~II, neutralised when necessary by Reichstein and Shoppee's procedure.[13]

Cholest-5-en-3α-yl iso*Cyanate*.—Cholest-5-ene-3α-carboxylic acid (500 mg.), dissolved in benzene, was refluxed with thionyl chloride (0·8 c.c.) for 2 hr.; complete evaporation in a vacuum gave the crude chloride as a sticky solid. The chloride, dissolved in dry acetone (35 c.c.) and dioxan (15 c.c.), was treated dropwise with a solution of sodium azide (200 mg.) in water (1·5 c.c.) with stirring. After 0·25 hr., the mixture was diluted and the precipitate filtered off, washed with water, and dried in a vacuum-desiccator. This material was refluxed in benzene for 1·5 hr. to ensure conversion into the *iso*cyanate; the product was a sticky solid which did not crystallise satisfactorily.

3α-*Cholesterylamine*.—The crude *iso*cyanate (200 mg.) was refluxed in benzene for 2 hr. with acetic acid (28 c.c.) and concentrated hydrochloric acid (7 c.c.). After evaporation of the solvent in a vacuum the product was basified with 4N-sodium hydroxide, extracted with ether, and worked up in the usual way. The oil obtained was chromatographed on aluminium oxide (15 g.). Elution with benzene yielded non-basic material whilst elution with ether–chloroform (1 : 1) gave 3α-cholesterylamine (100 mg.) as a colourless oil which tended to crystallise. Acetylation of the base with ether–acetic anhydride furnished 3α-acetamidocholest-5-ene which, after filtration of a pentane solution through aluminium oxide, crystallised from ethyl acetate as needles, m. p. and mixed m. p. 188°, $[\alpha]_D$ −32°.

N-*Methyl*-3α-*cholesterylamine*.—The crude *iso*cyanate (400 mg.), in ether, was treated with lithium aluminium hydride (100 mg.), heated under reflux for 2 hr., cooled, and carefully diluted with water. The precipitated aluminium hydroxide was filtered off, and the ethereal solution washed, dried, and evaporated to furnish an oil (390 mg.). The product was chromatographed on aluminium oxide (12 g.). Elution successively with benzene–pentane (1 : 19; 4 × 40 c.c.), benzene and benzene–ether (1 : 1) gave *N*-methyl-3α-cholesterylamine (270 mg.) which crystallised from acetone in needles, m. p. 85—86°, $[\alpha]_D$ −31° (*c*, 0·8). Methylation with formaldehyde and formic acid gave *NN*-dimethyl-3α-cholesterylamine, m. p. 69°, $[\alpha]_D$ −31° (*c*, 1·0).

NN-*Dimethyl*-3α-*cholesterylamine*.—*N*-Benzyl-3α-cholesterylamine (750 mg.) in formic acid (5 c.c.) and 40% aqueous formaldehyde (7 c.c.) was heated for 4 hr. at 100°. The solution was poured into water and basified with ammonia, the base was extracted with ether, and the ethereal extract washed with water, dried (Na_2SO_4) and evaporated, to yield *N*-benzyl-*N*-methyl-3α-cholesterylamine. This oil was refluxed in acetone (25 c.c.) with methyl iodide (0·5 c.c.) for 2 hr. Evaporation of the solvent, after washing with ether, yielded the *methiodide*, m. p. 220—230° (Found: C, 68·7; H, 8·7. $C_{36}H_{58}NI$ requires C, 68·5; H, 9·2%).

The methiodide (400 mg.) in aqueous ethanol (60 c.c.; 84% EtOH) was vigorously stirred with 2% sodium amalgam (20 g.) added during 8 hr. The solution was decanted, diluted with water, and extracted with ether. Evaporation of the ether gave a solid which after nitration of a pentane solution through aluminium oxide gave *NN*-dimethyl-3α-cholesterylamine, which crystallised from acetone as needles, m. p. and mixed m. p. 66—69°.

[11] Bridgwater and Shoppee, *J.*, 1953, 1709.
[12] Shoppee, *J.*, 1946, 1138.
[13] Reichstein and Shoppee, *Discuss. Faraday Soc.*, 1949, **7**, 205.

Coprostane-3α-carboxylic Acid.—Cholest-5-ene-3α-carboxylic acid (400 mg.), dissolved in acetic acid (200 c.c.), was shaken with platinum oxide (800 mg.) in an atmosphere of hydrogen. Hydrogenation was complete in 3 hr. After filtration the solution was diluted with water and extracted with ether. After working up in the usual way, the ethereal extract furnished a solid which crystallised from aqueous acetone as needles, m. p. 163—174°. The impure acid was esterified with diazomethane, and the oily ester chromatographed on neutralised aluminium oxide (15 g.). Successive elution with pentane–benzene (19 : 1; 8 × 50 c.c.) (9 : 1; 6 × 50 c.c.) (17 : 3; 4 × 50 c.c.) furnished *methyl coprostane-3α-carboxylate* (290 mg.) which crystallised from ether–methanol as needles, m. p. 71—72°, $[\alpha]_D$ +30° (*c*, 1·1) [Found (after drying at 20°/0·03 mm. for 8 hr.): C, 81·2; H, 11·6. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%].

Hydrolysis of methyl coprostane-3α-carboxylate with 2N-ethanolic potassium hydroxide gave *coprostane-3α-carboxylic acid* which crystallised from aqueous acetone as needles, m. p. 179°, $[\alpha]_D$ +31° (*c*, 1·0) [Found (after drying at 20°/0·03 mm.): C, 80·7; H, 11·6. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%].

3α-Acetamidocoprostane.—Coprostane-3α-carboxylic acid (200 mg.) was refluxed in benzene with thionyl chloride (1 c.c.) for 2 hr. Evaporation in vacuum gave the crude chloride. The chloride, in dry acetone (25 c.c.) and dioxan (5 c.c.), was treated with sodium azide (100 mg.) in water (1 c.c.). After 15 min. the mixture was diluted with water and extracted with benzene and chloroform, and after working up in the usual way yielded a semisolid residue. This was refluxed in benzene for 1·5 hr. Acetic acid (10 c.c.) and concentrated hydrochloric acid (4 c.c.) were added and the mixture heated for a further 2 hr. The solvent was removed in a vacuum, the hydrochloride basified with ethanolic potassium hydroxide solution, and the product worked up in the usual way. The resultant oil was acetylated with ether–acetic anhydride and the acetyl derivative chromatographed on aluminium oxide (3 g.). Elution with benzene gave *3α-acetamidocoprostane* (110 mg.), which crystallised from acetone as plates, m. p. 217—218°, mixed m. p. 216—218° [Found (after drying at 100°/0·01 mm.): C, 80·9; H, 11·9. $C_{29}H_{51}ON$ requires C, 81·0; H, 11·95%].

N-Benzylcoprostan-3α-ylamine.—3β-Chlorocoprostane (230 mg.) in benzylamine (5 c.c.) was refluxed for 14 hr. The usual working up yielded an oil (300 mg.), which was chromatographed on aluminium oxide (8 g.). Elution with pentane gave an oil (100 mg.), and benzene–pentane also gave oils (total, 90 mg.), whereafter ether–benzene gave oils (total, 30 mg.); the benzene–pentane fractions, $[\alpha]_D$ +30° (*c*, 1·20), did not crystallise but on treatment with hydrochloric acid gave *N-benzylcoprostan-3α-ylamine hydrochloride*, m. p. 136—140°, $[\alpha]_D$ +24° (*c*, 0·87) [Found (after drying at 20°/0·03 mm. for 16 hr.): C, 78·9; H, 10·9. $C_{34}H_{56}NCl$ requires C, 79·4; H, 11·0%].

N-Benzylcholestan-3α-ylamine.—3β-Bromocholestane (100 mg.) in benzylamine (10 c.c.) was refluxed for 18 hr. Working up in the usual way previously described gave an oil (80 mg.) which was chromatographed on aluminium oxide (5 g.). Elution with pentane–benzene (4 : 1) gave an oil (50 mg.) which solidified and on crystallisation from acetone yielded *N-benzylcholestan-3α-ylamine*, m. p. 75—77°, $[\alpha]_D$ +27° (*c*, 1·14) [Found (after drying at 20°/0·03 mm. for 3 hr.): C, 85·4; H, 11·4. $C_{34}H_{55}N$ requires C, 85·5; H, 11·6%]. Elution with benzene–ether (9 : 1) yielded a few mg. of a solid, which crystallised from acetone as plates, m. p. 113—114°, $[\alpha]_D$ 16° (*c*, 0·71), undepressed on admixture with *N*-benzylcholestan-3β-ylamine (*vide infra*).

N-(cycloHexylmethyl)cholestan-3α-ylamine and N-(cycloHexylmethyl)coprostan-3α-ylamine.—*N*-Benzyl-3α-cholesterylamine (500 mg.) in glacial acetic acid (20 c.c.) was hydrogenated in the presence of platinum oxide (100 mg.); after 3 hr. four mols. of hydrogen were absorbed. Working up in the usual way yielded an oil (450 mg.) which was chromatographed on aluminium oxide (14 g.). Elution with pentane–benzene (9 : 1) gave a sticky solid (90 mg.) which on crystallisation from acetone gave *N-(cyclohexylmethyl)cholestan-3α-ylamine* as plates, m. p. 114—115°, $[\alpha]_D$ +19° (*c*, 0·75) [Found (after drying at 20°/0·03 mm. for 3 hr.): C, 84·1; H, 12·3. $C_{34}H_{61}N$ requires C, 84·4; H, 12·7%). Elution with pentane–benzene (4 : 1) yielded oils (80 mg.) and pentane–benzene (1 : 1) and benzene gave an oil (200 mg.), $[\alpha]_D$ +31° (*c*, 1·30). This fraction formed *N-(cyclohexylmethylcoprostan)-3α-ylamine hydrochloride*, m. p. 238—242°, $[\alpha]_D$ +17° (*c*, 0·67) [Found (after drying at 20°/0·03 mm. for 16 hr.): C, 78·6; H, 11·85. $C_{34}H_{62}NCl$ requires C, 78·5; H, 12·0%].

N-(cycloHexylmethyl)cholestan-3α-ylamine.—*N*-Benzylcholestan-3α-ylamine (50 mg.) in glacial acetic acid (5 c.c.) was hydrogenated in the presence of platinum oxide (20 mg.). Isolation of the product in the usual way and crystallisation from acetone gave plates, m. p. 114—115°, $[\alpha]_D$ +21° (*c*, 0·84), undepressed by the specimen in the previous experiment.

N-(cycloHexylmethyl)coprostan-3α-ylamine.—*N*-Benzylcoprostan-3α-ylamine (50 mg.) on

hydrogenation yielded an oil which formed a hydrochloride, m. p. 240°, $[\alpha]_D$ +16° (*c*, 0·66), undepressed on admixture with the hydrochloride obtained from the reduction of *N*-benzyl-3α-cholesterylamine.

N-*Benzylcholestan*-3β-*ylamine*.—(*a*) 3α-Chlorocholestane (700 mg.) in benzylamine (10 c.c.) was refluxed for 14 hr. Dilution with 2N-hydrochloric acid gave *N*-benzylcholestan-3β-ylamine hydrochloride, which after filtration, washing with water, and basification with ammonia, was extracted with ether. The ethereal extract yielded an oil (700 mg.), which was chromatographed on aluminium oxide (20 g.). Elution with pentane gave cholest-2-ene (300 mg.; m. p. 68°). Elution with benzene–ether (9 : 1) yielded N-*benzylcholestan*-3β-*ylamine* (150 mg.) which crystallised from acetone as plates, m. p. 114—115°, $[\alpha]_D$ +19° (*c*, 0·87) [Found (after drying at 20°/0·03 for 2 hr.): C, 85·75; H, 11·4. $C_{34}H_{55}N$ requires C, 85·5; H, 11·6%].

(*b*) *N*-Benzyl-6-oxocholestan-3β-ylamine (500 mg.) in ethanol (20 c.c.) was refluxed for 0·5 hr. with hydrazine hydrate (4 c.c.) and potassium hydroxide (2 g.). Ethylene glycol (20 c.c.) was added and the refluxing continued for 3 hr. at 200°. The mixture was diluted with water, extracted with ether, and worked up in the usual way to yield an oil, which on crystallisation from ethyl acetate gave plates, m. p. 116—117°, undepressed by the above specimen.

N-(cyclo*Hexylmethyl*)*cholestan*-3β-*ylamine*.—(*a*) *N*-Benzyl-3β-cholesterylamine (350 mg.) in glacial acid (20 c.c.) was hydrogenated in the presence of platinum oxide (100 mg.). After 1 hr., the solution was poured into water and extracted with ether, and the ethereal extract washed with ammonia. Working up in the usual way gave a white solid, which on crystallisation from ethyl acetate gave N-(cyclo*hexylmethyl*)*cholestan*-3β-*ylamine* as neeedles, m. p. 143—145°, $[\alpha]_D$ +16° (*c*, 0·82) [Found (after drying at 20°/0·02 mm. for 3 hr.): C, 84·4; H, 12·7; N, 2·9. $C_{34}H_{61}N$ requires C, 84·4; H, 12·7; N, 2·9%].

(*b*) *N*-Benzylcholestan-3β-ylamine (200 mg.) in glacial acetic acid (20 c.c.) was hydrogenated in the presence of platinum oxide (80 mg.). After 2·5 hr. 3 mols. of hydrogen had been absorbed. Working up in the usual way gave *N*-(*cyclo*hexylmethyl)cholestan-3β-ylamine which crystallised from acetone as needles, m. p. 146—148°, $[\alpha]_D$ +18° (*c*, 0·79), undepressed on admixture with the above specimen.

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