170. *The Stereochemistry of the* 3 : 5-cyclo*Cholestan*-6-*ylamines.*

By D. E. Evans and G. H. R. Summers.

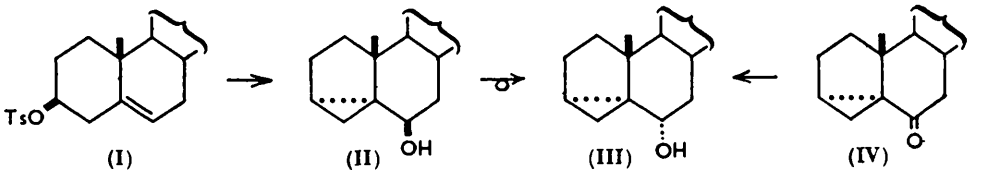
The configurations of the epimeric 3 : 5-*cyclo*cholestan-6-ylamines have been established from their methods of formation and from their behaviour on deamination.

Shoppee and Summers [1] have shown that the *i*-steroid rearrangement, whereby derivatives of 3β-hydroxy-Δ^5-steroids afford 6-substituted 3 : 5-*cyclo*steroids, is a stereospecific reaction leading to a predictable configuration at $C_{(6)}$. From a study of the hydrogenation of the 3 : 5-*cyclo*cholestan-6-ols, the 6-hydroxyl group in the alcohol formed by treatment of cholesteryl toluene-*p*-sulphonate (I) with potassium acetate in aqueous acetone [2] was shown to possess the axial β-configuration. Thus "*i*-cholesterol" and its epimer "*epi*-*i*-cholesterol," the latter formed by reduction of 3 : 5-*cyclo*cholestan-6-one (IV) with sodium–ethanol,[1] lithium aluminium hydride,[1,3] or aluminium *iso*propoxide,[4] are respectively 3 : 5-*cyclo*cholestan-6β- (II) and -6α-ol (III). Further proof of these formulations is provided by the conversion of the β-alcohol (II) into its epimer (III) by treatment with sodium ethoxide at 190—200°. The isomer (III) is clearly the 6α-alcohol and arises by inversion of the axial 6β-structure to the more thermodynamically stable, equatorial 6α-structure; the compound (III) is recovered unchanged after this treatment, consistently

[1] Shoppee and Summers, *J.*, 1952, 3361.
[2] Beynon, Heilbron, and Spring, *J.*, 1937, 1459.
[3] Wagner and Wallis, *J. Amer. Chem. Soc.*, 1950, **72**, 1047; Wagner, Wolff, and Wallis, *J. Org. Chem.*, 1952, **17**, 529.
[4] Heilbron, Hodges, and Spring, *J.*, 1938, 759.

with its method of preparation (reduction by sodium–ethanol) and the above epimerisation. The formation of the 6α-epimer by reduction of the ketone (IV) with lithium aluminium hydride, instead of the expected 6β-epimer (cf. reduction of cholestan-6-one [1] and its derivatives [1, 5]), will be discussed in a future publication.

These configurations at $C_{(6)}$ are nevertheless the reverse of those arrived at by Wagner, Wolff, and Wallis [3, cf. 6] from investigations on the dielectric constants of the 6-epimeric



(I) (II) (III) (IV)

(Ts = *p*-$C_6H_4Me{\cdot}SO_2$) M. p. 74—75° $[\alpha]_D$ +24° M. p. 85—86° $[\alpha]_D$ +81°

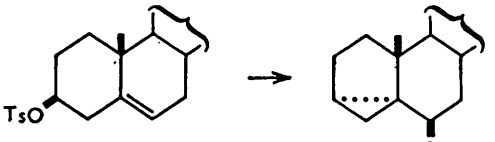
3 : 5-*cyclo*androstane-6 : 17β-diols and bromination of the 3 : 5-*cyclo*cholestan-6-ols (II and III). However, in a later publication Smith and Wallis [7] regard " *i*-stigmasteryl methyl ether " and " *epi-i*-stigmasterol " as the 6β- and the 6α-epimer respectively, in agreement with the original view of Shoppee and Summers [1] and the further evidence now adduced.

On the foregoing basis the substances described as *i*-cholesterylamine [8, 9, 10] (Va; R = NH_2), *N*-methyl-3 : 5-*cyclo*cholestan-6-ylamine [9, 11, 12] (Vb; R = NHMe), *NN*-dimethyl-3 : 5-*cyclo*cholestan-6-ylamine [9, 13] (Vc; R = NMe_2), *N*-benzyl-*i*-cholesterylamine [8, 14, 15] (Vd; R = $NH{\cdot}CH_2Ph$), *i*-cholesterylmalonic acid [16] [V; R = $CH(CO_2H)_2$], and 6-phenylthio-3 : 5-*cyclo*cholestane [17] (V; R = SPh) have by analogy been assigned the 6β-orientation. We now present further evidence that these assignments are correct.

Solvolysis of cholesteryl toluene-*p*-sulphonate (I) with ammonia and substituted ammonias furnish, besides 3β- and 3α-substituted Δ^5-amino-steroids, dextrorotatory bases isolated *via* their ether-soluble hydrochlorides. Thus, the ester (I) with ammonia, methylamine, dimethylamine, and benzylamine yields the bases (Va—d). That these compounds are derivatives of 3 : 5-*cyclo*cholestane has been demonstrated by direct conversion into known 3 : 5-*cyclo*steroids and indirectly by cleavage in an acid medium to various 3β-substituted Δ^5-steroids. Thus Julian, Magnani, Meyer, and Cole [8] degraded *N*-benzyl-3 : 5-*cyclo*cholestan-6β-ylamine (Vd) by hydrolysis of its chloramine, and isolated 3 : 5-*cyclo*cholestan-6β-ylamine (Va); similar treatment of the hydrochloride of this base (Va) afforded 3 : 5-*cyclo*cholestan-6-one (IV), identified by conversion into 3β-chlorocholestan-6-one. Rearrangement of the benzyl derivative (Vd) in benzylamine by the benzylammonium cation $[CH_2Ph{\cdot}NH_3]^+$ gave *N*-benzylcholest-5-en-3β-ylamine. Attempted methylation of the amines (Va—c) with formic acid and formaldehyde described by Haworth *et al.*[10] and by Labler and Sorm [12] yielded, in each case, cholesterol [some tertiary base (Vc) was formed from (Va)], and treatment of the tertiary base (Vc) with methyl iodide in acetone gave some cholesteryl iodide.[10] Finally pyrolysis of the hydrochloride of the dimethyl derivative (Vc) in hydrogen chloride gave cholesteryl chloride.[12] None of these transformations provides information about the stereochemistry at $C_{(6)}$.

[5] Shoppee and Summers, *J.*, 1952, 1787, 1790.
[6] Wolff and Wallis, *J. Org. Chem.*, 1952, **17**, 1361.
[7] Smith and Wallis, *ibid.*, 1954, **19**, 1628.
[8] Julian, Magnani, Meyer, and Cole, *J. Amer. Chem. Soc.*, 1948, **70**, 1834.
[9] Haworth, McKenna, and Powell, *J.*, 1953, 1110.
[10] Haworth, Lunts, and McKenna, *J.*, 1955, 986.
[11] Pierce, Shoppee, and Summers, *J.*, 1955, 690.
[12] Labler and Sorm, *Chem. Listy*, 1954, **48**, 1378.
[13] Labler, Sorm, and Czerny, *ibid.*, 1953, **47**, 418.
[14] Vavasour, Bolker, and McKay, *Canad. J. Chem.*, 1952, **30**, 933.
[15] Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694.
[16] Shoppee and Stephenson, *J.*, 1954, 2230.
[17] Shoppee, Richards, and Summers, *J.*, 1956, 4817.

3 : 5-*cyclo*Cholestan-6-one (IV) with hydroxylamine acetate gave, after chromatography, 3 : 5-*cyclo*cholestan-6-one oxime (VI), m. p. 128°, $[\alpha]_D$ +63° (Wallis, Chakravorty, and Ladenburg,[18] and Heilbron, Hodges, and Spring [4] give melting points 143—144° and



(I) (V)

Formula	M. p.	[α]	Ref.
(Va) R = NH_2 ...	77—79°	+34°	*a*
	84—85	+36	10
	77—78	+34	9
Ac derivative ...	142—143	—	*a*
	142—143	—	8
hydrochloride ...	212—214	—	8
(Vb) R = NHMe	52—54	+27	11
	57—58	+27	12
hydrochloride ...	260—261 *	+37	11

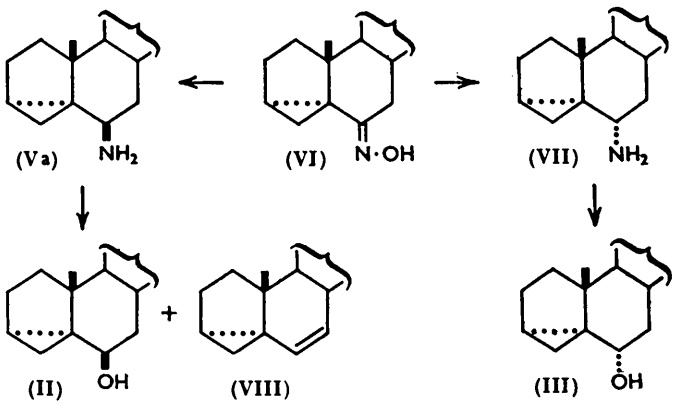
* Decomp.

Formula	M. p. (b. p.)	[α]	Ref.
(Vc) R = NMe_2	b. p. 116°/10^{-3} mm.	+61°	13
	b. p. 164—166°/0·05 mm.	+54	10
hydrochloride	196—197°	+45	10
methiodide	206—207	—	10
(Vd) R = $NH{\cdot}CH_2Ph$	—	+12	8
hydrochloride	217—218	+27	8

Ref. (*a*), this work.

122—123° respectively) which by reduction with lithium aluminium hydride furnishes exclusively, and in quantitative yield, 3 : 5-*cyclo*cholestan-6β-ylamine (Va) identical with the ammonolysis product of cholesteryl toluene-*p*-sulphonate (I). Reduction of the oxime (VI) with sodium–ethanol afforded the isomeric base 3 : 5-*cyclo*cholestan-6α-ylamine (VII), b. p. 190—200°/0·03 mm., $[\alpha]_D$ +60°, which on methylation gave cholesterol whilst pyrolysis of its hydrochloride afforded cholesteryl chloride, thus indirectly confirming that it is a 3 : 5-*cyclo*steroid amine. This formulation of the epimeric bases is in accord with their methods of preparation.

Recent studies [19] on the steric course of deamination of alicyclic amines, *e.g.*, *cyclo*hexylamines, decalylamines, and indanylamines, have shown the reaction to be conformationally specific, that in general both equatorial and axial amino-groups afford by deamination the appropriate equatorial alcohol, but that for axial amino-groups the inversion



(axial NH_2 ⟶ equatorial OH) is accompanied by some retention and much elimination with the formation of olefins. The deamination of steroid amines (including 6-amines) conforms to this pattern of behaviour with one important difference. Steroid axial amines, without exception, react with retention of configuration, accompanied by elimination, but with complete exclusion of inversion.[20,21]

[18] Wallis, Chakravorty, and Ladenburg, *J. Amer. Chem. Soc.*, 1939, **61**, 3483; cf. Wallis, Fernholz, and Gephart, *ibid.*, 1937, **59**, 137.
[19] Dauben, Tweit, and Mannerskantz, *ibid.*, 1954, **76**, 4420.
[20] Shoppee, Evans, and Summers, *J.*, 1957, 97.
[21] Evans and Summers, *J.*, 1956, 4821.

The steric course of deamination of the 3 : 5-*cyclo*cholestan-6-amines follows this generalisation; 3 : 5-*cyclo*cholestan-6α-ylamine (VII) yields 3 : 5-*cyclo*cholestan-6α-ol (III), whilst the 6β-amine (Va) affords 3 : 5-*cyclo*cholestan-6β-ol (II) and 3 : 5-*cyclo*cholest-6-ene (VIII). These results establish the correctness of the configurations assigned at $C_{(6)}$ in 3 : 5-*cyclo*steroid amines and their derivatives. Two further products common to both deaminations were cholesterol and 3 : 5-*cyclo*cholestan-6-one (IV). The former product arose from the rearrangement of the amines in the acidic reaction medium, a result which was verified by similar rearrangement of 3 : 5-*cyclo*cholestan-6β-yl methyl ether to cholesterol under the conditions of deamination. The formation of 3 : 5-*cyclo*cholestan-6-one (IV) cannot be adequately explained since under comparable conditions the 3 : 5-*cyclo*cholestan-6-ols are not oxidised but are partially rearranged to cholesterol.

Experimental

$[\alpha]_D$ refer to $CHCl_3$ solutions.

Non-epimerisation of 3 : 5-cyclo*Cholestan*-6α-*ol* [By G. D. Phillips].—3 : 5-*cyclo*Cholestan-6α-ol, $[\alpha]_D$ +79° (859 mg.), was heated in ethanol (10 c.c.) containing sodium (800 mg.) in a sealed tube at 190° for 18 hr. Dilution with water precipitated the product which was extracted with ether in the usual way, to yield an oil, $[\alpha]_D$ +78° (*c*, 1·12); *i.e.*, no epimerisation had occurred.

Epimerisation of 3 : 5-cyclo*Cholestan*-6β-*ol*.—A solution of 3 : 5-*cyclo*cholestan-6β-ol, $[\alpha]_D$ +23° (236 mg.), in ethanol (4 c.c.) containing sodium (250 mg.) was heated at 190° for 18 hr. The product, an oil, $[\alpha]_D$ +45° (230 mg.), was chromatographed on neutral aluminium oxide (11 g.). Elution with benzene gave a solid (143 mg.) which by crystallisation from cold aqueous methanol gave 3 : 5-*cyclo*cholestan-6β-ol, m. p. 74°, $[\alpha]_D$ +22°. Elution with ether–benzene (1 : 9) gave, as an oil (87 mg.), 3 : 5-*cyclo*cholestan-6α-ol, $[\alpha]_D$ +79° (*c* 1·1); *i.e.*, 37% of conversion occurred.

3 : 5-cyclo*Cholestan*-6-*one Oxime*.—3 : 5-*cyclo*Cholestan-6-one, m. p. 94—96°, $[\alpha]_D$ +40°, was refluxed with hydroxylamine acetate in methanol, and the product (4 g.) was chromatographed on aluminium oxide (120 g.). Elution with ether–benzene (1 : 1), ether, and chloroform furnished 3 : 5-*cyclo*cholestan-6-one oxime, m. p. 128°, $[\alpha]_D$ +63° (*c* 0·74) after crystallisation from methanol.

3 : 5-cyclo*Cholestan*-6β-*ylamine*.—3 : 5-*cyclo*Cholestan-6-one oxime (2 g.) was treated with lithium aluminium hydride (500 mg.) in refluxing ether overnight. The solution, worked up in the usual way, afforded an oil (1·6 g.) which was chromatographed on aluminium oxide (50 g.). Elution with benzene and ether gave a wax (1·5 g.) which by crystallisation from pentane afforded 3 : 5-*cyclo*cholestan-6β-ylamine, m. p. 77—78°, $[\alpha]_D$ +34° (*c* 0·96). Acetylation with acetic anhydride in ether at 15° furnished 6β-acetamido-3 : 5-*cyclo*cholestane, m. p. 142—143°.

3 : 5-cyclo*Cholestan*-6α-*ylamine*.—3 : 5-*cyclo*Cholestan-6-one oxime (1 g.) was treated with sodium (12 g.) in refluxing ethyl alcohol (100 c.c.) for 3·5 hr. Excess of sodium was destroyed with alcohol, and the oily product (950 mg.) obtained in the usual manner was chromatographed on aluminium oxide (30 g.). Elution with benzene, ether, and methylene dichloride furnished 3 : 5-cyclo*cholestan*-6α-*ylamine* (900 mg.), b. p. 190—200°/0·03 mm., $[\alpha]_D$ +60° (*c* 0·86) (Found: C, 83·6; H, 12·0. $C_{27}H_{47}N$ requires C, 84·1; H, 12·3%). With acetic anhydride in ether at 15° this afforded, after crystallisation from acetone, 6α-*acetamido*-3 : 5-cyclo*cholestane*, m. p. 213°, $[\alpha]_D$ +72° (*c* 0·76) [Found (after drying at 100°/0·03 mm. for 3 hr.): C, 81·3; H, 11·5. $C_{29}H_{49}ON$ requires C, 81·4; H, 11·5%].

Attempted Methylation of 3 : 5-cyclo*Cholestan*-6α-*ylamine*.—The base (100 mg.) was treated with 90% formic acid (4 c.c.) and 40% formaldehyde (3 c.c.) at 100° for 3 hr. The solution was diluted and extracted with ether and the ethereal solution washed with sodium hydrogen carbonate solution and water, dried, and evaporated to an oil (75 mg.) which was chromatographed on aluminium oxide (3 g.). Elution with benzene–pentane (1 : 1) and benzene gave oils (30 mg.) whilst ether–benzene (1 : 9) furnished a solid (39 mg.) which was crystallised from acetone to afford cholesterol, m. p. 146—148°.

Pyrolysis of 3 : 5-cyclo*Cholestan*-6α-*ylamine Hydrochloride*.—The hydrochloride, m. p. 286—288° (30 mg.), was heated at 290—295° for 5 min. in an atmosphere of hydrogen chloride. The

dark residue was extracted with ether and the oily product chromatographed on aluminium oxide (1 g.). Elution with pentane and crystallisation from acetone furnished cholesteryl chloride, m. p. 96°.

Deamination of 3 : 5-cyclo*Cholestan*-6β-*ylamine*.—3 : 5-*cyclo*Cholestan-6β-ylamine (1·95 g.) in 50% acetic acid (70 c.c.) and dioxan (20 c.c.) was treated with sodium nitrite (4 g.) in 50% acetic acid (30 c.c.) overnight at 20°. The mixture was diluted and neutralised at 0° with 4N-sodium hydroxide. Extraction with ether, followed by washing with water, drying, and evaporation, gave an oil. Hydrolysis with methanolic potassium hydroxide and isolation of the product in the usual manner gave an oil (1·86 g.) which was chromatographed on aluminium oxide (60 g.). Elution with pentane (4 × 200 c.c.) gave an oil *A* (500 mg.) which failed to crystallise, and benzene–pentane (1 : 1; 4 × 200 c.c.) gave an oil *B* (305 mg.). Elution with benzene gave a solid (210 mg.) which from acetone furnished cholesterol, m. p. 148°. Successive elution with ether–benzene (1 : 1) and ether yielded an oil (700 mg.) which with boiling acetic anhydride afforded 6β-acetamido-3 : 5-*cyclo*cholestane, m. p. 141°. Fraction *A* was rechromatographed on aluminium oxide (15 g.). Elution with pentane gave a series of oils (470 mg.) which by crystallisation from acetone–methanol gave a solid, m. p. 65—80°, $[\alpha]_D$ −11° (*c* 1·2). Elution with benzene–pentane (1 : 9) gave material (20 mg.) which from acetone–methanol afforded 3 : 5-*cyclo*cholestan-6-one, m. p. 96°. The pentane fractions were combined and treated with lithium aluminium hydride in refluxing ether for 2 hr. Excess of reagent was destroyed with 4N-hydrochloric acid at 0°, and the solution worked up in the usual manner to furnish an oil (195 mg.) which was chromatographed on aluminium oxide (6 g.). Elution with pentane gave an oil (120 mg.) whence crystallisation from acetone gave 3 : 5-*cyclo*cholest-6-ene, m. p. 72—73°, $[\alpha]_D$ −46° (*c* 1·0). Elution with benzene gave 3 : 5-*cyclo*cholestan-6α-ol (70 mg.), $[\alpha]_D$ +80°, formed by reduction of the 3 : 5-*cyclo*cholestan-6-one present.

Fraction *B* was kept with acetic anhydride in pyridine overnight at 20°. The product, an oil (300 mg.), was chromatographed on aluminium oxide (8 g.). Elution with pentane furnished an oil (285 mg.) which from acetone afforded 3 : 5-*cyclo*cholestan-6β-yl acetate, m. p. 72—73°, $[\alpha]_D$ +50° (*c* 1·2).

Deamination of 3 : 5-cyclo*Cholestan*-6α-*ylamine*.—3 : 5-*cyclo*Cholestan-6α-ylamine (830 mg.) in 50% acetic acid (20 c.c.) and dioxan (10 c.c.) was treated overnight with sodium nitrite (1·6 g.) in 50% acetic acid (20 c.c.). Ice was added and the acetic acid neutralised with ammonia solution. The solution was extracted with ether, and the ethereal extract washed with water, dried, and evaporated to an oil which was treated with acetic anhydride in pyridine overnight at 20°. The product, a yellow oil (820 mg.), was chromatographed on aluminium oxide (20 g.). Elution with pentane (5 × 100 c.c.) gave an oil (248 mg.), $[\alpha]_D$ +50°, and benzene–pentane (1 : 9; 2 × 100 c.c.) gave cholesteryl acetate (134 mg.), m. p. 114° (from acetone). Elution with benzene and ether gave an oil (420 mg.) which in boiling acetic anhydride furnished 6α-acetamido-3 : 5-*cyclo*cholestane, m. p. 213°.

The fractions eluted with pentane were hydrolysed with 5% methanolic potassium hydroxide (50 c.c.) for 1 hr. and the product, an oil (230 mg.), was chromatographed on aluminium oxide (7 g.). Elution with pentane gave an oil (190 mg.) which slowly crystallised and by recrystallisation from acetone–methanol afforded 3 : 5-*cyclo*cholestan-6-one, m. p. and mixed m. p. 95—96°. Elution with benzene gave an oil (35 mg.), $[\alpha]_D$ +65° (*c* 1·36), which was rechromatographed on aluminium oxide (1·5 g.). Elution with benzene gave as an oil (32 mg.), 3 : 5-*cyclo*cholestan-6α-ol, $[\alpha]_D$ +79° (*c* 1·2). This with acetic anhydride–pyridine at 20° for 16 hr. gave, after chromatography, 3 : 5-*cyclo*cholestan-6α-yl acetate as an oil, $[\alpha]_D$ +100° (*c* 2·0).

Attempted Oxidation of 3 : 5-cyclo*Cholestan*-6α-*ol and* -6β-*ol*.—3 : 5-*cyclo*Cholestan-6α-ol (500 mg.) in 50% acetic acid (30 c.c.) and dioxan (20 c.c.) was treated overnight with sodium nitrite (1 g.) in 50% acetic acid (30 c.c.). The acid was neutralised at 0° with 4N-sodium hydroxide, and the product isolated in the usual manner was hydrolysed with 5% methanolic potassium hydroxide (100 c.c.) for 1 hr. The oily product (490 mg.) was chromatographed on aluminium oxide (15 g.). Elution with benzene (5 × 100 c.c.) gave 3 : 5-*cyclo*cholestan-6α-ol (320 mg.), an oil, $[\alpha]_D$ +80° (*c* 2·1), and ether–benzene (1 : 4) gave cholesterol, m. p. 148° (150 mg.).

3 : 5-*cyclo*Cholestan-6β-ol (515 mg.) by similar treatment gave a product (500 mg.) which on chromatography on aluminium oxide gave 3 : 5-*cyclo*cholestan-6β-ol, $[\alpha]_D$ +24° (*c* 2·3) (360 mg.), and cholesterol, m. p. 148° (123 mg.).

Rearrangement of 3 : 5-cyclo*Cholestan*-6β-*yl Methyl Ether*.—3 : 5-*cyclo*Cholestan-6β-yl methyl

ether (390 mg.) in 50% acetic acid (10 c.c.) was left with sodium nitrite (800 mg.) in 50% acetic acid (10 c.c.) for 16 hr. at 20°. The solution was diluted, then extracted with benzene, and the benzene layer washed with sodium hydrogen carbonate solution and water, dried, and distilled, to furnish an oil which was hydrolysed with 5% methanolic potassium hydroxide. The oily product (380 mg.) was chromatographed on aluminium oxide (10 g.). Elution with pentane and benzene–pentane (1 : 9) afforded an oil (250 mg.) which from acetone–methanol furnished 3 : 5-*cyclo*holestan-6β-yl methyl ether, m. p. 77—79°. Elution with benzene and ether–benzene (1 : 4) gave a solid (120 mg.) which by crystallisation from acetone yielded cholesterol, m. p. 148°.

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