942. *Steroids and Walden Inversion. Part XXXV.* NN-*Dimethylcholest*-7-*en*-3α- *and* -3β-*ylamine.*

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

Solvolysis of cholest-7-en-3α- and -3β-yl toluene-*p*-sulphonate by bases has been shown to proceed with inversion of configuration by a bimolecular mechanism. The preparation and deamination of the epimeric cholest-7-enyl-3-amines are described. The *NN*-dimethylcholest-7-en-3β-ylamine of Bertho and Baumgart [1] has been shown to be the 3α-epimeride.

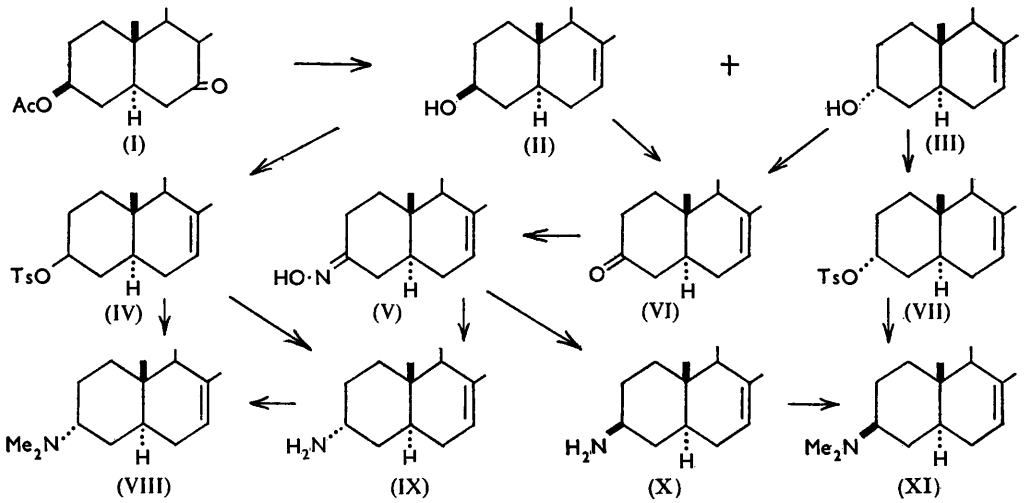
Solvolysis of the 3-toluene-*p*-sulphonates of A/B-*trans*- and A/B-*cis*-steroids by bases (*e.g.*, NH_3,[2,3] $NHMe_2$,[4,5] $C_6H_5{\cdot}CH_2{\cdot}NH_2$ [6]) proceeds by a bimolecular substitution with inversion of configuration, accompanied by some elimination. Thus cholestan-3β-yl and coprostan-3α-yl toluene-*p*-sulphonate on treatment with dimethylamine furnish *NN*-dimethylcholestan-3α-ylamine [4] and *NN*-dimethylcoprostan-3β-ylamine [5] respectively. By contrast, replacement reactions at $C_{(3)}$ in 3β-substituted Δ^5-steroids with bases (*e.g.*, NH_3, NH_2Me, $NHMe_2$, $C_6H_5{\cdot}CH_2{\cdot}NH_2$) [7] involve both a unimolecular heterolysis leading to retention of configuration at $C_{(3)}$, and a bimolecular substitution giving 3α-substituted steroid amines. Thus cholest-5-en-3β-yl toluene-*p*-sulphonate on treatment with dimethylamine yielded *NN*-dimethylcholest-5-en-3β-ylamine and *NN*-dimethyl-3 : 5-*cyclo*cholestan-6β-ylamine by the former mechanism, and *NN*-dimethylcholest-5-en-3α-ylamine by the latter mechanism.[4,5,7] In 1953 Bertho and Baumgart [1] repeated this reaction and isolated only the first product. By analogy, and possibly because of unfamiliarity with the S_N2 orientation rule,[8] Bertho and Baumgart [1] describe the product (m. p. 103—104°, $[\alpha]_D$ +17°) of the reaction of cholest-7-en-3β-yl toluene-*p*-sulphonate with dimethylamine (obtained in 72% yield) as *NN*-dimethylcholest-7-en-3β-ylamine. Although few solvolyses of 3-substituted Δ^7-steroids have been studied, it would not be expected that the π-electrons of the 7 : 8-double bond would influence replacement reactions at the distant reaction centre $C_{(3)}$ and cause retention of configuration. It was to examine the possibility of such interaction that the configuration of the supposed *NN*-dimethylcholest-7-en-3β-ylamine was investigated.

When 7-oxocholestan-3β-yl acetate (I) was subjected to the Bamford–Stevens reaction,[9] the product gave, after hydrolysis and chromatography, cholest-7-en-3α-ol (III), m. p. 176°, $[\alpha]_D$ +1° (cf. Buser [10]), and cholest-7-en-3β-ol (II), m. p. 125—127°, $[\alpha]_D$ +9° (cf.

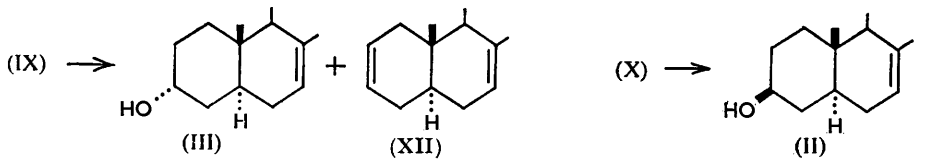
* Part XXXIV, preceding paper.

[1] Bertho and Baumgart, *Annalen*, 1953, **581**, 140.
[2] Haworth, Lunts, and McKenna, *J.*, 1955, 986.
[3] Shoppee, Evans, Richards, and Summers, *J.*, 1956, 1649.
[4] Haworth, McKenna, and Powell, *J.*, 1953, 1110.
[5] Šorm, Labler, and Czerny, *Chem Listy*, 1953, **47**, 418.
[6] Shoppee, Richards, Sly, and Summers, *J.*, 1956, 1054.
[7] Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694.
[8] Ingold, "Structure and Mechanism in Organic Chemistry," George Bell and Sons, London, 1953, p. 377.
[9] Bamford and Stevens, *J.*, 1952, 4735.

Wintersteiner and Moore,[11] and Fieser [12]). Cholest-7-en-3α-ol (III) evidently results by epimerisation of the more thermodynamically stable epimeride (II), although the yield (31%) is surprisingly high for such an equilibration (cf. Windaus and Uibrig [13]). Both alcohols by oxidation with chromium trioxide in pyridine furnished cholest-7-en-3-one (IV), which was converted into its oxime (V). Reduction of the oxime with lithium



aluminium hydride gave, after chromatography, cholest-7-en-3α- (IX), $[\alpha]_D$ +20°, and 3β-ylamine (X), $[\alpha]_D$ +8°, the latter being identical with the base obtained by reduction of the oxime (V) with sodium and butanol. Ammonolysis of cholest-7-en-3β-yl toluene-*p*-sulphonate (IV) also gave the amine (IX) accompanied by cholesta-2 : 7-diene (XII).



Although the configurations assigned to the bases (IX) and (X) follow from their method of preparation, confirmation was obtained by studying their reaction with nitrous acid. In a later paper [14] it will be established that, in the steroid series, equatorial amines are deaminated with retention of configuration whilst axial amines react with retention of configuration accompanied by elimination. Cholest-7-en-3β-ylamine (X) by treatment with nitrous acid gave exclusively cholest-7-en-3β-ol (II), whilst cholest-7-en-3α-ylamine (IX) afforded cholest-7-en-3α-ol (III) and cholesta-2 : 7-diene (XII). Methylation of the β-amine (X) with formaldehyde–formic acid gave *NN*-dimethylcholest-7-en-3β-ylamine (XI), also obtained by treatment of cholest-7-en-3α-yl toluene-*p*-sulphonate (IX) with dimethylamine. Methylation of the α-amine (IX) yielded *NN*-dimethylcholest-7-en-3α-ylamine (VIII), identical with the "*NN*-dimethylcholest-7-en-3β-ylamine" described by Bertho and Baumgart.[1] Consequently, the isomeric base, m. p. 78°, $[\alpha]_D$ +26°, obtained by these workers from *NN*-dimethylcholest-7-en-3α-ylamine (VIII) by treatment with platinum in acetic acid in hydrogen is *NN*-dimethylcholest-8(14)-en-3α-ylamine and not the 3β-isomer.

[10] Buser, *Helv. Chim. Acta*, 1947, **30**, 1385.
[11] Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503.
[12] Fieser and Herz, *ibid.*, 1953, **75**, 121.
[13] Windaus and Uibrig, *Ber.*, 1914, **47**, 2384: 1915, **48**, 857.
[14] Shoppee, Evans, and Summers, *J.*, in the press.

Solvolysis of 3β-substituted Δ^7-steroids thus proceeds with inversion of configuration by a bimolecular substitution and, by contrast with the solvolysis of Δ^5-unsaturated steroids, the π-electrons of the 7 : 8-double bond do not participate in the reaction. Further evidence is provided by the acetolysis of cholest-7-en-3β-yl toluene-*p*-sulphonate (IV), which gave (after alkaline hydrolysis) cholesta-2 : 7-diene (XII) and cholest-7-en-3α-ol (III).

Experimental

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

3β-*Acetoxycholestan-7-one Toluene*-p-*sulphonylhydrazone*.—3β-Acetoxycholestan-7-one (3·8 g.) was treated with toluene-*p*-sulphonhydrazide (2·4 g.) in refluxing ethanol for 1 hr. The solid product was crystallised from ether, to afford 3β-*acetoxycholestan-7-one toluene*-p-*sulphonylhydrazone*, m. p. 235—236° (decomp.), $[\alpha]_D$ −26·4° (*c* 0·8) [Found (after drying for 3 hr. at 100°/0·03 mm.) : C, 70·2; H, 9·0. $C_{36}H_{56}O_4N_2S$ requires C, 69·7; H, 9·2%].

Cholest-7-en-3α- and -3β-ol.—3β-Acetoxycholestan-7-one toluene-*p*-sulphonylhydrazone (3·5 g.) in refluxing ethylene glycol (350 c.c.) was treated during 1 hr. with sodium (12 g.). After refluxing for a further 3 hr. the solution was cooled, treated with ethanol to destroy excess of sodium, and worked up in the usual manner, to give a solid (2·7 g.) which was chromatographed on aluminium oxide (80 g.). Elution with ether–benzene (1 : 9) gave a solid (72 mg.) which by recrystallisation from aqueous ethanol gave cholest-7-en-3α-ol as needles, m. p. 175—176°, $[\alpha]_D$ +1° (*c* 0·68). Further elution with ether–benzene (1 : 9 and 1 : 1) gave a solid (1·6 g.) which on repeated crystallisation from ethanol furnished plates of cholest-7-en-3β-ol (1·35 g.), m. p. 125—127°, $[\alpha]_D$ +9° (*c* 1·6). Crystallisation of material in the mother liquors from aqueous ethanol afforded cholest-7-en-3α-ol, m. p. 175—176° (230 mg.). Elution with ether–chloroform and chloroform gave a solid (800 mg.) which by recrystallisation from ether furnished starting material, m. p. 235—236° (decomp.).

Cholest-7-en-3-one.—Cholest-7-en-3β-ol (2 g.) in commercial pyridine (20 c.c.) was added to a solution of chromium trioxide (2 g.) in commercial pyridine (20 c.c.) prepared by the procedure of Poos, Arth, Beyler, and Sarett.[15] The solution was vigorously shaken for 0·25 hr. and kept overnight at 25°. The solution was diluted with water and worked up in the usual manner, to give a solid (1·9 g.) which was chromatographed on aluminium oxide (60 g.). Elution with pentane and benzene–pentane (1 : 4) gave a solid (1·85 g.) which by recrystallisation from acetone furnished cholest-7-en-3-one, m. p. 148°, $[\alpha]_D$ +22° (*c* 2·1).

Cholest-7-en-3-one Oxime.—Cholest-7-en-3-one (1·9 g.) was oximated in ethanol with hydroxylamine acetate. The product was crystallised from ethyl acetate, to give cholest-7-en-3-one oxime, m. p. 228° (decomp.), $[\alpha]_D$ +24·6° (*c* 0·9) [Found (after drying at 100°/0·03 mm. for 3 hr.) : C, 81·1; H, 11·05. $C_{27}H_{45}ON$ requires C, 81·1; H, 11·3%].

Cholest-7-en-3β-ylamine.—Cholest-7-en-3-one oxime (320 mg.) in refluxing butan-1-ol was treated with sodium (3 g.), and heating was continued for 3 hr. The excess of sodium was destroyed with ethanol; the product isolated in the usual manner was an oil (250 mg.) which was chromatographed on aluminium oxide (10 g.). Successive elution with ether–benzene (1 : 1), ether, and chloroform yielded cholest-7-en-3β-ylamine as an oil, b. p. 165°/0·03 mm., $[\alpha]_D$ +8° (*c* 0·9). Acetylation with acetic anhydride in ether at 15° gave a solid which by recrystallisation from acetone afforded 3β-*acetamidocholest-7-ene* as plates, m. p. 252—254° (decomp.), $[\alpha]_D$ +3° (*c* 0·77) [Found (after drying at 100°/0·03 mm. for 3 hr.) : C, 81·3; H, 11·6. $C_{29}H_{49}ON$ requires C, 81·4; H, 11·5%].

Cholest-7-en-3α- and -3β-ylamine.—Cholest-7-en-3-one oxime (940 mg.) was treated with lithium aluminium hydride (800 mg.) in refluxing ether for 6 hr. The oily product (870 mg.) was chromatographed on aluminium oxide (27 g.). Elution with ether–benzene (1 : 1) and ether afforded an oil (327 mg.) which on distillation at 180—185°/0·03 mm. furnished cholest 7-en-3α-ylamine, $[\alpha]_D$ +20·3° (*c* 0·9). Acetylation with acetic anhydride in ether at 15° gave 3α-*acetamidocholest-7-ene* as needles (from acetone), m. p. 202—204°, $[\alpha]_D$ +28·4° (*c* 0·68) [Found (after drying at 100°/0·03 mm. for 10 hr.) : C, 81·0; H, 11·2%]. Elution with chloroform–ether (1 : 1) and chloroform yielded an oil (351 mg.) which was distilled at 160—170°/0·03 mm., to yield cholest-7-en-3β-ylamine, $[\alpha]_D$ +8° (*c* 0·9). Acetylation with acetic anhydride in ether at 15° gave 3β-acetamidocholest-7-ene, m. p. and mixed m. p. 250—253°.

Cholest-7-en-3α-ylamine.—Cholest-7-en-3β-yl toluene-*p*-sulphonate (m. p. 104°; 700 mg.) was heated at 95° with liquid ammonia in an autoclave; the product, an oil (590 mg.), was chromatographed on aluminium oxide (18 g.). Elution with pentane–benzene (1 : 1) gave an oil

[15] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.

(50 mg.) which by crystallisation from acetone afforded cholesta-2 : 7-diene, m. p. 72—74°. Elution with ether and chloroform gave an oil which on distillation at 180—185°/0·03 mm. furnished cholest-7-en-3α-ylamine, $[\alpha]_D$ +20° (*c* 1·1). Acetylation with acetic anhydride in ether at 15° gave 3α-acetamidocholest-7-ene, m. p. 202—204°.

Deamination of Cholest-7-en-3β-ylamine.—Cholest-7-en-3β-ylamine (200 mg.) in 50% acetic acid (20 c.c.) was treated overnight with a solution of sodium nitrite (400 mg.) in 50% acetic acid (20 c.c.). The oily product was hydrolysed with methanolic 5% potassium hydroxide solution (100 c.c.), and the product (187 mg.) chromatographed on aluminium oxide (6 g.). Elution with benzene gave a solid (130 mg.) which by recrystallisation from ethanol furnished cholest-7-en-3β-ol, m. p. and mixed m. p. 125—126°. Elution with ether gave an oil (40 mg.) which on acetylation and crystallisation from acetone yielded 3β-acetamidocholest-7-ene, m. p. 252—254° (decomp.).

Deamination of Cholest-7-en-3α-ylamine.—Cholest-7-en-3α-ylamine (120 mg.) in 50% acetic acid (20 c.c.) was treated overnight with sodium nitrite (240 mg.) in 50% acetic acid (20 c.c.). The solution was worked up in the usual manner and hydrolysed with methanolic 5% potassium hydroxide solution (20 c.c.), to furnish an oil (100 mg.) which was chromatographed on aluminium oxide (3 g.). Elution with pentane afforded an oil (35 mg.) which by crystallisation from methanol gave cholesta-2 : 7-diene, m. p. 70—72°, $[\alpha]_D$ −4° (*c* 0·9). Elution with benzene–pentane (1 : 1) gave a solid (30 mg.) which by recrystallisation from acetone furnished cholest-7-en-3α-ol, m. p. and mixed m. p. 172—174°. Elution with ether and chloroform gave an oil (25 mg.) which by acetylation furnished 3α-acetamidocholest-7-ene, m. p. 202—204°.

Cholest-7-en-3α-yl Toluene-p-*sulphonate.*—Cholest-7-en-3α-ol (300 mg.) in dry pyridine (10 c.c.) was treated with toluene-*p*-sulphonyl chloride (300 mg.) and left at 20° for 60 hr. The solid product, crystallised from methanol–acetone, gave *cholest-7-en-3α-yl toluene*-p-*sulphonate* as needles, m. p. 136°, $[\alpha]_D$ +17·3° (*c* 1·0) [Found (after drying at 100°/0·03 mm. for 10 hr.): C, 75·6; H, 9·9. $C_{34}H_{52}O_3S$ requires C, 75·5; H, 9·7%].

NN-*Dimethylcholest-7-en-3α-ylamine.*—(*a*) Cholest-7-en-3β-yl toluene-*p*-sulphonate (500 mg.) was treated with an ethanolic solution of dimethylamine (14 c.c.; 33% w/w) in a sealed tube at 110—115° for 5 hr. The product, worked up *via* an ether-insoluble hydrochloride, gave the base (300 mg.) which by crystallisation from methanol afforded *NN*-dimethylcholest-7-en-3α-ylamine as plates, m. p. 103—104°, $[\alpha]_D$ +20° (*c* 1·0).

(*b*) Cholest-7-en-3α-ylamine (90 mg.) was treated with 90% formic acid (1·9 c.c.) and 40% formaldehyde (1·5 c.c.) at 100° for 3 hr. Isolation of the base *via* its hydrochloride afforded an oil which on crystallisation from methanol gave *NN*-dimethylcholest-7-en-3α-ylamine, m. p. and mixed m. p. 102—104°.

NN-*Dimethylcholest-7-en-3β-ylamine.*—(*a*) Cholest-7-en-3α-yl toluene-*p*-sulphonate (173 mg.) was treated with ethanolic 30% (w/w) dimethylamine (10 c.c.) in a sealed tube at 110—115° for 5 hr. The oily product (90 mg.) was chromatographed on aluminium oxide (3 g.). Elution with pentane furnished an oil (30 mg.) which by crystallisation from acetone gave cholesta-2 : 7-diene, m. p. 73—74°. Elution with benzene–pentane (1 : 1) and benzene furnished an oil (45 mg.) which by crystallisation from acetone afforded NN-*dimethylcholest-7-en-3β-ylamine*, m. p. 112—113°, $[\alpha]_D$ +12° (*c* 0·92) [Found (after drying at 80°/0·03 mm. for 3 hr.): C, 84·2; H, 12·4.. $C_{29}H_{51}N$ requires C, 84·7; H, 12·4%].

(*b*) Methylation of cholest-7-en-3β-ylamine with formaldehyde and formic acid also gave *NN*-dimethylcholest-7-en-3β-ylamine, m. p. 110—112°.

Acetolysis of Cholest-7-en-3β-yl Toluene-p-*sulphonate.*—This toluene-*p*-sulphonate (645 mg.) in glacial acetic acid (15 c.c.) containing anhydrous sodium acetate (5 g.) was heated at 100° for 3 hr. The product, isolated in the usual way, was hydrolysed with lithium aluminium hydride in ether for 0·5 hr. and worked up, to give a semi-solid material (430 mg.) which was chromatographed on aluminium oxide (12 g.). Elution with pentane gave cholesta-2 : 7-diene, m. p. 70—72° (100 mg.), and elution with chloroform gave cholest-7-en-3α-ol, m. p. 170—175° (320 mg.).

One of us (D. E. E.) acknowledges the financial support of Monsanto Chemicals Ltd.; we thank Glaxo Laboratories Ltd. for performing high-pressure ammonolyses and for a gift of cholesterol. We are grateful for the interest and advice of Professor C. W. Shoppee, F.R.S.

UNIVERSITY OF WALES, UNIVERSITY COLLEGE OF SWANSEA. [*Received, July 20th,* 1956.]