438. *Aza-steroids. Part IV.* 3-Aza-5α- and -5β-cholestane, 4-Aza-5α- and -5β-cholestane, and Related Compounds.*

By C. W. Shoppee, R. W. Killick, and (in part) G. Krüger.

Routes to 3-aza-steroids by use of the Curtius and the Hofmann rearrangement are exemplified by preparation of 3-azacholest-5-en-4-one, 3-aza-5α-cholestan-4-one, and 3-aza-5α- and -5β-cholestane.

Routes to 4-aza-steroids by use of the Beckmann rearrangement of A-nor-steroid ketoximes and by various transformations of 3,4-seco-steroids are exemplified by preparation of 4-azacholest-5-en-3-one, 4-aza-5α- and -5β-cholestan-3-one, 4-azacholest-4-ene, and 4-aza-5α- and -5β-cholestane.

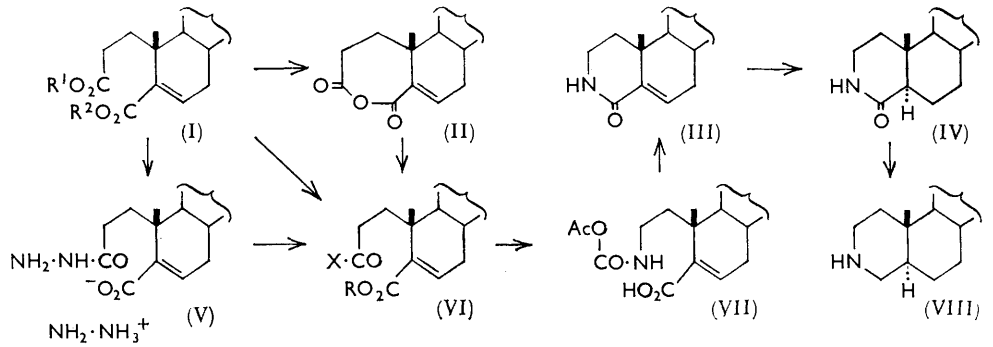
Replacement of trigonal sp^2-carbon by trigonal nitrogen, or of tetrahedral sp^3-carbon by tetrahedral positively charged nitrogen should produce little modification of size or molecular geometry, but should lead to marked alteration of chemical and physiological properties; aza-analogues of steroid hormones might therefore be capable of interaction with the same enzyme systems as the natural hormones and so be able to act as anti-hormones. In continuation of the programme indicated in Part I,[1] we have used compounds of the cholestane series as models for studies in progress in the pregnane and androstane series, and we now report work on 3-aza- and 4-aza-5α- and -5β-cholestane and related compounds.

We have devised routes to 3-aza-steroids by use of the Curtius and the Hofmann rearrangement. Diels's acid [2,3] (I; $R^1 = R^2 = H$) was converted into the anhydride (II), which with sodium azide in xylene at 140° gave the 3-azido-4-acid (VI; $X = N_3$, $R = H$). The reaction appears to involve bimolecular nucleophilic substitution (S_N2) at the less hindered and more positively charged carbonyl-carbon atom $C_{(3)}$, since the anhydride (II) did not react with hydrazoic acid even under forcing conditions. Rearrangement of the azide (VI; $X = N_3$, $R = H$) to the 3-isocyanate, which was not isolated but was hydrolysed with hydrochloric acid, gave the corresponding δ-amino-acid hydrochloride, which by basification cyclised spontaneously to 3-azacholest-5-en-4-one (III), $\lambda_{max.}$ 220 mμ (log ε 4·94), characterised as the *N*-acetyl derivative. Alternatively, Diels's acid was partially esterified with methanolic hydrogen chloride, to yield the 3-methyl ester [2] (I; $R^1 = Me$, $R^2 = H$), which with hydrazine gave the hydrazine salt of the 3-hydrazido-4-acid (V);

* Part III, *J.*, 1962, 1050.

[1] Shoppee and Sly, *J.*, 1958, 3458.
[2] Diels and Abderhalden, *Ber.*, 1903, **36**, 3177; 1904, **37**, 3092.
[3] Shoppee and Summers, *J.*, 1952, 2528.

this was converted by nitrous acid into the 3-azido-4-acid (VI; X = N_3, R = H). This azide rearranged in refluxing ether–acetic acid; it gave a crystalline product, which we regard as the mixed anhydride (VII) formed by addition of acetic acid to the precursor 3-isocyanato-4-acid, since thermal decomposition occurred smoothly at 215°/0·3 mm. with



elimination of carbon dioxide and acetic acid to yield the Δ^5-δ-lactam (III). Finally, Diels's acid, on esterification with ethereal diazomethane, gave the dimethyl ester [2,3] (I; $R^1 = R^2 =$ Me), which was partially hydrolysed by methanolic sodium hydroxide at 100° to the 4-methyl ester (I; $R^1 =$ H, $R^2 =$ Me); this, by conversion with thionyl chloride into the acid chloride-ester (VI; X = Cl, R = Me) and treatment with ammonia, gave the amide-ester (VI; X = NH_2, R = Me), which underwent the Hofmann rearrangement to yield the δ-amino-ester, and this cyclised spontaneously to the Δ^5-δ-lactam (III).

Hydrogenation of the Δ^5-δ-lactam (III) with palladium in ethanol or platinum oxide in acetic acid yielded 3-aza-5α-cholestan-4-one (IV), characterised as the *N*-acetyl derivative, accompanied by a little of the 5β-isomeride (XI) (see below). Reduction of the Δ^5-δ-lactam (III) with lithium aluminium hydride yielded, on one occasion only, 3-azacholest-5-ene, a strong base, rapidly absorbing carbon dioxide, and characterised as the hydrochloride; in all other experiments, the product was 3-aza-5β-cholestane (XII) (see below), characterised as the hydrochloride and the *N*-methyl derivative, and the hydrochloride and the methiodide of the latter.

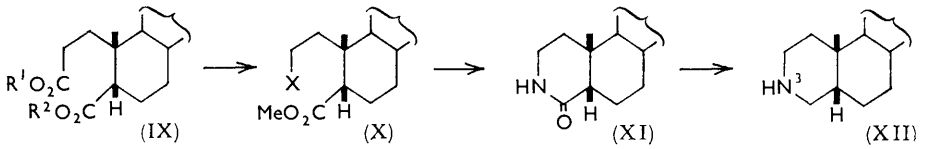
Reduction of the saturated δ-lactam (IV) with lithium aluminium hydride or sodium–butanol gave 3-aza-5α-cholestane (VIII), a strong base rapidly forming a carbonate in air and characterised as the hydrochloride and the *N*-methyl derivative, and the hydrochloride and methiodide of the latter.

3-Aza-5β-cholestan-4-one (XI), isolated above as a minor hydrogenation product, has been prepared as follows. Gardner and Godden's acid [4,5,6] (IX; $R^1 = R^2 =$ H) was converted by diazomethane into the dimethyl ester [7] (IX; $R^1 = R^2 =$ Me), which was partially hydrolysed with methanolic sodium hydroxide on the steam-bath to the 4-methyl ester (IX; $R^1 =$ H, $R^2 =$ Me). This with thionyl chloride gave the acid chloride-ester (X; X = COCl), converted by ammonia into the amide-ester (X; X = CO·NH_2), which by the Hofmann rearrangement furnished the amine-ester (X; X = NH_2); this cyclised spontaneously to the δ-lactam (XI). Reduction of the lactam (XI) with lithium aluminium hydride gave 3-aza-5β-cholestane (XII), a strong base, rapidly forming the carbonate in air, characterised as the hydrochloride, the *N*-methyl derivative, and the *N*-methyl methiodide.

The δ-lactam (XI) did not undergo inversion of configuration at $C_{(5)}$, to afford the epimer (IV), when boiled with methanolic sodium methoxide or with sodium pentyl oxide in pentanol. The δ-lactam (IV) was also unchanged under these conditions.

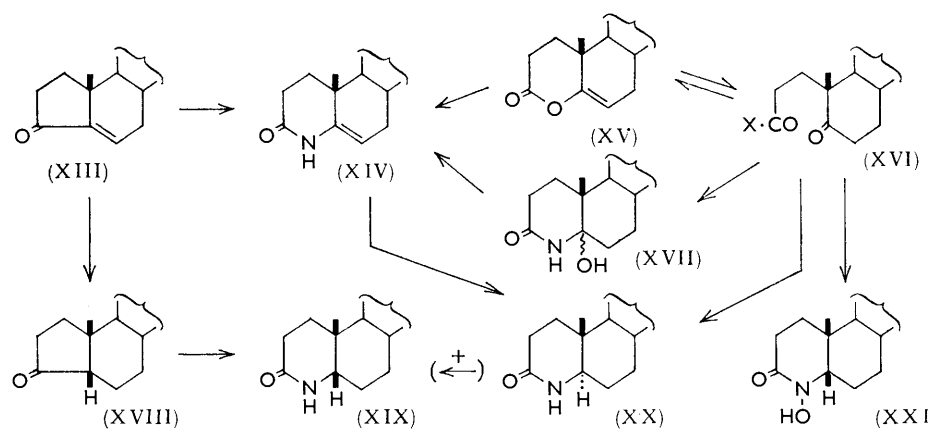
[4] Gardner and Godden, *Biochem. J.*, 1913, **7**, 588.
[5] Windaus and Kuhr, *Annalen*, 1937, **532**, 52; Windaus and Mielke, *ibid.*, 1938, **536**, 116.
[6] Langer, *Z. physiol. Chem.*, 1933, **216**, 189.
[7] Windaus, *Ber.*, 1916, **49**, 1724.

We have examined routes to 4-aza-steroids that involve Beckmann rearrangement of A-nor-steroid ketoximes and various transformations of 3,4-seco-steroids. The oxime of A-norcholest-5-en-3-one [3,8] (XIII), on Beckmann rearrangement with thionyl chloride at −20°, gives a single δ-lactam, 4-azacholest-5-en-3-one (XIV), m. p. 253°, $[\alpha]_D$ −92°, $\lambda_{max.}$ 235 mμ (log ε 4·1). This compound was reported by Doorenbos and Huang [9] and has



recently been described by Wildi; [10] in both cases, the Windaus keto-acid [11,12,13] (XVI; X = OH) was converted by treatment with acetic anhydride in presence of anhydrous sodium acetate into 4-oxacholest-5-en-3-one [13] (XV), which was heated with ammonia at 140—180° or 200° to afford the δ-lactam (XIV). We have obtained yields of 90% of lactam (XIV) directly from the Windaus keto-acid (XVI; X = OH) by addition of ammonium carbonate to supplement the supply of ammonia; the infrared spectrum of our specimen was identical with the original infrared curve kindly lent to us by Dr. Wildi, Monsanto Chemical Co., Dayton 7, Ohio. More recently, Gut and Uskokovics [14] converted the enol-lactone (XV) by treatment in benzene solution with ammonia at 20°; this procedure may give the amide (XVI; X = NH_2), the compound (XVII), or the δ-lactam (XIV),* or a mixture of these compounds readily converted into the δ-lactam by hot acetic acid.

Beckmann rearrangement of the oxime of A-nor-5β-cholestan-3-one [3,8] (XVIII) gave a



single δ-lactam, 4-aza-5β-cholestan-3-one (XIX). 4-Aza-5α-cholestan-3-one (XX) was first prepared by Bolt [15] from the oxime of the Windaus keto-acid (XVI; X = OH) by reduction with sodium–ethanol. We have repeated Bolt's preparation of the δ-lactam

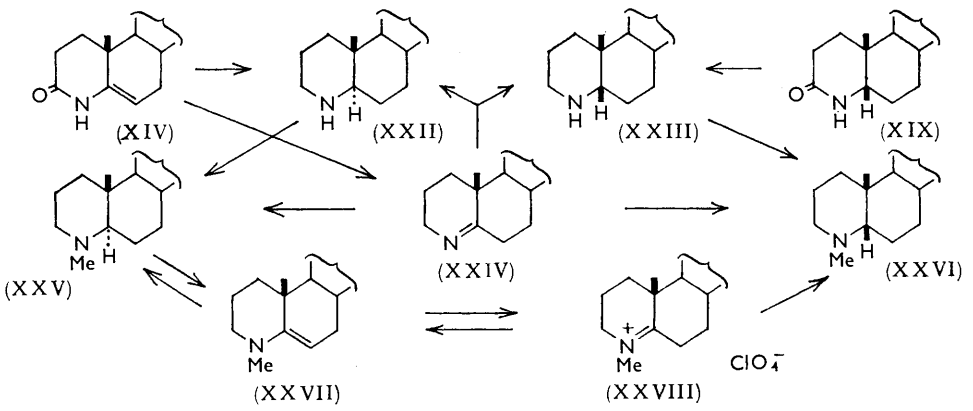
* Gut and Uskokovics [14] gave for their preparation, m. p. 189° (decomp.), [α] −77°, $\lambda_{max.}$ 233 mμ (log ε 4·13), $\nu_{max.}$ (in KBr) 3180, 3090 (NH), 1680, 1628 (CO·NH), and 846 cm.$^{-1}$ (Δ^5). The authenticity of their compound is thus unquestionable and their m. p. must be a typographical error; they point out that, whilst the ultraviolet data suggest a Δ^4-structure, the infrared data support a Δ^5-structure.

[8] Windaus, *Ber.*, 1912, **45**, 1316; 1919, **52**, 170.
[9] Doorenbos and Huang, Abs. 136th Amer. Chem. Soc. Meeting 30–0, Atlantic City, 1959.
[10] Wildi, U.S.P. 2,897,202; *Chem. Abs.*, 1960, **54**, 646.
[11] Windaus, *Ber.*, 1906, **39**, 2008.
[12] Lettré, *Annalen*, 1933, **218**, 67; 1933, **221**, 73.
[13] Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 583.
[14] Gut and Uskokovics, *Helv. Chim. Acta*, 1959, **42**, 2258.
[15] Bolt, *Rec. Trav. chim.*, 1938, **54**, 905.

(XX); McKenna and Tulley [16] have also done this. Hydrogenation of the oxime of the keto-acid [17] (XVI; X = OH) with platinum in acetic acid ceased after absorption of 1 mol. of hydrogen initially, to give the related hydroxyamino-acid, which cyclised spontaneously to the monohydrate of *N*-hydroxy-4-aza-5β-cholestan-3-one (XXI), recently described by Edward and Morand [18] and characterised as the *O*-methyl and the *O*-benzyl derivative. Formation of the *N*-hydroxy-δ-lactam (XXI) prevents further hydrogenation, but use of the oxime of the keto-ester [13] (XVI; X = OMe) avoids this difficulty and affords 4-aza-5α-cholestan-3-one (XX) and 4-aza-5β-cholestan-3-one (XIX), which were readily separated chromatographically, together with a little of the *N*-hydroxy-δ-lactam (XXI) formed by hydrolysis of the methoxycarbonyl group either before or after reduction of the hydroxyimino-group. 4-Aza-5α-cholestan-3-one (XX) so obtained was identical with the product prepared by hydrogenation, with platinum in acetic acid, of the Δ^5-δ-lactam (XIV); the 4-aza-5β-cholestan-3-one (XIX) was identical with the product previously prepared by Beckmann rearrangement of the oxime of A-nor-5β-cholestan-3-one (XVIII).

Reduction of the Δ^5-δ-lactam (XIV) with lithium aluminium hydride gave a mixture of 4-azacholest-4-ene (XXIV) and 4-azacholest-5-ene, exhibiting the broad absorption maximum at 230—240 mμ (log ε 2·24), characteristic of the enamine group NH·CH=CH. The major product, 4-azacholest-4-ene (XXIV), also described by Edward and Morand,[18] was readily isolated through the picrate; its ultraviolet spectrum showed only end-absorption, and its infrared absorption spectrum exhibited no N–H stretching vibration at ~3300 cm.$^{-1}$ but a strong sharp band at 1650 cm.$^{-1}$ (cf. ref. 18) corresponding to a C=N stretching vibration; it did not absorb carbon dioxide in air and so behaved as a weak tertiary base. It may be noted that Jacobs and Brownfield,[19] on reducing 6-azacholest-4-en-7-one with lithium aluminium hydride (4·6 mol.), also observed transposition of the double bond since the product was 6-azacholest-5-ene, $\lambda_{max.}$ none, $\nu_{max.}$ 1650 cm.$^{-1}$.

We have confirmed that reduction of the Δ^5-δ-lactam (XIV) with a large excess of lithium aluminium hydride [16] or with sodium–pentanol [15,16] yields 4-aza-5α-cholestane (XXII). According to Gaylord,[20] carbinolamines are intermediates in the reduction by lithium aluminium hydride of lactams to cyclic secondary amines and can undergo elimination to give cyclic azomethines, which according to the prevailing stereoelectronic



circumstances may survive or undergo further reduction. It seems possible that a conjugated azomethine –CH=N·C=CH– may be a precursor of 4-azacholest-4-ene (XXIV) and

[16] McKenna and Tulley, *J.*, 1960, 945.
[17] Cf. N.V. Organon, Dutch P. 47,226; *Chem. Zentr.*, 1940, I, 2829.
[18] Edward and Morand, *Canad. J. Chem.*, 1960, **38**, 1316.
[19] Jacobs and Brownfield, *J. Amer. Chem. Soc.*, 1960, **82**, 4033.
[20] Gaylord, " Reduction with Complex Metal Hydrides," Interscience Publ. Inc., New York, 1956, pp. 600, 619.

of 4-aza-5α-cholestane (XXII). Reduction of 4-aza-5β-cholestan-3-one (XIX) by lithium aluminium hydride gave 4-aza-5β-cholestane (XXIII).

Hydrogenation of 4-azacholest-4-ene (XXIV) with palladium in ethanol or with platinum oxide in dioxan in the presence of potassium hydroxide was ineffective, but it occurred with platinum oxide in acetic acid to give a mixture of 4-aza-5α-cholestane (XXII) (54%) and 4-aza-5β-cholestane (XXIII) (36%) which were readily separated by chromatography on aluminium oxide. Use of lithium aluminium hydride also gave the 5-epimeric 4-azacholestanes [XXII (66%); XXIII (33%)].

The configurations of *N*-methyl-4-aza-5α- (XXV) and -5β-cholestane (XXVI) have been established by McKenna and Tulley [16] by exhaustive methylation. The tertiary base (XXV) was prepared by these authors from the secondary base (XXII) by use of formaldehyde–formic acid at 100°; dehydrogenation of the base (XXV) with mercuric acetate furnished the Δ^5-tertiary base (XXVII), characterised as the Δ^4-methoperchlorate (XXVIII), which on hydrogenation with platinum oxide in ethanol gave *N*-methyl-4-aza-5α-cholestane (XXV) accompanied by the 5β-epimer (XXVI). We have confirmed the structure of the Δ^4-tertiary base (XXIV) by reduction with formic acid [21] then methylation with formaldehyde to furnish the tertiary bases (XXV, XXVI), and the structure of 4-aza-5β-cholestane (XXIII) by methylation with formaldehyde and formic acid to afford the tertiary base (XXVI). An attempt directly to convert the *N*-acetyl derivative of the saturated secondary base (XXII) by oxidation with potassium permanganate [22] in acetone into the *N*-acetyl derivative of the Δ^5-secondary base analogous to (XXVII) was unsuccessful.

Experimental

For general experimental directions, see *J.*, 1958, 3458. $[\alpha]_D$ are for $CHCl_3$ solutions. Ultraviolet absorption spectra were measured for EtOH solutions in a Hilger Uvispek spectrophotometer, and infrared absorption spectra were determined on a Perkin–Elmer model 21 or, for Nujol mulls, on an Infracord spectrophotometer.

3-*Azacholest*-5-*en*-4-*one* (III).—(*a*) *From Diels's acid* [G. K.]. 3,4-Secocholest-5-ene-3,4-dioic acid (m. p. 296° after softening from 285°; 1 g.) was refluxed with acetic anhydride (5 c.c.) for 4 hr. Acetic anhydride was removed at 100°/10 mm., and the residue chromatographed on silica gel (60 g.) prepared in pentane. Elution with ether–pentane (1 : 9 and 1 : 4) furnished a solid that recrystallised from pentane to give the *anhydride*, m. p. 124—126°, $\nu_{max.}$ (in Nujol) 1782, 1748, 1100, 1040, 1010, 985 cm.$^{-1}$ [Found (after drying at 60°/0·05 mm. for 4 hr.): C, 77·9; H, 10·3. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·2%]. The anhydride, finely powdered dry sodium azide (3 g.), and xylene (10 c.c.) were heated in a Carius tube at 130° for 40 hr. The gelatinous product was treated with ethereal hydrogen chloride, to give a granular precipitate, which was filtered off and washed with chloroform. The filtrate and washings were combined, dried, and evaporated at 10 mm. and then at 0·1 mm., yielding a yellowish glass (1 g.); this was dissolved in chloroform–benzene (1 : 20) and introduced on to a column of aluminium oxide (30 g.) prepared in benzene. Elution with chloroform–benzene (2 : 3 and 1 : 1) gave a substance (50 mg.), m. p. 174—175°, $\nu_{max.}$ (in Nujol) 3210, 1690, 1655, 1610, 1540, 1290, 905, 773, and 755 cm.$^{-1}$, which was not further investigated. Elution with chloroform gave 3-*azacholest*-5-*en*-4-*one* (200 mg.), m. p. and mixed m. p. 223—226°, $\nu_{max.}$ (in CCl_4) 3440, 3190 (NH), 1678, 1635 (CO·NH), $\nu_{max.}$ (in Nujol) 3420, 3210 (NH), 1680, 1667 (CO·NH) [Found (after sublimation at 190—205°/0·01 mm.): C, 80·7; H, 11·25; N, 3·6. $C_{26}H_{43}NO$ requires C, 81·0; H, 11·25; N, 3·6%]. Finely ground sodium azide was preferable to unground material.

When sodium azide was replaced by anhydrous hydrazoic acid (generated from dry sodium azide and concentrated sulphuric acid and collected in the Carius tube at −20°), no reaction occurred at 130° during 7 days; the anhydride could be isolated unchanged, and converted into Diels's acid by treatment with water.

(*b*) *From the* 3-*methyl ester* (I; R^1 = Me, R^2 = H). 3-Methyl 4-hydrogen 3,4-secocholest-5-ene-3,4-dioate [2] (1·2 g.) and hydrazine hydrate (1 c.c.) in ethanol (40 c.c.) were refluxed for 2 hr. After cooling, the crystalline product was filtered off and washed with ethanol, to give

[21] Hickinbottom, " Reactions of Organic Compounds," Longmans, Green & Co., London, 1957, p. 412.

[22] Hara, *Pharm. Bull.* (*Japan*), 1955, **3**, 297.

the 4-*hydrazine salt* (V), m. p. 228°, of 3,4-secocholest-5-ene-3,4-dioic acid 3-hydrazide [Found (after drying at 80°/0·1 mm. for 4 hr.): C, 67·5; H, 10·2. $C_{27}H_{50}N_4O_3$ requires C, 67·75; H, 10·5%]; further quantities of the salt (V) were obtained by concentration of the filtrate. The salt (V) in ethanolic hydrogen chloride gave hydrazine dihydrochloride, m. p. 197—198° (lit., 198°), and with 5-bromosalicylaldehyde in boiling ethanol–benzene (4 : 1) furnished NN-*di*-(5-*bromosalicylidene*)*hydrazine*, m. p. 317—319° alone or mixed with a specimen prepared from hydrazine hydrate and 5-bromosalicylaldehyde in refluxing ethanol [Found (after drying at 65°/0·1 mm. for 5 hr.): C, 42·7; H, 2·5; N, 7·5. $C_{14}H_{10}Br_2N_2O_2$ requires C, 42·3; H, 2·5; N, 7·0%]. The salt (V) (1 g.) was dissolved in warm acetic acid (40 c.c.) containing 4 drops of 10N-hydrochloric acid, cooled to 10°, and treated with sodium nitrite (500 mg.) with stirring. After 10 min. the solution was poured into water and extracted with ether (2 × 250 c.c.); the extract was washed three times with water, dried, and evaporated, to yield 3,4-secocholest-5-ene-3,4-dioic acid 3-azide (VI; X = N_3, R = H) as an oil, $\nu_{max.}$ 2130 cm.$^{-1}$ [$-CO\cdot N_3$], containing some acetic acid. The oil (1 g.) was dissolved in ether and refluxed for 40 hr.; a small quantity of precipitated product (190 mg.) was collected, and the filtrate was concentrated to yield the mixed *anhydride* (VII) (800 mg.), m. p. 213° (decomp.), $\nu_{max.}$ (in Nujol) 3575 (OH), 3300 (NH), 1700, 1670, 1630—1600 (CO·NH), 1237 (OAc), 742 cm.$^{-1}$, after recrystallisation from chloroform–methanol [Found (after drying at 80°/0·1 mm. for 4 hr.): C, 70·8; H, 10·1. $C_{29}H_{47}NO_5$ requires C, 71·1; H, 9·7%]. The anhydride (VII) (92 mg.) was heated at 215—220° (bath-temp.)/0·3 mm., whereupon it melted with effervescence and slowly distilled, to afford a solid (52 mg.); recrystallisation from acetone gave 3-*azacholest*-5-*en*-4-*one*, m. p. 225—226°, $[\alpha]_D$ −32° (*c* 0·6), $\lambda_{max.}$ 220 mμ (log ε 4·94), $\nu_{max.}$ (in $CHCl_3$) 3520 (NH), 1686, 1643 (CO·NH) [Found (after drying at 80°/0·1 mm. for 4 hr.): C, 80·7; H, 11·4; N, 4·0. $C_{26}H_{43}NO$ requires C, 81·0; H, 11·2; N, 3·6%]. The N-*acetyl* derivative, prepared by use of acetic anhydride–pyridine at 20°, had m. p. 164—165° after recrystallisation from methanol [Found (after drying at 80°/0·1 mm. for 3 hr.): C, 78·5; H, 10·5. $C_{28}H_{45}NO_2$ requires C, 78·6; H, 10·6%].

(*c*) *From the* 4-*methyl ester* (I; R^1 = H, R^2 = Me). Dimethyl 3,4-secocholest-5-ene-3,4-dioate [2,3] (m. p. 69°; 8·5 g.) was refluxed with 3·3N-potassium hydroxide (5·6 c.c.) and methanol (140 c.c.) for 2 hr. The solution was poured into water and extracted with benzene, which removed unchanged dimethyl ester (3·4 g.), m. p. and mixed m. p. 68—70°; the aqueous alkaline solution was acidified and extracted with ether, to give 4-*methyl* 3-*hydrogen* 3,4-*secocholest*-5-*ene*-3,4-*dioate*, m. p. 63—64° after crystallisation from methanol, which was extremely difficult to dry completely [Found (after drying at 20°/0·1 mm. for 10 hr.): C, 74·7; H, 10·0. $C_{28}H_{46}O_4$ requires C, 75·3; H, 10·4%]. The 4-methyl ester (9·95 g.) was refluxed with purified thionyl chloride (20 c.c.) in benzene (175 c.c.) for 2 hr., and the excess of the reagent and the solvent were removed in a vacuum; the residual acid chloride methyl ester was dissolved in ether and treated with a stream of ammonia for 0·25 hr. The ethereal solution was then washed with 2N-hydrochloric acid and with water, dried, and evaporated, to yield 3,4-*secocholest*-5-*ene*-3,4-*dioic acid* 3-*amide* 4-*methyl ester* (VI; X = NH_2, R = Me) (9·25 g.), m. p. 136—137°, after a single recrystallisation from acetone; further recrystallisation from ether–pentane gave a small sample, m. p. 140°, $\nu_{max.}$ (in Nujol) 3400, 3300 (NH), 1695 (CO_2Me), 1680, 1650 cm.$^{-1}$ (CO·NH) [Found (after drying at 80°/0·1 mm. for 3 hr.): C, 75·25; H, 10·25; N, 3·2. $C_{28}H_{47}NO_3$ requires C, 75·45; H, 10·6; N, 3·15%]. The amide ester (m. p. 137°; 2 g.), in methanol (55 c.c.), was treated with methanolic sodium methoxide [8 c.c., prepared from sodium (2·5 g.) and methanol (32 c.c.)] and a 20% v/v solution of bromine in methanol (2 c.c.) with stirring at 20° for 0·25 hr. The solution was then refluxed for 0·25 hr., poured into water, and acidified with 2N-hydrochloric acid, and the product was extracted with ether; the ethereal extract was washed twice with water, dried, and evaporated, and the residue recrystallised from acetone. The infrared spectrum of the product (1·5 g.), m. p. 220—221°, was similar to, but not identical with, that of 3-azacholest-5-en-4-one [preparation (*b*)]; it was therefore refluxed with 3% ethanolic potassium hydroxide (30 c.c.) for 0·5 hr., and the cooled solution was poured into water, acidified with acetic acid, and extracted with ether to furnish 3-azacholest-5-en-4-one, m. p. and mixed m. p. 225—226°, $\lambda_{max.}$ 220 mμ (log ε 4·94), $\nu_{max.}$ (in $CHCl_3$) 3520 (NH), 1686, 1643 cm.$^{-1}$ (CO·NH), after recrystallisation from acetone (*N*-acetyl derivative, m. p. and mixed m. p. 164—165°, after recrystallisation from methanol).

3-*Aza*-5α-*cholestan*-4-*one* (IV).—(*a*) 3-Azacholest-5-en-4-one (140 mg.) was shaken in hydrogen with platinum oxide (110 mg.) and acetic acid (40 c.c.) until absorption ceased. The usual working up gave 3-*aza*-5α-*cholestan*-4-*one* (135 mg.), m. p. 225—227°, $[\alpha]_D$ +17° (*c* 0·6),

$\nu_{max.}$ (in CCl_4) 3200 (NH), 1675 $cm.^{-1}$ (CO·NH)] [Found (after drying at 80°/0·1 mm. for 4 hr.): C, 80·3; H, 11·5. $C_{26}H_{45}NO$ requires C, 80·55; H, 11·7%]. A mixed m. p. with 3-azacholest-5-en-4-one was depressed to 205°. The N-*acetyl derivative*, prepared by using acetic anhydride–pyridine at 20°, had m. p. 103—104° after recrystallisation from methanol [Found (after drying at 55°/0·1 mm. for 4 hr.): C, 78·7; H, 11·1. $C_{28}H_{47}NO_2$ requires C, 78·3; H, 11·0%].

(*b*) 3-Azacholest-5-en-4-one (580 mg.) was shaken in hydrogen with 5% palladium–charcoal (1·05 g.) in ethanol (125 c.c.) until absorption ceased. The usual isolation procedure gave a colourless solid (560 mg.), which was chromatographed on a column of aluminium oxide (15 g.) prepared in hexane. Elution with ether–chloroform (7 : 3 and 6 : 4; 100 c.c.) gave fractions (30 mg., 150 mg.), m. p. ~165° and 195—210°, which by repeated chromatography furnished a small quantity of 3-aza-5β-cholestan-4-one (XI) (see below), m. p. and mixed m. p. 168—170°. Further elution with ether–chloroform (6 : 4 and 5 : 5) yielded 3-aza-5α-cholestan-4-one (320 mg.), m. p. 220—225° after recrystallisation from acetone.

(*c*) 3-Azacholest-5-en-4-one (550 mg.) was hydrogenated with 5% palladium–charcoal (1·15 g.) in ethanol (120 c.c.) containing 2 drops of 2N-potassium hydroxide until uptake ceased. Chromatography of the product (530 mg.) as in (*b*) and elution with ether–chloroform (7 : 3; 100 c.c.) gave a solid (80 mg.), m. p. 175—215°, which by repeated chromatography furnished a little 3-aza-5β-cholestan-4-one (XI), m. p. and mixed m. p. 168—170°. Further elution with ether–chloroform (7 : 3, 6 : 4, and 5 : 5) gave 3-aza-5α-cholestan-4-one (400 mg.), m. p. 225—230° after recrystallisation from acetone.

3-*Azacholest-5-ene*.—On a single occasion 3-azacholest-5-en-4-one (500 mg.) was treated with lithium aluminium hydride (1 g.) in ether (125 c.c.) at 20° for 48 hr. Moist ether and ice were added to decompose the excess of the reagent, the ethereal layer was decanted, and the residue was washed several times with ether. The combined ethereal extracts were dried rapidly and evaporated, to give 3-azacholest-5-ene (470 mg.) as an oil, $[\alpha]_D$ −50° (*c* 0·43); the base absorbed carbon dioxide rapidly and was analysed as the *hydrochloride*, m. p. 174—180° (from acetone) [Found (after drying at 80°/0·3 mm. for 4 hr.): N, 3·7. $C_{26}H_{46}ClN$ requires N, 3·4%].

In all other experiments, when 3-azacholest-5-en-4-one (700 mg.) was treated with lithium aluminium hydride (3 g.) in refluxing ether (125 c.c.) for 48 hr., and the mixture decomposed with moist ether and ice, the product was 3-aza-5β-cholestane (XII) (700 mg.), an oil $[\alpha]_D$ +30° (*c* 1·8), that absorbed carbon dioxide rapidly and was analysed as the *hydrochloride*, m. p. 245—250° (from acetone) [Found (after drying at 70°/0·1 mm. for 4 hr.): Cl, 7·95; N, 3·2. $C_{26}H_{48}ClN$ requires Cl, 8·6; N, 3·4. The *N*-methyl derivative, prepared by using formaldehyde–formic acid at 100°, chromatographed on aluminium oxide in hexane, and eluted with ether–hexane (1 : 9 to 3 : 7), had m. p. 82—83°, $[\alpha]_D$ +52° (*c* 0·82), after two recrystallisations from methanol; the *hydrochloride* had m. p. 275—280° after crystallisation from acetone [Found (after drying at 70°/0·1 mm. for 4 hr.): Cl, 8·4; H, 3·0. $C_{27}H_{50}ClN$ requires Cl, 8·35; N, 3·3%]. The N-*methyl derivative methiodide* had m. p. 282—284° after recrystallisation from acetone [Found (after drying at 80°/0·3 mm. for 3 hr.): C, 63·8; H, 9·7. $C_{28}H_{50}NI$ requires C, 63·75; H, 9·55%].

3-*Aza-5α-cholestane* (VIII).—3-Aza-5α-cholestan-4-one (320 mg.) was treated with lithium aluminium hydride (1·5 g.) in refluxing ether (125 c.c.) for 48 hr. The excess of the reagent was decomposed with moist ether and ice, the ethereal layer decanted, the residue washed several times with ether, and the combined ethereal extracts were rapidly dried and evaporated, to yield 3-aza-5α-cholestane (270 mg.) as an oil, $[\alpha]_D$ +45° (*c* 0·43), that rapidly formed the carbonate and was analysed as the *hydrochloride*, m. p. 280—285° (from acetone) [Found (after drying at 80°/0·3 mm. for 4 hr.): C, 76·2; H, 11·4. $C_{26}H_{48}ClN$ requires C, 76·2; H, 11·7%]. The N-*methyl derivative*, purified by chromatography on aluminium oxide in hexane and eluted with ether–hexane (1 : 9), had m. p. 87—88°, $[\alpha]_D$ +22° (*c* 0·4), after two recrystallisations from methanol [Found (after drying at 25°/0·1 mm. for 6 hr.): C, 83·8; H, 12·4. $C_{27}H_{49}N$ requires C, 83·65; H, 12·7%]; the *hydrochloride* had m. p. 300—303° after recrystallisation from methanol–acetone [Found (after drying at 80°/0·3 mm. for 4 hr.): C, 75·9; H, 11·5. $C_{27}H_{50}NCl$ requires C, 76·45; H, 11·9%]; the *methiodide* had m. p. 265—270° (from acetone) [Found (after drying at 90°/0·3 mm. for 4 hr.): C, 63·2; H, 9·95. $C_{28}H_{52}NI$ requires C, 63·5; H, 9·9%].

3-*Aza-5β-cholestan-4-one* (XI).—Dimethyl 3,4-seco-5β-cholestane-3,4-dioate [7] (IX; R^1 = R^2 = Me) (m. p. 60—61°; 2·1 g.) was refluxed with 4·5N-potassium hydroxide (1 c.c.) in methanol (40 c.c.) for 2 hr. The cooled solution was saturated with carbon dioxide,

concentrated in a vacuum to ~10 c.c., acidified with 2N-hydrochloric acid, and extracted with ether. The acidic fraction was removed with 2N-sodium carbonate; the neutral ethereal extract yielded unchanged dimethyl ester (930 mg.), m. p. and mixed m. p. 60°. The alkaline extract was acidified with 2N-hydrochloric acid and extracted with ether, to afford the methyl hydrogen ester as an oil (1 g.), which was chromatographed on a column of Davison silica gel (100—200 mesh; W. R. Grace & Co., Baltimore, Ind., U.S.A.; 30 g.) prepared in hexane. Elution with ether–hexane (1 : 4) gave *4-methyl 3-hydrogen 3,4-seco-5β-cholestane-3,4-dioate* (IX; R^1 = H, R^2 = Me), m. p. 127°, $\nu_{max.}$ (in Nujol) 1725 (CO_2Me), 1698 (CO_2H), 1158 (C–O), 935 cm.$^{-1}$ (OH) [Found (after drying at 20°/0·1 mm. for 4 hr.): C, 75·25; H, 10·6. $C_{28}H_{46}O_4$ requires C, 75·3; H, 10·4%]. The 4-methyl ester (1·15 g.) was refluxed with purified thionyl chloride (5 c.c.) in benzene (50 c.c.) for 2 hr.; the residual acid chloride methyl ester, obtained by complete evaporation under reduced pressure, was dissolved in ether and treated with a stream of ammonia for 10 min. The usual working up gave the *amide ester* (1 g.) (X; X = $CO{\cdot}NH_2$), m. p. 167°, $\nu_{max.}$ (in Nujol) 3390, 3320, 3180 (NH), 1720 (CO_2Me), 1675 (CO·NH), 1164 cm.$^{-1}$ (C–O) [Found (after drying at 80°/0·3 mm. for 4 hr.): C, 75·05; H, 11·0; N, 3·5. $C_{28}H_{49}NO_3$ requires C, 75·1; H, 11·0; N, 3·1%]. The amide methyl ester (400 mg.) was dissolved in warm methanol (11 c.c.), the solution cooled to 20°, and treated with methanolic sodium methoxide [8 c.c., prepared from sodium (0·5 g.) and methanol (32 c.c.)] and a 20% v/v solution (2 c.c.) of bromine in methanol. The clear solution was heated on a steam-bath for 0·25 hr., cooled, poured into 2N-hydrochloric acid, and extracted with ether; the extract gave an oil, which was refluxed with 2N-ethanolic potassium hydroxide (25 c.c.) for 0·5 hr. and then gave, after the usual working up, a semisolid material (360 mg.). This by chromatography on a column of aluminium oxide (11 g.) prepared in hexane and elution with ether–chloroform (7 : 3 and 6 : 4) yielded *3-aza-5β-cholestan-4-one* (200 mg.), m. p. 168—170°, $[\alpha]_D$ +68° (*c* 1·75), $\nu_{max.}$ (in CCl_4) 3200 (NH), 1665 (CO·NH), $\nu_{max.}$ (in Nujol) 3425, 3180 (NH), 1645, 1620 cm.$^{-1}$ (CO·NH) [Found (after drying at 80°/0·1 mm. for 24 hr.): C, 80·4; H, 11·3. $C_{26}H_{45}NO$ requires C, 80·55; H, 11·6%]. The compound was unaffected by treatment for 2 hr. with boiling 0·35N-methanolic sodium methoxide or with sodium pentyloxide in boiling methanol.

The 4-methyl 3-hydrogen ester (IX; R^1 = H, R^2 = Me) is reconverted by ethereal diazomethyl into the dimethyl ester (IX; R^1 = R^2 = Me), m. p. and mixed m. p. 58—61° (the 5α-epimer has m. p. 121—122°). This proves absence of inversion in the reactions involved and the 5β-configuration of the compounds of this series.

3-Aza-5β-cholestane (XII).—3-Aza-5β-cholestan-4-one (500 mg.) was refluxed with lithium aluminium hydride (2·5 g.) in ether (175 c.c.) for 48 hr. Moist ether and ice were added to decompose the excess of the reagent, the ethereal layer was decanted, and the residue washed several times with ether. The combined ethereal extracts were rapidly dried and evaporated, to furnish 3-aza-5β-cholestane (480 mg.), an oil, $[\alpha]_D$ +47° (*c* 0·6), which quickly formed the carbonate in air and was analysed as the *hydrochloride*, needles, m. p. 240—242° (from methanol–acetone), or plates, m. p. 230—235° (from acetone) [Found (after drying at 80°/0·2 mm. for 4 hr.): Cl, 8·1; N, 3·4. $C_{26}H_{48}ClN$ requires Cl, 8·6; N, 3·4%]. The *N-methyl derivative*, prepared in the usual way and purified chromatographically on aluminium oxide in hexane by elution with ether–hexane (1 : 9 and 1 : 4), was an oil, b. p. 180°/0·1 mm., $[\alpha]_D$ +57° (*c* 0·85), which crystallised on keeping, m. p. 80—83° (Found: C, 83·85; H, 12·9. $C_{27}H_{49}N$ requires C, 83·65; H, 12·75%); it gave a *methiodide*, m. p. 288° (from acetone) [Found (after drying at 80°/0·1 mm. for 3 hr.): C, 63·75; H, 9·95. $C_{28}H_{52}IN$ requires C, 63·5; H, 9·9%].

4-Azacholest-5-en-3-one (XIV).—(*a*) *From* A-*norcholest-5-en-3-one oxime* [3,8] (XIII) [G. K.]. The oxime (m. p. 174—177°; 380 mg.) was rapidly dissolved in purified thionyl chloride (5 c.c.) at −20° and the almost colourless solution immediately poured into 4N-potassium hydroxide (10 c.c.) previously heated to 90°. The product was extracted with ether, isolated in the usual way, and recrystallised several times from chloroform–ether, finally to give 4-azacholest-5-en-3-one (30 mg.), m. p. and mixed m. p. 252—253° (lit.,[10] 249—253°), $[\alpha]_D$ −90°, $\nu_{max.}$ (in CCl_4) 3420, 3210, 3085 (NH), 1680, 1667 (CO·NH), $\nu_{max.}$ (in Nujol) 3155, 3050 (NH), 1675 cm.$^{-1}$ (CO·NH), the latter spectrum being identical with that observed by Wildi in Nujol.[10] The material in the mother-liquor consisted mainly of unchanged oxime.

(*b*) *From 4-oxacholest-5-en-3-one* (XV). The lactone (m. p. 96°; 6·4 g.) was heated with ammonia solution (*d* 0·880; 200 c.c.) at 210° for 40 hr. The solid product was filtered off, dried, and recrystallised from acetone, to yield 4-azacholest-5-en-3-one (4·6 g.), m. p. 249—253°, $[\alpha]_D$ −92° (*c* 0·95), $\lambda_{max.}$ 235 (log ε 4·1), $\nu_{max.}$ (in Nujol) 3096, 1660 cm.$^{-1}$.

(*c*) *From 5-oxo-3,5-secocholestan-3-oic acid* (XVI; X = OH). (i) The keto-acid (4·8 g.) was heated with ammonia solution (*d* 0·880; 200 c.c.) and ammonium carbonate (5 g.) at 200° for 40 hr. The solid product was filtered off, washed with water, and dried; recrystallisation from chloroform–ether gave a polymorphic form of 4-azacholest-5-en-3-one, m. p. 227—229°, $[\alpha]_D$ −92·5° (*c* 0·4), $\nu_{max.}$ (in Nujol) 3096, 1660 cm.$^{-1}$, the infrared spectrum being identical with that of the modification of m. p. 249—253° which was obtained by recrystallisation from acetone or methanol. The *N*-acetyl derivative, prepared by using acetic anhydride–pyridine at 20°, had m. p. 122—123° (lit.,[10] 118°) after recrystallisation from methanol [Found (after drying at 80°/0·1 mm. for 4 hr.): C, 78·5; H, 10·4; N, 3·6. Calc. for $C_{28}H_{45}NO_2$: C, 78·6; H, 10·6; N, 3·3%]. (ii) The keto-acid (1 g.) and ammonia solution (150 c.c.) were heated at 200° for 20, 40, and 64 hr., to afford 650, 900, and 910 mg., respectively, of the crude Δ^5-δ-lactam (XIV).

4-Aza-5β-cholestan-3-one (XIX).—A-Nor-5β-cholestan-3-one oxime[3,8] (m. p. 123—127°; 360 mg.) was treated with purified thionyl chloride (4 c.c.) at 0°, and the resulting clear yellow solution at once poured slowly into 4N-potassium hydroxide with stirring at 20°. The product was isolated with ether in the usual way, giving *4-aza-5β-cholestan-3-one* (285 mg.), m. p. 193—196°, $[\alpha]_D$ +34° (*c* 1·0), $\nu_{max.}$ (in Nujol) 3200 (NH), 1665, 1615 cm.$^{-1}$ (CO·NH) [Found (after drying at 80/0·1 mm. for 4 hr.): C, 80·65; H, 11·75. $C_{26}H_{45}NO$ requires C, 80·55; H, 11·7%]. The N-*acetyl derivative* required purification by chromatography on aluminium oxide and distillation at 180—200°/0·2 mm. before it crystallised; after recrystallisation from methanol it had m. p. 70—72° [Found (after drying at 20°/0·1 mm. for 4 hr.): C, 78·2; H, 11·0. $C_{28}H_{47}NO_2$ requires C, 78·25; H, 11·05%].

4-Aza-5α-cholestan-3-one (XX).—(*a*) 4-Azacholest-5-en-3-one (280 mg.) was shaken with platinum oxide (135 mg.) and acetic acid (70 c.c.) in hydrogen for 3 hr. The solution was filtered, the filtrate diluted with water, and the precipitate collected; recrystallisation from acetone gave 4-aza-5α-cholestan-3-one (260 mg.), m. p. 253—255° alone or mixed with a specimen prepared by Bolt's method (*b*).[15] The *N*-acetyl derivative, prepared by using acetic anhydride–pyridine at 20° and recrystallised from methanol, had m. p. and mixed m. p. 137—138° (lit.,[15] 136—137°,[17] 135°).

(*b*) The oxime[15] (m. p. 188°; 0·9 g.) of 5-oxo-3,5-seco-A-norcholestan-3-oic acid (XVI; X = OH) was reduced with sodium (2 g.) in boiling ethanol (35 c.c.) for 1 hr. Isolated in the usual way, 4-aza-5α-cholestan-3-one had m. p. 253—255° after recrystallisation from acetone.

Hydrogenation of the Oxime of the Keto-acid (XVI; X = OH).—The oxime (320 mg.) was shaken in hydrogen with platinum oxide (110 mg.) and acetic acid (70 c.c.) for 15 hr. After filtration, the solution was evaporated in a vacuum, poured into sodium hydrogen carbonate solution, and extracted with ether. The usual working up gave *N*-hydroxy-4-aza-5α-cholestan-3-one (XXI) (300 mg.), as the monohydrate, m. p. 127—128°, $\nu_{max.}$ (in Nujol) 3300 (OH), 1610 cm.$^{-1}$ (CO·NH) [lit.,[18] m. p. 122—124°, $\nu_{max.}$ (in $CHCl_3$) 1607 cm.$^{-1}$, $\nu_{max.}$ (in CCl_4) 3240 cm.$^{-1}$], after recrystallisation from acetone [Found (after drying at 80°/0·1 mm. for 4 hr.): C, 74·0; H, 11·2; N, 3·7. Calc. for $C_{26}H_{47}NO_3$: C, 74·05; H, 11·25; N, 3·3%]. The compound did not sublime, but it distilled at 185—200°/0·1 mm. to yield unaltered material, m. p. 125—126° (mixed m. p. 126—127°) (from acetone).

Alternative Preparation of 4-Aza-5β-cholestan-3-one (XIX) *and 4-Aza-5α-cholestan-3-one* (XX).—Methyl 5-oxo-3,5-seco-A-norcholestan-3-oate[13] (XVI; X = OMe) was refluxed with hydroxylamine hydrochloride (5 g.) and sodium acetate trihydrate (7·5 g.) in 90% ethanol (220 c.c.) for 3 hr. The solvent was removed under reduced pressure, and the oxime extracted with ether and isolated in the usual manner. The resultant oil (2·7 g.) was chromatographed on a column of silica gel (75 g.) prepared in hexane; elution with ether–hexane (1 : 8) gave *methyl 5-hydroxyimino-3,5-seco-A-norcholestan-3-oate* (1·33 g.), m. p. 81—82°, $\nu_{max.}$ (in Nujol) 3450 (OH), 1740 (CO), 1020 (N·OH), 930 cm.$^{-1}$ (CO_2Me), after three recrystallisations from methanol [Found (after drying at 25°/0·1 mm. for 6 hr.): C, 74·2; H, 11·8. $C_{27}H_{49}NO_3$ requires C, 74·4; H, 11·4%]. The same compound was obtained from the oxime[15] of the keto-acid (XVI; X = OH) was esterified with 36N-sulphuric acid (3 drops) in refluxing methanol (110 c.c.) for 2 hr. The methyl ester oxime (1·55 g.) was shaken with platinum oxide (310 mg.) in acetic acid (100 c.c.) for 23 hr. After filtration, the filtrate was evaporated completely in a vacuum, and the residue dissolved in ether. The ethereal solution was washed with water, and extracted with N-sodium hydroxide (2 × 50 c.c.); an insoluble sodium salt was formed. This was separated with the aqueous phase, acidified with 2N-hydrochloric acid, and extracted with ether, to furnish the hydrate of *N*-hydroxy-4-aza-5β-cholestan-3-one (860 mg.), m. p. and

mixed m. p. 126—127° (from acetone). The neutral ethereal fraction was worked up in the usual way to give a mixed product (575 mg.), m. p. 130—230°, which was chromatographed on a column of aluminium oxide (20 g.) prepared in hexane. Elution with chloroform–ether (3 : 7, 100 c.c.) furnished 4-aza-5β-cholestan-3-one (90 mg.), m. p. and mixed m. p. 193—195°, $[\alpha]_D$ +35° (*c* 0·8) (after recrystallisation from acetone), whose infrared spectrum was identical with that of the specimen prepared by Beckmann rearrangement of the oxime of A-nor-5β-cholestan-3-one. Elution with chloroform–ether (4 : 6, 5 : 5; 2 × 100 c.c.) gave mixtures (250 mg.) of the 5β- and 5α-epimers; later elution with chloroform–ether (6 : 4, 100 c.c.) gave 4-aza-5α-cholestan-3-one (70 mg.), m. p. 247—249°, mixed m. p. 250—253° (from methanol), characterised as the *N*-acetyl derivative, m. p. and mixed m. p. 138—139° (from methanol).

Reduction of 4-*Azacholest*-5-*en*-3-*one* (XIV) *by Lithium Aluminium Hydride.*—(*a*) The Δ^5-δ-lactam (2·95 g.) was extracted from a thimble in a Soxhlet apparatus with ether into an ethereal solution of lithium aluminium hydride (1 g., 2·5 mol.) at 36° during 48 hr. After addition of moist ether and ice, the ethereal layer was decanted and the residue washed several times with ether. The usual working up gave a solid (2·15 g.), which was chromatographed on aluminium oxide (60 g.) prepared in hexane; elution with ether–hexane (1 : 9 to 3 : 7) yielded a mixture (1·55 g.) of 4-azacholest-4-ene and 4-azacholest-5-ene, that had m. p. 85—87°, $[\alpha]_D$ +28° (*c* 0·65), $\lambda_{max.}$ ~240 mμ (log ε 2·24), after repeated recrystallisation from acetone [Found (after drying at 25°/0·1 mm. for 4 hr.): C, 84·0; H, 12·7. Calc. for $C_{26}H_{45}N$: C, 84·0; H, 12·2%]. The mixed bases were dissolved in the minimum volume of ethanol, and an equal volume of saturated ethanolic picric acid was added. The solution was heated at 100° for 5 min., then cooled in ice, whereupon 4-*azacholest*-4-*ene picrate* crystallised (m. p. 189—195°); recrystallisation from ethanol gave a pure product, m. p. 203—204° [Found (after drying at 80°/0·1 mm. for 4 hr.): C, 64·3; H, 8·25; N, 9·3. $C_{32}H_{48}N_4O_7$ requires C, 64·0; H, 8·05; N, 9·3%]. The purified picrate (180 mg.) was dissolved in sufficient ether, and this solution thrice washed with small portions of ~5% v/v aqueous ethanolamine; the combined yellow aqueous washings were extracted twice with ether, and the combined colourless ethereal solutions washed with water, then with saturated sodium chloride solution, dried, and evaporated. The resultant oil (100 mg.) was chromatographed on aluminium oxide (3 g.) prepared in hexane; elution with ether–hexane (3 : 7, 4 : 6, and 5 : 5) furnished 4-azacholest-4-ene, m. p. 103°, $[\alpha]_D$ +88° (*c* 0·55), $\lambda_{max.}$ none, $\nu_{max.}$ (in CCl_4) 1650 $cm.^{-1}$ (C=N), no band at ~3300 $cm.^{-1}$ (NH) [lit.,[18] m. p. 101—102°, $\nu_{max.}$ (in CCl_4) 1649 $cm.^{-1}$] [Found (after drying at 25°/0·1 mm. for 4 hr.): C, 83·6; H, 12·1. Calc. for $C_{26}H_{45}N$: C, 84·0; H, 12·2%].

4-Azacholest-4-ene (90 mg.) was heated with 40% formaldehyde and formic acid at 100° for 6 hr. The mixture, after concentration at 10 mm., was poured into 4N-sodium hydroxide and extracted with ether to give, by the usual isolation procedure, an oil (90 mg.) which was chromatographed on aluminium oxide (3 g.) prepared in hexane. Elution with ether–hexane (1 : 9, 1 : 4; 3 : 7 and 5 : 5) gave fractions: (*a*) a mixture of *N*-methyl-4-aza-5α- and -5β-cholestane (45 mg.), $\nu_{max.}$ (film) 1024 [*N*-Me (*eq*)], 1012 $cm.^{-1}$ [*N*-Me (*ax*)]; (*b*) *N*-methyl-4-aza-5α-cholestane [15,16,17] (15 mg.), m. p. 70°, $\nu_{max.}$ (film) 1024 $cm.^{-1}$ (*N*-methyl methiodide,[16] m. p. 283—285°); (*c*) 4-azacholest-4-ene (20 mg.), $\nu_{max.}$ (film) 1650 $cm.^{-1}$, containing a trace of *N*-methyl-4-aza-5α-cholestane, $\nu_{max.}$ (film) 1024 $cm.^{-1}$; (*d*) 4-azacholest-4-ene (25 mg.), m. p. 97—100°, $\nu_{max.}$ (in Nujol) 1650 $cm.^{-1}$. Fraction (*a*) was rechromatographed similarly, elution with ether–hexane (1 : 9) giving three fractions: (i) *N*-methyl-4-aza-5β-cholestane [16] (XXVI) (20 mg.), an oil, $\nu_{max.}$ (film) 1012 $cm.^{-1}$; (ii) a mixture of *N*-methyl-4-aza-5α- and -5β-cholestane (10 mg.); (iii) *N*-methyl-4-aza-5α-cholestane (15 mg.), m. p. 70°, $\nu_{max.}$ (film) 1024 $cm.^{-1}$.

(*b*) The Δ^5-δ-lactam (530 mg.), on reduction with a large excess of lithium aluminium hydride (4 g., 47 mol.) for 30 hr., gave 4-aza-5α-cholestane (450 mg.), m. p. and mixed m. p. 115—116° (from methanol).

(*c*) The Δ^5-δ-lactam (7·5 g.), on reduction with sodium (75 g.) in boiling pentanol (550 c.c.) during 3 hr., gave 4-*aza*-5α-*cholestane* (4 g.), m. p. and mixed m. p. 113·5—115°, $[\alpha]_D$ +42° (*c* 0·7) (from methanol) [Found (after drying at 50°/0·1 mm. for 4 hr.): C, 83·55; H, 12·7. $C_{26}H_{47}N$ requires C, 83·6; H, 12·7%].

Reduction of 4-*Aza*-5β-*cholestan*-3-*one* (XIX) *by Lithium Aluminium Hydride.*—The 5β-lactam (300 mg.) was treated with lithium aluminium hydride (4 g.) in ether at 36° for 40 hr. After decomposition of the excess of reagent with moist ether and ice, the ethereal layer was decanted and the residual hydroxide washed several times with ether. The combined ethereal extracts furnished, by the usual procedure, an oil (280 mg.) which was chromatographed on

aluminium oxide (10 g.) prepared in hexane. Elution with ether–hexane mixtures (1 : 9, 2 : 8, and 3 : 7; 75 c.c.) yielded 4-aza-5β-cholestane (225 mg.), m. p. 50—52°, $[\alpha]_D$ +21° (*c* 0·6), $\nu_{max.}$ (in Nujol) 3250 cm.$^{-1}$ (NH) (lit.,[18] an oil, $[\alpha]_D$ +22°) [Found (after distillation at 180°/0·1 mm.): C, 83·9; H, 12·4. Calc. for $C_{26}H_{47}N$: C, 83·6; H, 12·7%]. The *hydrochloride* formed needles, m. p. 288—290°, from acetone [Found (after drying at 80°/0·1 mm. for 4 hr.): C, 76·0; H, 12·0. $C_{26}H_{48}NCl$ requires C, 76·15; H, 11·8%]. The N-*acetyl derivative*, prepared by using acetic anhydride–pyridine at 20°, was purified by elution from aluminium oxide with ether–hexane (3 : 7) and had m. p. 85—87° after crystallisation from methanol [Found (after drying at 20°/0·1 mm. for 3 hr.): C, 79·7; H, 11·85. $C_{28}H_{49}NO$ requires C, 80·9; H, 11·9%]. The *N*-methyl derivative methiodide, recrystallised from acetone, had m. p. 277—278° (lit.,[16] 267—268°) [Found (after drying at 80°/0·1 mm. for 3 hr.): C, 63·4; H, 10·1. Calc. for $C_{28}H_{52}NI$: C, 63·5; H, 9·9%].

Reduction of 4-*Azacholest*-4-*ene* (XXIV).—(*a*) *With lithium aluminium hydride.* 4-Azacholest-4-ene (80 mg.) was refluxed with the reagent (2 g., 400 mol.) for 40 hr. Moist ether and then ice were added, the ethereal layer was decanted, and the residue was washed several times with ether. The combined ethereal solutions were dried and evaporated, to afford crystals (80 mg.), m. p. 111—115°, which were chromatographed on aluminium oxide (3 g.) prepared in pentane. Elution with ether–hexane (1 : 9 and 1 : 4; 25 c.c.) gave oily 4-aza-5β-cholestane (25 mg.) whose infrared spectrum was identical with that of the authentic sample; it was characterised as the methiodide,[16] m. p. 275—277° alone or mixed with the specimen described above. Elution with ether–hexane (3 : 7 and 5 : 5; 25 c.c.) yielded 4-aza-5α-cholestane (50 mg.), m. p. and mixed m. p. 117° (from methanol).

(*b*) *With hydrogen and platinum.* 4-Azacholest-4-ene (80 mg.) was shaken in hydrogen with prereduced platinum oxide (100 mg.) in acetic acid (45 c.c.) for 5 hr. The usual working up afforded a solid (80 mg.), m. p. 112—115°, which was chromatographed as under (*a*), to give 4-aza-5β-cholestane (25 mg.) (an oil with the correct infrared spectrum and giving the methiodide,[16] m. p. and mixed m. p. 275—277°) and 4-aza-5α-cholestane (45 mg.), m. p. and mixed m. p. 117° (from methanol).

A similar result was obtained with platinum oxide in ether, but hydrogenation did not proceed in dioxan–ethanol (5 : 2) containing aqueous 2N-potassium hydroxide (5 drops) or 10% palladium–charcoal in ethanol with or without addition of a trace of potassium hydroxide.

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