196. *Aza-steroids. Part III.*[1] 3-*Aza*-A-*homocholest*-4a- *and* -5-*ene and Related Compounds.*

By C. W. Shoppee, G. Krüger, and R. N. Mirrington.

Cholest-4-en-3-one oxime, on Beckmann rearrangement, gives 3-aza-A-homocholest-4a-en-4-one, hydrogenated to the known 3-aza-A-homo-5α-cholestan-4-one, and reduced by lithium aluminium hydride to 3-aza-A-homocholest-4a-ene.

Cholest-5-en-3-one oxime undergoes the Beckmann rearrangement, to afford 4-aza-A-homocholest-5-en-3-one, hydrogenated to yield 4-aza-A-homo-5α- and -5β-cholestan-3-one. The structure of the 5α-ε-lactam is proved by hydrolysis and deamination to the known 4-oxa-A-homo-5α-cholestan-3-one. Reduction of the 5α- and the 5β-ε-lactam with lithium aluminium hydride gives, respectively, 4-aza-A-homo-5α- and -5β-cholestane.

As a model for the preparation of 3-aza-A-homoandrost-4a-en-4-one from the oxime of androst-4-en-3-one, described in Part II,[1] we examined the Beckmann rearrangement of

[1] Part II, Shoppee and Krüger, *J.*, 1961, 3641. [In that paper, formula (XVI) was misprinted; ring A should be seven-membered, with nitrogen at position 3.]

the oxime of cholest-4-en-3-one. This oxime has been reported [2] to exist in two forms, regarded as geometrical isomerides. The " B "-form,[3-6] m. p. 152—153°, and the " A "-form,[2] double m. p. 65°/152°, possess the same ultraviolet absorption spectra in acetic acid [2] and in ethanol; [2,4,5] they are interconvertible by crystallisation from appropriate solvents, and the " A "- gives the " B "-form when heated above 85°. The " A "-form gave a crystalline polybromo-derivative that lost hydrogen bromide very readily to give a product (presumed to be an isoxazole) containing one atom of bromine and incapable of acetylation, whilst the " B "-form gave a non-crystalline polybromo-derivative, losing hydrogen bromide relatively less readily but also incapable of acetylation. On this somewhat exiguous basis, Ralls concluded [2] that the " A "-form is the *syn*-isomer (OH *syn* to the 4,5-double bond). Because of the ready interconversion we at first regarded the two forms as polymorphs, but we have found that they behave differently in the Beckmann rearrangement and on the basis of the accepted *trans*-interchange in molecular rearrangements, we conclude, as a result of reactions to be detailed that the " A "-form is the *anti*-oxime (I) and the " B "-form, contrary to Ralls's conclusion,[2] is the *syn*-oxime (II). It is possible that conjugation in a six-membered ring leading to some degree of double-bond character in the 3,4-bond of the *anti*-oxime (I) may be responsible for resistance to the migration of that bond, which would be involved in a Beckmann rearrangement.

The oximes of αβ-unsaturated steroid ketones undergo the Beckmann rearrangement less readily than those of saturated steroid ketones. Rapid addition of the *syn*-oxime (II) of cholest-4-en-3-one to an excess of thionyl chloride cooled to −20° gave an almost colourless solution, becoming pale yellow; when this solution was at once poured into cold water, only traces of the Δ^{4a}-ε-lactam (III) could be isolated, but by immediate addition to 4N-sodium hydroxide at 20°, or better at 80°, a ~20% yield of the Δ^{4a}-ε-lactam (III) was obtained, with some unchanged oxime. The *anti*-oxime (I) failed to rearrange, even under more vigorous conditions; in benzene, where the *anti*- is converted into the *syn*-form, the product was the same lactam (III).

Formulation of the lactam as (III), rather than the isomeric 3-oxo-4-aza-structure [cf. (V)], is supported by the ultraviolet and infrared spectral characteristics (see Table 1), which are consistent with those of the unsaturated ε-lactam [7,8] (VI) [compare those of the isomeric lactam [7,8] (X)], of 3-aza-A-homoandrost-4a-en-4-one [1] (VII), and of the spirostan [9] (VIII); the similar maxima shown by (III) and (VII) (the structure of the latter is established [1]) are noteworthy.

Hydrogenation of the Δ^{4a}-ε-lactam (III) with palladium–calcium carbonate or palladium–charcoal in ethanol gave 3-aza-A-homo-5α-cholestan-4-one (IV), m. p. 294—296°, $[\alpha]_D$ +41°. This compound, but with m. p. 268—271°, $[\alpha]_D$ +16°, was described by Shoppee and Sly [10] as the sole product of the Beckmann rearrangement of 5α-cholestan-3-one, but it now appears (see Table 2) that this reputed compound is an inseparable mixture, or a molecular compound, of the 3-aza-A-homo-5α-cholestan-4-one (IV), and the isomeric Beckmann rearrangement product 4-aza-A-homo-5α-cholestan-3-one (XI).

Analogy suggests that the preparation, m. p. 166—174° (clear at 195°), $[\alpha]_D$ +42°, described by Shoppee and Sly [10] as 3-aza-A-homo-5β-cholestan-4-one may have been an inseparable mixture or a molecular compound of 3-aza-A-homo-5β-cholestan-4-one and 4-aza-A-homo-5β-cholestan-3-one (XII).

Reduction of the Δ^{4a}-lactam (III) with lithium aluminium hydride in ether eliminated

[2] Ralls, *J. Amer. Chem. Soc.*, 1938, **60**, 1744; 1940, **62**, 2459.
[3] Diels and Abderhalden, *Ber.*, 1904, **37**, 3092.
[4] Mohler, *Helv. Chim. Acta*, 1937, **20**, 289.
[5] Jones, Wilkinson, and Kerlogue, *J.*, 1942, 391.
[6] Shoppee, Evans, Richards, and Summers, *J.*, 1956, 1649.
[7] Montgomery and Dougherty, *J. Org. Chem.*, 1952, **17**, 823.
[8] Mazur, personal communication.
[9] Mazur, *J. Amer. Chem. Soc.*, 1959, **81**, 1454.
[10] Shoppee and Sly, *J.*, 1958, 3458.

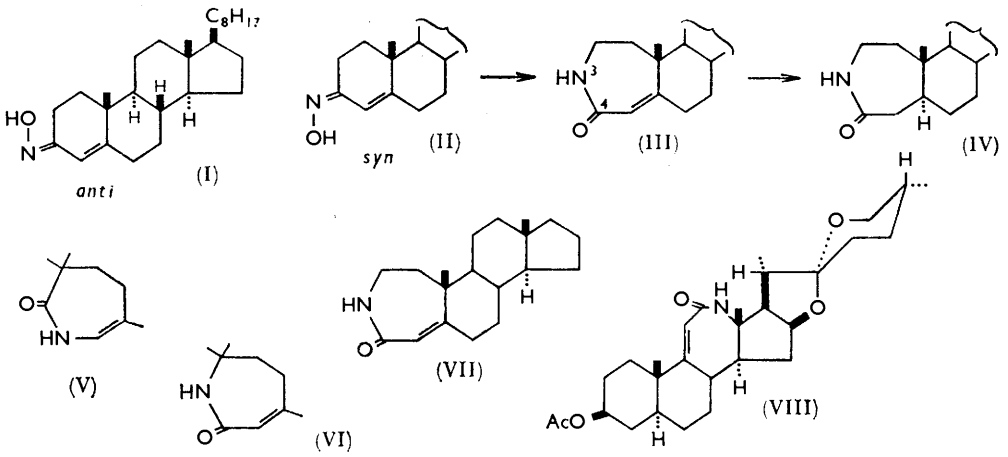


TABLE 1.

Lactam	$\lambda_{max.}$ (mμ)	log ε	$\nu_{max.}$ (cm.$^{-1}$) (in Nujol)
(III)	222	4·1	3250, 3140, 3040 (NH); 1665, 1635, 1615 (O:C·C:C)
(V)	237	3·86	
(VI)	218	4·07	
(VII)	222	4·15	3290, 3178, 3050 (NH); 1668, 1636, 1602 (O:C·C:C)
(VIII)	220	4·2	1658 (in KBr)

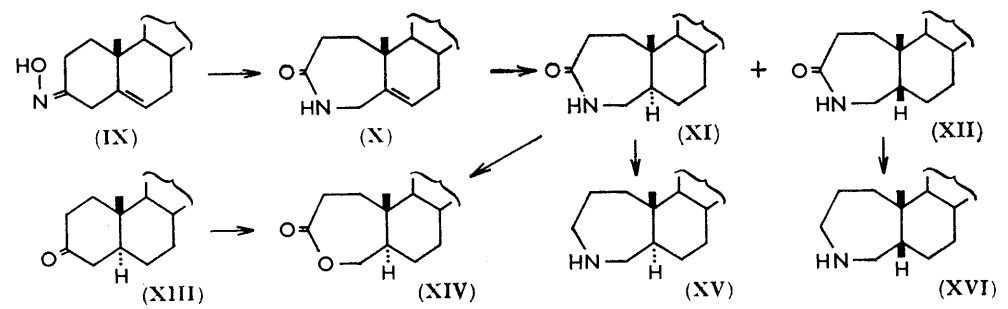
the 4-carbonyl group and gave 3-aza-A-homocholest-4a-ene, characterised as the *N*-acetyl derivative.

When the oxime (IX) of cholest-5-en-3-one [11] was treated with thionyl chloride at

TABLE 2.

	M. p.	$[\alpha]_D$	$\nu_{max.}$ (cm.$^{-1}$) (in Nujol) NH	CO·NH
3-Aza-4-ketone (IV)	295°	+41°	3310s, 3195s, 3075m	1680s, 1625s
4-Aza-3-ketone (XI)	295	−8	3280sh, 3175s, 3060s	1680s, 1625m
1 : 1 Mixture of (IV) and (XI)...	265—270	+20	— 3175s, 3050m	1660s, 1625s
Shoppee & Sly's " compound "	268—271	+16	— 3180s, 3055s	1665s, 1630s

−10° and the resulting pale yellow solution treated at once with 4N-potassium hydroxide at 90°, a 20% yield of a single Δ^5-ε-lactam (X) was obtained. This oxime (IX), unlike (II), thus appears to have the hydroxyl group *anti* to the 5,6-double bond. Hydrogenation



of 4-aza-A-homocholest-5-en-3-one (X) with platinum oxide–acetic acid containing a trace of perchloric acid gave the epimeric saturated lactams (XI) (65%) and (XII) (30%),

[11] Butenandt and Schmidt-Thomé, *Ber.*, 1936, **69**, 882.

which were readily separated by fractional crystallisation. The structure of the 5α-lactam (XI) was proved by deamination of the derived amino-acid with dinitrogen trioxide; the resulting hydroxy-acid lactonised immediately to furnish the known ε-lactone,[10,12] (XIV), the infrared absorption spectrum of which was identical with that of an authentic specimen prepared from 5α-cholestan-3-one (XIII) by oxidation with perbenzoic acid. The structure of the 5β-lactam (XII) follows by exclusion.

Reduction with lithium aluminium hydride of the epimeric lactams (XI, XII) gave, respectively, 4-aza-A-homo-5α- (XV) and -5β-cholestane (XVI).

Experimental

For general experimental directions see *J.*, 1958, 3458. $[\alpha]_D$ refer to $CHCl_3$ solutions; ultraviolet absorption spectra were measured on a Hilger Uvispek spectrophotometer for EtOH solutions, and infrared absorption spectra on a Perkin-Elmer model 21 double-beam spectrometer for CCl_4 solutions, or on an Infracord instrument in Nujol.

Cholest-4-en-3-one Oximes (I *and* II).—Cholest-4-en-3-one (m. p. 81—82°; 1·66 g.) was refluxed with hydroxylamine hydrochloride (4·4 g.) and sodium acetate trihydrate (6·6 g.) in methanol (90 c.c.) for 0·5 hr. and left to cool. The oxime (1·3 g.) had m. p. 152—153° (lit.,[3-6] 152—153°) after crystallisation from pentane. It (1 g.) was dissolved in warm propionic acid (<3 c.c.) and left to cool; within 5 min. crystals had separated, which were filtered off, washed with cold alcohol, and dried (850 mg.); these had double m. p. 65°/150—152° (lit.,[2] 65°/152°).

3-*Aza*-A-*homo-cholest*-4a-*en*-4-*one* (III).—(*A*) (*a*) The *syn*-oxime (m. p. 152—153°; 3·61 g.) was added as quickly as possible with stirring to purified thionyl chloride (32 c.c.) at −10°, and the solution immediately poured into 4N-potassium hydroxide at ~80°. The yellowish product was filtered off, washed with water, dried, and crystallised from chloroform–ether, to give 3-*aza*-A-*homocholest*-4a-*en*-4-*one* (532 mg.), m. p. 252—256°, $\nu_{max.}$ 3250, 3140, 3040 (NH), 1665, 1635, 1615 (CO·NH), 995 cm.$^{-1}$ (in Nujol) [Found (after sublimation at 210—220°/10^{-4} mm.): C, 81·15; H, 11·2; N, 3·5. $C_{27}H_{45}NO$ requires C, 81·15; H, 11·35; N, 3·5%]. The mother-liquor yielded some unchanged oxime, m. p. 148—152°.

(*b*) The *syn*-oxime (100 mg.), in pentane (8 c.c.), was treated with thionyl chloride (0·1 c.c.) in pentane (2 c.c.) at 20° for 5 hr. The brown precipitate (63 mg.) was separated on a centrifuge, and extracted briefly with ether at 36°, and with ether–pentane (1 : 1); the product (40 mg.), m. p. 245—254°, was sublimed at 200—205°/10^{-4} mm., to give 3-aza-A-homocholest-4a-en-4-one (22 mg.), m. p. 250—254° (Found: C, 81·4; H, 11·5; N, 3·6%).

(*B*) (*a*) The *anti*-oxime (double m. p. 65°/152°; 515 mg.) was added with swirling to purified thionyl chloride (5·2 c.c.) at −10°, and the colourless solution at once, or after 10 min. at 20° (100 mg. experiment), poured into 4N-potassium hydroxide (20 c.c.) at ~80°. Extraction with chloroform and the usual working up gave only unchanged oxime, double m. p. 65°/152°. When this oxime (100 mg.) was added to thionyl chloride (2 c.c.) at −10° similarly worked-up also gave unchanged oxime (95 mg.).

(*b*) The *anti*-oxime (260 mg.), dissolved in pyridine (3 c.c.), was treated with freshly prepared *p*-acetamidobenzenesulphonyl chloride [13] (300 mg.; recrystallised from benzene) and stirred for 0·5 hr. at 10°. After 1 hr. at 20°, the mixture was poured into ice-water, extracted with chloroform, and after the usual working up the extract was concentrated to ~1 c.c. Methanol (1·5 c.c.) was added, and the precipitate filtered off, and crystallised from methanol to give material, m. p. 130—145°. This by chromatography on aluminium oxide (10 g.; prepared in hexane) and elution with ether gave the p-*acetamidobenzenesulphonate*, m. p. 141—145°, of cholest-4-en-3-one *anti*-oxime (Found: C, 69·5; H, 8·6. $C_{35}H_{52}N_2O_4S$ requires C, 70·4; H, 8·8%), hydrolysed by hot 80% sulphuric acid to cholest-4-en-3-one *anti*-oxime (I), $\nu_{max.}$ (in Nujol) 3220 (OH), 1650 cm.$^{-1}$ (C=N).

(*c*) The *anti*-oxime (190 mg.) was dissolved in warm benzene (10 c.c.) and shaken overnight with *p*-acetamidobenzenesulphonyl chloride (220 mg.) at 20°. Powdered potassium hydroxide (500 mg.) and ethanol (10 c.c.) were added and the mixture refluxed for 1 hr. Extraction with ether (3 × 100 c.c.) furnished, after the usual working up, impure 3-aza-A-homocholest-4a-en-4-one (III) (25 mg.), m. p. ~250°, identified by hydrogenation with palladium–charcoal

[12] Reichstein and Burckhardt, *Helv. Chim. Acta*, 1942, **25**, 1434.
[13] Rosenkranz, Mancera, Sondheimer, and Djerassi, *J. Org. Chem.*, 1956, **21**, 520; cf. U.S.P. 2,335,616.

(105 mg.) in ethanol (25 c.c.) overnight to 3-aza-A-homo-5α-cholestan-4-one (IV), m. p. and mixed m. p. 295° after softening from 285°, $[\alpha]_D$ +45° (*c* 0·4), $\nu_{max.}$ (in Nujol) 3310, 3195 (NH), 1680, 1625 cm.$^{-1}$ (CO·NH), the infrared trace being almost identical with that of a genuine specimen of the lactam (IV).

3-*Aza*-A-*homo*-5α-*cholestan*-4-*one* (IV).—(*a*) The Δ^{4a}-ε-lactam (III) (500 mg.) was shaken in hydrogen with palladium–charcoal (500 mg.) in ethanol (115 c.c.) overnight. The catalyst was removed by filtration through Celite, and the filtrate worked up in the usual way to yield, after recrystallisation from chloroform–ether, 3-aza-A-homo-5α-cholestan-4-one [10] (450 mg.), m. p. 294—296°, $[\alpha]_D$ +41° (*c* 1·0), $\nu_{max.}$ (in CCl_4) 3400, 3200 (NH), 1660 (CO·NH), and (in Nujol) 3310, 3195, 3075, 1680, 1625 cm.$^{-1}$ [Found (after drying at 120°/0·1 mm. for 3 hr.): C, 80·65; H, 11·9. Calc. for $C_{27}H_{47}NO$: C, 80·7; H, 11·8%].

(*b*) A similar hydrogenation with 10% palladised calcium carbonate gave material of m. p. 294—297°.

Sublimation of a 1 : 1 mixture of 3-aza-A-homo-5α-cholestan-4-one (IV) and 4-aza-A-homo-5α-cholestan-3-one (XI) at 190—210°/0·15 mm. for 2 hr. gave a product, m. p. 265—270°, $[\alpha]_D$ +20° (*c* 0·7), $\nu_{max.}$ (in Nujol) 3175s, 3050m (NH), 1660s, 1625m (CO·NH).

3-*Aza*-A-*homocholest*-4a-*ene*.—3-Aza-A-homocholest-4a-en-4-one (200 mg.) was treated with lithium aluminium hydride (500 mg.) in ether (200 c.c.) at 36° for 24 hr. The excess of the reagent was decomposed with ice-water; the ethereal solution was decanted, the residual inorganic material was extracted thrice with ether, and the combined ethereal solutions were washed with sodium hydrogen carbonate solution, dried briefly, and evaporated rapidly. The resultant oil (162 mg.) was distilled at 190°/0·05 mm. The distillate crystallised immediately when moistened with pentane, furnishing 3-*aza*-A-*homocholest*-4a-*ene*, m. p. 55—60°, $\nu_{max.}$ (in Nujol) 3300 (NH), 1640 (C=C) cm.$^{-1}$ (Found: C, 83·8; H, 12·6. $C_{27}H_{47}N$ requires C, 84·1; H, 12·3%). The *N*-acetyl derivative failed to crystallise.

Cholest-5-*en*-3-*one Oxime*.—Cholest-5-en-3-one [11] was prepared in 60% yield by oxidation of cholesterol with chromium trioxide–acetone [14] in nitrogen [15] or in 65% yield from 5α,6β-dibromocholesterol and sodium dichromate in acetic acid at 90° with subsequent debromination; [16] after chromatography on silica gel (B.D.H) with elution by ether–pentane (1 : 4) and recrystallisation from methanol the ketone had m. p. 128° and showed no absorption at 240 mμ characteristic of the isomeric cholest-4-en-3-one.

The ketone (25 g.), in warm hexane (500 c.c.), was shaken with a 20% methanolic solution (100 c.c.) of hydroxylamine acetate (prepared by grinding hydroxylamine hydrochloride with sodium acetate trihydrate, addition of methanol, and filtration) at 20° for 3 hr. Evaporation of the hexane phase gave material, m. p. 170—173°, which by a single recrystallisation from methanol gave the oxime (17·7 g.), m. p. 178—181° (lit.,[11] 188°), no absorption at 200—400 mμ.

4-*Aza*-A-*homocholest*-5-*en*-3-*one* (X).—Cholest-5-en-3-one oxime (1·6 g.) was added gradually during 20 min. with stirring to purified thionyl chloride (16 c.c.) at −10°; the mixture was at once poured very slowly into 4N-potassium hydroxide at 90° with stirring. The cooled suspension was extracted with chloroform–ether (1 : 1), and the extract worked up in the usual way to give a cream-coloured solid (1·6 g.), which was chromatographed on aluminium oxide (60 g.) prepared in hexane. Elution with chloroform–ether (1 : 1) gave 4-*aza*-A-*homocholest*-5-*en*-3-*one* (770 mg.), m. p. 264—265°, $[\alpha]_D$ −37° (*c* 1·0), $\lambda_{max.} < 205$ mμ [Found (after drying at 100°/0·1 mm. for 12 hr.): C, 81·3, 80·95; H, 11·5, 11·2; N, 4·0, 3·8. $C_{27}H_{45}NO$ requires C, 81·15; H, 11·35; N, 3·5%]. The N-*acetyl derivative*, prepared by use of acetic anhydride–pyridine at 80° for 2 hr., had m. p. 177—178° (from methanol) [Found (after drying at 60°/0·1 mm. for 12 hr.): C, 79·0; H, 10·8. $C_{29}H_{47}NO_2$ requires C, 78·85; H, 10·7%].

4-*Aza*-A-*homo*-5α- *and* -5β-*cholestan*-3-*one* (XI, XII).—4-Aza-A-homocholest-5-en-3-one (900 mg.) was shaken in hydrogen with platinum oxide (500 mg.) in acetic acid (160 c.c.) containing 60% perchloric acid (2 drops) overnight. After filtration, threefold dilution of the filtrate with water gave a granular precipitate, which was separated, washed with water, and dried at 20°/0·3 mm. for 0·5 hr. Dissolution in the minimum amount of chloroform and addition of ether afforded 4-*aza*-A-*homo*-5α-*cholestan*-3-*one* (250 mg.), m. p. 295°, $[\alpha]_D$ −8°

[14] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, **39**; Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402; Bowers, Halsall, Jones, and Lemin, *ibid.*, p. 2548.

[15] Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547; cf. Fieser, Greene, Bischoff, Lopez, and Rupp, *J. Amer. Chem. Soc.*, 1955, **77**, 3928.

[16] Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4377, 5421; cf. *Org. Synth.*, 1955, **35**, 43.

(*c* 0·75), $\nu_{max.}$ (in Nujol) 3180 (NH), 1680, 1639 cm.$^{-1}$ (CO·NH) [Found (after drying at 100°/0·1 mm. for 12 hr.): C, 80·6; H, 11·7; N, 3·4. $C_{27}H_{47}NO$ requires C, 80·7; H, 11·8; N, 3·5%]; repeated fractional crystallisation gave a total yield of 430 mg.

The mother-liquors afforded the more soluble 4-*aza*-A-*homo*-5β-*cholestan*-3-*one* (170 mg.), m. p. 194—195°, $[\alpha]_D$ +21° (*c* 0·75), $\nu_{max.}$ (in Nujol) 3210 (NH), 1695, 1645 cm.$^{-1}$ (CO·NH) [Found (after drying at 100°/0·1 mm. for 12 hr.): C, 80·5; H, 11·75%].

Hydrolysis and Deamination of 4-*Aza*-A-*homo*-5α-*cholestan*-3-*one* (XI).—The lactam (160 mg.) was introduced into a small Carius tube, and concentrated hydrochloric acid (1·6 c.c.; boiled to remove oxygen) was added; the mixture was frozen in liquid air, and the tube evacuated to 0·4 mm., sealed, and heated at 130° for 16 hr. The product was transferred to a mixture of ether (200 c.c.; saturated with dinitrogen trioxide) with water (50 c.c.), and the whole shaken at 20° for 20 hr. The ethereal phase was separated, washed with sodium hydrogen carbonate solution (6 × 40 c.c.), then with water, dried, and evaporated, to afford a colourless solid, m. p. 175—180°, which was chromatographed on silica gel (10 g.; B.D.H.) prepared in hexane. Elution with ether–hexane (1 : 9) gave 4-hydroxy-3,4-*seco*-5α-cholestan-3-oic acid lactone (XIV), m. p. 187—188°, mixed m. p. 187°, $\nu_{max.}$ (in Nujol) 1740 cm.$^{-1}$ (CO·O).

4-*Aza*-A-*homo*-5α-*cholestane* (XV).—4-Aza-A-homo-5α-cholestan-3-one (200 mg.) was refluxed with lithium aluminium hydride (500 mg.) in ether (200 c.c.) for 20 hr. The excess of reagent was decomposed with moist ether and ice; the inorganic hydroxides were filtered off and washed several times with ether. The combined ethereal solutions were dried and evaporated, to yield 4-*aza*-A-*homo*-5α-*cholestane* (110 mg.), m. p. 95—100°, $\nu_{max.}$ (in Nujol) 3450 cm.$^{-1}$ (NH) [Found (after distillation at 180°/0·1 mm.): C, 83·75; H, 13·0. $C_{27}H_{49}N$ requires C, 83·65; H, 12·75%]. The N-*acetyl derivative*, prepared from the aza-steroid (50 mg.), acetic anhydride, and pyridine at 20° for 16 hr. and crystallised from methanol (40 mg.), had m. p. 150—151°, $\nu_{max.}$ (in Nujol) 1625 cm.$^{-1}$ (no peak at 3450 cm.$^{-1}$) [Found, after drying at 60°/0·1 mm. for 12 hr.): C, 80·65; H, 11·9. $C_{29}H_{51}NO$ requires C, 81·0; H, 12·0%].

4-*Aza*-A-*homo*-5β-*cholestane* (XVI).—4-Aza-A-homo-5β-cholestan-3-one (100 mg.) was similarly reduced with lithium aluminium hydride (250 mg.) in ether (100 c.c.) at 36° for 20 hr., to yield a glass, which slowly crystallised. Distillation at 200°/0·3 mm. and moistening of the distillate with pentane caused crystallisation of 4-*aza*-A-*homo*-5β-*cholestane*, m. p. 72—75°, $\nu_{max.}$ (in Nujol) 3278 cm.$^{-1}$ (NH) [Found (after distillation as above): C, 83·6; H, 12·6. $C_{27}H_{49}N$ requires C, 83·6; H, 12·7%].

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Department of Organic Chemistry, The University of Sydney, N.S.W., Australia. [*Received, July 24th,* 1961.]