62. *Steroids and Walden Inversion. Part XLI.* The Deamination of Some* A-*Nor-*, B-*Nor-, and* 17-*Amino-steroids.*

By C. W. Shoppee and J. C. P. Sly.

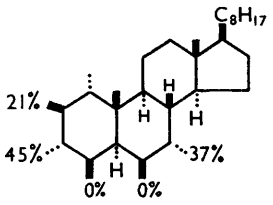
Amino-groups attached to flexible five-membered carbocyclic systems, *e.g.*, *cyclo*pentane, *cis*-perhydroindane, appear to possess mixed equatorial-axial character. Amino-groups attached to rigid five-membered carbocyclic systems, *e.g.*, *trans*-perhydroindane, or to such systems forming part of the nuclei of A-nor-5α-, A-nor-5β-, and 14α-steroids, at positions adjacent to a bridgehead, appear to possess either equatorial character disclosed by deamination with retention of configuration, or axial character disclosed by deamination with ready and exclusive elimination (Saytzew orientation); nor-steroids with amino-groups not adjacent to a bridgehead, like aliphatic amino-groups, undergo deamination with predominant inversion of configuration accompanied by some elimination.

Previous studies [1,2] of the stereochemical course of deamination of amino-steroids in aqueous acetic acid disclosed an unexpected divergence from the steric behaviour of amino-*cyclo*hexanes and aminodecalins. For all three groups of compounds the reaction is conformationally specific: equatorial amines undergo deamination with retention of

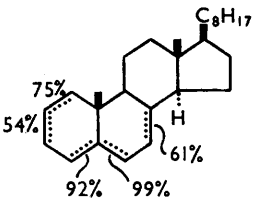
* Part XL, *J.*, 1958, 3048.

[1] Shoppee, Evans, and Summers, *J.*, 1957, 97.
[2] Shoppee, Cremlyn, Evans, and Summers, *J.*, 1957, 4364.

configuration but, whereas axial steroid amines display complete retention accompanied by elimination, axial amino*cyclo*hexanes and axial aminodecalins exhibit nearly complete inversion with concomitant elimination.[3,4]



(I)



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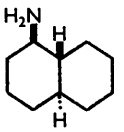
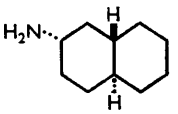
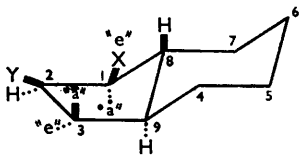


(III)

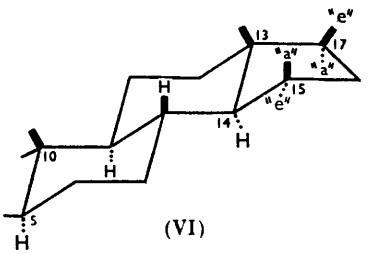


(IV)

Thus the axial 2β-, 3α-, 4β-, 6β-, and 7α-amino-5α-cholestanes * (I; substituent = NH_2) furnish with preservation of configuration the corresponding axial alcohols (I; substituent = OH) in the yields shown in (I), accompanied by the appropriate olefins, formed in accordance with the Saytzew orientation, in the yields indicated in (II).[1,2] By contrast, *cis*-1-amino-*trans*-decalin (III; NH_2, axial) and *trans*-2-amino-*trans*-decalin (IV; NH_2, axial) both yield 27% of the appropriate alcohol with the inverted configuration, and only 3% of that with the retained configuration, accompanied by 70% of olefins.[4]



(V) ‡§



(VI)

The principal mechanical difference between the polycyclic steroid nucleus (I) and the *bicyclo*[4 : 4 : 0]decane structures (III, IV) is the greater conformational stiffness of the former, not only in regard to bond-rotation, but also in respect of bond-angle deformation. *cyclo*Pentane is non-planar,[5] and therefore must possess some small degree of conformational flexibility; this is, however, so limited that *trans*-fusion to a single *cyclo*hexane ring ‡ (V), or to a multi*cyclo*hexane ring system (VI), produces an inflexible system. It was therefore of interest to prepare some A-nor-, B-nor-, and 17-amino-steroids and to examine the stereochemistry of their deamination.

Unlike the *trans*-perhydroindane system (V), the *cis*-perhydroindane system (VII, VIII) possesses flexibility which permits a 1-substituent (and in the case of an 8-methyl-*cis*-perhydroindane, a 3-substituent) to acquire either equatorial or axial character. Transformation occurs through systems in which the six-membered ring assumes the boat conformation: (i) a boat form with ends at $C_{(4)}$ and $C_{(7)}$ furnishing a structure with a plane of symmetry, or (ii) equivalent boat forms with ends at $C_{(5)}$ and $C_{(8)}$, or at $C_{(6)}$ and $C_{(9)}$.

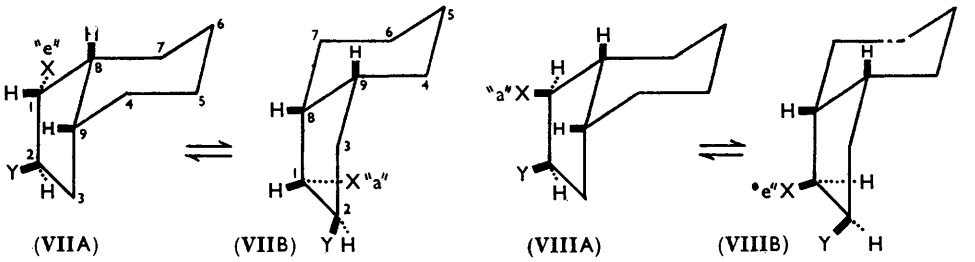
* Use of 5α- and 5β-cholestane in place of cholestane and coprostane, respectively, follows the I.U.P.A.C. 1957 Nomenclature Rules for Steroids (I.U.P.A.C. 1957 Rules for Organic Nomenclature, Butterworths, London, 1958) (cf. *J.*, 1958, 3458).

‡ This system is inflexible apart from transformation of the six-membered ring into boat conformations with ends (i) at $C_{(5)}$ and $C_{(8)}$, or (ii) at $C_{(6)}$ and $C_{(9)}$, neither of which affects the geometry at the bridgehead positions.

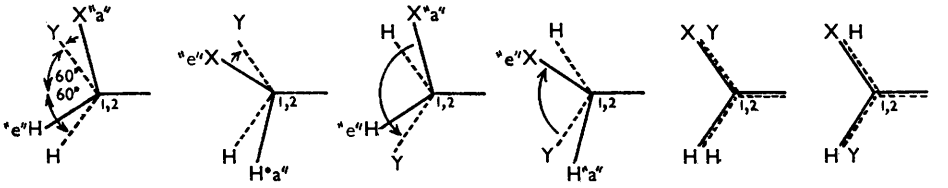
§ This structure represents one of a pair of stereoisomers.

[3] Mills, *J.*, 1953, 260; Bose, *Experientia*, 1953, **9**, 256.
[4] Dauben, Tweit, and Mannerskantz, *J. Amer. Chem. Soc.*, 1954, **76**, 4420.
[5] Kilpatrick, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2483.

The preferred conformation of *cyclo*pentane [6] possesses C_2 symmetry, and has $C_{(2)}$, $C_{(4)}$, and $C_{(5)}$ coplanar, with $C_{(1)}$ lying above that plane and $C_{(3)}$ lying an equal distance below that plane. This arrangement requires rotation of $C_{(1)}$ and $C_{(3)}$ in (V, VII, and



VIII) [and of $C_{(15)}$ and $C_{(17)}$ in (VI)] through equal and opposite angles, and permits staggering of bonds attached to the adjacent atoms $C_{(1)}$ and $C_{(2)}$ [and $C_{(3)}$](A, B, C, D), as compared with the eclipsed disposition of the bonds in a planar *cyclo*pentane system (E, F).



θ is the angle (=78°) between the two substituent bonds [$C_{(1)}$–X, $C_{(2)}$–Y] when projected on to a plane perpendicular to the $C_{(1)}$–$C_{(2)}$ bond-axis.

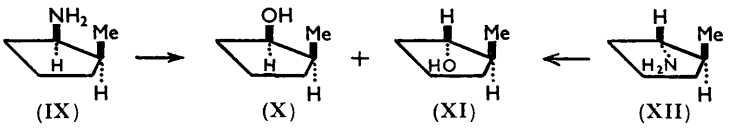
Substituents at $C_{(1)}$ [and, when appropriate, at $C_{(3)}$] in *trans*-perhydroindanes (V), *cis*-perhydroindanes (VII, VIII), and A-norsteroids should accordingly possess equatorial or axial character in the same way as 17-substituted steroids.[7]

Deamination in a simple *cyclo*pentane system can be exemplified by the work of Hückel and Kupka.[8] *cis*-1-Amino-2-methyl*cyclo*pentane (IX) yields 54% of the *cis*-alcohol (X), 23% of the *trans*-alcohol (XI), and 23% of olefins, whilst *trans*-1-amino-2-methyl*cyclo*pentane (XII) affords 32% of each of the epimeric alcohols (X, XI) and 35% of olefins. This reaction pattern recalls that of the epimeric amino*cyclo*hexanes and aminodecalins (see p. 345) and suggests the operation of conformational influences. It may be significant that, whereas in the *cis*-epimer (IX) steric compressions are equal in conformations (A) and (B) [X = NH_2, Y = Me], in the *trans*-epimer (XII) such compressions are less in conformation (C) [X = NH_2, " axial "] than in conformation (D) [X = NH_2, " equatorial "], leading to the development of more axial character in (XII) and resulting in less retention, more inversion, and more elimination.

The deamination of aminoperhydroindanes has been investigated by Hückel *et al.*[9] The symmetry of the *trans*-perhydroindane system (V) permits the existence of only a single racemic 2-substituted derivative. *trans*-Perhydroindan-2-one and its oxime by reduction, with sodium–ethanol or catalytically, give 2-hydroxy-*trans*-perhydroindane

[6] Le Fèvre and Le Fèvre, *J.*, 1956, 3549; Brutcher, Roberts, Barr, and Pearson, *J. Amer. Chem. Soc.*, 1956, **78**, 1507.
[7] Barton, *Experientia*, 1950, **6**, 316.
[8] Hückel and Kupka, *Chem. Ber.*, 1956, **89**, 1694.
[9] Hückel, Sachs, Yantschulewitsch, and Nerdel, *Annalen*, 1935, **518**, 155; Hückel, *ibid.*, 1937, **33**, 1.

(V; X = H, Y = OH) and 2-amino-*trans*-perhydroindane (V; X = H, Y = NH_2) respectively. Deamination of the latter gives the former together with a little unsaturated hydrocarbon,[9] so that here a mechanistically complete inversion would be observed as



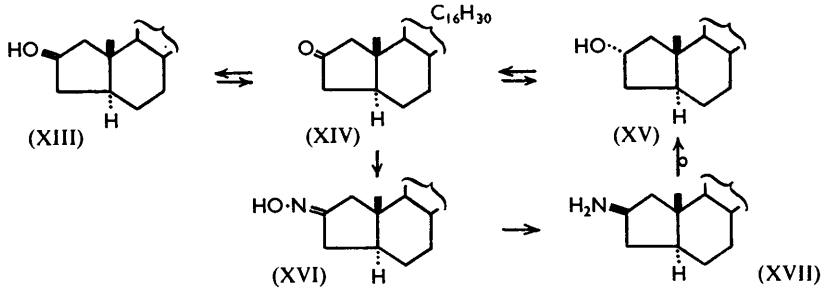
complete retention. *cis*-1-Amino-*cis*-perhydroindane (VII; X = NH_2, Y = H) by deamination gives ~52% of *cis*- (VII; X = OH, Y = H), ~13% of *trans*-1-hydroxy-*cis*-perhydroindane (VIII; X = OH, Y = H), and ~35% of olefins. The epimeric *trans*-1-amino-*cis*-perhydroindane (VIII; X = NH_2, Y = H) by deamination gives, however, only ~7% of the alcohol (VIII; X = OH, Y = H) with retained configuration, but yields ~63% of the alcohol (VII; X = OH, Y = H) with inverted configuration, and ~30% of olefins.[9] These results resemble those given by the 1-amino-2-methyl*cyclo*pentanes (IX, XII) and again suggest that conformational influences are operative. Conformational analysis shows that the number of molecules of *trans*-1-amino-*cis*-perhydroindane in conformation (VIIIA; NH_2, " axial ") as compared with conformation (VIIIB; NH_2, " equatorial ") depends only on the relative energy difference associated with an " axial " and an " equatorial " bond, but that stereoelectronic interactions compel the number of molecules of *cis*-1-amino-*cis*-perhydroindane in conformation (VIIA; NH_2, " equatorial ") greatly to exceed the number of molecules in conformation (VIIB; NH_2, " axial "). The amino-group in (VII) should therefore possess less axial character than that in (VIII), so that, by analogy with the reaction pattern characteristic of amino*cyclo*hexanes and aminodecalins, deamination of form (VII) should lead to more retention and less inversion (Found: ~52%, ~13%) than in the case of form (VIII) (Found: ~7%, ~63%). The epimeric 2-amino-*cis*-perhydroindanes should possess neither equatorial nor axial character and on deamination might be expected to exhibit the reaction pattern of aliphatic amines—predominant inversion with some elimination;[10] the single known 2-amino-*cis*-perhydroindane, which may be either *trans*- (VII ≡ VIII; X = H, Y = NH_2) or *cis*-2-amino-*cis*-perhydroindane (VII ≡ VIII; X = H, Y = NH_2 but with configuration at $C_{(2)}$ reversed), by deamination gives 80% of the alcohol with inverted configuration, 20% of the alcohol with retained configuration, and unsaturated hydrocarbon in undetermined amount.[9]

The present study involves the preparation of A-nor-5α-cholestan-1- and -2-one, and A-nor-5β-cholestan-1-, -2-, and -3-one, and, by way of their oximes, the five derived pairs of epimeric primary amines; we now report that part of this programme which has been realised.

A-Nor-5α-cholestan-2-one[11] (XIV) by reduction with sodium–ethanol or aluminium *iso*propoxide–propan-2-ol, or by hydrogenation in presence of platinum in acetic acid, gives a mixture of epimeric alcohols. One epimer,[12] m. p. 130°, $[\alpha]_D$ +38°, giving an insoluble digitonide and forming the major product of sodium–ethanol reduction, has been regarded as A-nor-5α-cholestan-2β-ol by analogy with 5α-cholestan-2β-ol,[13] and with the compound, m. p. 148°, $[\alpha]_D$ +2°, provisionally considered to be A-nor-5α-androstan-2β-ol,[14] which also afford insoluble digitonides. The other epimer, m. p. 155°, $[\alpha]_D$ + 28°, giving no insoluble digitonide and forming the major product of Meerwein–Ponndorf reduction,

[10] Brewster, Hiron, Hughes, Ingold, and Rao, *Nature*, 1950, **166**, 178.
[11] (*a*) Windaus and Dalmer, *Ber.*, 1919, **52**, 162, 170; Langer, *Z. physiol. Chem.*, 1933, **216**, 189; (*b*) Lettré, *ibid.*, 1933, **221**, 73.
[12] Kawasaki, *J. Pharm. Soc. Japan.*, 1936, **56**, 896; Marker, Kamm, Jones, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1363.
[13] Ruzicka, Plattner, and Furrer, *Helv. Chim. Acta*, 1944, **27**, 727; Fürst and Plattner, *ibid.*, 1949, **32**, 275.
[14] Ruzicka, Prelog, and Meister, *ibid.*, 1945, **28**, 1651.

has been regarded as A-nor-5α-cholestan-2α-ol by analogy with 5α-cholestan-2α-ol,[13] and the substance, m. p. 121°, $[\alpha]_D$ +3°, provisionally considered to be A-nor-5α-androstan-2α-ol.[14] The ketoxime (XVI) by reduction with sodium and pentyl alcohol, or by hydrogenation (platinum–acetic acid), gave a single 2-amino-A-nor-5α-cholestane, characterised as the crystalline acetyl derivative.



Digitonide formation is a function of the crystal lattice, and an unreliable guide to molecular configuration; [15] it is, however, generally agreed that molecular rotatory power can give reliable indications of configuration.[16] Klyne's principle of enantiomeric types [16] cannot be used to indicate the configurations of the epimeric A-nor-5α-cholestan-2-ols because both ΔOH(16α) and ΔOH(16β) are negative and similar in magnitude (−33°, −20°), so that both ΔOH(2α : A-nor-5α) and ΔOH(2β : A-nor-5α) are expected to be positive and similar in size. The optical rotatory properties of the A-nor-5α-cholestane ($[M]_D$ +90°) and 5α-cholestane ($[M]_D$ +91°) systems are however closely similar, and the molecular rotations and molecular-rotation differences for (*a*) the epimeric A-nor-5α-cholestan-2-ols and 5α-cholestan-2-ols and their acetates,[13] and (*b*) the single 2-amino-A-

Compound	$[M]_D$ ROH	$[M]_D$ RH	ΔM_D OH	$[M]_D$ ROAc	$[M]_D$ RH	ΔM_D (OAc)
A-Nor-5α-cholestan-2α-ol, m. p. 130°	+142°	+90°	+52°	+4°	+90°	−86°
A-Nor-5α-cholestan-2β-ol, m. p. 155°	+105	+90	+15	+104	+90	+14
5α-Cholestan-2α-ol	+101	+91	+10	+61	+91	−30
5α-Cholestan-2β-ol	+132	+91	+41	+114	+91	+23
	R·NH_2	RH	NH_2	R·NHAc	RH	NHAc
2β-Amino-A-nor-5α-cholestane	+93	+90	+3	+162	+90	+72
2α-Amino-5α-cholestane	+77	+91	−14	−61	+91	+152
2β-Amino-5α-cholestane	+110	+91	+19	+118	+91	+27

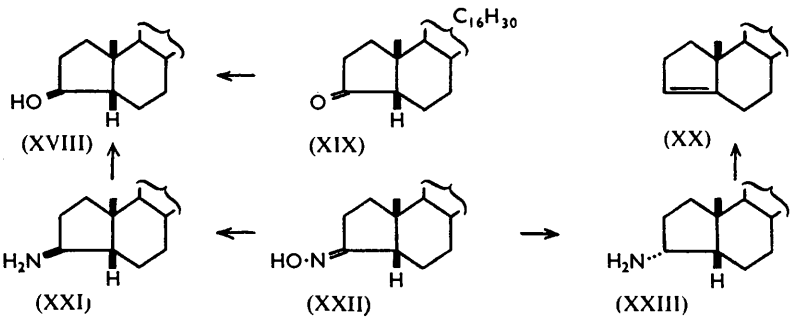
nor-5α-cholestane, the epimeric 2-amino-5α-cholestanes,[2] and their acetyl derivatives [2] are given in the Table. The sign of the increments ΔM_D(OAc) appear especially significant. The ΔOAc values strongly suggest that the accepted configurations of the A-nor-5α-cholestan-2-ols should be reversed; the epimer, m. p. 130°, is A-nor-5α-cholestan-2α-ol (XV), whilst the epimer, m. p. 155°, is A-nor-5α-cholestan-2β-ol (XIII). These new assignments are consistent with the reduction of the ketone (XIV) by sodium–ethanol to afford 75% of the 2α- (XV) and 25% of the 2β-alcohol (XIII); provided that equilibration occurs, these figures give a measure of the relative thermodynamic stabilities of the epimers, which must reflect the 1 : 3-interactions [(XV; 2α-OH/5α-H), (XIII; 2β-OH/10β-Me)] since these constitute their sole conformational difference. It seems probable that the configurations provisionally assigned [14] to the epimeric 5α-androstan-2-ols may have likewise to be reversed.

The Δ values also suggest that the base obtained by reduction of the ketoxime (XVI) is 2β-amino-A-nor-5α-cholestane (XVII). This by deamination furnishes 93% of A-nor-5α-cholestan-2α-ol (XV) with 3% of unsaturated hydrocarbon (probably a mixture of

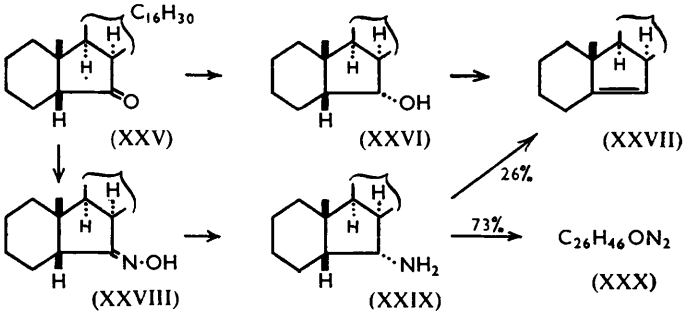
[15] Shoppee, in Robinson and Rodd's "Chemistry of Carbon Compounds," Elsevier Publ. Co., 1953, Vol. II*B*, p. 804.
[16] Klyne, *J.*, 1952, 2916.

A-nor-5α-cholest-1- and -2-ene); thus deamination here appears to proceed with substantially complete inversion of configuration.

A-Nor-5β-cholestan-3-one [11] (XIX) resisted hydrogenation in presence of platinum in



acetic acid–perchloric acid, but was reduced by sodium and pentyl alcohol or by lithium aluminium hydride in ether at 36° to 3β-hydroxy-A-nor-5β-cholestane (XVIII; OH, " equatorial "). The ketoxime (XXII) was reduced by sodium and pentyl alcohol to give 3β-amino-A-nor-5β-cholestane (XXI; NH_2, " equatorial "), and smoothly hydrogenated (platinum–acetic acid) to 3α-amino-A-nor-5β-cholestane (XXIII; NH_2, " axial "). Deamination of the 3β-amine gave, with retention of configuration, 40% of the 3β-alcohol (XVIII) accompanied by 59% of A-norcholest-3(5)-ene [11b] (XX); deamination of the 3α-amine (XXIII) furnished ~100% of the hydrocarbon (XX), unaccompanied by alcohol.

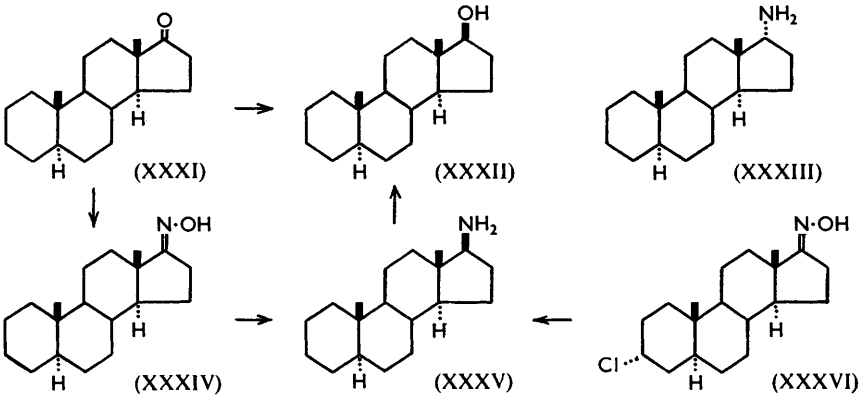


Barium 6 : 7-*seco*-5α-cholestane-6 : 7-dioate on pyrolysis at 400°/1 mm. yields a ketone,[17] which we formulate as B-nor-5β : 8α-cholestan-6-one (XXV) on the grounds that *cis*-perhydroindan-1-one [9] and *cis*-perhydroindan-4-one [18] are more stable than their *trans*-isomerides. Ring B then conforms to the Le Fèvre model for *cyclo*pentanone [6] with $C_{(6)}$, $C_{(9)}$, and $C_{(10)}$ coplanar, and $C_{(5)}$ below and $C_{(8)}$ above that plane; the 6β-position is greatly hindered by the 10β-methyl group, the 11β-hydrogen atom, and the 13β-methyl group, whilst the 6α-position is relatively unhindered. The ketone (XXV) by reduction with sodium and pentyl alcohol or with lithium aluminium hydride gives a single alcohol, which we accordingly regard as B-nor-5β : 8α-cholestan-6α-ol (XXVI), readily dehydrated by thionyl chloride–pyridine at 20° to B-nor-8α-cholest-5-ene (XXVII). The ketoxime [17] (XXVIII) resisted catalytic hydrogenation, but was reduced by sodium and pentyl alcohol or by lithium aluminium hydride to a single amine, which we formulate by analogy with the alcohol (XXVI) as 6α-amino-B-nor-5β : 8α-cholestane (XXIX). Deamination of this base gave 26% of B-nor-8α-cholest-5-ene (XXVII) accompanied by 73% of a colourless compound, $C_{26}H_{46}ON_2$, double m. p. 121°/136° (XXX), whose infrared absorption spectrum

[17] Stange, *Z. physiol. Chem.*, 1933, **218**, 74.
[18] Dimroth and Jonsson, *Ber.*, 1941, **74**, 520.

showed no characteristic absorption bands [the nitroso-group furnishes intense bands: C–N:O, 1310—1420 or 1350—1400; N–N:O, 1400 and 1653; O–N:O, 1613—1625 and 1653—1681 cm.$^{-1}$]. One of the two nitrogen atoms of compound (XXX) appears to be the original amino-nitrogen atom, whilst the other must be derived from the nitrosonium ion NO^+; the only primary nitrosamines, Ar·NH·NO, are yellow unstable substances.[19] An addition compound of dinitrogen trioxide and the hydrocarbon (XXVII), or an isomeride arising by rearrangement, is excluded by the presence of only one oxygen atom in (XXX).

5α-Androstan-17-one [20] (XXXI) by reduction with sodium and pentyl alcohol [21] or with lithium aluminium hydride [22] affords almost exclusively 5α-androstan-17β-ol [20,23] (XXXII); similarly, the ketoxime (XXXIV) by reduction with sodium and ethanol, lithium aluminium hydride, or hydrogen–platinum–acetic acid gives exclusively the crystalline 17β-amino-5α-androstane (XXXV; NH_2, "equatorial"); this is probably identical with the base, b. p. 110°/0·01 mm., obtained from 3α-chloro-5α-androstan-17-one oxime (XXXVI) by reduction with sodium and pentyl alcohol.[21] Deamination of 17β-amino-5α-androstane (XXXV) gives with complete retention and in almost



quantitative yield 5α-androstan-17β-ol (XXXII) (cf. ref. 21). Attempts to prepare 17α-amino-5α-androstane (XXXIII) by treatment of 5α-androstan-17β-yl toluene-*p*-sulphonate at 100° with ammonia, alone or in the presence of sodamide, failed; Elkes and Shoppee [22] found similarly that acetolysis gave only about 5% of 17α-acetoxy-5α-androstane.

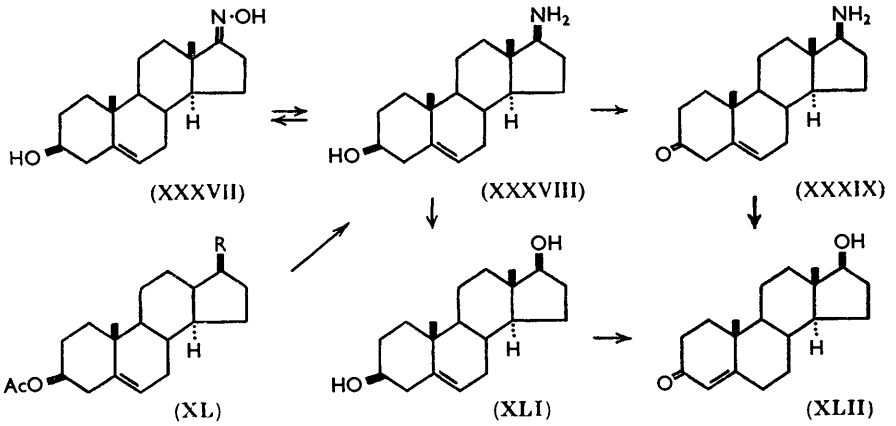
Androsterone oxime by reduction with sodium and ethanol [21,24] or catalytically [24] gives 17β-amino-5α-androstan-3α-ol, also obtained from 3α-acetoxy*allo*etianic acid as the azide by the Curtius rearrangement, in which the configuration of the migrating group is known to be preserved,[25] and hydrolysis of the resulting 17β-*iso*cyanate. Deamination of 17β-amino-5α-androstan-3α-ol proceeds with retention of configuration to yield 5α-androstane-3α : 17β-diol.[21,26] Dehydro*epi*androsterone oxime (XXXVII) by reduction with sodium and ethanol gives 17β-aminoandrost-5-en-3β-ol [27] (XXXVIII), which we have also obtained by use of lithium aluminium hydride in ether at 36°. The base (XXXVIII) can be prepared [28,29] (*a*) from 3β-acetoxyeti-5-enic acid (XL; R = CO_2H) as the azide (XL;

[19] Hantzsch, *Ber.*, 1912, **45**, 3036; 1930, **63**, 1280.
[20] Rosenkranz, Kaufmann, and Romo, *J. Amer. Chem. Soc.*, 1949, **71**, 3689.
[21] Marker, *ibid.*, 1936, **58**, 480.
[22] Elks and Shoppee, *J.*, 1953, 241.
[23] Shoppee, *Chem. and Ind.*, 1950, 454.
[24] CIBA, B.P. 451,352/1936.
[25] (*a*) Jones and Wallis, *J. Amer. Chem. Soc.*, 1926, **48**, 169; (*b*) Kenyon and Campbell, *J.*, 1946, 25.
[26] CIBA, Swiss P. 191,339/1936; I.G. Farbenind., B.P. 478,583/1936.
[27] Ruzicka and Goldberg, *Helv. Chim. Acta*, 1936, **19**, 107.
[28] Schmidt-Thomé, *Chem. Ber.*, 1955, **88**, 895.
[29] CIBA, Swiss P. 193,468/1936; I.G. Farbenind., French P. 819,975/1937; 819,975/1939; B.P. 501,421/1937; Erhardt, Rushig, and Aumuller, *Angew. Chem.*, 1939, **52**, 363.

R = CON_3) by the Curtius rearrangement, to yield the 17β-*iso*cyanate (XL; R = NCO) and acid hydrolysis thereof, and (*b*) from pregnenolone acetate oxime (XL; R = CMe:N·OH) by the Beckmann rearrangement (in which the configuration of the migrating group is also known to be retained [25b, 30]) and subsequent hydrolysis; we have repeated these preparations and characterised the base (XXXVIII) by preparation of the 3β : 17β-diacetyl derivative.

Deamination of the 17β-amine (XXXVIII; NH_2, " equatorial ") occurs with complete retention of configuration, to yield androst-5-ene-3β : 17β-diol (XLI) (cf. patents in ref. 29). Similarly, 17β-aminoandrost-5-en-3-one (XXXIX; NH_2, " equatorial ") by deamination is reported [29] to give testosterone (XLII), with retention of configuration, whilst (+)-œstrone-b oxime by reduction with sodium and ethanol gives 17β-aminoœstra-1 : 3 : 5(10)-triene, deaminated with retention of configuration to œstradiol-17β.[31]

The foregoing evidence suggests that amino-groups attached to flexible five-membered carbocyclic systems, *e.g.*, *cyclo*pentane, *cis*-perhydroindane, possess mixed equatorial-axial character according to the conformational exigencies of the situation. Amino-groups attached to rigid five-membered carbocyclic systems, *e.g.*, *trans*-perhydroindane, or to such systems forming part of the nuclei of A-nor-5α- A-nor-5β-, and normal 14α-steroids, and



placed adjacent to a bridgehead appear to possess either equatorial character characterised by deamination with retention of configuration accompanied by some elimination (Saytzew orientation), or axial character characterised by deamination with ready and exclusive elimination (Saytzew orientation) [cf. 4β- and 6β-amino-5α-cholestane (NH_2, " axial ") which by deamination give 100% of cholest-4-ene and cholest-5-ene respectively [2]; amino-groups not adjacent to a bridgehead appear to resemble aliphatic amino-groups and to undergo deamination with predominant inversion of configuration, accompanied by some elimination.

The complete absence of elimination products (derivatives of 5α-androst-16-ene or of ψ-androstene) in the deamination of 17β-amino-steroids (NH_2, " equatorial ") may reflect the presence of the angular 18-methyl group on the adjacent bridgehead carbon atom and suggests that the diazonium ion, rather than a carbonium ion, is the important intermediate.

Experimental

M. p.s were determined on a Kofler block and are therefore corrected (error ±2°). Solvents for chromatography were rigorously purified and dried, and, unless stated otherwise, aluminium

[30] Kenyon and Young, *J.*, 1941, 263.
[31] Schering A.G., G.P. 711,378/1932; B.P. 428,133/1933.

oxide (Spence type H, activity ~II) was used. The phrase " usual isolation " implies extraction with ether, washing with 2N-hydrochloric acid and/or 2N-sodium carbonate, and with water, and brief drying (Na_2SO_4). Ultraviolet absorption spectra were determined for ethanol solutions in a Hilger Uvispek spectrophotometer, and infrared absorption spectra were measured for carbon tetrachloride solutions in a Perkin-Elmer Model 21 double-beam instrument. $[\alpha]_D$ refer to chloroform solutions.

A-*Nor*-5α-*cholestan*-2-*one* (XIV).—Cholestanol (11 g.) was oxidised [32] with chromium trioxide (11·5 g.) in 90% acetic acid at 70—75° for 2·5 hr. to 2 : 3-*seco*-5α-cholestane-2 : 3-dioic acid (8·5 g.), m. p. 196—197° (from ether–pentane), which when refluxed with acetic anhydride and then distilled at 300°/1·5 mm. gave, after the usual work up, A-nor-5α-cholestan-2-one [11] (4·6 g.), m. p. 100—101° (from methanol) [oxime, m. p. 201—203° (from ethyl acetate)].

A-*Nor*-5α-*cholestan*-2α- *and* -2β-*ol* (XV, XIII).—A-Nor-5α-cholestan-2-one by reduction with excess of sodium in refluxing ethanol, or with aluminium *iso*propoxide in slowly distilling (7 hr.) propan-2-ol, gave a mixture of the epimeric alcohols, which were separated by treatment overnight with a 4% ethanolic solution of digitonin. The insoluble digitonide, on decomposition with pyridine, gave A-nor-5α-cholestan-2α-ol,[12] m. p. 128°, $[\alpha]_D$ +38° (*c* 1·2) {acetate, m. p. 80°, $[\alpha]_D$ +1° (*c* 0·8)}; the material not precipitated by digitonin gave, on recrystallisation from methanol, A-nor-5α-cholestan-2β-ol [12] as a solvate, m. p. 120° with transition to needles, m. p. >135°, which after sublimation at 160°/0·5 mm. had m. p. 153°, $[\alpha]_D$ +28° (*c* 1·0) {acetate, m. p. 93°, $[\alpha]_D$ +25° (*c* 0·4)}.

2β-*Amino*-A-*nor*-5α-*cholestane* (XVII).—(*a*) A-Norcholestan-2-one oxime (600 mg.) in refluxing pentyl alcohol (200 c.c.) was saturated with sodium during 2 hr.; after a further 1·5 hr., excess of sodium was destroyed with ethanol, and the basic product isolated in the usual way. The resultant oil (580 mg.) was chromatographed on a column of aluminium oxide (18 g.) prepared in benzene. Elution with benzene (7 × 60 c.c.) gave unchanged oxime (109 mg.); elution with ether, chloroform, and finally methanol yielded 2β-*amino*-A-*nor*-5α-*cholestane* (430 mg.), b. p. 150°/0·01 mm., $[\alpha]_D$ +25·5° (*c* 0·9) (Found: C, 83·3; H, 12·4. $C_{26}H_{47}N$ requires C, 83·55; H, 12·7%), converted by acetic anhydride into the *acetyl derivative*, m. p. 190—191° (from acetone), $[\alpha]_D$ +39° (*c* 1·0) [Found (after drying at 25°/0·03 mm. for 4 hr.): C, 80·5; H, 11·7; N, 3·1. $C_{28}H_{49}ON$ requires C, 80·9; H, 11·9; N, 3·4%].

(*b*) The ketoxime (500 mg.) was hydrogenated with platinum oxide (200 mg.) in acetic acid (50 c.c.); reaction was complete in 6 hr. After removal of acetic acid in a vacuum the base was isolated in the usual way and acetylated with acetic anhydride, and the solid product purified by chromatography on a column of aluminium oxide (15 g.) prepared in pentane. Elution with benzene–pentane (1 : 1; 6 × 50 c.c.) gave 2β-acetamido-A-nor-5α-cholestane (410 mg.), m. p. 189—191° (from acetone), identical with the specimen prepared as under (*a*) above.

A-*Nor*-5β-*cholestan*-3-*one* (XIX).—3 : 4-*seco*Cholest-5-ene-3 : 4-dioic acid [Diels's acid], m. p. 296°, was prepared by Diels and Abderhalden's method [33] as modified by Shoppee and Summers,[34] and converted by refluxing it with acetic anhydride and pyrolysing the product at 300—320°/1·5 mm. into A-norcholest-5-en-3-one, m. p. 95°, hydrogenated with palladium oxide in ether–acetic acid to A-nor-5β-cholestan-3-one, m. p. 74°. The *oxime* of the latter had m. p. 129—130°, $[\alpha]_D$ +74° (*c* 0·9), after crystallisation from methanol [Found (after drying at 20°/0·03 mm. for 8 hr.): C, 80·55; H, 11·4. $C_{26}H_{45}ON$ requires C, 80·55; H, 11·7%].

A-*Nor*-5β-*cholestan*-3β-*ol* (XVIII).—(*a*) A-Nor-5β-cholestan-3-one (250 mg.) in refluxing ethanol was treated with an excess of sodium during 2 hr.; the usual isolation gave an oil (240 mg.), which was chromatographed on a column of aluminium oxide prepared in benzene. Elution with ether–benzene (1 : 9, 3 × 20 c.c.; 1 : 4, 3 × 20 c.c.) gave A-*nor*-5β-*cholestan*-3β-*ol* (200 mg.), double m. p. 89°/107° (from methanol), $[\alpha]_D$ +51° (*c* 0·9) [Found (after drying at 25°/0·5 mm. for 12 hr.): C, 83·0; H, 12·0. $C_{26}H_{46}O$ requires C, 83·35; H, 12·35%].

(*b*) The ketone (85 mg.) was refluxed with lithium aluminium hydride (50 mg.) in ether for 1 hr. to yield, after the usual isolation procedure, an oil (85 mg.), which by chromatography as under (*a*) furnished A-nor-5β-cholestan-3β-ol (69 mg.), m. p. and mixed double m. p. 89°/106°.

The ketone (100 mg.) resisted hydrogenation in presence of platinum oxide (44 mg.) in ether–acetic acid (1 : 4; 20 c.c.) containing 2 drops of 60% perchloric acid, and was recovered unchanged (97 mg.; m. p. and mixed m. p. 74°).

[32] Cf. Windaus and Uibrig, *Ber.*, 1914, **47**, 2384.
[33] Diels and Abderhalden, *Ber.*, 1903, **36**, 3177.
[34] Shoppee and Summers, *J.*, 1952, 2528.

3α-Amino- and 3β-Amino-A-nor-5β-cholestane (XXIII, XXI).—(*a*) The ketoxime (XXII) (600 mg.) in refluxing pentyl alcohol (120 c.c.) was saturated with sodium during 3 hr. After another hour, excess of sodium was destroyed with ethanol, and the solution poured into water, and extracted with ether; working up through the ether-insoluble hydrochloride gave 3β-amino-A-nor-5β-cholestane (400 mg.), b. p. 181—185°/0·5 mm., $[\alpha]_D$ +46° (*c* 0·8) (Found: C, 83·4; H, 12·8; N, 3·62. $C_{26}H_{47}N$ requires C, 83·55; H, 12·7; N, 3·75%). Acetic anhydride afforded the *acetyl derivative*, m. p. 246—247°, $[\alpha]_D$ +48° (*c* 0·9), after recrystallisation from acetone [Found (after drying at 20°/0·03 mm. for 20 hr.): C, 80·6; H, 11·75. $C_{28}H_{49}ON$ requires C, 80·9; H, 11·9%].

(*b*) The ketoxime (250 mg.) was hydrogenated in presence of platinum oxide (100 mg.) in acetic acid (35 c.c.) in 0·75 hr. The base was isolated in the usual way as an oil (220 mg.) and chromatographed on a column of aluminium oxide (7 g.) prepared in benzene. Elution with ether–benzene, ether, chloroform, and finally methanol gave *3α-amino-A-nor-5β-cholestane*, m. p. 66—68° (from methanol), $[\alpha]_D$ +9° (*c* 1·1) [Found (after distillation at 150°/0·02 mm.): C, 83·2; H, 12·5. $C_{26}H_{47}N$ requires C, 83·55; H, 12·7%]. Acetic anhydride furnished the *acetyl derivative*, m. p. 166—168°, $[\alpha]_D$ +67° (*c* 0·9), after recrystallisation from acetone [Found (after drying at 20°/0·03 mm. for 20 hr.): C, 80·6; H, 11·6. $C_{28}H_{49}ON$ requires C, 80·9; H, 11·9%].

B-*Nor*-5β- : 8α-*cholestan*-6-*one* (XXV).—3β-Hydroxy-6 : 7-*seco*-5α-cholestane-6 : 7-dioic acid,[35,36] m. p. 239°, was oxidised with chromium trioxide in acetic acid to the 3-oxo-acid,[35,37] m. p. 254—255°, which by Clemmensen reduction gave only 27% of 6 : 7-*seco*-5α-cholestane-6 : 7-dioic acid.[37] The 3-oxo-acid (8·3 g.) was therefore refluxed in ethylene glycol (215 c.c.) containing hydrazine hydrate (7 c.c.) with sodium (8·3 g.) for 1 hr.; the temperature was allowed to rise to 185°, and refluxing continued for 6 hr.; working up gave 6 : 7-*seco*-5α-cholestane-6 : 7-dioic acid (7·3 g.), m. p. 272—273° (from acetic acid). The dry barium salt by pyrolysis at 400—420°/1·5 mm. for 3 hr. gave an oily distillate, which by the usual isolation procedure gave B-nor-5β : 8α-cholestan-6-one,[17] m. p. 92—93° (from aqueous acetone at 0°). The oxime [17] had m. p. 185—187° (from methanol).

B-*Nor*-5β : 8α-*cholestan*-6α-*ol* (XXVI).—(*a*) B-Nor-5β : 8α-cholestan-6-one (200 mg.) in refluxing pentyl alcohol (80 c.c.) was saturated with sodium during 1·5 hr.; after 2 hr., excess of sodium was destroyed with ethanol, and the mixture worked up in the usual way, giving an oil (170 mg.), which was chromatographed on a column of aluminium oxide (6 g.) prepared in pentane. Elution with benzene–pentane (1 : 1; 8 × 20 c.c.) afforded B-*nor*-5β : 8α-*cholestan*-6α-*ol* (144 mg.), m. p. 85—87°, $[\alpha]_D$ +42° (*c* 1·0) (from aqueous acetone) [Found (after drying at 25°/0·04 mm. for 20 hr.): C, 83·0; H, 12·0. $C_{26}H_{46}O$ requires C, 83·35; H, 12·35%].

(*b*) The ketone (300 mg.) in ether was refluxed with excess of lithium aluminium hydride for 14 hr. Excess of the reagent was destroyed with ice-water, and the ethereal solution worked up to give an oil (290 mg.); chromatography as under (*a*) gave by elution with pentane (6 × 30 c.c.) unchanged ketone (145 mg.), m. p. 92°, and by elution with benzene–pentane (1 : 1; 7 × 25 c.c.) B-nor-5β : 8α-cholestan-6α-ol (120 mg.), m. p. and mixed m. p. 85—87° (from aqueous acetone). The alcohol, on treatment with thionyl chloride–pyridine at 20° overnight, gave B-nor-8α-cholest-5-ene (XXVII), as an oil giving a yellow colour with tetranitromethane in chloroform, but the quantity was insufficient for purification.

6α-Amino-B-nor-5β : 8α-cholestane (XXIX).—(*a*) The ketoxime (XXVIII) (215 mg.) in refluxing pentyl alcohol was saturated with sodium during 2·5 hr.; refluxing was continued for 4 hr., excess of sodium destroyed with ethanol, the mixture poured into water, and the product isolated with ether. The resultant oil (200 mg.) was chromatographed on a column of aluminium oxide (6 g.) prepared in pentane. Elution with benzene–pentane (1 : 1), and benzene gave unidentified oils, but elution with benzene–ether (1 : 1), ether, and finally chloroform gave *6α-amino-B-nor-5β : 8α-cholestane*, b. p. 220—230°/1 mm., $[\alpha]_D$ +33° (*c* 1·1) (Found: C, 83·1; H, 12·2. $C_{26}H_{47}N$ requires C, 83·55; H, 12·7%), converted by acetic anhydride into the *acetyl derivative*, which after distillation at 180—190°/0·4 mm. crystallised from acetone, then having m. p. 178—180°, $[\alpha]_D$ +14° (*c* 1·1) [Found (after drying at 25°/0·05 mm. for 12 hr.): C, 80·65; H, 11·8; N, 3·7. $C_{28}H_{49}ON$ requires C, 80·9; H, 11·9; N, 3·4%].

(*b*) The ketoxime (XXVIII) (110 mg.) in dioxan (30 c.c.) was refluxed with excess of lithium

[35] Windaus and Stein, *Ber.*, 1904, **37**, 3699.
[36] Shoppee, *J.*, 1948, 1032.
[37] Windaus and von Staden, *Ber.*, 1921, **54**, 1059.

aluminium hydride for 16 hr. After addition of ice-water and filtration of the precipitate of aluminium hydroxide, the filtrate was diluted with water and extracted with ether, to give by the usual isolation procedure an oil (110 mg.). This was acetylated with acetic anhydride and the product chromatographed on a column of aluminium oxide (4 g.) prepared in pentane. Elution with benzene and ether–benzene (1 : 4) and recrystallisation from acetone gave 6-acetamido-B-nor-5β : 8α-cholestane, m. p. and mixed m. p. 178—180°, with the specimen prepared as under (*a*) above.

The ketoxime (XXVIII) (120 mg.) resisted hydrogenation in presence of platinum oxide (50 mg.) in acetic acid (30 c.c.) containing 4 drops of 60% perchloric acid at 20° and at 55—60°, and was recovered unchanged (115 mg.; m. p. and mixed m. p. 186—188°).

17β-*Amino*-5α-*androstane* (XXXIV).—(*a*) 5α-*Androstan*-17-*one oxime* (XXXIV) [m. p. 173—176° (from ether–methanol) (Found: N, 4·9. $C_{19}H_{31}ON$ requires N, 4·8%); 1 g.] in refluxing ethanol was saturated during 1 hr. with sodium excess of which was destroyed by adding ethanol. The cooled mixture was poured into saturated sodium chloride solution, and the base isolated, through the ether-insoluble hydrochloride, as an oil which on crystallisation from acetone gave 17β-amino-5α-androstane, m. p. 138—141° [Found (after sublimation at 130°/0·02 mm.): C, 82·65; H, 12·0. $C_{19}H_{33}N$ requires C, 82·85; H, 12·1%]. Treatment with acetic anhydride at 100° for 15 min. gave the *acetyl derivative*, m. p. 208—209° (from ethyl acetate) [Found (after sublimation at 180°/0·02 mm.): C, 79·25; H, 11·1. $C_{21}H_{35}ON$ requires C, 79·45; H, 11·1%].

(*b*) The ketoxime (XXXIV) (500 mg.) in ether (100 c.c.) was refluxed with lithium aluminium hydride (1 g.) for 3 hr. The usual working up gave 17β-amino-5α-androstane (480 mg.), m. p. and mixed m. p. 138—140° (from acetone).

(*c*) The ketoxime (XXXIV) (400 mg.) was hydrogenated in presence of platinum oxide (100 mg.) in acetic acid (50 c.c.) containing 2 drops of 60% perchloric acid. The reaction was complete in 1 hr., and after removal of acetic acid in a vacuum the base was isolated in the usual way, furnishing 17β-amino-5α-androstane (380 mg.), m. p. and mixed m. p. 138—141°.

17β-*Aminoandrost*-5-*en*-3β-*ol* (XXXVIII).—(*a*) 3β-Acetoxyandrost-5-en-17-one oxime (1·5 g.) in refluxing ethanol (100 c.c.) was treated with excess of sodium. The usual isolation gave 17β-aminoandrost-5-en-3β-ol (1·3 g.), m. p. 160° (from ethyl acetate), $[\alpha]_D$ −80° (*c* 1·0). Acetic anhydride at 140° afforded 17β-*acetamidoandrost*-5-*en*-3β-*yl acetate*, m. p. 196°, $[\alpha]_D$ −88° (*c* 0·5), after recrystallisation from ether–methanol [Found (after drying at 70°/0·02 mm. for 6 hr.): C, 70·8; H, 9·3; N, 3·4. $C_{23}H_{35}O_3N$ requires C, 70·9; H, 9·5; N, 3·6%].

(*b*) 3β-Acetoxyandrost-5-en-17-one oxime (500 mg.) in ether (50 c.c.) was refluxed with excess of lithium aluminium hydride for 3 hr. The usual isolation gave 17β-aminoandrost-5-en-3β-ol (450 mg.), m. p. 159—160° (from ethyl acetate) [Found (after drying at 70°/0·02 mm. for 6 hr.): C, 78·6; H, 11·5. Calc. for $C_{19}H_{33}ON$: C, 78·3; H, 11·4%].

(*c*) 3β-Acetoxyeti-5-enic acid (500 mg.) in benzene (20 c.c.) was refluxed with purified thionyl chloride (1 c.c.) for 2 hr. The chloride, obtained by complete evaporation in a vacuum, was dissolved in acetone–dioxan (2 : 1, 60 c.c.), and treated dropwise with a solution of sodium azide (300 mg.) in water (1·2 c.c.) with stirring. After 0·5 hr., water was added, and the precipitate filtered off, washed with water, and dried in a vacuum-desiccator overnight; this material was heated in benzene for 1·5 hr. to ensure conversion into the 17β-*iso*cyanate, which was hydrolysed by addition of acetic acid (20 c.c.) and concentrated hydrochloric acid (7 c.c.) and refluxing for 2 hr. After evaporation in a vacuum, the product was refluxed with 15% methanolic sodium hydroxide for 1 hr., and the base isolated through the ether-insoluble hydrochloride as an oil (245 mg.), which was chromatographed on a column of aluminium oxide (7 g.) prepared in pentane. Elution with benzene (4 × 25 c.c.) gave 17β-aminoandrost-5-en-3β-ol (175 mg.), m. p. and mixed m. p. 158—160°, identical with the specimens prepared as under (*a*) and (*b*) above, and characterised as the 3β : 17β-diacetyl derivative, m. p. 196°.

Deaminations.—In the following six experiments the steroid amine was dissolved in 50% acetic acid and where necessary dioxan was added to give complete dissolution. Sodium nitrite (approximately 2—3 times the weight of the amine) in 50% acetic acid was added dropwise with stirring at 20°, and the mixture left overnight. After basification with 4N-sodium hydroxide the product was isolated by extraction with ether, and then hydrolysed for 0·5 hr. with 5% methanolic potassium hydroxide, or acetylated with acetic anhydride at 100°.

(1) 2β-Amino-A-nor-5α-cholestane (XVII) (205 mg.) gave a product which, by chromatography on aluminium oxide (6 g.) prepared in pentane, yielded: (*a*) an oil (5 mg.; eluted with pentane), which did not crystallise satisfactorily, but gave a positive test for unsaturation

with tetranitromethane in chloroform, and is probably A-nor-5α-cholest-1- and/or -2-ene; (*b*) A-nor-5α-cholestan-2α-ol (XV) (125 mg.; eluted with ether–benzene (1 : 4, 1 : 1)], m. p. and mixed m. p. 128° after crystallisation from methanol; and (*c*) an oil (60 mg.; eluted with chloroform and methanol) which by acetylation gave 2β-acetamido-A-nor-5α-cholestane, m. p. and mixed m. p. 189° (from acetone).

(2) 3β-Amino-A-nor-5β-cholestane (XXI) (600 mg.) gave a product from which most of the basic material was separated by treatment with dry hydrogen chloride in ether. The ether-insoluble hydrochloride (290 mg.) yielded (on acetylation) 3β-acetamido-A-nor-5β-cholestane, m. p. and mixed m. p. 244—246° (from acetone). The residual material (315 mg.) by chromatography on aluminium oxide (10 g.) in pentane furnished: (*a*) A-norcholest-3(5)-ene [11b] (XX) (177 mg.; eluted with pentane), m. p. 80°, $[\alpha]_D$ +53° (*c* 1·1) {lit., m. p. 80°; $[\alpha]_D$ +55°} (after crystallisation from methanol); (*b*) A-nor-5β-cholestan-3β-ol (XXVIII) [119 mg.; eluted with benzene and ether–benzene (1 : 4)], double m. p. 88°/107° (from methanol) undepressed on admixture with an authentic specimen; and (*c*) oil (14 mg.; eluted with ether), which on acetylation gave 3β-acetamido-A-nor-5β-cholestane, m. p. and mixed m. p. 244—246° (from acetone).

(3) 3α-Amino-A-nor-5β-cholestane (XXIII) (210 mg.) gave a product (195 mg.) which, by chromatography on aluminium oxide in pentane, yield (*a*) A-norcholest-3(5)-ene (XX) (82 mg.; eluted with pentane), m. p. 79—80° (from methanol), and (*b*) oils (105 mg.; eluted with benzene, ether, and finally methanol), which on acetylation gave 3α-acetamido-A-nor-5β-cholestane, m. p. and mixed m. p. 165° (from acetone).

(4) 6α-Amino-B-nor-5β : 8α-cholestane (XXIX) (300 mg.) gave a product (280 mg.) which on chromatography on aluminium oxide (9 g.) furnished: (*a*) B-nor-8α-cholest-5-ene (XXVII) (50 mg.; eluted with pentane), which did not crystallise but gave a yellow colour with tetranitromethane in chloroform; (*b*) a *substance*, $C_{26}H_{46}ON_2$ [146 mg.; eluted with benzene–pentane (1 : 1) and benzene], which was crystallised with difficulty from aqueous acetone, then having double m. p. 121°/136—138° [Found (after drying at 20°/0·02 mm. for 12 hr.): C, 77·7; H, 11·7; O, 4·4; N, 6·7%; *M* (Rast), 390. $C_{26}H_{46}ON_2$ requires C, 77·55; H, 11·5; O, 4·0; N, 6·9%; *M*, 402]; and (*c*) an oil (75 mg.; eluted with ether and methanol), which on acetylation afforded 6α-acetamido-B-nor-5β : 8α-cholestane, m. p. and mixed m. p. 178° (from acetone). A second experiment gave a similar result

(5) 17β-Amino-5α-androstane (XXXV) (130 mg.) yielded 5α-androstan-17β-ol (XXXII) (125 mg.), m. p. and mixed m. p. 168—170° (from hexane).

(6) 17β-Aminoandrost-5-en-3β-ol (XXXVIII) (500 mg.) gave androst-5-ene-3β : 17β-diol (XLI) (485 mg.), m. p. and mixed m. p. 177—180° (from ethyl acetate).

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