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STEROIDS AND WALDEN INVERSION—LVII*

DEAMINATION OF SOME ALLYLIC AMINES

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Professor Henry Stephen *in memoriam*

Abstract—Solvolysis of 3β-chlorocholest-4-ene (Cl, quasiequatorial) or of 3α-chlorocholest-4-ene (Cl, quasiaxial) gave the same mixture of cholest-4-en-3β-ol (48%) and cholest-4-en-3α-ol (52%); these proportions are taken to give a measure of stereochemical partition at C-3 of the mesomeric cholest-4-enyl cation.

Deamination in aqueous acetic acid of 3β-aminocholest-4-ene (NH_2, quasiequatorial) gave, as the sole product isolated, cholest-4-en-3β-ol, formed with retention of configuration, whilst 3α-aminocholest-4-ene (NH_2, quasiaxial), gave only cholesta-2,4-diene.

Deamination in aqueous acetic acid of 3β-amino-5α-cholest-1-ene (NH_2, quasiequatorial) gave a mixture of at least seven compounds, but only the major product 5α-cholest-1-en-3β-ol, formed with retention of configuration, could be isolated. 3α-Aminocholest-1-ene could not be obtained in quantity sufficient for deamination.

These results suggest that the main reaction path in deamination of allylic cyclohexenylamines involves an internal substitution [S_Ni] of a solvated close diazonium ion-pair, and that the incidence of an S_N1 process involving a solvated carbonium ion is very limited.

IT HAS been shown[1] that deamination of aliphatic primary amines must comprise a stage having the form of an S_N1 process, and may involve a carbonium ion:[2-4] $R{-}NH_2 \rightarrow R{-}\overset{+}{N}{\equiv}N \rightarrow \overset{+}{R} \rightarrow R{-}OH$. It has however been suggested that conformation,[5-8] especially in cyclic systems, may confer importance on the precursor diazonium ion.[9] Provision of a potentially mesomeric carbonium ion should enable the reactions of the diazonium ion to be distinguished from those of the carbonium ion. An example of the use of this device is discussed, and attempts to apply the device to a study of the deamination of some allylic steroid amines are recorded.

3-Methylallylamine (= crotylamine; I) and 1-methylallylamine (= methylvinylamine; II) by deamination with aqueous nitrous acid each give a mixture of crotyl

* Part LVI, *J. Chem. Soc.*, 6458 (1965).

[1] P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold and P. A. D. S. Rao, *Nature, Lond.* **166**, 179 (1950).

[2] J. D. Roberts and M. Halmann, *J. Amer. Chem. Soc.* **75**, 5759 (1953); O. A. Reutov and T. N. Shatkina, *Tetrahedron* **18**, 237 (1962).

[3] G. J. Karabatsos and C. E. Orzech, *J. Amer. Chem. Soc.* **84**, 2838 (1962); P. S. Skell and I. Starer, *Ibid.* **82**, 2971 (1960); **84**, 3962 (1962).

[4] M. S. Silver, *J. Amer. Chem. Soc.* **82**, 3971 (1960); **83**, 3482 (1961).

[5] D. J. Cram and J. E. McCarty, *J. Amer. Chem. Soc.* **79**, 2866 (1957).

[6] A. Streitwieser and W. D. Schaeffer, *J. Amer. Chem. Soc.* **79**, 2888 (1957); A. Streitwieser, *J. Org. Chem.* **22**, 861 (1957).

[7] R. J. W. Cremlyn, D. L. Garmaise and C. W. Shoppee, *J. Chem. Soc.* 1847 (1953).

[8] C. W. Shoppee, D. E. Evans and G. H. R. Summers, *J. Chem. Soc.* 97 (1957).

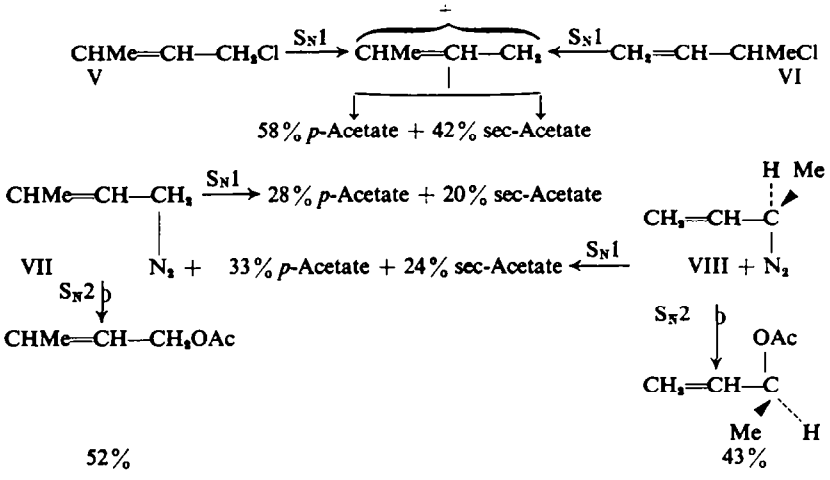
[9] R. Huisgen and C. Rüchardt, *Liebigs Ann.* **601**, 1 (1956).

alcohol (47% from I, 31% from II) and methylvinylcarbinol (53% from I, 69% from II);[10] 1-diazobut-2-ene (III) and 3-diazobut-1-ene (IV) by treatment with aqueous perchloric acid each afford again a mixture of crotyl alcohol and methylvinylcarbinol (50% from I, 50%, 70% from II), but by treatment with ethereal 3,5-dinitrobenzoic acid afford only crotyl 3,5-dinitrobenzoate and methylvinylcarbinyl 3,5-dinitrobenzoate respectively[11] by way of the respective conjugate acids, i.e., the diazonium ions, by an S_N2 process.

I $CHMe{=}CH{-}CH_2NH_2$ $\quad$ $CH_2{=}CH{-}CHMeNH_2$ II

III $CHMe{=}CH{-}\overset{-}{C}H{-}\overset{+}{N}{\equiv}N$ $\quad$ $CH_2{=}CH{-}\overset{-}{C}Me{-}\overset{+}{N}{\equiv}N$ IV

Deamination of the allylic amines (I, II) in acetic acid was also investigated by Semenov *et al.*[12] Acetolysis of 3-methylallyl chloride (V) and 1-methylallyl chloride (VI) was taken to give the proportions of *p*-acetate (58%) and sec-acetate (42%) formed from the mesomeric methylallyl cation. Deamination of the amines (I, II) was found to yield excessive amounts (80%, 67%) of unrearranged acetates (*p*-acetate from (I), sec-acetate from II). In the deamination, if the rearranged acetates (20% sec-acetate from I, 33% *p*-acetate from II) arise from the mesomeric methylallyl cation, a proportion of the unrearranged acetates (80 − 28 = 52% from I, 67 − 24 = 43% from II), must be formed by some other path. We suggest that this other path is S_N2 substitution of the respective diazonium ions (VII, VIII).



This suggestion appears to be supported by analysis of the data recorded by Young *et al.*[12] for deamination in acetic acid of the optically active amine (II), which was found to give 58% of inverted unrearranged sec-acetate. If 37.2% of this product was formed by S_N2 substitution of the optically active diazonium ion (VIII), there would also be formed by S_N1 substitution of the optically active diazonium ion (VIII) 21% of racemic unrearranged sec-acetate,* which is equivalent to 10.5% of inverted

* One of us (C.W.S.) pointed out to Professor W. G. Young, during a visit to Los Angeles in 1959, that the S_N1 pathway accounts for only 24% of racemic unrearranged sec-acetate, and not, as stated,[13] 57%—a figure which includes 33% of optically inactive rearranged primary acetate.

[10] J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.* **73**, 2509 (1951).

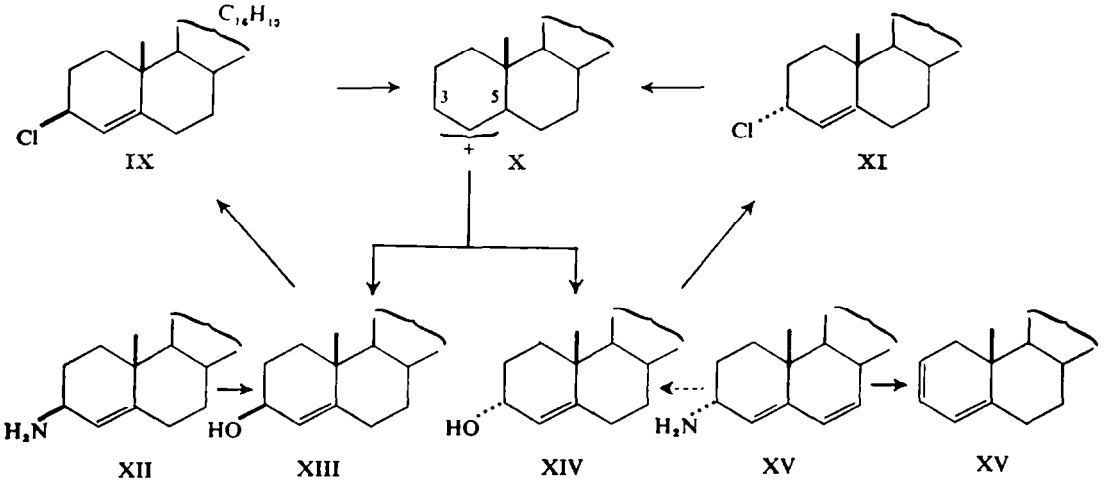
[11] D. Y. Curtin and S. M. Gerber, *J. Amer. Chem. Soc.* **74**, 4052 (1952).

[12] D. Semenov, C-H. Shih and W. G. Young, *J. Amer. Chem. Soc.* **80**, 5472 (1958).

unrearranged sec-acetate, giving a total of ~48% of inverted unrearranged sec-acetate (Found: 58%).

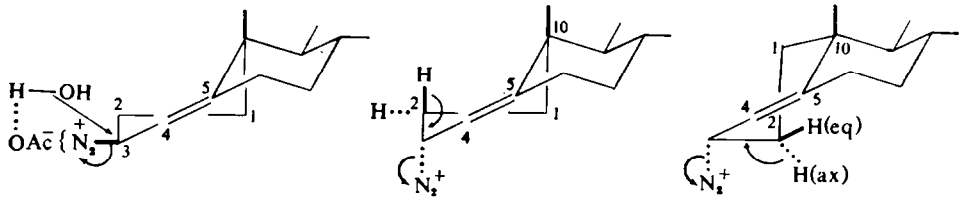
A single example of deamination of epimeric allylic steroid amines has been reported;[13] 7β-aminocholest-5-en-3β-ol (NH_2, quasiequatorial), gave with retention of configuration cholest-5-ene-3β,7β-diol (84%) apparently unaccompanied by cholest-5-ene-3β,7α-diol, whereas 7α-aminocholest-5-en-3β-ol (NH_2, quasiaxial) gave with retention of configuration cholest-5-ene-3β,7α-diol (22%), apparently unaccompanied by cholest-5-ene-3β,7β-diol, together with cholesta-5,7-dien-3β-ol (70%). It seemed therefore of interest to try to discover if this simple stereochemical pattern, which appears to involve decomposition of the diazonium ion with predominant retention of configuration and not the potentially mesomeric carbonium ion, applies to other allylic steroid amines.

Solvolysis of 3β-chlorocholest-4-ene (IX: Cl, quasiequatorial) has been reported[14] to give approximately equal amounts (40%) of cholest-4-en-3β-ol (XII) and cholest-4-en-3α-ol (XIV) together with cholesta-3,5-diene (15%); we find by analysis of the integral of the signals for the vinyl protons at τ 4·69 of the 3β-ol (XII) and at τ 4·52 of the 3α-ol (XIV) in the NMR spectrum of the solvolysis product that there is present 48% of the 3β-epimer and 52% of the 3α-epimer. Solvolysis of 3α-chlorocholest-4-ene (XI: Cl, quasiaxial) yields the same products (XII, XIV) in the same proportions; analysis of the integral of the signals for the vinyl protons of the 3β-ol (XII) and the 3α-ol (XIV) in the NMR spectrum of the solvolysis product shows the presence of 48% of the 3β-epimer and 52% of the 3α-epimer. Further, the first order rate constants for solvolysis of the chlorides (IX, XI) in ethanol–dioxan at 25° are almost the same (10^4 k 6·2 and 5·0 sec^{-1}).[14] These facts indicate the formation, by an S_Ni heterolysis, of the common mesomeric cation (X) and its subsequent sterochemical partition at C-3; the absence of products arising from stereochemical partition at C-5 is noteworthy and may be related to the tertiary character of this bridge head carbon atom.



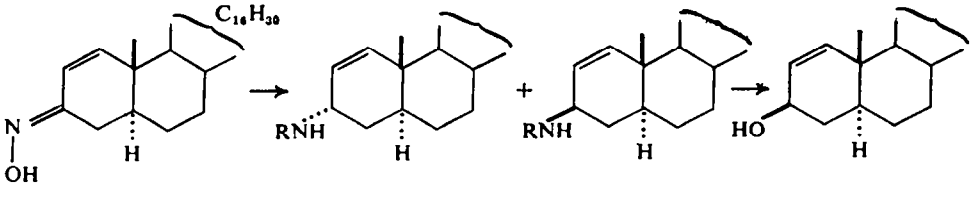
[13] C. W. Shoppee, R. F. W. Cremlyn, D. E. Evans and G. H. R. Summers, *J. Chem. Soc.* 4364 (1957).
[14] W. G. Young, R. E. Ireland, T. I. Wrigley, C. W. Shoppee, B. D. Agashe and G. H. R. Summers, *J. Amer. Chem. Soc.* **81**, 1452 (1959).

3β-Aminocholest-4-ene[15] (XII) and 3α-aminocholest-4-ene[15] (XV) were obtained by brief reduction of cholest-4-en-3-one oxime[16] (m.p. 152°; mixture of 60% *syn*- and 40% *anti*-oxime) with LAH. Deamination in aqueous acetic acid of 3β-aminocholest-4-ene (XII: NH_2, quasiequatorial) gave by column chromatography only cholest-4-en-3β-ol (XIII) with retention of configuration.* This observation is consistent with an internal substitution reaction [S_Ni] of the solvated diazonium ion pair (A);[8,17] the absence of the epimeric cholest-4-en-3α-ol (XIV) appears to exclude an S_N1 process leading to the mesomeric carbonium ion (X), since this should furnish approximately equal proportions of the epimeric alcohols (XIII, XIV), and also to exclude S_N2 substitution of the solvated diazonium ion with inversion of configuration. Deamination of 3α-aminocholest-4-ene (XV: NH_2, quasiaxial) gave only cholesta-2,4-diene (XVI).* The absence here of the expected cholest-4-en-3α-ol (XIV) suggests that the solvated diazonium ion of the half-chair conformation (B),[18] and not of the alternative conformation (C),[18] undergoes a facile base-induced *trans*-axial/quasiaxial E2 elimination reaction, since the carbonium ion (X) gives by expulsion of a proton not cholesta-2,4-diene (XVI) but cholesta-3,5-diene.



(A) (B) (C)

Reduction of 5α-cholest-1-en-3-one anti-oxime[19] (XVII: R = H) with LAH in tetrahydrofuran, followed by acetylation, gave 3β-acetamido-5α-cholest-1-ene (XVIII: R = Ac) accompanied by traces of 3α-acetamido-5α-cholest-1-ene (XIX: R = Ac) and some unchanged oxime as the acetate[19] (XVII: R = Ac). The NMR spectrum of the 3β-acetamido-compound, after deuteration, showed signals for two vinyl protons, H-2 at τ 4·02 ($J_{2,1}$ 9·4, $J_{2,3}$ 2·5 c/s), and H-1 at τ 4·67 ($J_{1,2}$ 9·4 c/s broadened by long range spin-spin coupling with the allylic 3α-proton; the quasiaxial 3α-proton appeared as a very broad multiplet centred at τ 5·5 ($W_{1/2h}$ 17 c/s).



XVII XVIII XIX XX

* We hope to check this result by NMR spectroscopy and VPC.

[15] C. W. Shoppee, D. E. Evans, H. C. Richards and G. H. R. Summers, *J. Chem. Soc.* 1649 (1956).
[16] C. W. Shoppee, R. F. Lack and B. C. Newman, *J. Chem. Soc.* 3388 (1964).
[17] C. W. Shoppee, M. I. Akhtar and R. E. Lack, *J. Chem. Soc.* 877 (1964).
[18] C. W. Shoppee, P. Ram and R. E. Lack, *J. Chem. Soc.* in press (1966).
[19] C. W. Shoppee, R. E. Lack, R. N. Mirrington and L. R. Smith, *J. Chem. Soc.*, 6450 (1965).

3β-Acetamido-5α-cholest-1-ene (XIX: R = Ac) by alkaline hydrolysis gave 3β-amino-5α-cholest-1-ene (XIX: R = H; NH_2, quasiequatorial) as an oil, homogeneous by TLC, which was deaminated in aqueous acetic acid. The product was a mixture, shown by TLC to contain at least seven substances, and probably consisting of 5α-cholesta-1,3-diene, the epimeric 5α-cholest-1-en-3-ols and 5α-cholest-2-en-1-ols and their acetates. After brief alkaline hydrolysis of the mixture, column chromatography on silica gave, as the only compound isolated, 5α-cholest-1-en-3β-ol (XX), formed with retention of configuration and identical with an authentic sample prepared by reduction of 5α-cholest-1-en-3-one with LAH.[20] The quantity of 3α-acetamido-5α-cholest-1-ene (XVIII: R = Ac) available was insufficient for hydrolysis and deamination.

Isolation of XX indicates the occurrence of an internal S_Ni substitution reaction of a solvated diazonium ion-pair (cf. A). The multiplicity of alcohols (and their acetates) formed in small amount suggests the incursion of an S_N1 process involving a mesomeric carbonium ion in which both possible sites of attack, C-1 and C-3, are secondary; operation of the linear S_N2 substitution mechanism on a limited scale is not excluded.

Attempts to prepare the 6ξ-aminocholest-4-enes and the 4ξ-aminocholest-5-enes were unsuccessful. Cholest-4-en-6-one oxime by reduction with sodium-pentanol unexpectedly gave mainly 6α-amino-5α-cholestane,[8] identified as the N-acetyl derivative and as the hydrochloride, whose NMR spectrum showed no signals for a vinyl proton. Although 6α-amino-5α-cholestane was the only product isolated in several independant experiments, VPC of the mixture from the acetylation of the crude product, showed it to be a mixture of at least three compounds, whilst the presence of a low intensity signal for a vinyl proton in the NMR spectrum indicated the presence of small amounts of a 6ξ-acetaminocholest-4-ene. It may be noted that sodium ethanol reduction of cholest-4-en-3-one oxime gives some 3β-amino-5α-cholestane.[15] Deamination of 6α-amino-5α-cholestane gave 5α-cholestan-6α-ol.

Cholest-4-en-6-one oxime by reduction with LAH for 16 hr yielded mainly the saturated 6β-amino-5α-cholestane,[8] accompanied by some 6α-amino-5α-cholestane,[8] as disclosed by TLC on silica in chloroform. The NMR spectrum of 6β-acetamido-5α-cholestane showed signals at τ 8·99 for the 19-methyl group (shifted downfield 18 ppm due to shielding by the axial 6β-acetamido group; τ 9·17 for the 19-methyl group in 5α-cholestane), and at τ 7·87 for the axial 6β-acetamido group (shifted downfield 10 ppm due to shielding by the axial 19-methyl group). The mixture of 6-acetamido-compounds, obtained by acetylation of the crude reduction product, showed signals derived from 6α-acetamido-5α-cholestane at τ 9·09 (19-methyl group), τ 9·35 (18-methyl group), and τ 7·97 (6α-acetamido group), and signals derived from 6β-acetamido-5α-cholestane at τ 8·99 (19-methyl group), τ 9·37 (18-methyl group), and τ 7·87 (6β-acetamido group). Reduction of cholest-4-en-6-one oxime with LAH for only 6 hr gave inseparable mixtures of saturated and unsaturated amines as shown by the NMR spectrum and VPC.

Cholest-5-en-4-one oxime by reduction with sodium-pentanol gave mainly 4α-acetamido-5α-cholestane, after acetylation of the reaction product. The NMR spectrum disclosed the presence of 90% of 4α-acetamido-5α-cholestane,[13] which exhibited high intensity signals at τ 9·12 (C-19 methyl group), τ 9·34 (C-18 methyl group), and

[20] W. Bergmann, M. Kita and D. J. Giancola, *J. Amer. Chem. Soc.* **76**, 4974 (1954).

τ 8·03 (4α-acetamido group), and of 10% of 4β-acetamido-5α-cholestane,[13] which showed low intensity signals at τ 9·02 for the 19-methyl group (shifted downfield 15 ppm due to shielding by the axial 4β-acetamido group), τ 9·32 (C-18 methyl group), and τ 7·97 for the axial 4β-acetamido group (shifted downfield 6 ppm due to shielding by the axial 19-methyl group).

Reduction of cholest-5-en-4-one oxime with LAH for 6 to 32 hr gave inseparable mixtures of amines, as shown by NMR spectroscopy and VPC.

EXPERIMENTAL

For general experimental directions see *J. Chem. Soc.* 345 (1959). $[\alpha]_D$ are for $CHCl_3$ solutions. UV absorption spectra were measured for EtOH solutions in a Perkin–Elmer model 4000 A spectrophotometer and IR absorption spectra for CCl_4 solutions in a Perkin–Elmer model 221 spectrophotometer. NMR spectra were determined using a Varian D.P. 60 instrument at 60 Mc/s. with $CDCl_3$ as solvent and tetramethylsilane as internal reference. For chromatography alumina [Spence, type H, activity ~II, or Woelm neutral] or silica gel [Davison, 40–200 mesh] were used.

Cholest-4-en-3β- and -3α-ol (XIII, XIV)

(a) Cholest-4-en-3-one (3 g) was reduced with LAH (300 mg) in tetrahydrofuran (60 ml) at 65° for 30 min. The usual working up gave a crystalline product, shown by TLC on silica in hexane to consist largely of cholest-4-en-3β-ol with a trace[21] of the 3α-ol. Column chromatography on silica (250 g) in pentane and elution with ether–pentane (1:5) gave a mixture (50 mg) of the epimeric 3-ols. Further elution with the same eluant gave cholest-4-en-3β-ol (2·9 g), m.p. 130–132°, $[\alpha]_D$ +50° (*c* 1·0) (lit.[21] m.p. 131–132°, $[\alpha]_D$ +45°), whose NMR spectrum showed signals for the 19-methyl and 18-methyl groups at τ 8·95 and 9·32, for the quasiaxial 3α-proton at τ 5·88, and for the vinyl 4-proton as a singlet[21] at τ 4·69.

(b) Cholest-4-en-3-one (3 g) was reduced with LAH in ether at 36°[21] to give a mixture of the epimeric 3-ols as shown by TLC. The mixture could not be separated by column chromatography on silica; cholest-4-en-3β-ol was therefore precipitated with digitonin[22,24] to leave cholest-4-en-3α-ol (1·07 g), which was isolated in the usual way and had m.p. 83°, $[\alpha]_D$ +110° (lit.[22] m.p. 83–84°, $[\alpha]_D$ +115;[24] m.p. 84°, $[\alpha]_D$ +121° [in benzene]) from acetone, and showed NMR signals for the 19-methyl and 18-methyl groups at τ 9·02 and 9·32, for the quasi-equatorial 3β-proton at τ 5·9, and for the vinyl 4-proton as a doublet at τ 4·52.

3β-Chloro- and 3α-Chlorocholest-4-ene (IX, XI)

(a) Cholest-4-en-3β-ol (1 g) in ether (10 ml) was treated with thionyl chloride (0·3 ml) at 0° for 5 min, whereafter the solution was washed with $NaHCO_3$ aq., dried, and evaporated to give 3β-chlorocholest-4-ene, m.p. 116-117°, $[\alpha]_D$ +22° (*c* 0·85) from ether (lit.[14] m.p. 116–120°, $[\alpha]_D$ +26°; m.p. 111–113°, $[\alpha]$ +25°).

(b) Cholest-4-en-3α-ol (500 mg) in ether (10 ml) was treated with thionyl chloride (0·2 ml) at 0° for 5 min. Working up as under (a) gave 3α-chlorocholest-4-ene, m.p. 94–98°, $[\alpha]_D$ +170° from acetone (lit.[14] m.p. 89–95°, $[\alpha]$ +169°; m.p. 96–98°, $[\alpha]$ +140°); shown by TLC on silica in hexane to contain a trace of cholesta-3,5-diene, which could not be removed by column chromatography.

Solvolysis of 3β-chloro- and 3α-chlorocholest-4-ene

(a) 3β-Chlorocholest-4-ene (1 g) was solvolysed in aqueous acetone in the presence of $NaHCO_3$ at 45–55° for 1·5 hr as described by Young *et al.*[14] The product, isolated in the usual way, was chromatographed on silica (100 g) in pentane. Elution with pentane gave cholesta-3,5-diene (180 mg), m.p. and mixed m.p. 74°, whilst elution with ether–pentane (1:1) gave a mixture of the 3-epimeric

[21] P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **32**, 265 (1949); cf. H. McKennis and G. W. Gaffney, *J. Biol. Chem.* **75**, 217 (1948).
[22] D. J. Collins, J. J. Hobbs and S. Sternhell, *Tetrahedron Letters* No. 10, 623 (1963).
[23] R. Schoenheimer and E. A. Evans, *J. Biol. Chem.* **114**, 567 (1936).
[24] C. W. Shoppee, B. D. Agashe and G. H. R. Summers, *J. Chem. Soc.* 3107 (1957).

cholest-4-en-3-ols (790 mg), m.p. 110–142°. The NMR spectrum of this mixture showed it to contain 48% of the 3β-ol (XIII), and 52% of the 3α-ol (XIV); the spectrum also revealed signals for the 18-methyl groups at τ 9·32, for the 19-methyl groups at τ 8·95 and 9·02 for the vinyl 4-protons at τ 4·69 (3β-ol, XIII) and τ 4·52 (3α-ol, XIV), whilst the signals for the epimeric 3-protons appeared as a complex corresponding to one proton at τ 5·98.

(b) 3α-Chlorocholest-4-ene (500 mg) in acetone (45 ml) was treated with $NaHCO_3$ (1·5 g) and water (5 ml) at 45–55° for 1 hr. The product was isolated in the usual way and chromatographed on silica (50 g) in pentane. Elution with pentane gave cholesta-3,5-diene (165 mg), m.p. and mixed m.p. 78–80°, λ_{max} 235 mμ. Elution with ether–pentane (1:1) gave a mixture of the 3-epimeric cholest-4-en-3-ols (300 mg), m.p. 98–142°, shown by its NMR spectrum to contain 48% of the 3β-ol (XIII) and 52% of the 3α-ol (XIV).

3β-Amino- and 3α-aminocholest-4-ene (XII, XV)

Cholest-4-en-3-one oxime[18] (m.p. 152°; 2 g) was refluxed with LAH (2 g) in ether (200 ml) for 1 hr. Excess of the reagent was destroyed with moist ether, and the basic products isolated as the ether-insoluble hydrochlorides; the free bases were liberated in the usual way and acetylated with Ac_2O–pyridine at 20° overnight. The 3-epimeric N-acetyl derivatives (1·2 g) were separated by chromatography on alumina (50 g) in pentane. Elution with benzene–pentane (1:1) gave fractions (300 mg), which by fourfold crystallization from AcOEt yielded 3α-acetamidocholest-4-ene (175 mg), m.p. 187–190°, $[\alpha]_D$ +90° (*c* 0·8) (lit.[15] m.p. 190°, $[\alpha]_D$ +94°). Further elution with benzene–pentane, benzene, and ether–benzene mixtures gave material (900 mg), which after sixfold crystallization from AcOEt furnished 3β-acetamidocholest-4-ene (400 mg), m.p. 228–230°, $[\alpha]_D$ +9° (*c* 0·75) (lit.[15] m.p. 231°, $[\alpha]_D$ +5°).

The 3α-N-acetyl compound (160 mg) by hydrolysis with conc. HCl–EtOH (1:2) under reflux for 10 hr, isolation of the base hydrochloride and regeneration of the base, gave 3α-aminocholest-4-ene as an oil, b.p. 165–170°/0·05 mm, $[\alpha]_D$ +93° (*c* 0·8); a portion by acetylation regenerated the N-acetyl derivative, m.p. and mixed m.p. 186–190°. The 3β-N-acetyl compound similarly afforded 3β-aminocholest-4-ene, b.p. 180°/0·05 mm, $[\alpha]_D$ +51° (*c* 1·1); a portion by acetylation regenerated the N-acetyl derivative, m.p. and mixed m.p. 227–230°. The epimeric 3-amines were deaminated immediately after their preparation.

3α-Amino- and 3β-amino-5α-cholest-1-ene (XVIII, XIX: R = H)

5α-Cholest-1-en-3-one *anti*-oxime[19] (m.p. 148–150°; 400 mg) was refluxed with LAH (600 mg) in tetrahydrofuran (75 ml) for 3 hr and left at 20° for 18 hr. Excess of the reagent was destroyed with moist ether, and with ice-water; insoluble material was filtered off and washed with ether. The crude bases, isolated from the ethereal solution, were acetylated with Ac_2O–pyridine at 20° for 15 hr. The N-acetyl derivatives were chromatographed on silica (50 g) in ether–pentane (1:20). Elution with ether–pentane (1:10, 5 × 20 ml) gave 5α-cholest-1-en-3-one *anti*-oxime acetate (111 mg), m.p. and mixed m.p. 150–152° from acetone (lit.[19], m.p. 150–152°). Elution with ether (3 × 10 ml) gave a mixture of XVIII (R = Ac) and XIX (R = Ac), giving two spots with closely similar R_F values on TLC on silica in chloroform, and whose NMR spectrum showed the signal for the quasiequatorial 3β-proton in XVIII (R = Ac) as a narrow multiplet at τ 5·42 superimposed on the broad multiplet signal centred at τ 5·5 for the quasiaxial proton 3α-proton in XIX (R = Ac). Further elution with ether (7 × 20 ml) gave *3β-acetamido-5α-cholest-1-ene* (172 mg), m.p. 240–243°, ν_{max} 3442, 1677 cm^{-1}, from acetone. (Found after drying at 100°/0·1 mm for 4 hr: C, 81·2; H, 11·6. $C_{29}H_{49}NO$ requires: C, 81·45; H, 11·55%.) The compound was homogeneous by TLC and its NMR spectrum showed three signals, each as a singlet equivalent to three protons, corresponding to the 18-methyl group at τ 9·34, the 19-methyl group at τ 9·12, and the N-acetyl group at τ 8·05, in addition to signals for H-2 at τ 4·02 [$J_{2,1}$ 9·4, $J_{2,3}$ 2·5 c/s], H-1 at τ 4·67 [$J_{1,2}$ 9·4 c/s], and 3α-H at τ 5·5 [$W_{\frac{1}{2}h}$ 17 c/s]. 3β-Acetamido-5α-cholest-1-ene (350 mg) was hydrolysed by refluxing with conc. HCl (250 ml) and EtOH (350 ml) for 48 hr to yield 3β-amino-5α-cholest-1-ene as an oil, which was isolated in the usual way and deaminated immediately.

Deaminations of amines (XII, XV, XIX: R = H)

The base was dissolved in 50% AcOH, and where necessary dioxan was added to cause complete dissolution. $NaNO_2$ (2–3 × the wt of amine) in 50% AcOH was added dropwise with stirring and

the mixture left overnight at 20°. After neutralization with 4N NaOH, the product was isolated by extraction with ether and then hydrolysed for 0·5 hr with 5% methanolic KOH, or acetylated with Ac_2O–pyridine at 20°.

(a) [S.K.R.] 3β-Aminocholest-4-ene (70 mg) gave a product which was chromatographed on alumina (3 g) in pentane; elution with benzene gave cholest-4-en-3β-ol (30 mg), m.p. and mixed m.p. 129–130°, $[\alpha]_D$ +42° (*c* 0·6) from acetone (lit.[21] m.p. 131–132°, $[\alpha]_D$+45°). Elution with ether–MeOH gave non-crystalline material (30 mg) which by acetylation gave 3β-acetamidocholest-4-ene, m.p. and mixed m.p. 228–230° (lit.[15] m.p. 231°).

(b) [S.K.R.] 3α-Aminocholest-4-ene (35 mg) yielded an oil, which was chromatographed on alumina (2 g) in pentane; elution with pentane gave cholesta-2,4-diene (15 mg), m.p. 65–67°, $[\alpha]_D$ +165° (*c* 0·5), λ_{max} 268, 274 mμ, from acetone (lit.[25] m.p. 68°, $[\alpha]_D$ +168°, λ_{max} 267, 275 mμ, log ε 3·83, 3·80). Elution with ether–MeOH gave an oil (15 mg), which by acetylation furnished 3α-acetamidocholest-4-ene, m.p. and mixed m.p. 186–189° (lit.[15] m.p. 190°).

(c) [R.E.L.] 3β-Amino-5α-cholest-1-ene (300 mg) gave by ether extraction a product (which was not saponified), shown to contain at least seven compounds by TLC on silica in benzene. The product, dissolved in pentane, was chromatographed on a column of silica (50 g) prepared in ether–pentane (1:20), and washed free from ether with pentane. Elution with pentane (9 × 25 ml) gave 5α-cholesta-1,3-diene (25 mg) as an oil, R_F 0·76, λ_{max} 265 mμ, log ε 3·95. Elution with ether–pentane (1:50, 10 × 25 ml) gave non-crystalline fractions (155 mg) containing possibly 3 compounds, R_F 0·45–0·65 (overlapping spots), ν_{max} 1738 cm^{-1} (OAc). Elution with ether–benzene (1:5, 5 × 25 ml) gave non-crystalline fractions (52 mg) containing 4 compounds (one major and three minor components), R_F 0·2–0·35, thought to be a mixture of the epimeric 5α-cholest-1-en-3-ols and 5α-cholest-2-en-1-ols.

The fractions containing acetates and alcohols were recombined and saponified, and the product (140 mg) rechromatographed on a column of silica (15 g) in pentane. Elution with ether–pentane (1:20) gave oils, but use of ether–pentane (1:15) gave 5α-cholest-1-en-3β-ol (60 mg), m.p. and mixed m.p. 131°, $[\alpha]_D$ +57° from MeOH, which was homogeneous on TLC and whose IR spectrum was identical with that of a genuine sample (lit.[20], m.p. 131°, $[\alpha]_D$ +55°).

Reduction of cholest-4-en-6-one oxime

Cholest-4-en-6-one[26,27] (m.p. 108–109°; $[\alpha]_D$ +36°; 3 g) was oximated in the usual way to give the *oxime*, m.p. 163–165°, from MeOH. (Found after drying at 100°/0·2 mm for 2 hr: C, 81·0; H, 11·35; N, 3·6. $C_{27}H_{45}NO$ requires: C, 81·1; H, 11·35; N, 3·5%.)

(a) The oxime (1·6 g) was dissolved in refluxing pentanol (200 ml) and the solution saturated with Na (16 g) during 3 hr. The cooled reaction mixture was poured into water, and the product extracted with ether; treatment of the dry ethereal extract with HCl gave the ether-insoluble *hydrochloride*, m.p. 257–258°. (Found after sublimation at 220°/1 mm: C, 76·4; H, 11·8; N, 3·3. $C_{27}H_{49}N$. HCl requires: C, 76·45; H, 11·9; N, 3·3%), converted in the usual manner into 6α-amino-5α-cholestane, b.p. 180°/0·1 mm, $[\alpha]_D$ +40° (*c* 0·8) (lit.[8] b.p. 140°/0·02 mm, m.p. 125–127°, $[\alpha]_D$ +38·5°), which was identified as the N-acetyl derivative, double m.p. 116–118°/186–188°, $[\alpha]_D$ +65° (lit.[8] double m.p. 117–118°/185–187°. $[\alpha]_D$ +62°). 6α-Amino-5α-cholestane was also obtained using Na–EtOH.

(b) The oxime (500 mg) was refluxed with LAH (1 g) in ether (100 ml) for 16 hr. Excess of the reagent was destroyed with moist ether, ice-water added, and the product isolated with ether–chloroform. The crude bases were acetylated with Ac_2O–pyridine at 20°; TLC of the product on silica in chloroform gave two spots with similar R_F values, whilst the NMR spectrum disclosed the presence of 60% 6β-acetamido-5α-cholestane, τ 8·99 (19-methyl group) accompanied by 40% of 6α-acetamido-5α-cholestane, τ 9·09 (19-methyl group). Column chromatography on alumina (20 g) in hexane, and elution with ether gave 6β-acetamido-5α-cholestane as a hydrate, m.p. 95–100°, [lit.[8], m.p. 189–190° (anhydrous)], which was homogeneous on TLC but which could not be obtained

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completely anhydrous by drying at 60°/1 mm. (Found: C, 79·6; H, 11·7; N, 2·85. Calc. for $C_{29}H_{51}NO$: C, 81·05; H, 11·95; N, 3·25 for $C_{29}H_{51}NO.H_2O$: C, 77·8; H, 11·95; N, 3·15%.)

Reduction of cholest-5-en-4-one oxime

Cholest-5-en-4-one[17,18] (m.p. 110°, $[\alpha]_D$ −32°) was oximated in the normal manner to afford the *oxime*, m.p. 168–170° from MeOH. (Found after drying at 50°/1 mm for 4 hr: C, 80·7; H, 11·4; N, 3·4. $C_{27}H_{45}NO$ requires: C, 81·1; H, 11·35; N, 3·5%.)

(a) [P.R.] The oxime (500 mg) was dissolved in refluxing pentanol (200 ml) and the solution saturated with Na (4 g) during 4 hr. The product was treated with Ac_2O–pyridine at 20° to give the N-acetyl derivative, m.p. 235° with transformation to needles, m.p. 239–240°. The NMR spectrum of this product showed the absence of vinyl protons and disclosed the presence of 90% of 4α-acetamido-5α-cholestane,[18] which exhibited high intensity signals at τ 9·12 (C-19 methyl), τ 9·34 (C-18 methyl) and τ 8·03 (4α-NHAc), and 10% of 4β-acetamido-5α-cholestane,[18] which showed low intensity signals at τ 9·02 (C-19 methyl), τ 9·32 (C-18 methyl) and τ 7·97 (axial 4β-NHAc). The ratio 9:1 was confirmed by VPC on an F and M 400 instrument fitted with a 200 Disc integrator using a 4 ft. column packed with 3·8% silicone rubber SE 30 on 80–100 Diatoport S and with helium as carrier gas at an oven temperature of 240°.

(b) [P.R.] The oxime (500 mg) was refluxed with LAH (1 g) in ether (80 ml) for 6 hr. The crude product was acetylated with Ac_2O–pyridine at 20° to give an oil, which failed to crystallize and was inseparable by column chromatography; the NMR spectrum showed 4 peaks between τ 8·1 and 7·9 indicating the product to contain at least four N-acetyl derivatives. Longer reaction times of 16 hr and 32 hr gave mixtures of products as shown by TLC and the NMR spectrum. These could not be separated by column chromatography, or crystallization.

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