Steroids. Part II.[1] Deamination of 5α-Amino- and 6α-Amino-5β-hydroxy-steroids

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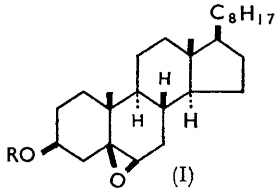
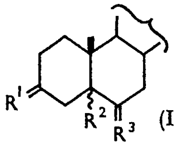
Aprotic deamination of 3β,6β-diacetoxy-5α-aminocholestane gave a Westphalen rearrangement in which an increased ratio of Hofmann to Saytzeff product is obtained. Deamination of 6α-aminocholestane-3β,5β-diol gave 3β-hydroxy-A-homo-B-nor-5β-cholestan-4a-one.

Snatzke and Veithen[2] have recently reported that deamination of 3β,6β-diacetoxy-5α-aminocholestane (IIc) in aqueous acetic acid and dioxan gave the Westphalen diol diacetate (III) (46%) and small quantities of the $\Delta^{1(10)}$-isomer (IV) (30%) and the Δ^4-isomer (9%). This product distribution is similar to that obtained from the Westphalen rearrangement of the 5α-hydroxy-compound (IId) with potassium hydrogen sulphate–acetic anhydride.[3] We have studied the aprotic deamination of (IIc), since it was felt that the solvent change involved might well affect the fate of the C(5)-carbonium ion (VI) generated in these reactions.

a; R = Ac
b; R = H

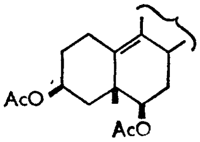


(I)

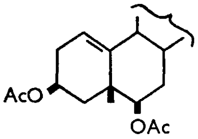


(II)

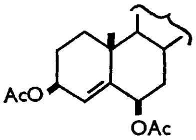
	R^1	R^2	R^3
a;	β-OAc,α-H	α-N_3	β-OH,α-H
b;	β-OAc,α-H	α-N_3	β-OAc,α-H
c;	β-OAc,α-H	α-NH_2	β-OAc,α-H
d;	β-OAc,α-H	α-OH	β-OAc,α-H
e;	β-OAc,α-H	β-OH	α-N_3,β-H
f;	β-OH,α-H	β-OH	α-N_3,β-H
g;	β-OH,α-H	β-OH	α-NH_2,β-H
h;	O	β-OH	α-N_3,β-H



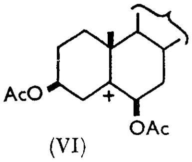
(III)



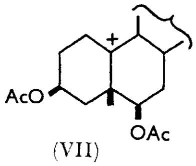
(IV)



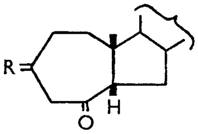
(V)



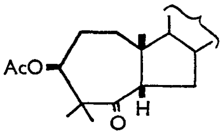
(VI)



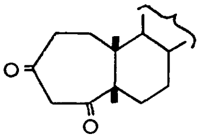
(VII)



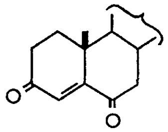
(VIII) a; R = β-OH,α-H
b; R = O



(IX)



(X)



(XI)

The amine (IIc) was prepared by way of the azide (IIa) by Ponsold's method.[4] Reaction of the epoxide (Ia)[5] with sodium azide–sulphuric acid in dimethyl sulphoxide gave the azide (IIa), the isomeric compound (IIe), and some starting material (Ia). The mixture was chromatographed on a column to give (IIa) contaminated with the hydrolysis product (IIf), and (IIe) contaminated with (Ia). Compound (IIa) was purified by preparative t.l.c. and on acetylation gave the azide (IIb). Reduction of (IIb) with hydrazine hydrate and Raney nickel gave the amine (IIc). The isomer (IIe), which was detected by Snatzke and Veithen[2] but not by Ponsold,[4] was subsequently obtained by way of the dihydroxy-azide (IIf). The mixture of (IIe) and (Ia) was hydrolysed and chromatographed to give (IIf) and (Ib). Acetylation of (IIf) gave the azide (IIe).

The hydrochloride of (IIc), in chloroform, gave, on treatment with an excess of 3-methylbutyl nitrite, and after preparative t.l.c., the Westphalen diol diacetate (III) (40%) and essentially pure $\Delta^{1(10)}$-isomer (IV) (47%). The ^{1}H n.m.r. spectrum of the latter suggested that it was contaminated with a little of the Δ^4-isomer (V) (<10%), but one crystallisation from aqueous methanol gave pure $\Delta^{1(10)}$-isomer (IV).[3]

The change from protic to aprotic conditions apparently results in a greater ratio of Hofmann to Saytzeff product from the deamination. Since the $\Delta^{1(10)}$-isomer (IV) gives no detectable $\Delta^{9(10)}$-isomer (III) when set aside in aqueous acetic acid for 2 hr., it seems unlikely that (IV) is first formed under protic conditions and then equilibrates to (III). The explanation may involve the difference in size of the basic species[6] attacking the C(10)-carbonium ion (VII), presumably an intermediate in both reactions.* The ease of removal of a proton from C-1 in (VII) by a water molecule is probably about the same as that for deprotonation at C-9, and under aqueous conditions the expected[7] Saytzeff elimination occurs. However, in the aprotic reaction, the base is

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* The reaction may be to some extent concerted, so that the classical ions (VI) and (VII) do not exist.

[1] Part I, M. J. Harrington and B. A. Marples, *Chem. and Ind.*, 1968, 484.

[2] G. Snatzke and A. Veithen, *Annalen*, 1967, **703**, 159.

[3] G. Snatzke and H. W. Fehlhaber, *Annalen*, 1964, **676**, 188.

[4] K. Ponsold, *Chem. Ber.*, 1962, **95**, 1727.

[5] (*a*) E. J. Tarlton, Dissertation, Harvard, 1953; (*b*) L. F. Fieser and M. Fieser, 'Steroids,' Reinhold, New York, 1959, p. 198.

[6] E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt, New York, 1959, p. 483.

[7] C. W. Shoppee, R. J. W. Cremlyn, D. E. Evans, and G. H. R. Summers, *J. Chem. Soc.*, 1957, 4364.

probably 3-methylbutyl nitrite and this will be more sterically demanding than water. The C-9 proton in (VII) appears, from models, to be subject to 1,3-diaxial interactions with hydrogen atoms at positions 12, 14, and possibly 7, whereas the protons at C-1 appear to be relatively unhindered. Consequently, increased attack at C-1 and formation of more of the Hofmann product (IV) than in the reaction under protic conditions would be anticipated. 'Back-bone rearranged'[8] products were not detected.

The indicated stereochemistry of the azide (IIe) was assumed by Snatzke and Veithen[2] by analogy with the reported diequatorial opening (in part) of (Ia) with lithium aluminium hydride.[9] The ^1H n.m.r. data for the dihydroxy-azide (IIf) and the acetate (IIe) confirm this stereochemistry, which is also consistent with results of the deamination of the corresponding amine (IIg) described below. In the ^1H n.m.r. spectra of (IIf) and (IIe), the C-3 methine proton signal, at τ 5·8 and 4·8 respectively, has a half-height band width of 7—9 c./sec., which confirms its equatorial conformation and that the A/B-ring junction is *cis*. The C-6 methine proton in (IIf) and (IIe) is axial, since the signal at τ 6·4 has a half-height band width of *ca.* 20 c./sec. Reduction of the dihydroxy-azide (IIf) with hydrazine hydrate and Raney nickel gave the amine (IIg), and deamination of this in aqueous acetic acid gave the anticipated A-homo-B-norketol (VIIIa). The ketol is assigned a *cis*-A/B-ring junction since it gives a positive c.d. curve and is closely analogous to the ketone (IX) which gives a positive Cotton effect.[10] The migration of the C(5)–C(10) bond in the deamination is forseeable, since it has the required antiperiplanar conformation with the departing equatorial diazonium group.[11] Oxidation of (VIIIa) with Jones reagent[12] gave the β-diketone (VIIIb) which in alkaline solution showed an intense u.v. absorption: $\lambda_{max.}$ 294 mμ (ε 20,800). In neutral solution only a weak absorption was evident; these data compare well with those reported[13] for the compound (X).

Oxidation of the diol (IIf) with Jones reagent[12] gave the ketol (IIh). Attempted retroaldolisation of this gave, surprisingly, cholest-4-ene-3,6-dione (XI).[14] T.l.c. indicates that (XI) is formed (along with other unidentified materials) by rearrangement of an initial labile compound, at present unknown. The i.r. spectrum, indicates that the azide group is removed in the treatment with base. The mechanism of this reaction is being further investigated.

EXPERIMENTAL

Solutions were dried over anhydrous sodium sulphate. Column chromatography was carried out with deactivated (grade III) Camag or Weolm neutral alumina. Merck Kieselgel P_{254} silica gel was used for preparative t.l.c. Light petroleum refers to the fraction b.p. 40—60°.

I.r. spectra were determined with Perkin-Elmer 237 and 257 spectrophotometers. U.v. spectra were determined for solutions in ethanol with a Unicam SP 800 spectrophotometer and ^1H n.m.r. spectra were determined (for solutions in carbon tetrachloride unless otherwise specified) at 60 Mc./sec. with a Perkin-Elmer R10 spectrometer. Rotations were measured at 22° with a Bendix polarimeter 143C for solutions in chloroform.

Azides (IIa) and (IIf).[2,4]—The epoxide (Ia)[5] (2 g.) and sodium azide (6 g.) in dimethyl sulphoxide (200 ml.) containing a few drops of 98% sulphuric acid were heated for 48 hr. on a steam-bath. The mixture was poured into brine and extracted with chloroform; the extract was dried and gave a colourless oil. Chromatography of this with light petroleum as eluant gave a mixture of azide (IIe) and epoxide (Ia) (1·1 g.). Elution with 5% ether–light petroleum gave a mixture of the azide (IIa) and the hydrolysis product (IIf). Preparative t.l.c. of the latter mixture on silver nitrate-impregnated silica (10%) gave the azide (IIa) (647 mg.), m.p. 184—188° (lit.,[2] 188°), $\nu_{max.}$ 3350 (OH), 2090 (N_3), and 1740 and 1710 (C=O, partially hydrogen bonded) cm.$^{-1}$, τ 4·7—5·3 (m, AcO·C*H*), 6·1—6·4 (m HO·C*H*), 8·0 (s, AcO), 8·84 (s, 19-Me), and 9·35 (s, 18-Me), and the *azide* (IIf) (227 mg.), m.p. 126—128° $[\alpha]_D$ +40°, $\nu_{max.}$ 3440 (OH) and 2090 (N_3) cm.$^{-1}$, τ 5·7—5·9 (m HO·C*H*), 6·2—6·7 (m, N_3C*H*), 9·1 (s, 19-Me), and 9·35 (s, 18-Me) (Found: C, 72·85; H, 10·35; N, 9·2. $C_{27}H_{47}N_3O_2$ requires C, 72·75; H, 10·65; N 9·45%).

The mixture of (Ia) and (IIe) was heated under reflux in 10% aqueous methanolic potassium hydroxide for 15 min., poured into water, and extracted with ether. The crude product was chromatographed; elution with 20% ether–light petroleum gave the azide (IIf) (700 mg.), m.p. 125—126° (see above). Elution with 40% ether–light petroleum gave the epoxide (Ib) (200 mg.), m.p. 128—130° (lit.,[5] 132°).

Azides (IIb) *and* (IIe).—The appropriate azide was treated with an excess of acetic anhydride in pyridine at room temperature overnight. The solution was poured into cold water, set aside for a few min., and extracted. The extract was washed successively with water, sodium hydrogen carbonate solution until neutral, and finally water, and dried. Removal of the solvent left the crude acetate which was crystallised from methanol.

(*a*) Azide (IIa) (640 mg.) gave azide (IIb) (540 mg.), m.p. 146—148° $[\alpha]_D$ −73° (lit.,[4] m.p. 146°, $[\alpha]_D$ −70°), $\nu_{max.}$ 2095 (N_3) and 1740 (AcO) cm.$^{-1}$, τ 4·8—5·3(m, 2 AcO·C*H*), 7·96 and 8·05 (each s, AcO), 8·86 (s, 19-Me), and 9·34 (s, 18-Me).

(*b*) Azide (IIf) (700 mg.) gave azide (IIe) (630 mg.), m.p. 115—116°, $[\alpha]_D$ +41° (lit.,[2] m.p. 112—115°, $[\alpha]_D$ +40·5°), $\nu_{max.}$ 3600 (OH), 2100 (N_3), and 1740 (AcO) cm.$^{-1}$, τ 4·7—4·9 (m, AcO·C*H*), 6·2—6·6 (m, C*H*·N_3), 7·92 (s, AcO), 9·06 (s, 19-Me), and 9·35 (s, 18-Me).

Amines (IIc) *and* (IIg).—To the azide in ethanol was added hydrazine hydrate (1 ml. per 300 mg. of azide) and a little Raney nickel. The mixture was heated under reflux for 15 min. ether was added, and the solution was

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[8] J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1966, **22**, 3195.

[9] Pl. A. Plattner, H. Heusser, and M. Feurer, *Helv. Chim. Acta*, 1949, **32**, 587.

[10] T. G. Halsall, Sir Ewart R. H. Jones, E. L. Tan, and (in part) G. R. Chaudhry, *J. Chem. Soc.* (*C*), 1966, 1374.

[11] Cf. the deamination of D-homo-hydroxy-amino-steroids: W. Klyne and C. W. Shoppee, *Chem. and Ind.*, 1952, 470; R. J. W. Cremlyn, D. L. Garmaise, and C. W. Shoppee, *J. Chem. Soc.*, 1953, 1847.

[12] C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

[13] J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1966, **22**, 1421.

[14] Ref. 5(*b*), p. 44.

set aside until gas evolution ceased. It was then washed with water and dried, and the solvent was removed to leave the crude amine which was purified by t.l.c. and crystallised from methanol.

(*a*) Azide (IIb) (600 mg.) gave the amine (IIc) (500 mg.), m.p. 141—142°, $[\alpha]_D$ −32° (lit.,[2] m.p. 142—145°, $[\alpha]_D$ −36·8°), $\nu_{max.}$ 3310 and 3390 (NH_2), 1740 (AcO), and 1610 (NH_3) cm.$^{-1}$, τ 4·5—5·2 and 5·3—5·6 (each m, AcO·C*H*), 7·99 and 8·07 (each s, AcO), 8·86 (s, 19-Me), and 9·32 (s, 18-Me).

(*b*) Azide (IIf) (200 mg.) gave the *amine* (IIg) (180 mg.), m.p. 141—143°, $[\alpha]_D$ +33°, $\nu_{max.}$ 3400br (OH and NH_2) cm.$^{-1}$, τ ($CDCl_3$) 5·8—6·1 (m, C*H*·OH), 7·0—7·4 (m, C*H*·NH_2), 9·1 (s, 19-Me), and 9·35 (s, 18-Me) (Found: C, 76·95; H, 11·85; N, 3·5. $C_{27}H_{49}NO_2$ requires C, 77·25; H, 11·75; N, 3·35%).

Aprotic Deamination of the Amine (IIc).—Dry hydrogen chloride was bubbled briefly through a solution of the amine (IIc) (150 mg.) in dry ether. The solvent was removed *in vacuo* and the residual hydrochloride was treated in chloroform with an excess of 3-methylbutyl nitrite (5 drops). The solution was set aside at room temperature for 1·5 hr. and then evaporated to dryness *in vacuo*. Preparative t.l.c. gave (III) (59 mg.), m.p. 126—127° (from aqueous acetone), $[\alpha]_D$ +85·5° (lit.,[3] m.p. 127°, $[\alpha]_D$ +84°), $\nu_{max.}$ 1740 (AcO) cm.$^{-1}$, τ 4·8—5·1 and 5·1—5·6 (each m, AcO·C*H*), 8·0 (s, AcO), 8·82 (s, 19-Me), and 9·18 (s, 18-Me), and (IV) (68 mg.), m.p. 81—82° (from methanol), $[\alpha]_D$ −7° (lit.,[3] m.p. 85°, $[\alpha]_D$ −10°) $\nu_{max.}$ 1740 (AcO) cm.$^{-1}$, τ 4·5—4·8 (m, C*H*:C), 4·8—5·6 (m, 2AcO·C*H*), 7·99 and 8·02 (each s, AcO), 8·80 (s, 19-Me), and 9·33 (s, 18-Me).

Deamination of the Amine (IIg).—The amine (IIg) (500 mg.) in 80% aqueous acetic acid (50 ml.) at 10° was treated with concentrated sodium nitrite solution (containing 2 g.). After 1 hr., the solution was poured into water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution until neutral, and then water, and finally dried. Removal of the solvent left an oil (400 mg.) which after preparative t.l.c. gave the A-*homo*-B-*nor-ketol* (VIIIa) (220 mg.), m.p. 148° (from methanol) $[\alpha]_D$ +21°, $\nu_{max.}$ 3400 (OH) and 1695 (C=O) cm.$^{-1}$, τ 6·1—6·6 (m, C*H*·OH), 7·2—7·6 (m, C*H*$_2$·CO·C*H*), 8·85 (s, 19-Me), and 9·35 (s, 18-Me), c.d. (cyclohexane) $\lambda_{max.}$ 293, 298, and 307 mμ, Δε +1·40, +1·55, and +1·39 (Found: C, 80·85; H, 11·35. $C_{27}H_{46}O_2$ requires C, 80·55; H, 11·5%).

Ketol (IIh) *and Diketone* (VIIIb).—The appropriate alcohol was treated in AnalaR acetone at 20° with an excess of chromic acid solution [chromium trioxide (6·25 g.) in 20% sulphuric acid (25 ml.) [12]] for 15 min. The solution was diluted with water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution until neutral and then with water, and dried. The solvent was removed to leave the crude ketone which was crystallised.

(*a*) The azide (IIf) (260 mg.) gave the *ketol* (IIh) (250 mg.), m.p. 182—184° (decomp.) (from methanol), $[\alpha]_D$ +84°, $\nu_{max.}$ 3490 (OH), 2100 (N_3), and 1720 (C=O) cm.$^{-1}$, τ ($CDCl_3$) 6·1—6·5 (m, N_3C*H*), 8·97 (s, 19-Me), and 9·28 (s, 18-Me) (Found: C, 73·15; H, 10·0; N, 9·45. $C_{27}H_{45}N_3O_2$ requires C, 73·1; H, 10·2; N, 9·45%).

(*b*) The ketol (VIIIa) (25 mg.) gave the *diketone* (VIIIb) (22 mg.), m.p. 138—139° (from aqueous acetone), $\nu_{max.}$ 1695 (C=O) cm.$^{-1}$, τ 6·4—6·8 (m, CO·C*H*$_2$·CO), 8·99 (s, 19-Me), and 9·35 (s, 18-Me), $\lambda_{max.}$ (KOH–EtOH) 294 mμ (ε 20,800) (Found: C, 81·05; H, 11·25. $C_{27}H_{44}O_2$ requires C, 80·95; H, 11·05%).

Attempted Retroaldolisation of the Ketol (IIh).—The ketol (IIh) (150 mg.) was heated under reflux in methanolic potassium hydroxide (150 mg. in 25 ml.) for 0·5 hr. The solution was poured into water and extracted with ether–chloroform (1 : 1). The extract was dried and filtered through a small quantity of alumina. Removal of the solvent left a product (120 mg.) which showed no azide absorption in the i.r. spectrum. Attempted purification by preparative t.l.c. gave the ketone (XI), m.p. 122—123° (from methanol), $[\alpha]_D$ −41°, $\lambda_{max.}$ 253 mμ (ε 10,500) {lit.,[14] m.p. 125°, $[\alpha]_D$ −40°, $\lambda_{max.}$ 254 mμ (ε 11,200)}, $\nu_{max.}$ 1690 (C:C·C:O) and 1600 (C:C) cm.$^{-1}$, τ 3·95 (s, C*H*:C), 8·8 (s, 19-Me), and 9·25 (s, 18-Me).

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