Steroids. Part XIX.[1] Westphalen Rearrangement of 6β-Azido- and 6β-Cyano-5α-hydroxy-steroids. Neighbouring Group Participation by the Azido-group

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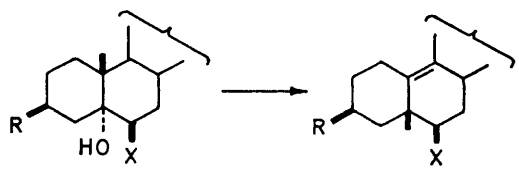
The 6β-azido-5α-hydroxy-compound (3) and the 6β-cyano-5α-hydroxy-compound (4) rearrange to Δ^9-compounds. The major product from the azido-compound (3) is 3β,5-diacetoxy-6β-azido-5α-cholestane (11), indicating significant neighbouring group participation by the azido-group. The effect of the 6β-cyano-group on reaction rate is comparable to that of a 6β-fluoro-substituent.

THE Westphalen rearrangement of 5α-hydroxy-6β-substituted steroids (1) to the Δ^9-compounds (2), in H_2SO_4–Ac_2O–AcOH, is well known.[2] The rearrangement proceeds most efficiently when the substituent X is electronegative and relatively inefficient as a participating neighbouring group (*e.g.* X = F). It was of interest to compare the efficiency of the azido-group and the cyano-group in promoting the Westphalen rearrangement. Both are electronegative,[3] but some differences in their abilities to participate as neighbouring groups would be anticipated. A number of examples of neighbouring group effects are claimed for the azido-group,[4] though the generality of this has been questioned.[5] We know of no similar vicinal effects with nitriles, although some intramolecular Ritter reactions have been reported.[6] We find that the 6β-azido-5α-hydroxy-compound (3)[7] rearranges to the Δ^9-compound (8) in low yield (*ca.* 8%; variable), the major product being the tertiary acetate (11) (36%), whereas the 6β-cyano-5α-hydroxy-compound (4) rearranges smoothly to the Δ^9-compound (9) (41%). Efficient neighbouring group participation by the azido-group is thus indicated. Comparison of the rate of reaction of the 6β-cyano-5α-hydroxy-compound (4) with that for the 6β-acetoxy-5α-hydroxy-compound (6)[2b,8] indicates that the rate-retarding effect of the 6β-cyano-group is comparable to that of a 6β-fluoro-substituent.[2a]

The Δ^9-azido-compound (8) and the diacetate (11) were separated from other minor products by preparative t.l.c. The ^{1}H n.m.r. spectrum of the Δ^9-azido-compound (8) showed characteristic signals[2b]



(1) (2)

at τ 4·9 (m, $W_{\frac{1}{2}}$ 9 Hz, 3-H), 6·67 (q, J_{app} 11 and 5 Hz, 6-H), 8·84 (s, 5β-Me), and 9·17 (s, 13β-Me), and the i.r. spectrum confirmed the retention of the azido-group ($\nu_{max.}$ 2100 cm^{-1}). The ^{1}H n.m.r. spectrum of the diacetate (11) showed important signals at τ 5·31 (m, 6α-H), 7·22 (q, J_{app} 14 and 5 Hz, 4α-H), and 7·94 and 8·04 (s, 3- and 5-OAc). The remarkable deshielding influence of a 5α-acetoxy-group on the 4α- and 6α-protons has been previously noted.[9] A sample of the

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[3] J. E. Huheey, *J. Phys. Chem.*, 1966, **70**, 2086.

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[5] (*a*) G. Swift and D. Swern, *J. Org. Chem.*, 1967, **32**, 511; (*b*) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 1965, 6956.

[6] L. I. Krimen and D. J. Cota, *Org. Reactions*, 1969, **17**, 213.

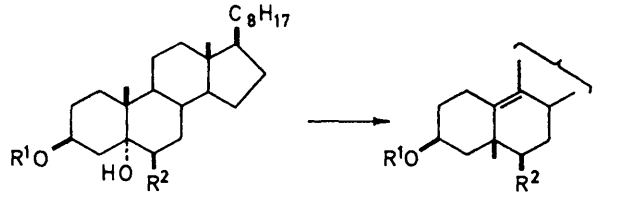
[7] K. Ponsold, *Chem. Ber.*, 1962, **95**, 1727.

[8] J. G. Ll. Jones and B. A. Marples, *J. Chem. Soc.* (*C*), 1971, 572.

[9] C. R. Narayanan and M. R. Sarma, *Tetrahedron Letters*, 1968, 1553.

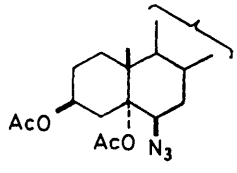
diacetate (11) was prepared, for comparison, by acetylation of the 5α-hydroxy-compound (3) with toluene-*p*-sulphonic acid in acetic acid–acetic anhydride. Basic hydrolysis of the diacetate (11) yielded 5,6α-epoxy-5α-cholestan-3β-ol, affording further evidence in support of the assigned structure.

The 6β-cyano-5α-hydroxy-compound (4) was prepared by the reaction of 5,6α-epoxy-3β-methoxy-5α-cholestane [10] with KCN in dimethyl sulphoxide containing a small quantity of sulphuric acid. Preparative t.l.c. of the reaction mixture from the 6β-cyano-5α-hydroxy-compound (4) afforded the Δ^9-cyano-compound (9) and several minor components. The ^{1}H n.m.r. spectrum of the Δ^9-cyano-compound (9) showed characteristic signals [2b] for the 5β-methyl (τ 8·66) and the 13β-methyl (τ 9·2) groups, and the i.r. spectrum confirmed the presence of the nitrile group ($\nu_{max.}$ 2240 cm^{-1}). Insufficient quantities of the minor components of the reaction mixture were obtained for complete characterisation. However, spectral data suggested they were typical by-products of Westphalen-type rearrangements.

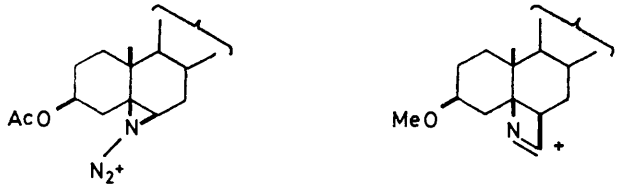


(3) R^1 = Ac, R^2 = N_3
(4) R^1 = Me, R^2 = CN
(5) R^1 = Ac, R^2 = F
(6) R^1 = Me, R^2 = OAc
(7) R^1 = Ac, R^2 = OAc

(8) R^1 = Ac, R^2 = N_3
(9) R^1 = Me, R^2 = CN
(10) R^1 = Ac, R^2 = F



(11)



(12) (13)

The isolation of the diacetate (11) from the reaction of the 6β-azido-5α-hydroxy-compound (3) supports the intermediacy of the *N*-diazonio-aziridine (12). The diacetate (11) would be formed by the preferred diaxial cleavage of the aziridine by acetate ion. We assume that as usual the reaction medium does not bring about simple esterification of the 5α-hydroxy-group. The alternative diequatorial mode of cleavage would lead to a 5β-azido-6α-acetoxy-compound. Isolation of this isomer would provide direct evidence of the intermediate (12); however, we have been unable to detect it.

The relatively efficient rearrangement of the 6β-cyano-5α-hydroxy-compound (4) suggests that the cyano-group does not participate effectively, and that the intermediate (13) is relatively unimportant. The electronegativity [3] and size [11] of the cyano-group are similar to those for a fluorine atom, and it was of interest to compare the effects of 6β-CN and 6β-F on the reaction rate. The rearrangements of 0·01M-solutions of the 6β-cyano-5α-hydroxy-compound (4) in acetic acid, which were 0·05M in sulphuric acid and 0·5M in acetic anhydride, were followed polarimetrically at 25° as originally described by Kirk and Hartshorn.[2a,b] Guggenheim plots afforded a first-order rate constant of $4{\cdot}3 \times 10^{-4}$ s^{-1}. Under the same conditions, the first-order rate constant for the 6β-acetoxy-5α-hydroxy-3β-methoxy-compound (6) was $5{\cdot}4 \times 10^{-3}$ s^{-1}. This value compares well with those previously determined.[2b,8] The ratio of the rates of compounds (4) and (6) is thus 1 : 12·6 and this compares well with that for the 6β-fluoro-compound (5) and the 6β-acetoxy-compound (7) (1 : 10).[2a] The considerably lower yield of the Δ^9-cyano-compound (9) relative to that of the Δ^9-fluoro-compound (10) (81%) [2a] obtained from the compound (5), may be, in part, a result of the presence of the 3β-methoxy- rather than the 3β-acetoxy-substituent.[2b]

EXPERIMENTAL

Solutions were dried over anhydrous sodium sulphate and solvents were removed *in vacuo* on a rotary evaporator. Plates (1 m × 0·5 mm thick) of Kieselgel PF 254 (Merck) were used for preparative t.l.c. Camag deactivated (Grade III) neutral alumina was used for column chromatography.

I.r. spectra were determined with Perkin-Elmer 237 and 257 spectrophotometers. ^{1}H N.m.r. spectra were determined at 60 and 90 MHz with Perkin-Elmer R10 and R32 spectrometers, and mass spectra were recorded with an A.E.I. MS 902 spectrometer. Rotations were measured for solutions in chloroform with a Bendix polarimeter 143C.

Rearrangement of 6β-Azido-5α-hydroxycholestan-3β-yl Acetate (3).—A solution of sulphuric acid in acetic acid (0·25M; 5 ml) was added to a solution of the azido-hydroxy-compound (3) (510 mg) in acetic acid (20 ml) and acetic anhydride (3 ml). After 1 h, the solution was poured into water, and after 30 min was extracted (×3) with ether. The extracts were washed free of acid with sodium hydrogen carbonate solution, dried, and evaporated to give a green-yellow oil (500 mg). Preparative t.l.c. [2 elutions with ether–petroleum (b.p. 40—60°) (1 : 5)], gave 6β-*azido-5-methyl-19-nor-5β-cholest-9-en-3β-yl acetate* (8) (40 mg), m.p. 73—75° (from methanol–acetone), $[\alpha]_D$ +129° (*c* 1·8),

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[11] J. A. Hirsch, *Topics Stereochem.*, 1967, **1**, 199.

$\nu_{max.}$ (mull) 2100 (N_3) and 1745 (acetate) cm^{-1}, τ ($CDCl_3$) 4·9 (m, $W_{\frac{1}{2}}$ 9 Hz, 3-H), 6·67 (q, J_{app} 11 and 5 Hz, 6-H), 7·92 (s, OAc), 8·84 (s, 5β-Me), 9·08 (d, 20-Me), 9·12 (d, 25-Me_2), and 9·17 (s, 13β-Me) [Found: $M^{+\cdot}$, 469 (detectable at low source temperature); $(M - N_2)^{+\cdot}$, 441·3605. $C_{29}H_{47}N_3O_2$ requires 469 and 441·3607]; and 6β-*azido*-5α-*cholestane*-3β,5-*diyl diacetate* (11) (200 mg), m.p. 128—129° (from aqueous methanol–acetone), $[\alpha]_D$ −60° (*c* 0·8), $\nu_{max.}$ (mull) 2100 (N_3) and 1745 (acetate) cm^{-1} τ (CCl_4) 5·1—5·6 (m, 3α-H), 5·31 (m, 6α-H), 7·22 (q, J_{app} 14 and 5 Hz, 4α-H), 7·94 (s, 3-OAc), 8·04 (s, 5-OAc), 5·82 (s, 10β-Me), 9·12 (d, side chain methyls), and 9·3 (s, 13β-Me) (Found: C, 70·0; H, 10·0; N, 8·1. $C_{31}H_{51}N_3O_4$ requires C, 70·3; H, 9·7; N, 7·95%).

Hydrolysis of the Azido-diacetate (11).—A solution of the diacetate (11) (200 mg) in aqueous ethanolic KOH (1%) was heated under reflux for 3 h. Dilution with water and extraction with ether afforded 5,6α-epoxy-5α-cholestan-3β-ol (110 mg), m.p. 141—143° (from methanol), $[\alpha]_D$ −45° (*c* 0·8) (lit.,[12] m.p. 142°, $[\alpha]_D$ −46°).

Acetylation of 6β-*Azido*-5α-*hydroxycholestan*-3β-*yl Acetate* (3).—A solution of the tertiary alcohol (3) (55 mg) in acetic anhydride (5 ml) containing a catalytic amount of toluene-*p*-sulphonic acid was heated at 100° for ½ h. The solution was poured onto crushed ice, allowed to warm to room temperature, and extracted with ether (×3). The extracts were washed free of acid with sodium hydrogen carbonate solution. Evaporation, and crystallisation of the residue from aqueous methanol–acetone, gave the diacetate (11) (40 mg), m.p. 128—129°.

5-*Hydroxy*-3β-*methoxy*-5α-*cholestane*-6β-*carbonitrile* (4).—Concentrated sulphuric acid (2 drops) was added at 2 h intervals, over a period of 72 h, to a stirred solution of 5,6α-epoxy-3β-methoxy-5α-cholestane (4·4 g) and potassium cyanide (10 g) in dimethyl sulphoxide (180 ml) at 80°. The mixture was cooled, poured into water, and extracted with ether. The extracts were washed with water and evaporated to give an oil which was chromatographed on an alumina column. Elution with toluene–ethyl acetate (19 : 1, 9 : 1, 4 : 1) gave the 5α,6α-epoxide (0·9 g) and the 6β-*cyano*-5α-*hydroxy-compound* (4) (3·16 g), m.p. 164—166° (from methanol), $[\alpha]_D$ −17° (*c* 1·4) $\nu_{max.}$ (mull) 3340 (OH) and 2230 (CN) cm^{-1}, τ (CCl_4) 6·3—6·9 (m, 3-H), 6·72 (s, MeO), 7·5 (m, 6-H), 8·76 (s, 10β-Me), 9·12 (d, side chain methyls), and 9·27 (s, 13β-Me) (Found: C, 78·4; H, 10·8. $C_{29}H_{49}NO_2$ requires C, 78·5; H, 11·15%).

Rearrangement of 5-*Hydroxy*-3β-*methoxy*-5α-*cholestane*-6β-*carbonitrile* (4).—A solution of sulphuric acid in acetic acid (0·25M; 10 ml) was added to a solution of the cyano-hydroxy-compound (4) (1·0 g) in acetic acid (40 ml) and acetic anhydride (5 ml). After ½ h, the product was worked-up as above (yield 860 mg). Preparative t.l.c. [2 elutions with ether–petroleum (b.p. 40—60°) (1 : 8)] gave 3β-*methoxy*-5-*methyl*-19-*nor*-5β-*cholest*-9-*ene*-6β-*carbonitrile* (9) (395 mg), m.p. 52—54° (from methanol), $[\alpha]_D$ +109° (*c* 0·9), $\nu_{max.}$ (mull) 2240 cm^{-1} (CN), τ (CCl_4) 6·4—6·7 (m, 3-H), 6·70 (s, MeO), 8·66 (s, 5β-Me), 9·14 (d, side chain methyls), and 9·20 (s, 13β-Me) (Found: C, 81·4; H, 11·3; N, 3·6. $C_{29}H_{47}NO$ requires C, 81·8; H, 11·1; N, 3·3%), and other minor products.

Kinetic Runs.—The reactions were followed polarimetrically at 589 nm as described before [8] by use essentially of the techniques of Kirk and Hartshorn and their co-workers.[2a,b]

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