Steroids and Walden Inversion. Part LXVII.[1] Substitution Reactions of the 19-Nor-5α-cholestan-2-ols

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19-Nor-5α-cholestan-2α-ol and phosphorus pentachloride give with inversion of configuration 2β-chloro-19-nor-5α-cholestane (90%) together with 2α-chloro-19-nor-5α-cholestane (<10%). 19-Nor-5α-cholestan-2β-ol and phosphorus pentachloride give with inversion of configuration 2α-chloro-19-nor-5α-cholestane (70%) and considerable amounts of olefin(s) (30%). The results obtained by use of thionyl chloride at 20° show predominant retention for the 19-nor-2α-ol, but predominant inversion for the 19-nor-2β-ol.

In Part LXV,[2] the stereochemical course of the replacement of a hydroxy-group by chlorine at position 2 in the 5α-cholestane series was recorded. We now report the results of a parallel study in the 19-nor-5α-cholestane series.

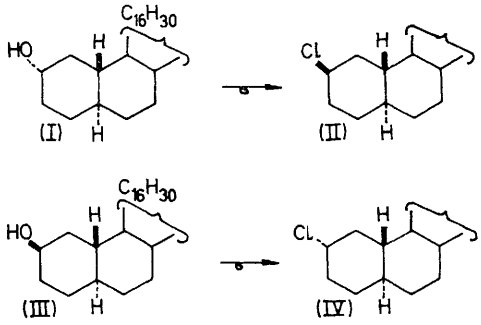
19-Nor-5α-cholestan-2α-ol [3] (I; OH*eq*) with phosphorus pentachloride in chloroform at 20° gave with inversion of configuration 2β-chloro-19-nor 5α-cholestane (90%) (II;

[1] Part LXVI, C. W. Shoppee and B. C. Newman, *J. Chem. Soc.* (*C*), 1969, 2767.

[2] C. W. Shoppee, T. E. Bellas, and R. E. Lack, *J. Chem. Soc.*, 1965, 6450.

[3] C. W. Shoppee, J. C. Coll, and R. E. Lack, *J. Chem. Soc.* (*C*), in the press.

Cl*ax*); the structure of the product was confirmed by its i.r. [$\nu_{max.}$ 720 cm.$^{-1}$ (*cf.* ref. 4)] and n.m.r. spectra [τ 5·42 (narrow m, W_H 8 c./sec., 2α-H*eq*)] (*cf.* ref. 5). G.l.c. of the product disclosed the production with retention of configuration of 2α-chloro-19-nor-5α-cholestane (<10%) (IV; Cl*eq*).



19-Nor-5α-cholestan-2β-ol[3] (III; OH*ax*) with phosphorus pentachloride in chloroform at 20° gave with inversion of configuration 2α-chloro-19-nor-5α-cholestane (70%) (IV; Cl*eq*), with a considerable amount of 19-nor-5α-cholest-1- and/or -2-ene. The structure (IV) is confirmed by the i.r. [$\nu_{max.}$ 795 and 750 cm.$^{-1}$ (*cf.* ref. 4)] and n.m.r. spectra [τ 6·2br (m, W_H 30 c./sec., 2β-H*ax*)] (*cf.* ref. 5).

The 19-nor-2α-ol (I) reacted incompletely with thionyl chloride in benzene at 20° to yield the 2α-chloride (IV) and the 2β-chloride (II), in the ratio of 3 : 1 (*i.e.* with predominant retention), and 19-nor-5α-cholestan-2α-yl sulphite, $\nu_{max.}$ 1200 and 758 cm.$^{-1}$, hydrolysed by methanolic potassium hydroxide to the parent alcohol (I). In benzene at 80° reaction was complete to yield the 2α-chloride (IV) and the 2β-chloride (II) in the ratio of 58 : 42 (*i.e.* essentially with racemisation); no starting material (I), 2α-yl sulphite, or olefin(s) could be detected in the product by t.l.c.

The 19-nor-2β-ol (III) reacted incompletely with thionyl chloride (used as both reagent and reaction medium) at 20° to furnish the 2β-chloride (II) and the 2α-chloride (IV) in the ratio of 38 : 62 (*i.e.* with predominant inversion), 19-nor-5α-cholestan-2β-yl sulphite, $\nu_{max.}$ 1400, 1200, and 758 cm.$^{-1}$, and 19-nor-5α-cholest-1- and/or -2-ene, τ 9·33 (13β-Me) and 4·35 (vinyl protons).

Replacement of the hydroxy-group in a series of saturated secondary equatorial steroid alcohols, *viz.* 5α-cholestan-6α-ol,[6] 3β-acetoxy-,[7] 3α-acetoxy-,[7] and 3β-chloro-5α-cholestan-6α-ol,[7] 5α-cholestan-4α-ol,[8] and 5α-cholestan-2α-ol,[2] by chlorine, with phosphorus pentachloride, takes place with exclusive or predominant retention of configuration. This unusual stereochemical pattern, also observed in part when thionyl chloride is used, has been attributed[6] to molecular congestion at the seat of substitution leading to suppression of the S_N2 mechanism in favour of the S_Ni mechanism. Such molecular congestion at steroid nuclear positions should decrease in the order 11 > 6 > 4 > 2; ring B (doubly locked by *trans* fusions with rings A and C) is of fixed conformation, whereas ring A possesses some degree of conformational flexibility which is less marked at position 4 (adjacent to a bridgehead) than at position 2 (capable of partial conformational inversion to produce a boat-form with 'ends' at positions 2 and 5).

In brief, substitution with retention of configuration should effectively be complete at position 6, nearly complete at position 4, and markedly less complete at position 2. When phosphorus pentachloride is used as the substituting agent, the ratios of epimeric chlorides formed are 6α-Cl to 6β-Cl, 100 : 0 (ref. 6); 4α-Cl to 4β-Cl, 97 : 3 (ref. 8); and 2α-Cl to 2β-Cl, 67 : 33 (ref. 2). When thionyl chloride is used as the substituting agent, retention of configuration is a marked feature but only the 6α-chloride (90% yield),[6] the 4α-chloride,[8] and the 2α-chloride (66% yield)[2] were isolated; the situation is less clear than with phosphorous pentachloride because of increasing production of olefin(s), and partial diversion of the starting alcohol to the sulphite.

The principal contributor to steric hindrance at position 2 is the axial 10β-methyl group; its replacement by an axial 10β-hydrogen atom should permit the S_N2 mechanism, normally associated with substitution of the hydroxy-group by chlorine in saturated secondary alcohols with phosphorus pentachloride,[9] to operate and to lead to complete or predominant inversion of configuration. This is the pattern now observed for the reactions of the 19-nor-5α-cholestan-2-ols (I) and (III) with phosphorus pentachloride.

Mechanistic interpretation of the reactions of the 19-nor-5α-cholestan-2-ols with thionyl chloride is more difficult. The 19-nor-2α-ol (I) exhibits substitution with retention (75%, S_Ni) and substitution with inversion (25%, S_N2); these figures could alternatively imply substitution with retention (50%, S_Ni) and substitution with racemisation (25%, S_N1), but this interpretation seems improbable because no olefin is formed. The 19-nor-2β-ol (III) displays substitution with retention (38%, S_Ni) and substitution with inversion (62%, S_N2); this result cannot be interpreted as substitution with racemisation (62%, S_N1 !) although *ca.* 5% of olefin is produced, because more than 50% racemisation is impossible, and appears to reflect the decreased steric hindrance by the 10β-hydrogen atom at position 2 (β-face).

EXPERIMENTAL

For general directions see *J. Chem. Soc.*, 1959, 345.

I.r. spectra were determined for solutions in carbon disulphide with a Perkin-Elmer 221 spectrophotometer.

[4] D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J. Chem. Soc.*, 1956, 331.
[5] A. Hassner and C. Heathcock, *J. Org. Chem.*, 1964, **29**, 1350.
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[7] C. W. Shoppee, R. E. Lack, and B. McLean, *J. Chem. Soc.*, 1964, 4996.
[8] C. W. Shoppee, R. E. Lack, and S. C. Sharma, *J. Chem. Soc.* (*C*), 1968, 2083.
[9] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Bell and Sons Ltd., London, 1953, 392.

N.m.r. spectra were measured for solutions in deuteriochloroform with Varian A60 and HA100 instruments, with tetramethylsilane as internal reference. Mass spectra were measured with an MS9 double-focusing spectrometer. Thionyl chloride was twice distilled (b.p. 77—78°); phosphorus pentachloride was freshly sublimed before use. T.l.c. was carried out on silica (Davison; 100—200 mesh); for preparative t.l.c. plates were sprayed with berberine hydrochloride (1% solution in methanol) and examined in u.v. light. G.l.c. was performed on an F and M 400 machine, fitted with a disc integrator, by use of a column [1·75 m. × 3 mm. (internal diam.)] packed with 1% silicone rubber (nitrile) XE60 on acid-washed 100—140 mesh silanised Gas Chrom P at 218°, with helium as the carrier gas at a flow rate of 60 ml./min.

2α-*Chloro- and* 2β-*Chloro*-19-*nor*-5α-*cholestane*, (II) *and* (IV).—(*a*) 19-Nor-5α-cholestan-2α-ol (I) (m.p. 165—167°; 15 mg.) in chloroform (0·5 ml.) was treated with phosphorus pentachloride (50 mg.), and the mixture was stirred with a glass rod for 15 min. Quenching with ice and extraction with ether gave 2β-*chloro*-19-*nor*-5α-*cholestane* (II) (12 mg.), m.p. 60—62° (from acetonitrile), $\nu_{max.}$ 720 cm.$^{-1}$, τ 9·34 (13β-Me) and 5·42 (W_H 8 c./sec., 2α-H) [Found: *M* (mass spectrometry), 392·3210. $C_{26}H_{45}Cl$ requires *M*, 392·3210], *m/e* 392 (100%), 356 (10), 252 (25), and 237 (100), isotopic abundances: *M* (100%), *M* + 1 (40), *M* + 2 (50), and *M* + 3 (10). G.l.c. of the reaction product gave the following retention times and composition: 2β-chloro-19-nor-5α-cholestane (90%), 13·6 min.; 2α-chloro-19-nor-5α-cholestane (10%), 15·0 min.

(*b*) 19-Nor-5α-cholestan-2β-ol (III) (m.p. 135—137°; 15 mg.) in chloroform was treated with phosphorus pentachloride (50 mg.) as in (*a*). The product was placed on a t.l.c. silica plate and run in hexane; repeated extraction of the upper band with ether afforded a mixture of 19-nor-5α-cholest-1- and 2-enes (4 mg.), τ 9·33 (13β-Me) and 4·36 (2 vinyl protons); repeated extraction of the lower band with ether gave 2α-*chloro*-19-*nor*-5α-*cholestane* (IV) (9 mg.), m.p. 78—80° (from acetonitrile), $\nu_{max.}$ 795 and 750 cm.$^{-1}$, τ 9·38 (13β-Me) and 6·2 (W_H 30 c./sec., 2β-H) [Found: *M* (mass spectrometry), 392·3213. $C_{26}H_{45}Cl$ requires *M*, 392·3210], *m/e* 392 (100%), 356 (10), and 237 (20), isotopic abundances: *M* (100%), *M* + 1 (40), *M* + 2 (50), and *M* + 3 (10). The reaction product had a retention time of 15·0 min. on g.l.c., which showed the presence of no other compounds.

(*c*) The 2α-ol (I) (10 mg.) in benzene (1 ml.) was added with stirring to thionyl chloride (1 ml.) at 0° and the mixture was kept at 20° overnight. Addition of ice–water and extraction with ether furnished the product, which was adsorbed on a preparative t.l.c. silica plate, and run in pentane. The mixed epimeric chlorides, (II) and (IV) (2·5 mg.) were removed by repeated extraction of the upper band with ether ($\nu_{max.}$ 795, 750, and 720 cm.$^{-1}$), and the mixture was shown by g.l.c. to contain the 2α-chloride (IV) (ret. time 15 min.; 75%) and the 2β-chloride (II) (ret. time 13·6 min.; 25%). The plate was then re-run twice in benzene; by this device 19-nor-5α-cholestan-2α-yl sulphite (2·5 mg.), $\nu_{max.}$ 1200 (RO–SO–OR) and 758 cm.$^{-1}$ (yielding by hydrolysis with methanolic 2N-potassium hydroxide 19-nor-5α-cholestan-2α-ol, identified by t.l.c.) was separated from unchanged 19-nor-5α-cholestan-2α-ol (3·5 mg.) (bands extracted with ether).

(*d*) The 2α-ol (I) (10 mg.) in benzene (1 ml.) was added with stirring to refluxing thionyl chloride (2 ml.) during 5 min. and the mixture was refluxed for 1 hr. The procedure described in (*c*) gave the epimeric chlorides, (II) and (IV) (6 mg.), ($\nu_{max.}$ 795, 750, and 720 cm.$^{-1}$), shown by g.l.c. to contain the 2α-chloride (IV) (ret. time 15 min.; 58%) and the 2β-chloride (II) (ret. time 13·6 min.; 42%); no 2α-yl sulphite, olefin(s), or unchanged 2α-ol was detected by t.l.c.

(*e*) The 2β-ol (III) (30 mg.) was treated with thionyl chloride (1 ml.) at 20° for 1 hr. After addition of ice–water and extraction with ether, the procedure described in (*c*) yielded (i) 19-nor-5α-cholest-1- and/or -2-ene (1 mg.), τ (micro-cell, 100 Mc. instrument) 9·33 (13β-Me) and 4·35 (2 vinyl H); (ii) a mixture of the epimeric chlorides (II) and (IV) (7 mg.), $\nu_{max.}$ 795, 750, and 720 cm.$^{-1}$, containing (g.l.c.) the 2α-chloride (IV) (ret. time 15 min.; 62%) and the 2β-chloride (II) (ret. time 13·6 min.; 38%); (iii) 19-nor-5α-cholestan-2β-yl sulphite (2 mg.), $\nu_{max.}$ 1400, 1200 (RO–SO–OR), and 758 cm.$^{-1}$; and (iv) unchanged 2β-ol (10 mg.), identified by t.l.c.

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