Steroids and Walden Inversion. Part LXIX.[1] Substitution Reactions of the 5α-Androstan-11-ols

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5α-Androstan-11α-ol (IV) on treatment with phosphorus pentachloride does not undergo substitution; elimination occurs instead to give 5α-androst-9(11)-ene and its chlorine addition product 9α,11β-dichloro-5α-androstane. However treatment of the alcohol (IV) with thionyl chloride results in substitution with retention of configuration to give 11α-chloro-5α-androstane (40%) and 5α-androst-9(11)-ene (22%). Treatment of 5α-androstan-11β-ol with phosphorus pentachloride or with thionyl chloride yields only 5α-androst-9(11)-ene.

It has been shown previously that a series of saturated secondary equatorial steroid alcohols, *viz.* 5α-cholestan-6α-ol,[2] 3β-acetoxy-,[3] 3α-acetoxy-,[3] and 3β-chloro-5α-cholestan-6α-ol,[3] 5α-cholestan-4α-ol,[4] and 5α-cholestan-2α-ol[5] undergo substitution on treatment with phosphorus pentachloride with exclusive or predominant retention of configuration. This unique stereochemical pattern, also observed in part when thionyl chloride (in the absence of tertiary bases) is used as the substituting agent, has been attributed to molecular congestion at the seat of substitution.[2] Ingold's S_N2 Rule: 'Substitution by mechanism S_N2 involves inversion of configuration, independently of all constitutional details'[6] is universally true. Violation of the S_N2 Rule is avoided by change from mechanism S_N2 to mechanism S_Ni, which is believed to be immune from steric retardation, and which leads to substitution with retention of configuration. Molecular congestion at steroid nuclear positions should decrease in the order position 11 > 6 > 4 > 2; we have therefore investigated the reactions of the 5α-androstan-11-ols with phosphorus pentachloride and with thionyl chloride.

Androst-4-ene-3,11,17-trione (adrenosterone)[7-9] (I), from cortisone, was hydrogenated over palladium–calcium carbonate in ethanol to give a quantitative yield of 5α-androstane-3,11,17-trione[7,9,10] (II). Use of palladium–charcoal in ethyl acetate, as recommended by Giroud *et al.*,[9] or in ethanol or methanol, gave a complex mixture containing the triketone (II), isolated with difficulty in low yield, and products shown by n.m.r. spectroscopy to be acetals arising from the acidity of the catalyst.

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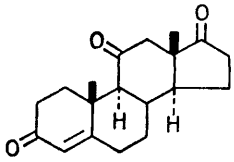
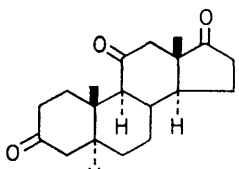
5α-Androstan-11-one [7,9,11,12] (III; R = O) was prepared in 60% yield from the 3,11,17-triketone (II) by conversion into the 3,3:17,17-bisthioacetal and desulphurisation with nickel. Low pressure Wolff-Kishner



(I)



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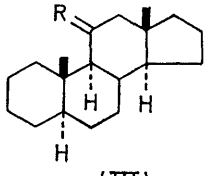


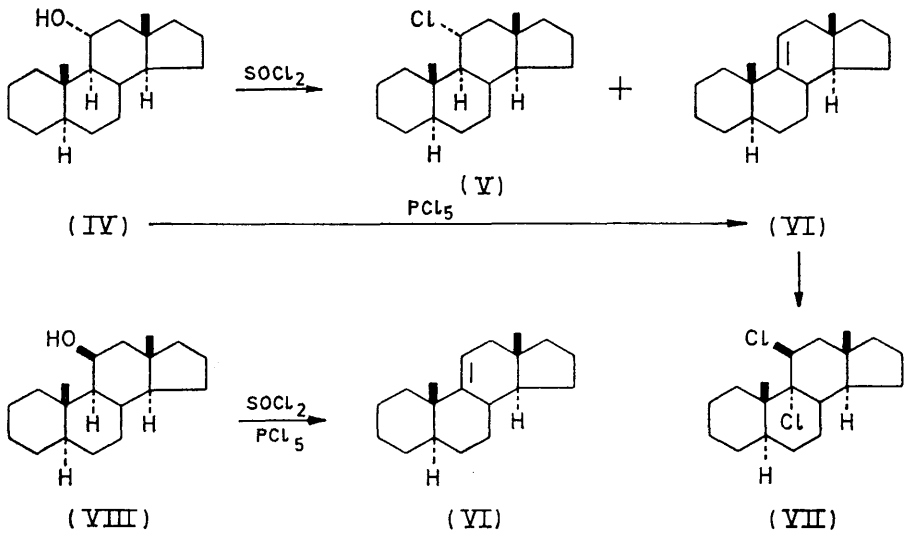
(III)

reduction of the triketone (II), recommended by Giroud *et al.*,[9] did not proceed smoothly; only *ca.* 20% of the required 11-ketone (III; R = O) was isolated and the main product was the 11-hydrazone, isolated as the azine (III; R = N·N=CMe_2) formed by reaction with acetone during work-up. The 11-ketone (III; R = O) was also obtained in 22% yield from the triketone (II) by low pressure Wolff-Kishner reduction of the 3,17-dihydrazone (*cf.* ref. 11). 5α-Androstan-11α-ol [9,12] (IV) was prepared by reduction of the 11-ketone with sodium in refluxing propan-2-ol; 5α-androstan-11β-ol [13] (VIII) was prepared by reduction of the 11-ketone with lithium aluminum hydride in tetrahydrofuran at 20°.

The 11α-ol (IV; OH*eq*), on brief treatment with phosphorus pentachloride in chloroform at 25°, gave a 93% yield of 5α-androst-9(11)-ene (VI), of which 30% had been converted into the 9α,11β-dichloride (VII) by *trans*-diaxial addition of chlorine, derived from the equilibrium [14] $PCl_5 \rightleftharpoons PCl_3 + Cl_2$. Treatment of the 11α-ol (IV; OH*eq*) with thionyl chloride in ether or benzene at 20° afforded only the 9(11)-olefin (VI), but with thionyl chloride alone at 20° furnished 11α-chloro-5α-androstane (V) (40%), $\nu_{max.}$ 750 cm^{-1} (giving on reduction 5α-androstane) and the 9(11)-olefin (VI) (22%).

The 11β-ol (VIII; OH*ax*), on brief treatment with phosphorus pentachloride in chloroform at 25° or with thionyl chloride in ether at 25°, gave only the 9(11)-olefin (VI) (70 and 60% yields, respectively), by *trans*-diaxial elimination.

The 11-position is the most sterically hindered site in the steroid nucleus. Esterification of axial 11β-ols is difficult; [15] however, esterification of equatorial 11α-ols is easy [16] and steric hindrance by 1β-H is minimal. An equatorial 11α-chlorosulphite or 11α-chlorophosphonate should therefore be formed relatively readily and give with retention of configuration an 11α-chloride, whereas the analogous 11β-esters would not be formed and an 11β-ol should (and does) undergo *trans*-diaxial elimination to afford the 9(11)-olefin.[17,18] Equatorial 11α-ols and their esters,[18-20] however, readily undergo *cis*-equatorial–axial elimination to give 9(11)-olefins. The reason for this is not fully understood, but may be



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connected with the conversion of ring C, in a rigid and highly strained chair conformation [21] in structure (IV), into the half-chair conformation [22] in a 9(11)-olefin (VI).*

Failure of the 11α-ol (IV) to give the 11α-chloride (V) on treatment with phosphorus pentachloride was unexpected. Since chlorosulphites have a smaller tendency to ionise than chlorophosphonates, it appears that the 11α-chlorosulphite reacts by internal collapse of a close ion-pair, $\overset{\delta+}{R}|OS\overset{\delta-}{O}Cl$, whereas the 11α-chlorophosphonate reacts to give an open ion-pair, $\overset{+}{R}||\bar{O}PCl_4$, with subsequent loss of a proton from $\overset{+}{R}$, to give the 9(11)-olefin (VI).

EXPERIMENTAL

M.p.s were determined with a Köfler hot-stage apparatus. I.r. spectra (solutions in carbon tetrachloride) were measured with a Perkin-Elmer 221 spectrophotometer. N.m.r. spectra were measured with Varian A60 or HA100 instruments with deuteriochloroform as solvent and tetramethylsilane as internal reference. Mass spectra were measured with an A.E.I. MS9 double-focus spectrometer. Column chromatography was performed on alumina deactivated by washing with 2N-acetic acid or on silica gel (Davison; 100—200 mesh). T.l.c. was carried out on silica plates in benzene; plates were developed by spraying with conc. sulphuric acid and heating. Preparative t.l.c. was carried out on silica plates in ether-hexane (1 : 4); plates were sprayed with berberine hydrochloride solution and examined in u.v. light.

5α-*Androstane*-3,11,17-*trione*.—Adrenosterone (m.p. 220°; 2·0 g) (lit.,[7] 222—224°; lit.,[8] 220°; lit.,[9] 223°) in ethanol was hydrogenated over palladium–calcium carbonate (10%) to give 5α-androstane-3,11,17-trione (2·0 g), m.p. 178—179° (from ether) (lit.,[7] 178—179°; lit.,[9] 175°; lit.,[10] 174—176°; lit.,[11] 178—180°), $\nu_{max.}$ 1740 and 1705 cm^{-1}. The n.m.r. spectrum showed no vinyl proton signal. If palladium–charcoal (10%) in ethanol, methanol, or ethyl acetate was used, the product was a complex mixture containing compounds shown by n.m.r. to be acetals.

3,3:17,17-*Bisethylenedithio*-5α-*androstan*-11-*one*.—5α-Androstane-3,11,17-trione (2 g) in ethanedithiol (8 ml) was treated with boron trifluoride–ether complex (3 ml) at 25° for 4 h. The mixture was poured into water and extracted with dichloromethane to give the *bisthioacetal* (2·2 g, 80%), m.p. 196—198°, $\nu_{max.}$ 1705 cm^{-1} [C(11)=O]; δ 0·89 (3H, s, 18-H_3), 1·02 (3H, s, 19-H_3), and 3·28 (8H, 2 × S[CH_2]$_2$S) (Found: C, 60·7; H, 7·6; S, 27·8%; M^+, 464·1499. $C_{23}H_{34}OS_4$ requires C, 60·75; H, 7·65; S, 28·0%; *M*, 464·1492).

5α-*Androstan*-11-*one*.—(*a*) The bisthioacetal (1 g) in ethanol (180 ml) was heated under reflux with Raney nickel (W6; 15 g) for 3 h. The catalyst was filtered off and the filtrate diluted with water and extracted with ether. The product was chromatographed on alumina in hexane to give 5α-androstan-11-one (500 mg), m.p. 50—51° (after evaporation of an ethereal solution) (lit.,[7] 50—52°; lit.,[9] 49°; lit.,[11] 49—50°; lit.,[13] 49—50°), $\nu_{max.}$ 1705 cm^{-1} [C(11)=O] (lit.,[11] 1700 cm^{-1}); δ 0·7 (3H, s, 18-H_3), 1·02 (3H, s, 19-H_3), and 2·2 (2H, 12-H_2, J_{gem} 12 Hz [23]).

(*b*) 5α-Androstane-3,11,17-trione (2 g) in ethylene glycol (130 ml) and hydrazine hydrate (8 ml) were heated under reflux for 45 min. Potassium hydroxide (2 g) was added, and solvent was removed until the temperature of the distillate had risen to 200°. The mixture was then heated under reflux for 2 h, cooled, poured into water, and extracted with ether. Material insoluble in ether and water was filtered off. This crude solid (1·5 g) was extracted with acetone; evaporation of the extract gave 11-*isopropylidenehydrazono*-5α-*androstane* (III; R = N·N=CMe_2) as a gum, showing no i.r. carbonyl absorption; δ 0·59 (3H, s, 18-H_3), 1·0 (3H, s, 19-H_3), and 1·82 and 1·94 (each 3H, s, =CMe_2) (Found: M^+, 328·2875. $C_{22}H_{36}N_2$ requires *M*, 328·2878). The ethereal extract gave 5α-androstan-11-one (0·3 g), m.p. 50—51°, identical with the sample prepared in (*a*).

(*c*) 5α-Androstane-3,11,17-trione (1 g) in ethanol (75 ml) was treated with hydrazine hydrate (3 ml) under reflux for 45 min; the mixture was poured into water and extracted with dichloromethane to yield the crude 3,17-dihydrazone as a solid, which decomposed on heating or attempted recrystallisation from methanol, $\nu_{max.}$ 3400 (NH_2), 1705 [C(11)=O], 1640, and 1260 cm^{-1}; δ 0·81 (3H, s, 18-H_3), 1·05 (3H, s, 19-H_3), 2·42 (2H, s, 12-H_2), and 4·58 (2 × NH_2). The crude dihydrazone (2 g) in refluxing ethylene glycol (130 ml) was treated with potassium hydroxide (3 g); solvent was removed until the temperature of the distillate had risen to 200° and the mixture was refluxed at 200° for 2 h, cooled, poured into water, and extracted with ether to give 5α-androstan-11-one (0·4 g), m.p. 50—51°, identical with the sample obtained in (*a*).

5α-*Androstan*-11α-*ol*.—5α-Androstan-11-one (160 mg) in propanol-2-ol (18 ml) was refluxed with sodium (500 mg); the reaction was followed by t.l.c. After 2 h, no starting material remained and the cooled solution was poured into water and extracted with ether to give 5α-androstan-11α-ol (120 mg), m.p. 107—108° (from methanol) (lit.,[9] 108°), $\nu_{max.}$ 3640 cm^{-1}; δ 0·71 (3H, s, 18-H_3), 0·90 (3H, s, 19-H_3), and 3·65 (1H, m, $W_{\frac{1}{2}}$ 22 Hz, 11β-H [23,24]).

5α-*Androstan*-11β-*ol*.—5α-Androstan-11-one (120 mg) in tetrahydrofuran was treated with lithium aluminium hydride (50 mg) at 25°; the reaction was followed by t.l.c. Initially the 11β-ol and starting material only were observed, but after 45 min a third less polar spot had developed, probably due to 5α-androst-9(11)-ene, and the reaction was stopped after 1 h. The mixture was decomposed with sodium sulphate solution and extracted with ether to give an oil (120 mg), which was purified by preparative t.l.c. on silica (in 10% ether–hexane) to give 5α-androstan-11β-ol (40 mg), m.p. 89—90° (from aqueous methanol) (lit.,[13] 89—91°), $\nu_{max.}$ 3620 cm^{-1}; δ 0·90 (3H, s, 18-H_3), 1·00 (3H, s, 19-H_3), and 4·18 (1H, m, $W_{\frac{1}{2}}$ 9 Hz, 11α-H [23,24]). Also isolated was unchanged 5α-androstan-11-one, m.p. and mixed m.p. 50—51°.

Reactions with Phosphorus Pentachloride.—(*a*) 5α-Androstan-11α-ol (30 mg) in purified chloroform (10 drops) was treated with resublimed phosphorus pentachloride (100 mg)

* Strain initially confined to ring C becomes distributed over both rings B and C; the 13,17- and 14,15-bonds remain truly equatorial,[22] so that the C/D-ring strain situation is unchanged, but the 10β-Me/11β-H/13β-Me repulsions are reduced.

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for 15 min at 25°. The crude product, isolated in the usual way, was separated by preparative t.l.c. on silica in pentane to give 5α-*androst*-9(11)-*ene* (18 mg), m.p. 38—40°; δ 0·62 (3H, s, 18-H_3), 0·90 (3H, s, 19-H_3), and 4·75 (1H, m, 11α-H) (Found: C, 88·2; H, 11·5%; M^+, 258·2345. $C_{19}H_{30}$ requires C, 88·4; H, 11·6%; M, 258·2347), and 9α,11β-*dichloro*-5α-*androstane* (8 mg), m.p. 127—128° (from acetone), $\nu_{max.}$ (CS_2) 740 cm^{-1} (C–Cl*ax*); δ 1·00 (3H, s, 18-H_3); 1·32 (3H, s, 19-H_3), 2·20 (12β-H, $J_{12\beta,12\alpha}$ 16, $J_{12\beta,11\alpha}$ 3 Hz), 2·34 (12α-H, $J_{12\alpha,12\beta}$ 16, $J_{12\alpha,11\alpha}$ 6 Hz), and 4·66 (11α-H, $J_{11\alpha,12\beta}$ 3, $J_{11\alpha,12\alpha}$ 6 Hz) (Found: C, 69·4; H, 9·2; Cl, 21·5%; M^+, 328·1720.* $C_{19}H_{30}Cl_2$ requires C, 69·3; H, 9·1; Cl, 21·6%; M, 328·1705). This 9α,11β-dichloride was prepared in quantitative yield from 5α-androst-9(11)-ene by brief treatment with chlorine in chloroform solution, m.p. and mixed m.p. 127—128°.

(*b*) 5α-Androstan-11β-ol (15 mg) in purified chloroform (3 drops) was treated with resublimed phosphorus pentachloride (50 mg) for 15 min at 25°. The crude product, isolated in the usual way, was purified by preparative t.l.c. on silica in pentane to give 5α-androst-9(11)-ene, m.p. 38—40: (10 mg), identical with the sample obtained in (*a*).

Reactions with Thionyl Chloride.—(*a*) 5α-Androstan-11α-ol (20 mg) in ether was treated with redistilled thionyl chloride at 20°; the reaction was followed by t.l.c. After 12 h, no starting material remained; the mixture was poured on ice, and extracted with ether. The crude oil was purified by preparative t.l.c. on silica in pentane to give 5α-androst-9(11)-ene, m.p. 38—40° (from acetone), identical with a sample prepared previously.

(*b*) 5α-Androstan-11α-ol (20 mg) in benzene was treated with redistilled thionyl chloride as in (*a*). The only product was 5α-androst-9(11)-ene, identical with the sample obtained in (*a*).

(*c*) 5α-Androstan-11α-ol (50 mg) was treated with thionyl chloride (15 ml) at 20° for 1 h. The mixture was poured on ice, and extracted with ether to give a crude oil shown by t.l.c. to contain two components. Preparative t.l.c. on silica in pentane gave 11α-*chloro*-5α-*androstane* as an oil (20 mg), homogeneous by t.l.c., $\nu_{max.}$ (CS_2) 750 and 800 cm^{-1} (C–Cl*eq*); δ 0·70 (3H, s, 18-H_3), 0·95 (3H, s, 19-H_3), 4·2 (1H, m, $W_{\frac{1}{2}}$ 25 Hz, 11β-H), and 2·30 and 2·43 (2H, q, 12-H_2) (Found: M^+, 294·2110.† $C_{19}H_{31}Cl$ requires M, 294·2114), and 5α-androst-9(11)-ene (10 mg), identical with the samples prepared before.

(*d*) 5α-Androstan-11β-ol (15 mg) in ether (1·5 ml) was treated at 0° with redistilled thionyl chloride and left at 20° for 8 h. The crude product was purified by preparative t.l.c. on silica to give 5α-androst-9(11)-ene (8 mg), m.p. 38—40°, identical with samples previously obtained.

Reduction of 11α-*Chloro*-5α-*androstane to* 5α-*Androstane.*—The 11α-chloride (10 mg) was refluxed in 48% hydriodic acid–acetic acid (1 : 1; 5 ml) with red phosphorus for 1 h. After work-up, t.l.c. showed two components; the less polar component, isolated by preparative t.l.c. on silica in pentane and recrystallised from aqueous acetone, was 5α-androstane, m.p. and mixed m.p. 42°; δ 0·70 (3H, s, 18-H_3) and 0·80 (3H, s, 19-H_3) (no other peaks). The more polar component was unchanged 11α-chloride.

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* Isotopic peaks at *m/e* 330 (^{35}Cl, ^{37}Cl) and 332 (^{37}Cl, ^{37}Cl).
† Isotopic peak *m/e* 296 (^{37}Cl).