Preparation of 3β-Hydroxy-5α-androstan-16-one

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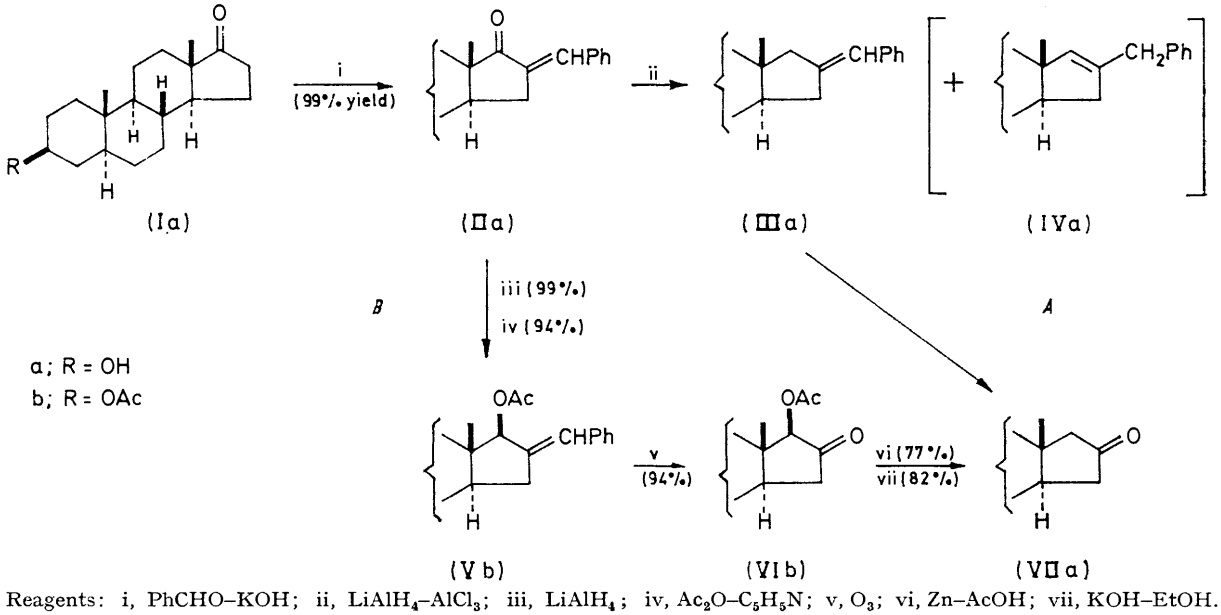
3β-Hydroxy-5α-androstan-16-one is conveniently prepared from the readily available 3-hydroxy-17-ketone by a simple sequence which gives an overall yield of 53%

In an earlier paper [1] on transposing an oxo-function and an adjacent methylene group we summarised methods used previously and described two new sequences: one (*A*) for preparing 16-oxo-5α-androstanes from the readily available 17-ketones, and the second (as in *B*) for obtaining 2-oxo- from 3-oxo-steroids; subsequently other methods for ketone transposition in alicyclic systems have been developed.[2]

Although sequence *A* is convenient and efficient for the parent 16-ketone (VII; R = H), the presence of a hydroxy-group in the starting material leads to the formation of sparingly soluble complexes in the dichloroaluminium hydride stage, which then requires forcing conditions. Several repetitions of this reaction with the 3β-hydroxy-compound (Ia) have now shown that the reported 16-benzylidene product (IIIa) [1] is accompanied by various amounts of the endocyclic isomer (IVa). (The reported difficulty [3] in using sequence *A* with a 3-aza-A-homo-5α-androstan-17-one may stem from partial isomerisation during the reduction with dichloroaluminium hydride.) Sequence *B*, although longer, is simple manipulatively, and since one product is formed almost exclusively at each stage purification of intermediates is unnecessary. Overall yields of 51—56% have been obtained in runs giving the product (VIIa) in 5—20 g quantities.



Reagents: i, PhCHO–KOH; ii, $LiAlH_4$–$AlCl_3$; iii, $LiAlH_4$; iv, Ac_2O–C_5H_5N; v, O_3; vi, Zn–AcOH; vii, KOH–EtOH.

EXPERIMENTAL

General directions are as described in *J. Chem. Soc.* (*C*), 1968, 2674, except that ^1H n.m.r. spectra were measured at 100 MHz. Small quantities of all the intermediates were purified and used for characterisation; with compounds already described in ref. 1 the present materials were identified by comparison (mixed m.p.; spectrometric examinations) with authentic specimens, and the constants found here are not reported. Petrol refers to light petroleum, b.p. 60—80 °C.

Sequence B *giving* 3β-*Hydroxy*-5α-*androstan*-16-*one* (VIIa).—3β-Hydroxy-5α-androstan-17-one (Ia) (15 g) was condensed with benzaldehyde (8 ml) as described earlier [1] to give the benzylidene ketone (IIa) [1] (19.3 g). This ketone (19 g) was added to a solution of $LiAlH_4$ (3 g) in dry tetrahydrofuran (600 ml), and the mixture was boiled under reflux for 3 h. Work-up gave material (19 g) which was dissolved in Ac_2O (80 ml)–C_5H_5N (40 ml) at 50 °C. After 48 h at 20 °C the solution was worked up to give 3β,17β-*diacetoxy*-16-*benzylidene*-5α-*androstane* (Vb) (22 g), m.p. 152—154° (from petrol), $[\alpha]_D$ −49.5° (*c* 3.0) (Found: C, 77.5; H, 8.6. $C_{30}H_{40}O_4$ requires C, 77.55; H, 8.7%), $\nu_{max.}$ 1 740 cm^{-1}, τ 3.79 (s, =CH–), 4.64 (s, 17α-H), 5.38 (m, 3α-H), 7.83 (17β-OAc), 8.00 (3β-OAc), 9.16 (19-H), and 9.26 (18-H). A solution of the diacetate (22 g) in dry EtOAc (300 ml)–MeOH (300 ml) was ozonised at −78 °C until a blue colour persisted (*ca.* 3—4 h), and N_2 was then passed through the solution for 15 min. Glacial AcOH (80 ml)–H_2O (20 ml) was added, the solution was stirred at 0 °C, and Zn dust (35 g) was added in portions during 10 min. The mixture was stirred at 20 °C for 6 h, and then worked up to give 3β,17β-diacetoxy-5α-androstan-16-one (VIb) (17.4 g), m.p. 179—181° (from Me_2CO-petrol), $[\alpha]_D$ −113° (*c* 1.1) (lit.,[4]

[1] J. E. Bridgeman, C. E. Butchers, Sir Ewart R. H. Jones, A. Kasal, G. D. Meakins, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1970, 244.

[2] J. A. Marshall and H. Roebke, *J. Org. Chem.*, 1969, **34**, 4188; B. M. Trost, K. Hiroi, and S. Kurozumi, *J. Amer. Chem. Soc.*, 1975, **97**, 438.

[3] R. B. Rao and L. Weiler, *Tetrahedron Letters*, 1973, 4971.

[4] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.*, 1954, **76**, 2943.

m.p. 179—181°, $[\alpha]_D$ −120°), τ 5.0 (s, 17α-H), 5.35 (m, 3α-H), 7.85 (17β-OAc), 7.98 (3β-OAc), 9.14 (19-H), and 9.18 (18-H). The diacetoxy-ketone (17 g) in glacial AcOH (750 ml) was heated under reflux with Zn dust (750 g; activated by washing twice with 2N-HCl, then successively with H_2O, MeOH, Et_2O, and dry Et_2O) until starting material was not detected by t.l.c. (*ca.* 28 h). The cooled mixture was filtered, the filtrate was evaporated at 100 °C and 2 cmHg, and H_2O (200 ml) was added to the residue. Extraction with EtOAc gave 3β-acetoxy-5α-androstan-16-one (11.4 g), m.p. 112—114° (from Me_2CO–petrol), $[\alpha]_D$ −157° (*c* 0.9) (lit.,[5] m.p. 109—110°, $[\alpha]_D$ −171°), τ 5.35 (m, 3α-H), 8.00 (3β-OAc), 9.13 (18- and 19-H). The foregoing acetoxy-ketone (11.2 g) in EtOH (300 ml) was boiled under reflux for 1 h with KOH (6 g) in H_2O (20 ml). Work-up and crystallisation of the bulk product from Me_2CO–petrol gave 3β-hydroxy-5α-androstan-16-one (VIIa) [1] (7.9 g), m.p. and mixed m.p. 185—187°.

Reduction of 16-*Benzylidene*-3β-*hydroxy*-5α-*androstan*-17-*one* (IIIa) *with Dichloroaluminium Hydride.*—The 17-ketone (2.5 g) in bis-(2-methoxyethyl) ether (180 ml) was added during 30 min to a solution of $AlCl_3$ (10.5 g) and $LiAlH_4$ (1.5 g) in Et_2O (150 ml) which was stirred under N_2, and the mixture was boiled under reflux for 72 h. After work-up the product (2.43 g) was chromatographed on neutral Al_2O_3 (300 g). Et_2O–petrol (2 : 1) eluted 16-*benzyl*-5α-*androst*-16-*en*-3β-*ol* (IVa) (0.81—0.87 g in various experiments), m.p. 130—132° (from Me_2CO–petrol), $[\alpha]_D$ −16° (*c* 0.6) (Found: C, 85.7; H, 10.2. $C_{26}H_{36}O$ requires C, 85.7; H, 9.95%), $\nu_{max.}$ 3 620 cm^{-1}, τ 2.78 (5 H, m, C_6H_5), 4.54 (1 H, s, =CH–), 6.46 (1 H, m with $W_{\frac{1}{2}}$ 20 Hz, 3α-H), 6.67 (2 H, s, =C–CH_2Ph), 9.19 (H-19), and 9.24 (H-18), *m/e* 364 (20%, M^+) and 349 (100%, M^+ − Me), followed by 16-benzylidene-5α-androstan-3β-ol (IIIa) [1] (1.53—1.59 g), m.p. and mixed m.p. 194—196°.

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