Studies in the Steroid Group. Part LXXX.[1] Preparation of 2- and 16-Oxo-, and 3,16- and 2,16-Dioxo-5α-androstane, and 2-Oxo-5α-cholestane

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16-Oxo-5α-androstanes are readily obtained from the 17-ketones in three stages, *viz.*, condensation with benzaldehyde to 16-benzylidene-17-ketones, reduction with lithium aluminium hydride–aluminium chloride to 16-benzylidene-androstanes, and ozonolysis. This sequence is not suitable for the 3 ⟶ 2 transposition of oxo-groups in ring-A. Here the 2-arylidene-3-ketones are reduced with sodium borohydride and acetylated before ozonolysis: the acetoxy-groups of the 3β-acetoxy-2-ketones are removed by reduction with zinc and acetic acid.

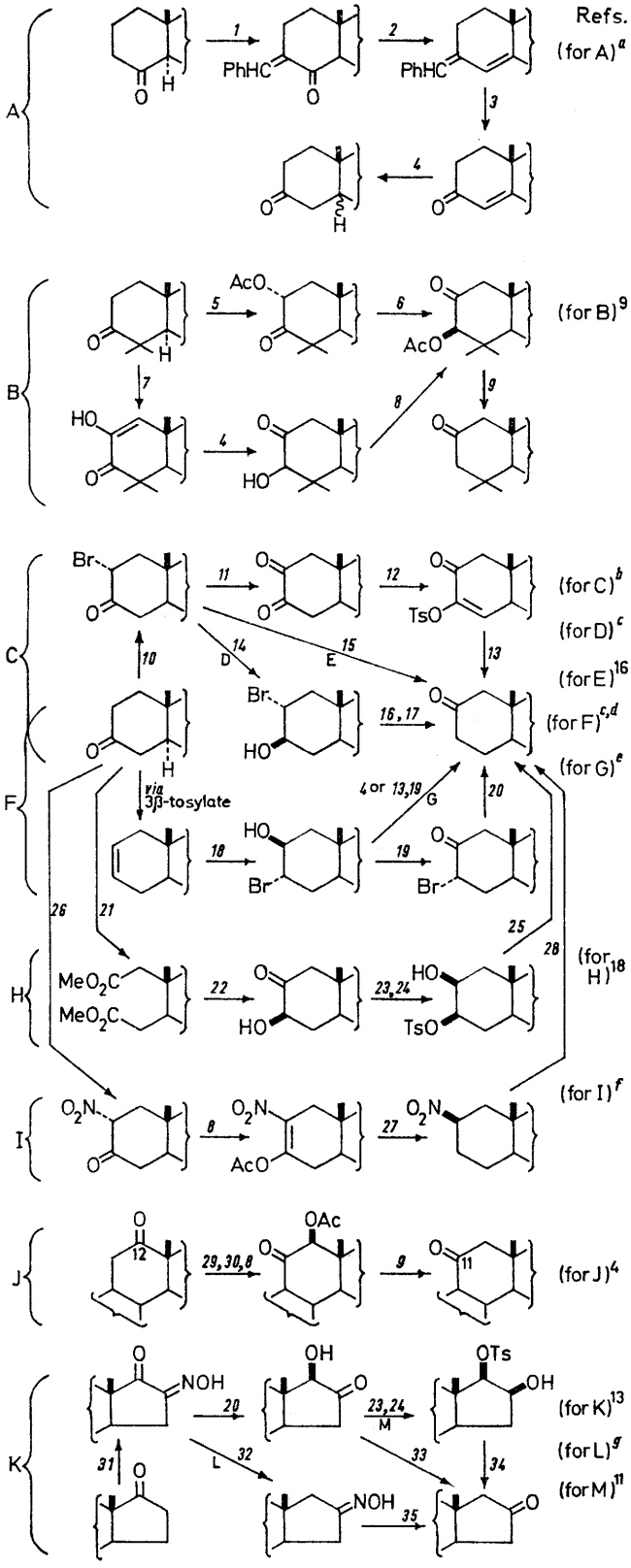
With 5α-androstane-3,17-dione the longer route afforded 5α-androstane-2,16-dione in 24% yield overall.

In studying the microbiological hydroxylation of steroids we required oxygenated steroids of the less common types. This paper deals with the synthesis of the compounds listed in the Title: the microbiological work, some aspects of which have been reported briefly,[2] will be described later.

The readily available 3- and 17-oxo-steroids were obvious starting materials for preparing 2- and 16-ketones, and the problem was a general one, the transposing of a keto-function and an adjacent methylene group. Methods used previously for this purpose in steroidal and terpenoid systems are summarised in Scheme 1. Only the outlines are shown: no attempt is made to specify the particular compounds involved and, for brevity, some of the intermediates are omitted. Main sequences are denoted by brackets and capital letters on the left of the Scheme, and variations by capital letters within the Scheme. The recent method

[1] Part LXXIX, R. T. Aplin, G. D. Meakins, K. Z. Tuba, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1969, 1602.

[2] J. E. Bridgeman, J. W. Browne, P. C. Cherry, M. G. Combe, J. M. Evans, E. R. H. Jones, A. Kasal, G. D. Meakins, Y. Morisawa, and P. D. Woodgate, *Chem. Comm.*, 1969, 463.



SCHEME 1 Methods for the conversion $-CH_2-CO- \longrightarrow -CO-CH_2-$

Reagents: *1*, PhCHO–NaOH; *2*, $Al(OPr^i)_3$; *3*, O_3 at −60°; *4*, H_2–Pd; *5*, $Pb(OAc)_4$–BF_3; *6*, *e.g.* Al_2O_3; *7*, O_2–$KOBu^t$; *8*, Ac_2O–C_5H_5N; *9*, Ca–NH_3; *10*, *e.g.* $C_5H_6N^+Br_3^-$; *11*, Kröhnke reaction; *12*, TsCl + K salt; *13*, H_2–Ni; *14*, $LiAlH(OBu^t)_3$; *15*, PrSH–$CHCl_3$; *16*, KOH–MeOH; *17*, $LiAlH_4$; *18*, *N*-bromosuccinimide–$HClO_4$; *19*, H_2CrO_4–Me_2CO; *20*, Zn–AcOH; *21*, oxidation to diacid (see ref. 14), then CH_2N_2; *22*, Na–NH_3; *23*, TsCl–C_5H_5N; *24*, $NaBH_4$; *25*, collidine; *26*, Bu^tONO_2–$KOBu^t$; *27*, $NaBH_4$ then H^+; *28*, Nef reaction; *29*, Br_2–C_6H_6; *30*, NaOH–H_2O–Bu^tOH; *31*, $C_5H_{11}ONO$–$KOBu^t$; *32*, mild Huang-Minlon reduction; *33*, Zn(Hg)–HCl–EtOH; *34*, NaOH–$MeOCH_2{\cdot}CH_2OH$; *35*, $NaHSO_3$ then H^+.

[a] H. H. Zeiss and W. B. Martin, *J. Amer. Chem. Soc.*, 1953, **75**, 5935. [b] L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, 1944, **27**, 524; C. Djerassi, R. Yashin, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1950, **72**, 5750. [c] J. E. Gurst and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 5542. [d] R. Gardi, R. Vitali, and A. Ercoli, *Gazzetta*, 1962, **92**, 632. [e] R. L. Clarke and S. J. Daum, *J. Org. Chem.*, 1965, **30**, 3786; P. D. Klimstra, R. Zigman, and R. E. Counsell, *J. Medicin. Chem.*, 1966, **9**, 924. [f] A. Hassner, J. M. Larkin, and J. E. Dowd, *J. Org. Chem.*, 1968, **33**, 1733. [g] J. Just and Y. C. Lin, *Chem. Comm.*, 1968, 1350.

of Fetizon *et al.*[3] is discussed later, since it is closely related to the present work.

It is unfortunate that some of the best methods are applicable only to certain transformations. For example, the excellent sequence *J* depends upon the relative stabilities of the isomeric 11,12-hydroxyketones[4] and similar special features are the basis of methods *B*, *H* and *K*. In others (*e.g.*, *C* and *F*) certain stages require particular stereochemical relations between the groups involved. The novel route (*I*), utilising a nitro-ketone intermediate, appears promising for steroids, but less suitable in the triterpene series.[5] Having in mind a 'double' transposition (**3**, **17** ⟶ **2**, **16**) at a later stage we turned to an older method (*A*) which, being unsatisfactory in its original form, has received little attention. After development, this led to the new route for preparing 16-ketones shown in the upper part of Scheme 2. (The detailed nature of the Scheme, which includes percentage yields, obviates the need for lengthy discussion. New compounds are indicated by the symbol † in Schemes **2**, **3**, and **4**: references to known compounds are given in the Experimental section.)

The key stage is the removal of the 17-oxo-group from the benzylidene-ketones (IV), and here the mixed hydride reagent was markedly superior to the other methods investigated. While a $LiAlH_4 : AlCl_3$ ratio of 1 : 3 (giving a reagent formulated as dichloroaluminium hydride, $AlCl_2H$) [6] has been used frequently in this type of reduction, the yields in the present cases were significantly improved by the presence of an appreciable excess of the hydride. With the benzylidene-ketone (IVa) unsubstituted at position **3** the reaction proceeded satisfactorily in boiling ether, but the formation of insoluble salts from the 3-hydroxy-compound (IVb) made it

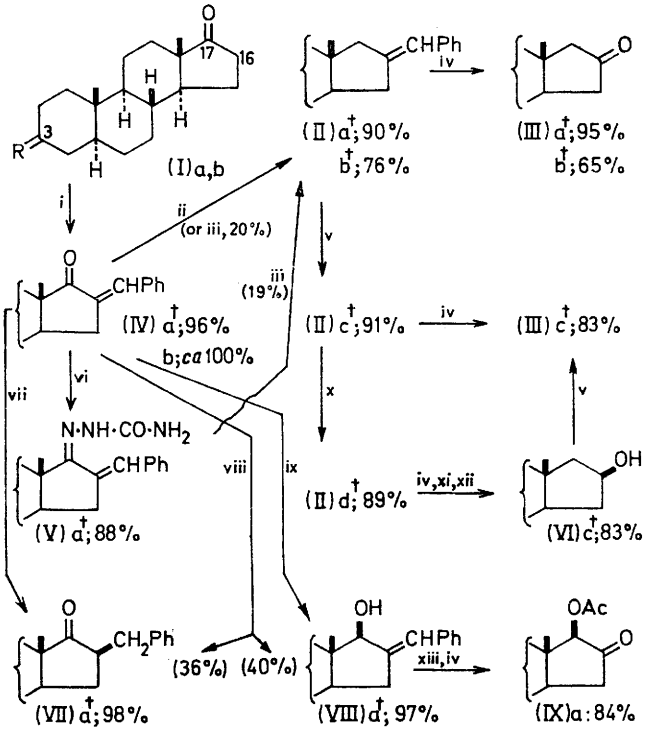
[3] M. Fetizon, J.-C. Gramain, and I. Hanna, *Compt. rend.*, 1967, **265**, 929.

[4] J. Elks, G. H. Phillips, T. Walker, and L. J. Wyman, *J. Chem. Soc.*, 1956, 4330; J. H. Chapman, J. Elks, G. H. Phillips, and L. J. Wyman, *ibid.*, p. 4344.

[5] P. M. Everard, Part II Thesis, Oxford, 1969.

[6] J. H. Brewster, H. O. Bayer, and S. F. Osman, *J. Org. Chem.*, 1964, **29**, 110; E. C. Ashby and B. Cook, *J. Amer. Chem. Soc.*, 1968, **90**, 1625.

necessary to use a 1 : 1 mixture of ether–diglyme. The 16β-configuration of the benzyl ketone (VIIa) suggested by the routes leading to it is supported, but not rigorously established, by ^{1}H n.m.r. evidence: with the benzylidene



Scheme 2 Preparation of 16-oxo- and 3,16-dioxo-5α-androstane

a; R = H_2. b; R = 3β-OH, 3α-H. c; R = O.

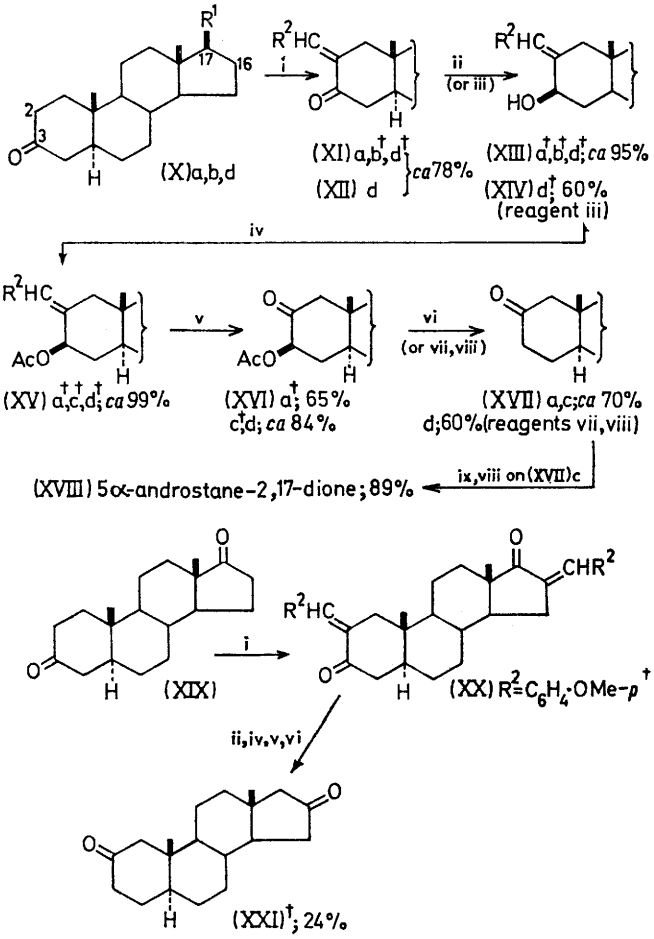
d; R = 3-ethylenedioxy

Reagents: i, PhCHO–KOH–EtOH; ii, $LiAlH_4$–$AlCl_3$; iii, Huang–Minlon reduction; iv, O_3; v, H_2CrO_4–Me_2CO; vi, $H_2N{\cdot}NH{\cdot}CO{\cdot}NH_2$; vii, H_2–Pt; viii, Zn–AcOH; ix, $NaBH_4$; x, $HO{\cdot}[CH_2]_2{\cdot}OH$–TsOH; xi, $LiAlH(OBu^t)_3$; xii, Me_2CO–TsOH; xiii, Ac_2O.

alcohol (VIIIa) the 17β-structure follows from its conversion into the known 17β-acetoxy-ketone (IXa).[7]

After the preliminary announcement of this route,[8] Professor M. Fetizon kindly supplied us with details, considerably before publication,[3] of his similar studies in ring-A. To facilitate comparison with the French authors' results we used anisylidene rather than benzylidene derivatives in most of our subsequent work. As discussed below, the short 17 ⟶ 16 route is not directly applicable to the 3 ⟶ 2 conversion, but modifications led to a longer sequence of general applicability as portrayed in Scheme 3.

Reduction of the arylidene-ketones (XI) and (XII) followed by acetylation and ozonolysis gives 3-acetoxy-2-ketones (XVI), the 3β-configurations of these intermediates being supported by spectrometric examination and by relating some of them to compounds of established structures (see Experimental section). Removal of the acetoxy-groups using calcium in ammonia [4,9a] was not easily controlled: in the cholestane series (XVId) over-reduction could not be avoided and mild oxidation was required [9b] to regenerate the 2-ketone (XVIId). The more convenient method, zinc in acetic acid, was, somewhat surprisingly, more effective. With rigid cyclic



Scheme 3 Preparation of 2-oxo-, and 2,17- and 2,16-dioxo-5α-steroids

a; R^1 = H. b; R^1 = OH. c; R^1 = OAc. d; R^1 = C_8H_{17}. (XI), (XIII), and (XV; R^2 = $C_6H_4{\cdot}OMe$-*p*). (XII) and (XIV) R^2 = Ph.

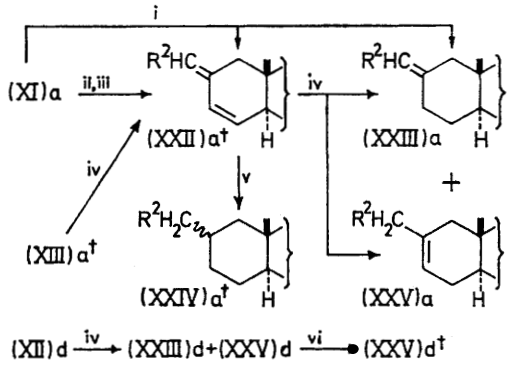
Reagents: i, R^2CHO–KOH–EtOH; ii, $NaBH_4$; iii, $LiAlH_4$; iv, Ac_2O–C_5H_5N; v, O_3; vi, Zn–AcOH; vii, Ca–NH_3; viii, H_2CrO_4–Me_2CO; ix, KOH–MeOH.

α-acetoxy-ketones it has been shown that only axial acetoxy-groups are removed easily.[10] The present results suggest that the flexibility of ring-A allows the departing group to adopt a quasi-axial conformation. Application of the sequence to the 3,17-diketone (XIX)

[7] C. Djerassi and D. Herbst, *J. Org. Chem.*, 1961, **26**, 4675.
[8] J. E. Bridgeman, E. R. H. Jones, G. D. Meakins, and J. Wicha, *Chem. Comm.*, 1967, 898.
[9] (*a*) A. Lablache-Combier, B. Lacoume, and J. Levisalles, *Bull. Soc. chim. France*, 1966, 897; (*b*) D. H. R. Barton, D. Giacopello, P. Manitto, and D. L. Struble, *J. Chem. Soc.* (*C*), 1969, 1047.
[10] R. S. Rosenfeld and T. F. Gallagher, *J. Amer. Chem. Soc.* 1955, **77**, 4367.

gave the doubly transposed 2,16-isomer (XXI) in satisfactory yield. Here the duration of the final reduction is of critical importance. The 3β-acetoxy-group is removed considerably faster than is the more rigidly confined 17β-group, and it is necessary to compromise between further reduction (of the 2-oxo-group) in ring-A and incomplete removal of the 17β-substituent in ring-D.

Fetizon *et al.*[3] have shown that the anisylidene-ketone (XIa) is reduced by mixed hydride [$LiAlH_4$–$AlCl_3$(1 : 3)] in refluxing tetrahydrofuran to a mixture consisting mainly of inseparable olefins [(XXIIIa) and (XXVa), 40%] and various 3-alcohols. Ozonolysis of the olefin fraction afforded 5α-androstan-2-one in 24% yield. Thus, success in the short 16 ⟶ 17 conversion (Scheme 2) stems from the higher relative stability of the conjugated olefin system exocyclic to ring-D as already discussed.[3] Further studies in ring-A are depicted in Scheme 4. These establish that the mixed



SCHEME 4 Mixed hydride reduction of 2-arylidene-3-ketones a; R^1 = H, R^2 = C_6H_4·OMe-*p*. b; R^1 = C_8H_{17}, R^2 = Ph.

Reagents: i, $LiAlH_4$–$AlCl_3$ (1 : 4)–Et_2O, 5°; ii, $LiAlH_4$ at 5° then 20°; iii, $AlCl_3$ at 5° then 20°; iv, as i at 35°; v, H_2–Pd; vi, TsOH–C_6H_6, reflux.

hydride reactions proceed *via* the diene (XXIIa), which is readily obtained by sequential reduction of the anisylidene-ketone (XIa) (83%) or by treating the allylic alcohol (XIIIa) with the mixed reagent at low temperature (73%). Experiments with the benzylidene-cholestanone (XIId) suggest that the endocyclic olefin (XXVd) is more stable than its conjugated exocyclic isomer (XXIIId).

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: the signals of end-products (as opposed to intermediates) are not given here since they will appear in Part I of our series dealing with microbiological hydroxylation of steroids. Petrol refers to light petroleum, b.p. 60—80°. Experimental procedures are described fully only where they are first mentioned: the numbering of experiments facilitates references to these operations.

Work in Scheme 2.—Experiment 1. A solution of benzaldehyde (freshly distilled; 4·4 g.) and 5α-androstan-17-one (Ia) (4·4 g.) in EtOH (115 ml.) containing KOH (0·64 g.) was kept in the dark at 20° for 16 hr. Filtration afforded 16-*benzylidene-5α-androstan-17-one* (IVa) (5·6 g., m.p. 154—156°), m.p. 157—159° (from EtOH), $[\alpha]_D$ +40° (*c* 0·9) (Found: C, 86·2; H, 9·8. $C_{26}H_{34}O$ requires C, 86·1; H, 9·5%), $\nu_{max.}$ 1730 $cm.^{-1}$, $\lambda_{max.}$ 294 nm. (ε 24,700).

Experiment 2. The above product (IVa) (8·9 g.) in dry Et_2O (450 ml.) was added during 20 min. to a stirred solution made by dissolving $AlCl_3$ (10·7 g.) and then $LiAlH_4$ (1·8 g.) in dry Et_2O (225 ml.). The solution was boiled under reflux for 2·5 hr., and was then added slowly to ice–water (2000 ml.) containing 2N-HCl (100 ml.). Standard manipulation gave 16-*benzylidene-5α-androstane* (IIa) (7·65 g.), m.p. 123·5—124° (from Me_2CO), $[\alpha]_D$ −72° (*c* 1·1) (Found: C, 89·7; H, 10·3. $C_{26}H_{36}$ requires C, 89·6; H, 10·4%), $\lambda_{max.}$ 256 nm. (ε 22,050), τ 9·20 (19-H) and 9·23 (18-H).

Experiment 3. The benzylidene derivative (IIa) (2 g.) in MeOH (500 ml.)–EtOAc (200 ml.) was ozonised at −20° until a blue colour persisted, and N_2 was then passed through the solution for 10 min. After the addition of glacial AcOH (100 ml.), the mixture was warmed to 30°, stirred, and kept at 30—35° by cooling while Zn dust (40 g.) was added during 20 min. The mixture was filtered, the excess of Zn being washed with EtOAc, and the combined filtrates were concentrated at 60°/2 cm. to a volume of *ca.* 200 ml. Addition of water, extraction with CH_2Cl_2, and filtration of the product in 5% Et_2O–petrol through neutral Al_2O_3 (deactivated with 5% of H_2O) afforded 5α-androstan-16-one (IIIa) (1·46 g.), m.p. 106—107° (from MeOH), $[\alpha]_D$ −185° (*c* 0·8) (lit.,[11] m.p. 108°, $[\alpha]_D$ −172°), $\nu_{max.}$ 1745 $cm.^{-1}$.

Experiment 4. A solution of the benzylidene-ketone (IVa) (1·5 g.) and hydrazine hydrate (9 ml.) in diethylene glycol (45 ml.) was boiled gently under reflux for 1 hr. The solution was distilled until it reached 170° and kept at 170° for 40 min. KOH (3 g.) was added and after a further 30 min. at 170°, the solution was distilled until it reached 200°, and kept at 200° for 3·5 hr. The addition of H_2O followed by isolation with Et_2O and filtration through Al_2O_3 gave the benzylidene derivative (IIa) (250 mg.).

Experiment 5. The benzylidene-ketone (IVa) was converted by the standard method into the *semicarbazone* (Va) (88%), m.p. 213—215° (from EtOH), $[\alpha]_D$ −41° (*c* 1·0 in C_5H_5N) (Found: C, 77·0; H, 8·7; N, 9·9. $C_{27}H_{37}N_3O$ requires C, 77·3; H, 8·9; N, 10·0%), $\lambda_{max.}$ 305 nm. (ε 16,500). A solution of this compound (250 mg.) and KOH (250 mg.) in diethylene glycol (5 ml.) was heated at 210° for 20 hr. Work-up as in expt. 4 gave the benzylidene derivative (IIa) (40 mg.).

Experiment 6. Hydrogenation of the benzylidene-ketone (IVa) (830 mg.) in EtOAc (22 ml.)–AcOH (3 ml.) over pre-reduced PtO_2 (50 mg.) until hydrogenation absorption became slow, followed by oxidation of the product in Me_2CO with 8N-H_2CrO_4 gave 16β-*benzyl-5α-androstan-17-one* (VIIa) (814 mg., m.p. 160—162°), m.p. 165—166° (from EtOH), $[\alpha]_D$ +128° (*c* 1·1) (Found: C, 85·5; H, 10·0. $C_{26}H_{36}O$ requires C, 85·7; H, 10·0%), $\nu_{max.}$ 1739 $cm.^{-1}$, τ 6·84 and 7·37 (two q, *J* 13 and 4, and 13 and 9, Hz respectively; benzylic CH_2), 9·22 (19-H), and 9·32 (18-H). Freshly cut Na (300 mg.) and then the ketone (VIIa) (100 mg.) were added to MeO^2H (5·5 ml.)–^2H_2O (2 ml.) and the mixture was boiled under reflux for 5 days to give material (95 mg.), m.p. 165—166° (from EtOH), shown by its mass spectrum

[11] (*a*) D. Varech and J. Jacques, *Bull. Soc. chim. France*, 1965, 67; (*b*) M. N. Huffman, M. H. Lott, and A. Tillotson, *J. Biol. Chem.*, 1955, **217**, 107.

to contain 15% of starting material and 85% of a compound formulated as 16α-^{2}H (VIIa), τ 6·84 and 7·37 (two d, each with J 14 Hz), 9·22 (19-H), and 9·33 (18-H).

Experiment 7. A solution of $NaBH_4$ (3·6 g.) in H_2O (20 ml.) was added to a stirred solution of the ketone (IVa) (5·3 g.) in EtOH (650 ml.) at 20°. After 2 hr. the solution was poured into H_2O and extracted with Et_2O to give 16-*benzylidene*-5α-*androstan*-17β-*ol* (VIIIa) (5·16 g.; m.p. 192—195°), m.p. 198—199° (from EtOH), $[\alpha]_D$ −115° (*c* 0·9) (Found: C, 85·4; H, 10·1. $C_{26}H_{36}O$ requires C, 85·7; H, 10·0%), $\lambda_{max.}$ 258 nm. (ε 23,900), τ 3·50 (olefinic H), 5·98 (17α-H), 9·19 (19-H), and 9·31 (18-H). A solution of this compound (5 g.) in Ac_2O (20 ml.) was heated gradually during 1 hr. to its b.p. The cooled solution was poured into H_2O (200 ml.)–C_5H_5N (0·5 ml.) and the mixture was stirred at 20° for 30 min. It was then filtered, and the precipitation was washed with H_2O and dried to afford 16-*benzylidene*-5α-*androstan*-17β-*yl acetate* (5·48 g.; m.p. 153—155°), m.p. 156—157° (from EtOH), $[\alpha]_D$ −41° (*c* 1·0) (Found: C, 82·6; H, 9·3. $C_{28}H_{38}O_2$ requires C, 82·7; H, 9·4%), $\nu_{max.}$ 1742 cm.$^{-1}$.

Ozonolysis of this acetate (100 mg.) in MeOH (50 ml.) at −20° for 30 min. followed by treatment as in expt. 3 gave 16-oxo-5α-androstan-17β-yl acetate (IXa) (75 mg.), m.p. 152—153° (from MeOH) (lit.,[7] m.p. 153—153·5°), identified by comparison with material prepared as in ref. 7.

Experiment 8. Zn dust (40 g.) was added in portions (10 g.) at 15 min. intervals to a stirred solution of the benzylidene-ketone (IVa) (250 mg.) in glacial AcOH (75 ml.) at 20°. After a further 3 hr. the excess of Zn was filtered off, washed with AcOH (2 × 25 ml.), and the combined filtrates were evaporated at 60°/20 mm. The residue was suspended in H_2O and extracted with Et_2O to give material which was chromatographed on 5% deactivated neutral Al_2O_3 (30 g.). Elution with petrol–Et_2O (1 : 1) afforded the benzyl-ketone (VIIa) (90 mg.; m.p. 164—165°) followed by the benzylidene-alcohol (VIIIa) (100 mg.; m.p. 198—199°).

Experiment 9. Solutions of 3β-hydroxy-5α-androstan-17-one (15 g.) and benzaldehyde (freshly distilled; 8 ml.) in EtOH (200 ml.), and KOH (3 g.) in EtOH (20 ml.)–H_2O (2 ml.) were mixed, boiled under reflux for 10 min., and diluted with H_2O (5 ml.). After 12 hr. at 20°, the mixture was cooled to 10°; filtration gave the conjugated ketone (IVb) (19·5 g.; m.p. 177—180°), m.p. 181—182° (from EtOH) (lit.,[12] m.p. 181·5—182·5°), $\lambda_{max.}$ 298 nm. (ε 22,500).

Experiment 10. A solution of the conjugated ketone (13·5 g.) in diglyme (400 ml.) was added during 20 min. to a stirred solution of $AlCl_3$ (60 g.) and $LiAlH_4$ (10 g.) in ether (400 ml.), and the mixture was boiled under reflux for 60 hr. Work-up as in expt. 2, isolation with $CHCl_3$, and filtration of the solution in C_6H_6 through SiO_2 gave 16-*benzylidene*-5α-*androstan*-3β-*ol* (11b) (14·2 g., m.p. 189—193°), m.p. 196—197° (from MeOH), $[\alpha]_D$ −60° (*c* 0·8) (Found: C, 85·3; H, 10·1. $C_{26}H_{36}O$ requires C, 85·7; H, 9·95%), $\lambda_{max.}$ 258 nm. (ε 20,500), $\nu_{max.}$ 3620 cm.$^{-1}$.

Experiment 11. Ozonolysis of the above product (IIb) (1·6 g.) in CH_2Cl_2 (50 ml.) $-C_5H_5N$ (5 ml.) at −60° afforded 3β-hydroxy-5α-androstan-16-one (IIIb) (0·91 g.), m.p. 186—187° (lit.,[13c] m.p. 186—187°) $\nu_{max.}$ 1744 cm.$^{-1}$.

Experiment 12. Oxidation of the hydroxy-ketone (IIIb) (8·4 g.) in Me_2CO with 8N-H_2CrO_4 gave 16-*benzylidene*-5α-*androstan*-3-*one* (IIc) (7·7 g., m.p. 140—144°), m.p. 145—146° (from Me_2CO), $[\alpha]_D$ −69° (*c* 0·6) (Found: C, 85·8; H, 9·5. $C_{26}H_{34}O$ requires C, 86·1; H, 9·45%), $\nu_{max.}$ 1715 cm.$^{-1}$.

Ozonolysis of the product (220 mg.) as in expt. 11 afforded 5α-androstane-3,16-dione (IIIc) (145 mg.), m.p. 161—162° (from C_6H_{12}), $[\alpha]_D$ −149° (*c* 0·4) (lit.,[13d] m.p. 157—159°, $[\alpha]_D$ −162°), $\nu_{max.}$ 1747 and 1715 cm.$^{-1}$.

Experiment 13. A solution of 16-benzylidene-5α-androstan-3-one (IIc) (6·2 g.) and p-$MeC_6H_4{\cdot}SO_3H,H_2O$ (0·2 g.) in $HO{\cdot}[CH_2]_2{\cdot}OH$ (40 ml.)–C_6H_6 (200 ml.) was boiled under reflux in a Dean–Stark apparatus for 20 hr. The solution was washed with aq. KOH and then worked up to give 3,3-*ethylenedioxy*-16-*benzylidene*-5α-*androstane* (IId) (6·15 g.), m.p. 181—182°, $[\alpha]_D$ −72° (*c* 0·6) (Found: C, 82·8; H, 9·8. $C_{28}H_{38}O_2$ requires C, 82·7; H, 9·4%), $\nu_{max.}$ 1270 and 1230 cm.$^{-1}$.

The material obtained by ozonising this product (6·15 g.) as in expt. 11 was dissolved in tetrahydrofuran (250 ml.), and the solution was stirred at 20° for 12 hr. with $LiAlH(OBu^t)_3$ (6 g.). After the addition of 2N-HCl and isolation with $CHCl_3$, the product was dissolved in Me_2CO (100 ml.) containing p-$MeC_6H_4{\cdot}SO_3H,H_2O$ (0·5 g.); the solution was kept at 20° for 18 hr. The addition of H_2O (50 ml.), evaporation at 80°/2 cm., extraction into C_6H_6, washing with aq. $KHCO_3$, drying, and filtration through SiO_2 afforded 16β-*hydroxy*-5α-*androstan*-3-*one* (VIc) (3·65 g., m.p. 148—153°), m.p. 152—154° (from C_6H_{12} and then Me_2CO), $[\alpha]_D$ +10° (*c* 1·0) (Found: C, 78·2; H, 10·4. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%), $\nu_{max.}$ 3625 and 1715 cm.$^{-1}$, the 16β-configuration being confirmed [14] by signals at τ 8·97 (19-H) and 9·02 (18-H). Oxidation of this product (400 mg.) as in expt. 12 gave 5α-androstane-3,16-dione (IIIc) (390 mg.), m.p. and mixed m.p. 161—162°.

Work in Schemes 3 *and* 4.—*Experiment* 14. A solution of anisaldehyde (freshly distilled; 5 ml.) and 5α-androstan-3-one (Xa) (5 g.) in EtOH (340 ml.)–H_2O (10 ml.) containing KOH (17 g.) was kept in the dark at 20° for 6 hr. Filtration, and crystallisation from EtOH afforded 2-p-methoxybenzylidene-5α-androstan-3-one (XIa) (5·47 g.), m.p. 184—185°, $[\alpha]_D$ −232° (*c* 1·1), $\lambda_{max.}$ 320 nm. (ε 15,500) {lit.,[3] m.p. 184—185°, $[\alpha]_D$ −324° (dioxan), $\lambda_{max.}$ 320 nm. (ε 15,000)}.

The 17β-hydroxy-ketone (Xb) (5 g.) gave 17β-*hydroxy*-2-*p*-*methoxybenzylidene*-5α-*androstan*-3-*one* (XIb) (5·5 g.), m.p. 208·5—210·5° (from EtOH), $[\alpha]_D$ −209° (*c* 0·8) (Found: C, 76·5; H, 9·1. $C_{27}H_{36}O_3$,EtOH requires C, 76·6; H, 9·3%), $\nu_{max.}$ 1685 cm.$^{-1}$. 5α-Cholestan-3-one (Xd) (5 g.) gave, after 6 days with anisaldehyde (5 ml.) in EtOH (485 ml.)–H_2O (15 ml.) containing KOH (22 g.), 2-p-*methoxybenzylidene*-5α-*cholestan*-3-*one* (XId) (4·8 g.), m.p. 167—169°, $[\alpha]_D$ −180° (*c* 1·2) (Found: C, 83·7; H, 10·3. $C_{35}H_{52}O_2$ requires C, 83·7; H, 10·4%), $\lambda_{max.}$ 320 nm. (ε 19,400); with benzaldehyde (5 ml.), 2-benzylidene-5α-cholestan-3-one (XIId) (4·8 g.), m.p. and mixed m.p. 147—148° (lit.,[15] 146—147°), $\lambda_{max.}$ 290 nm. (ε 16,000); and with veratraldehyde (5 g.), 2-(3,4-*dimethoxybenzylidene*)-5α-*cholestan*-3-*one* (2·9 g.), m.p. 148—150°, $[\alpha]_D$ −54° (*c* 1·2) (Found: C, 80·5;

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H, 10·1. $C_{36}H_{54}O_3$ requires C, 80·0; H, 10·2%), $\lambda_{max.}$ 332 nm. (ε 14,400).

Experiment 15. A solution of the ketone (XIa) (12·7 g.) in tetrahydrofuran (300 ml.)–MeOH (50 ml.) was stirred with $NaBH_4$ (750 mg.) at 20° for 2·5 hr., and was then poured into ice–water, and extracted with Et_2O to give 2-p-*methoxybenzylidene*-5α-*androstan*-3β-*ol* (XIIIa) (12·1 g., m.p. 138—145°), m.p. 146—147° (from $CHCl_3$–petrol), $[\alpha]_D$ −59° (*c* 0·9) (Found: C, 82·5; H, 9·7. $C_{27}H_{38}O_2$ requires C, 82·2; H, 9·7%), $\nu_{max.}$ 3620 cm.$^{-1}$, $\lambda_{max.}$ 254 nm. (ε 15,000), τ 5·81 (m, $w_{\frac{1}{2}}$ 16 Hz, 3α-H).

The ketone (XIb) (5·19 g.) gave similarly 2-p-*methoxybenzylidene*-5α-*androstane*-3β,17β-*diol* (XIIIb) (4·95 g.), m.p. 124·5—127° (from Me_2CO), $[\alpha]_D$ −53° (*c* 0·7) (Found: C, 78·95; H, 9·2. $C_{27}H_{38}O_3$ requires C, 79·0; H, 9·3%).

Reduction of the ketone (XId) (2 g.) as in expt. 7 gave 2-p-*methoxybenzylidene*-5α-*cholestan*-3β-*ol* (XIIId) (1·95 g.), m.p. 161—163° (from EtOH), $[\alpha]_D$ −53° (*c* 1·1) (Found: C, 82·8; H, 10·8. $C_{35}H_{54}O$ requires C, 82·9; H, 10·9%), $\lambda_{max.}$ 255 nm. (ε 16,000), τ 5·85 (m, $w_{\frac{1}{2}}$ 19 Hz, 3α-H).

Experiment 16. A solution of the ketone (XIId) (2 g.) in Et_2O (100 ml.) was added during 20 min. to a stirred solution of $LiAlH_4$ (2 g.) in Et_2O (40 ml.). The solution was boiled under reflux for 3 hr., and poured into ice–water (300 ml.) containing glacial AcOH (5 ml.). Isolation with Et_2O gave material which, after filtration in benzene–petrol (1 : 1) through deactivated Al_2O_3, afforded 2-*benzylidene*-5α-*cholestan*-3β-*ol* (XIVd) (1·2 g.), m.p. 111—113° (from EtOH), $[\alpha]_D$ −47° (*c* 1·1) (Found: C, 85·5; H, 11·1. $C_{34}H_{52}O$ requires C, 85·7; H, 11·0%), $\lambda_{max.}$ 244 nm. (ε 14,300).

Experiment 17. The alcohol (XIIIa) was dissolved in C_5H_5N (50 ml.), Ac_2O (50 ml.) was added, and the solution kept at 20° for 6 hr. Work-up gave 2-p-*methoxybenzylidene*-5α-*androstan*-3β-*yl acetate* (XVa) (12·4 g.), as an oil, $[\alpha]_D$ −83° (*c* 1·0) (Found: C, 79·7; H, 9·3. $C_{29}H_{40}O_3$ requires C, 79·8; H, 9·2%), $\nu_{max.}$ 1732 cm.$^{-1}$, τ 4·80 (q, *J* 11 and 8 Hz, 3α-H).

The alcohols (XIIIb) and (XIIId) similarly gave quantitative yields of, respectively, 3β,17β-*diacetoxy*-2-p-*methoxybenzylidene*-5α-*androstane* (XVc), m.p. 121—123·5° (from C_6H_{14}), $[\alpha]_D$ +2° (*c* 1·0) (Found: C, 75·35; H, 8·8. $C_{31}H_{42}O$ requires C, 75·3; H, 8·6%), τ 4·78 (q, *J* 11 and 8 Hz, 3α-H), and 2-p-*methoxybenzylidene*-5α-*cholestan*-3β-*yl acetate* (XVd), m.p. 139—141°, $[\alpha]_D$ −57° (*c* 1·2) (Found: C, 80·8; H, 10·4. $C_{37}H_{56}O_3$ requires C, 80·9; H, 10·3%).

Experiment 18. The acetate (XVa) (2·32 g.) in MeOH (105 ml.)–EtOAc (43 ml.) was ozonised at −70° as in expt. 3 and was worked up with AcOH (20 ml.) and Zn (25 g.) to give 2-*oxo*-5α-*androstan*-3β-*yl acetate* (XVIa) (1·16 g.), m.p. 165—167° (from MeOH), $[\alpha]_D$ +74° (*c* 1·1) (Found: C, 75·7; H, 9·7. $C_{21}H_{32}O_5$ requires C, 75·9; H, 9·7%), $\nu_{max.}$ 1752 and 1732 cm.$^{-1}$.

The diacetate (XVc) (4·85 g.) similarly gave 3β,17β-*diacetoxy*-5α-*androstan*-2-*one* (XVIc) (3·2 g.), m.p. 153·5—155·5° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +60° (*c* 0·9) (Found: C, 70·5; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·9%). On ozonolysis at −20°, the acetate (XVd) (1 g.) gave the keto-acetate (XVId) (0·68 g.), m.p. 146—147°, $[\alpha]_D$ +72° (*c* 1·4), $\nu_{max.}$ 1751 and 1734 cm.$^{-1}$ (lit.,[16] m.p. 145·5—146°, $[\alpha]_D$ +75·5°).

Experiment 19. Activated Zn dust (200 g.) was added to a stirred solution of the keto-acetate (XVIa) (4·13 g.) in glacial AcOH (150 ml.) and the mixture was boiled under reflux for 2 hr. The Zn was filtered off, washed with AcOH, and the combined filtrates were poured into ice–water. The precipitate was collected, dried, and chromatographed on SiO_2 (150 ml.). Elution with petrol–ether (19 : 1) gave 5α-androstan-2-one (XVIIa) (2·34 g.), m.p. 120—122° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +43° (*c* 0·8) {lit.,[3] m.p. 122—123°, $[\alpha]_D$ +36° (dioxan)} (Found: C, 83·0; H, 11·0. Calc. for $C_{19}H_{30}O$: C, 83·2; H, 11·0%). Starting material (0·44 g.) was eluted with petrol–ether (17 : 3). An increase in the reaction time gave a lower yield of the ketone (XVIIa), hydrocarbons (probably 5α-androst-2-ene and 5α-androstane) being formed slowly.

The keto-diacetate (XVIc) (2·74 g.) similarly gave 2-oxo-5α-androstan-17β-yl acetate (XVIIc) (1·67 g.), m.p. 146—148° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +26° (lit.,[17] m.p. 149—150°, $[\alpha]_D$ +27°) (Found: C, 76·0; H, 9·7. Calc. for $C_{21}H_{32}O_3$: C, 75·9; H, 9·7%). Hydrolysis, by boiling the keto-acetate (1·13 g.) for 1 hr. in MeOH (30 ml.) containing KOH (1 g.), afforded 17β-hydroxy-5α-androstan-2-one (951 mg.), m.p. 179—180° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +44° (*c* 1·1) (lit.,[18] m.p. 180—181°, $[\alpha]_D$ +49°). This hydroxy-ketone (825 mg.) was oxidised as in expt. 12 to 5α-androstane-2,17-dione (XVIII) (720 mg.), m.p. 153—155° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +112° (*c* 0·9) (lit.,[17] m.p. 155—157°, $[\alpha]_D$ +114·6°).

Experiment 20.—A solution of the keto-acetate (XVId) (800 mg.) in dry PhMe (40 ml.) was added over 10 min. to a stirred solution of Ca (600 mg.) in liquid NH_3 (freshly distilled from Na; 120 ml.). After a further 15 min., PhMe–MeOH (1 : 1) was added until the blue colour disappeared. The material isolated by dilution with H_2O and extraction with Et_2O was oxidised as in expt. 12 to give 5α-cholestan-2-one (XVIId) (0·34 g.), m.p. 126—127° (from MeOH), $[\alpha]_D$ +43° (*c* 1·1) (lit.,[19] m.p. 128—129°, $[\alpha]_D$ +48°).

Experiment 21. 5α-Androstane-3,17-dione (XIX) (5·97 g.) was added to a boiling solution of KOH (15 g.) in EtOH (300 ml.)–H_2O (10 ml.). After 1 min., anisaldehyde (12 ml.) was added, and the mixture was boiled under reflux for a further 5 min. Filtration at 20° gave 2,16-*di*-(p-*methoxybenzylidene*)-5α-*androstane*-3,17-*dione* (XX) (9·62 g., m.p. 212—216°), m.p. 217—219° (from EtOH), $[\alpha]_D$ −244° (*c* 1·1) (Found: C, 80·1; H, 7·8. $C_{35}H_{40}O_4$ requires C, 80·1; H, 7·7%). This diketone, in tetrahydrofuran (220 ml.)–MeOH (22 ml.) was reduced with $NaBH_4$ (977 mg.), as in expt. 15, to give 2,16-*di*-(p-*methoxybenzylidene*)-5α-*androstane*-3β,17β-*diol* (9·59 g.; m.p. 161—165°), m.p. 166·5—168·5° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ −56° (*c* 0·44) (Found: C, 77·65; H, 8·3. $C_{35}H_{44}O_4$,Me_2CO requires C, 77·8; H, 8·6%), τ 9·29 (19-H) and 9·36 (18-H). Acetylation of the 3,17-diol as in expt. 17, and chromatography on SiO_2 afforded the 3β,17β-*diacetate* (9·4 g.) as an oil, $[\alpha]_D$ −49° (*c* 0·9) (Found: C, 76·35; H, 7·9. $C_{39}H_{48}O_6$ requires C, 76·4; H, 7·9%), τ 9·30 (19-H and 18-H), which was judged pure by t.l.c. Ozonolysis of this oil, as in expt. 18, gave 3β,17β-*diacetoxy*-5α-*androstane*-2,16-*dione* (3·62 g.), m.p. 218—221° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ −52° (*c* 1·1) (Found: C, 68·5; H, 7·9. $C_{23}H_{32}O_6$ requires C, 68·3; H, 8·0%), $\nu_{max.}$ 1767, 1749, and 1733 cm.$^{-1}$, τ 9·18 (19-H and 18-H).

Reduction of this diacetate (2 g.) in AcOH (75 ml.) with

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Zn (100 g.), as in expt. 19 but for 8 hr., afforded *5α-androstane-2,16-dione* (XXI) (658 mg.), m.p. 158—159° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ −142° (*c* 1·0) (Found: C, 79·0; H, 9·6. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%), $\nu_{max.}$ 1746 and 1713 $cm.^{-1}$.

Experiment 22. A solution of $LiAlH_4$ (28 mg.) in dry Et_2O (30 ml.) was added during 5 min. to a stirred solution of the ketone (XIa) (500 mg.) in Et_2O (70 ml.) at 5°. The mixture was stirred for 2 hr. at 20°, and was then cooled to 5°. A solution of $AlCl_3$ (388 mg.) in Et_2O (50 ml.) was added during 20 min., and stirring was continued for 1 hr. at 5° and for 1·5 hr. at 20°. Standard manipulation followed by elution from SiO_2 with petrol–ether (49 : 1) gave *2-p-methoxybenzylidene-5α-androst-3-ene* (XXIIa) (400 mg.), m.p. 121—124° (from Me_2CO–MeOH–H_2O), $[\alpha]_D$ −124° (*c* 1·0) (Found: C, 86·4; H, 9·8. $C_{27}H_{36}O$ requires C, 86·2; H, 9·8%), $\lambda_{max.}$ 290 nm. (ε 21,500), τ 3·89 (q, *J* 10 and 2 Hz), 4·60 (q, *J* 10 and 1·5 Hz) and 9·30 (19-H and 18-H).

Hydrogenation of the diene (48 mg.) in EtOAc over Pd–on–C for 1 hr. afforded *2β(?)-p-methoxybenzyl-5α-androstane* (XXIVa) (40 mg.), m.p. 97—99° (from MeOH), $[\alpha]_D$ +3° (*c* 0·9) [Found: C, 83·5; H, 10·5%; *M* (mass spectrometry), 380. $C_{27}H_{40}O$, 0·5 MeOH requires C, 83·2; H, 10·6%, and $C_{27}H_{40}O$ requires *M*, 380].

Experiment 23. Et_2O (30 ml.) was added during 5 min. with stirring to $AlCl_3$ (246 mg.) at 5°. After 10 min., a solution of $LiAlH_4$ (17·5 mg.) in Et_2O (20 ml.) was added during 10 min., and the solution was stirred for a further 15 min. at 5°. A solution of the alcohol (XIIIa) (300 mg.) in Et_2O (20 ml.) was added during 20 min., and stirring was continued for 2 hr. at 5°. Work-up gave the diene (XXIIa) (208 mg.).

Experiment 24. Treatment of the ketone (XIa) (500 mg.) as in expt. 23, but with the final stirring continued for 5 hr. at 5°, gave material which was separated by preparative t.l.c. into the ketone (XIa) (359 mg.) and a mixture (130 mg.) of olefins. Analysis by n.m.r. showed this mixture to consist of the diene (XXIIa) (90 mg.; key signal, τ 3·89), the Δ^2-olefin (XXVa) (20 mg.; τ 4·60), and the conjugated olefin (XXIIIa) (20 mg.; τ 3·75). A solution of the mixture in Et_2O (3 ml.) was added at 5° to Et_2O (10 ml.) containing $AlCl_3$ (74 mg.) and $LiAlH_4$ (5·3 mg.), and the solution was boiled under reflux for 2·5 hr. Analysis of the product showed it to contain about equal amounts of the olefins (XXIIIa) and (XXVa), but none of the diene (XXIIa).

Experiment 25. The ketone (XIId) (1·8 g.) was treated, as in expt. 2, with $AlCl_3$ (1·95 g.) and $LiAlH_4$ (0·14 g.). Chromatography on neutral Al_2O_3 and elution with petrol–benzene (1 : 1) gave material (805 mg.) containing equal amounts of the olefins (XXIIId) (τ 3·81) and (XXVd) (τ 4·68). This was dissolved in benzene (100 ml.) containing *p*-$MeC_6H_4{\cdot}SO_3H,H_2O$ (1·5 g.), and the solution was boiled under reflux for 1 hr. Trituration of the product with Me_2CO gave *2-benzyl-5α-cholest-2-ene* (XXVd) (520 mg.), m.p. 69—71° (from EtOH), $[\alpha]_D$ +44° (*c* 1·5) (Found: C, 88·5; H, 11·5. $C_{34}H_{52}$ requires C, 88·6; H, 11·4%), $\lambda_{max.}$ 250 nm. (ε 1700), τ 6·92 (Ar-CH_2), 4·68 (3-H).

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