Hydroxy-steroids. Part XIX.[1] Preparation and Reactions of 4,4-Dimethyl-5α-androstan-2-one and Lupan-2-one

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4,4-Dimethyl-5α-androstan-2-one and lupan-2-one, prepared from the 3-ketones by general methods for transposing oxo-groups, undergo substitutions at position 3. Acetoxylation and bromination proceed easily and introduce 3α-substituents; formylation to the 3-hydroxymethylene-2-ketones is difficult and gives poor yields even under forcing conditions.

THERE have been several investigations into the methods of preparation [2,3] and the reactions of steroidal 2-ketones; [4-6] much less is known about the 4,4-dimethyl analogues, the most important study, of 4,4-dimethyl-5α-cholestan-2-one, being that of Levisalles and co-

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workers.[7,8] The object of the present work was to prepare the simplest steroidal 4,4-dimethyl-2-ketone (Xa) and a related triterpene (Xb) (lupan-2-one), and to compare their reactions with those of 5α-androstan-2-one (Ic).

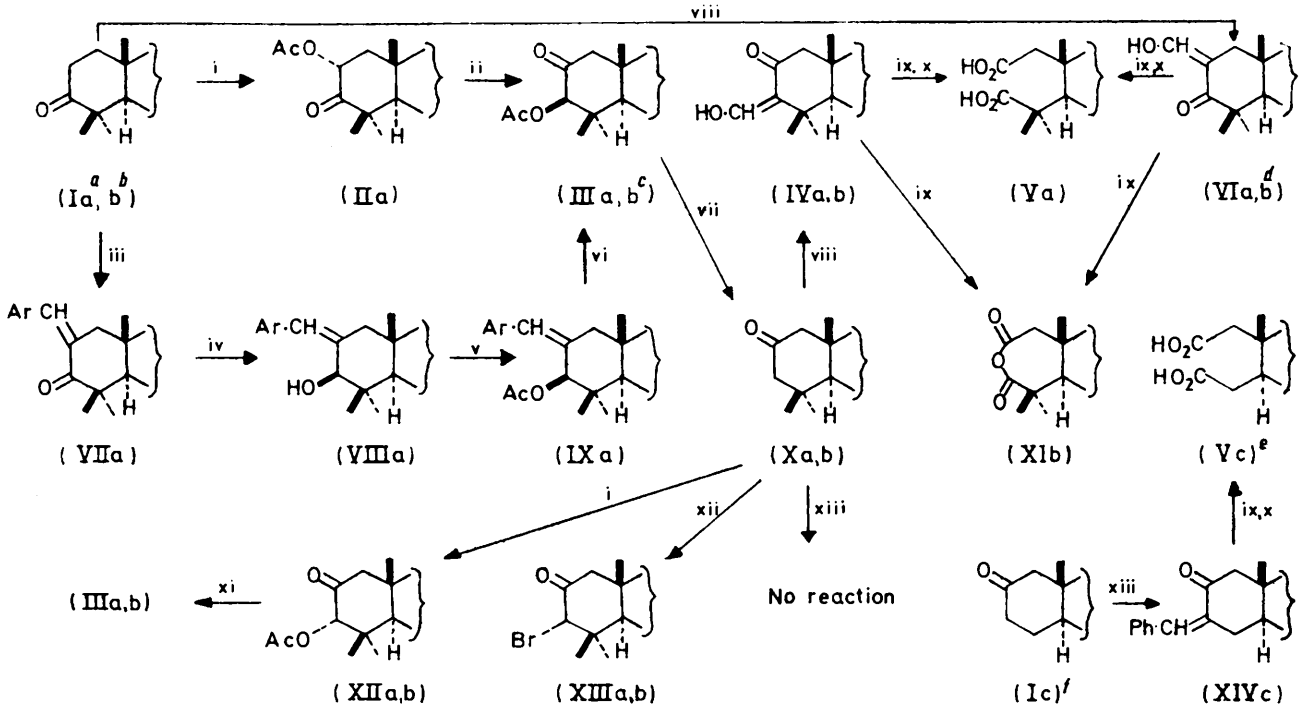
The preparations started with 4,4-dimethyl-5α-androstan-3-one [9] (Ia) and lupan-3-one [10] (Ib) and are outlined in the Scheme. Reduction of 2-oxolupan-3β-yl acetate [11] (IIIb), obtained by isomerising the 2α-acetoxy-3-ketone] gave lupan-2-one (Xb). Two methods [3,7,8] were used to prepare 2-oxo-4,4-dimethyl-5α-androstan-3β-yl acetate (IIIa). The isomerisation stage (2α-AcO,3-CO ⟶ 3β-AcO,2-CO) of the shorter route gave an equilibrium mixture; although the 3β-acetate predominated, purification was hampered by the unusually high solubility of this compound in organic solvents. The alternative sequence based on 2-arylidene intermediates is longer, but each stage is efficient and the overall yield is appreciably higher.

5α-Androstan-2-one is formylated at position 3,[6] and gives the 3β-acetoxy-derivative with lead tetra-acetate;[5] brominations employing long reaction times of both 5α-cholestan-2-one [4] and 4,4-dimethyl-5α-cholestan-2-one [7] lead to mixtures of 3α- and 3β-bromo-compounds.

Formylation, inefficient even under forcing conditions, of the 2-ketones (Xa and b) gave products whose structures were established by oxidation to a diacid (Va) or an anhydride (XIb) which were also obtained from the isomeric 2-hydroxymethylene-3-ketones (VIa and b). [Formation of the anhydride (XIb) by ozonolysis is unusual, but occurs also with 2-arylidenelupan-3-ones;[12] work on a similar case [13] suggests that Baeyer–Villiger type oxidation of the intermediate 2,3-diketone is involved.] The presence of the 4,4-dimethyl substituents inhibits condensation with benzaldehyde which in the case of the unhindered 5α-androstan-2-one (Ic) occurs at the 3-position. Acetoxylation and bromination, the latter carried out for the minimum time required, gave derivatives [(XIIa and b) and (XIIIa and b)] formulated as the 3α-isomers on the basis of spectrometric comparisons with related compounds (see Experimental section) and, for the acetates, isomerisation under acidic conditions to the more stable 3β-compounds (IIIa and b).

SCHEME Preparation and reactions of 2-ketones

Derivatives of 4,4-dimethyl-5α-androstane (series a), lupane (series b), and 5α-androstane [series c]. References are given to known compounds; the rest are new.



Reagents: i, $Pb(OAc)_4$–BF_3; ii, Al_2O_3 (alkaline), or $NaHCO_3$–$EtCO_2H$, reflux; iii, *p*-MeO·C_6H_4·CHO–NaOH; iv, $NaBH_4$; v, Ac_2O–C_5H_5N; vi, O_3, then Me_2S; vii, Zn–AcOH; viii, HCO_2Et–NaH; ix, O_3; x, tetrahydrofuran–aq. H_2SO_4; xi, HBr–AcOH; xii, Br_2–AcOH; xiii, PhCHO–NaOEt.

[a] Ref. 9. [b] Ref. 10. [c] Ref. 11. [d] Ref. 15. [e] Ref. 16. [f] Ref. 3.

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The results of the reactions under kinetic control (those with lead tetra-acetate and bromine) show that 4,4-dimethyl-2-ketones enolise more quickly towards the 3- than the 1-position, as do the unsubstituted 2-ketones. Although quantitative comparisons have not been made the ease of the present reactions suggests that the 4,4-dimethyl group has only a small effect on them. It is not known whether formylation under the conditions used here is subject to kinetic or thermodynamic control;[14] substitution again occurs at the 3-position, but the 4,4-dimethyl group causes marked inhibition, probably by impeding the final stage in which the exocyclic double bond is formed.

EXPERIMENTAL

For general directions see *J.C.S. Perkin I*, 1972, 2081 and ref. 11. The c.d. data, kindly supplied by Professor W. Klyne, refer to solutions in dioxan. Petrol refers to light petroleum, b.p. 60—80°.

Preparation of the 2-Ketones (Xa *and* b).—(a) *Shorter route* (*see Scheme*). Treatment[11] of 4,4-dimethyl-5α-androstan-3-one[9] (Ia) (5·2 g) in AcOH (650 ml)–Ac_2O (50 ml)–BF_3,Et_2O (12 ml) under N_2 with $Pb(OAc)_4$ (15 g) at 20 °C gave 4,4-*dimethyl*-3-*oxo*-5α-*androstan*-2α-*yl acetate* (IIa) (3·1 g), m.p. 135—138° (from MeOH), $[\alpha]_D$ −100° (*c* 1·0) (Found: C, 76·8; H, 10·1. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%), $\nu_{max.}$ 1749 and 1725 (more intense band) cm^{-1}, τ 4·34 (4 lines, *J* 13 and 5 Hz, 2β-H), c.d. λ 287 (Δε −0·61) and 296 nm (−0·49). Isomerisation of the 2α-acetate (600 mg) on alkaline Al_2O_3[11] gave material (540 mg) shown by n.m.r. examination to contain the 3β-acetate (IIIa) and the 2α-acetate (IIa) in a ratio of *ca.* 10 : 1. Two crystallisations from small volumes of MeOH gave the 3β-acetate (IIIa) (204 mg), m.p. 139—143°, $[\alpha]_D$ +62°, identified by comparison with authentic material described below. Isomerisation of the 2α-acetate (600 mg) with $NaHCO_3$–$EtCO_2H$[11] gave the 3β-acetate (IIIa) (195 mg).

Reduction of the 3β-acetate (IIIa) (1·5 g) with Zn dust (50 g) in glacial AcOH (70 ml) as in experiment 19 of ref. 3 gave 4,4-*dimethyl*-5α-*androstan*-2-*one* (Xa) (820 mg), m.p. 113—116° (from MeOH), $[\alpha]_D$ +23° (*c* 0·9) (Found: C, 83·1; H, 11·4. $C_{21}H_{34}O$ requires C, 83·4; H, 11·3%), $\nu_{max.}$ 1712 cm^{-1}, τ 9·31 (18-H), 9·11 (19-H and 4β-Me), and 8·96 (4α-Me), c.d. λ 289 (Δε +1·13), 297 (+1·36), and 305 nm (+1·31). Similarly 2-oxolupan-3β-yl acetate[11] (IIIb) (1·5 g) gave *lupan*-2-*one* (Xb) (885 mg), m.p. 205—207° (from MeOH), $[\alpha]_D$ +9° (*c* 0·9) (Found: C, 84·6; H, 12·0. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%), $\nu_{max.}$ 1712 cm^{-1}, c.d. λ 290 (Δε +3·69), 298 (+4·50), and 307 nm (+4·26).

(b) *Longer route* (*see Scheme*). 4,4-Dimethyl-5α-androstan-3-one (Ia) (4·8 g), KOH (7·5 g), and anisaldehyde (3·2 ml) in EtOH (200 ml) gave[3] the 2-p-*anisylidene*-4,4-*dimethyl*-5α-*androstan*-3-*one* (VIIa) (5·7 g), m.p. 125—127° (from MeOH), $[\alpha]_D$ −143° (*c* 1·1) (Found: C, 82·8; H, 9·6. $C_{29}H_{40}O_2$ requires C, 82·8; H, 9·6%). Reduction[3] of this ketone (5·5 g) with $NaBH_4$ (400 mg) gave 2-p-*anisylidene*-4,4-*dimethyl*-5α-*androstan*-3β-*ol* (VIIIa) (5·2 g), m.p. 156—158° (from petrol), $[\alpha]_D$ −252° (*c* 1·1) (Found: C, 82·4; H, 10·0. $C_{29}H_{42}O_2$ requires C, 82·4; H, 10·0%). Treatment[3] of this alcohol (5·1 g) with Ac_2O (35 ml)–C_5H_5N (35 ml) gave 2-p-*anisylidene*-4,4-*dimethyl*-5α-*androstan*-3β-*yl acetate* (IXa) (5·05 g), m.p. 142—144° (from MeOH), $[\alpha]_D$ −200° (*c* 0·9) (Found: C, 80·0; H, 9·5. $C_{31}H_{44}O_3$ requires C, 80·1; H, 9·55%). A solution of this acetate (4·9 g) in EtOAc (300 ml)–MeOH (700 ml) was ozonised at −40 °C until a blue colour persisted, and then flushed with N_2 for 15 min. Me_2S (10 ml) was added, and the cooling bath was removed. Work-up after 12 h gave 2-*oxo*-4,4-*dimethyl*-5α-*androstan*-3β-*yl acetate* (IIIa) (2·9 g), m.p. 142—144° (from MeOH), $[\alpha]_D$ +57° (*c* 1·1) (Found: C, 76·6; H, 10·1. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%), $\nu_{max.}$ 1750 and 1730 (bands about equally intense) cm^{-1}, τ 5·03 (s, $W_{\frac{1}{2}}$ 2 Hz, 3α-H), c.d. λ 290 (Δε +1·22) and 298 nm (+1·33).

The Hydroxymethylene-ketones (IVa *and* b) *and* (VIa *and* b).—Treatment[14b] of 4,4-dimethyl-5α-androstan-3-one (Ia) (520 mg) in C_6H_6 (40 ml) containing HCO_2Et (2 ml) with NaH (520 mg) gave 2-*hydroxymethylene*-4,4-*dimethyl*-5α-*androstan*-3-*one* (VIa) (410 mg), m.p. 81—83° (from MeOH), $[\alpha]_D$ +27° (*c* 0·9) (Found: C, 79·7; H, 10·1. $C_{22}H_{36}O_2$ requires C, 79·95; H, 10·4%), $\nu_{max.}$ ($CHCl_3$) 1630 and 1590 cm^{-1}.

A solution of the foregoing ketone (122 mg) in EtOAc (22 ml)–CH_2Cl_2 (9 ml) was ozonised at −50 °C for 5 min, flushed with N_2 for 15 min, and evaporated at 20 °C and 25 mmHg. The product was dissolved in tetrahydrofuran (4 ml)–H_2O (0·8 ml)–H_2SO_4 (0·1 ml) and kept at 20 °C for 3 days. Work-up gave 4,4-*dimethyl*-2,3-*seco*-5α-*androstane*-2,3-*dioic acid* (Va) (72 mg), m.p. 210—214° (from petrol), $[\alpha]_D$ (EtOH) +1° (*c* 0·9) (Found: C, 71·5; H, 9·6. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·7%).

NaH (160 mg) was added to a solution of 4,4-dimethyl-5α-androstan-2-one (175 mg) in C_6H_6 (25 ml) containing HCO_2Et (5 ml) under N_2 at 20 °C. The flask was stoppered and shaken, three further portions of NaH (each 160 mg) being added at daily intervals. Work-up after 7 days gave material which was chromatographed on SiO_2 (80 g). Light petroleum eluted unchanged 2-ketone (115 mg). Petrol–Et_2O eluted material (54 mg) which crystallised from MeOH to give 3-*hydroxymethylene*-4,4-*dimethyl*-5α-*androstan*-2-*one* (IVa) (25 mg), m.p. 139—140·5° (Found: C, 79·8; H, 10·3. $C_{22}H_{36}O_2$ requires C, 79·95; H, 10·4%), $\nu_{max.}$ ($CHCl_3$) 1633 and 1591 cm^{-1}. Ozonolysis of this ketone (40 mg) and treatment with aq. H_2SO_4 as described above gave the diacid (Va) (15 mg), m.p. and mixed m.p. 209—213°.

Similarly, lupan-2-one (Xb) (250 mg) gave 3-*hydroxymethylenelupan*-2-*one* (IVb) (35 mg), m.p. 194—196° (after crystallisation from MeOH) (Found: C, 81·4; H, 11·3. $C_{31}H_{50}O_2$ requires C, 81·9; H, 11·1%), $\nu_{max.}$ ($CHCl_3$) 1632 and 1590 cm^{-1}. A solution of this ketone (125 mg) in EtOAc (25 ml)–CH_2Cl_2 (8 ml) was ozonised at −50 °C for 5 min, flushed with N_2, and evaporated at 20 °C and 25 mmHg. Crystallisation from petrol gave 3-*oxa*-A-*homolupan*-2,4-*dione* (XIb) (65 mg), m.p. 248—251°, $[\alpha]_D$ +35° (*c* 0·9) (Found: C, 78·7; H, 10·6. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·7%), $\nu_{max.}$ 1798 and 1759 cm^{-1}. This anhydride (82 mg) was also obtained by ozonolysis of 2-hydroxymethylenelupan-3-one[15] (VIb) (138 mg).

3-*Benzylidene*-5α-*androstan*-2-*one* (XIVc).—PhCHO (filtered twice through Al_2O_3; 0·3 ml) was added to 5α-androstan-2-one[3] (Ic) (252 mg) in 5% NaOEt in EtOH (10 ml). After 90 min at 20 °C the insoluble material was collected and crystallised from EtOH to give the *benzylidene-ketone* (XIVc) (215 mg), m.p. 205—206°, $[\alpha]_D$ −72° (*c* 1·1)

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(Found: C, 85·7; H, 9·6. $C_{26}H_{34}O$ requires C, 86·1; H, 9·4%), $\nu_{max.}$ 1680 cm^{-1}. Ozonolysis of this ketone (70 mg) followed by treatment with aq. H_2SO_4 gave 2,3-seco-5α-androstane-2,3-dioic acid [16] (Vc) (43 mg), m.p. and mixed m.p. 234—237°, $[\alpha]_D$ −7° (*c* 0·9 in EtOH).

The 2-ketones (Xa and b) were recovered unchanged after treatment with PhCHO in NaOEt–EtOH at 20 °C for times up to 4 days.

The 3-*Bromo*-2-*ketones* (XIIIa *and* b).—Br_2 (190 mg) in AcOH (2 ml) was added to 4,4-dimethyl-5α-androstan-2-one (Xa) (288 mg) in AcOH (44 ml) at 20 °C. The solution became colourless after 6 min, and was then worked up. P.l.c. [1 large plate, 2 × petrol–Et_2O (19 : 1)] gave 3α-*bromo*-4,4-*dimethyl*-5α-*androstan*-2-*one* (XIIIa) (195 mg, m.p. 152—155°, after crystallisation from MeOH), $[\alpha]_D$ +142° (*c* 1·1) (Found: C, 66·3; H, 8·7. $C_{21}H_{33}BrO$ requires C, 66·1; H, 8·7%), $\nu_{max.}$ (CCl_4) 1720 cm^{-1}, τ (CCl_4) 6·15 [d, *J* 1·6, 3β-H with small couplings to (?) 1β-H], c.d. λ 317 (Δε + 7·2) and 227 nm (−2·1). [The values for 3α-bromo-4,4-dimethyl-5α-cholestan-2-one in the same solvents are $\nu_{max.}$ 1720 cm^{-1}, τ 6·17 (s), c.d. λ 319 nm (Δε +7·6), and for the 3β-bromo-isomer $\nu_{max.}$ 1735 cm^{-1}, τ 5·53, c.d. λ 296 (Δε +1·11) and 304 nm (+1·16).]

Lupan-2-one (Xb) (212 mg) similarly gave 3α-*bromolupan*-2-*one* [144 mg, m.p. 218—222° (decomp.), after crystallisation from MeOH], $[\alpha]_D$ +97° (*c* 0·8) (Found: C, 71·4; H, 9·5. $C_{30}H_{49}BrO$ requires C, 71·3; H, 9·8%), $\nu_{max.}$ 1721 cm^{-1}, τ (CCl_4) 6·15 (d, *J* 1·4, 3β-H), c.d. λ 319 nm (Δε +6·9).

The 3α-*Acetoxy*-2-*ketones* (XIIa *and* b).—Treatment [11] of 4,4-dimethyl-5α-androstan-2-one (Xa) (240 mg) in AcOH (35 ml)–Ac_2O (4 ml)–BF_3,Et_2O (0·5 ml) under N_2 with $Pb(OAc)_4$ (1 g) at 20 °C for 2·5 h, and purification of the product by p.l.c. [1 large plate, 2 × petrol–Me_2CO (12 : 1) gave 2-*oxo*-4,4-*dimethyl*-5α-*androstan*-3α-*yl acetate* (XIIa) (135 mg, m.p. 149—152° after crystallisation from MeOH), $[\alpha]_D$ +6° (*c* 1·1) (Found: C, 76·5; H, 10·0. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%), $\nu_{max.}$ 1748 (more intense band) and 1728 cm^{-1}, τ 5·19 (s, $W_{\frac{1}{2}}$ 2 Hz, 3β-H), c.d. λ 290 (Δε +1·04) and 298 nm (+0·94).

Similarly lupan-2-one (Xb) (250 mg) gave 2-*oxolupan*-3α-*yl acetate* (165 mg, m.p. 221—223°, after crystallisation from MeOH), $[\alpha]_D$ +12° (*c* 1·1) (Found: C, 79·4; H, 10·95. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%), $\nu_{max.}$ 1748 (more intense band) and 1728 cm^{-1}, τ 5·24 (s, $W_{\frac{1}{2}}$ 1·7 Hz, 3β-H), c.d. λ 292 (Δε +1·43), 298 (+1·36), and 309 nm (+0·85). [The c.d. peak (MeOH) of 2-oxo-5α-cholestan-3α-yl acetate is at 300 nm (Δε 1·45), and that of the 3β-isomer at 289 (+3·2).[17]]

Treatment of these acetoxy-ketones (XIIa and b) (70 mg) in AcOH (3 ml) with 48% HBr–AcOH (0·1 ml) at 20 °C for 2 days, work-up, and crystallisation of the products from MeOH gave the corresponding 3β-acetoxy-2-ketones [(IIIa), 25 mg] and [(IIIb), 52 mg], identical (i.r. and n.m.r. spectra) with authentic materials.

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