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# STEROIDAL ANALOGUES OF UNNATURAL CONFIGURATION—VII[1]

## TOTAL SYNTHESIS OF 17β-HYDROXY-9-METHYL-9β,10α-OESTR-4-EN-3-ONE, A NOVEL RETROTESTOSTERONE ISOMER[2]

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**Abstract**—Conjugate methylation of 17β-hydroxy-des-A-oestr-9-en-5-one (**1**) and the derived 4,5-seco-steroid (**6b**) afforded the respective 9β-methyl compounds. Base-catalysed alkylation of 17β-hydroxy-9-methyl-des-A-9β-oestran-5-one (**3a**) resulted in attack at C(6); this result was used to prepare the anthrasteroid (**5**). Ring closure of the 9β-methyl-4,5-seco-steroid (**8**) derived from **6b** afforded 17β-hydroxy-9-methyl-9β,10α-oestr-4-en-3-one (**9a**). Conjugate methylation of 17β-hydroxyoestra-4,9-dien-3-one (**11**) resulted in 1,4-addition to the dienone system.

The synthesis of 9β,10α-steroids has attracted much attention[3–5] since it was demonstrated[6] that certain members of this class of compounds display potent physiological activity. Current concepts of the relationship between structure and hormonal activity do not readily account for this finding since the B,C-*cis* ring fusion profoundly affects molecular geometry and consequently, disallows facile comparisons with skeletally normal steroid hormones.[7]

The 9β,10α- and 19-nor-9β,10α-series[1] have been extensively investigated, but structural variations suggested by the cucurbitacin nucleus *viz*, the 19-nor-9-methyl-9β,10α-[or 19(10→9β)*abeo*-10α-[1]] series, have not hitherto been synthesised. Clearly the known[8] aptitude for migration of the steroidal 10β-Me group to the 9-position *via* 9-carbonium ion processes can be adapted to this purpose. We chose, however, to examine more versatile totally synthetic pathways, leading to hormone analogues unencumbered by C-ring functionality.

The des-A-steroid (**1**) which is an intermediate in the epochal total syntheses developed by Roussel-Uclaf,[9] afforded an attractive starting point since it was reasoned that the known[10] *cis*-stereoselectivity of copper-catalysed conjugate methylation to the bridgehead position of appropriate octalones would apply. Consequently, it would be possible to prepare a 9β-methyl-des-A-steroid, to which the A-ring elements could be added by unexceptional methods, or to carry out the key methylation upon a derivative of **1**[9] to which the four-carbon side-chain at C(10) had already been added.

Preliminary experiments were performed by treating **1** with methylmagnesium iodide in the presence of catalytic amounts of cupric acetate, but the major product (50%) was shown by spectroscopic data [$M^+$, 218; $\lambda_{max}$ 239 nm (ε 18400); no CO absorption in IR] to be the transoid diene (**2**), which clearly arose through 1,2-methylation and subsequent dehydration. The desired product (**3a**, *vide infra*) was obtained in only 10% yield.

Treatment of **1** with methylcopper[11] (generated by treating cuprous iodide with 1 mol of methyl lithium) afforded only the 1,4-alkylation product (**3a**) albeit very slowly. GLC monitoring revealed that after 5 hr at 0°, the reaction had proceeded to 30%. However, the reaction of **1** with dimethyl copper lithium[11] (DCL) proceeded rapidly (2·5 hr at 0°) and regiospecifically to give a quantitative yield of **3a**. Careful examination of the product failed to reveal any trace of the 9α-isomer.

The assignment of 9β-configuration to **3a** was supported[12] by CD evidence [$\lambda_{max}$ 288 nm (Δε + 0·51) in methanol], and confirmed by NMR examination of the derived[13] t-butyl ether (**3b**) under the influence of added tris (1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato) europium (III)[14] [Eu(fod)$_3$]. The t-butyl ether was chosen as a protective function to inhibit complexation of the shift reagent with the D-ring site, thereby preventing excessive shifts of potentially interfering resonances. The observed ΔEu[15] values of the 17α- and t-Bu protons (Table 1) reveal that this was successful, and the induced shifts of B-ring protons in **3b** displayed linearity in the range of examination [0–0·29 mol. Eu(fod)$_3$]. The signals were readily identified and assigned by consideration of the well-known ψ-contact relationship:[16] the shift behaviour of assigned proton signals accords with expectations for a con-

Table 1. NMR data* for 17β-t-butoxy-9-methyl-des-A-9β-oestran-3-one (3b)

| Chemical shift (ppm) | Multiplicity and coupling (Hz) | ΔEu | Assignment |
|---|---|---|---|
| *ca* 1·97 | br. d, $J_{gem}$ 14 | 17·45 | 6β-H |
| *ca* 1·57 | d, $J_{gem}$ 14 | 16·3 | 10β-H |
| *ca* 2·13 | t.d, $J_{gem}$ 14; $J_{aa}$ 14; $J_{ae}$ 7 | 13·57 | 6α-H |
| 2·63 | d, $J_{gem}$ 14 | 13·3 | 10α-H |
| *ca* 1·92 | t.t, $J_{gem}$ 14; $J_{aa}$ 14; $2\times J_{ae}$ 4·5 | 7·57 | 7β-H |
| 0·92 | s, | 6·15 | 9β-Me |
| 0·73 | s, | 1·77 | 13β-Me |
| 3·41 | t, $2\times J$ 8 | 1·46 | 17α-H |
| 1·08 | s | 0·45 | t-Bu |

*NMR data in Tables 1, 2 and 3 were determined at 100 MHz for 0·001 M-solutions of substrate in $CCl_4$ with TMS as internal reference. Shift spectra were obtained for each of successive additions of $Eu(fod)_3$ up to 0·3–0·5 mol. Approximate chemical shifts refer to values obtained by extrapolation. s, singlet; d, doublet; br. d, broadened doublet; t.d, triplet of doublets; t, triplet; t.t, triplet of triplets; q, quarter; m, multiplet.

formationally rigid cyclohexanone,[17] in that ΔEu values decrease in the order, *α-eq* > *α-ax* > *β-ax* > *β-eq*.

The signal for the axial β-removed proton at C(7) was separated from interfering signals at 0·144 mol $Eu(fod)_3$ and appeared as a triplet of triplets ($J$ 14 and 4·5 Hz) (Fig 1), to which the couplings $J_{7\beta,7\alpha} \sim J_{7\beta,6\alpha} = 14$ Hz and $J_{7\beta,6\beta} \sim J_{7\beta,8\beta} = 4{\cdot}5$ Hz are uniquely assigned. This signal is compatible only with 9β-configuration for the introduced Me group, since a B,C-*trans* ring junction would give rise to one small (*ax-eq*) and three large (two *ax-ax* and one *gem*) couplings for the axial C(7) proton. Other signals for the B-ring protons are consistent with the structural assignment (Table 1).

It was expected, by consideration of the factors governing relative stabilities of the possible enolates,[18] that enolisation of the 5-CO group in 3 would proceed preferentially toward C(10) and hence, that base-catalysed alkylation would favour this position. However, prolonged treatment of **3a** with 1,3-dichlorobut-2-ene [DCB; *ca* 1:9 mixture of (*E*)- and (*Z*)-isomers (NMR)] in refluxing toluene in the presence of sodium hydride afforded in low yield, an oily product which was assigned structure **4**. The evidence for alkyl attachment at C(6) was based upon the presence of a doublet ($J$ 14 Hz) at δ 2·76 in the NMR spectrum. This signal is very similar to those seen for the 10α-proton in **3a** and **3b** [δ 2·73 ($J$ 15 Hz) and 2·63 ($J$ 14 Hz), respectively], and indicates that the 10-position of **4** is also unsubstituted.

Further evidence for preferential C(6) alkylation was obtained by annelation of **3b** with methyl vinyl ketone, under conditions described[19] for the successful synthesis of 9β,10α-steroids from 9β-H, 10β-Me analogues of 3. The only product isolated (65% of reacted **3b**) was assigned the

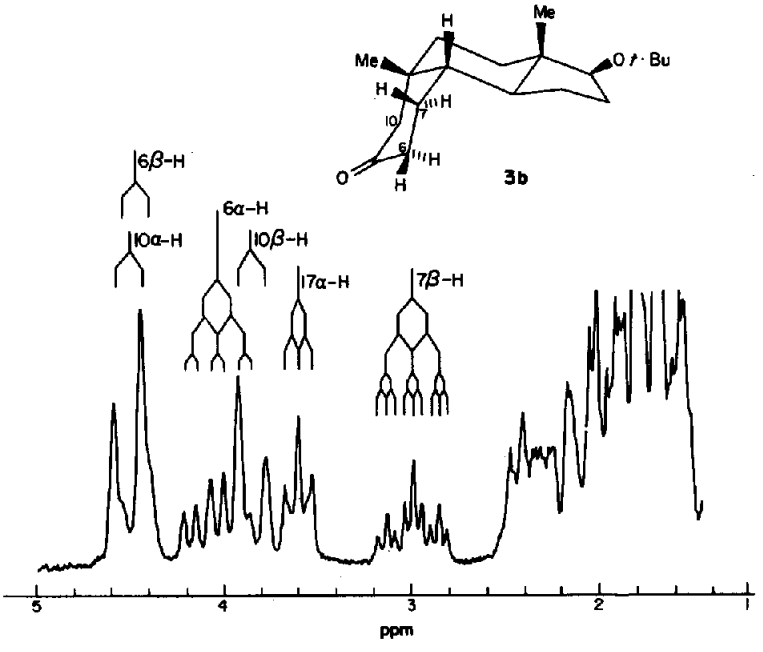
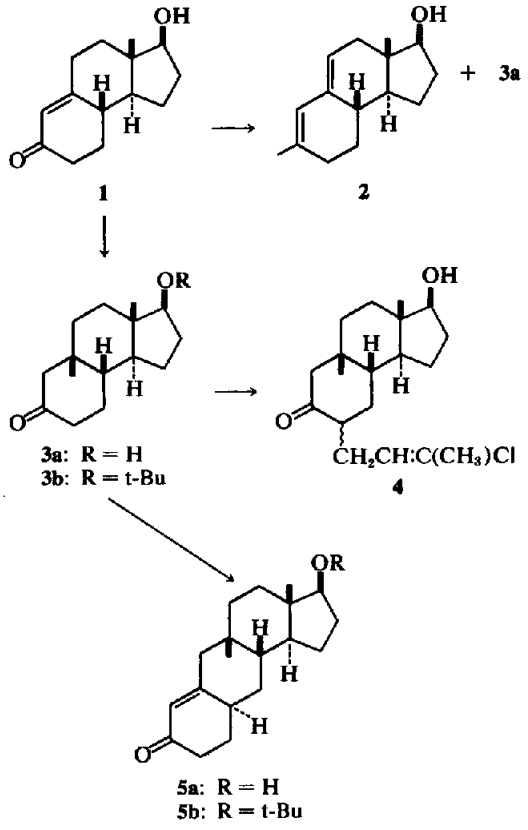



Fig 1.




anthrasteroid structure (**5b**) since the CD spectrum [$\lambda_{max}$ 311 ($\Delta\epsilon - 1{\cdot}04$) and 242 nm ($\Delta\epsilon + 10{\cdot}0$) in methanol] is incompatible with that expected[20] for a 3-oxo-$\Delta^4$-retrosteroid. The structural assignment was supported by shift spectral data on **5b** (Table 2) which revealed the presence of an AB system (*J ca* 15 Hz), whose mutual relationship was confirmed by double resonance. The lower field portion of this system was visible at $\delta$ 2·85 in the unshifted spectrum, as a doublet distinctly broadened by long-range coupling. Irradiation of the signal caused the olefinic proton triplet (*J* 2 Hz) at $\delta$ 5·64, to collapse to a doublet (*J* 2 Hz). These data accord with the anthrasteroid structure (**5b**) if the AB system is ascribed to the protons at C(10), the lower field signal being assigned to the 10$\alpha$-proton which is suitably orientated for allylic coupling with the olefinic 4-proton.[21] The presence of a further small coupling to the latter proton suggests that **5b** has 6$\alpha$-configuration, since the ring junction proton thereby enjoys a similar relative disposition toward C(4). This conclusion is also reached by inspection of Dreiding models since a 6$\beta$,9$\beta$-skeleton would require the adoption of a twist-boat conformation by the B- or C-ring. Such a conformation would be manifestly less stable than the all-chair conformation of the 6$\alpha$,9$\beta$-skeleton. It is equally evident that the aforegoing spectral data cannot accommodate the retrosteroid structure (**9**). Hydrolysis of **5b** afforded the 17-hydroxy-compound (**5a**) which differs from the authentic retrosteroid (**9a**, *vide infra*).

Table 2. NMR data for 17$\beta$-t-butoxy-9-methyl-1(10 → 6$\alpha$H)*abeo*-9$\beta$-oestr-4-en-3-one (**5b**)

| Chemical shift (ppm) | Multiplicity and coupling (Hz) | $\Delta$Eu | Assignment |
|---|---|---|---|
| *ca* 2·3 | d.t, $J_{gem}$ 17; $J_{e'e'}$ 5·5; $J_{e'e'}$ 4 | 14·4 | 2$\beta$-H |
| *ca* 2·1 | t.d, $J_{gem}$ 17; $J_{a'a'}$ 13; $J_{a'e'}$ 4 | 13·5 | 2$\alpha$-H |
| 5·64 | t, *J* 2 | 12·96 | 4-H |
| *ca* 1·38 | d, $J_{gem}$ 15 | 3·84 | 10$\beta$-H |
| 2·73 | br. d, $J_{gem}$ 15; $w_{1/2}$ *ca* 4 | 3·5 | 10$\alpha$-H |
| 0·91 | s | 1·44 | 9$\beta$-Me |
| 0·69 | s | 0·6 | 13$\beta$-Me |
| 3·38 | t, *J* 8 | 0·6 | 17$\alpha$-H |
| 1·08 | s | 0·28 | t-Bu |

The failure to alkylate **3** at C(10) is surprising in view of the expectation, based upon analogous systems,[19,22] that enolisation should occur preferentially toward that position. An explanation based upon the failure of **3** to form a 5(10)-enolate is clearly untenable since deuterium exchange upon **3b** under mild conditions [0·5 N-NaOD in dioxan-$D_2O$ (2:3) at 20° under $N_2$ for 16 hr] revealed (MS) that all four $\alpha$-hydrogens had been replaced. Although the sequence of exchange was not determined, it is clear that both of the possible enolates are readily formed.

A rationalisation of the relative reactivity of the 5(10)- and 5(6)-enolates must therefore be sought in the influence of the 9$\beta$-Me group. Dreiding models reveal that $\alpha$-face approach to the 5(10)-enolate of **3** is severely obstructed by the 12$\alpha$- and 14$\alpha$-protons, and that otherwise favoured anti-parallel attack must therefore be inhibited. However, $\beta$-directed attack would require approach of the electrophile along a co-ordinate parallel to the $\psi$-axial 9$\beta$-Me group (Fig 2). Since

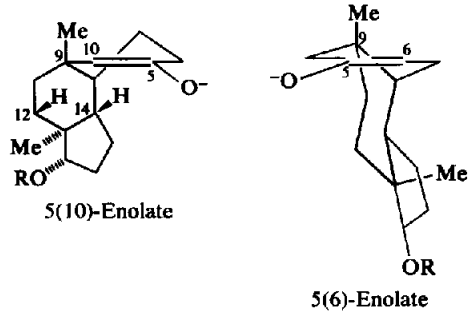



Fig 2.

it has been demonstrated[19,23] that alkylation of a related 9β-H,10-Me 5(10)-enolate is β-directed, the steric factor imposed by a 9β-Me group must suffice to suppress C(10) attack altogether in **3**, thereby allowing the reaction with the less stable, but more accessible 5(6)-enolate to take place (Fig 2).

It was therefore clear that it would be necessary to introduce the A-ring elements before the 9β-Me group. Accordingly, the pyrrolidine dienamine of **1** was treated with DCB to give **6a** (75%). That alkylation had proceeded in the desired manner[9,24] was shown by spectroscopic data. The compound (**6a**) and its derived benzoate[25] (**6b**) failed to crystallise, presumably because the (*E*):(*Z*)-isomer distribution in the reactant (DCB) is also reflected in the products (*vide infra*).

Conjugate alkylation of **6a** with DCL afforded the 9β-Me compound **7a** (41%). This step proceeded less efficiently than did **1** → **2** and, since the vinyl chloride moiety appears to be inert to DCL, the lower reactivity of **6a** is a probable stereoelectronic consequence of tetrasubstitution at the 9,10-position. No separation of (*E*)- and (*Z*)-isomers of **7a** was detected, but the product was purified by crystallisation. Upon conversion of unrecrystallised **7a** to the t-butyl ether (**7b**), however, a minor isomer, insufficient for characterisation, was detected during chromatography.

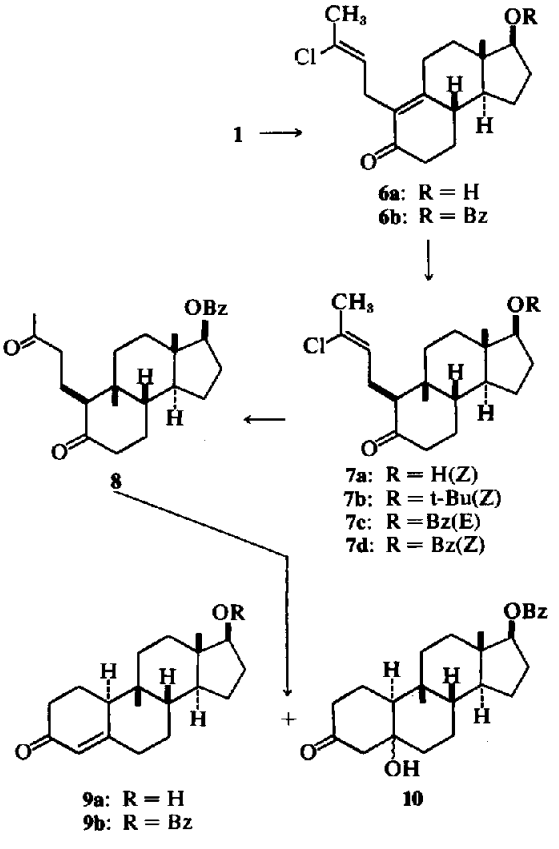
The (*Z*)-isomer (**7b**) was subjected to successive additions of Eu(fod)$_3$ during NMR examination, and the configuration at C(9) was firmly established (Table 3). In this instance, the axial 7-proton appeared as a multiplet composed of $J_{7\beta,7\alpha} = 14$ Hz, $J_{7\beta,6\alpha} = 10$ Hz and $J_{7\beta,6\beta} \sim J_{7\beta,8\beta} = 3$ Hz, the major difference compared to **3b** being the non-equivalence of the *gem* and *ax-ax* couplings. The chemical shift (δ 2·71) of the 10-proton signal compares well with that of the 10α-proton in **3b** (2·63 ppm), and it was inferred that the side chain in **7b** has β-configuration.

Benzoylation of unrecrystallised **7a** afforded the separable (*E*)- and (*Z*)-isomers (**7c** and **7d**). However, the preferred sequence for obtaining these products was by prior benzoylation of **6a** to give **6b** which underwent conjugate methylation with DCL in higher yield (62%) than did the 17-hydroxy-compound (**6a**). The spectral properties of the separated isomers **7c** and **7d** revealed incidental differences associated with the side chain stereochemistry, and the possibility that the two products were 10-isomers was discounted, since both underwent exchange of three protons in alkaline dioxan-$D_2O$, but failed to undergo mutual interconversion under these conditions.

Hydrolysis of the vinyl chloride moiety of **7c** or **7d** with sulphuric acid in dichloromethane[26] proceeded smoothly to give the same diketone (**8**). Although this product failed to crystallise, it was obtained as an analytically pure glass upon distillation, and exhibited the expected spectral properties. Treatment of **8** with methanolic N-KOH at 20° for 16 hr afforded 17β-hydroxy-9-methyl-9β,10α-oestr-4-en-3-one (alternatively[1,2] named 19(10 → 9β)*abeo*-10α-testosterone) (**9a**) (93%). Milder reaction conditions (0·4 N-KOH at 20° for 3 hr) gave **9a** (47%), together with two minor products whose properties are consistent with those expected for the intermediates **9b** (24%) and **10** (5%). The CD spectrum of **9a** clearly dis-

Table 3. NMR data for 17β-t-butoxy-3-chloro-9-methyl-4,5-seco-9β,10α-oestr-2-en-5-one (**7b**)

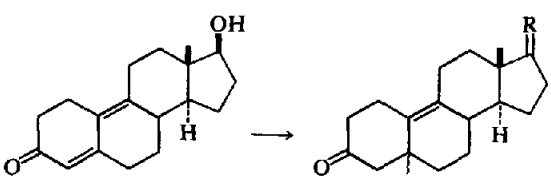
| Chemical shift (ppm) | Multiplicity and coupling (Hz) | ΔEu | Assignment |
|---|---|---|---|
| 2·71 | q, *J* 7 and 5 | 10·7 | 10α-H |
| *ca* 2·3 | t.d, $J_{gem}$ 14; $J_{aa}$ 14; $J_{ae}$ 6 | 10·45 | 6α-H |
| 5·61 | t.d, *J* 7, 7 and 1 | 9·3 | 2-H |
| *ca* 2·14 | m, $J_{gem}$ 14; $J_{aa}$ 10; $2 \times J_{ae}$ 3 | 6·45 | 7β-H |
| 0·78 | s | 5·0 | 9β-Me |
| 3·48 | t, $2 \times J$ 7·5 | 1·87 | 17α-H |
| 0·75 | s | 1·56 | 13β-Me |
| 1·1 | s | 0·8 | t-Bu |
| 2·01 | br. s, $w_{1/2}$ *ca* 3 | 0·34 | 4-$H_3$ |



played the characteristic n → π* and π → π* transitions [$\lambda_{max}$ 315 (Δε + 2·2) and 246 nm (Δε − 8·7)] associated with 9β,10α-stereochemistry.[20]

The most efficient sequence for the preparation of the final product [1 → 6a → 6b → 7c (7d) → 8 → 9a] proceeded in *ca* 28% overall yield.

A seemingly facile extension of the aforegoing synthesis would involve 1,6-alkylation[27] of 17β-hydroxy-oestra-4,9-dien-3-one (11) to give the desired product (9a) in one step. In the event, the reaction of 11 in THF at 0° with DCL proceeded slowly to give after 6 hr a product 12a (35%) contaminated with traces of an isomer. The absence of 9a in the reaction product was confirmed by comparative TLC, and the major product was purified by chromatography. While the compound 12a is clearly isomeric with 9a, it is not a 9β-methyl-$\Delta^{5(10)}$-3-one arising from deconjugative protonation[27] of the dienolate intermediate of 1,6-alkylation, since it failed to isomerise under acidic or alkaline conditions. The only alternative compatible with the spectral data is that of 1,4-alkylation to give a 5-Me compound (12a).



11

12a: R = β-OH, α-H
12b: R = O

An assertion regarding configuration at C(5) cannot be made since the properties of 12a do not correspond to those reported[28] for the known 17β-hydroxy-5-methyl-5β-oestr-9-en-3-one, nor do the properties of the derived diketone (12b) agree exactly with those of a compound purported[29] to be 5-methyl-5α-oestr-9-ene-3,17-dione. However, in the absence of factors which would otherwise exert steric control of 1,4-addition to 11 it seems more likely that α-attack will be favoured, and that the major product (12a) is the 5α-Me compound.

## EXPERIMENTAL

For general directions see Ref 30. GLC was performed with 1% OV-101 on 80–100 mesh Supelcoport (2m × 2·2 mm) at 165°.

*17β-Hydroxy-9-methyl-des-*A*-9β-oestran-5-one* (3a)

Dimethyl copper lithium (DCL) was prepared by the slow addition of ethereal MeLi (*ca* 1·3 M) to a stirred slurry of cuprous iodide (1·2 g) in anhyd ether (10 ml) at 0° under $N_2$, until the yellow ppt of methyl copper just dissolved to give a clear colourless soln (*ca* 9 ml MeLi soln required). The enone 1 (0·33 g) in anhyd ether (50 ml) was added and the mixture was stirred at 0° for 2·5 hr. Sat $NH_4Cl$aq was added and the mixture was diluted with EtOAc. The organic phase was washed repeatedly with brine, dried over $Na_2SO_4$, and evaporated to give yellow crystalline material which was decolourised by filtration through alumina (5 g) with benzene-EtOAc (1:1). A portion of the product (0·355 g) was crystallised from hexane to give an analytical sample of 3a, m.p. 86–88°, $[\alpha]_D$ −15° (*c* 1·1), $\nu_{max}$ 3610 and 1701 $cm^{-1}$, δ 0·81 (13β-Me), 0·96 (9β-Me), 2·73 (1H, d, *J* 15 Hz, 10α-H) and 3·76 (1H, t, *J* 8 Hz, 17α-H) (Found: C, 76·3; H, 10·3%; $M^+$, 236. $C_{15}H_{24}O_2$ requires: C, 76·2; H, 10·2%; M, 236).

*17β-t-Butoxy-9-methyl-des-*A*-9β-oestran-5-one* (3b)

The compound 3a (0·05 g) and isobutene (*ca* 15 ml, generated by refluxing t-BuOH over oxalic acid and drying the liberated gas before condensation at −70°, whereafter it was redistilled before use) were added to 100% phosphoric acid (0·039 g) and $BF_3$-etherate (0·05 ml) in $CH_2Cl_2$ (3 ml). The mixture at 20°, was shaken for 12 hr in a pressure flask, cooled, and poured into 2N-$NH_4OH$ (15 ml). Extraction with benzene (2 × 100 ml) followed by the usual work-up afforded a brown oil (0·077 g) which was adsorbed on silica gel (7 g). Elution with benzene-EtOAc (8:1) gave brown crystalline material (0·046 g) which was decolourised by filtration through alumina (2·5 g) with benzene, and crystallised from hexane to give 3b, m.p. 82–84°, $[\alpha]_D$ +2° (*c* 1·0), $\nu_{max}$ 1710 $cm^{-1}$, δ 0·73 (13β-Me), 0·92 (9β-Me), 1·08 (t-Bu), 2·63 (1H, d, *J* 14 Hz, 10α-H), and 3·41 (1H, t, *J* 8 Hz, 17α-H) (Found: C, 78·1; H, 11·0%; $M^+$, 292. $C_{19}H_{32}O_2$ requires: C, 78·0; H, 11·0%; M, 292).

*Base-catalysed alkylation of* 3a *with* 1,3-*dichlorobut-2-ene*

The compound 3a (0·022 g) in dry toluene (5 ml) was added to NaH (50% dispersion in mineral oil, 0·048 g) under $N_2$. The mixture was stirred at 20° for 0·5 hr, and 1,3-dichlorobut-2-ene (0·3 ml) was added, after which the mixture was heated under reflux for 10 hr. Benzene was added and the organic phase was washed, dried, and evaporated to give a yellow oil (0·069 g) which was adsorbed on silica gel (5 g). Elution with benzene-EtOAc (7:3) yielded a product which was chromatographically homogeneous, and which was assumed to be 4, as a colourless oil (0·01 g), δ 0·79 (13β-Me), 0·92 (9β-Me), 2·05 (3′-Me), 2·76 (1H, d, 14 Hz, 10α-H), 3·75 (1H, t, *J* 8 Hz, 17α-H), and 5·49 (1H, t, *J* 7 Hz, 2′-H) (Found: $M^+$, 324 and 326. $C_{19}H_{29}ClO_2$ requires M, 324 and 326).

*17β-t-Butoxy-9-methyl-*1(10 → 6αH)abeo-9β-*oestr-4-en-3-one* (5b)

An aliquot (0·32 ml) of a suspension of NaOH (0·05 g) in t-BuOH (5 ml) was added to 3b (0·3 g) in t-BuOH (6 ml) at 35° under $N_2$. Over a period of 0·5 hr, freshly distilled methyl vinyl ketone (0·085 ml) in benzene (0·6 ml) was then added. The soln, which rapidly turned yellow, was kept at 50° for 0·5 hr. Benzene was added and the mixture was worked up in the usual way to give a yellow oil (0·34 g) which was adsorbed on silica gel (40 g). Elution with benzene-EtOAc (8:1) afforded starting material 3b (0·205 g) followed by the *anthrasteroid* 5b (0·073 g), m.p. 166–169° (from EtOH), $[\alpha]_D$ +6° (*c* 1·0), $\nu_{max}$ 1662 and 1617 $cm^{-1}$, δ 0·69 (13β-Me), 0·91 (9β-Me), 1·08 (t-Bu), 2·73 (1H, br. d, *J* 15 Hz and $w_{1/2}$ *ca* 4 Hz, 10α-H), 3·38 (1H, t, *J* 8 Hz, 17α-H) and 5·64 (1H, t, 2 Hz; 4-H) (Found: C, 80·3; H, 10·45%; $M^+$, 344. $C_{23}H_{36}O_2$ requires: C, 80·2; H, 10·5%; M, 344).

*17β-Hydroxy-9-methyl-1(10 → 6αH)abeo-9β-oestr-4-en-3-one* (**5a**)

A soln of **5b** (0·04 g) and toluene *p*-sulphonic acid (0·025 g) in benzene (2·5 ml) was heated under reflux in $N_2$ for 1 hr. Benzene was added and the soln was washed, dried ($Na_2SO_4$) and evaporated. Chromatography of the residue (0·035 g) on silica gel (7 g) with benzene-EtOAc (1:1) afforded the product **5a** (0·018 g), m.p. 145–146° (from ether-hexane), $[\alpha]_D$ −23° (*c* 0·7), $\nu_{max}$ 3603, 1663 and 1619 $cm^{-1}$, δ 0·73 (13β-Me), 0·98 (9β-Me), 2·71 (1H, br. d, *J* 14 Hz and $w_{1/2}$ *ca* 4 Hz, 10α-H), 3·66 (1H, t, *J* 7 Hz, 17α-H) and 5·76 (1H, t, *J* 2 Hz, 4-H) (Found: C, 78·75; H, 10·1%; $M^+$, 288. $C_{19}H_{28}O_2$ requires: C, 79·1; H, 9·8%; M, 288).

*3-Chloro-17β-hydroxy-4,5-seco-oestra-2,9-dien-3-one* (**6a**)

Pyrrolidine (1·3 ml) was added to **1** (2·23 g) in MeOH (10 ml) at 20° under $N_2$ and the soln which rapidly turned yellow, was kept at 20° for 1·5 hr. The solvent and excess reagent were removed *in vacuo* at 20°, and KI (2 g) and dry DMF (12 ml) were added to the yellow crystalline residue. 1,3-Dichlorobut-2-ene (2·5 ml) was added to the mixture under $N_2$. After 17 hr at 20° the mixture was treated with NaOAc-AcOH-water (1:2:2; 20 ml) at 100° for 3·5 hr. EtOAc was added and the organic phase was washed with $NaHCO_3$aq, water, dried over $Na_2SO_4$ and evaporated to give a dark oil (3·85 g) which was chromatographed on silica gel (450 g) with benzene-EtOAc (1:1) to give **6a** (2·34 g) as a pale yellow oil which required storage at 0° under $N_2$ to prevent decomposition to dark, uncharacterised products. A fresh sample of **6a** had $[\alpha]_D$ −26° (*c* 1·5), $\nu_{max}$ 3603, 1658 and 1604 $cm^{-1}$, δ 0·89 (13β-Me), 1·03 (4-$H_3$), 3·68 (1H, t, *J* 8 Hz, 17α-H), and 5·28 (1H, t, *J* 6·5 Hz, 2-H) (Found: $M^+$, 308·1569. $C_{18}H_{25}ClO_2$ requires: M, 308·1542).

Treatment of **6a** (1·9 g) in pyridine (25 ml) at 20° with benzoyl chloride (1·55 g) for 1·5 hr, and chromatography on silica gel (350 g) with benzene-EtOAc (5:1) afforded the *benzoate* **6b** (1·924 g) as a yellow oil which decomposed slowly in the presence of air. The product had $[\alpha]_D$ +39° (*c* 0·5), $\nu_{max}$ 1714 and 1662 $cm^{-1}$, δ 1·08 (13β-Me) 2·03 (3H, d, *J* 1 Hz, 4-$H_3$), 3·19 (2H, d, *J* 7 Hz, 1-$H_2$), 4·89 (1H, t, *J* 8 Hz, 17α-H), 5·29 (1H, d. t, *J* 7 and 1 Hz, 2-H), 7·28 (3H, m, 2'-, 4'- and 6'-H) and 8·04 (2H, m, 3'- and 5'-H) (Found: $M^+$, 412·1804. $C_{25}H_{29}ClO_3$ requires: M, 412·1804).

*3-Chloro-17β-hydroxy-9-methyl-4,5-seco-9β,10α-oestr-2-en-5-one* (**7a**)

The enone **6a** (0·37 g) in ether (10 ml) was added to an ethereal soln of DCL [prepared from cuprous iodide (0·98 g) and MeLi] at 0° under $N_2$. After 2·5 hr at 0°, the product (0·373 g) was isolated and adsorbed on silica gel (40 g). Elution with benzene-EtOAc (2:1) afforded starting material **6a** (0·086 g) followed by the *9β-methyl compound* **7a** (0·132 g), m.p. 140–142° (from $CH_2Cl_2$-ether), $[\alpha]_D$ −88° (*c* 1·0), $\nu_{max}$ 3604 and 1705 $cm^{-1}$, δ 0·76 (9β-Me), 0·78 (13β-Me), 1·96 (3H, br. s, $w_{1/2}$ 3 Hz, 4-$H_3$), 2·74 (1H, t, *J* 6 Hz, 10α-H), 3·76 (1H, t, *J* 8 Hz, 17α-H) and 5·56 (1H, br. t, *J* 7 and $w_{1/2}$ 3 Hz, 2-H) (Found: C, 70·45; H, 8·9%; $M^+$, 324 and 326. $C_{19}H_{29}ClO_2$ requires: C, 70·2; H, 9·0%; M, 324 and 326).

Treatment of **7a** (0·037 g) with isobutene, as described in a previous experiment, followed by chromatography on silica gel (8 g) with benzene afforded traces of a product which was not characterised, followed by the *t-butyl ether* **7b** (0·022 g), m.p. 103–104° (from hexane), $[\alpha]_D$ −50° (*c* 1·1), $\nu_{max}$ 1704 $cm^{-1}$, δ 0·75 (9β-Me), 0·78 (13β-Me), 1·1 (t-Bu), 2·01 (4-$H_3$), 2·71 (1H, q, *J* 7 and 5 Hz, 10α-H), 3·48 (1H, t, *J* 7·5 Hz, 17α-H) and 5·61 (1H, d.t, *J* 7 and 1 Hz, 2-H) (Found: C, 72·5; H 9·85%; $M^+$, 380 and 382. $C_{23}H_{37}ClO_2$ requires: C, 72·5; H, 9·8%; M, 380 and 382).

*17β-Benzoyloxy-3-chloro-9-methyl-4,5-seco-9β,10α-oestr-2-en-5-one* (**7c, 7d**)

(a) The benzoate **6b** (1 g) in anhyd ether (8 ml) was treated with DCL [prepared from cuprous iodide (2·76 g) and MeLi] as described. After 4·5 hr at 0°, the product (1·05 g) was isolated and adsorbed on silica gel (170 g). Elution with benzene-EtOAc (20:1) afforded the (E)-*isomer* **7c** (0·109 g), m.p. 112–114° (from hexane), $[\alpha]_D$ + 88° (*c* 1·5), $\nu_{max}$ 1709 $cm^{-1}$, δ 0·82 (9β-Me), 1·02 (13β-Me), 2·06 (3H, br. s, $w_{1/2}$ 3 Hz, 4-$H_3$), 2·77 (1H, d.d, *J* 9 and 2 Hz, 10α-H), 5·01 (1H, t, *J* 8 Hz, 17α-H), 5·55 (1H, br. t, *J* 6 and $w_{1/2}$ 3 Hz, 2-H), 7·44 (3H, m, 2'-, 4'- and 6'-H), and 8·04 (2H, m, 3'- and 5'-H) (Found: C, 72·8; H, 7·85%; $M^+$, 428 and 430. $C_{26}H_{33}ClO_3$ requires: C, 72·8; H, 7·75%; M, 428 and 430).

Further elution with the same solvent afforded mixed fractions (0·123 g) followed by the (Z)-*isomer* **7d** (0·423 g), m.p. 88–95° (from hexane), $[\alpha]_D$ −10° (*c* 1·3), $\nu_{max}$ 1709 $cm^{-1}$, δ 0·82 (9β-Me), 1·02 (13β-Me), 2·01 (3H, br. s, $w_{1/2}$ 3 Hz, 4-$H_3$), 2·81 (1H, t, *J* 6 Hz, 10α-H), 4·99 (1H, t, *J* 8 Hz, 17α-H), 5·58 (1H, br. t, *J* 6 and $w_{1/2}$ 3 Hz, 2-H), 7·44 (3 H, m, 2'-, 4'- and 6'-H), and 8·04 (2H, m, 3'- and 5'-H) (Found: C, 72·8; H, 7·85%; $M^+$, 428 and 430). Further elution with the same solvent afforded starting material **6b** (0·076 g).

Rechromatography of the mixed fractions (0·123 g) on silica gel (27 g) gave further **7c** (0·033 g) and **7d** (0·069 g).

(b) The hydroxy-ketone **7a** (0·065 g) in pyridine (1 ml) at 20° under $N_2$, was treated with benzoyl chloride (0·055 g) for 0·75 hr. Chromatography of the product (0·107 g) on silica gel (14 g) with benzene-EtOAc (8:1) afforded **7c** (0·005 g) and **7d** (0·071 g). The products were identical with those described.

*17β-Benzoyl-9-methyl-4,5-seco-9β,10α-oestrane-3,5-dione* (**8**)

(a) The vinyl chloride **7d** (0·412 g) in $CH_2Cl_2$ (40 ml) at 0° under $N_2$, was stirred vigorously with conc $H_2SO_4$ (0·75 ml) for 0·75 hr. The mixture was poured onto ice and the product (0·423 g) was isolated by extraction with benzene. Chromatography on silica gel (65 g) with benzene-EtOAc (3:1) afforded the *diketone* **8** (0·314 g) as a colourless oil. Attempted sublimation (110–160°, $8 \times 10^{-5}$ Torr) afforded an analytical sample as a glass, $[\alpha]_D$ + 59° (*c* 0·6), $\nu_{max}$ 1712 $cm^{-1}$, δ 0·82 (9β-Me), 1·02 (13β-Me), 2·08 (4-$H_3$), 4·98 (1H, t, *J* 8 Hz, 17α-H), 7·46 (3H, m, 2'-, 4'- and 6'-H) and 8·03 (2H, m, 3'- and 5'-H) (Found: C, 75·95; H, 8·1%; $M^+$, 410·2483. $C_{26}H_{34}O_4$ requires: C, 76·05; H, 8·35%; M, 410·2457).

(b) The (*E*)-isomer **7c** (0·01 g) was hydrolysed as described to give after chromatography, the diketone (**8**), identified by TLC and spectral data.

*17β-Hydroxy-9-methyl-9β,10α-oestr-4-en-3-one* (**9a**)

(a) The compound **8** (0·245 g) was treated with methanolic N-KOH (20 ml) at 20° under $N_2$ for 16 hr. The product (0·22 g) was isolated by extraction with EtOAc and adsorbed on silica gel (18 g). Elution with $CHCl_3$-EtOAc (1:1) afforded the *compound* **9a** (0·16 g), m.p. 135–137° (from ether), $[\alpha]_D$ −84° (*c* 1·6), $\nu_{max}$ 3602, 1665 and 1612 $cm^{-1}$, δ 0·9 (13β-Me), 0·97 (9β-Me),

2·76 (1H, br. m, collapsing to q, $J$ 9 and 5 Hz, upon irradiation of the δ 5·9 signal, 10α-H), 3·74 (1H, t, $J$ 8 Hz, 17α-H), 5·9 (1H, br. s, $w_{1/2}$ 4 Hz, 4-H) (Found: C, 79·1; H, 9·9%; $M^+$, 288·2087. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%; M, 288·2089).

(b) Treatment of **8** (0·039 g) with methanolic 0·4 N KOH (1 ml) at 20° under $N_2$ for 3 hr and chromatography on silica gel (7 g) with benzene-EtOAc (1:1) afforded the *benzoate* **9b** (0·016 g), m.p. 188–191° (from dichloromethane-ether), $\nu_{max}$ 1711, 1663 and 1607 $cm^{-1}$, δ 0·89 (13β-Me), 0·99 (9β-Me), 2·84 (1H, br. m, 10α-H), 4·99 (1H, t, $J$ 8 Hz, 17α-H), 5·93 (1H, br. s, $w_{1/2}$ 4 Hz, 4-H), 7·45 (3H, m, 2′-, 4′- and 6′-H) and 8·03 (2H, m, 3′- and 5′-H) (Found: $M^+$, 392. $C_{26}H_{32}O_3$ requires: M, 392), followed by material (0·002 g) assumed to be **10**, m.p. 189–194° (Found: $M^+$, 410. $C_{26}H_{34}O_4$ requires: M, 410), and **9a** (0·013 g), identical with the product obtained previously.

*Conjugate methylation of* 17β-*hydroxy-oestra*-4,9-dien-3-*one* (**11**)

The compound **11** (0·544 g) in anhyd THF (12 ml) was added to an ethereal soln of DCL [prepared from cuprous iodide (1·52 g) and MeLi] at 0° under $N_2$. After 6 hr at 0° the product (0·53 g) was isolated and adsorbed on silica gel (100 g). Elution with $CHCl_3$-MeOH (99:1) afforded mixed fractions (0·13 g) followed by **12a** (0·073 g), m.p. 192–196° (from acetone), $[\alpha]_D$ −186° ($c$ 1·0), $\nu_{max}$ 1705 $cm^{-1}$, δ 0·78 (13β-Me), 1·08 (5ξ-Me), and 3·59 (1H, t, $J$ 8 Hz, 17α-H) (Found: C, 78·8; H, 9·6%; $M^+$, 288. $C_{19}H_{28}O_2$ requires: C, 79·1; H, 9·8%; M, 288). Further elution with the same solvent gave starting material (0·26 g).

Rechromatography of the mixed fractions (0·13 g) on silica gel (20 g) afforded further **12a** (0·085 g) m.p. 190–194°, but a persistent impurity (TLC) in the remaining material could not be isolated.

*Oxidation of* 17β-*hydroxy*-5-*methyl*-5ξ-*oestr*-9-*en*-3-*one* (**12a**)

The compound **12a** (0·067 g) in acetone (20 ml) at 0° was treated with 8 N-chromic acid. After 10 min the product was isolated and crystallised from EtOAc-MeOH to give the diketone **12b** (0·045 g), m.p. 130–133°, $[\alpha]_D$ −113° ($c$ 1·2), $\nu_{max}$ 1740 and 1705 $cm^{-1}$, δ 0·89 (13β-Me) and 1·1 (5ξ-Me) (Found: C, 79·4; H, 9·0%; $M^+$, 286. $C_{19}H_{26}O_2$ requires: C, 79·7; H, 9·15%; M, 286).

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