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# MODIFIED STEROID HORMONES—XLIX[1]

## 7-SUBSTITUTED 6-OXO-3α,5α-CYCLOSTEROIDS—1. THE PREPARATION OF 7-METHYL-6-OXO-3α,5α-CYCLOSTEROIDS

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**Abstract**—The preparation of some 7α- and 7β-methyl-6-oxo-3α,5α-cyclosteroids via 7-methylene intermediates is described.

7-METHYLATED steroids may be obtained through reaction of methylmagnesium halides with 3-oxo-4,6-dienes[2] and with 7-oxo-5-enes.[3–5] In the first procedure, 1,6-addition of the Grignard reagent leads to 3-oxo-4-ene-7(α + β)-methyl derivatives. In the second procedure, 1,2-addition leads via initially-formed 7-hydroxy-7-methyl intermediates to 7-methylene-5-ene derivatives, which may then be converted into 7-methyl steroids by hydrogenation of the exocyclic methylene group. 7-Methylene-5-enes may also be prepared by reaction of 5-enic-7-oxosteroids with triphenylphosphonium methylide.[4,6] The courses of both the 1,6-Grignard addition[2] and the hydrogenation[4] of 7-methylene-5-enes are by no means stereospecific and may be greatly influenced by the presence and orientation of an oxygen function at $C_{11}$. The object of the work reported herein was to develop a route by which one 7-Me isomer would be formed stereospecifically, and to provide a situation in which this isomer could be readily converted into its epimer. It was anticipated that the presence of a 6-oxo function would permit equilibration of a 7-alkyl substituent.

Some fairly readily accessible 6-oxo-3α,5α-cyclosteroids (cf I) were chosen as starting materials for the present investigation. They were prepared by standard transformations[7] involving solvolysis of 3β-tosyloxy-5-enic steroids to 6β-hydroxy-3α,5α-cyclo compounds and subsequent oxidation, preferably with chromium trioxide/pyridine,[8] to the corresponding 6-ketones. 17α-Methyl-3α,5-cyclo-5α-androstan-17β-ol-6-one, 3α,5-cyclo-5α-androstan-17β-ol-6-one and 17α-acetoxy-3α,5-cyclo-5α-pregnane-6,20-dione were obtained during this work, and do not appear to have been described hitherto.

The direct alkylation with iodomethane of the 6-oxo-3α,5α-cyclosteroid starting materials was contra-indicated by the observation of Julia *et al.*[9] that methylation of 17,17-ethylenedioxy-3α,5-cyclo-5α-androstan-6-one gives predominantly the 7,7-dimethyl derivative together with only small amounts of apparently monomethylated material of unknown stereochemistry. Attempts to apply to 6-oxo-3α,5α-cyclosteroids the Stork enamine procedure[10] for the monoalkylation of ketones proved abortive as enamine formation at $C_6$ could not be achieved. An alternative approach to this problem appeared to be through the preparation of 7-methylene-6-oxo-3α,5α-

cyclosteroids, catalytic hydrogenation of which was expected to give the corresponding 7-Me steroids.

Steroidal α-alkylaminoketones may be prepared from certain ketosteroids, e.g. 5-androsten-3β-ol-17-one, by the Mannich reaction, and subsequently converted into α-keto exocyclic methylene derivatives.[11] When 17α-methyl-3α,5-cyclo-5α-androstan-17β-ol-6-one (I) was treated with dimethylamine hydrochloride and paraformaldehyde in hot dioxan, only a surprisingly insignificant quantity of basic material was found. The major product, isolated in high yield, was not the expected Mannich base, but a neutral compound to which the constitution 17α-methyl-7-methylene-3α,5-cyclo-5α-androstan-17β-ol-6-one (cf II) has been assigned on the basis of physical evidence presented below. It is assumed that a Mannich base (7-dimethylaminomethyl-17α-methyl-3α,5-cyclo-5α-androstan-17β-ol-6-one) was formed as an intermediate in this reaction, and that elimination from it of secondary amine had occurred under the experimental conditions employed. The 7-methylene derivatives of 3α,5-cyclo-5α-androstan-17β-ol-6-one, 17β-acetoxy-3α,5-cyclo-5α-androstan-6-one[12] 3α,5-cyclo-5α-androstane-6,17-dione,[7] 17α-acetoxy-3α,5-cyclo-5α-pregnane-6,20-dione and 3α,5-cyclo-5α-pregnane-6,20-dione[13] respectively, were similarly prepared and obtained in satisfactory yields. Under the experimental conditions employed in this work, only slight attack (<10%) at $C_{16}$ (in the case of the 17-oxo steroid) and at $C_{21}$ (in the cases of the 20-oxo steroids) occurred.

The presence of the 7-methylene-6-oxo-3α,5α-cyclo system in the foregoing compounds is indicated by the following evidence. The carbonyl stretching frequency of the 6-oxo- group is shifted from 1690 $cm^{-1}$ in the spectra of the parent saturated cyclopropyl ketones to ca 1675 $cm^{-1}$, the change being accompanied by the appearance of a new intense C=C stretching band at 1599 $cm^{-1}$. The ratio of the apparent extinction coefficients of these bands, $\varepsilon^{app}_{C=O}/\varepsilon^{app}_{C=C}$ = 2·8 to 4·0, indicates the presence of a cisoid conjugated enone system.[14]

This change in the IR spectra is accompanied by a corresponding bathochromic shift of the short wavelength UV absorption maximum from 210 mμ to 233–235 mμ. Application of the modified Woodward rules for conjugated enones[15] to the 7-methylene-6-oxo-system leads to the prediction of an absorption maximum at 230 mμ. It is difficult to estimate the effect of cross-conjugation with the cyclopropyl ring upon the position of the absorption maximum, in view of the markedly different contributions from cross-conjugation in cisoid as opposed to transoid systems (cf steroidal 1,4-diene-3-ones and 4-methylene-5α-steroidal-1-ene-3-ones.[16] However, since the degree of conjugation between the cyclopropyl- and 6-oxo- groups in the parent 6-oxo-3α,5α-cyclosteroids is quite low,[17] the 7-methylene derivatives might be expected to exhibit the principal UV absorption characteristics of a simple 7-methylene-6-oxo-chromophore. The observed low intensity of this absorption (ε = ca 9,000) furthermore suggests a cisoid enone,[18] the corresponding transoid system, as in steroidal 3α,5α-cyclo-6-oxo-7-enes,[19] giving rise to $\lambda_{max}$ 249 mμ (ε = 13,500).

The NMR spectra of these 7-methylene-6-oxo-3α,5α-cyclosteroids (see Table 1) show, in addition to the features normally associated with the substituents at $C_{17}$, signals for two olefinic protons (two multiplets, separated by ca. 0·6 ppm), two tertiary Me groups ($C_{10}$ and $C_{13}$), but NO olefinic Me proton resonances. No discrete signals due to the cyclopropyl ring protons are observed suggesting that

they are heavily deshielded and resonate below 9·1 τ. Examination of Dreiding models indicates that the exo-methylene group and the CO function are almost coplanar, and the lower field resonance must therefore arise from that proton nearer to the centre of the CO bond.[16,20] Weak coupling (0–3·5 c/s) is to be expected[21] between the two olefinic protons, and further weaker coupling of both these protons to the allylic $C_{8\beta}$—hydrogen nucleus is possible. Since the axial $C_{8\beta}$—H bond seems to be virtually perpendicular to the plane of the methylene function, maximal allylic coupling (0–2 c/s)[22] is anticipated.

Analysis of these signals in the spectrum of 17α-acetoxy-7-methylene-3α,5-cyclo-5α-pregnane-6,20-dione has been performed, by spin-spin decoupling at 60 Mc/s, at which frequency the two methylene proton peaks appear as triplets separated by 3·9 c/s. Decoupling of each proton from the other produces a doublet, the coupling constants between these protons and the $C_{8\beta}$-proton both being 2·0 c/s. The position of the $C_{8\beta}$-proton resonance was established (to within ±0·05 ppm) by irradiating different parts of the region above 7 τ whilst observing the olefinic proton peaks, using a necessarily high irradiation energy in both field and frequency sweep experiments. The general exo-methylene coupling constant was found to be 1·5 c/s. The chemical shift of the $C_{8\beta}$-proton, 7·25 τ, indicates that this hydrogen nucleus has undergone greater deshielding than would be expected for olefinic methyl, methylene or methine hydrogens,[23] due presumably to some specific magnetic anisotropy effect dependent upon the relative positions of the angular hydrogen and the conjugated methylene group.

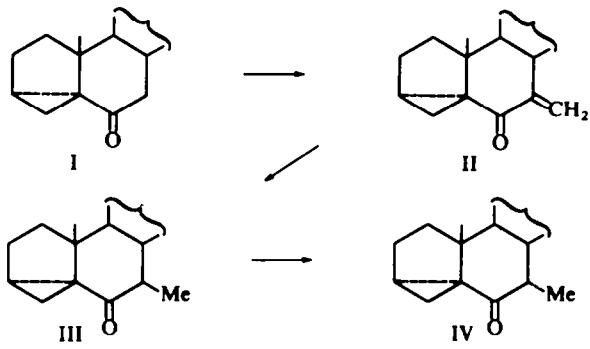
Catalytic hydrogenation of 17α-methyl-7-methylene-3α,5-cyclo-5α-androstan-17β-ol-6-one (II), employing a Pd/C catalyst, gave in high yield (88%) a single compound regarded as 7β,17α-dimethyl-3α,5-cyclo-5α-androstan-17β-ol-6-one (III), transformed by methanolic alkali into its 7α-Me epimer (IV). The physical evidence upon which these and analogous structures (*vide infra*) are based is presented and discussed in Part 2. The 7β-Me derivatives of 3α,5-cyclo-5α-androstan-17β-ol-6-one, 17β-acetoxy-3α,5-cyclo-5α-androstan-6-one, 3α,5-cyclo-5α-androstane-6,17-dione, 17α-acetoxy-3α,5-cyclo-5α-pregnane-6,20-dione and 3α,5-cyclo-5α-pregnane-6,20-dione were similarly prepared in high yield by hydrogenation of the corresponding 7-methylene-3α,5α-cyclo-6-oxo-steroids. Base-catalysed epimerization of the foregoing 7β-methyl-5α-androstane derivatives afforded 7α,17α-dimethyl-3α,5-cyclo-5α-androstan-17β-ol-6-one, 7α-methyl-3α,5-cyclo-5α-androstan-17β-ol-6-one and 7α-methyl-3α,5-cyclo-5α-androstane-6,17-dione, respectively. Treatment of the two 7β-methyl-pregnane compounds with alkali gave complex mixtures from which crystalline material could not be isolated. It is likely that side reactions involving the 17β-acetyl side-chain had occurred under the alkaline conditions employed.

The physical data obtained for the 7-methylene-3α,5α-cyclo-6-oxo-steroids (II) described herein do not provide positive evidence for the presence in the molecule of the cyclopropyl ring. The NMR spectra of the 7α-Me derivatives (IV), however, show definite cyclopropyl proton signals.[17] Furthermore, the IR, UV and ORD curves given by both 7α- and 7β-methyl derivatives (IV and III) show features also given by the unsubstituted 6-oxo-3α,5α-cyclosteroid precursors (I). These observations are consistent with the preservation of the 3α,5α-cyclosteroid structure throughout the series of transformations I → II → III → IV.

TABLE 1. BAND POSITIONS (TAU SCALE) IN THE NMR SPECTRA OF 7-METHYLENE-6-OXO-3α,5α-CYCLOSTEROIDS (SOLNS IN $CDCl_3$, CA. 5% W/V, OF SAMPLE. TMS AS INTERNAL REFERENCE)

| Compounds | Angular methyl protons (3-proton singlets) $C_{10}$ | $C_{13}$ | Olefinic protons (1-proton multiplets)* | Other features |
|---|---|---|---|---|
| 7-Methylene-3α,5-cyclo-5α-androstan-17β-ol-6-one | 8·95 | 9·13 | 4·19; 4·75 | 8·31 OH (1, s) ca 6·30 (C-17αH) (1, m) |
| 17β-Acetoxy-7-methylene-3α,5-cyclo-5α-androstan-6-one | 8·98 | 9·09 | 4·14; 4·77 | 7·95 (17β-OAc, 3, s) ca 5·30 (C-17αH) (1, m) |
| 7-Methylene-3α,5-cyclo-5α-androstane-6,17-dione | 8·94 | 8·99 | 4·03; 4·77 | — |
| 7-Methylene-3α,5-cyclo-5α-pregnane-6,20-dione | 8·96 | 9·23 | 4·14; 4·78 | 7·87 (C-21 $C\underline{H}_3$, 3, s) |
| 17α-Methyl-7-methylene-3α,5-cyclo-5α-androstan-17β-ol-6-one | 8·94 | 9·02 | 4·14; 4·76 | 8·76 (C-17α-$CH_3$) (3, s) 8·25 (OH, 1, s) |
| 17α-Acetoxy-7-methylene-3α,5-cyclo-5α-pregnane-6,20-dione | 8·96 | 9·26 | 4·11; 4·77 | 7·88, 7·93 (2 × 3, s) 17α-$OCOC\underline{H}_3$, -17β-$COC\underline{H}_3$ |

* Positions of principal bands in multiplets, at 40 Mcs/s.




## EXPERIMENTAL

M.ps were determined under current British Pharmaceutical conditions and are corrected. UV spectra were determined in spectrograde EtOH. IR spectra were determined on a Hilger H800 instrument (NaCl prism) in $CCl_4$ soln unless otherwise stated. NMR spectra were determined at 40 Mcs, except for the spin-decoupling experiments (60 Mcs), using a Perkin–Elmer permanent magnet instrument in both cases. Optical rotations were determined on ca 1% solns in $CHCl_3$ at room temp unless otherwise stated.

17α-*Methyl*-3α,5-*cyclo*-5α-*androstane*-6β,17β-*diol*

(a) A soln of 17α-methyl-3β-toluene-*p*-sulphonyloxy-5-androsten-17β-ol[24] (12·5 g) and AcOK (15 g) in acetone (350 ml) and water (350 ml) was refluxed for 26 hr. The acetone was removed under reduced press and the precipitated solid was crystallized from acetone to give the product, 6·1 g (73%), m.p. 170–172°, $[\alpha]_D$ +13·5° (*c*, 1·1 in dioxan); $\nu_{max}^{CH_2Cl_2}$ 3628 $cm^{-1}$. (Found: C, 78·75; H, 10·55. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%).

(b) A soln of 3α,5-cyclo-5α-androstan-6β-ol-17-one[7] (10 g) in ether (100 ml) was added to a stirred soln of the Grignard reagent prepared from Mg (3·3 g) and bromomethane (8 ml) in ether (100 ml). The mixture was stirred at room temp for 4 hr, excess reagent was decomposed with sat $NH_4Cl$ aq, and the product was isolated with ether. Crystallization from acetone gave 7 g (66%), m.p. 170–172°, identical with that obtained in (a).

17α-*Methyl*-3α,5-*cyclo*-5α-*androstan*-17β-*ol*-6-*one*. A soln of 17α-methyl-3α,5-cyclo-5α-androstane-6β,17β-diol (10·5 g) in pyridine (100 ml) was added to a suspension of the complex prepared from $CrO_3$ (10 g) and pyridine (100 ml). The mixture was kept overnight at room temp, diluted with EtOAc (ca. 500 ml) and filtered. The filtrate was washed with dilute HCl aq and water, dried over $Na_2SO_4$ and evaporated. Crystallization of the residue from ether gave the 6-ketone 7·8 g (75%), m.p. 202–203°; $[\alpha]_D$ +11·2°; $\nu_{max}$ 3615, 1689 $cm^{-1}$ (OH, C=O). (Found: C, 78·85; H, 9·95. $C_{20}H_{30}O_2$ requires: C, 79·4; H, 10·0%).

3α,5-*Cyclo*-5α-*androstan*-17β-*ol*-6-*one*. A soln of 17β-acetoxy-3α,5-cyclo-5α-androstan-6-one[12] (15·2 g) in 5% methanolic KOH (150 ml) was kept at room temp for 3 hr. Dilution with water, and crystallization of the precipitated solid from acetone, gave the product, 11·9 g (90%) m.p. 191°; $[\alpha]_D$ +35·3°; $\nu_{max}$ 3620, 1690 $cm^{-1}$ (OH, C=O). (Found: C, 78·1; H, 9·5. $C_{19}H_{28}O_2$ requires: C, 79·1; H, 9·8%).

17α-*Acetoxy*-3α,5-*cyclo*-5α-*pregnane*-6,20-*dione*. 17α-Acetoxy-3α,5-cyclo-5α-pregnan-6β-ol-20-one[25] (72·8 g) in pyridine (700 ml) was oxidised with the $CrO_3$-pyridine complex (70 g/700 ml) as before. The product, 43·5 g (60%) crystallized from EtOH, had m.p. 225–226°; $[\alpha]_D$ +15·2° (*c*, 0·95 in dioxan); $\nu_{max}$ 1741, 1721, 1692 $cm^{-1}$ (17-OAc, $C_{20}$=O, $C_6$=O). (Found: C, 73·95; H, 8·75. $C_{23}H_{32}O_4$ requires: C, 74·15; H, 8·65%).

17α-*Methyl*-7-*methylene*-3α,5-*cyclo*-5α-*androstan*-17β-*ol*-6-*one*. A mixture of 17α-methyl-3α,5-cyclo-5α-androstan-17β-ol-6-one (43 g), dimethylammonium chloride (24 g), paraformaldehyde (8·5 g) and dioxan (700 ml) was stirred and refluxed for 4 hr and poured into water (ca. 7 l). The ppt was collected, dissolved in $CH_2Cl_2$ and the soln was washed with dilute HCl aq and water. (No material was obtained when these washings were made alkaline and extracted with ether.) Evaporation of the $CH_2Cl_2$ and crystallization of the residue from di-isopropyl ether gave the product, 31·6 g (70%), m.p. 147–148°; $[\alpha]_D$ −10·3° (*c*, 1·05 in

dioxan); $\lambda_{max}$ 234 mμ (ε, 8850); $\nu_{max}$ 3600, 1675 and 1599 $cm^{-1}$ (OH, C=O, C=C). (Found: C, 79·2; H, 9·2. $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6%).

*7-Methylene-3α,5-cyclo-5α-androstane-6,17-dione*, prepared in the same way from 3α,5-cyclo-5α-androstane-6,17-dione, crystallized from MeOH (74%), m.p. 175°; $[\alpha]_D$ +147·9° (*c*, 1·2 in dioxan); $\lambda_{max}$ 233 mμ (ε, 9310); $\nu_{max}$ 1745, 1678, 1603 $cm^{-1}$ ($C_{17}$=O, $C_6$=O, C=C). (Found: C, 79·8; H, 8·5. $C_{20}H_{26}O_2$ requires: C, 80·5; H, 8·8%).

*7-Methylene-3α,5-cyclo-5α-androstan-17β-ol-6-one*, prepared in the same way from 3α,5-cyclo-5α-androstan-17β-ol-6-one, crystallized from MeOH (66%), m.p. 198°; $[\alpha]_D$ +39·7°; $\lambda_{max}$ 234 mμ (ε, 9370); $\nu_{max}$ 3620, 1675, 1602 $cm^{-1}$ (OH, C=O, C=C). (Found: C, 79·65; H, 9·35. $C_{20}H_{28}O_2$ requires: C, 79·95; H, 9·4%).

*17β-Acetoxy-7-methylene-3α,5-cyclo-5α-androstan-6-one*, prepared in the same way from 17β-acetoxy-3α,5-cyclo-5α-androstan-6-one, crystallized from MeOH (61%), m.p. 123–124°; $[\alpha]_D$ +36·7° (*c*, 0·55 in dioxan); $\lambda_{max}$ 235 mμ (ε, 9320); $\nu_{max}$ 1737, 1676, 1599 $cm^{-1}$ (OAc, C=O, C=C). (Found: C, 77·05; H, 8·7. $C_{22}H_{30}O_3$ requires: C, 77·15; H, 8·85%).

*17α-Acetoxy-7-methylene-3α,5-cyclo-5α-pregnane-6,20-dione*, prepared in the same way from 17α-acetoxy-3α,5-cyclo-5α-pregnane-6,20-dione, crystallized from MeOH (79%), m.p. 197–198°; $[\alpha]_D$ +11·6° (*c*, 1·0 in dioxan); $\lambda_{max}$ 236 mμ (ε, 9250); $\nu_{max}$ 1739, 1718, 1676, 1598 $cm^{-1}$ (OAc, $C_{20}$=O, $C_6$=O, C=C). (Found: C, 74·55; H, 8·1. $C_{24}H_{32}O_4$ requires: C, 74·95; H, 8·4%).

*7-Methylene-3α,5-cyclo-5α-pregnane-6,20-dione*, prepared in the same way from 3α,5-cyclo-5α-pregnane-6,20-dione, crystallized from ether (60%), m.p. 141°; $[\alpha]_D$ +107·1°; $\lambda_{max}$ 234 mμ (ε, 9080); $\nu_{max}$ 1707, 1673, 1598 $cm^{-1}$ ($C_{20}$=O, $C_6$=O, C=C). (Found: C, 80·85; H, 9·1. $C_{22}H_{30}O_2$ requires: C, 80·95; H, 9·25%).

*7β,17α-Dimethyl-3α,5-cyclo-5α-androstan-17β-ol-6-one*

A soln of 17α-methyl-7-methylene-3α,5-cyclo-5α-androstan-17β-ol-6-one (18 g) in EtOH (500 ml) containing 5% Pd–C (0·5 g) was stirred at room temp under $H_2$ until absorption ceased. The catalyst was removed by filtration and the filtrate was evaporated under reduced press. Crystallization of the residue from di-isopropyl ether gave the product, 15·9 g (88%), m.p. 146°; $[\alpha]_D$ +16·8° (*c*, 0·7 in dioxan); $\nu_{max}$ 3600, 1675 $cm^{-1}$ (OH, C=O). (Found: C, 79·55; H, 10·15. $C_{21}H_{32}O_2$ requires: C, 79·75; H, 10·2%).

*7β-Methyl-3α,5-cyclo-5α-androstane-6,17-dione*, prepared in the same way from 7-methylene-3α,5-cyclo-5α-androstane-6,17-dione, crystallized from di-isopropyl ether (80%), m.p. 128–129°; $[\alpha]_D$ +128° (*c*, 1·0 in dioxan); $\nu_{max}$ 1742, 1678 $cm^{-1}$ ($C_{17}$=O, $C_6$=O). (Found: C, 79·5; H, 9·15. $C_{20}H_{28}O_2$ requires: C, 79·95; H, 9·4%).

*7β-Methyl-3α,5-cyclo-5α-androstan-17β-ol-6-one*

(a) 7-Methylene-3α,5-cyclo-5α-androstan-17β-ol-6-one was hydrogenated as described above. The product crystallized from ether (77%), m.p. 136°; $[\alpha]_D$ +23·7°; $\nu_{max}$ 3622, 1676 $cm^{-1}$ (OH, C=O). (Found: C, 79·3; H, 10·05. $C_{20}H_{30}O_2$ requires: C, 79·4; H, 10·0%).

(b) To a soln of 7β-methyl-3α,5-cyclo-5α-androstane-6,17-dione (26·6 g) in THF (75 ml) was added, at 0°, a soln of $LiBH_4$ in THF (2M, 12 ml). After 2 hr at 0° the mixture was poured into saturated $NH_4Cl$aq (500 ml) and extracted with ether. Evaporation of the extract gave a residue which was dissolved in benzene–chloroform (7:3) and filtered through alumina (400 g). Evaporation of the eluate and crystallization of the residue from ether gave a product (14·7 g, 55%), m.p. 135–136°, identical with that obtained in (a) above.

*17β-Acetoxy-7β-methyl-3α,5-cyclo-5α-androstan-6-one*

(a) 17β-Acetoxy-7-methylene-3α,5-cyclo-5α-androstan-6-one was hydrogenated as described above. The product crystallized from MeOHaq (10%), m.p. 71°; $[\alpha]_D$ +8·9°; $\nu_{max}$ 1736, 1675 $cm^{-1}$ (OAc, C=O). (Found: C, 76·5; H, 9·5. $C_{22}H_{32}O_3$ requires: C, 76·7; H, 9·35%). Attempts to isolate further material from the mother liquors gave only small quantities of the 7α-methyl isomer (see later).

(b) 7β-Methyl-3α,5-cyclo-5α-androstan-17β-ol-6-one (2·7 g) was acetylated with $Ac_2O$-pyridine. The product, crystallized from MeOHaq (85%), had m.p. 70–71° and was identical with that obtained in (a) above.

*17α-Acetoxy-7β-methyl-3α,5-cyclo-5α-pregnane-6,20-dione*, prepared by similar hydrogenation of 17α-acetoxy-7-methylene-3α,5-cyclo-5α-pregnane-6,20-dione, crystallized from MeOH (86%), m.p. 207°; $[\alpha]_D$ +10·1° (*c*, 1·0 in dioxan); $\nu_{max}$ 1739, 1719, 1678 $cm^{-1}$ (OAc, $C_{20}$=O, $C_6$=O). (Found: C, 73·55; H, 8·65. $C_{24}H_{34}O_4$ requires: C, 74·55; H, 8·85%).

*7β-Methyl-3α,5-cyclo-5α-pregnane-6,20-dione*, prepared in the same way from 7-methylene-3α,5-cyclo-

5α-pregnane-6,20-dione, crystallized from di-isopropyl ether (90%), m.p. 131°; $[\alpha]_D$ +104·4° (*c*, 1·15 in dioxan); $\nu_{max}$ 1709, 1677 $cm^{-1}$ ($C_{20}$=O, $C_6$=O). (Found: C, 80·75; H, 9·7. $C_{22}H_{32}O_2$ requires: C, 80·45; H, 9·8%).

7α,17α-*Dimethyl*-3α,5-*cyclo*-5α-*androstan*-17β-ol-6-*one*

A soln of 7β,17α-dimethyl-3α,5-cyclo-5α-androstan-17β-ol-6-one (5 g) in 1·5% methanolic KOH (30 ml) was refluxed for 15 hr and then concentrated under reduced press. A soln of the residue in ether–benzene (4:1) was washed with 2NHCl and water and evaporated. Crystallization of the residue from ether gave the product (1·9 g, 38%), m.p. 189°; $[\alpha]_D$ +48°; $\nu_{max}$ 3600, 1690 $cm^{-1}$ (OH, C=O). (Found: C, 79·45; H, 10·15. $C_{21}H_{32}O_2$ requires: C, 79·75; H, 10·2%).

7α-*Methyl*-3α,5-*cyclo*-5α-*androstane*-6,17-*dione*, prepared as above from 7β-methyl-3α,5-cyclo-5α-androstane-6,17-dione, crystallized from di-isopropyl ether (73%), m.p. 217°; $[\alpha]_D$ +150·9°; $\nu_{max}$ 1743, 1690 $cm^{-1}$ ($C_{17}$=O, $C_6$=O). (Found: C, 80·25; H, 9·45. $C_{20}H_{28}O_2$ requires: C, 79·95; H, 9·4%).

7α-*Methyl*-3α,5-*cyclo*-5α,*androstan*-17β-*ol*-6-*one*, prepared in the same way from 7β-methyl-3α,5-cyclo-5α-androstan-17β-ol-6-one, crystallized from ether (47%), m.p. 183°; $[\alpha]_D$ +60·6°; $\nu_{max}$ 3625, 1689 $cm^{-1}$ (OH, C=O). (Found: C, 79·5; H, 9·95. $C_{20}H_{30}O_2$ requires: C, 79·4; H, 10·0%).

The 17β-acetate, prepared with $Ac_2O$-pyridine and crystallized from di-isopropyl ether, had m.p. 221°; $[\alpha]_D$ +52·8°; $\nu_{max}$ 1739, 1690 $cm^{-1}$ (OAc, C=O). (Found: C, 75·95; H, 9·25. $C_{22}H_{32}O_3$ requires: C, 76·7; H, 9·35%).

## REFERENCES


1 Part XLVIII, C. Burgess, G. Cooley, P. Feather and V. Petrow, *Tetrahedron* **23**, 4111 (1967).
2 J. A. Campbell and J. C. Babcock, *J. Am. Chem. Soc.* **81**, 4069 (1959).
3 C. H. Robinson, O. Gnoj, W. Charney, M. L. Gilmore and E. P. Oliveto, *Ibid.* **81**, 408 (1959); C. H. Robinson, O. Gnoj and E. P. Oliveto, *J. Org. Chem.* **24**, 121 (1959).
4 R. E. Beyler, A. E. Oberster, F. Hoffman and L. H. Sarett, *J. Am. Chem. Soc.* **82**, 170 (1960).
5 J. A. Zderic, H. Carpio and H. J. Ringold, *Ibid.* **81**, 432 (1959).
6 F. Sondheimer and R. Mechoulam, *Ibid.* **79**, 5029 (1957).
7 A. Butenandt and L. A. Suranyi, *Chem. Ber.* **75**, 591 (1942).
8 G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Am. Chem. Soc.* **75**, 422 (1953).
9 S. Julia, C. Neuville and M. Davis, *Bull. Soc. Chim. Fr.* 297 (1960).
10 G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.* **85**, 207 (1963).
11 See, for example, P. L. Julian, E. W. Meyer and H. C. Printy, *Ibid.* **70**, 3872 (1948); M. J. Brienne, C. Ouannes and J. Jaques, *Bull. Soc. Chim. Fr.* 1773 (1964).
12 C. H. Robinson, O. Gnoj and F. C. Carlon, *Tetrahedron* **21**, 2509 (1965).
13 R. Goutarel, A. Cave, L. Tan and M. Leboeuf, *Bull. Soc. Chim. Fr.* 646 (1962).
14 R. L. Erskine and E. S. Waight, *J. Chem. Soc.* 3425 (1960) and refs cited therein.
15 A. I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products* Chap. 2. Pergamon Press, Oxford (1964).
16 W. H. W. Lunn, *J. Org. Chem.* **30**, 2925 (1965).
17 F. K. Butcher, R. A. Coombs, M. T. Davies and V. Petrow, *Tetrahedron* Part 2 of this paper.
18 cf. Relative intensities of UV absorption of steroidal 4-en-6-ones and 7-en-6-ones. J. S. Dusza, M. Heller and S. Bernstein, *Ultraviolet Absorption* in *Physical Properties of the Steroid Hormones*, (Edited by L. L. Engel) p. 84. Pergamon Press, Oxford (1963).
19 G. H. R. Summers, *J. Chem. Soc.* 4489 (1958).
20 L. Jackman, *Applications of NMR Spectroscopy in Organic Chemistry* Chap. 7 and refs cited therein. Pergamon Press, Oxford (1959).
21 Ref. 20, page 85.
22 S. Sternhell, *Rev. Pure Appl. Chem.* **14**, 15 (1964).
23 cf Ref 20, Table 4.8.
24 D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 665 (1957).
25 J. A. Zderic, O. Halpern and J. Iriarte, U.S. Patent 3,071,581 (1963); O. Halpern, J. A. Edwards and J. A. Zderic, *Chem. & Ind.* 1571 (1962).