527. *Studies in the Steroid Group. Part LXXVI.* The Methylation of Enol Acetates and Bromo-ketones. Nuclear Magnetic Resonance Spectra of* 11-*Keto-steroids*

By Sir Ewart R. H. Jones and D. A. Wilson

9α-Methyl-11-keto-steroids (VI) have been prepared by treatment of $\Delta^{9(11)}$-enol acetates (V) with methylmagnesium iodide–methyl iodide, under conditions previously used with the 9α-bromo-11-ketone (II*a*). The $\Delta^{17(20)}$-enol acetates similarly give 17α-methyl-20-ketones. Some 9,12- and 17,21-dialkylated steroids have been isolated from these reactions. Improved conditions for the methylation of the bromo-ketones are also described. The nuclear magnetic resonance spectra of 11-keto-steroids with 9- and 12-substituents are recorded and discussed.

Part LXXV * described the conversion of 3β-acetoxy-9α-bromo-5α-androstan-11-one (II*a*) into the 9α-methyl-steroid (VI*a*) as one step in the correlation of the structure and stereochemistry of the steroids with that of the pentacyclic triterpenes. The method used was based on that described by Tishler and his colleagues:[1] the bromo-ketone (II*a*) was treated with an excess of methylmagnesium iodide and a massive excess of methyl iodide in ether–tetrahydrofuran and, after acetylation, the 9α-methyl-steroid (VI*a*) was separated from unmethylated ketone (I*a*) by chromatography. A similar result was obtained with the 5α-ergostane derivative (II; R = C_9H_{19}). However, attempts similarly to methylate 9α-bromo-11-keto-5α-steroids with oxygen functions at C-20 and C-17 (II*b*, II*c*, and X; R = Br) were largely unsuccessful. Further investigation of the alkylation procedure has revealed conditions under which the required 9α-methyl compounds (VI*b* and VI*c*) can be prepared from the bromo-ketones in 40—60% yields. Of greater interest is the discovery that it is possible to methylate the related $\Delta^{9(11)}$-enol acetates (V*a*, V*b*, and V*c*).

In a series of experiments with the 9α-bromo-ketones (II*b* and II*c*) it was first shown that tetrahydrofuran was an essential reagent, even though it produces precipitates on addition to the solutions of the Grignard reagent. As "co-solvents" ether (giving a reaction temperature of about 35°) or di-n-butyl ether (reaction temperature *ca.* 55°) were used. The bromo-ketone in tetrahydrofuran was added to the Grignard reagent prepared in the ether containing a large excess of methyl iodide. The effects of reaction time and temperature are set out in Table 1. Gas–liquid chromatography permits the detection of as little as 5% of methylated product. None could be detected when analogous steroids of the 5β-series were employed.

In each case, the products from the 5-min. reactions were subjected to dehydrobromination conditions (Li_2CO_3–dimethylformamide) but no Δ^8-11-ketone (VII) could be observed, proving that the bromo-ketone is very quickly converted into the enolate anion. It seemed likely that the enolate anion might also be generated from an enol acetate, using a

* Part LXXV, S. Binns, J. S. G. Cox, Sir Ewart R. H. Jones, and B. G. Ketcheson, *J.*, 1964, 1161.

[1] R. E. Beyler, F. Hoffman, L. H. Sarett, and M. Tishler, *J. Org. Chem.*, 1961, **26**, 2426.

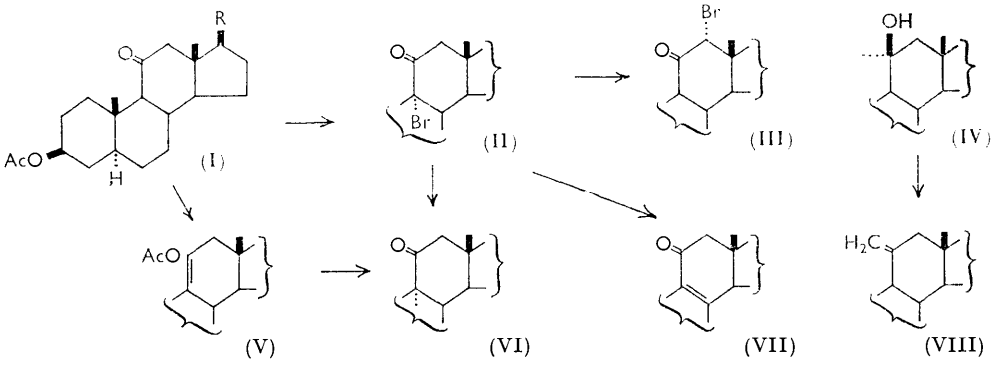
TABLE 1

Percentage of 9α-methylsteroid in recovered steroid

Reaction time (min.)	5	30	60	105	150	240
(II*b*) in Et_2O–THF *	8	15	—	20	—	—
(II*b*) in Bu_2O–THF	18	30	—	—	40 †	—
(II*c*) in Et_2O–THF	5	20	30	—	—	50
(II*c*) in Bu_2O–THF	20	40	50	—	60 †	—

* THF = Tetrahydrofuran. † Plus some dialkylated material.

Grignard reagent, and that alkylation could be effected without preparing the bromo-ketone. With the original alkylation procedure, from the pure enol acetate (V*b*) and from (V*a*) and (V*c*) containing some ketone, yields (estimated by g.l.c.) of the methylated ketones (VI*a*, *b*, and *c*) of 25—40% have been obtained. Higher reaction temperatures (dibutyl ether–tetrahydrofuran) lead to 40—60% yields, but some dialkylation ensues (see below). If enol acetate–ketone mixtures have to be employed [as with (V*a*) and (V*c*)] then tertiary alcohols (IV) are formed [2] which contaminate the methylated ketones (VI).



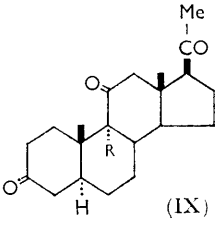
a, R = H; *b*, R = β-CH(OAc)·CH_3; *c*, R = OAc

Hence an acid treatment was introduced to form [2] the exocyclic methylene steroids (VIII) and the desired methyl ketones were then separated from these and from parent ketones by alumina chromatography and characterised, in particular by n.m.r. spectroscopy. The 9α-methyl signal (Table 3) of (VI*b*) was overlapped by one arm of the doublet from the C-21 protons; the triketone (IX; R = Me) was therefore prepared, in which the 9α-methyl absorption was clearly seen. The 3α,5β-isomer of (Vb) gave no methylated product, a result consistent with the failure of the original alkylation reaction with 9α-bromo-11-keto-5β-steroids for which an explanation of steric hindrance was suggested.[3] 3β-Acetoxy-9α-methyl-5α-androstan-11-one (VI*a*) obtained by the enol acetate procedure, identical with that previously obtained by the bromo-ketone method,[3] has been converted into the corresponding alcohol (XI; R = Me) and diketone (XII; R = Me), required for another investigation.

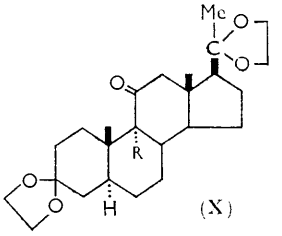
In the alkylations with dibutyl ether–tetrahydrofuran, both bromo-ketones (II*b* and II*c*) and enol acetates (V*b* and *c*) have afforded quantities (up to 20%) of material with longer g.l.c. retention time than the 9α-methyl-steroids (VI*b* and VI*c*), indicating a larger molecular weight. These compounds, which might have arisen by Grignard attack on the extremely hindered 11-carbonyl group of the monoalkylated steroids, have been shown to be 9α,12β-dimethyl-11-keto-steroids. The compound in the pregnane series (*i.e.*, XIII) was shown by analysis and n.m.r. spectroscopy to have a (secondary) methyl group more than (VI*b*). It lacked a peak at 1430 $cm.^{-1}$ (CCl_4 solution), present in the infrared spectra of both (I*b*) and (VI*b*) showing that the $CO{\cdot}CH_2$-group [4] was no longer present, and

[2] D. N. Kirk and V. Petrow, *J.*, 1961, 2091.
[3] S. Binns, J. S. G. Cox, Sir Ewart R. H. Jones, and B. G. Ketcheson, *J.*, 1964, 1161.
[4] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Co., London, 1958, p. 23.

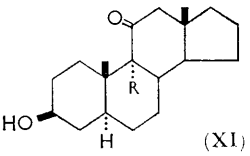
the 11-ketone absorbed at 1695 cm.$^{-1}$ rather than at 1710 cm.$^{-1}$ as in (VI*b*) (cf. ref. 5). The n.m.r. spectrum of (XIII) showed one proton, as a quartet, although not all visible, at 7·82 p.p.m. The β-configuration for the new methyl group was suggested by the n.m.r. spectrum, which showed the 9α-methyl signal at the same chemical shift as in (VI*b*). Had the 12-methyl group had the α-configuration, then the strong 1,3-diaxial interaction of these two methyl groups should have caused a change in shift for the 9α-methyl group. Clearer evidence was obtained by comparison of molecular rotations. The steroid (VI*b*) had M_D +294°, while the compound (XIII) had a very similar value of M_D +268°, pointing to a 12β (equatorial) configuration. Hydrolysis of (XIII) to the corresponding diol [under acidic conditions, which should epimerise a methyl group at C-12 to its more stable configuration (cf. ref. 5); it is reported [6] that base does not epimerise a 12α-methyl-11-ketone] and oxidation gave the triketone (XIV) with M_D +561°. The corresponding 9α-methyl triketone (IX; R = Me) has M_D +558° and clearly no epimerisation took place on hydrolysis. The optical rotatory dispersion curve of ketone (XIII) was almost identical (positive Cotton effect, *a*, +79) with that of ketone (VIb) (*a*, +66) showing that the extra methyl group made virtually no contribution, *i.e.*, it was equatorial. The analogous



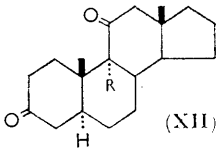
(IX)



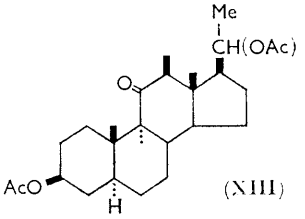
(X)



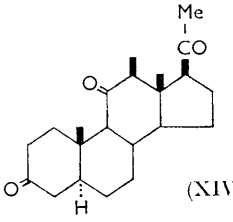
(XI)



(XII)



(XIII)



(XIV)

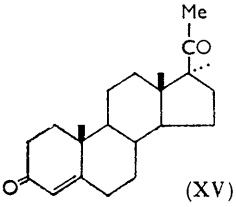
compound in the 17-acetoxy-androstane series, not completely pure, has been characterised by spectra only, but has, we believe, structure (XIII, but with 17β-OAc). This second methylation presumably involves the Grignard reagent acting as a base, the hindered carbonyl function giving it opportunity of showing its strength; it is not possible to decide whether the 12α- or the 12β-methyl compound is initially formed.

The reaction between a Grignard reagent and an α-bromo-ketone may take several paths,[7] and the formation of the enolate anion is most likely when the carbonyl group is sterically hindered. However, preliminary results [8] suggest that, apart from the 9α-bromo-11-ketones described, only 5α-bromo-6-keto-steroids afford reasonable yields of simple alkylated products. The enol acetate method, generating the enolate anion without the intermediacy of a bromo-ketone, should therefore be preferred, but alkylation may be complicated by further reaction of the initial product, as with the formation of 9α,12β-dimethyl-steroids, whilst with a less hindered carbonyl group methylation followed by normal Grignard reaction seems likely.

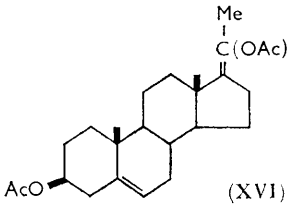
Since 17α-methyl-20-ketopregnanes are reported to be unreactive towards Grignard

[5] Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.
[6] B. G. Christensen, R. G. Strachan, N. R. Trenner, B. H. Arison, R. Hirschman, and J. M. Chemerda, *J. Amer. Chem. Soc.*, 1960, **82**, 3995.
[7] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice Hall, New York, 1954, p. 181.
[8] With J. J. Smolicz, unpublished observations.

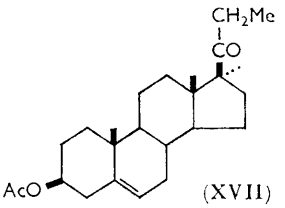
reagents,[9,10] the enol acetate method seemed indicated here, and in fact made possible a three-stage preparation of 17α-methylprogesterone (XV) from pregnenolone. The mixture



(XV)



(XVI)



(XVII)

of stereoisomeric enol acetates (XVI) (75%)[11] from pregnenolone, on alkylation gave 17α-methylpregnenolone (about 60%) separated from pregnenolone with Girard's reagent,[9] and oxidised[12] to 17α-methylprogesterone (XV). Some (10%) of dialkylated material was produced and a longer reaction time gave a dialkylated ketone isolated as its acetate (XVII) by chromatography, with infrared and n.m.r. spectra consistent with the replacement of an acetyl by a propionyl group.

Table 2 gives the molecular rotations of the steroids used and prepared in this work and molecular rotation differences for the conversions indicated in the footnote.

TABLE 2

(Rotations were measured for $CHCl_3$ solutions at room temperature)

Compound	$M_D°$	ΔM_D *	Ref.	Compound	$M_D°$	ΔM_D *	Ref.
(I) *a*	+130		3	(VI) *a*	+302	−172	3
(I) *b*	+142		13	(VI) *b*	+294	−152	
(I) *c*	+20		14	(VI) *c*	+160	−140	
(II) *a*	+660	−530		(VII) *c*	+365	−345	
(II) *b*	+710	−568		(VIII) *b*	+79	+63	2
(II) *c*	+565	−545		(VIII) *c*	−31	+51	
(III) *a*	−301	+431		(IX) R = H	+402	—	15
(III) *b*	−208	+350		(IX) R = Br	+930	−528	
(IV) *a*	−42	+172		(IX) R = Me	+558	−156	
(IV) *b*	+83	+59	2	(XI) R = H	+174	—	3
(IV) *c*	−65	+85		(XI) R = Me	+358	−184	
(V) *b*	+216	−64		(XII) R = H	+254	—	3
(V) *c*	+91	−71		(XII) R = Me	+387	−133	

* For compounds (II—VIII) ΔM_D is quoted as M_D (I)–M_D (compound); for compounds (IX, XI, and XII), ΔM_D is quoted as M_D (compound R = H) −M_D (compound).

TABLE 3

Nuclear magnetic resonance line positions (in τ units) ‡

Compound	C-18	C-19	C-21	OAc	C-12	Others
(I) *a*	9·33	8·94		7·98	7·70	
(I) *b*	9·43	8·98	8·85*d* $J = 6$	7·97, 7·97	7·62	
(I) *c*	9·27	8·96		7·99, 7·97	7·72	
(II) *a*	9·32	8·81		7·97	7·73*d* (β) 6·67*d* (α) $J = 13$	
(II) *b*	9·39	8·79	8·82*d* $J = 6$	7·96, 7·92	7·68*d* (β) 6·55*d* (α) $J = 13·5$	
(II) *c*	9·24	8·79		7·99, 7·97	7·76*d* (β) 6·61*d* (α) $J = 14$	

[9] M. J. Weiss, R. E. Schaub, G. R. Allen, J. F. Poletto, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, 1964, **20**, 357.
[10] R. Deghenghi, Y. Lefebvre, P. Mitchell, P. F. Morand, and R. Gaudry, *Tetrahedron*, 1963, **19**, 289.
[11] L. F. Fieser and Huang-Minlon, *J. Amer. Chem. Soc.*, 1949, **71**, 1840.
[12] Pl. A. Plattner, H. Heusser, and P. Th. Herzig, *Helv. Chim. Acta*, 1949, **32**, 270.
[13] *Inter al.*, J. Romo, G. Stork, G. Rosenkranz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 2919.
[14] H. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger, and O. Jeger, *Helv. Chim. Acta*, 1952, **35**, 295.
[15] *Inter al.*, C. Djerassi, O. Mancera, J. Romo, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 3505.

TABLE 3 (*Continued*)

Compound	C-18	C-19	C-21	OAc	C-12	Others
(III) *a*	9·12	8·93		7·97	5·91 (β)	
(III) *b*	9·24	8·95	8·79*d* $J = 6$	7·97, 7·94	5·98 (β)	
(IV) *a*	9·08	8·84		7·97		C-11-Me 8·57
(IV) *b*	9·17	8·86	8·86*d* $J = 6$	7·97, 7·95		8·60
(IV) *c*	9·03	8·87		8·00, 7·98		8·60
(V) *b*	9·37	8·92	8·85*d* $J = 6·5$	8·02, 7·99 7·94		
(V) *c*	9·22	8·95		8·12, 8·07 8·05		
(VI) *a*	9·29	8·90		7·98	7·75 * 7·50*d* (α) $J = 13$	C-9-Me 8·82
(VI) *b*	9·39	8·91	8·84*d* $J = 6$	7·96, 7·96	7·71 * 7·40*d* (α) $J = 13·5$	8·83
(VI) *c*	9·24	8·91		7·99, 7·97	7·77 * 7·41*d* (α) $J = 13$	8·85
(VII) *a*	9·27	8·89		7·99		
(VII) *b*	9·33	8·89	8·84*d* $J = 6·5$	7·97, 7·95		
(VII) *c*	9·18	8·83		7·98, 7·96	7·79*d* (α) 7·45*d* (β) $J = 16$	
(VIII) *a*	9·38	8·95		8·06		C-11=CH_2 5·15
(VIII) *c*	9·29	8·95		7·99, 7·97		5·10
(IX) R = H	9·38	8·76	7·87			
(IX) R = Br	9·36	8·62	7·87		7·42*d* (β) 6·38*d* (α) $J = 13$	
(IX) R = Me	9·37	8·74 †	7·91			C-9-Me 8·79 † O·CH_2·CH_2·O 6·07
(X) R = H	9·27	8·95	8·74			
(X) R = Br	9·27	8·81	8·74		7·44*d* (β) 6·59*d* (α) $J = 14$	6·06
(XIII)	9·34	8·97	8·85*d* $J = 6$	7·98, 7·98	7·82(*q*) $J = 8$	C-9α-Me 8·87 C-12-Me 8·76*d* $J = 8$
(XIV)	9·28	8·84 or 8·79	7·90	C-9α-Me 8·79 or 8·84		C-12-Me 8·72*d* $J = 8$
(XIII) (but 17β-OAc) §	9·14	8·94		C-9α-Me 7·97, 7·97	8·88	C-12-Me 8·86*d* $J = 7$
3β-Acetoxy-5α-androstane				9·30		9·16
3β,20β-Diacetoxy-5α-pregnane				C-18 9·38		C-19 9·17
3β,17β-Diacetoxy-5α-androstane				9·22		9·16

* The major arm of the high field doublet: the minor arm is hidden beneath the OAc absorption. † Probable assignment; see text. ‡ Spectra measured at 60 Mc./sec. for *ca.* 0·25M-solutions in $CHCl_3$ [CCl_4 for (Vc) and (VIIIa)] with tetramethylsilane as internal reference. All signals are singlets, unless otherwise indicated (*d* = doublet, *q* = quartet, with *J* in cps.), of the correct relative intensity for the assigned protons. § Sample 85% pure.

Recent compilations of n.m.r. data for steroids, particularly of chemical shifts for C-18 and C-19 protons, will prove most valuable. As additions to these lists, which contain very few 11-ketones and their derivatives, Table 3 gives the n.m.r. spectral data for the steroids discussed in this Paper, in addition to which the 12α-bromo-ketones (III*a* and III*b*) were prepared. The last three compounds are given for comparison, using chemical

shifts calculated from the Paper by Zurcher.[16] Where the actual compounds have been examined (*e.g.*, ref. 17) agreement is excellent. The discussion that follows refers to spectra measured in chloroform solutions, except when otherwise indicated.

Introduction of an 11-ketone group into the steroid nucleus results in a shift to high field (0·04 p.p.m.) of the C-18 protons, while the C-19 protons are moved downfield (0·20 p.p.m.), as quoted by Zurcher. Similarly, the 11-methylene group gives a small shift (0·07 p.p.m.) upfield for the C-18 protons, and a larger downfield shift (0·20 p.p.m.) for the C-19 protons. The Δ^8-11-ketone system effects a small downfield shift (0·04 p.p.m.) on the C-18 protons, and a fairly large downfield shift (0·29 p.p.m.) of the C-19 protons. In the spectra of 11-ketones in chloroform solution, a 9α-bromo-substituent brings the C-19 protons downfield (*ca.* 0·16 p.p.m.) while having little effect on the C-18 protons; the 12α-bromo-substituent brings the C-18 protons downfield (*ca.* 0·20 p.p.m.), while causing little shift of the C-19 protons. A 9α-methyl group brings both C-18 and C-19 protons downfield (*ca.* 0·05 p.p.m.) [it is on this basis that the assignments for (IX; R = Me) are made], and while both bromo- and methyl-substituents might be expected to have similar effects on the geometry of the molecule, the larger effect of the bromo-substituent on the angular methyl group 1,2-diaxial to it reflects the polarity of the C–Br bond. The 11α-methyl-11β-alcohols (IV) show the effect of a methyl group close to an electronegative atom, a point which Zurcher [16] considers in some detail.

The C-12 protons in the ketones (I) are observed as a singlet, albeit broader than the angular methyl signals (chloroform solution). The introduction of a 9α-substituent (Br or Me) removes this accidental coincidence of chemical shift, resulting in an AB quartet being observed. The 12β-proton has essentially the same chemical shift as in the unsubstituted ketone, but the 12α-proton occurs at lower field. In the 9α-bromo-ketones (II), the 12α-proton is shifted downfield (*ca.* 1·0 p.p.m.), and is seen as a doublet, considerably broadened compared with the 12β-proton doublet (these protons are thus distinguishable; coupling between the 12α-proton and C-18 protons has recently been suggested in an 11-ketone [18]). Similarly, the 9α-methyl group shifts the 12α-proton to lower field (by *ca.* 0·3 p.p.m.). Of relevance to these observations is the report [19] that a 3α-proton is shifted downfield (by 0·5 p.p.m.) by a 5α-hydroxyl group. Another example of a substituent deshielding a proton that is in a 1,3-diaxial position relative to it is seen in a 5α-chloro-steroid which shows a shift of the 3α-proton to low field (0·8 p.p.m.) compared with the 5α-H steroid.[20]* The Δ^8-11-ketone (VII*c*) also showed the C-12 protons as an AB quartet, and in this case the 12α-proton was the one at higher field.

The spectra of these 11-ketones measured in benzene solution show marked changes from the spectra in chloroform solution. An example of an 11-ketone with hydrogen at C-9 is recorded [21] in which the C-12 protons, a broad singlet in chloroform, show as an AB quartet in benzene, with the 12β-proton as a sharp doublet at lower field than the broader 12α-proton doublet. Compounds (I*b*) and (I*c*), in benzene, show similar AB quartets. The 9α-bromo-ketones (II*b*) and (II*c*) show the C-12 protons as a quartet in benzene, as they did in chloroform. The 12β-proton is at slightly lower field in benzene, while the 12α-proton has the same chemical shift in both solvents. The 9α-methyl compounds (VI*b*) and (VI*c*), which show the AB quartet in chloroform (see Table 3) show the C-12 protons as a broad singlet in benzene. The Δ^8-11-ketone (VI*c*) shows similar movements for the 12α- and 12β-protons on change of solvent as the unsubstituted ketones, although the 12α-proton

* *Added in proof*).—K. Tori and K. Komeno (*Tetrahedron*, 1965, **21**, 309) have recently reported a number of examples of this effect which is now well recognised, and discuss it in detail (p. 325).

[16] R. F. Zurcher, *Helv. Chim. Acta*, 1961, **44**, 1380; 1963, **46**, 2054.
[17] A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.*, 1963, **85**, 3223.
[18] C. W. Shoppee, F. P. Johnson, R. Lack, and S. Sternhell, *Tetrahedron Letters*, 1964, 2319.
[19] S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, 1963, 1517.
[20] J. R. Bull and G. D. Meakins, personal communication.
[21] N. S. Bhacca and D. H. Williams, results referred to in Varian advertisement, " N.M.R. at work, No. 89."

moves upfield by a smaller amount. The chemical shifts (in τ units) for these protons in benzene solution are annexed.

	(I*b*)	(I*c*)	(II*b*)	(II*c*)	(VI*b*)	(VI*c*)	(VII*c*)
12β	7·49(*d*)	7·62(*d*)	7·56(*d*)	7·65(*d*)	7·63	7·69	7·29(*d*)
12α	7·95(*d*)	7·98(*d*)	6·56(*d*)	6·62(*d*)	7·63	7·69	7·88(*d*)
J (c./sec.)	12·5	12·5	13·5	14			14

Experimental

Melting points were determined on a Kofler hot-stage apparatus. Rotations (±1% for $[\alpha]_D$ >20°, becoming progressively less accurate; *e.g.*, ±5% for $[\alpha]_D$ 5°) were measured for chloroform solutions at room temperature with a Bendix–Ericsson polarimeter (type 143A). Infrared spectra, unless otherwise specified, were determined in carbon tetrachloride; ultraviolet spectra in ethanol and optical rotatory dispersion curves were measured in methanol. For gas–liquid chromatographic (g.l.c.) analysis, a column (4 ft. × 4 mm.) of 1% Silicone E301 (Imperial Chemical Industries Limited, Nobel Divison) on Gas-Chrom P (100—120 mesh) prepared as described by Horning *et al.*,[22] at 200—225°, with an inlet heater at *ca.* 300° and an inlet pressure of 10 lb. in.$^{-2}$ was used, in conjunction with a Pye Argon β-ray detector. Retention times of 10—30 min. were obtained. The alumina used was prepared by treating Peter Spence Grade " H " alumina with 5% (by volume) of 10% acetic acid. Silica gel is Crosfield " Sorbsil " (60—120 mesh) and light petroleum had b. p. 60—80° unless otherwise stated.

Androstane Series

Enol Acetylation of 3β-*Acetoxy*-5α-*androstan*-11-*one*.—A solution of 3β-acetoxy-5α-androstan-11-one [3] (1·14 g.) and toluene-*p*-sulphonic acid monohydrate (670 mg.) in acetic anhydride (170 c.c.) was heated under reflux with slow distillation for 8 hr., and more anhydride (40 c.c.) was added after 4 hr. The solvent was removed at 30 mm. and isolation *via* ether gave a gum which was adsorbed from benzene on alumina (10 g.). Elution with benzene (200 c.c.) gave an oil (1·38 g.) containing (by g.l.c.) the starting ketone (40%) and the enol acetate (V*a*) with a longer retention time (r.t.). Further treatment under the same reaction conditions failed to increase substantially the proportion of enol acetate present. Binns [23] was only able to obtain the enol acetate contaminated with 20% of the ketone after extensive chromatographic purification.

Methylation of the Enol Acetate–Ketone Mixture with Grignard Reagent–Methyl Iodide.—A mixture (1·3 g.) of the above 3β,11-diacetoxy-5α-androst-9(11)-ene (*ca.* 60%) and 3β-acetoxy-5α-androstan-11-one (*ca.* 40%) in tetrahydrofuran (240 c.c.; distilled from sodium) was added to methylmagnesium iodide [prepared from magnesium (5 g.) in ether (100 c.c.) and methyl iodide (20 c.c.) in ether (100 c.c.) and filtered under nitrogen]. The reaction mixture was heated under reflux for 2 hr., methyl iodide (400 c.c.) was added, and heating was continued for 20 hr. Aqueous ammonium chloride was added, and after acetylation (acetic anhydride–pyridine) the product (1·12 g.) showed two peaks on g.l.c. analysis, one (20%) corresponding to 3β-acetoxy-5α-androstan-11-one, and the other (80%) to 3β-acetoxy-9α-methyl-5α-androstan-11-one,[3] but being due also to the tertiary alcohol, below. This material, in ether, deposited crystals (140 mg.), m. p. 149—153°. Recrystallisation from ether–light petroleum (b. p. 40—60°) afforded 3β-*acetoxy*-11α-*methyl*-5α-*androstan*-11β-*ol* (IV*a*). m. p. 152—153°, $[\alpha]_D$ −12° (*c* 0·98); $\nu_{max.}$ 3610 (OH), 1735, 1250, and 1030 cm.$^{-1}$ (acetate) (Found: C, 75·4; H, 10·6. $C_{22}H_{36}O_3$ requires C, 75·8; H, 10·4%). The tertiary alcohol was identical (including $[\alpha]_D$, see below) with that obtained from the action of methylmagnesium iodide on the pure 3β-acetoxy-5α-androstan-11-one as described by Binns,[23] who recorded $[\alpha]_D$ +8° (*c* 0·87) for the alcohol (IV*a*), but this value, which we now believe to be erroneous, was measured on a visual polarimeter. The remaining material (*ca.* 630 mg.) was heated under reflux in benzene (75 c.c.) containing toluene-*p*-sulphonic acid monohydrate (350 mg.) for 1 hr. Normal work-up gave a gum (490 mg.) again showing two peaks on g.l.c. analysis, one (45%) with the same retention time as 3β-acetoxy-9α-methyl-5α-androstan-11-one, and the other (55%) with the same retention time as the unmethylated ketone, but which contained also the product of dehydration of the tertiary alcohol. With allowance made for the alcohol already isolated, this represents, in the crude alkylation product, 40% alkylated ketone (VI*a*) (see below), 20% unmethylated

[22] E. C. Horning, W. J. A. Vander Heuvel, and B. G. Creech, *Methods Biochem. Analysis*, 1963, **11**, 69.
[23] S. Binns, D.Phil. Thesis, Oxford, 1961.

ketone (I*a*), and 40% tertiary alcohol (IV*a*), which in turn means that about 60% of the starting enol acetate was converted into methylated ketone. The dehydration product was chromatographed on alumina (150 g.) with the same eluant as above. The first fraction (1 l.) gave a gum (108 mg.) which was essentially pure and which was shown by n.m.r. (Table 3) to be 3β-acetoxy-11-methylene-5α-androstane (VIII*a*); $\nu_{max.}$ 1730, 1240, 1025 (acetate), 1635, 905, and 895 cm.$^{-1}$ (methylene). Subsequent fractions afforded 3β-acetoxy-9α-methyl-5α-androstan-11-one (VI*a*; 120 mg.), m. p. 138—143° (lit.,[3] 144—145°), identical with an authentic sample (g.l.c., t.l.c., and mixed m. p.).

3β-*Acetoxy*-12α-*bromo*-5α-*androstan*-11-*one* (III*a*).—3β-Acetoxy-5α-androstan-11-one (995 mg.) was brominated as described below for the pregnane derivative (I*b*) for 3 hr. at 50°. The crude product was heated at 100° for 2 hr. with lithium carbonate (5 g.) in dimethylformamide (100 c.c.) and then chromatographed on alumina (200 g.). The first fraction (250 c.c.; benzene–light petroleum, 55 : 45) afforded a solid (160 mg.) which was twice crystallised from ethanol–light petroleum to give the 12α-*bromo-ketone*, m. p. 176—178°, $[\alpha]_D$ −73° (*c* 1·03), $\lambda_{max.}$ 3175 Å (ε 159) [cf. 3β-acetoxy-5α-androstan-11-one [3] $\lambda_{max.}$ 2980 Å (ε 27)]; $\nu_{max.}$ (in CS_2), 1730, 1240, 1030 (acetate), 1715 (ketone), and 715 cm.$^{-1}$ (C–Br) (Found: C, 61·4; H, 7·8. $C_{21}H_{31}BrO_3$ requires C, 61·4; H, 7·55%). Later fractions afforded the non-crystalline 3β-acetoxy-5α-androst-8-en-11-one (VI*a*).[3]

3β-*Hydroxy*-9α-*methyl*-5α-*androstan*-11-*one* (XI; R = Me).—3β-Acetoxy-9α-methyl-5α-androstan-11-one (140 mg.) was hydrolysed in methanol (25 c.c.) containing aqueous sulphuric acid (1 c.c., 20% v/v) for 2 hr. under reflux. The product, crystallised from ether, was the 9α-*methyl-alcohol*, m. p. 154—157°, $[\alpha]_D$ +117·5° (*c* 1·01), $\nu_{max.}$ (in CS_2) 3540, 1040 (OH), and 1700 cm.$^{-1}$ (ketone) (Found: C, 79·0; H, 10·7. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

9α-*Methyl*-5α-*androstane*-3,11-*dione* (XII; R = Me).—The above alcohol (89 mg.) in acetone was oxidised with 8N-chromic acid in sulphuric acid [24] to the *diketone*, m. p. 118—120° [from ether–light petroleum (b. p. 40—60°)], $[\alpha]_D$ +128° (*c* 1·01); $\nu_{max.}$ (in CS_2) 1710 and 1700 cm.$^{-1}$ (ketones) (Found: C, 79·4; H, 10·15. $C_{20}H_{30}O_2$ requires C, 79·6; H, 10·0%).

Pregnane Series

3β,20β-*Diacetoxy*-9α-*bromo*-5α-*pregnan*-11-*one* (II*b*).[25]—3β,20β-Diacetoxy-5α-pregnan-11-one (5·0 g.) was dissolved in acetic acid (30 c.c.) containing hydrogen bromide (3% w/v) at 40° under nitrogen and in the dark. Bromine (0·8 c.c.) in acetic acid–hydrogen bromide (7·5 c.c.) was added to the stirred solution, and after 3 min. aqueous sodium sulphite was added. Isolation *via* ether and three crystallisations from ethanol gave pure 3β,20β-*diacetoxy*-9α-*bromo*-5α-*pregnan*-11-*one* (II*b*) (2·3 g.), m. p. 188—191° (change of crystal form at *ca.* 178°), $[\alpha]_D$ +140° (*c* 0·79), $\lambda_{max.}$ 3190 Å (ε 87) [cf. 3β,20β-diacetoxy-5α-pregnan-11-one $\lambda_{max.}$ 2965 Å (ε 29)]; $\nu_{max.}$ (in CS_2) 1730, 1240, 1025 (acetates), 1710 (ketone), and 745 cm.$^{-1}$ (C–Br) [cf. 3β,20β-diacetoxy-5α-pregnan-11-one, $\nu_{max.}$ (in CS_2) 1710 cm.$^{-1}$ (ketone)] (Found: C, 60·8; H, 7·6; Br, 16·1. $C_{25}H_{37}BrO_5$ requires C, 60·4; H, 7·5; Br, 16·1%).

3β,20β-*Diacetoxy*-12α-*bromo*-5α-*pregnan*-11-*one* (III*b*).—The above bromination was repeated, except that the reaction time was 5 min. The first crystalline product was filtered through alumina in benzene–light petroleum (1 : 1), and the product was again crystallised from ethanol to give material, m. p. 156—170° $[\alpha]_D$ +92°, corresponding to 75% of 9α-Br and 25% of 12α-Br ketones. Some (990 mg.) of this mixture was heated at 100° with dimethylformamide (100 c.c.) and lithium carbonate (5 g.) for 2 hr. Isolation with ether afforded a gum (830 mg.) which was adsorbed on alumina (200 g.) and eluted with benzene–light petroleum (1 : 1 increasing to 3 : 1) and then pure benzene. The first material from the column crystallised from ethanol to give the 12α-*bromo-ketone* (III*b*) (160 mg.), m. p. 195—197°, $[\alpha]_D$ −41° (*c* 1·01), $\lambda_{max.}$ 3170 Å (ε 145); $\nu_{max.}$ (in CS_2) 1730, 1240, 1025 (acetates), 1710 (ketone), and 720 cm.$^{-1}$ (C–Br) (Found: C, 60·1; H, 7·3; Br, 15·9. $C_{25}H_{37}BrO_5$ requires C, 60·4; H, 7·5; Br, 16·1%). The later fractions gave a gum, which could not be obtained crystalline, but was essentially 3β,20β-diacetoxy-5α-pregn-8-en-11-one (VI*c*), $\lambda_{max.}$ 2520 Å, $\nu_{max.}$ 1735, 1240, 1030, 1020 (acetates), 1665 (ketone), and 1590 cm.$^{-1}$ (8-ene).

9α-*Bromo*-5α-*pregnane*-3,11,20-*trione* (IX; R = Br).—A solution of 3β,20β-diacetoxy-9α-bromo-5α-pregnan-11-one (715 mg.) in methanol (30 c.c.) containing aqueous sulphuric acid (3 c.c.; 20% v/v) was heated under reflux for 3·5 hr. Isolation *via* ether gave material (600 mg.)

[24] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J.*, 1953, 2555.

[25] We thank Dr. A. H. Harrison for preliminary experiments.

which was treated in acetone (100 c.c.) with a small excess of 8N-chromic acid in sulphuric acid. The product (560 mg.) crystallised from acetone–chloroform to give the *bromo-triketone*, m. p. 169—172° (decomp.), $[\alpha]_D$ +227° (*c* 0·96); $\nu_{max.}$ (in CS_2) 1725sh, 1715 (ketones), 760, and 745 cm.$^{-1}$ (C–Br) (Found: C, 61·5; H, 6·9; Br, 19·7. $C_{21}H_{29}BrO_3$ requires C, 61·7; H, 7·1; Br, 19·5%).

9α-*Bromo*-3,3:20,20-*bisethylenedioxy*-5α-*pregnan*-11-*one* (X; R = Br).—9α-Bromo-5α-pregnane-3,11,20-trione (750 mg.) was heated under reflux for 8 hr. in benzene (80 c.c.) containing ethylene glycol (12 c.c.) and toluene-*p*-sulphonic acid monohydrate (150 mg.) with azeotropic removal of water. The product (885 mg.), crystallised from acetone containing a little water, was the *bisethylenedioxy-ketone* m. p. 184—187°, $[\alpha]_D$ +140° (*c* 1·18), $\nu_{max.}$ (in CS_2) 1715 (ketone), 1080 (ketals), and 740 cm.$^{-1}$ (C–Br) (Found: C, 60·6; H, 7·7; Br, 16·2. $C_{25}H_{37}BrO_5$ requires C, 60·4; H, 7·5; Br, 16·1%).

Attempted Alkylation of 9α-*Bromo-ketones*.—The method found to be successful [3] with 9α-bromo-ketones of the 5α-androstane and 5α-ergostane series was employed. 3β,20β-Diacetoxy-9α-bromo-5α-pregnan-11-one (500 mg., 1 mmole) in dry tetrahydrofuran (100 c.c.) was added to methylmagnesium iodide (70 mmoles) [from magnesium (1·75 g.) in ether (40 c.c.) and methyl iodide (7·5 c.c.) in ether (40 c.c.) prepared and filtered under nitrogen]. The mixture was heated under reflux for 1 hr., methyl iodide (180 c.c., 1·5 mole) was added, and heating was continued for 20 hr. Addition of aqueous ammonium chloride and acetylation of the product gave material (390 mg.) that contained (by g.l.c.) less than 5% of, possibly, alkylated ketone and which was essentially debrominated ketone, m. p. and mixed m. p. 159—162° (from ethanol–light petroleum). A similar experiment, but displacing the ether used as solvent for the Grignard preparation with dichloromethane and adding the steroid in the same solvent, gave no alkylated material. 9α-Bromo-3,3:20,20-bisethylenedioxy-5α-pregnan-11-one was used in a similar reaction using the ether–tetrahydrofuran procedure, when initial isolation (omitting acetylation step) gave crude debrominated ketal (X; R = H) and again no alkylated material (by g.l.c.).

Alkylation of 9α-*Bromo*-11-*ketones*.—The following general procedure was used with 3β,20β-diacetoxy-9α-bromo-5α-pregnan-11-one (II*b*) and 3β,17β-diacetoxy-9α-bromo-5α-androstan-11-one (II*c*) to furnish the results in Table 1. To magnesium (250 mg.) in ether (10 c.c. ethyl or butyl) was slowly added methyl iodide (5 c.c.) in the ether (10 c.c.) under nitrogen. To this Grignard solution (10 mmole with about 50 mmole excess of methyl iodide) was added the bromo-ketone (100 mg., about 0·2 mmole) in tetrahydrofuran (25 c.c.) and the mixture was immediately set to reflux. After the allotted time, the mixture was cooled, and saturated ammonium chloride solution (50 c.c.) was added. Extraction with ether was followed by acetic anhydride–pyridine treatment at 100° for 1 hr., and g.l.c. analysis Material from reactions allowed only 5 min. under reflux was also heated at 100° for 2 hr. in dimethylformamide (10 c.c.) containing lithium carbonate (250 mg.). The isolated product was then also examined by ultraviolet spectroscopy.

3β,11,20β-*Triacetoxy*-5α-*pregn*-9(11)-*ene* (V*b*).[25]—3β,20β-Diacetoxy-5α-pregnan-11-one (15·5 g.) was heated under reflux in acetic anhydride (350 c.c.) containing toluene-*p*-sulphonic acid monohydrate (5·0 g.) for 9 hr. [more anhydride (50 c.c.) added after 3 hr.] with slow distillation of solvent, which was finally removed at 30 mm. The residue, crystallised from ether–light petroleum (b. p. 40—60°) gave the *enol acetate* (6·67 g.), m. p. 155—156°, $[\alpha]_D$ +46° (*c* 1·01), $\nu_{max.}$ 1740, 1245, 1225, 1025 (acetates), 1750sh, 1210, 1035 (enol acetate), and 1650 cm.$^{-1}$ [9(11)ene] (Found: C, 70·6; H, 8·8. $C_{27}H_{40}O_6$ requires C, 70·4; H, 8·75%).

3β,20β-*Diacetoxy*-9α-*methyl*-5α-*pregnan*-11-*one* (IV*b*).—3β,11,20β-Triacetoxy-5α-pregn-9(11)-ene (500 mg.) was treated with methylmagnesium iodide–methyl iodide following the procedure described above for the first attempted alkylation of 3β,20β-diacetoxy-9α-bromo-5α-pregnan-11-one, except that the mixture was heated under reflux for 2 hr. before the addition of methyl iodide. The product (465 mg.) from acetylation showed two peaks on g.l.c. analysis, one (60%) with the same retention time as the 11-ketone (I*b*) and the other (40%) with a longer retention time (longer by a factor of about 1·3; the same relative retention times were observed between methylated and unmethylated ketones in the 5α-androstane series above, and the 17β-acetoxy-5α-androstane series below). The mixture was adsorbed on alumina (150 g.) and eluted with light petroleum containing increasing amounts of benzene (15—35%). Fractions containing more than 90% of the longer retention time material (total *ca.* 100 mg.) were combined and crystallised from methanol to afford the 9α-*methyl ketone*, m. p. 192—195°,

$[\alpha]_D$ +69° (*c* 0·78); $\nu_{max.}$ 1740, 1245, 1020 (acetates), and 1710 cm.$^{-1}$ (ketone) (Found: C, 72·45; H, 9·6. $C_{26}H_{40}O_5$ requires C, 72·2; H, 9·3%); o.r.d. [*M*] (4000 Å), +960; (3230), +4870; (2780), −3060; (2200), +3640°.

9α-*Methyl*-5α-*pregnane*-3,11,20-*trione* (IX; R = Me).—3β,20β-Diacetoxy-9α-methyl-5α-pregnan-11-ene (180 mg.) was hydrolysed with aqueous acid in methanol (as above), oxidised,[24] and the product (107 mg.) crystallised from ethanol–chloroform to give the 9α-*methyl triketone*, m. p. 206—210°, $[\alpha]_D$ +168° (*c* 1·00); $\nu_{max.}$ (in $CHCl_3$) 1715sh and 1705 cm.$^{-1}$ (ketones) (Found: C, 75·8; H, 9·3. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%).

3β,20β-*Diacetoxy*-9α,12β-*dimethyl*-5α-*pregnan*-11-*one* (XIII).—3β,11,20β-Triacetoxy-5α-pregnan-11-one (V*b*) (2·0 g.) in tetrahydrofuran (500 c.c.) was added to methylmagnesium iodide [from magnesium (6 g.) in di-n-butyl ether (200 c.c.) and methyl iodide (40 c.c.) in the ether (160 c.c.) under nitrogen]. After 1 hr. methyl iodide (200 c.c.) was added, and the mixture was heated under reflux for 19 hr. The usual isolation and acetylation afforded material that contained (by g.l.c.) about 20% of a steroid of longer retention time than (VI*b*). Chromatography on alumina (400 g.) and rechromatography of the early fractions afforded the 9α,12β-*dimethyl steroid*, m. p. 168—171°, $[\alpha]_D$ +60° (*c* 0·39); $\nu_{max.}$ 1740sh, 1735, 1245, 1025 (acetates), and 1695 cm.$^{-1}$ (ketone) (Found: C, 72·4; H, 9·55. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·5%); o.r.d. [*M*] (4000 Å), +1020; (3260), +4330; (2820), −2300; (2270), +3990°.

9α,12β-*Dimethyl*-5α-*pregnane*-3,11,20-*trione* (XIV).—The above diacetate (40 mg.) was heated under reflux in methanol (5 c.c.) containing aqueous sulphuric acid (0·5 c.c., 20% v/v) for 7 hr. and the product oxidised [24] to give, after crystallisation from ethanol–chloroform, the *dimethyl triketone*, m. p. 209—212° $[\alpha]_D$ +155° (*c* 0·56); $\nu_{max.}$ 1715 (3,20-ketones), 1705sh (11-ketone) (Found: C, 76·85; H, 9·3. $C_{23}H_{34}O_3$ requires C, 77·05; H, 9·6%).

Attempted Alkylation of 3α,11,20β-*Triacetoxy*-5β-*pregn*-9(11)-*ene*.—This enol acetate [26] (250 mg.) was allowed to react under the conditions used for the 3β,5α-isomer (V*b*) above. The product, after acetylation, was at least 95% (by g.l.c.) 3α,20β-diacetoxy-5β-pregnan-11-one,[27] m. p. 160—163°.

Alkylation of 3β,20-*Diacetoxypregna*-5,17(20)-*diene* (XVI).—To methylmagnesium iodide [from magnesium (2 g.) in butyl ether (100 c.c.) and methyl iodide (50 c.c.) in butyl ether (100 c.c.) prepared and filtered under nitrogen] was added 3β,20-diacetoxypregna-5,17(20)-diene [11] (1·0 g.) in tetrahydrofuran (250 c.c.). The mixture was heated under reflux for 4·5 hr. and cooled, and saturated ammonium chloride solution was added. The crude product contained, by g.l.c., pregnenolone, 17α-methylpregnenolone, and 17α,21-dimethylpregnenolone in the ratio 1 : 6 : 3. The mixture was acetylated and chromatography on alumina afforded, in the first fractions, 3β-*acetoxy*-17α,21-*dimethylpregn*-5-*en*-20-*one* (XVII) (120 mg.), m. p. 152—153°, $[\alpha]_D$ −51° (*c* 0·85); $\nu_{max.}$ 1740, 1245, 1035 (acetate), 1708 cm.$^{-1}$, and no peak at about 1355 cm.$^{-1}$ present in pregnenolone acetate and its 17α-methyl-homologue, attributable to the $CO{\cdot}CH_3$ group (Found: C, 77·3; H, 10·2. $C_{25}H_{38}O_3$ requires C, 77·7; H, 9·9%).

The later chromatography fractions afforded 3β-acetoxy-17α-methylpregn-5-en-20-one (310 mg.), m. p. 191—193° (lit.,[12] 185—187°), $[\alpha]_D$ −58° (*c* 0·98) (lit.,[10] −54°); $\nu_{max.}$ 1740, 1245, 1035 (acetate), 1706 (ketone), and 1354 cm.$^{-1}$ ($CO{\cdot}CH_3$): the n.m.r. spectrum showed the same chemical shifts as quoted for the alcohol,[9] except that the assignments for 19-H_3 and 17-CH_3 should be reversed (Found: C, 77·1; H, 9·5. Calc. for $C_{24}H_{36}O_3$: C, 77·4; H, 9·7%).

A similar experiment, with the reaction time of 3 hr., afforded a crude product that contained, by g.l.c., pregnenolone, 17α-methylpregnenolone, and 17α,21-dimethylpregnenolone in the ratio 3 : 6 : 1. Separation using Girard reagent T, as described by Schaub and his co-workers [9] gave 17α-methylpregnenolone (450 mg.) contaminated with about 5% of the dialkylated material. From this was prepared 17α-methylprogesterone (XV), m. p. 130—134° (lit.,[9,12] 131—138°, 129—131°); the n.m.r. spectrum showed the same chemical shifts as have been reported.[9]

17β-*Acetoxyandrostane Series*

3β-*Acetoxy*-5α-*androstane*-11,17-*dione*.—This diketone was prepared by the method of Williams *et al.*,[28] using the conditions developed by Kirk and Petrow [2] for a similar transformation. 3β-Acetoxy-5α-pregn-16-ene-11,20-dione 20-oxime [28] (30 g.) was dissolved in dry

[26] E. R. H. Jones and D. J. Wluka, *J.*, 1961, 907.
[27] L. H. Sarett, *J. Amer. Chem. Soc.*, 1948, **70**, 1690.
[28] D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2091. We thank Professor Djerassi for a copy of this Paper before publication.

pyridine (140 c.c.) at 0°, and to the stirred solution phosphoryl chloride (60 c.c.) in pyridine (160 c.c.) was added during a few minutes. Stirring at 0° was continued for 3 hr. when the solution was poured on concentrated hydrochloric acid (500 c.c.) and ice (*ca.* 500 g.) with external cooling to keep the temperature below 50°. The cooled mixture was extracted with ether (2 × 500 c.c.) and the product from the washed extracts was crystallised from aqueous ethanol to give the diketone (19·2 g.), m. p. 162—165° (lit.,[28] 161—163°), $[\alpha]_D$ +99° (*c* 1·01) (lit.,[28] +98°).

3β,17β-*Diacetoxy*-5α-*androstan*-11-*one* (I*c*).—The above dione (20 g.) was treated in methanol (500 c.c.) at 0° with sodium borohydride (2 g.) for 45 min. Acetic acid (40 c.c.) in acetone (40 c.c.) was slowly added. The solution was kept at 20° for 30 min., and was then poured into water (1 l.). After 30 min., extraction with ether, acetylation with acetic anhydride in pyridine at 100° for 1 hr., and crystallisation of the product from aqueous ethanol afforded material (20 g.), m. p. 149—153°, $[\alpha]_D$ +7°, that contained (by g.l.c.) 10—15% of (presumably) 3β,17β-diacetoxy-5α-androstan-11β-ol. This mixture was treated, in acetone, with a small excess of chromic acid in sulphuric acid, and the product (now pure by g.l.c.) was crystallised from aqueous ethanol to give 3β,17β-diacetoxy-5α-androstan-11-one, m. p. 165—167° (lit.,[14] 153—154°), $[\alpha]_D$ +5° (*c* 0·98) (lit.,[14] +14° ± 4°) (Found: C, 70·65; H, 8·9. Calc. for $C_{23}H_{34}O_5$: C, 70·7; H, 8·8%).

3β,17β-*Diacetoxy*-9α-*bromo*-5α-*androstan*-11-*one* (II*c*).—Bromine (2·4 g.) in acetic acid (7·8 c.c.) was added to a stirred solution of 3β,17β-diacetoxy-5α-androstan-11-one (5·0 g.) in acetic acid (50 c.c.) containing hydrogen bromide (3% w/v) at 40—45°, under nitrogen in the dark. After 4 min. aqueous sodium sulphite was added, and the product was isolated *via* ether. Crystallisation from ethanol gave the 9α-*bromo-ketone* (4·25 g.), m. p. 172—174°, $[\alpha]_D$ +123° (*c* 1·00), $\lambda_{max.}$ 3170 Å (ε 97·5) [cf. 3β,17β-diacetoxy-5α-androstan-11-one, $\lambda_{max.}$ 297 Å (ε 25)]; $\nu_{max.}$ (in CS_2) 1745, 1240, 1050, 1030 (acetates), 1715 (ketone), and 745 cm.$^{-1}$ (C–Br) [cf. 3β,17β-diacetoxy-5α-androstan-11-one, $\nu_{max.}$ 1715 cm.$^{-1}$ (ketone)] (Found: C, 59·1; H, 7·1; Br, 17·2. $C_{23}H_{33}BrO_5$ requires C, 58·9; H, 7·1; Br, 17·05%).

This bromo-ketone (II*c*), treated under the original alkylation conditions described above for the bromopregnane derivatives, gave a product that contained (by g.l.c.) only about 8% of material of longer retention time than the debrominated ketone (I*c*), the major product. This small amount of, possibly alkylated, product was not investigated further. However, alkylation by the modified procedure (see above) gave yields indicated in Table 1.

3β,17β-*Diacetoxy*-5α-*androst*-8-*en*-11-*one* (VII*c*).—A solution of 3β,17β-diacetoxy-9α-bromo-5α-androstan-11-one (150 mg.) in dimethylformamide (10 c.c.) containing lithium carbonate (250 mg.) was kept at 100° for 2 hr. Isolation *via* ether and crystallisation from aqueous ethanol gave the *ketone* (110 mg.), m. p. 177—179°, $[\alpha]_D$ +94° (*c* 0·91), $\lambda_{max.}$ 2530 Å (ε 9100); $\nu_{max.}$ 1745sh, 1740, 1245, 1025 (acetates), 1670 (ketone), and 1595 cm.$^{-1}$ (8-ene) (Found: C, 70·8; H, 8·0. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

3β,17β-*Diacetoxy*-11α-*methyl*-5α-*androstan*-11β-*ol* (IV*c*).—3β,17β-Diacetoxy-5α-androstan-11-one (1·0 g.) in ether (80 c.c.) was added to methylmagnesium iodide [from magnesium (2 g.) in ether (100 c.c.) and sufficient of a solution of methyl iodide (18 c.c.) in ether (50 c.c.) to react with all the metal], and tetrahydrofuran (30 c.c.) was then added. The mixture was heated under reflux for 1 hr, and normal isolation, followed by acetylation, gave material (1·1 g.) that contained (by g.l.c.) 10% unreacted ketone. Crystallisation from aqueous ethanol gave the *tertiary alcohol*, m. p. 118—121°, $[\alpha]_D$ −16° (*c* 0·87); $\nu_{max.}$ (in $CHCl_3$) 3600 (OH), 1730, 1260, and 1030 (acetates) (Found: C, 70·6; H, 9·45. $C_{24}H_{38}O_5$ requires C, 70·9; H, 9·4%).

3β,17β-*Diacetoxy*-11-*methylene*-5α-*androstane* (VIII*c*).—3β,17β-Diacetoxy-11α-methyl-5α-androstan-11β-ol (200 mg.) was heated under reflux in benzene (40 c.c.) containing toluene-*p*-sulphonic acid monohydrate (150 mg.) for 1 hr. The product was crystallised from light petroleum (b. p. 40—60°) to give the *methylene-steroid* m. p. 153—156°, $[\alpha]_D$ −8° (*c* 0·97); $\nu_{max.}$ (in CS_2) 1745, 1740, 1245, 1035 (acetates), 905 and 895 cm.$^{-1}$ (11-methylene) (Found: C, 74·6; H, 9·35. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

3β,11,17β-*Triacetoxy*-5α-*androst*-9(11)-*ene* (V*c*).—3β,17β-Diacetoxy-5α-androstan-11-one (5·4 g.) was heated under reflux in acetic anhydride (350 c.c.) containing toluene-*p*-sulphonic acid monohydrate (3 g.) for 6 hr. with slow distillation of solvent. The solvent was then removed at 30 mm. and the residue was taken up in benzene and adsorbed on silica gel (50 g.). Elution with benzene (20 c.c.) gave material containing (by g.l.c.) starting ketone and the enol acetate (*ca.* 70%) which was allowed to crystallise from ether–light petroleum (b. p. 40—60°)

(1 : 1). The first two crops (total 900 mg.) were pure 11-ketone, but the next crop (1·23 g.) when crystallised from ethyl acetate–light petroleum gave the pure *enol acetate*, m. p. 116—118°, $[\alpha]_D$ +21° (*c* 1·03); $\nu_{max.}$ 1740, 1245, 1225, 1025 (acetates), 1750sh, 1210, and 1035 cm.$^{-1}$ (enol acetate) (Found: C, 69·4; H, 8·3. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). This enol acetate is more readily hydrolysed than the pregnane analogue (V*b*), and yields of pure compound are variable.

3β,17β-*Diacetoxy*-9α-*methyl*-5α-*androstan*-11-*one* (VI*c*).—The enol acetate (V*c*) (1 g. containing *ca.* 10% of 11-ketone) in tetrahydrofuran (200 c.c.) was added to methylmagnesium iodide [from magnesium (4 g.) in ether (80 c.c.) and methyl iodide (20 c.c.) in ether (80 c.c.) prepared and filtered under nitrogen] and the mixture was heated under reflux for 90 min. Methyl iodide (320 c.c.) was added to the cooled mixture, and heating was continued for 20 hr. The usual isolation and acetylation procedure gave material that showed, on g.l.c. analysis, two peaks, one (60%) of the same retention time as the 11-ketone (I*c*) and the other of longer retention time. This mixture was treated with toluene-*p*-sulphonic acid monohydrate (500 mg.) in benzene (50 c.c.) as above, and the product (990 mg.) had a g.l.c. analysis showing *ca.* 10% of 11-methylene compound (VII*c*), *ca.* 60% of unmethylated ketone (I*c*), and *ca.* 25% of methylated product. The mixture was adsorbed on alumina (250 g.) and eluted with light petroleum containing increasing amounts of benzene (45—70%). The first fractions contained the 11-methylene-steroid (*ca.* 140 mg.) and those immediately following contained the material with the longest retention time. These (total 190 mg.) were combined and crystallisation from aqueous ethanol gave the 9α-*methyl-steroid* (VI*c*), m. p. 171—173°, $[\alpha]_D$ +39·5° (*c* 0·96); $\nu_{max.}$ 1745sh, 1740, 1245, 1045, 1025 (acetates), and 1710 cm.$^{-1}$ (ketone) (Found: C, 70·75; H, 8·9. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%). The last fractions gave, after intermediate mixtures, the unmethylated ketone (I*a*).

From similar alkylations of this enol acetate and of the bromo-ketone (II*c*) in butyl ether–tetrahydrofuran (see pregnane series for general experimental conditions and Table 1 for yields) there was obtained, after several chromatographic separations, a small amount of a compound (about 85% pure) that had the n.m.r. and infrared spectra expected for 3β,17β-diacetoxy-9α,12β-dimethyl-5α-androstan-11-one; $\nu_{max.}$ 1740sh, 1730, 1245, 1045, 1025 (acetates), and 1695 cm.$^{-1}$ (11-ketone).

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