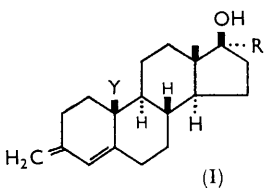
825. 2- *and* 3-*Methylene-steroids.*

By D. D. Evans, D. E. Evans, G. S. Lewis, and P. J. Palmer.

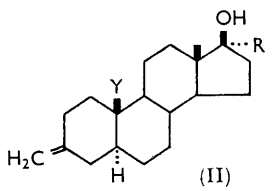
3-Methylene-steroids of the androstane, androst-4-ene, and the related 19-nor series have been prepared by reaction of the corresponding 3-keto-steroids with methylenetriphenylphosphorane. 2-Methylene-Δ^4-3-keto-steroids have been prepared by aldol condensation of the 2-ethoxalyl-Δ^4-3-keto-derivatives with formaldehyde. 17α-Methyl-2-methylenetestosterone has also been prepared by reaction of the corresponding 2-ethoxalyl derivative with chloromethyl methyl ether.

In attempts to synthesise steroids with greater biological activity or fewer side-effects we have prepared a series of steriods containing a 2- or 3-methylene group.

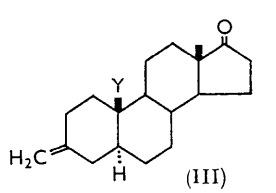
The 3-methylene steroids (I; R = H, Me, or Et; Y = H or Me) (Table 1) and (II; R = H, Me, or Et; Y = H or Me) (Table 2) were prepared by reaction of the corresponding 3-keto-steroids with methylenetriphenylphosphorane, and the 17α-ethynyl analogues (II; Y = Me or H, R = CH≡C) were prepared by reaction of ethynylmagnesium iodide



(I)



(II)

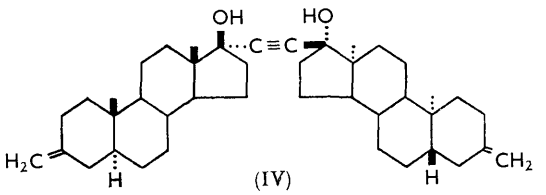


(III)

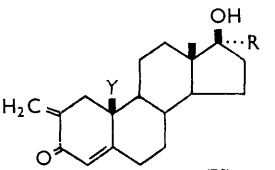
with the 17-ketones (III; Y = Me or H), which were obtained by oxidation of the 17β-alcohols (II; Y = Me or H, R = H). Ethynylation of 3-methylene-5α-androstan-17-one (III; Y = Me) gave a second product which was shown to be 17,17′-ethynylenedi-(3-methylene-5α-androstan-17β-ol) (IV).

3-Methyleneandrost-4-en-17β-ol [1] (I; Y = Me, R = H) was oxidised to the corresponding 17-ketone with chromium trioxide in pyridine [2] since Δ^4-3-methylenes are reported [1] to be unstable to acids. 3-Methylene-19-norandrost-4-en-17β-ol (I; Y = R = H), isolated only as an oil, was characterised as its 17-acetate, and esters (Table 3) of the alcohols (I and II; Y = Me, R = H) were also prepared.

The 2-methylene-steroids (V; Y = H or Me, R = H, Me, Et, or C≡CH) (Table 4) were prepared by a potassium carbonate-catalysed aldol condensation of the corresponding



(IV)



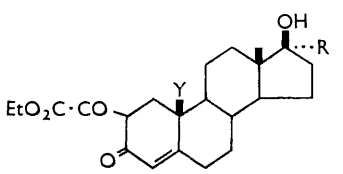
(V)

2-ethoxalyl derivatives [3,4] (VI) with formaldehyde in aqueous methanol. 17β-Hydroxy-17α-methyl-2-methyleneandrost-4-en-3-one (V; Y = R = Me) was also prepared by reaction of 2-ethoxalyl-17α-methyltestosterone [3] (VI; Y = R = Me) with chloromethyl methyl ether. In both cases the initial reaction is followed by a reversed Claisen condensation and we assume that subsequent loss of a hydroxyl or methoxyl ion from an intermediate (VIIa or b) gives the 2-methylene derivative. This is supported by the reaction of chloromethyl methyl ether with diethyl sodiomalonate [5] to give diethyl (methoxymethyl)-malonate and with ethyl sodioacetoacetate which yields ethyl (α-methoxymethyl)acetoacetate.[6]

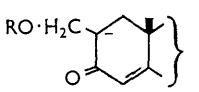
Oxidation of the alcohols (V; Y = Me or H, R = H) with Jones's chromic acid [7] gave good yields of the corresponding ketones (VIII; Y = Me and H).

Various attempts were made to synthesise the 2-methylene analogues of saturated 3-keto-steroids but without success. The inaccessibility of such compounds has been attributed [8] to the ready formation of methylenebisketones.

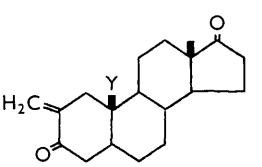
The 3-methylene-steriods absorb in the infrared region at 880—887 cm.$^{-1}$. The 2-methylene-Δ^4-3-keto-system is characterised by its absorption both in the ultraviolet



(VI)



(VII) a, R = H; b, R = Me



(VIII)

spectrum at 260—261 mμ,[9] and in the infrared in the 1655—1660, 1610—1618, 930—940, and 883—890 cm.$^{-1}$ regions. The absorption at 1655—1660 and 1610—1618 cm.$^{-1}$, appearing as twin peaks of almost equal intensity, is a characteristic feature. In the infrared spectrum of 2-methylenecortisone the absorption at 940 cm.$^{-1}$ has been attributed [10]

[1] Sondheimer and Mechoulam, *J. Amer. Chem. Soc.*, 1957, **79**, 5029.
[2] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[3] Ringold, Batres, Halpern, and Necoechea, *J. Amer. Chem. Soc.*, 1959, **81**, 427.
[4] B.P. 809,485; *Chem. Abs.*, 1959, **53**, 17,201.
[5] Simonsen, *J.*, 1908, **93**, 1777.
[6] Oda and Teramura, *Bull. Inst. Chem. Res. Kyoto Univ.*, 1951, **26**, 88 (*Chem. Abs.*, 1953, **47**, 3223c).
[7] Cf. Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.
[8] de Stevens, and Halamandaris, *J. Org. Chem.*, 1961, **26**, 1614; Waid and Taurins, *Canad. J. Chem.*, 1960, **38**, 1983.
[9] U.S.P. 2,847,430.
[10] Carrington, Long, and Turner, *J.*, 1962, 1572.

to the exocyclic methylene group. The presence of absorption in the 930—940 cm.$^{-1}$ region, and overtones at 1860—1880 cm.$^{-1}$ in the present series of 2-methylene-Δ^4-3-keto-steroids, appears to confirm this assignment, notwithstanding absorption at 883—890 cm.$^{-1}$, which, in the 3-methylene-steroids, is characteristic of the exocyclic methylene group. A discussion of the spectra will be reported elsewhere.

Biological Activities.—Certain members of the series have favourable myotrophic-androgenic ratios due, primarily, to decreased androgenicity. Details of the endocrine effects of the compounds will be given elsewhere.[11]

Experimental

M. p.s were determined on a Kofler block. Rotations are for chloroform solutions at room temperature. Ultraviolet spectra were determined for ethanol solutions, and infrared spectra for Nujol mulls, unless otherwise specified. Deactivated alumina refers to Spence's grade "H" deactivated with 5% by volume of 10% aqueous acetic acid,[12] and neutral alumina to Woelm neutral alumina deactivated with water to give activity II or III. Light petroleum of b. p. 40—60° was used unless specified otherwise.

Compounds whose preparation do not require detailed description are recorded in Tables 1—4.

General Method for the Methylenetriphenylphosphorane Reaction.—Phenyl-lithium (5 mol.), as a molar solution in ether, was added slowly to a stirred suspension of methyltriphenylphosphonium bromide (5 mol.) in anhydrous ether under nitrogen at room temperature. The mixture was stirred for 2 hr., treated with the steroid (1 mol.) dissolved in anhydrous ether or ether–benzene, stirred for a further 4 hr., and set aside overnight under nitrogen. Ether was then distilled off, whilst being replaced by an approximately equal volume of anhydrous tetrahydrofuran, until the internal temperature reached 60—65°. The mixture was refluxed for 5—6 hr., set aside overnight at room temperature, diluted with water, and extracted with ether. In the case of the 5α-saturated steroids the ethereal extracts were washed with dilute acid and then water; acid washing of the 3-methylene-Δ^4-steroid extracts was omitted. In all cases except (II; Y = R = Me) the residue after evaporation of the ethereal extract was dissolved in ethanol, the solution diluted with half its volume of water, and the product, if solid, filtered off. When an oil was produced by this treatment the mixture was extracted several times with light petroleum, and the extracts were washed with water, dried, and evaporated. In either case, except where otherwise described, the product was chromatographed on neutral alumina. The alcohol (II; Y = R = Me) was isolated by repeated chromatography of the residue from the ethereal extract.

3-Methylene-19-norandrost-4-en-17β-yl Acetate.—3-Methylene-19-norandrost-4-en-17β-ol (I; Y = R = H) (550 mg.), obtained as an oil from 19-nortestosterone, was acetylated in pyridine (10 ml.) with acetic anhydride (1·0 ml.), to yield *3-methylene-19-norandrost-4-en-17β-yl acetate* (200 mg.), m. p. 89—92°, $[\alpha]_D$ +120° (*c* 0·93), $\lambda_{max.}$ 240 mμ (ε 26,000) $\nu_{max.}$ 1740, 1636, 1605, 1244, and 885 cm.$^{-1}$ (Found: C, 80·7; H, 9·8. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

3-Methylene-5α-androstan-17-one (III; Y = Me).—3-Methylene-5α-androstan-17β-ol (II; Y = Me, R = H) (1·0 g.), oxidised with chromium trioxide (1·0 g.) in pyridine [2] (50 ml.), gave a white solid (903 mg.) which after crystallisation from methanol yielded 3-methylene-5α-androstan-17-one (III; Y = Me) (772 mg.), m. p. 143—145°. Two recrystallisations from acetone gave a sample of m. p. 145—147°, $[\alpha]_D$ +88° (*c* 1·14), $\nu_{max.}$ 1745, 1644, and 892 cm.$^{-1}$ {lit.,[13] m. p. 145·5—146·5°, $[\alpha]_D$ +91° and $\nu_{max.}$ (in $CHCl_3$) 1740, 1647, and 889 cm.$^{-1}$} (Found: C, 84·1; H, 10·8. Calc. for $C_{20}H_{30}O$: C, 83·9; H, 10·6%).

The 17-ketone (III; Y = Me) was also prepared by oxidation of the corresponding alcohol (II; Y = Me, R = H) with Jones's chromic acid.[7]

3-Methylene-5α-œstran-17-one (III; Y = H).—3-Methylene-5α-œstran-17β-ol (II; Y = R = H) (1·0 g.) in acetone (100 ml.) was oxidised with Jones's chromic acid [7] (1·0 ml.) at 15°, and after chromatography on neutral alumina and crystallisation from methanol yielded *3-methylene-5α-œstran-17-one* (III; Y = H) (680 mg.), m. p. 95—97°, $[\alpha]_D$ +119° (*c* 1·0), $\nu_{max.}$

[11] Humphrey, *Endocrinol.*, to be published.
[12] Jones, Meakins, and Stephenson, *J.*, 1958, 2156.
[13] Sondheimer and Mechoulam, *J. Amer. Chem. Soc.*, 1958, **80**, 3087.

TABLE 1.

Compounds (I)

Y	R	M. p.	$[\alpha]_D$	Yield (%)	$\lambda_{max.}$ (mμ)	ε	$\nu_{max.}$ (cm.$^{-1}$)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Me	Me	134—137°	+151°	20	240	24,060	3435, 1628, 1595, 885	84·0	10·7	$C_{21}H_{32}O$	83·9	10·7
Me	Et	91—97	+132	25	239	24,500	3555, 1632, 1599, 881	84·35	11·15	$C_{22}H_{34}O$	84·0	10·9
H	Me	106—109	+86	6	240	22,740	3375, 1640, 1612, 886	84·1	10·9	$C_{20}H_{30}O$	83·9	10·6
H	Et	120—123	+105	10	239	23,460	3430, 1640, 1608, 885	83·7	11·0	$C_{21}H_{32}O$	83·9	10·7

TABLE 2.

Compounds (II).

Y	R	M. p.	$[\alpha]_D$	Yield (%)	$\nu_{max.}$ (cm.$^{-1}$)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Me	Me	179—181°	−19°	45	3600, 1640, 887	83·2	11·5	$C_{21}H_{34}O$	83·4	11·3
Me	Et	140—142	−11	45	3480, 1636, 881	83·9	11·7	$C_{22}H_{36}O$	83·5	11·5
H	H	136—137	+24	50	3255, 1644, 881	82·9	11·4	$C_{19}H_{30}O$	83·15	11·0
H	Me	152—154	+3	40	3320, 1648, 886	83·25	11·6	$C_{20}H_{32}O$	83·3	11·2
H	Et	115—116	+8	40	3270, 1653, 885	83·2	11·8	$C_{21}H_{34}O$	83·4	11·3

TABLE 3.

17β-Acyloxy-3-methylene-androstanes and -androstenes.

Acyl		M. p.	$[\alpha]_D$	Yield (%)	$\lambda_{max.}$ (mμ)	ε	$\nu_{max.}$ (cm.$^{-1}$)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Ac	Δ^4	111—112°	+157°	80	238	25,240	1740, 1634, 1605, 1241, 881	80·7	9·5	$C_{22}H_{32}O_2$	80·4	9·8
Et·CO	Δ^4	80—82	+155	71	238	25,100	1715, 1653, 1608, 894 *	80·7	10·0	$C_{23}H_{34}O_2$	80·9	9·8
Ph·CH_2·CH_2·CO·	Δ^4	101—103	+149	21	240	24,600	1730, 1632, 1599, 1171, 880	83·0	9·1	$C_{29}H_{38}O_2$	83·2	9·15
Ac	5α-H	105—107	+6	67	—	—	1740, 1644, 890	79·8	10·4	$C_{22}H_{34}O_2$	80·0	10·4
Et·CO	5α-H	103—105	+9	70	—	—	1736, 1644, 884	80·0	10·4	$C_{23}H_{36}O_2$	80·2	10·5

* In $CHCl_3$.

TABLE 4.

Compounds (V).

Y	R	M. p.	$[\alpha]_D$	Yield (%)	$\lambda_{max.}$ (mμ)	ε	$\nu_{max.}$ (cm.$^{-1}$)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Me	Et	145—147° & 156—158°	+138°	34	261	14,000	3448, 1657, 1615, 940, 889 †	80·6	10·0	$C_{22}H_{32}O_2$	80·4	9·8
Me	CH≡C	183—185	+74	18	260·5	14,400	3600, 3335, 1661, 1618, 940, 889 †	81·45	9·0	$C_{22}H_{28}O_2$	81·4	8·7
H	H	124—126	+63	20	260	14,000	3448, 1653, 1608, 935, 883	79·5	9·1	$C_{19}H_{26}O_2$	79·7	9·15
H	Me	122—123	+28	7	260	14,400	3405, 1655, 1618, 929, 887	79·6	9·4	$C_{20}H_{28}O_2$	79·95	9·4
H	Et	Oil	+18	17	260	13,880	3405, 1661, 1615, 935, 884	—	—	$C_{21}H_{30}O_2$	—	—
H	CH≡C	123—124	−42	20	260	14,900	3555, 3270, 1664, 1615, 936, 888 ‡	81·0	7·9	$C_{21}H_{26}O_2$	81·25	8·4

† $CHCl_3$. ‡ In CCl_4.

(in $CHCl_3$) 1736, 1648, and 896 cm.$^{-1}$ (Found: C, 84·0; H, 10·4. $C_{19}H_{28}O$ requires C, 83·8; H, 10·4%).

17α-*Ethynyl*-3-*methylene*-5α-*androstan*-17β-*ol* (II; Y = Me, R = CH≡C).—3-Methylene-5α-androstan-17-one [13] (III; Y = Me) (1·0 g.) in anhydrous tetrahydrofuran was added to a solution of ethynylmagnesium iodide [prepared by reaction of acetylene with methylmagnesium iodide [14] (3 g.) in tetrahydrofuran], the mixture was refluxed for 20 min., then cooled and treated with dilute sulphuric acid, and the product was extracted with ether. The ethereal extract was washed with water, dilute sodium thiosulphate solution, and water, dried, and evaporated, leaving a solid. Several crystallisations from acetone gave 17,17′-*ethynylenedi*-(3-*methylene*-5α-*androstan*-17β-*ol*) (IV) (74 mg.), m. p. 282—285°, $[\alpha]_D$ −58° (*c* 0·7), $\nu_{max.}$ (in $CHCl_3$) 3545, 2216, (C≡C), 1645, and 889 cm.$^{-1}$ (Found: C, 83·9; H, 10·6. $C_{42}H_{62}O_2$ requires C, 84·2; H, 10·4%). No band corresponding to the C≡CH group was present.

The material recovered from the mother-liquors was chromatographed and after crystallisation from acetone gave 17α-*ethynyl*-3-*methylene*-5α-*androstan*-17β-*ol* (505 mg.) (II; Y = Me, R = CH≡C), m. p. 155—156°. An analytical sample prepared by sublimation at 120—130°/0·5 mm. had m. p. 155—156°, $[\alpha]_D$ −39° (*c* 0·83), $\nu_{max.}$ (in $CHCl_3$) 3545, 3270 (C≡CH), 2106 (C≡C), 1645, and 889 cm.$^{-1}$ (Found: C, 84·6; H, 10·3. $C_{22}H_{32}O$ requires C, 84·6; H, 10·3%).

17α-*Ethynyl*-3-*methylene*-5α-*œstran*-17β-*ol* (II; Y = H, R = CH≡C).—Ethynylation of 3-methylene-5α-œstran-17-one (III; Y = H) (800 mg.) by the above procedure and chromatography of the product on neutral alumina gave a solid (539 mg.), m. p. 108—112°, which after crystallisation from light petroleum yielded 17α-*ethynyl*-3-*methylene*-5α-*œstran*-17β-*ol* (II; Y = H, R = CH≡C), m. p. 110—112°, $[\alpha]_D$ −22° (*c* 1·0), $\nu_{max.}$ 3530, 3340, 1645, and 890 cm.$^{-1}$ (Found: C, 84·8; H, 10·3. $C_{21}H_{30}O$ requires C, 84·5; H, 10·1%).

3-*Methyleneandrost*-4-*en*-17-*one*.—Oxidation of 3-methyleneandrost-4-en-17β-ol with chromium trioxide in pyridine [2] gave, after several crystallisations from methanol, 3-*methyleneandrost*-4-*en*-17-*one* (21%), m. p. 104—108°. An analytical sample, crystallised from methanol, had m. p. 106—108°, $[\alpha]_D$ +253° (*c* 1·33), $\nu_{max.}$ 1740, 1636, 1605, and 880 cm.$^{-1}$ (Found: C, 84·1; H, 9·5. $C_{20}H_{28}O$ requires C, 84·45; H, 9·9%).

2-*Ethoxalyl Derivatives*.—The 2-ethoxalyl derivatives (VI; Y = Me, R = Et and CH≡C) were prepared by sodium hydride-catalysed [3] condensation of the corresponding ketones with diethyl oxalate at 50—60° in benzene. Similar condensations at room temperature with sodium methoxide as catalyst gave esters (VI; Y = R = H; Y = H, R = Me).[4] The preparation of 2-ethoxalyl-17α-ethyl- (VI; Y = H, R = Et) and 2-ethoxalyl-17α-ethynyl-19-nortestosterone (VI; Y = H; R = CH≡C) from the corresponding ketones was achieved in t-butyl alcohol at 60° with sodium methoxide as catalyst.[4,15]

17α-*Methyl*-2-*methylenetestosterone* (V; Y = R = Me).—(*a*) A stirred solution of 2-ethoxalyl-17α-methyltestosterone [3] (VI; Y = R = Me) (5·2 g.) in methanol (150 ml.) was treated dropwise with 36% w/v aqueous formaldehyde (52 ml.) and, after 30 min., with a solution of potassium carbonate (5·2 g.) in water (80 ml.), which was added during 60 min. Stirring was continued for a further 90 min., and the mixture extracted with methylene chloride. The washed, dried, filtered, and evaporated extract gave an oil (4·3 g.) which was chromatographed on deactivated alumina. Evaporation of the benzene eluates gave a solid (2·64 g.) which, after crystallisation from acetone, yielded 17α-*methyl*-2-*methylenetestosterone* (V; Y = R = Me) (1·7 g.), m. p. 175—178°. Recrystallisation from acetone gave a sample, m. p. 177—180°, $[\alpha]_D$ +151° (*c* 0·99), $\lambda_{max.}$ 261 mμ (ε 14,850), $\nu_{max.}$ (in $CHCl_3$) 3533, 1661, 1617, 931, and 889 cm.$^{-1}$ (Found: C, 80·5; H, 9·85. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

(*b*) Chloromethyl methyl ether (9·0 ml.) was added portion-wise to a mixture of potassium carbonate (9·0 g.) and 2-ethoxalyl-17α-methyltestosterone (VI; Y = R = Me) (3·0 g.) in acetone (30 ml.). After being stirred for 30 min. the mixture was refluxed for 4 hr. and kept at room temperature overnight. Most of the solvent was removed *in vacuo*, the residue extracted with a mixture of ether and water, and the ethereal extract washed neutral with water, dried, filtered, and evaporated. The residual oil, which solidified on trituration, was chromatographed, and the solid, obtained from the benzene–light petroleum and benzene eluates, gave on crystallisation from acetone 17α-methyl-2-methylenetestosterone (V; Y = R = Me), m. p. 175—180° (410 mg.). Recrystallisation from acetone gave a sample, m. p.

[14] Sondheimer, Mancera, Flores, and Rosenkranz, *J. Amer. Chem. Soc.*, 1956, **78**, 1742.
[15] Natham, Magerlein, and Hogg, *J. Org. Chem.*, 1959, **24**, 1517.

179—182°, $\lambda_{max.}$ 260 mμ (ε 14,400), identical in infrared spectrum with the sample prepared as above.

2-*Methylenetestosterone* (V; Y = Me, R = H) (37%), m. p. 160—162°, $[\alpha]_D$ +166 (*c* 1·0), $\lambda_{max.}$ 260 mμ (ε 14,650), $\nu_{max.}$ (in $CHCl_3$) 3448, 1661, 1618, 941, and 889 cm.$^{-1}$ (Found: C, 80·0; H, 9·6. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%), was prepared by a method similar to (*a*) above, as were the 2-methylene-steroids of Table 4.

2-*Methyleneandrost*-4-*ene*-3,17-*dione* (VIII; Y = Me).—2-Methylenetestosterone (V; Y = Me, R = H) (1·5 g.), when oxidised with Jones's chromic acid,[7] gave 2-*methyleneandrost*-4-*ene*-3,17-*dione* (VIII; Y = Me) (1·2 g.), m. p. 195—198°, $[\alpha]_D$ +217° (*c* 1·02), $\lambda_{max.}$ 260 mμ (ε 14,240), $\nu_{max.}$ 1730, 1661, 1612, 947, and 887 cm.$^{-1}$ (Found: C, 80·4; H, 8·8. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%).

2-*Methylene*-19-*norandrost*-4-*ene*-3,17-*dione* (VIII; Y = H).—Similar oxidation of 2-methylene-19-nortestosterone (V; Y = R = H) gave 2-*methylene*-19-*norandrost*-4-*ene*-3,17-*dione* (VIII; Y = H) (66%), m. p. 134—137°, $[\alpha]_D$ +135° (*c* 1·035), $\lambda_{max.}$ 260 mμ (ε 14,300), $\nu_{max.}$ (in $CHCl_3$) 1740, 1664, 1620, 941, and 886 cm.$^{-1}$ (Found: C, 79·7; H, 8·55. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%).

Esters.—The alcohols (I, II, and V; Y = Me, R = H) (2 mmoles) were esterified in pyridine (10—12 ml.) with an acid anhydride (2—3 mmoles) or acid chloride at room temperature for 1—2 days. Purification was achieved either by crystallisation or by chromatography followed by crystallisation. In this way 3-methylene-5α-androstan-17β-ol (II; Y = Me, R = H) and 3-methyleneandrost-4-en-17β-ol (I; Y = Me, R = H) gave the esters described in Table 3; 2-methylenetestosterone (V; Y = Me, R = H) gave the *propionate* (73%), m. p. 153—156°, $[\alpha]_D$ +134° (*c* 1·09), $\lambda_{max.}$ 260 mμ (ε 14,800), $\nu_{max.}$ (in $CHCl_3$) 1720, 1661, 1615, 940, and 888 cm.$^{-1}$ (Found: C, 77·7; H, 8·9. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·05%), the β-*phenylpropionate* (41%), m. p. 161—163°, $[\alpha]_D$ +133° (*c* 1·035), $\lambda_{max.}$ 260 mμ (ε 14,500), $\nu_{max.}$ (in $CHCl_3$) 1730, 1664, 1620, 942, and 891 cm.$^{-1}$ (Found: C, 80·1; H, 8·5. $C_{29}H_{36}O_3$ requires C, 80·5; H, 8·3%), and the *hexahydrobenzoate* (22%), m. p. 176—178°, $[\alpha]_D$ +134° (*c* 0·96), $\lambda_{max.}$ 260 mμ (ε 14,960), $\nu_{max.}$ (in $CHCl_3$) 1720, 1664, 1620, 942, and 890 cm.$^{-1}$ (Found: C, 78·7; H, 9·5. $C_{27}H_{38}O_3$ requires C, 79·0; H, 9·3%).

The authors thank Dr. R. E. Bowman for his encouragement and many helpful suggestions, especially that of using chloromethyl methyl ether; also Miss E. M. Tanner for determination of rotations and spectra, Mr. F. H. Oliver for the microanalyses, and Mr. R. R. Humphrey of Parke Davis and Company, Research Laboratories, Ann Arbor, U.S.A., for the pharmacological assays.

Research Laboratories, Parke, Davis & Company.
Staines Road, Hounslow, Middlesex.

[*Received, March 7th*, 1963.]