674. *A Novel Method for the Preparation of Steroid Esters.*

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The reaction of steroid halogenomagnesium alkoxides with acid chlorides has been used to prepare three representative types of ester, *viz.*, acetates, β-phenylpropionates, and hemisuccinates. Steroid alcohols with a Δ^4- or $\Delta^{1,4}$-3-keto-grouping were successfully esterified either *per se* or when the keto-groups were protected as enol ethers or ethylenedioxy-derivatives. A saturated 3-keto-group was protected as its ethylenedioxy-derivative prior to esterification of the alcohol function. Esterification of a phenolic group was also achieved by this method.

The large number of steroid esters synthesised [1] for biological assay have been prepared, almost exclusively, by the reaction of an acid chloride or anhydride with the alcohol in pyridine. We now describe a novel method for the esterification of steroid alcohols by reaction of their halogenomagnesium alkoxides with an acid chloride.

$$R{\cdot}OH + EtMgBr \longrightarrow R{\cdot}OMgBr + C_2H_6$$
$$R{\cdot}OMgBr + R'CO{\cdot}Cl \longrightarrow R{\cdot}O{\cdot}CO{\cdot}R' + MgBrCl$$

Although the method is new to steroid chemistry it has been reported [2] that certain non-steroidal alcohols can be esterified by this type of reaction. We have used it to prepare secondary and tertiary esters of steroidal alcohols, and it has proved to be of particular value for the synthesis of relatively inaccessible esters.

[1] (*a*) Junkmann and Witzel, "Monographs on Therapy," The Squibb Institute for Medical Research, New Brunswick, New Jersey, 1958, Vol. 3 (Supplement), p. 1; Junkmann, *Recent Progr. Hormone Res.*, 1957, **13**, 389; Shapiro, Weinberg, and Freedman, *J. Org. Chem.*, 1956, **21**, 1300; Gould, Finckenor, Hershberg, Cassidy, and Perlman, *J. Amer. Chem. Soc.*, 1957, **79**, 4472; Giannini and Fedi, *Boll. chim. farm.*, 1960, **99**, 24; U.S.P. 2,868,809 (*Chem. Abs.*, 1959, **53**, 10,306); U.S.P. 2,964,537; (*b*) U.S.P. 2,846,455 (*Chem. Abs.*, 1959, **53**, 4352).

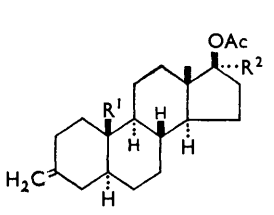
[2] Henecka in Houben-Weyl, "Methoden der Organischen Chemie" (Ed. Müller), 1952, Vol. VIII, p. 550.

Reaction of the halogenomagnesium alkoxides with an acid chloride was carried out in ether or di-isopropyl ether at room temperature or at the boiling point of the solvent, and although halogenomagnesium alkoxides could be replaced by the corresponding lithium alkoxides the yield of ester was lower. When sodium alkoxides were used no esters were formed and the use of sodium and lithium alkoxides was not pursued. Addition of pyridine had little effect on the rate or course of the esterification reaction. Working up of the reactions involving acid chlorides, which are only slowly hydrolysed by dilute aqueous alkali, was best carried out by adding anhydrous dimethylaminopropylamine to the reaction mixture and washing out the resulting basic amide with dilute acid.

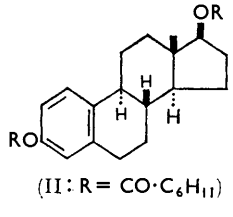
Initially the reaction was examined for the preparation of the acetates (Ia), (Ib), and (Ic), and œstradiol dicyclohexanecarboxylate [1b] (II), since these compounds have no other functional group capable of reacting with the Grignard reagent.

Steroids having αβ-unsaturated keto-groups in the molecule also yielded halogenomagnesium salts readily. In this case prolonged contact of the steroid with the Grignard reagent was undesirable and was avoided either by filtering off the alkoxide or, preferably, by adding excess of acid chloride as soon as the alkoxide was formed. By these means representative types of ester, *viz.*, acetate (IIIa), β-phenylpropionate (IIIb), and hemisuccinate (IIId), were prepared. The latter was prepared by selective hydrolysis of the methyl steroid succinate (IIIc) with dilute alkali at room temperature. That the reaction could also be applied to αβ-unsaturated ketones of the œstrane series and $\Delta^{1,4}$-3-keto-steroids was shown by the preparation of 17β-(β-phenylpropionyloxy)œstr-4-en-3-one [3] (IIIe), 17β-acetoxy-17α-methylandrosta-1,4-dien-3-one (IVa), and the corresponding hydrogen succinate (IVb).

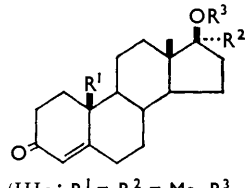
The use of protected keto-groups and regeneration of the ketone after esterification of the hydroxyl group also appeared to offer a method of avoiding undesirable side-reactions



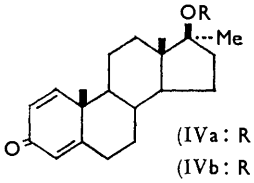
(Ia: $R^1 = R^2 = Me$)
(Ib: $R^1 = Me$, $R^2 = C{:}CH$)
(Ic: $R^1 = H$, $R^2 = Me$)



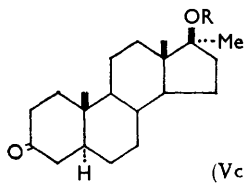
(II: $R = CO{\cdot}C_6H_{11}$)



(IIIa: $R^1 = R^2 = Me$, $R^3 = Ac$)
(IIIb: $R^1 = R^2 = Me$, $R^3 = CO{\cdot}[CH_2]_2{\cdot}Ph$)
(IIIc: $R^1 = R^2 = Me$, $R^3 = CO{\cdot}[CH_2]_2{\cdot}CO_2Me$)
(IIId: $R^1 = R^2 = Me$, $R^3 = CO{\cdot}[CH_2]_2{\cdot}CO_2H$)
(IIIe: $R^1 = R^2 = H$, $R^3 = CO{\cdot}[CH_2]_2{\cdot}Ph$)



(IVa: R = Ac)
(IVb: $R = CO{\cdot}[CH_2]_2{\cdot}CO_2H$)



(Va: R = Ac)
(Vb: $R = CO{\cdot}[CH_2]_2{\cdot}Ph$)
(Vc: $R = CO{\cdot}[CH_2]_2{\cdot}CO_2H$)

due to the keto-group. Although enamines were unsuitable, alcohols having the keto-group protected as its enol ether gave good yields of keto-esters by esterification followed by hydrolysis of the enol ether. Thus 3-ethoxy-17α-methylandrost-3,5-dien-17β-ol, prepared from 3-ethoxyandrost-3,5-dien-17-one,[4] gave the β-phenylpropionate (IIIb) and the succinate (IIIc), and the β-phenylpropionate (IIIe) was prepared from 3-methoxy-œstra-2,5(10)-dien-17β-ol.

[3] B.P. 826,028 (*Chem. Abs.*, 1960, **54**, 11,089).
[4] Riegel and Liu, *J. Org. Chem.*, 1951, **16**, 1610.

When an αβ-unsaturated or saturated keto-group was protected as its ethylenedioxy-derivative good yields of keto-esters were obtained by esterification followed by hydrolysis of the ketal. The 3-ethylenedioxy-derivative of the secondary alcohol 17β-hydroxyœstr-4-en-3-one was prepared by conventional means.[5] Since tertiary alcohol groups tend to lose water [6] under the ketalisation conditions 3-ethylenedioxy-17α-methyl-5α-androstan-17β-ol was prepared by reaction of methyl-lithium with 3-ethylenedioxy-5α-androstan-17-one, which was obtained by oxidation of the corresponding 17β-alcohol. Examples of esters prepared *via* the 3-ethylenedioxy-derivatives are (IIIe) and 17β-acetoxy-17α-methyl-5α-androstan-3-one (Va) and the β-phenylpropionate (Vb) and hemisuccinate (Vc).

The reaction is not confined to 17β-hydroxy-groups, since 3β,17β-diacetoxy-17α-methylandrost-5-ene was prepared by this method. In all probability the reaction is applicable to any steroid alcohol group which forms a halogenomagnesium alkoxide.

Experimental

Melting points were determined on a Kofler block. Specific rotations are for chloroform solutions (unless otherwise specified) at room temperature. Ultraviolet spectra were determined for ethanol solutions, and infrared specta in Nujol, unless otherwise indicated. In purification of esters by chromatography the products were eluted from Woelm neutral alumina, activity II or III.

The expression " in the usual way " indicates that the reaction mixture was diluted with water, extracted with ether or methylene chloride, the extract washed with saturated sodium hydrogen carbonate solution, and with water until neutral, dried ($MgSO_4$), filtered, and evaporated to dryness. When the reaction is described as being worked up by addition of 3-dimethylaminopropylamine, the amine was added (in excess) to the reaction mixture, which was set aside for 5—10 min., and acidified with 2N-hydrochloric acid before being worked up in the usual way.

Esterification Reactions.—(*a*) *Non-ketonic steroids.* A solution of 17α-ethynyl-3-methylene-5α-androstan-17β-ol [7] (312·5 mg., 1 mmole) in anhydrous ether (20 ml.) was treated with an approximately molar solution of ethylmagnesium bromide (3·23 ml., 2·5 mmoles) and, after a few minutes, with acetyl chloride (0·175 ml., 2·5 mmoles). The mixture was set aside overnight and worked up in the usual way. The solid (138 mg.) obtained by chromatography gave the 17β-*acetate* (Ib) (120 mg.), m. p. 162—164° (from methanol), $[\alpha]_D$ −38° (*c* 0·98), $\nu_{max.}$ 3270, 1745, 1644, and 896 cm.$^{-1}$ (Found: C, 81·0; H, 9·7. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·7%).

By a similar method the following compounds were prepared: 17β-*acetoxy*-17α-*methyl*-3-*methylene*-5α-*androstane* (Ia) (64%), m. p. 128—131°, $[\alpha]_D$ ±0° (*c* 1·0), $\nu_{max.}$ 1736, 1644, 1261, and 896 cm.$^{-1}$ (Found: C, 80·5; H, 10·6. $C_{23}H_{36}O_2$ requires C, 80·2; H, 10·5%); 17β-*acetoxy*-17α-*methyl*-3-*methylene*-5α-*œstrane* (Ic) (66%), m. p. 75—77°, $[\alpha]_D$ +14°, $\nu_{max.}$ 1740, 1653, 886 cm.$^{-1}$ Found: C, 80·15; H, 10·5. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·4%); 3β,17β-diacetoxy-17α-methylandrost-5-ene (11%), m. p. 140—145°, $[\alpha]_D$ −56° (*c* 0·985 in ethanol) (lit.,[8] m. p. 145—146, $[\alpha]_D$ −59°). Œstradiol dicyclohexanecarboxylate (II) (51%), m. p. 180—183° (lit.,[1b] m. p. 182—183°), $\nu_{max.}$ (in $CHCl_3$) 1750, 1730, 1612, and 1584 (Found: C, 78·4; H, 8·7. Calc. for $C_{32}H_{44}O_4$: C, 78·0; H, 9·0%), was also prepared but required refluxing for 5 hr. after the initial period at room temperature.

(*b*) *Unsaturated 3-keto-steroids.* A stirred solution of 17β-hydroxy-17α-methylandrosta-1,4-dien-3-one [9] (600 mg., 2 mmoles) in anhydrous ether (60 ml.) was treated successively with an approximately molar solution of ethylmagnesium bromide (2·6 ml., 2·2 mmoles) and acetyl chloride (0·21 ml., 3 mmoles), and the reaction mixture refluxed for 5 hr. The product was isolated in the usual way, and chromatography gave the 17β-*acetate* (IVa) (250 mg.), m. p. 134—136° (from n-hexane–acetone), $[\alpha]_D$ +14·5° (*c* 1·07), $\lambda_{max.}$ 244 mμ (ε 15,900), $\nu_{max.}$ 1726, 1653, 1619, 1599, and 1254 cm.$^{-1}$ (Found: C, 77·3; H, 8·9. $C_{22}H_{30}O_3$ requires C, 77·15; H, 8·8%).

Other compounds prepared by this method include: 17α-*methyl*-17β-(β-*phenylpropionyloxy*)-*androst*-4-*en*-3-*one* (IIIb) (27%), m. p. 131—133°, $[\alpha]_D$ +77° (*c* 1·045), $\lambda_{max.}$ 241 mμ (ε 16,400),

[5] Rao, *J. Org. Chem.*, 1960, **25**, 1058.
[6] Campbell, Babcock, and Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 4717.
[7] D. D. Evans, D. E. Evans, Lewis, and Palmer, *J.*, in the press.
[8] Meischer and Klarer, *Helv. Chim. Acta*, 1939, **22**, 962.
[9] Meystre, Frey, Voser, and Wettstein, *Helv. Chim. Acta*, 1956, **39**, 734.

$\nu_{max.}$ 1730, 1677, and 1616 cm.$^{-1}$ (Found: C, 80·2; H, 8·7. $C_{29}H_{38}O_3$ requires C, 80·1; H, 8·8%); 17β-(β-*methoxycarbonylpropionyloxy*)-17α-*methylandrost*-4-*en*-3-*one* (IIIc) (40%), m. p. 119—121°, $[\alpha]_D$ +75° (*c* 0·98), $\lambda_{max.}$ 241 mμ (ε 16,200), $\nu_{max.}$ 1750s, 1736, 1661, and 1608 cm.$^{-1}$ (Found: C, 72·2; H, 8·5. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·7%); 17β-acetoxy-17α-methylandrost-4-en-3-one (IIIa) (59%), m. p. 174·5—176·5° (lit.,[8] m. p. 176—176·5°), $[\alpha]_D$ +83° (*c* 1·005) (lit.,[10] $[\alpha]_D$ +89°), $\nu_{max.}$ 1726, 1657, 1615, and 1268 cm.$^{-1}$.

These compounds were also prepared by allowing the reaction to proceed at room temperature for 1—3 days.

(*c*) *Ethylenedioxy-derivatives.* A mixture prepared from 3-ethylenedioxy-17α-methyl-5α-androstan-17β-ol (5·04 g., 15 mmoles), ethylmagnesium bromide (19 ml., 20 mmoles), and β-phenylpropionyl chloride (4·1 g., 24 mmoles) in di-isopropyl ether (350 ml.) was refluxed for 24 hr. and worked up by addition of 3-dimethylaminopropylamine. The ketal-ester ($\nu_{max.}$ 1726, 1149, and 1090 cm.$^{-1}$) obtained was dissolved in acetone (250 ml.) containing toluene-*p*-sulphonic acid (1·0 g.), and the solution refluxed for 1 hr. The reaction mixture was worked up in the usual manner, and chromatography yielded the 17β-(β-*phenylpropionate*) (Vb) (2·45 g.), m. p. 116—118° (from ether–n-hexane), $[\alpha]_D$ +18° (*c* 1·015), $\nu_{max.}$ 1726 and 1196 cm.$^{-1}$ (Found: C, 79·4; H, 9·3. $C_{29}H_{40}O_3$ requires C, 79·8; H, 9·2%).

By using similar reaction mixtures, but allowing reaction to proceed for 1—3 days at room temperature in ether, the following compounds were prepared: 17β-*acetoxy*-17α-*methyl*-5α-*androstan*-3-*one* (Va) (50%), m. p. 152—154°, $[\alpha]_D$ +17° (*c* 0·99), $\nu_{max.}$ 1726 and 1266 cm.$^{-1}$ (Found: C, 76·7; H, 9·9. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·9%); 17β-(β-phenylpropionyloxy)œstr-4-en-3-one (IIIe) (37%), m. p. 94—96°, $[\alpha]_D$ +53° (*c* 0·99) (lit.,[3] m. p. 95—96°, $[\alpha]_D$ +58°), $\nu_{max.}$ (in $CHCl_3$) 1720, 1657, and 1615 cm.$^{-1}$.

(*d*) *Enol ethers.* A mixture prepared from 3-ethoxy-17α-methylandrosta-3,5-dien-17β-ol (4·29 g., 13 mmoles), ethylmagnesium bromide (18 ml., 15 mmoles), and β-phenylpropionyl chloride (3·03 g., 18 mmoles) in anhydrous ether (300 ml.) was left at room temperature for 65 hr. and worked up by the addition of 3-dimethylaminopropylamine. The product was dissolved in acetone (50 ml.) containing concentrated hydrochloric acid (2·4 ml.) and the reaction mixture left for 45 min. before working up in the usual manner. The solid obtained after chromatography gave the phenylpropionate (IIIb) (2·6 g), m. p. 130—132° (from methanol).

Compounds prepared in a similar manner include the β-methoxycarbonylpropionate (IIIc) (46%), m. p. 119—121°, and the β-(β-phenylpropionate) (IIIe) (23%), m. p. 93—96° [from 3-methoxyœstra-3,5(10)-dien-17β-ol [11]].

17α-*Methyl*-3-*oxoandrost*-4-*en*-17β-*yl Hydrogen Succinate* (IIId).—A solution of the β-methoxycarbonylpropionate (IIIc) (750 mg., 1·8 mmoles) in methanol (50 ml.) was treated with 1·0N-sodium hydroxide (3·6 ml.) under nitrogen and the solution was left at room temperature for 24 hr. After acidification with 2N-sulphuric acid the methanol was removed *in vacuo* at 35°, and the oily residue dissolved in ether. The ethereal solution was extracted twice with ice-cold 2N-sodium hydroxide (50 ml.) and the combined extracts washed with ether. The aqueous alkaline solution was acidified, extracted with ether, and the extract worked up in the usual way. Trituration of the residual oil (410 mg.) with acetone yielded a solid which gave the *hemisuccinate* (IIId) (320 mg.), double m. p. 148—150° and 168—170° (from ether–n-hexane). Recrystallisation from ether–n-hexane afforded a sample of m. p. 149—150°, $[\alpha]_D$ +75·5° (*c* 1·015), $\lambda_{max.}$ 240 mμ (ε 16,200), $\nu_{max.}$ 1726, 1640, and 1605 cm.$^{-1}$ (Found: C, 71·5; H, 8·1. $C_{24}H_{34}O_5$ requires C, 71·6; H, 8·5%). When repeated on a larger scale, this experiment gave a 73% yield.

The following hemisuccinates were prepared in a similar manner although no attempt was made to purify the intermediate β-methoxycarbonylpropionates: 17α-*methyl*-3-*oxo*-5α-*androstan*-17β-*yl hydrogen succinate* (Vc) (37%, based on 3-ethylenedioxy-17α-methyl-5α-androstan-17β-ol), m. p. 124—126° and 144—146°, $[\alpha]_D$ +14° (*c* 0·82), $\nu_{max.}$ 1726, 1640, and 1605 cm.$^{-1}$ (Found: C, 71·2; H, 8·8. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%), and 17α-*methyl*-3-*oxo*-*androsta*-1,4-*dien*-17β-*yl hydrogen succinate* (IVb) (41%, based on 17β-hydroxy-17α-methylandrosta-1,4-dien-3-one), m. p. 171—173°, $[\alpha]_D$ +18·5 (*c* 1·02), $\lambda_{max.}$ 245 mμ (ε 16,400), $\nu_{max.}$ 1726s, 1705, 1648, and 1599 cm.$^{-1}$ (Found: C, 72·1; H, 8·1. $C_{24}H_{32}O_5$ requires C, 72·0; H, 8·05%).

3-*Ethoxy*-17α-*methylandrosta*-3,5-*dien*-17β-*ol*.—A solution of 3-ethoxyandrosta-3,5-dien-17-one [6] (7·0 g.) in anhydrous ether (400 ml.) was added to a solution of methyl-lithium [from

[10] Julia and Heusser, *Helv. Chim. Acta*, 1952, **35**, 2080.
[11] Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5366.

lithium (3·08 g.) and methyl iodide (13·7 ml.)] in ether. The reaction mixture was refluxed for 1 hr., cooled, and worked up in the usual way. The solid residue, crystallised from methanol containing a small volume of pyridine, yielded the *enol ether*, m. p. 70—80° ($\nu_{max.}$ 3435, 3195, 1653, 1628, and 1177 cm.$^{-1}$) which was used without further purification.

3-*Ethylenedioxy*-5α-*androstan*-17β-*ol*.—A mixture of dihydrotestosterone [12] (5 g.) in ethylene glycol (50 ml.), benzene (100 ml.), and toluene-*p*-sulphonic acid (20 mg.) was refluxed, with azeotropic removal of water, for 7 hr., and worked up in the usual way to give a solid (2·13 g.), m. p. 169—170° (from benzene). Recrystallisation from ethyl acetate yielded the *ketal*, m. p. 171—173°, $[\alpha]_D$ +8·5° (*c* 1·035), $\nu_{max.}$ 3350, 1101, and 1083 cm.$^{-1}$ (Found: C, 74·9; H, 10·5. $C_{21}H_{34}O_5$ requires C, 75·4; H, 10·25%).

3-*Ethylenedioxy*-5α-*androstan*-17-*one*.—Chromium trioxide (4 g.) was added portion-wise to a well stirred solution of 3-ethylenedioxy-5α-androstan-17β-ol (4·41 g.) in anhydrous pyridine (50 ml.) maintained below 20° by cooling in ice. The reaction mixture was left overnight at room temperature, diluted with ether, and filtered. The filtrate was washed with sodium chloride solution, dried, and evaporated. The residue, crystallised from methanol containing a few drops of pyridine, gave 3-*ethylenedioxy*-5α-*androstan*-17-*one* (3·26 g.), m. p. 156—158°, $[\alpha]_D$ +79° (*c* 1·01), $\nu_{max.}$ 1740 and 1096 cm.$^{-1}$ (Found: C, 76·3; H, 9·9. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%).

3-*Ethylenedioxy*-17α-*methyl*-5α-*androstan*-17β-*ol*.—3-Ethylenedioxy-5α-androstan-17-one (2·98 g.) in anhydrous ether (100 ml.) was added to an ethereal solution of methyl-lithium [from lithium (2·52 g.) and methyl iodide (11·1 ml.)] and the reaction mixture refluxed for 1 hr. before working up in the usual manner. The residue, crystallised from benzene–light petroleum (b. p. 40—60°), gave 3-*ethylenedioxy*-17α-*methyl*-5α-*androstan*-17β-*ol* (2·03 g.), m. p. 190—193°, $[\alpha]_D$ −11° (*c* 1·05), $\nu_{max.}$ 3459, 1101, and 1087 cm.$^{-1}$ (Found: C, 75·7; H, 10·7. $C_{22}H_{36}O_3$ requires C, 75·8; H, 10·4%).

The authors thank Dr. R. E. Bowman for his encouragement and many helpful suggestions, especially that of using dimethylaminopropylamine, Miss E. M. Tanner for the determination of rotations and spectra, and Mr. F. H. Oliver for the microanalyses.

PARKE, DAVIS AND COMPANY, HOUNSLOW, MIDDLESEX. [*Received, December 10th*, 1962.]

[12] Weisenborn and Applegate, *J. Amer. Chem. Soc.*, 1959, **81**, 1960.