Studies in the Steroid Group. Part LXXVIII.† The Conversion of Hydroxy-steroids (R^1OH) into *O*-Substituted Glycollic Esters ($R^1O{\cdot}CH_2{\cdot}CO_2R^2$)

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O-Substituted glycollic esters ($R^1O{\cdot}CH_2{\cdot}CO_2R^2$) are readily prepared by treating hydroxy-steroids (R^1OH) with alkyl diazoacetates in the presence of fluoroboric acid.

In connection with other work we wished to convert hydroxy-steroids (R^1OH) into *O*-substituted glycollic esters ($R^1O{\cdot}CH_2{\cdot}CO_2R^2$). The well known methylation of alcoholic hydroxy-groups by the acid-catalysed reaction with diazomethane [1] suggested that esters of diazoacetic acid might be used for this purpose. Ethyl ethoxyacetate is formed (in unspecified amount) from ethanol, ethyl diazoacetate, and fluoroboric acid,[2] and in the presence of chloroacetic acid ethyl diazoacetate converts phenol into ethyl phenoxyacetate.[3]

Exploratory work showed that while weak acids (*e.g.*, chloroacetic acids) do not promote reaction between diazoesters and hydroxy-steroids, even when the latter are phenolic, fluoroboric acid is an effective catalyst. After finding that 18N-fluoroboric acid in ether–dichloromethane, the standard reagent in methylation,[1] required a long reaction time (24 hr.) and led to an undesirable by-product (see Table), the following simple procedure was developed. A solution of the steroid and the diazoester in dichloromethane was stirred for 6 hr. at 20° with a small amount of strong aqueous fluoroboric acid. After chromatographic purification the 3β-glycollates (Ib and Ic) from 5α-androstan-3β-ol were obtained in good yield: the methyl ester (Ib) was

† Part LXXVII, E. L. McGinnis, G. D. Meakins, and D. J. Morris, *J. Chem. Soc.* (*C*), 1967, 1238.

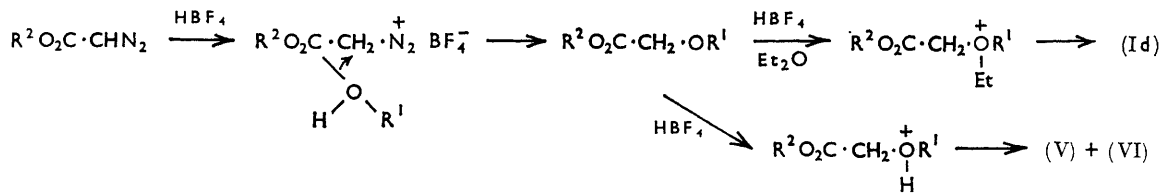
[1] M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, 1959, **6**, 36.

[2] J. D. Roberts, C. M. Regan, and I. Allen, *J. Amer. Chem. Soc.*, 1952, **74**, 3679.

[3] J. N. Brönsted and R. P. Bell, *J. Amer. Chem. Soc.*, 1931, **53**, 2478.

isolated in 58% yield by direct crystallisation of the reaction mixture. With the axial alcohol (IIa) these conditions afforded the derived ester (IIb) and some unchanged material. Three successive additions of fluoroboric acid at intervals of 2 hr. gave slightly more product (IIb), together with an appreciable quantity of olefin (V) and a small amount of 3α-methoxy-5α-androstane (IIe). [Structural details of the new compounds described in this work were established by spectrometric examinations (see Experimental section).] The more hindered 17β-hydroxy-compound (IIIa) required repeated additions of methyl diazoacetate and fluoroboric acid; rearrangement, probably to ψ-androstene [4] [which may have structure (VII)] occurred to only a small extent. Conversion of the phenolic compound (IVa) to the glycollic ester (IVb) was slower and less satisfactory than the reactions with the alcoholic hydroxy-steroids.

When fluoroboric acid in ether–dichloromethane was used with the 3β-alcohol (Ia) and ethyl diazoacetate the required product (Ic) was accompanied not only by small amounts of 5α-androst-2-ene (V) and 3α-fluoro-5α-androstane, as was the case using aqueous fluoroboric acid, but also by a considerable quantity of the 3β-ethoxy-compound (Id). The alcohol (Ia) was largely unchanged by treatment with this fluoroboric acid solution, but the glycollic ester (Ic) reacted slightly to give (Id), (V), and (VI) in proportions similar to those observed in the first experiment. In a reaction using methyl-, rather than ethyl-diazoacetate, with alcohol (Ia) the same by-products were formed, in similar amounts. Thus, the by-products arise from partial decomposition of the main products (Ic and Ib), the ethyl group of 3β-ethoxy-5α-androstane (Id) originating from solvent ether. Although related studies of systems involving alkyl diazoacetates, fluoroboric acid, and ethers [5] suggest various mechanistic interpretations of the present results, the simplest representation seems to be as follows:



The formation of the steroidal glycollates by nucleophilic displacement on the protonated diazoester explains the slowness of the reaction with the phenolic compound (IV); in the acidic medium ionisation to the phenoxide ion will be suppressed, and the neutral molecule will be a weaker nucleophile than the alcoholic hydroxy-steroids. Protonation of the glycollic ester gives an intermediate which may undergo elimination to olefin (V) or substitution to the fluoro-compound (VI).

The high proportion of the olefin formed in the reaction of the axial alcohol (IIa) is understandable, but the mechanism of the reaction whereby two hydroxy-steroids (II and IV) give small amounts of methyl ethers is obscure. Formation of the steroidal oxonium ion from the glycollic ester requires generation of a species equivalent to Et^+ from diethyl ether, and there is precedent for this under comparable conditions.[5b]

The doublet C=O stretching absorptions shown by the steroidal glycollates are being studied, and the results will be reported elsewhere. A paper appearing after the completion of our work describes reactions between alcohols and diazoesters in the presence of copper salts; [6] glycollate esters are formed, but this carbenoid route give rather low yields.

EXPERIMENTAL

Infrared, n.m.r., and u.v. spectra were recorded on Perkin-Elmer 237 and R14 (100 Mc./sec.) spectrometers, and a Unicam SP 800 spectrometer using solutions in CS_2, $CDCl_3$, and EtOH respectively. General procedures are described fully only with the first set of experiments. Silica gel used for chromatography was deactivated with water (3%).

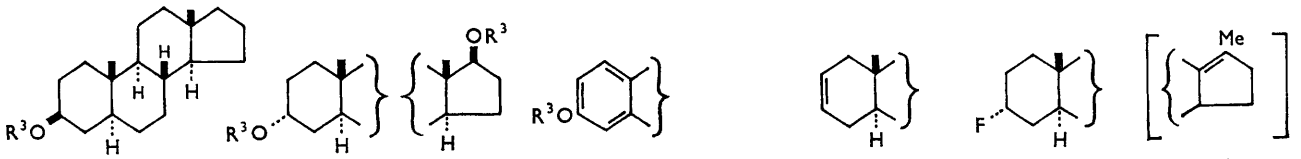
Reactions of 5α-Androstan-3β-ol (1a).—(a) *With ethyl diazoacetate and fluoroboric acid.* A solution of ethyl diazoacetate (1·4 g.) in dichloromethane (10 ml.) was added to a solution of 5α-androstan-3β-ol (1 g.) in dichloromethane (20 ml.). 18N-Fluoroboric acid (1 drop) was added, and the mixture stirred for 6 hr. at 20°. 2N-Hydrochloric acid (20 ml.) was added and the stirring continued for 20 min. After separation of the layers, the aqueous layer was extracted with dichloromethane. The organic layers were combined and washed with 2N-hydrochloric acid, water, 2N-sodium hydrogen carbonate, and water. Evaporation of the dried solution gave material which was chromatographed on silica gel (80 g.). Light petroleum (b.p. 40—60°) eluted *5α-androst-2-ene* (37 mg.), m.p. 71—72° (from ethanol), $[\alpha]_D$ +51° (*c* 0·8) (Found: C, 88·0; H, 11·5. $C_{19}H_{30}$ requires C, 88·3; H, 11·7%). Elution with light petroleum–ether (49 : 1) gave *3α-fluoro-5α-androstane* (32 mg.), m.p. 62—64° (from ethanol), $[\alpha]_D$ +1° (*c* 0·5) (Found: C, 82·0; H, 10·9. $C_{19}H_{31}F$ requires C, 82·0; H, 10·9%). Light petroleum–ether (1 : 1) eluted *ethyl 5α-androstan-3β-yloxyacetate* (Ic) (920 mg.), m.p. 68—69·5° (from ethanol), $[\alpha]_D$ −8° (*c* 1·9) (Found: C, 76·3; H, 10·3. $C_{23}H_{38}O_3$ requires C, 76·2; H, 10·6%).

(b) *With ethyl diazoacetate and fluoroboric acid in the presence of ether.* A solution of ethyl diazoacetate (10·3 g.)

[4] (*a*) H. Kägi and K. Miescher, *Helv. Chim. Acta*, 1939, **22**, 683; (*b*) G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, E. E. Richards, and T. L. Whateley, *J. Chem. Soc.* (*C*), 1966, 1266.

[5] (*a*) E. Müller and H. Huber-Emden, *Annalen*, 1961, **649**, 70; (*b*) S. Patai, 'The Chemistry of the Ether Linkage,' Interscience, New York, 1967, p. 267.

[6] T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and T. Shimizu, *J. Org. Chem.*, 1968, **33**, 544.



(I) (II) (III) (IV) (V) (VI) (VII)

a, $R^3 = H$; b, $R^3 = CH_2 \cdot CO_2Me$; c, $R^3 = CH_2 \cdot CO_2Et$; d, $R^3 = Et$; e, $R^3 = Me$

R^1OH	$N_2CH \cdot CO_2R^2$	Acid	Products (yield %)			
(Ia)	R^2 = Et	HBF_4	(Ic)(70)	(V)(4)	(VI)(3)	
,,	R^2 = Me	,,	(Ib)(71)	(V)(4)	(VI)(2)	
(IIa)	,,	,,	(IIb)(68)	(IIa)(15)		
,,	,,	,,(extra)	(IIb)(72)	(V)(20)	(IIe)(3)	
(IIIa)	,,	HBF_4	(IIIb)(68)	(IIIa)(7)	(VII)(5)	
(IVa)	,,	,,	(IVb)(43)	(IVe)(9)		
(Ia)	R^2 = Et	$CH_2Cl \cdot CO_2H$	(Ia)(92)			
(IVa)	R^2 = Me	$CH_2Cl \cdot CO_2H$ / $CHCl_2 \cdot CO_2H$	(IVa)(>90)			
(Ia)*	R^2 = Et	HBF_4–Et_2O	(Ic)(64)	(Id)(19)	(V)(3)	(VI)(2)
,,	R^2 = Me	,,	(Ib)(63)	(Id)(16)	(V)(3)	(VI)(2)
,,	Absent	,,	Little reaction (t.l.c. examination)			
[(Ic)	,,		(Ic) (Id), (V), and (VI), proportions similar to those in experiment.*]			

Reactions of hydroxy-steroids (R^1OH), in CH_2Cl_2, with alkyl diazoacetates ($N_2CH \cdot CO_2R^2$). HBF_4 refers to an 18N-aqueous solution

in dichloromethane (100 ml.) and a solution of fluoroboric acid [33 ml. of a solution made from 18N-fluoroboric acid (1·5 ml.), ether (225 ml.), and dichloromethane (75 ml.)] were added separately but simultaneously over 20 min. to a stirred solution of 5α-androstan-3β-ol (7·5 g.) in dichloromethane (150 ml.) at 20°. After stirring for 24 hr., 2N-hydrochloric acid (150 ml.) was added, the mixture was worked up as above, and the product chromatographed on silica gel (500 g.). Light petroleum eluted 5α-androst-2-ene (205 mg.). Light petroleum–ether (49 : 1) eluted 3α-fluoro-5α-androstane (150 mg.). Light petroleum–ether (19 : 1 and 9 : 1) eluted 3β-*ethoxy*-5α-*androstane* (1·57 g.), m.p. 75·5—76° (from ethanol), $[\alpha]_D$ −4° (*c* 0·9) (Found: C, 83·1; H, 11·7. $C_{21}H_{36}O$ requires C, 82·8; H, 11·9%). Light petroleum–ether (1 : 1) eluted the glycollate (Ic) (6·26 g.).

(c) *With methyl diazoacetate and fluoroboric acid.* Methyl diazoacetate (4·5 g.), 5α-androstan-3β-ol (3·75 g.) and fluoroboric acid (1 drop) were used as in experiment (a), and the product chromatographed on silica gel (250 g.). Light petroleum eluted 5α-androst-2-ene (141 mg.), m.p. and mixed m.p. 70—72°, and light petroleum–ether (49 : 1) eluted 3α-fluoro-5α-androstane (76 mg.), m.p. and mixed m.p. 62—64°. Light petroleum–ether (7 : 3) eluted *methyl* 5α-*androstan*-3β-*yloxyacetate* (Ib) (3·36 g.), m.p. 84—86° (from ethanol), $[\alpha]_D$ −6° (*c* 1·0) (Found: C, 75·95; H, 10·3. $C_{22}H_{36}O_3$ requires C, 75·8; H, 10·4%).

The above experiment was repeated using methyl diazoacetate (2·2 g.), 5α-androstan-3β-ol (1·87 g.), and fluoroboric acid (1 drop). Direct crystallisation of the product from ethanol gave the glycollate (Ib) (1·42 g.), m.p. 84—86°, identified by i.r. examination.

(d) *With methyl diazoacetate and fluoroboric acid in the presence of ether.* The procedure of experiment (b) was employed with methyl diazoacetate (4·5 g.), fluoroboric acid in ether–dichloromethane (16·5 ml.), and 5α-androstan-3β-ol (3·75 g.). Chromatography, using light petroleum containing increasing amounts of ether, gave in turn 5α-androst-2-ene (105 mg.), 3α-fluoro-5α-androstane (75 mg.), 3β-ethoxy-5α-androstane (662 mg., m.p. and mixed m.p. 75—76°), and the glycollate (Ib) (2·98 g.).

(e) *With other reagents.* Fluoroboric acid [2 ml. of the solution in ether–dichloromethane described in experiment (b)] was added to 5α-androstan-3β-ol (495 mg.) in dichloromethane (10 ml.) and the solution was stirred for 20 hr. at 20°. Analysis of the product by t.l.c. showed the presence of only trace amounts of 5α-androst-2-ene and 3α-fluoro-5α-androstane. Chromatography on silica gel afforded 5α-androstan-3β-ol (465 mg.), m.p. and mixed m.p. 150—151°.

The procedure of experiment (a) was employed using 5α-androstan-3β-ol (110 mg.) with methyl diazoacetate (200 mg.) and chloroacetic acid (10 mg.). 5α-Androstan-3β-ol (101 mg.) was recovered unchanged.

Treatment of Ethyl 5α-*Androstan*-3β-*yloxyacetate* (Ib) *with Fluoroboric Acid in the Presence of Ether.*—Fluoroboric acid (2 ml. of the solution in ether–dichloromethane) was added to the glycollate (480 mg.) in dichloromethane (10 ml.) and the solution was stirred for 24 hr. at 20°. The usual work-up and t.l.c. analysis of the product showed 5α-androst-2-ene, 3α-fluoro-5α-androstane, 3β-ethoxy-5α-androstane, and starting material in the same relative proportions as in experiment (b).

Reactions of 5α-*Androstan*-3α-*ol* (IIa).—18N-Fluoroboric acid (1 drop) was added to a stirred solution of 5α-androstan-3α-ol (1·38 g.) and methyl diazoacetate (2·5 g.) in dichloromethane (50 ml.) at 20°. Three further additions of 18N-fluoroboric acid (each 1 drop) were made at intervals of 2 hr., and the product was chromatographed on silica gel (100 g.). Light petroleum–ethyl acetate (50 : 1) eluted 5α-androst-2-ene (264 mg.), m.p. 70—72°, and then an oil (88 mg.) which was rechromatographed. Light petroleum–ethyl acetate (19 : 1) eluted *methyl* 5α-*androstan*-3α-*yloxyacetate* (IIb) (1·093 g.) as an oil, $[\alpha]_D$ −3° (*c* 1·0) (Found: C, 75·8; H, 10·55. $C_{22}H_{36}O_3$ requires C, 75·9; H, 10·4%). The oil (88 mg.) was chromatographed on silica gel (10 g.). Light petroleum–ethyl acetate (100 : 1) eluted 3α-*methoxy*-5β-*androstane* (IIe) (40 mg.), m.p. 55—57° (from methanol), $[\alpha]_D$ −3° (*c* 0·2) (Found: C, 82·9; H, 12·0. $C_{20}H_{34}O$ requires C, 82·8; H, 11·7%). Light petroleum–ethyl acetate (50 : 1) eluted the glycollate (IIb) (41 mg.).

For comparison, a specimen of 3α-methoxy-5α-androstane

was prepared by treating 5α-androstan-3α-ol with diazomethane under the standard conditions.[1] The product (86%) had m.p. 55—57°, alone and on admixture with the material described above.

The glycollate (IIb) was boiled under reflux for 1 hr. with 5% methanolic potassium hydroxide. Standard manipulation gave *5α-androstan-3α-yloxyacetic acid* (88%), m.p. 130—133° (from light petroleum), $[\alpha]_D$ 0° (*c* 0·8) (Found: C, 75·4; H, 10·2. $C_{12}H_{34}O_3$ requires C, 75·5; H, 10·2%).

Reaction of 5α-Androstan-17β-ol (IIIa).—18N-Fluoroboric acid (1 drop) was added to a stirred solution of 5α-androstan-17β-ol (200 mg.) and methyl diazoacetate (254 mg.) in dichloromethane (26 ml.) at 20°. Three further additions of methyl diazoacetate [each 250 mg. in dichloromethane (6 ml.)] followed by 18N-fluoroboric acid (each 1 drop) were made at intervals of 20 min. Preparative t.l.c. of the product on silica using benzene–ethyl acetate (19 : 1) for development gave (i) an oil (9 mg., probably ψ-androstene [4]) showing n.m.r. signals at τ 8·74 (s, ?Me–C=C) and 9·30 (19-H), but no absorption (i.r. and n.m.r.) corresponding to *H*–C=C; (ii) *methyl 5α-androstan-17β-yloxyacetate* (IIIb) (171 mg.), m.p. 77·5—79° (from methanol), $[\alpha]_D$ −3° (*c* 1·0) (Found: C, 75·5; H, 10·1. $C_{22}H_{36}O_3$ requires C, 75·8; H, 10·4%), and (iii) starting material (IIIa) (14 mg.), m.p. and mixed m.p. 166—168°.

Reactions of Oestra-1,3,5(10)-trien-3-ol (IVa).—18N-Fluoroboric acid (1 drop) was added to a stirred solution of the steroid (IVa) (500 mg.) and methyl diazoacetate (680 mg.) in dichloromethane (30 ml.) at 20°. After 24 hr. the mixture was worked up as usual. Preparative t.l.c. on silica using benzene–ethyl acetate (19 : 1) for development gave two fractions. The one of lower R_F was *methyl oestra-1,3,5(10)-trien-3-yloxyacetate* (IVb) (275 mg.), m.p. 84·5—85·5° (from ethanol), $[\alpha]_D$ +66° (*c* 0·8) (Found: C, 76·5; H, 8·6. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%); $\lambda_{max.}$ 277 (ε 1800) and 286 mμ (ε 1700). The fraction of higher R_F was 3-methoxy-oestra-1,3,5(10)-triene (IVe) (46 mg.), m.p. and mixed m.p. 75·5—76·5° (lit.,[7] m.p. 76·5°).

Experiments corresponding to reaction (e) under 5α-androstan-3β-ol were carried out with the oestratrienol (IVa); the starting material was recovered in each case.

N.m.r. Signals and I.r. Peaks.—Assignments are given only where a particular signal is first encountered. Multiplicities are denoted by letters [s, d, t, q, se (septet), and m], $W_{\frac{1}{2}}$ and *J* values are in c./sec.

Compound (Ib), τ 5·88 (s, $MeO_2C{\cdot}CH_2{\cdot}O$), 6·26 (s, CO_2Me), 6·68se, $W_{\frac{1}{2}}$ 24(H-3α); $\nu_{max.}$ 1766, 1738 cm.$^{-1}$. (IIb), τ 5·93s, 6·27s, 6·39m, $W_{\frac{1}{2}}$ 7(H-3β); $\nu_{max.}$ 1762, 1740. (IIIb), τ 5·89s, 6·26s, 6·61 [t, J_{total} 16(H-17α)]; $\nu_{max.}$ 1767, 1741. (IVb), τ 2·82 [d, *J* 8(H-1)], 3·34 [2d, *J* 8 and 3(H-2)], 3·38 (s, H-4), 5·43s, 6·22s; $\nu_{max.}$ 1770, 1744. (Ic), τ 5·79q and 8·77 (t, CO_2Et), 5·91s, 6·67se, $W_{\frac{1}{2}}$ 23; $\nu_{max.}$ 1756, 1734. (Id), τ 6·49q and 8·80 (t, O*Et*), 6·80se, $W_{\frac{1}{2}}$ 24; $\nu_{max.}$ 1112, 1098. (IIe), τ 6·58m, $W_{\frac{1}{2}}$ 8, 6·70 (s, O*Me*); $\nu_{max.}$ 1090. (V), τ 4·42 and 4·45 (Δ^2-system [4b]); $\nu_{max.}$ 3020, 665. (VI), τ 5·22 (d, *J* 49·2), $W_{\frac{1}{2}}$ (each component) 8 (H-3β); $\nu_{max.}$ 992, 983. 5α-Androstan-3α-yloxyacetic acid, τ 0·07 (s, CO_2H), 5·93s, 6·31m, $W_{\frac{1}{2}}$ 6; $\nu_{max.}$ 1782 and 1725 (the higher frequency band arising from an internally bonded form, as in aryloxyacetic acids [8]).

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