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MODIFIED STEROID HORMONES—XXXIII[1]

STEROIDAL 6-FORMYL-3-ALKOXY-3, 5-DIENES AND SOME OF THEIR TRANSFORMATIONS

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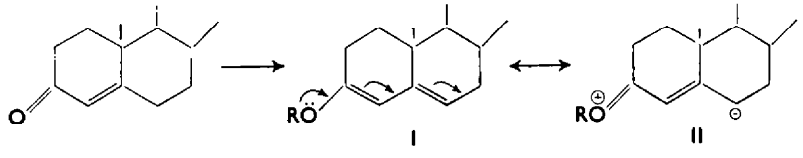
Abstract—Reaction between steroidal 3-alkoxy-3,5-dienes and the Vilsmeier reagent leads to high yields of the corresponding 6-formyl derivatives. These intermediates are reduced to 3-alkoxy-6-hydroxymethyl-3,5-dienes which undergo dehydration with acids to 6-methylene-4-en-3-ones.

SEVERAL methods for introducing a carbon substituent at C_6 in the steroid molecule have been reported. These include reaction of (i) 5α,6α-epoxy[2,3] derivatives and of 6-ketones[2] with a Grignard reagent, (ii) 3β-hydroxypregn-5-enes with carbon monoxide and hydrogen in the presence of dicobalt octacarbonyl (the "oxo reaction")[4] and (iii) 3-enol ethers of 4-en-3-ketones with a carbon tetrahalide.[5] Subsequent transformations of the initially-formed products have been directed in each case towards the preparation of 6α-methyl-4-en-3-ketones.

As the foregoing procedures are often inefficient and of doubtful reproducibility, we sought an alternative route and now report upon a new procedure which is both convenient and highly effective.

During the past few years, 6-hydroxy,[6] nitro[7] and halo-4-en-3-ketones[8] have been prepared by reaction of enolic derivatives of 4-en-3-ketones with electrophilic reagents such as per-acids, nitric acid and sources of "positive" halogen (e.g. N-chlorosuccinimide, perchloryl fluoride). These transformations may be rationalized by assuming that the enolic derivative (I) functions in a polarized form (II) in which C_6 is electro-



I II

negative. Application of the concept of electrophilic attack upon enol derivatives to the preparation of C_6-carbon substituted steroids clearly necessitates the provision of

[1] Part XXXII, M. T. Davies and V. Petrow, Tetrahedron **19**, 1771 (1963).
[2] D. Burn, B. Ellis, V. Petrow, I. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4092 (1957).
[3] G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957).
[4] A. L. Nussbaum, T. L. Popper, E. P. Oliveto, S. Friedman and I. Wendler, *J. Amer. Chem. Soc.* **81**, 1228 (1959); P. F. Beal, M. A. Rebensdorf and J. E. Pike, *Ibid.* **81**, 1231 (1959).
[5] S. Liisberg, W. O. Godtfredsen and S. Vangedal, *Tetrahedron* **9**, 149 (1960).
[6] J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Org. Chem.* **19**, 1509 (1954).
[7] A. Bowers, L. C. Ibanez and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 3707 (1959).
[8] H. J. Ringold, E. Batres, A. Bowers, J. Edwards and J. Zderic, *J. Amer. Chem. Soc.* **81**, 3485 (1959); S. Nakanishi, K. Morita and E. V. Jensen, *Ibid.* **81**, 5259 (1959).

a suitable electrophilic reagent in which the reactive centre is a carbon atom. To this end we examined several reagents which have been successfully employed for aromatic and heterocyclic electrophilic substituents, but only one of these, the Vilsmeier reagent,[9] gave encouraging results. The 3-enol ethers, acylates and enamines of 4-en-3-ketones were all examined but only the enol ethers gave the desired conversions.

The Vilsmeier reagent is a cationic species regarded by Arnold[10] as having the structure

$$R_2\overset{\oplus}{N}{=}CHX \longleftrightarrow R_2N{-}CH\overset{\oplus}{X}$$

where X is halogen (Cl or Br) atom or other electronegative group such as —O·PO·Cl_2. It is prepared by treating a formamide, generally dimethyl formamide, with phosgene or phosphoryl chloride, when reactions are thought to occur as follows:

(a)

$$Me_2N{-}CH{=}O + COCl_2 \rightarrow Me_2\overset{\oplus}{N}{=}CH{-}O{-}CO.Cl + Cl^-$$

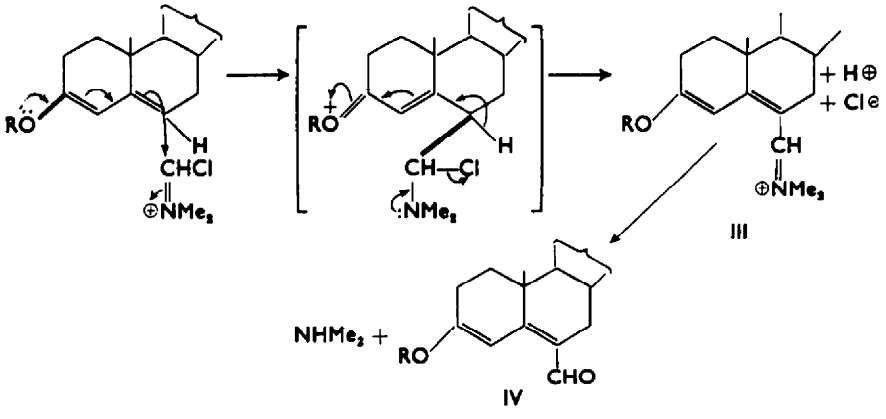
$$Me_2\overset{\oplus}{N}{=}CH{-}O \rightarrow Me_2\overset{\ominus}{N}{=}CHCl + CO_2$$

(b)

$$Me_2N{-}CH{=}O + POCl_3 \rightarrow Me_2\overset{\oplus}{N}{=}CH{-}O{-}POCl_3 + Cl^-$$

Its application to aliphatic ketomethylene systems has been studied by Arnold *et al.*[11]

We have found that the Vilsmeier reagent, formed from dimethyl formamide and phosgene, reacts with 3-alkoxy-3,5-dienes in an anhydrous medium to give an iminium intermediate, regarded as (III), which passes on hydrolysis into the corresponding 6-formyl 3-enol ether (IV). The transformations may be interpreted as follows:



General methods for the preparation of the Vilsmeier reagent and for its reaction with 3-enol ethers of a wide variety of steroidal 4-en-3-ketones are described in the Experimental Section.

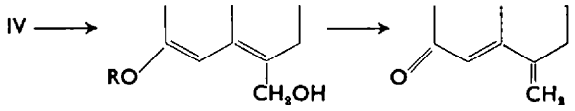
The high-order efficiency of the 6-formylation reaction proved to be independent of the nature of the ether grouping at C_3. Considerations based upon solubilities and other properties of the formylation products, however, pointed to the use of methyl

[9] See H. H. Bosshard and Hch. Zollinger, *Helv. Chim. Acta* **42**, 1659 (1959) and references there cited.
[10] Z. Arnold, *Coll. Czech. Chem. Comm.* **24**, 4048 (1959).
[11] See e.g. Z. Arnold and J. Zemlicka, *Coll. Czech. Chem. Comm.* **24**, 786 (1959).

enol ethers as the starting materials of choice. The Vilsmeier reagent, employed in the ratio of 1·1 to 1·3 molar proportions per molar proportion of steroid under the conditions defined in the Experimental Section, had little effect upon most functional groups except epoxy and some hydroxyl groups. 16α,17α-Epoxypregnan-20-ones were converted into chlorohydrins from which the epoxide ring could be regenerated by mild alkali treatment of the product. 16β-Methyl-16α,17α-epoxypregnan-20-ones were converted into 17α-hydroxy-16-methylene-20-ones. A molar excess of reagent was required for optimum yields of 6-formylated products in both the foregoing circumstances and in most cases in which an hydroxyl group was initially present. The behaviour of the last grouping depended upon character and position. Thus, whereas secondary 17β- and some tertiary 17β-hydroxyl groups (as in 17α-alkyl testosterone 3-enol ethers) underwent formylation, the 17α-hydroxy group of the cortical side-chain emerged unchanged from the reaction. 3,3-Ethylenedioxy-5-ene steroids were converted by the Vilsmeier reagent into 6-formyl derivatives of the corresponding 3-(β-hydroxy ethoxy)-3,5-dienes. Worthy of note is the observation* that the reagent promoted isomerization of the 3-methoxy estra-2,5(10)-diene system, when the 6-formyl derivative of the corresponding 3-methoxy estra-3,5-diene was obtained.

6-Formyl-3-enol ethers (IV) are, with few exceptions, well-defined crystalline solids with melting points often somewhat higher than those of the parent enol ethers. The UV absorption spectra show λ_{max} 219–221 mμ (ε10,000 to 12,000) and λ_{max} 319–323 mμ (ε14,000 to 16,000), and in the infrared spectra, bands (in Nujol) appear at 1639–1645 (medium intensity), 1604–1606 (very intense) and 1572–1577 cm^{-1} (weak). The 3-alkoxy-6-formyl-3,5-diene system proved unexpectedly stable to hot acetic acid and to other conditions of acidity which normally cause rapid regeneration of 4-en-3-ketones from unsubstituted 3-alkoxy-3,5-dienes. Surprisingly, simple crystallization of a 6-formyl enol *ethyl* ether from methanol often resulted in partial or even complete conversion to the corresponding *methyl* enol ether. Ether interchange may therefore occur with great facility, and caution must be exercised during crystallization of 6-formyl derivatives of higher enol ethers from lower alkanolic solvents.

The 6-formyl group present in compounds (IV) was readily reduced to a 6-hydroxymethyl group (see V) by catalytic hydrogenation, and by a variety of reagents including sodium and lithium borohydrides, and diborane, the method of choice



V VI

being dictated by the presence or absence of interfering groups in the derivative (IV). Thus, sodium borohydride in methanol, or lithium borohydride in tetrahydrofuran, could be employed for the reduction of certain derivatives such as the 17α-acetoxypregnan-20-ones in which the ketonic function is difficulty reducible. Careful use of the last reagent also avoided attack upon ester linkages. In contrast, the 6-formyl and 20-oxo functions of 6-formyl cortisone 21-acetate 3-enol ether were reduced by the borohydrides at comparable rates, but a hydrogenation procedure (see Experimental) employing a platinum-charcoal catalyst in a slightly basic medium permitted

* By Mr. C. Burgess of this Dept.

selective reduction of the formyl group at C_6. In this way, the 6-hydroxymethyl 3-enol ethers (V) derived from cortisone acetate, desoxycorticosterone acetate and androst-4-ene-3,17-dione were prepared in good yield. Hydrogenation in the presence of Raney nickel also proved useful.

Compounds of type V are sometimes difficult to obtain in crystalline condition. They have UV spectra with λ_{max} 248–251 mμ (ϵ16,000 to 20,000); the IR spectra show the principal features of the parent enol ethers. Unlike their 6-formyl precursors, 6-hydroxymethyl 3-enol ethers proved extremely sensitive to acids, and for this reason were crystallized best from solvents rendered slightly basic by the addition, for example, of a trace of pyridine. Brief treatment with aqueous acetic or methanolic mineral acids resulted in hydrolysis of the 3-enol ether systems with concomitant dehydration of the 6-hydroxymethyl groups, to give the corresponding 6-methylene-4-en-3-ketones (VI), generally in excellent yield.

Most 6-methylene derivatives (VI) crystallize well. They are strongly dextrorotatory, and have IR absorption with maxima (in methylene dichloride) at *circa* 1644, 1623 (poorly resolved) and 1599 cm^{-1}. The UV absorption spectra show a characteristic gradual and continuous increase in intensity with increase in wavelength from 220 mμ (ϵ ca. 3,400) to 260 mμ (ϵ11,500 to 14,000), after which the curves decline abruptly.

The 6-formyl derivative (IV) of testosterone acetate 3-enol methyl ether readily formed an oxime. Treatment of the 6-hydroxymethyl derivative (V) of testosterone acetate 3-enol methyl ether with acetic anhydride–pyridine gave an amorphous acetate, which, on attempted purification by recrystallization, passed into 6-methylene testosterone acetate (VI). Hydrogenation of the last compound, employing a palladium on charcoal catalyst, furnished 6β-methyl testosterone acetate,[12] from which the 6α-methyl isomer may be obtained by epimerization procedures.[12]

EXPERIMENTAL

Optical rotations, UV (in ethanol solution) and IR absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc.

General procedures for the preparation of hitherto undescribed 3-enol ethers of 4-ene-3-ketosteroids

Method A. Methyl or ethyl orthoformate (1 part) and toluene-*p*-sulphonic acid (1/20 part) or conc. H_2SO_4 (1/50 part) were added to the 4-ene-3-ketosteroid (1 part) in "AnalaR" dioxan (10–15 parts), and the mixture stirred at room temp for 20 mins, or until a clear solution was obtained and thereafter for a further 10 mins. After the addition of pyridine (1/5 part), the mixture was treated with sufficient water to effect crystallization of the enol ether. The product was purified usually from aqueous methanol containing a few drops of pyridine.

Method B. The 4-ene-3-ketosteroid (1 part) was suspended in a mixture of dry tetrahydrofuran (10–12 parts), methyl- or ethyl orthoformate (1–2 parts) and the corresponding alcohol (1 part). After the addition of toluene-*p*-sulphonic acid (1/50 part), the mixture was stirred until the steroid had dissolved and thereafter for a further 30 min. Pyridine (1/10 part) was added, followed by water and the product was isolated with ether. Excess orthoformate was removed under reduced pressure and the residue purified as in Method A.

Method C. Higher enol ethers were prepared by procedures[13] involving ether-exchange or azeotropic distillation.

[12] M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 4099 (1957).

[13] A. Ercoli and R. Gardi, *J. Amer. Chem. Soc.* **82**, 746 (1960).

Method D (for cortisone 17,21-acetonide 3-enol methyl ether). Cortisone (15 g), dimethylformamide (30 ml), dimethoxypropane (120 ml) and toluene-sulphonic acid (75 mg) were heated for 6 hr under reflux in an apparatus fitted with a variable take-off head. About 10 ml distillate were removed hourly. Methylorthoformate (15 ml) was then added, followed 10 min later by pyridine (5 ml). The mixture was concentrated under reduced pressure to about 40 ml, water added, and the product collected and purified from methylene dichloride–ethanol to which a trace of pyridine had been added.

General procedures for the 6-formylation of 3-enol ethers of 4-ene-3-ketosteroids

Method A. The Vilsmeier reagent was prepared as follows:

A freshly prepared solution of phosgene (2 parts) in ethylenedichloride (20–30 parts) was added dropwise during 30 min to a stirred solution of freshly distilled dimethylformamide (3 parts) in anhydrous ethylenedichloride (10 parts) maintained between 0° and 5°. A white ppt appeared, accompanied by the evolution of carbon dioxide. After a further 10 min, the steroidal enol ether (6 parts) in ethylene dichloride (30–60 parts) containing pyridine (½ part) was added all at once to the reagent slurry. Stirring was continued at 0°–20° for 1–2 hr, when a clear red solution was obtained. A 5% aqueous solution of sodium acetate (4 parts) was added and the mixture stirred vigorously for 10 min, then poured into water. Sufficient ether was added to produce an upper organic phase, and the two phases were separated. Coloured impurities in the ether phase were removed by repeatedly washing with water. After removal of the solvents from the dried extract, the residual crude 6-formyl derivative was purified from methanol or other suitable solvent. Yields of 6-formyl 3-enol ethers approached 90% in favourable cases.

Method B. The relative proportions of solvents and reactants were similar to those employed in the foregoing procedure. The steroidal enol ether, however, was not added to the prepared Vilsmeier reagent but was incorporated in the dimethylformamide–ethylenedichloride mixture prior to the addition of the phosgene solution. The product was isolated as above.

Method C. The process differed from Method A in that twice as much phosgene and dimethylformamide were employed.

Method D. As Method A, but three times as much phosgene and dimethylformamide were employed.

Freshly distilled phosphoryl chloride could be used in place of phosgene in any of the foregoing methods; successful reactions were carried out using, in place of dimethylformamide, the higher formamides N-methylformanilide, N-formylpiperidine, N-formylmorpholine and N,N- diethylformamide.

Preparation of 6-hydroxymethyl 3-enol ethers

Method A. The 6-formyl 3-enol ether (10 parts) in methanol (100 parts) was treated with sodium borohydride (1 part) and the mixture stirred for 15 min at room temp. The product was isolated by addition of water and extraction with ether, and was purified from aqueous methanol containing a trace of pyridine.

Method B. The 6-formyl derivative (20 parts) in anhydrous tetrahydrofuran (100–200 parts) was treated with lithium borohydride (1 part) in tetrahydrofuran (20–30 parts). The mixture was kept for 10 min at room temp then poured into water and the product isolated as above.

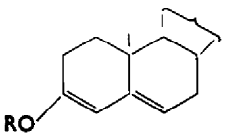
Method C. Raney nickel sludge (2 ml for each 1g of steroid) was repeatedly washed with methanol by decantation until the washings were only weakly alkaline, then treated with a 1:1 mixture of methanol and methyl acetate. The mixture was allowed to stand overnight, the solvents decanted, and replaced by a fresh 3:1 mixture of methanol and methyl acetate (10 ml per 1g of steroid to be used). The catalyst was hydrogenated to equilibrium at atm. press. a solution or suspension of the 6-formyl derivative in methanol (5–10 parts) was added, and hydrogenation allowed to proceed until a molar proportion of hydrogen had been absorbed. The catalyst was removed, and the product isolated and purified as above.

Method D. A 5% platinum on charcoal catalyst (1 part) was hydrogenated in methanol. The 6-formyl derivative (2 parts) and sodium acetate (2 parts) in methanol (10–30 parts) were added and the mixture hydrogenated until one equivalent proportion of hydrogen had been absorbed. After removal of the catalyst, water was added and the product purified as above.

Yields of 6-hydroxymethyl derivatives obtained by one or other of the foregoing methods approached 95% in favourable cases.

TABLE I

HITHERTO UNDESCRIBED 3-ENOL ETHERS



Parent compound	Method of prep.	R	M.p.	$[\alpha]_D^{\circ}$	λ_{max} (ε)	Formula	Analysis (%) Found C	Found H	Reqd. C	Reqd. H
Testosterone acetate[a]	A	Me	168–173°	−141°(di)	240(18,900)	$C_{23}H_{32}O_3$	76·3	9·2	76·7	9·4
Testosterone[b]	—	Me	125–127°	−128°(di)	240(17,540)	$C_{20}H_{30}O_2$	79·1	9·9	79·4	10·0
2α-Methyl testosterone acetate	A	Et	188–190°	−122°(py)	243(19,440)	$C_{24}H_{36}O_3$	77·2	9·6	77·35	9·75
17α-Methyl testosterone acetate	A	Me	112–114°	−141°(chf)	240(18,780)	$C_{23}H_{34}O_3$	76·8	9·1	77·05	9·6
17α-Vinyl testosterone propionate[c]	A	Et	103–104°	−96°(chf)	—	$C_{26}H_{38}O_3$	77·9	9·4	78·3	9·6
17α-Prop-1′-ynyl testosterone propionate[c]	A	Et	106–107°	−192°(chf)	—	$C_{27}H_{38}O_3$	79·2	9·2	79·0	9·3
17α-Chlorethynyl testosterone	A	Me	87–89°	−220°(chf)	240(18,260)	$C_{22}H_{29}ClO_2$	73·1	8·25	73·2	8·1
Androst-4-enc-3,17-dione	C	$C_6H_5CH_2$	172–176°	−49°(di)	241(22,330)	$C_{26}H_{32}O_2$	82·5	8·5	82·9	8·6
Progesterone	A	Me	158–160°	−65°(di)	240(19,150)	$C_{23}H_{32}O_2$	80·25	9·75	80·45	9·85
17α-Acetoxy progesterone[f]	A	Me	175–180°	−148°(di)	240(19,360)	$C_{24}H_{34}O_4$	74·7	9·0	74·6	8·9
17α-Acetoxy progesterone	A	Et	147–154°	−144°(di)	240(20,340)	$C_{25}H_{36}O_4$	75·1	9·0	75·0	9·1
17α-Acetoxy-21-fluoro progesterone	A	Me	192–194°	−164°(di)	240(19,090)	$C_{24}H_{33}FO_4$	70·5	8·3	71·2	8·2
17α-Acetoxy-16-methylene progesterone	B	Me	225–227°	−242°(chf)	241(19,300)	$C_{25}H_{34}O_4$	75·3	8·5	75·3	8·6
17α-Acetoxy-16-ethylidene progesterone	B	Me	205–208°	−231°(chf)	—	$C_{26}H_{36}O_4$	75·3	8·8	75·7	8·8
17α-Acetoxy-16α-methyl progesterone	A	Me	198–200°	−114(di)	240(19,550)	$C_{25}H_{36}O_4$	74·5	8·9	75·0	9·0
16β-Bromo-17α-hydroxy progesterone	B	Me	190–193°	−80(di)	240(20,370)	$C_{22}H_{31}BrO_3$	63·0	6·9	62·4	7·4
16α-Cyano-progesterone	A	Me	167–169°	−69°(chf)	240(18,525)	$C_{22}H_{31}NO_2$	78·0	8·8	78·1	8·8
16α,17α-Cyclomethylene progesterone	A	Me	201–202°	−24°(di)	240(19,680)	$C_{23}H_{32}O_2$	81·1	9·3	81·1	9·4
16α-17α-Isopropylidendioxy progesterone	A	Me	194–196°	−75°(di)	—	$C_{25}H_{36}O_4$	75·5	9·35	74·95	9·05
16α,17α-Isopropylidendioxy progesterone	A	Et	216–217°	−64°(chf)	—	$C_{26}H_{38}O_4$	75·3	9·35	75·3	9·2
21-Benzylidene-16α,17α-isopropylidenedioxy progesterone[d]	—	Et	183–190°	−75°(di)	240(20,760)	$C_{33}H_{42}O_4$	78·8	8·4	78·8	8·4
16α,17α-Epoxyprogesterone[g]	B	Me	196–202°	—	240(19,590)	$C_{22}H_{30}O_3$	76·7	8·7	77·15	8·8
16α,17α-Epoxy-16β-methyl progesterone	B	Me	128–130°	−71°(chf)	240(19,600)	$C_{23}H_{32}O_3$	77·5	8·9	77·5	9·05

20β-Acetoxypregn-4-en-3-one	A	Et	126–129°	−81°(di)	241(19,990)	$C_{25}H_{38}O_3$	77·15	9·6	77·65	9·9
20β-Hydroxypregn-4-en-3-one[b]	—	Et	141–144°	−152°(di)	241(19,740)	$C_{23}H_{36}O_2$	79·75	10·7	80·2	10·55
21-Acetoxypregna-4,17(20)-diene-3,11-dione	A	Me	141–143°	−41°(di)	239(17,270)	$C_{24}H_{32}O_4$	75·1	8·3	75·0	8·4
Deoxycorticosterone acetate[h]	A	Me	158–160°	−15°(di)	240(19,330)	$C_{24}H_{34}O_4$	74·35	8·95	74·55	8·85
Deoxycorticosterone acetate	A	Et	134–137°	−25°(chf)	241(19,500)	$C_{25}H_{36}O_4$	75·05	9·4	74·95	9·05
21-Acetoxy-17α-hydroxypregna-4,9(11)-diene-3,20-dione	B	Me	158–166°	−84°(di)	241(19,700)	$C_{24}H_{32}O_5$	71·5	8·1	72·0	8·05
Cortisone 17α,21-diacetate	A	Me	162–167°	−60°(di)	240(18,980)	$C_{26}H_{34}O_7$	67·8	7·4	68·1	7·65
Cortisone 17α,20:20,21-bismethylenedioxy derivative	A	Et	167–169°	−137°(chf)	241(18,560)	$C_{25}H_{34}O_6$	69·55	7·8	69·75	7·95
Cortisone 17α,21-methoxymethylenedioxy derivative	A	Me	147–152°	−31°(di)	240(15,000)	$C_{24}H_{32}O_6$	68·9	7·9	69·2	7·7
Cortisone 17α,21-isopropylidenedioxy derivative	D	Me	188–196°	−31°(di)	238(20,190)	$C_{25}H_{34}O_5$	72·4	8·25	72·4	8·3
Diosgenone	A	Et	171–174°	−179°(chf)	241(20,800)	$C_{29}H_{44}O_3$	79·2	9·8	79·0	10·1
3-(17β-Hydroxy-3-oxo-androst-4-en-17α-yl)propionic acid lactone	A	Et	174–175°	−171°(chf)	—	$C_{24}H_{34}O_3$	77·7	9·0	77·8	9·2

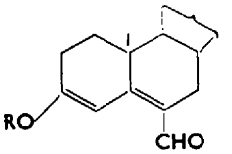
[a] At 18–25° in ca. 1% solution in dioxan (di), chloroform (chf) or pyridine (py).
[b] Prepared by saponification of the foregoing compound.
[c] Preparation of 4-ene-3-oxo steroid starting material is described herein.
[d] Prepared from the foregoing compound by condensation with benzaldehyde
[e] Ref. 14 gives m.p. 176–180°, $[\alpha]_D$ −152°(1% pyridine in $CHCl_3$), λ_{max} 234 mμ (19,500)
[f] Ref. 15 gives m.p. 195–198°, $[\alpha]_D$ −135°(1% pyridine in $CHCl_3$), λ_{max} 239 mμ (21,000)
[g] Ref. 14 gives m.p. 192–194°, $[\alpha]_D$ −49·8° (1% pyridine in $CHCl_3$), λ_{max} 238 mμ (19,800)
[h] Ref. 14 gives m.p. 153–155°, $[\alpha]_D$ +3·6° (1% pyridine in $CHCl_3$), λ_{max} 240 mμ (19,700)

The 3-enol methyl ether of 11α-acetoxy testosterone acetate was obtained in an amorphous state and was characterised by its infrared spectrum which had bands at 1655 and 1630 cm^{-1}.

[14] M. Freifelder, *J. Org. Chem.* **27**, 4046 (1962).
[15] J. P. Dusza, J. P. Joseph and S. Bernstein, *J. Org. Chem.* **28**, 92 (1963).

TABLE 2

6-FORMYL 3-ENOL ETHERS



Parent compound	Method of prep.	R	M.p.	$[\alpha]_D$	λ_{max} (ε)	Formula	Analysis (%)			
							Found		Reqd.	
							C	H	C	H
Testosterone acetate	A,B	Me	160–162°	−153°(chf)	220(10,240) 320(14,930)	$C_{21}H_{28}O_4$	74·0	8·7	74·2	8·7
Testosterone acetate	A	Et	101-104°	−140°(chf)	220(10,710) 323(15,890)	$C_{24}H_{34}O_4$	74·5	8·8	74·6	8·9
Testosterone acetate	A	$C_6H_5CH_2$	199–201°	−143°(chf)	— 322(16,285)	$C_{29}H_{36}O_4$	77·4	7·8	77·6	8·1
Testosterone[a]	C	Me	105–110°	−144°(chf)	220(10,050) 322(15,100)	$C_{21}H_{30}O_2$	76·1	9·1	76·3	9·15
2α-Methyl testosterone acetate	A	Et	118–119°	−123(chf)	221(10,250) 323(15,250)	$C_{25}H_{36}O_4$	74·4	8·9	74·9	9·05
11α-Acetoxy testosterone acetate[b]	B	Me	196–199°	−231°(chf)	220(10,420) 320(14,460)	$C_{25}H_{34}O_6$	69·4	7·7	69·7	8·0
17α-Methyl testosterone acetate	A	Me	118–123°	−141°(di)	220(10,550) 322(15,690)	$C_{24}H_{34}O_4$	74·5	8·8	74·6	8·9
19-Nortesterone acetate[c]	A	Me	144–147°	−250°(chf)	220(9,895) 322(16,380)	$C_{22}H_{32}O_4$	73·6	8·5	73·7	8·45
Androst-4-ene-3,17-dione	A	Me	191–193°	−92°(chf)	220(10,380) 322(15,040)	$C_{21}H_{28}O_2$	76·8	8·6	76·8	8·6
Androst-4-ene-3,17-dione	A	$C_6H_5CH_2$	213–216°	−96°(chf)	— 322(16,140)	$C_{17}H_{22}O_2$	80·4	7·9	80·2	8·0
17α-Acetoxy progesterone	A,B	Me	218–223°	−158°(chf)	220(10,570) 320(14,930)	$C_{23}H_{32}O_4$	72·4	8·6	72·4	8·3

17α-Acetoxy-21-fluoro progesterone	A	Me	247–249°	−147°(di)	220(10,380) 322(14,580)	$C_{25}H_{33}FO_5$	68·8	7·6	69·4	7·6
17α-Acetoxy-16-methylene progesterone	A	Me	219–222°	−255°(di)	220(11,370) 321(16,540)	$C_{26}H_{34}O_5$	72·8	8·0	73·2	8·0
17α-Hydroxy-16-methylene progesterone[a]	A	Me	199–201°	−276°(chf)	— 322(14,835)	$C_{24}H_{32}O_4$	74·5	8·4	75·0	8·4
17α-Acetoxy-16-ethylidene progesterone	A	Me	203–204°	−255°(chf)	— 320(15,290)	$C_{27}H_{36}O_5$	74·0	8·25	73·6	8·25
17α-Acetoxy-16α-methyl progesterone	A	Me	220–222°	−132°(chf)	218(11,100) 320(15,000)	$C_{26}H_{36}O_5$	72·7	8·3	72·9	8·4
16β-Bromo-17α-hydroxy progesterone	C	Me	235–237°	−90°(chf)	220(10,840) 324(14,220)	$C_{23}H_{31}BrO_4$	61·5	6·8	61·2	6·9
16α,17α-Cyclomethylene progesterone	A	Me	205–207°	−53°(di)	215(12,600) 321(15,400)	$C_{24}H_{32}O_3$	78·0	8·6	78·2	8·7
16α,17α-Isopropylidenedioxy progesterone	A	Et	203–206°	−85°(chf)	220(11,510) 323(15,935)	$C_{27}H_{38}O_5$	73·7	8·8	73·3	8·65
21-Benzylidene-16α,17α-isopropylidenedioxy progesterone	A	Et	161–165°	−275°(chf)	224(18,790) 298(23,190)	$C_{34}H_{42}O_5$	77·0	8·1	76·95	8·0
16α,17α-Epoxy progesterone[a]	C	Me	173–176	−88°(chf)	217(12,080) 320(15,635)	$C_{23}H_{30}O_4$	74·6	8·1	74·6	8·2
20β-Acetoxypregn-4-en-3-one	A	Et	185–189°	−61°(chf)	223(10,820) 322(13,520)	$C_{25}H_{38}O_4$	75·7	9·3	75·3	9·25
21-Acetoxypregna-4,17(20)-diene-3,11-dione[a]	A	Me	80–91°	−108(chf)	— 320(14,000)	$C_{25}H_{32}O_5$	71·6	7·95	72·8	7·8
Pregna-4,17(20)-dien-3-one 21-oate ethyl ester	A	Et	146–147°	−165°(chf)	223(26,565) 323(14,750)	$C_{25}H_{36}O_4$	76·1	8·7	75·7	8·8
Desoxycorticosterone acetate	A	Me	128–130°	−60°(chf)	219(10,280) 320(15,420)	$C_{25}H_{34}O_5$	72·2	8·15	72·4	8·25
21-Acetoxy-17α-hydroxypregna-4,9(11)-diene-3,20-dione	C	Me	180–184°	−95°(chf)	220(12,100) 322(15,400)	$C_{25}H_{32}O_6$	69·7	7·4	70·1	7·5
Cortisone 21-acetate	C	Me	200–204°	−15°(chf)	218(10,890) 322(14,980)	$C_{25}H_{32}O_7$	67·0	7·1	67·6	7·3

TABLE 2 (Contd)

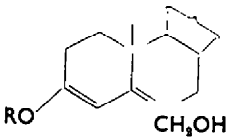
Parent compound	Method of prep.	R	M.p.	$[\alpha]_D$	λ_{max}	Formula	Analysis (%) Found C	Found H	Reqd C	Reqd H
Cortisone 21-acetate	C	Et	194–197°	−15°(chf)	218(11,320) 320(14,860)	$C_{26}H_{34}O_7 \cdot CH_3OH$	66·1	7·8	66·1	7·5
Cortisone 21-acetate[f]	C	CH_2— | CH_2OH	146–150°	−2°(chf)	219(10,500) 321(13,900)	$C_{26}H_{34}O_8 \cdot H_2O$	63·35	7·6	63·4	7·4
Cortisone 17α,21-diacetate	A	Me	203–206°	−74°(chf)	—	$C_{27}H_{34}O_8$	66·8	6·7	66·65	7·0
Cortisone 17α,20:20,21-bismethylenedioxy derivative	A	Et	212–215°	−154°(chf)	219(11,280) 321(15,680)	$C_{26}H_{34}O_7$	68·3	7·55	68·1	7·45
Cortisone 17α,21-methoxymethylenedioxy derivative	A	Me	185–190°	—	219(11,560) 322(14,500)	$C_{25}H_{32}O_7$	68·0	7·5	67·55	7·3
Cortisone 17α,21-isopropylidenedioxy derivative	A	Me	195–199°	−41°(chf)	219(12,830) 320(15,220)	$C_{26}H_{34}O_6$	70·3	7·6	70·6	7·7
3-(17β-Hydroxy-3-oxoandrost-4-en-17α-yl) propionic acid lactone	A	Et	199–201°	—	—	$C_{25}H_{34}O_4$	75·1	8·5	75·3	8·6

[a] The compound named was obtained after alkali treatment of the isolated reaction product.
[b] Prepared from an amorphous 3-enol ether precursor.
[c] 17β-Acetoxy-3-methoxyestra-2,5(10)-diene was employed as starting material.
[d] 16α,17α-Epoxy-16β-methyl progesterone 3-methyl enol ether was employed as starting material.
[e] The crystals were solvated: satisfactory analyses could not be obtained.
[f] The 3,3-ethylenedioxy derivative of cortisone acetate was employed as starting material.

The 6-formyl derivatives of the following enol ethers were obtained in an amorphous state, and were characterized from the UV absorption maxima at 220 and 320 mμ: progesterone 3-methyl enol ether, 17α-vinyl testosterone propionate, 17α-prop-1′-ynyl testosterone propionate, 20β-hydroxypregn-4-en-3-one, and diosgenone 3-ethyl enol ethers.

TABLE 3

6-HYDROXYMETHYL 3-ENOL ETHERS



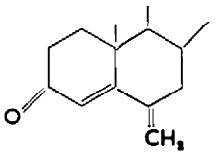
Parent compound	Method of prep.	R	M.p.	$[\alpha]_D$	$\lambda_{max}(\varepsilon)$	Formula	Analysis % Found C	Found H	Reqd. C	Reqd. H
Testosterone acetate	A,B,C.	Me	144–149°	−168°(di)	250(19,775)	$C_{23}H_{34}O_4$	73·5	9·2	73·8	9·15
Testosterone acetate	A	Et	114–119°	−163°(di)	251(20,050)	$C_{24}H_{36}O_4$	73·8	9·3	74·2	9·3
Testosterone acetate	A	$C_6H_5CH_2$	128–130°	−155°(di)	251(21,440)	$C_{29}H_{38}O_4$	77·6	8·5	77·3	8·5
Testosterone	A	Me	116–119°	−155°(di)	250(18,620)	$C_{21}H_{32}O_3$	75·45	9·8	75·9	9·7
2α-Methyl testosterone acetate	B	Et	140–141°	−138°(di)	252(19,730)	$C_{25}H_{38}O_4$	74·6	9·05	74·6	9·5
11α-Acetoxy testosterone acetate	B	Me	162–166°	−216°(di)	250(18,950)	$C_{25}H_{36}O_6$	68·9	8·3	69·4	8·4
17α-Methyl testosterone[a]	—	Me	109–111°	−142°(chf)	—	$C_{22}H_{34}O_2$	76·4	9·8	76·3	9·9
17α-Prop-1′-ynyl testosterone propionate[b]	B	Et	156–158°	−207°(chf)	251(17,315)	$C_{28}H_{40}O_4$	76·2	9·0	76·3	9·1
Androst-4-ene-3,17-dione	D	Me	143–146°	−111°(di)	249(19,000)	$C_{21}H_{30}O_2$	76·2	8·9	76·3	9·15
Progesterone[b]	C	Me	112–114°	−97°(di)	250(18,890)	$C_{23}H_{34}O_2$	76·8	10·3	77·05	9·55
17α-Acetoxyprogesterone	A	Me	197–201°	−137°(di)	250(19,660)	$C_{25}H_{36}O_5$	72·0	8·7	72·1	8·7
17α-Acetoxy-16-methylene progesterone	A	Me	171–173°	−252°(chf)	247(19,160)	$C_{26}H_{36}O_5$	72·5	8·3	72·8	8·4
17α-Acetoxy-16α-methyl progesterone	B	Me	202–204°	−147°(chf)	247(19,460)	$C_{26}H_{38}O_5$	72·3	9·0	72·5	8·8
16α,17α-Isopropylidenedioxy progesterone	B	Et	163–164°	−104°(di)	251(19,830)	$C_{27}H_{40}O_5$	72·8	9·3	72·9	9·1
20β-Acetoxypregn-4-en-3-one	B	Et	142–144°	−126°(di)	249(19,120)	$C_{26}H_4O_4$	75·3	9·55	74·95	9·7
Desoxycorticosterone acetate	D	Me	128–130°	−53°(chf)	249(18,280)	$C_{25}H_{36}O_5$	71·5	9·05	72·1	8·7
Cortisone 21-acetate	C,D.	Me	126–130°	0°(di)	249(15,900)	$C_{25}H_{34}O_7 \cdot \frac{1}{2}H_2O$	66·0	7·6	65·9	7·7
Cortisone 17α,20:20,21-bismethylenedioxy derivative	A	Et	201–203°	−175°(chf)	249(18,880)	$C_{26}H_{36}O_7$	67·2	7·8	67·8	7·9
Cortisone 17α,21-isopropylidenedioxy derivative	C,D	Me	174–180°	−45°(di)	248(17,000)	$C_{26}H_{36}O_6$	69·8	8·3	70·2	8·2

[a] Prepared by lithium aluminum hydride reduction of the 6-formyl derivative of 17α-methyl testosterone acetate enol ether.
[b] Prepared from an amorphous 6-formyl 3-enol ether precursor.

The 6-hydroxymethyl derivatives of the following enol ethers were obtained in the amorphous state, and were characterised from the UV absorption maxima at 250 mμ; 19-nortestosterone acetate, 17α-acetoxy-21-fluoroprogesterone, 17α-acetoxy-16-ethylidene progesterone, 16α,17α-cyclomethylene progesterone, 16α,17α-epoxy progesterone, cortisone-17α,21-diacetate 3-enol methyl ethers, 17α-vinyl testosterone propionate,[b] 21-benzylidene-16α,17α-isopropylidenedioxy progesterone, 20β-hydroxy pregn-4-en-3-one,[b] pregna-4,17(20)-dien-3-one 21-oate ethyl ester, and diosgenone 3-enolethyl ethers.[b]

TABLE 4

6-METHYLENE-4-EN-3-KETOSTEROIDS



Parent compound	M.p.	$[\alpha]_D$[a]	$\lambda_{max}(\varepsilon)$	Formula	Analysis(%) Found C	Found H	Reqd. C	Reqd. H
Testosterone acetate	139–141°	+266°	260(11,540)	$C_{23}H_{30}O_3$	77·1	8·7	77·15	8·8
Testosterone[b]	175°	+292°	259(11,000)	$C_{20}H_{28}O_2$	80·0	9·4	79·95	9·4
2α-Methyl testosterone acetate	179–181°	+243°	259(11,120)	$C_{23}H_{32}O_3$	77·7	9·15	77·5	9·05
17α-Methyl testosterone	140–145°	+245°	260(10,970)	$C_{21}H_{30}O_2$	80·5	9·6	80·2	9·6
17α-Methyl testosterone acetate[c]	129–130°	+219°(di)	260(11,800)	$C_{23}H_{32}O_3$	77·0	9·4	77·5	9·05
17α-Vinyl testosterone propionate[c]	129–130°	+261°	260(11,360)	$C_{25}H_{34}O_3$	78·3	8·9	78·5	9·0
17α-Prop-1′-ynyl testosterone propionate	141–142°	+161°	260(10,650)	$C_{26}H_{34}O_3$	79·2	8·7	79·15	8·7
19-Nortestosterone acetate[c]	*ca.* 150°	+186°	265(11,310)	$C_{21}H_{28}O_3$	76·3	8·6	76·8	8·6
Androst-4-ene-3,17-dione	163–165°	+387°	261(11,140)	$C_{20}H_{26}O_2$	80·7	8·6	80·5	8·8
Progesterone	133–135°	+373°	260(11,200)	$C_{21}H_{30}O_2$	80·7	9·15	80·95	9·25
17α-Acetoxy progesterone[d]	238–244°	+226°	260(13,960)	$C_{24}H_{32}O_4$	75·0	8·7	75·0	8·4
17α-Acetoxy-21-fluoroprogesterone	205–207°	+272°	260(10,770)	$C_{24}H_{31}FO_4$	71·3	8·0	71·6	7·7
17α-Acetoxy-16-methylene progesterone	223–225°	—	—	$C_{25}H_{32}O_4$	75·7	8·1	76·2	8·0
17α-Acetoxy-16-ethylidene progesterone[e]	194–198°	+105°	261(11,600)	$C_{26}H_{34}O_4$	76·4	8·25	76·1	8·35
16α,17α-Cyclomethylene progesterone[e]	168–169°	+362°	260(11,170)	$C_{22}H_{30}O_2$	81·8	8·7	81·6	8·9
16α,17α-Isopropylidenedioxy progesterone	225°	+253°	260(11,200)	$C_{25}H_{34}O_4$	74·7	8·7	75·3	8·6
21-Benzylidene-16α,17α-isopropylidenedioxy progesterone[e]	*ca* 315°	+37°(di)	299(18,490)	$C_{32}H_{38}O_4$	78·65	7·6	79·0	7·9
16α,17α-Epoxy progesterone[e]	185–187°	+305°	261(11,610)	$C_{22}H_{28}O_3$	78·0	8·6	77·6	8·3
20β-Acetoxypregn-4-en-3-one	176–178°	+274°	256(11,000)	$C_{24}H_{34}O_3$	77·4	9·3	77·8	9·25
20β-Hydroxypregn-4-en-3-one[e]	189–191°	+225°	257(11,070)	$C_{21}H_{32}O_2$	80·55	9·75	80·45	9·85
Pregna-4,17(20)-dien-3-one 21-oate ethyl ester[e]	161–162°	+251°	259(11,680)	$C_{24}H_{32}O_3$	78·4	8·7	78·2	8·75
Desoxycorticosterone acetate	114–115°	+306°	260(11,700)	$C_{23}H_{32}O_4$	71·1	8·55	74·9	8·4
Desoxycorticosterone[e]	145–147°	+329°	260(11,230)	$C_{21}H_{30}O_3$	76·8	8·75	77·15	8·85
Cortisone 21-acetate	191–193°	+355°	258(11,980)	$C_{23}H_{30}O_6$	69·1	7·2	69·5	7·3
Cortisone 17α,21-diacetate[e]	229–230°	+234°	257(10,910)	$C_{25}H_{32}O_7$	68·8	7·2	68·4	7·1
Cortisone 17α,20:20,21-bismethylenedioxy derivative	201–203°	+202°	259(11,480)	$C_{24}H_{30}O_6$	69·4	7·0	69·5	7·3
Diosgenone[e]	204–205°	+149°	260(11,310)	$C_{28}H_{40}O_3$	79·5	9·7	79·2	9·5

[a] Determined in chloroform solution unless otherwise indicated.
[b] Prepared by alcoholic mineral acid hydrolysis of the foregoing compound.
[c] Prepared from an amorphous 6-hydroxymethyl 3-enol ether precursor.
[d] U.S.Pat. 2,980,711 gives m.p. 248–251°, λ_{max} 262–263 mμ (ε11,650).
[e] Prepared from the foregoing compound by hydrolysis under nitrogen with aqueous alcoholic potassium hydrogen carbonate.

Preparation of 6-methylene-4-ene-3-ketosteroids

The 6-hydroxymethyl 3-enol ether (1 part) in 80% aqueous acetic acid (10 parts) was heated for 10–30 min at 85–100°. Addition of water gave a crystalline product which was purified from a suitable solvent. Alternatively, and in the absence of other hydrolysable groups, the 6-hydroxymethyl derivative (1 part) in methanol (10 parts) was treated with conc. HCl acid or 8N H_2SO_4 (0.2 parts) and the mixture stirred for 30 min at room temp. Yields were greater than 80% in favourable cases.

17α-*Vinyl testosterone propionate*, prepared by heating 17α-vinyl testosterone (5 g) in propionic anhydride (25 ml) and pyridine (25 ml) for 4 hr under reflux, crystallized from aqueous methanol, in needles, m.p. 126–127°, $[\alpha]_D^{24}$ +104° (*c*, 1·1 in $CHCl_3$). (Found: C, 77·6; H, 9·1. $C_{24}H_{34}O_3$ requires: C, 77·8; H, 9·2%).

17α-*Prop*-1′-*ynyl testosterone propionate*, prepared similarly, crystallized from aqueous methanol, in laths, m.p. 128–129°, $[\alpha]_D^{26}$ +9° (*c*, 1·0 in $CHCl_3$) (Found: C, 78·6; H, 9·0. $C_{25}H_{34}O_3$ requires: C, 78·5; H, 9·0%).

Oxime of 6-Formyl testosterone acetate 3-enol methyl ether, prepared by heating the 6-formyl derivative (10 g) and hydroxylamine hydrochloride in abs. ethanol (200 ml) and pyridine for 20 min under reflux crystallized from aqueous ethanol in prisms, m.p. 184–186°, $[\alpha]_D^{16}$ −204·5° (*c*, 0·78 in $CHCl_3$.) λ_{max} 216–218 (ε, 8,870) and 293 mμ (ε, 21,580), ν_{max} (in CCl_4) 3591, 1739, 1634 cm^{-1} (Found: C, 71·2; H, 8·6; N, 3·4. $C_{23}H_{33}NO_4$ requires: C, 71·3; H, 8·6; N, 3·6%).

6β-*Methyl testerone acetate*. 6-Methylene testosterone acetate (2 g) in methanol (70 ml) was hydrogenated in the presence of a pre-hydrogenated 2% Pd—C catalyst (0·1 g). The reaction was stopped when one equivalent proportion of hydrogen had been absorbed, the catalyst was removed, and the product isolated with ether. Crystallization from aqueous methanol gave 6β-methyl testosterone acetate, m.p. 154–156°, not depressed in admixture with an authentic specimen.[13]

21-*Acetoxy-6-formyl-3-methoxypregna*-3,5-*dien*-20-*one*. 21-Acetoxy-3-ethoxypregna-3,5-dien-20-one was formylated using procedure A. The crude product m.p. 100–106°, was recrystallized from methanol to give 21-acetoxy-6-formyl-3-methoxypregna-3,5-dien-20-one, m.p. 128–130°, identical with an authentic sample prepared from 21-acetoxy-3-methoxypregna-3,5-dien-20-one. The nature of the ether grouping in the crude and final products was clearly demonstrated by NMR spectra.