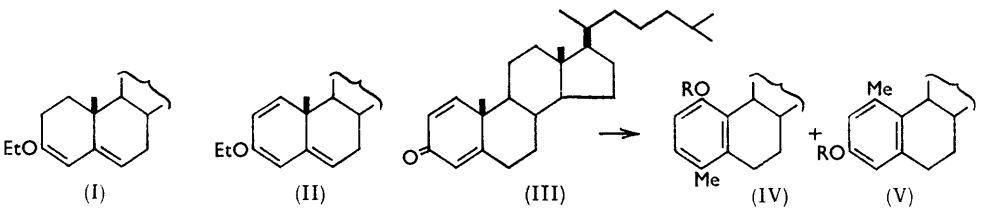
892. *Compounds Related to the Steroid Hormones. Part III.*[1] *Phenolic Ethers from the Dienone–Phenol Rearrangement of* $\Delta^{1,4}$*-3-Oxo-Steroids.*

By J. Elks, J. F. Oughton, and L. Stephenson.

Cholesta-1,4-dien-3-one is converted by a mixture of an alcohol, ethyl orthoformate, and sulphuric acid into the 1-alkoxy-4-methyl-19-norcholesta-1,3,5(10)-triene and, in smaller amount, the 3-alkoxy-1-methyl-19-norcholesta-1,3,5(10)-triene.

The acid-catalysed reaction of ethyl orthoformate with saturated 3-oxo-steroids gives diethyl ketals, which can be converted by pyrolysis into enol ethers;[2a] under similar conditions, Δ^4-3-oxo-compounds yield the enol ethers (I) directly.[2] We hoped that a $\Delta^{1,4}$-3-ketone might give the analogous 3-ethoxy-$\Delta^{1,3,5}$-compound (II), but neither prednisone acetate (21-acetoxy-17-hydroxypregna-1,4-diene-3,11,20-trione) nor cholesta-1,4-dien-3-one (III) was affected by treatment with ethyl orthoformate and sulphuric acid in dioxan under conditions known to convert Δ^4-3-ketones into their enol ethers.[2b] However, if the dioxan was replaced by ethanol, cholesta-1,4-dien-3-one yielded an oil showing neither the absorption maximum at 242 mμ of the starting material nor that at ~300 mμ which would be expected of a compound of type (II). Chromatography on alumina split the material into two fractions, neither of them crystalline; the ultraviolet spectrum of each showed a weak band at ~280 mμ, but in the infrared the major fraction showed a strong band at 794 cm.$^{-1}$, whereas the minor fraction showed a band at 852 cm.$^{-1}$. The infrared



(I) (II) (III) (IV) (V)

spectrum of each compound also showed bands attributable to an ether, although the major product was not cleaved under the conditions of the Zeisel alkoxyl determination, and the other gave a very low value.

Acid-catalysed aromatisation of steroid $\Delta^{1,4}$-3-ketones is known to proceed by two paths; under the conditions most commonly used (*i.e.*, a strong-acid catalyst in an acid anhydride), the sole product is the 1-acyloxy-4-methyl-compound [3] (*i.e.*, type IV) * unless the steroid also contains a 6,7-double bond, when the 3-acyloxy-1-methyl-compound (type V) results [4] (see also following paper). However, treatment of androsta-1,4-diene-3,17-dione with concentrated aqueous hydrogen bromide or hydrogen chloride gives a mixture of the "*para*"-phenol (cf. IV; R = H) and the "*meta*"-phenol (cf. V; R = H), in which the latter predominates.[5] It seemed probable that our reaction was giving a mixture of the two types of phenol, as their ethyl ethers, since the absorption of the two products in the 800—850 cm.$^{-1}$ region was consistent with the major and minor products'

* The earlier literature incorrectly ascribes the 3-acyloxy-1-methyl-structure (V) to such compounds.

[1] Part II, Green and Long, *J.*, 1961, 2532.

[2] (*a*) Fieser and Fieser, "Steroids," Reinhold Publ. Corp., New York, 1959, p. 310; (*b*) Meystre and Miescher, *Helv. Chim. Acta*, 1949, **32**, 1758; Sarett, Feurer, and Folkers, *J. Amer. Chem. Soc.*, 1951 **73**, 1777; Julian, Meyer, Karpel, and Cole, *ibid.*, p. 1982; Engel and Just, *ibid.*, 1954, **76**, 4909; Patel, Petrow, Royer, and Stuart-Webb, *J.*, 1952, 161.

[3] Woodward and Singh, *J. Amer. Chem. Soc.*, 1950, **72**, 494; Woodward, Inhoffen, Larson, and Menzel, *Chem. Ber.*, 1953, **86**, 594; Dreiding and Voltman, *J. Amer. Chem. Soc.*, 1954, **76**, 537.

[4] Djerassi, Rosenkranz, Romo, Pataki, and Kaufmann, *J. Amer. Chem. Soc.*, 1950, **72**, 4540; Dreiding and Pummer, *ibid.*, 1953, **75**, 3162.

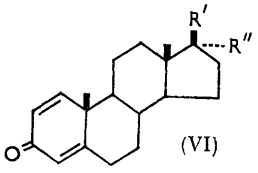
[5] Dreiding, Pummer, and Tomasewski, *J. Amer. Chem. Soc.*, 1953, **75**, 3159.

being 1-ethoxy-4-methyl- (IV; R = Et) and 3-ethoxy-1-methyl-19-norcholesta-1,3,5(10)-triene (V; R = Et), respectively.[5,6] Since the "*para*-compound" (IV; R = Et) could not readily be converted into the known 4-methyl-19-norcholesta-1,3,5(10)-trien-1-ol [7] (IV; R = H) (see above), this phenol was treated with diethyl sulphate, to give its ethyl ether (IV; R = Et), whose spectra and rotation were identical with those of the major product of our ethyl orthoformate reaction. The structure of the isomer (V; R = Et) rests upon its infrared spectrum and rotation (see below).

In the same way, treatment of cholesta-1,4-dien-3-one (III) with ethyl orthoformate and sulphuric acid in methanol gave as the major product the known 1-methoxy-4-methyl-19-norcholesta-1,3,5(10)-triene (IV; R = Me);[7] the minor one is assigned the "*meta*"-structure (V; R = Me) on reasoning similar to that applied to the ethoxy-compound.

A method that has commonly been used to protect saturated 3-oxo- and Δ^4-3-oxo-steroids involves their conversion into the cyclic ethylene ketals, the double bond in the latter compounds moving to the 5,6-position. When cholesta-1,4-dien-3-one (III) was treated with toluene-*p*-sulphonic acid in ethylene glycol at *ca.* 100° under reduced pressure,[8] the product was again seen from its infrared and ultraviolet spectra to have been aromatised. Chromatography yielded two fractions whose analyses, rotations, and spectra were consistent with their being the hydroxyethoxy-compounds (IV and V; R = $HO{\cdot}CH_2{\cdot}CH_2$). A similar mixture resulted from treatment of the dienone (III) with ethyl orthoformate and sulphuric acid in ethylene glycol at 100° at atmospheric pressure; in the absence of ethyl orthoformate the dienone was unaffected.

In the Table are shown the changes in molecular rotation accompanying the conversion of $\Delta^{1,4}$-3-ketones into known 3-methoxy-1-methyl- and 1-methoxy-4-methyl-$\Delta^{1,3,5}$-compounds; the values for the two types are distinct. The corresponding values for the ethers described in this paper, given in the lower half of the Table [where formulæ (VI) are as inset here], are in good agreement, thus supporting the structures proposed.



(VI)

Two groups of workers [9] have reported their failure to prepare ketals from $\Delta^{1,4}$-3-ketones but they apparently did not observe aromatisation of ring-A under their conditions. Against this, Hogg and his co-workers have referred in a note [10] and in patents [11] to the protection of the $\Delta^{1,4}$-3-oxo-grouping of methyl 3,11-dioxopregna-1,4,17(20)-trien-21-oate as its cyclic ethylene ketal; however, the lack of detail in these publications makes it difficult to comment upon them.

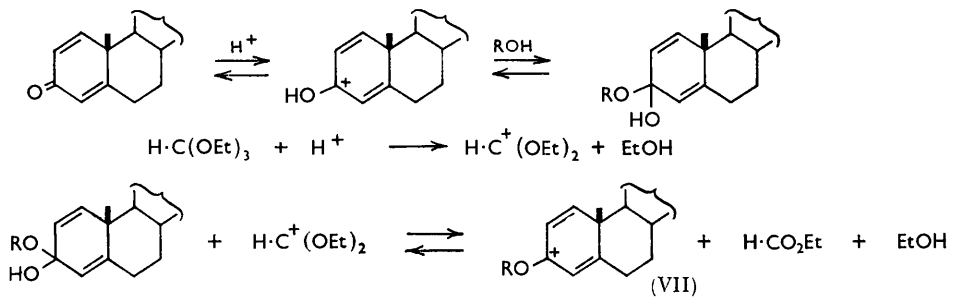
			(VI)	(V)		(IV)	
R *	R'	R''	$[M]_D$	$[M]_D$	$\Delta[M]_D$	$[M]_D$	$\Delta[M]_D$
Me	C_8H_{17}	H	+115° [a]			+713° [b]	+598°
Me	:O		+338 [a]	+710° [c]	+372°	+885 [a]	+547
Me	COMe	H	+374 [d]	+678 [e]	+304		
Me	COMe	OH	+126 [a]	+404 [e]	+278		
Me	$CO{\cdot}CH_2{\cdot}OAc$	H	+495 [f]			+1060	+565
Me	C_8H_{17}	H	+115 [a]	+448	+333		
Et	C_8H_{17}	H	+115 [a]	+451	+336	+710	+595
$HO{\cdot}CH_2{\cdot}CH_2{\cdot}$	C_8H_{17}	H	+115 [a]	+490	+375	+670	+555

[a] Petit and Mathieu, "Pouvoir Rotatoire Naturel, I. Steroïdes," Masson et Cie., Paris, 1956. [b] This paper. [c] Ringold, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 2477. [d] Sondheimer, Velasco, and Rosenkranz, *J. Amer. Chem. Soc.*, 1955, **77**, 5673. [e] Djerassi, Lippman, and Grossman, *J. Amer. Chem. Soc.*, 1956, **78**, 2479. [f] Vischer, Meystre, and Wettstein, *Helv. Chim. Acta*, 1955, **38**, 835. [g] Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1949, **71**, 3962.

* R is, of course, present only in (IV) and (V), not in (VI).

[6] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 2nd edn., pp. 75—79.
[7] Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1712.
[8] Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529; Allen, Bernstein, and Littell, *J. Amer. Chem. Soc.*, 1954, **76**, 6116.
[9] Sondheimer, Velasco, and Rosenkranz, *J. Amer. Chem. Soc.*, 1955, **77**, 5673; Gentles, Moss, Herzog, and Hershberg, *ibid.*, 1958, **80**, 3702.
[10] Hogg, Lincoln, Nathan, Hanze, Schneider, Beal, and Korman, *J. Amer. Chem. Soc.*, 1955, **77**, 4438.
[11] U.S.P. 2,873,271, 2,873,285; B.P. 799,493.

The aromatisation is of some interest in being, we believe, the first example of the direct preparation of phenol ethers by the dienone–phenol rearrangement. As to mechanism, one may invoke a modification of that proposed by MacKenzie and Stocker [12] to explain ketalisation with ethyl orthoformate and an alcohol. The ion (VII), rather than reacting with another molecule of alcohol to give the ketal, or losing a proton to give the enol ether, undergoes the well-understood rearrangement of such ions (in which R = H or acyl) to give the aromatic compounds that we have found.[3,5,13] We, like MacKenzie and Stocker, found (except in the one instance discussed below) that both the alcohol and the orthoformate were required and also that the alkoxy-group in the product was that of the dominant alcohol rather than that associated with the orthoformate molecule.



The instance when no ethyl orthoformate was required was special, in that the reaction was carried out under conditions in which water would have been removed as it was formed; the modification (shown below) to the above scheme can reasonably be advanced to deal with this reaction.

Experimental

Rotations and ultraviolet spectra were measured for solutions in chloroform and ethanol, respectively. Infrared spectra were determined in a Perkin–Elmer model 21 spectrophotometer with rock-salt optics. In this and later Parts, assignment of infrared peaks to "*meta*-type" refers to formulæ of type (V) and to "*para*-type" refers to formulæ of type (IV).

1-*Ethoxy*-4-*methyl*- (IV; R = Et) *and* 3-*Ethoxy*-1-*methyl*-19-*norcholesta*-1,3,5(10)-*triene* (V; R = Et).—Cholesta-1,4-dien-3-one (1·0 g.), absolute ethanol (40 ml.), ethyl orthoformate (10 ml.), and concentrated sulphuric acid (0·14 ml.) were boiled together under reflux for 1 hr. The dark red solution was cooled and poured into an excess of aqueous sodium hydrogen carbonate, and the mixture was extracted with ether. The extract was washed, dried ($MgSO_4$), and evaporated under reduced pressure to afford a yellow oil (1·18 g.), $\lambda_{max.}$ 277 mμ ($E^{1\%}_{1\,cm.}$ 46·5). This product was chromatographed on alumina (40 g.) made up in light petroleum (b. p. 40—60°). The first petroleum eluates afforded 1-*ethoxy*-4-*methyl*-19-*norcholesta*-1,3,5(10)-*triene* as a colourless oil (0·60 g., 56%), resistant to crystallisation, having $[\alpha]_D$ +169·5° (*c* 0·7), $\lambda_{max.}$ 277—286 mμ ($E^{1\%}_{1\,cm.}$ 45·2), $\nu_{max.}$ (in CS_2) 1240, 1114, and 1068 (aromatic ether), and 794 $cm.^{-1}$ (*para*-type) (the infrared spectrum resembled that of the authentic material described below) (Found: C, 84·6; H, 11·3; OEt, 0. $C_{29}H_{46}O$ requires C, 84·8; H, 11·3; OEt, 11·0%).

Light petroleum–benzene (9 : 1) eluted 3-*ethoxy*-1-*methyl*-19-*norcholesta*-1,3,5(10)-*triene* as a colourless oil (0·148 g., 14%), resistant to crystallisation, having $[\alpha]_D$ +110° (*c* 0·4), $\lambda_{max.}$ 277—286 mμ ($E^{1\%}_{1\,cm.}$ 51·9), $\nu_{max.}$ (in CS_2) 1300, 1154, and 1054 (aromatic ether), and 852 $cm.^{-1}$ (*meta*-type) (Found: C, 84·2; H, 11·2; OEt, 2·0%).

[12] MacKenzie and Stocker, *J. Org. Chem.*, 1955, **20**, 1695.
[13] Woodward, "Perspectives in Organic Chemistry," ed. Sir Alexander Todd, Interscience Publishers Inc., London, 1956, p. 178.

Preparation of 1-*Ethoxy*-4-*methyl*-19-*norcholesta*-1,3,5(10)-*triene* (IV; R = Et) *from the Corresponding Phenol.*—4-Methyl-19-norcholesta-1,3,5(10)-trien-1-ol [7] (4·4 g.) in ethanol (17 ml.) was warmed and treated alternately with aqueous sodium hydroxide (38% w/w; 1·8 ml.) and diethyl sulphate (2·5 ml.), four additions of each being made. The mixture was set aside for 15 min., water was added, and the mixture was extracted with ether. The extract was washed, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The oily product (0·51 g.) was dissolved in light petroleum (b. p. 40—60°) and filtered through alumina (10 g.); evaporation of the eluate gave 1-ethoxy-4-methyl-19-norcholesta-1,3,5(10)-triene as a colourless oil (0·36 g.), $[\alpha]_D$ +173° (*c* 1·0), $\lambda_{max.}$ 278—285 mμ ($E^{1\%}_{1cm.}$ 43·6) (Found: C, 84·8; H, 11·1; OEt, 0%).

1-*Methoxy*-4-*methyl*- (IV; R = Me) *and* 3-*Methoxy*-1-*methyl*-19-*norcholesta*-1,3,5(10)-*triene* (V; R = Me).—Cholesta-1,4-dien-3-one (1·0 g.), anhydrous methanol (40 ml.), ethyl orthoformate (10 ml.), and concentrated sulphuric acid (0·14 ml.) were boiled together under reflux for 1½ hr. The product was worked up as above to yield a yellow oil (1·09 g.) which was chromatographed on alumina (40 g.). The early petroleum fractions, on crystallisation from methanol, gave 1-methoxy-4-methyl-19-norcholesta-1,3,5(10)-triene (0·58 g., 56%), m. p. 99—100°, $[\alpha]_D$ +180° (*c* 1·0), $\lambda_{max.}$ 278—285 mμ ($E^{1\%}_{1cm.}$ 48·5), $\nu_{max.}$ (in CS_2) 1242 and 1080 (aromatic ether) and 795 cm.$^{-1}$ (*para*-type) (Found: C, 84·7; H, 11·2; OMe, 0. Calc. for $C_{28}H_{44}O$: C, 84·8; H, 11·2; OMe, 7·8%).

An authentic specimen of 1-methoxy-4-methyl-19-norcholesta-1,3,5(10)-triene, prepared by the method of Wilds and Djerassi,[7] had m. p. 104—105°, $[\alpha]_D$ +180° (*c* 1·0) (Found: C, 84·5; H, 11·2; OMe, 0%). Wilds and Djerassi [7] give m. p. 104·5—105°, $[\alpha]_D$ +165°. Its infrared spectrum resembled that of material prepared as described above

Light petroleum–benzene (9 : 1) eluted 3-methoxy-1-methyl-19-norcholesta-1,3,5(10)-triene as a colourless oil, resistant to crystallisation, having $[\alpha]_D$ +113° (*c* 0·6), $\lambda_{max.}$ 279 mμ ($E^{1\%}_{1cm.}$ 45), $\nu_{max.}$ (in CS_2) 1300, 1145, and 1060 (aromatic ether), and 852 cm.$^{-1}$ (*meta*-type).

Treatment of Cholesta-1,4-*dien*-3-*one with Ethylene Glycol.*—Cholesta-1,4-dien-3-one (1·0 g.), ethylene glycol (40 ml.), and toluene-*p*-sulphonic acid (4 mg.) were boiled together under reflux at 20 mm. pressure for 20 hr. The cooled product was poured into aqueous sodium hydrogen carbonate, and the mixture was extracted with ether. The extract was washed, dried ($MgSO_4$), and evaporated and the residual oil (1·1 g.) was chromatographed on alumina (50 g.). Ether eluted 1-2′-*hydroxyethoxy*-4-*methyl*-19-*norcholesta*-1,3,5(10)-*triene* (0·76 g.) which, after treatment with charcoal, gave a colourless oil, $[\alpha]_D$ +157° (*c* 1·0), $\lambda_{max.}$ 278—285 mμ ($E^{1\%}_{1cm.}$ 44), $\nu_{max.}$ (in CS_2) 3620 and 1052 (OH), 1236 and 1080 (aromatic ether), and 794 cm.$^{-1}$ (*para*-type) (Found: C, 81·45; H, 11·2. $C_{29}H_{46}O_2$ requires C, 81·6; H, 10·9%). Chloroform eluted 3-2′-*hydroxyethoxy*-1-*methyl*-19-*norcholesta*-1,3,5(10)-*triene* as an oil (0·18 g.), $[\alpha]_D$ +115° (*c* 0·8), $\lambda_{max.}$ 278—285 mμ ($E^{1\%}_{1cm.}$ 34), $\nu_{max.}$ (in CS_2) 3620 and 1050 (OH), 1300, 1150, and 1050 (aromatic ether), and 850 cm.$^{-1}$ (*meta*-type) (Found: C, 81·2; H, 11·0%).

Treatment of Cholesta-1,4-*dien*-3-*one with Ethylene Glycol and Ethyl Orthoformate.*—A mixture of cholesta-1,4-dien-3-one (0·1 g.), ethylene glycol (3 ml.), ethyl orthoformate (1 ml.), and concentrated sulphuric acid (0·015 ml.) was heated at 100° for 1 hr. The cooled solution was worked up as above to give an oil (0·11 g.), $\lambda_{max.}$ 278—285 mμ ($E^{1\%}_{1cm.}$ 39), whose infrared spectrum was similar to that of the mixture obtained as described above.

Repetition of this experiment, but with the omission of ethyl orthoformate, gave unchanged cholesta-1,4-dien-3-one.

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