Ready Formation of Enol Ethers in Steroidal 20β-Hydroxy-18-methyl-18-ketones

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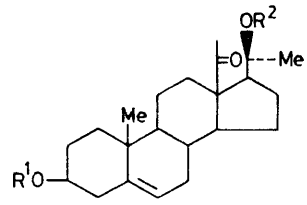
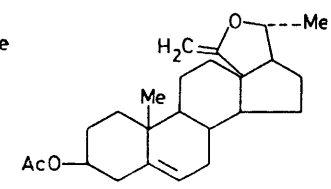
Summary Treatment of 20β-hydroxy-18-methyl-18-oxo-steroids with silica formed the stable enol ethers, while reaction with lead tetra-acetate formed the stable acetoxylated enol ethers instead of the expected α-acetoxy-ketones.

As part of a programme to prepare 18-substituted steroids related to the natural mineralcorticoids, we have prepared a series of compounds containing the 20β-hydroxy and 18-methyl-18-ketone side chains. Reaction of the 18→20 lactone, derived from pregnenolone acetate,[1] with MeMgBr gave 18-methyl-18-oxopregn-5-en-20β-ol (**1**).[2] Acetylation gave a mixture of the 3-mono-acetate (**2**) and the 3,20β-diacetate (**3**).† These compounds exist in the open hydroxy-ketone form, as shown by a strong carbonyl i.r. absorption for the 18-ketone between 1695 and 1705 cm^{-1}, and the absence of additional signals in the n.m.r. spectrum for the epimers of the hemi-acetal. When (**2**) was chromatographed on silica, it was converted in 70% yield into the enol ether (**4**), m.p. 139—141·5 °C, which could be slowly converted back into (**2**) by aqueous toluene-*p*-sulphonic acid.

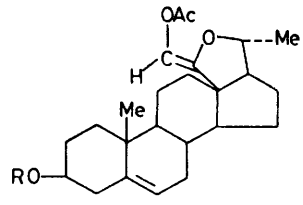
Although the hydroxy-ketone groups in these steroids do not exist in the hemi-acetal form, the ready formation of (**4**) suggested that the reaction developed by Kirk for the conversion of the hemi-acetal of 18-hydroxyprogesterone into 18-hydroxydeoxycorticosterone acetate would be applicable to this steroid system.[3] Reaction of either (**2**) or its enol ether (**4**), with excess of lead tetra-acetate in acetic acid, followed by quenching with glycerine and dilution with water, gave a new product (**5**), m.p. 192—203 °C, in 90—92% yield which was, however, not the expected α-acetoxyketone but its enol ether. The enol ether (**5**) showed two different carbonyl groups at 1740 and 1730 cm^{-1}, and a sharp 1H singlet at δ 6·70 for the vinyl enol hydrogen. The (*Z*)-configuration was assigned based on molecular models, which demonstrated severe steric interactions between the acetoxy-group and the 19-methyl and the axial hydrogens at C-6, -8, and -11 in the (*E*)-isomer while the (*Z*)-isomer was sterically unencumbered. A similar reaction with (**1**) yielded (**6**), m.p. 163—165·5 °C, in 77% yield, while treatment of the 3-keto-4-ene derivative of (**1**) furnished (**7**), m.p. 166·5—172·5 °C, in 79% yield. These acetoxylated enol ethers are remarkably stable compounds, being inert to silica gel chromatography and were recovered unchanged after attempted hydrolysis for 8 h with excess of toluene-*p*-sulphonic acid.



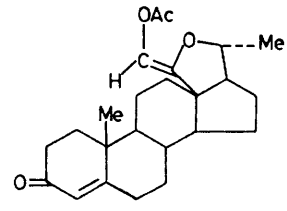
(1) $R^1 = R^2 = H$
(2) $R^1 = Ac, R^2 = H$
(3) $R^1 = R^2 = Ac$



(4)



(5) R = Ac
(6) R = H



(7)

The apparent reason for the isolation of enol ethers in these steroids is steric. The 18-methyl group attached to a trigonal carbon atom in the 18-ketones and as part of enol vinyl groups is relatively unencumbered by the remainder of the steroid. However, in the tetrahedral hemi-acetal form, which is an intermediate in the acetoxylation reaction, severe steric interactions occur between the 18-methyl group, in either the (*R*)- or (*S*)-configuration, and the 10-methyl group and the axial protons at C-8, -11, and -15; resulting in elimination to the enol ether. These same steric interactions are the reason that the 20β-hydroxy-18-methyl-18-one system does not exist in the hemi-acetal form as does 18-hydroxyprogesterone. Polarization of the 18-ketone *via* protonation or complexation causes addition of the hydroxy-group and subsequent enol ether formation as in the formation of (**4**) from (**2**).

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† All new compounds described gave appropriate microanalytical and spectral (i.r., u.v., n.m.r., and mass) data.

[1] K. Heusler, P. Wieland, and Ch. Meystre, *Org. Synth.*, 1973, Coll. Vol. V, 692.
[2] G. V. Baddeley, H. Carpio, and J. A. Edwards, *J. Org. Chem.*, 1966, **31**, 1026; V. Černý, A. Kasal, and F. Šorm, *Coll. Czech. Chem.*