THE LACK OF ALLYLIC OXIDATION IN THE MOFFATT OXIDATION. PREPARATION OF 5α-LANOST-8-EN-3-ONE.

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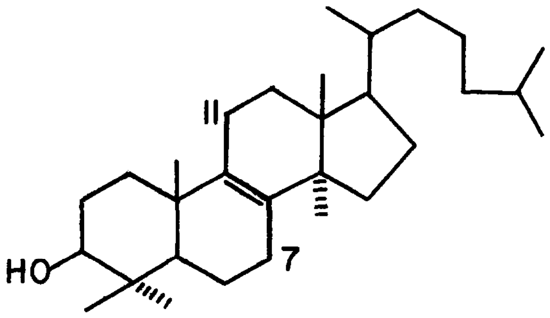
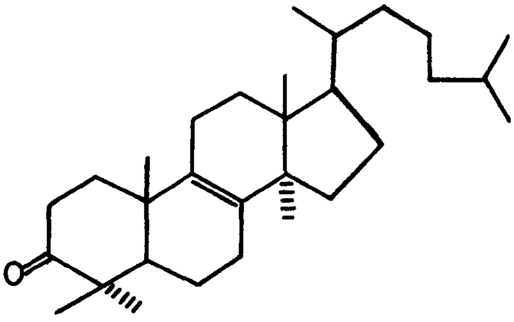
Abstract

The Moffatt oxidation (dimethyl sulfoxide-dicyclohexylcarbodiimide) is successful in oxidizing 5α-lanost-8-en-3β-ol (I) to 5α-lanost-8-en-3-one (II) without any detectable trace of the usual competing allylic oxidation products.

In connection with studies on the stereoselectivity of reduction of cyclic ketones (1,2,3) we have needed to prepare 5α-lanost-8-en-3-one (II), and it has been particularly important to our work that we could achieve the simple oxidation of 5α-lanost-8-en-3β-ol (dihydrolanosterol) (I) to 5α-lanost-8-en-3-one (II), without the concomitant allylic oxidation at the 7 and 11 positions.



I



II

Allylic oxidation contamination has long been a problem in steroid oxidations of this type, especially in the widely-studied cholesterol series (4,5). The conditions generally used for the oxidation at hand (I→II) are those of the Jones oxidation, using chromium trioxide in acetone (6). We have repeatedly tried these conditions and, even using very short reaction times, have found it impossible to obtain a product entirely free from conjugated ketones. Although the reaction certainly gives mainly the desired ketone II in good yield and in a degree of purity quite satisfactory for most purposes, even a 0.05% impurity of compounds with α,β-unsaturated carbonyl chromophores vitiates any experiments, like ours (2), which depend upon examination of the weak n,π* absorption of ketone II. The best we have achieved with the chromic acid method is ~95%, and we have not been able to raise this to the desired 99.99% by chromatography and repeated crystallizations. It is relevant to point out that variation of the reaction conditions can give extensive allylic oxidation and, indeed, chromium trioxide has been used to deliberately introduce oxygen at the 7 and 11 positions (7,8,9).

We have, therefore, considered other methods of oxidation of I in order to eliminate this problem of competing allylic oxidation. We wish to report that the Moffatt oxidation (dimethyl sulfoxide-dicyclohexylcarbodiimide) (10), which has been shown to be a mild and specific method of oxidizing alcohols to aldehydes without overoxidation to the carboxylic acid (10), and of oxidizing β,γ-unsaturated alcohols to the corresponding ketones without double bond isomerization (11), is also highly successful in the present situation. Oxidation of I to II can be accomplished in 90% yield with no trace of conjugated ketone detectable by glc or UV spectroscopy. This implies that the upper limit to which 7- and/or 11- ketones are present is 0.01%.

Experimental

To a solution of 5α-lanost-8-en-3β-ol (1.04 g, 2.3 mmol) in benzene (50 ml) were added a solution of dicyclohexylcarbodiimide (1.50 g, 7.3 mmol) in dimethyl sulfoxide (10 ml), and pyridinium trifluoroacetate (225 mg, 1.1 mmol). The reaction mixture was maintained at 35° for 50 hr. Ether (75 ml) was added, followed by solid oxalic acid (1.0 g, 11.1 mmol), and the mixture was stirred overnight, filtered, washed with water (3 X 20 ml), dried (Na_2SO_4), and evaporated (12). The residue was taken up in methanol (500 ml) and again stirred with oxalic acid (1.0 g) overnight. The mixture was evaporated, dissolved in ether (75 ml), washed with water (3 X 10 ml), dried (Na_2SO_4), and evaporated to yield 5α-lanost-8-en-3-one (0.94 g, 94%). Glc analysis (OV 210, 250°) of the product indicated the only impurity to be 5α-lanost-8-en-3β-ol (4%). Final purification was achieved by chromatography on alumina (Woelm neutral, Activity III), the product being eluted with 10% ether in benzene, and recrystallizations from ether-ethanol, giving plates with mp 118-119°, $\nu_{max}(CHCl_3)$ 1700 cm^{-1}, $\lambda_{max}(EtOH)$ 295 nm (ε, 24). (Lit. (13) m.p. 119.5-120.5°).

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12. The oxalic acid removes the dicyclohexylcarbodiimide most effectively when in methanol solution. However, if methanol is added in the first work-up, difficulty is experienced removing dimethyl sulfoxide. Thus the first work-up removes all dimethyl sulfoxide and most dicyclohexylcarbodiimide; the second work-up removes the remaining dicyclohexylcarbodiimide.
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