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A NEW HYDROXYLATION ROUTE: INTRODUCTION OF THE TRIMETHYLSILYLOXY GROUP

G. M. Maume (1) and E. C. Horning

Institute for Lipid Research, Baylor University College of Medicine, Houston, Texas 77025

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The reaction of lead tetraacetate with an enol acetate leads to the formation of the acetate of an α-hydroxy ketone. This method was used by Nambara and Fishman (2) for the synthesis of the diacetate of 5α-androstan-3β,16α-diol-17-one. The reaction presumably involves an acetoxy free radical as the reacting species.

In the course of a study of enol trimethylsilyl (TMSi) ethers (3), an analogous oxidative reaction was discovered. This reaction has been studied for two ketosteroids. The mechanism presumably involves a trimethylsilyloxy free radical which is generated in the reaction mixture, and which reacts with the enol TMSi ether to form the trimethylsilyl derivative of an α-hydroxy ketone. Ultraviolet light and benzoyl peroxide may be used as catalysts. When benzoyl peroxide is present, a small amount of an α-benzoyloxy ketone is formed as a by-product, apparently through the same type of reaction. Since TMSi ethers may be hydrolyzed easily to the parent compounds, this reaction may be regarded as equivalent to a hydroxylation reaction, and it may be particularly useful in the steroid field.

The experimental work was carried out in the following way. 5-Androsten-3β-ol-17-one (I) and 5-androsten-3β,17β-diol-16-one (II) were converted to enol TMSi ethers by heating at 90° C with a mixture of N-trimethylsilylimidazole, bis-trimethylsilylacetamide and trimethylchlorosilane (3). Portions of the reaction mixtures were then exposed to three reaction conditions: (a) heating with benzoyl peroxide (1:1 w/w with respect to the steroid) at 60° C for 24 hr, (b) exposure to ultraviolet light (quartz cell, mercury lamp) for 24 hr with the addition of benzoyl peroxide (1:1 w/w), and (c) exposure to ultraviolet light (quartz cell, mercury lamp) for 24 hr. An internal standard was added, and a GLC analysis of the reaction mixture was carried out. The results are in Table 1.

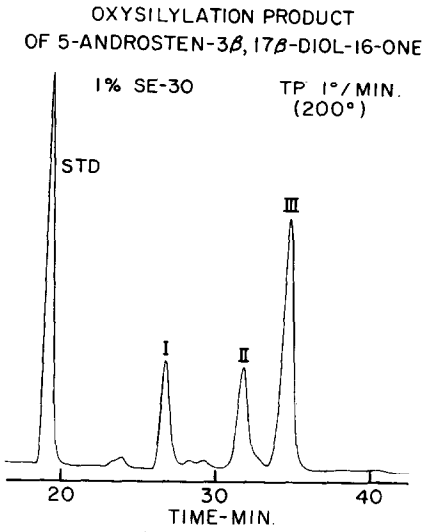
TABLE I

Effect of Reaction Conditions upon Yield

Compound	Conditions A	B	C
I	5%-TMSi 4%-Benz	18%-TMSi 3%-Benz	10%-TMSi ----
II	27%-TMSi 15%-Benz	60%-TMSi 5%-Benz	60%-TMSi -----

Condition A: Silylation mixture + benzoyl peroxide, 60° C.
Condition B: Silylation mixture + benzoyl peroxide, UV light.
Condition C: Silylation mixture, UV light.

The chief reaction product from I was the TMSi ether of 5-androsten-3β, 16α-diol-17-one. The structure was established by comparison of gas-liquid chromatographic (GLC) properties and mass spectra (LKB Model 9000 mass spectrometer) for an authentic sample of the steroid TMSi ether. While the mass spectra for the 16α- and 16β-isomers would be expected to be almost identical, the MU values (4) (SE-30, OV-17 and OV-22 columns, Table 2) of the two stereoisomers would be different. A corresponding product was obtained in higher yield



from II; by analogy this has been assigned the structure 5-androsten-3β, 15α, 17β-triol-16-one. The GLC properties of the TMSi ether (formed as the reaction product) are in Table 2. The Figure shows a GLC analysis of a reaction mixture containing 5-androsten-3β, 17β-diol-16-one (I), the enol ether (II), the reaction product 5-androsten-3β, 15α, 17β-tritrimethylsilyloxy-16-one (III), and an internal standard (hexacosane, STD). The separation was carried out with a 12 ft 1% SE-30 column and with temperature programming at the rate of 1^{o}/min from 200^{o} C.

TABLE 2

Methylene Unit (MU) Values for Reaction Products

Compound	SE-30	OV-17	OV-22
5-Androsten-3β, 16α-diol-17-one			
3β, 16α-ditrimethylsilyloxy	27.14*	29.18	29.55
3β-trimethylsilyloxy-16α-benzoyloxy	27.45		29.81
5-Androsten-3β, 15α, 17β-triol-16-one			
3β, 15α, 17β-trimethylsilyloxy	28.85		29.98
3β, 17β-ditrimethylsilyloxy-15α-benzoyloxy	27.70		30.23

* This value should replace the incorrect value (27.26) in the literature (4, 5).

Low resolution mass spectra for the minor products obtained in the presence of benzoyl peroxide indicated that a benzoyloxy group was present. The high resolution mass spectrum (CEC 110B mass spectrometer) for the product from 5-androsten-3β-ol-17-one showed an ion corresponding to the benzoyl group (C_7H_5O). By analogy, the reaction products (Table 2) are regarded as the 3β-TMSi-16α-benzoyl derivative of 5-androsten-3β, 16α-diol-17-one, and the 3β, 17β-di-TMSi-15α-benzoyl derivative of 5-androsten-3β, 15α, 17β-triol-16-one, respectively.

This new oxidative reaction may be regarded as being equivalent to an hydroxylation reaction. The stereospecific nature of the reaction is probably due to steric effects guiding the addition of the bulky trimethylsilyloxy group. The precursor(s) of the trimethylsilyloxy radical has not been identified. This may be one or more of the silylation reagents, or ditrimethylsilyl ether which may also be present. Additional studies of the scope of this reaction

are in progress.

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