A NEW MILD AND SPECIFIC KETALISATION METHOD. THE REACTIONS OF AMIDE-ACETALS I.

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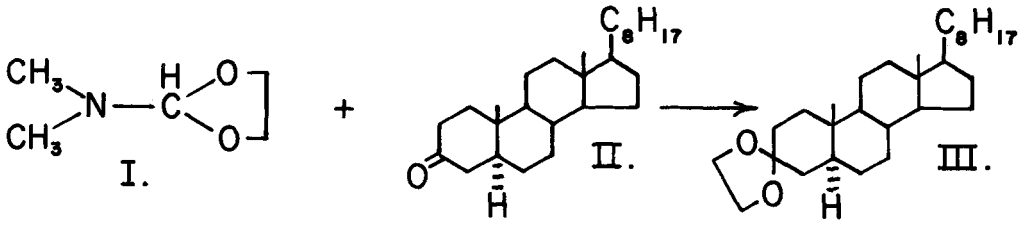
Received December 24, 1962

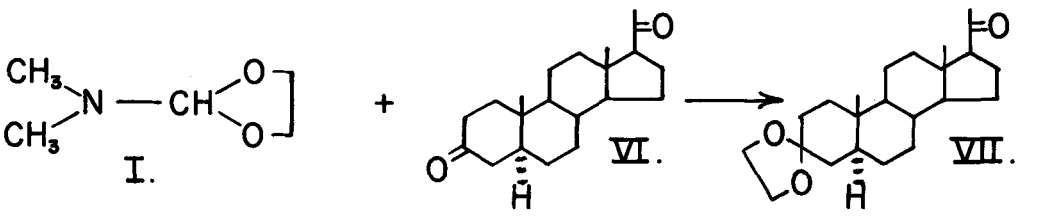
The ethylene-acetal of dimethylformamide (I) reacts specifically with steroidal 3-ketones to give the 3-ethylene ketal in the presence of other saturated or unsaturated keto functions.

Recently, H. Meerwein et al.[1,2] described the preparation and chemical properties of a variety of amide and lactam-acetals. The high reactivity of these weakly basic compounds aroused our interest in their possible preparative applications. Among these compounds the ethylene-acetal of dimethylformamide (I)[2] seemed to be a promising reagent for trans-ketalisation, especially of steroid ketones.

In boiling methylene chloride or benzene the reagent (I) reacted with the relatively unhindered carbonyl group in cholestan-3-one (II) under the catalytic influence of added acetic acid to give an 83% yield of cholestan-3-one ethylene-ketal (III)[3].



The added acetic acid formed glycol acetates in a competing reaction.[4] The more hindered pivalic acid formed also glycol esters but gave a slower rate of reaction. Experiments with other acids such as borontrifluoride-etherate or p-toluenesulfonic acid were unsuccessful. On applying this reaction to carbonyl groups in different positions in the steroid skeleton, it was found that 17-and 20-ketones or the Δ^4-3-ketones did not react under these conditions. It was thus possible to prepare in one step from 5α-androstane-3, 17-dione (IV) the known 5α-androstane-3, 17-dione 3-ethylene-ketal (V)[5] in 89% yield and from 5α-pregnane-3, 20-dione (VI) the hitherto unknown 5 α -pregnane-3, 20-dione 3-ethylene-ketal (VII) in 70% yield.



The structure of (VII) is supported by the analysis and the NMR spectrum, which showed signals of the C-21-methyl group adjacent to the C-20 carbonyl group at δ = 2, 02 ppm and the methylene groups of the ethylene ketal at δ = 3, 8 ppm.

This constitutes therefore a new method to prepare selectively the ethylene ketal of steroidal 3-ketones under very mild conditions in the presence of other saturated or unsaturated carbonyl groups, which is not possible with any of the known methods.[6] It is hoped to extend and investigate this reaction and its mechanism in the near future.

EXPERIMENTAL PART

The melting points were determined in capillaries on a Thomas Hoover melting point apparatus and are not corrected. The reactions were followed by thin-layer chromatography on silicagel G (E. Merck, Darmstadt) with the solvent systems benzene-ethylacetate 20:1 (for compounds (II) and (III))and 5:1 (for compounds (IV) - (VII)). The rotations were measured in chloroform solution. The microanalysis was performed by Mr. E. Meier and the NMR spectrum determined by Dr. L. Durham on a Varian A-60 spectrometer with tetramethylsilane as internal standard.

Cholestan-3-one ethylene ketal (III).

Cholestan-3-one (II) (387 mg) was boiled under reflux for 26 hours in dry methylene chloride (30 ml) with 2 ml of the ethylene acetal of dimethylformamide (I)[2] and 2 ml of acetic acid under exclusion of humidity. After cooling with ice, the mixture was poured on 25 ml of 10% potassium hydroxide solution and shaken for 5 minutes. The layers were separated, the aqueous phase extracted twice with methylene chloride and the combined organic phase dried with magnesium sulfate and evaporated. The residue was dissolved in hexane-benzene (4:1) and filtered through a column of 18 g of neutral alumina (A II). The first 100 ml eluate with the same solvent mixture gave on evaporation and recrystallization from acetone-methanol 355 mg (83%) of cholestan-3-one ethylene ketal, m.p. 113-114°. The melting point was not depressed on admixture with an authentic sample[3].

5 α -Androstane-3, 17-dione 3-ethylene ketal (V).

5 α -Androstane-3, 17-dione (IV) (288 mg) was boiled under reflux for 26 hours with 2 ml of reagent (I)[2] and 2 ml of acetic acid as described above. After working up and evaporating the methylene chloride solution, the crude product was shaken for 15 minutes with hexane (50 ml) and saturated sodium bicarbonate solution (25 ml), the layers separated, the hexane phase washed twice with water, dried with magnesium sulfate and evaporated. The crude product gave on recrystalliza-

tion from hexane 258 mg (89%) of 5 α -Androstane-3, 17-dione 3-ethylene ketal (V), m.p. 150-151°. Recrystallization from hexane gave the analytical sample m.p. 155-155.5° $[\alpha]_D = +84.5°$ (c=1.26) (Lit.[4] m.p. 155-156° $[\alpha]_D = +81.5°$).

5 α -Pregnane-3, 20-dione 3-ethylene ketal (VII).

5 α -Pregnane-3, 20-dione (VI) (316 mg) was reacted as described above for the preparation of (V). The crystalline residue was recrystallized from hexane to yield 250 mg (70%) of 5 α -Pregnane-3,20-dione 3-ethylene ketal (VII) m.p. 126.5-127°. Recrystallization from hexane gave the analytical sample m.p. 127-127.5°, $[\alpha]_D = +99°$ (c=0.65).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.57; H, 10.12.

Acknowledgement: The author is grateful to Professor C. Djerassi for his support and encouragement, and to Dr. A. D. Cross of Syntex S.A., Mexico City, for the steroid samples.

References.

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