REDUCTIVE REMOVAL OF THE 17α-HYDROXYL GROUP OF THE CORTICAL SIDE-CHAIN

by

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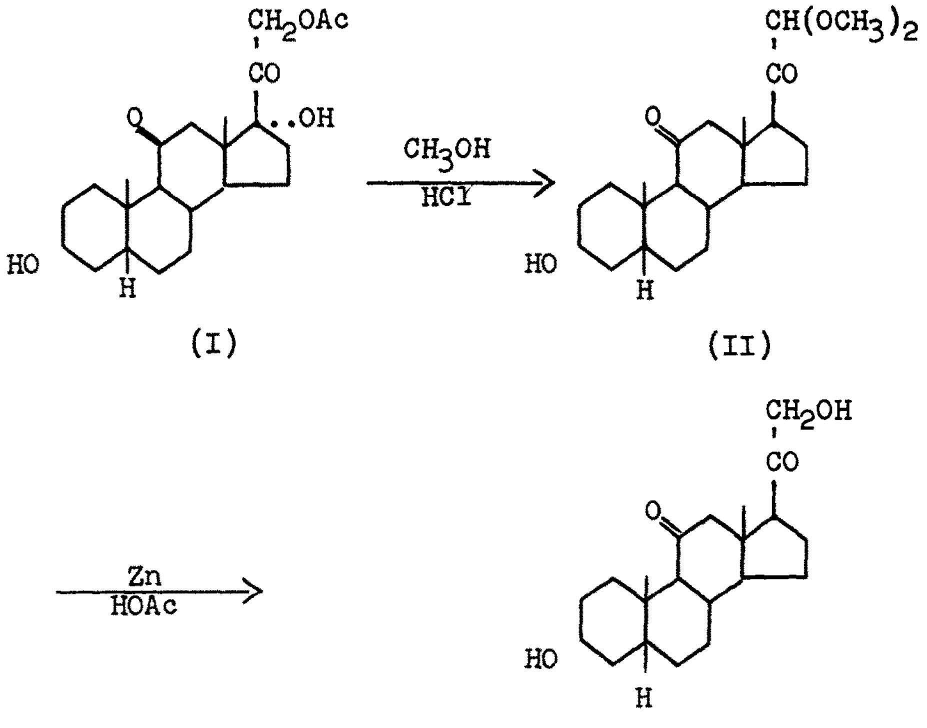
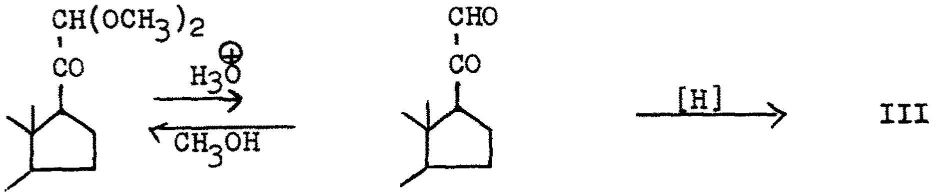
Several methods for the reductive removal of the 17α-hydroxyl group of the cortical side-chain have been recorded.[1,2,3,4] The method presently reported, in contrast to the foregoing, makes possible the reductive removal of the 17α-hydroxyl group by a simple two-step process with concluding isolation of the desired product by direct crystallization. This sequence consists, in effect, of a Mattox rearrangement with methanolic hydrogen chloride[5] followed by reduction with zinc in aqueous acetic acid. By this procedure 3α,17α,21-trihydroxy-5β-pregnane-11,20-dione 21-acetate (I) was converted _via_ the acetal (II) to 3α,21-dihydroxy-5β-pregnane-11,20-dione (III) in 45-50% yield.



(I) (II) (III)

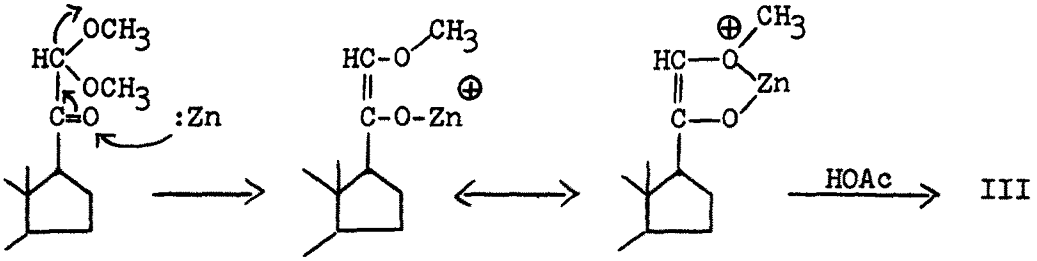
Reich and Reichstein had previously shown that 20-keto-21-aldehyde dimethylacetals are capable of finite cleavage in the presence of hydrochloric-acetic acids at room temperature.[6] In view thereof, it was felt that hot aqueous acetic acid alone might produce an equilibrium concentration of keto-aldehyde (i → ii) and that in the presence of zinc subsequent reduction[5] would display the equilibrium to the right through the formation of III.



i ii

In fact, a positive ammoniacal silver nitrate test for aldehyde was produced when pure II was refluxed with aqueous acetic acid alone.

The transformation of I → III might be alternatively considered to proceed by way of iii and iv.[7]



iii iv

EXPERIMENTAL

3α-Hydroxy-21,21-dimethoxy-5β-pregnane-11,20-dione (II).- 3α,17α,21-Trihydroxy-5β-pregnane-11,20-dione 21-acetate (I) (100 g.) was dissolved in 2.2 l. of methanol, treated with a solution of 42 g. of hydrogen chloride in 280 ml. of methanol and stirred at room temperature for 48 hours. The reaction mixture was then quenched by neutralizing with a solution of 80 g. of potassium carbonate in 80 ml. of water. After removal of the methanol *in vacuo*, the product was extracted several times with chloroform, the chloroform layer washed with water, dried over sodium sulfate and concentrated to dryness to yield 102 g. of amorphous product. The latter by TLC (alumina G., acetone) contained only a trace of starting material (21-ol) and was used without further purification for the next step. A sample of this product was characterized by conversion to the 3α-acetate, m.p. 106-107° (reported[5] m.p. 107-107.5°). The infrared spectrum of this material was in conformity with the proposed structure.

3α,21-Dihydroxy-5β-pregnane-11,20-dione (III).- To 100 g. of 3α-hydroxy-21,21-dimethoxy-5β-pregnane-11,20-dione (II) (crude from above) and 1.2 kg. of zinc dust was added 6 l. of acetic acid and 12 l. of water. The mixture was refluxed for 3-1/2 hours with vigorous stirring. The clear solution was then filtered hot from the zinc and the zinc washed a few times with chloroform. The combined filtrates were cooled and neutralized under stirring and ice-cooling with a solution of about 3 kg. of sodium hydroxide in 5 l. of water. The product was extracted with four 2 l. portions of chloroform and the chloroform extract washed with water, dried over sodium sulfate and concentrated to dryness. The crude residue was refluxed for two hours with 380 ml. of ether followed by stirring overnight at room temperature. The white crystalline product thus formed was filtered and washed with ether to yield 46.5 g. of crude III, m.p. 190-215°. The latter was dissolved in boiling acetone, concentrated on a steambath to a small volume, treated with n-hexane and the solution cautiously concentrated again until a few crystals started to form. After allowing to come to room temperature, the mixture was kept in the refrigerator overnight. The crystals were filtered and washed on the funnel with ether, yielding a first crop, 26.5 g., m.p. 217(softens)-222-228°(melts) (reported[8] m.p. 217-222°; an analytical sample melted at 222.5-228.5°). From the mother liquod there was obtained a second crop, 7.7 g., m.p. 217(softens)-222-228°(melts), and a third crop, 3.3 g., m.p. 217(softens)-222-228°(melts). Total yield 37.5 g. (47.5% from I). The analytical sample had m.p. 217(softens)-222-228° (melts), $[\alpha]_D^{25}$ + 102.4° (dioxane), (reported[8] + 110°, dioxane) was 98± 2% pure by phase solubility and single spot by TLC (silica gel G., ethylacetate-acetone, 3:2). The infrared spectrum was in conformity with the proposed structure.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.66; H, 9.05.

A sample of the diol III was acetylated to give the corresponding diacetate, m.p. 107-109° (reported[3a] m.p. 107-109°). The infrared spectrum was identical with an authentic sample.[9]

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.66; H, 8.65.

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9. Prepared by Dr. L. H. Sarett of these laboratories.