SYNTHESIS OF 11β,21-DIHYDROXY-1,4,17(20)-[CIS]-PREGNATRIEN-3-ONE FROM METHYL 3,11-DIKETO-1,4,17(20)-[CIS]-PREGNATRIEN-21-OATE

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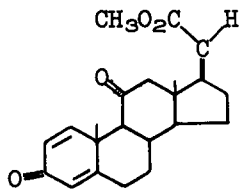
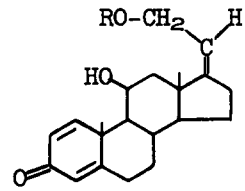
In a previous publication[1] from These Laboratories the conversion of methyl 3,11-diketo-1,4,17(20)-[cis]-pregnatrien-21-oate (1) to 11β,21-dihydroxy-1,4,17(20)-[cis]-pregnatrien-3-one (2) was reported without full experimental detail. Lithium aluminum hydride reduction of 1 after treatment with pyrrolidine (Method A) or ethylene glycol (Method B) and followed by hydrolytic procedures led to the isolation of 2.



1.



2. R=H

3. R=Ac

Subsequently there have been several references[2,3,4] to unsuccessful attempts to protect the $\Delta^{1,4}$-3-keto system of related steroids by ketal or enol ether formation. In order to provide an accurate evaluation of the feasibility of this type of transformation we now report the full detail of our experiments.

In method A the intermediate enamine of 1 was not isolated in pure crystalline form. However, its presence in substantial amount was indicated

by the ultraviolet absorption data and nitrogen analysis as well as by the subsequent isolation of approximately 20% of 2.

In alternate method A, using milder conditions, and in method B no direct evidence of the formation of ring-A blocking was noted; however, after reduction and hydrolysis authentic 2 and 3 respectively were isolated from the final products. From this we at first[1] concluded that a small amount of ring-A protection was achieved. Later it was shown that the reduction of 1 directly with lithium aluminum hydride essentially as in method B without attempted blocking at C-3 afforded a product containing 2 as identified by paper chromatography.

EXPERIMENTAL

11β,21-Dihydroxy-1,4,17(20)-[cis]-pregnatrien-3-one (2) Method A: Via Enamine Blocking. Two grams of methyl 3,11-diketo-1,4,17(20)-[cis]-pregnatrien-21-oate (1), 1.0 g. of pyrrolidine, 50 mg. of p-toluenesulfonic acid in 50 ml. of benzene was heated under reflux for 17 hrs. The distillate was passed through a Dean-Stark separator. The solvent was distilled under vacuum. The dark residue showed $\lambda_{max.}^{MeOH}$ 279 mμ, ε 12,400, 223 mμ, ε 14,500.

Anal. Calcd. for $C_{26}H_{32}NO_3$: N, 3.45. Found: 3.09.

The crude oil was dissolved in 40 ml. of anhydrous ether and added to 1.0 g. of lithium aluminum hydride suspended in 100 ml. of ether. After heating under reflux for 1 hr., there was added 5 ml. of ethyl acetate followed by 15 ml. of water. The ether was removed by distillation under vacuum. To the residue were added 100 ml. of methanol and 20 ml. of 5% sodium hydroxide. The resulting mixture was heated at 50° for 10 min. The alkali was neutralized by the addition of acetic acid. The methanol was distilled under vacuum. The product was isolated by extraction with methylene chloride. The methylene chloride solution was percolated through 150 g. of Florisil[5] and the column was eluted with Skellysolve B[6] containing increasing amounts of acetone. The fraction eluted with Skellysolve B - 20% acetone (451 mg.), after recrystallization from methanol, weighed 360 mg. and melted at 152-164°. Recrystallization afforded 230 mg. of 2, m.p. 167-170°, $[\alpha]_D$ +116° (chf.), λ_{max}^{EtOH} 243 mμ, ε 14,700. The infrared absorption spectrum of this product and its paper chromatographic characteristics[7] were identical with those of 2.

Alternate Method A. In a similar experiment, except that in the enamine stage only 3 mg. of p-toluenesulfonic acid was used as the catalyst and time of reflux was 45 min., the final crude product weighed 131 mg. but failed to crystallize. The presence of 2 was indicated by paper chromatography. The crude 2 (131 mg.) was dissolved in 4 ml. of boiling methanol and 0.09 ml. of pyrrolidine added. After standing for 1 hr. the methanol was distilled under vacuum. The residue was dissolved in methylene chloride,

washed with dilute hydrochloric acid, dried and chromatographed on 10 g. of Florisil. The fractions (33 mg.) eluted with Skellysolve B - 20% and 30% acetone crystallized slowly though paper chromatography indicated 2 of high purity. This material was rechromatographed on 5 g. of Florisil. The fraction eluted with Skellysolve B - 17% acetone (20 mg.) was recrystallized from methanol to give 4.5 mg. of 2, m.p. 154-160°. Recrystallization from methanol afforded 1.4 mg. of 2, m.p. 167-171.5°, identified by its infrared absorption spectrum, paper chromatography characteristics, and mixture m.p.

Method B. A mixture of 60 g. of ester 1, 300 ml. of ethylene glycol, 6 l. of benzene, and 6 g. of p-toluenesulfonic acid was heated under reflux for 5.5 hrs., the distillate being passed through a Dean-Stark trap. The cooled solution was washed with 1% sodium bicarbonate solution, dried and percolated through 6 kg. of Florisil. The fraction eluted with methylene chloride (32 l.) weighed 18.0 g. This fraction was dissolved in 840 ml. of benzene and added to a mixture of 18.0 g. of lithium aluminum hydride in 600 ml. of ether. The mixture was heated at reflux for 0.5 hr. To the cooled solution was added 600 ml. of water followed by 2.4 l. of methylene chloride. The organic phase was separated, dried, and evaporated. The residue was dissolved in 1.25 l. of acetone and 1.56 l. of water containing 1.5 ml. of conc. sulfuric acid added. After 24 hrs. at ambient temperature, the reaction mixture was neutralized and the acetone evaporated under vacuum. Distillation of the solvent afforded 15.8 g. of residue which showed the presence of 2, by paper chromatography. This solid was chromatographed on 1.4 kg. of Florisil. Selected fractions (2.83 g.), eluted with Skellysolve B - 15% to 30% acetone, were combined on the basis of their paper chromatography analysis. This oil was dissolved in 100 ml. of boiling methanol and 3 ml. of pyrrolidine added. After 1 hr. the solvent was evaporated. The residue was dissolved in methylene chloride and washed with dilute acid, thus removing that quantity of 3-keto Δ^4-steroidal material which is formed by lithium aluminum hydride reduction of the Δ^1 bond in unprotected starting material. Chromatography over 80 g. of Florisil afforded 605 mg. of crude 2. The fractions, eluted with Skellysolve B - 15% to 30% acetone, were selected on the basis of paper chromatographic analysis. Crude 2 (605 mg.) was treated with 3 ml. of acetic anhydride and 3 ml. of pyridine for 17 hrs. The crude product obtained after the usual work-up was chromatographed over 40 g. of Florisil and the fractions (44 mg.) eluted with Skellysolve B - 9% and 12% acetone combined on the basis of paper chromatographic analysis. The crude acetate was recrystallized from ethyl acetate - Skellysolve B to yield 40 mg. of 3, m.p. 193-197°. Several recrystallizations from the same solvent raised the m.p. to 209-212°. Its mixture melting point with known acetate 3, m.p. 219-221°, was not lowered and its infrared absorption spectrum and paper chromatographic characteristics confirmed its identity as acetate 3.

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