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SHORT COMMUNICATION

AN IMPROVED SYNTHESIS OF 16β-HYDROXY DEHYDROEPIANDROSTERONE

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SUMMARY

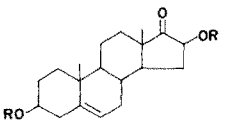
A convenient method for the preparation of large quantities of 16β-hydroxy dehydroepiandrosterone is described.

The need for large quantities of the very unstable 16β-hydroxy dehydroepiandrosterone (3β,16β-dihydroxy-5-androsten-17-one) in our laboratory necessitated a study of the conditions under which the hydrolysis of the corresponding diacetate proceeds without rearrangement of the ketol grouping.

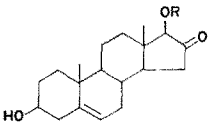
The synthesis of the diacetate (3β,16β-diacetoxy-5-androsten-17-one, II) has been described by Johnson *et al.*[1] in 1957. The acetate may be obtained easily in 100 g quantities under laboratory conditions. However, difficulties arise when the diacetate is exposed to alkaline or acidic conditions in order to prepare the parent ketal having the 16β-hydroxy-17-oxo grouping. This system is extremely unstable and, under mildest enolising conditions, undergoes rearrangement to the stable 17β-hydroxy-16-oxo compound[2].

To our knowledge two methods have been described for hydrolysis of the diacetate II to the ketol I: by enzymatic deacetylation[3] and hydrolysis with methanolic hydrochloric acid[4]. The first method is suitable only for preparation of small quantities of the ketol though the yield and purity of the product are good. The second method gives about 16% of a product which is not pure and, probably, according to the optical rotation contains about 17% of the rearranged product (3β,17β-dihydroxy-5-androsten-16-one, III). Attempts to improve this method have failed. Analysis of the reaction mixture revealed, next to minor components, the presence of about 30% of the methylether IV, about 40% of the rearranged ketol III, and about 10% of desired ketol I. Chromatography of the mixture caused further rearrangement of the desired isomer. We found only crystallization as a suitable method advisable for isolation of the desired product. We succeeded in isolating the pure product (m.p. 195–200°C; $[\alpha]_D^{20}$ +15° (dioxan), +17° (methanol)) by repeatedly crystallizing the crude reaction mixture from chloroform–ether but the yield was only about 5% and there was no possibility to recover any starting material.

In the course of our studies of steroid conjugates we needed about 5 g of the 16β-hydroxy dehydroepiandrosterone and therefore a new method had to be developed. The approach we have found to provide the best yields involved the hydrolysis of the diacetate II with sulfuric acid in dioxane–water mixture. The resulting reaction mixture was found to contain four principle products: the starting material (about 40%), the two isomeric monoacetates (about 10% of each) and about 30% of the desired ketol I: only traces of the rearranged products were detected. Repeated crystallization yielded 19% of a pure product, m.p. 200–204°C; $[\alpha]_D^{20}$ +17° (methanol). The mother liquors were combined, acetylated and purified by chromatography to yield 46% of the starting material.



I, R = H
II, R = Ac



III, R = H
IV, R = CH_3

EXPERIMENTAL

(a) *Hydrolysis with methanolic hydrochloric acid.* The diacetate II (2 g) was hydrolyzed as described[4]. Similar working-up and purification yielded 310 mg of a product, m.p. 184–188°, $[\alpha]_D$ −19° (dioxan) as reported. Crystallization of this product from chloroform–ether until the levorotatory ketol III was removed and the optical rotation reached +15° (dioxan) and +17° (methanol) yielded 105 mg of ketol I, m.p. 195–200°C, $[\alpha]_D^{20}$ +17° (methanol).

The mother liquors (1.65 g; $[\alpha]_D^{20}$ −183° in chloroform) consisted essentially of two components, present in about equal quantities. Chromatographic separation over silicagel (250 g) in ether yielded fractions with the lipophilic component. Work-up gave 680 mg of a product which after crystallization from ethyl acetate–ligroin yielded 510 mg of the methylether IV, m.p. 148–151°C, $[\alpha]_D^{20}$ −167° (c, 1.43 in chloroform). N.m.r.: (Varian HA-100, deuteriochloroform, tetramethylsilane as internal reference 0.83 (s, 18-H, 3H), 1.05 (s, 19-H, 3H), 3.35 (s, 17α-H, 1H), 3.57 (s, —OCH_3, 3H), 3.55 (broad m, 3α-H, 1H), 5.38 (m, 6-H, 1H)). For $C_{20}H_{30}O_3$ (318.4) calculated: C 75.43%, H 9.50%; found: C 75.38%, H 9.46%. Elution with ether afforded fractions with the polar component identified as the rearranged ketol III; the yield was 630 mg, m.p. 202–205°C, $[\alpha]_D^{20}$ −195° (ethanol).

(b) *Hydrolysis with sulphuric acid.* To a solution of the diacetate II (15 g) in dioxan (1200 ml) and water (300 ml) was added 6 N sulphuric acid (150 ml) and the reaction mixture allowed to stand at 35°C for 48 h. The progress of the reaction was followed by t.l.c.; the plates were developed twice in ether. The use of methanol in the developing solvent mixture should be avoided because rearrangement may take place. The reaction mixture was diluted with ethyl acetate (2000 ml) and water (4000 ml), the organic layer was washed with sodium hydrogen carbonate and water, dried and the solvent removed by distillation *in*

vacuo. The oily residue was dissolved in ether (70 ml) and allowed to crystallize at 0°C for 2 days. The solid (4 g) was separated by suction, washed with ether and crystallized from chloroform–ligroin to yield 3.4 g of a product, m.p. 189–195°C (Kofler block), $[\alpha]_D^{20}$ +11° (methanol) pure on t.l.c. Further crystallization from methanol raised the constants to m.p. 200–204°C (Kofler block), $[\alpha]_D^{20}$ +17° (c, 1.65 in methanol). The n.m.r. data were in agreement with those described for the pure product[3]. The mother liquors after crystallizations were combined, acetylated with acetic anhydride in pyridine in the usual way and the acetylated mixture (11.7 g) was chromatographed on a silica gel column (400 g) in benzene–ether (9:1 v/v) to yield 7.1 g of the pure diacetate II.

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