IMPROVED METHOD OF OBTAINING 16α-METHYL-5α-PREGNANE-17α,21-DIOL-3,20-DIONE, A DEXAMETHASONE INTERMEDIATE

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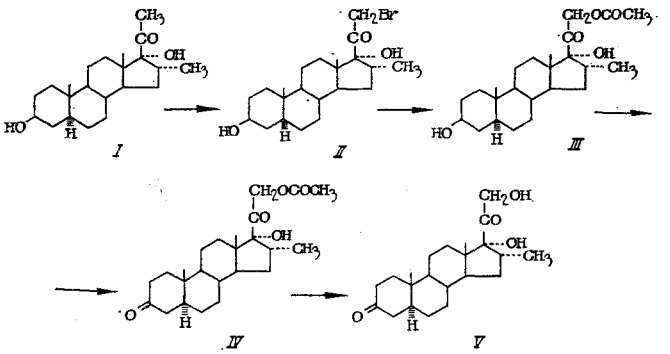
The use of tigogenin isolated from the perennial plant Yucca gloriosa (family Agavaceae) for obtaining 16α-methyl-5α-pregnane-3β,17α-diol-20-one (I) has been reported previously [1, 2]. Compound (I) is a key compound in the synthesis of dexamethasone.

The aim of the present investigation was the synthesis of 16α-methyl-5α-pregnane-17α,21-diol-3,20-dione (V) which is an intermediate used in the microbiological transformation to introduce a hydroxyl at position 11. Synthesis of (V) was carried out by us according to the following scheme:



The synthesis of dexamethasone via 16α-methyl-5α-pregnane-3β-ol-20-one has been described in the literature [3].

Modern methods of introducing functional groups were used in the present work which made it possible to obtain the compound in good yield and to simplify the procedure.

The properties of compounds (III) and (IV) corresponded with literature data [3, 4] but there are no data in the literature on compounds (II) and (V).

Bromination of 16α-methyl-5α-pregnane-3β,17α-diol-20-one (I) was carried out in methylene chloride using a small excess of bromine (1.05 mole per mole steroid). At the end of the reaction the 21-bromide (II) was precipitated from the reaction solution in 82-84% yield (TLC data).

Replacement of the 21-bromine in (II) by an acetoxy group was effected under homogeneous conditions, as described for other steroids in [5], by the action of triethylamine and acetic acid in acetone solution. Reaction time was reduced by half in comparison with literature data [3, 4] where acetoxylation at position 21 was described under heterogeneous conditions in DMF (dimethylformamide) or in acetone with sodium or potassium acetate.

For the oxidation of the compound (III) trihydroxyl groups into a keto group of two-phase variant was used by us, viz., steroid in methylene chloride solution and an aqueous solution of chromic acid (Jones' reagent) [6]. In contrast to oxidation in acetone using the Jones reagent the reaction occurred under more mild conditions as a result of the brief contact with the oxidizing agent. Yield was 82%. According to literature data the oxidation of 16α-methyl-5α-pregnane-3β,17α,21-triol-20-one 21-acetate was carried out in acetone [3] in which (III) dissolved poorly and also with N-bromoacetamide [4] and N-bromosuccinimide for 22 h [7].

Of the methods of deacetylating a primary 21-acetoxy group described in the literature the transesterification method with lower alcohols under the action of alkali salts of car-

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bonic acid has the most practical value [8]. Saponification of the 21-acetoxy group in (IV) has been carried out with a large excess of potassium bicarbonate in methanol [4].

Deactylation of compound (IV) was carried out by us in methanol in the presence of catalytic quantities of potassium hydroxide (0.15 mole per mole steroid) at room temperature for 2 h. The yield of chromatographically pure (V) was 90-92%.

EXPERIMENTAL

Compounds (II) and (V) were chromatographed on Silufol UV-254 plates in the system cyclohexane–acetone (5:3) and were visualized by spraying with sulfuric acid and heating. R_f 0.39 (II) and 0.42 (V).

21-Bromo-16α-methyl-5α-pregnane-3β,17α-diol-20-one (II). A 10% solution of hydrochloric acid in methanol (0.6 ml) and then bromine (0.97 g) in methylene chloride (10 ml) dropwise during 1 h were added to a solution of 16α-methyl-5α-pregnane-3β,17α-diol-20-one (I) (2 g) in methylene chloride (40 ml) at 20-22°C. At the end of adding bromine a crystalline precipitate of the 21-bromide (II) began to form. The reaction mixture was stirred for 1 h at room temperature, cooled, and neutralized with sodium bicarbonate solution. Compound (II) was obtained (2.06 g; 86.7%) of mp 205-207°C (with decomposition), $[\alpha]_D^{20}$ + 33.2° (c = 0.1, chloroform). Found, %: Br 18.87. $C_{22}H_{35}BrO_3$. Calculated, %: Br 18.69.

16α-Methyl-5α-pregnane-3β,17α,21-triol-20-one 21-acetate (III). A solution of dry triethylamine (10 ml: 7.22 g) and acetic acid (5 ml) in acetone (10 ml) was poured into a boiling solution of (II) (1.5 g) in acetone (25 ml). The mixture was boiled for 4 h, concentrated to one third volume, and poured into water. Compound (III) (1.2 g: 82%) was obtained of mp 192-194.5°C, $[\alpha]_D^{20}$ +29° (c = 0.1, chloroform).

16α-Methyl-5α-pregnane-17α,21-diol-3,20-dione 21-acetate (IV). Jones' reagent, obtained from chromic anhydride (0.32 g) and concentrated sulfuric acid (0.32 ml) in distilled water (1.5 ml), was poured into a solution of (III) (1 g) in methylene chloride (30 ml) at 10°C. After this the mixture was stirred at 20-22°C for 2 h. The organic layer was poured off and concentrated. Compound (IV) was obtained (0.81 g: 81.8%) of mp 203-205°C, $[\alpha]_D^{20}$ +41° (c = 0.1, chloroform).

16α-Methyl-5α-pregnane-17α,21-diol-3,20-dione (V). A solution of potassium hydroxide (0.02 g) in methanol (7 ml) was added to a suspension of (IV) (0.8 g) in methanol (30 ml) which had been purified by distillation from zinc dust in a current of argon. The reaction mixture was stirred for 2 h at room temperature, concentrated to one-third volume, and poured into water. Compound (V) (0.65 g: 91.5%) was isolated and had mp 172-174°C, $[\alpha]_D^{20}$ +33° (c = 0.1, methanol). Found, %: C 73.20; H 9.60. $C_{22}H_{34}O_4$. Calculated, %: C 72.87; H 9.44.

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