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AN IMPROVED PREPARATION OF 3α-ACETOXY-11,20-DIKETO-(5β)-PREGNANE, THE KEY INTERMEDIATE IN THE SYNTHESIS OF 11-OXYGENATED CORTICOSTEROIDS.

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Although microbiological methods of introducing oxygen at C-11 of the steroid molecule are effective, it is obvious that purely synthetic ways of producing cortisone and its analogues from bile acids or hecogenin have never been abondoned. Thus, we succeeded to obtain 3α-acetoxy-11,20-diketo-(5β)-pregnane XI, the key intermediate in the synthesis of 11-oxygenated corticosteroids in a very improved yield exceeding 13% calculated on starting desoxycholic acid I* by the following sequence of reactions:

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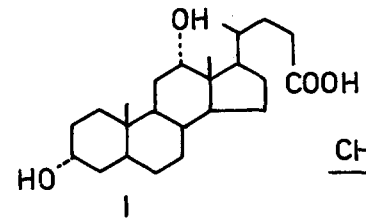
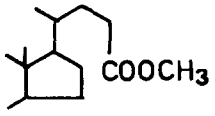
* Product of Chem. & Pharm. Ind. "Galenica", Beograd



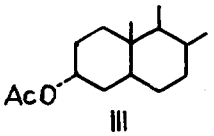
I

CH_3OH/HCL



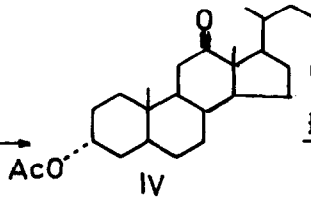
II

JBr
AcOH



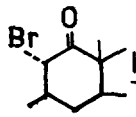
III

CrO_3



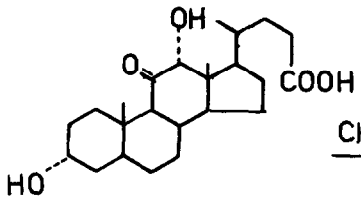
IV

$Br_2/AcOH$



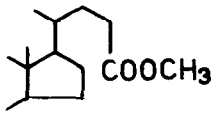
V

KOH/MeOH



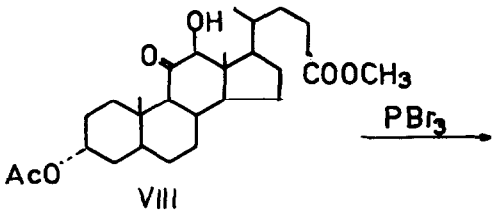
VI

CH_3OH/HCL



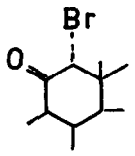
VII

Ac_2O



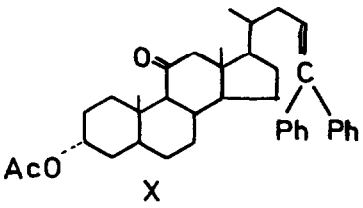
VIII

PBr_3



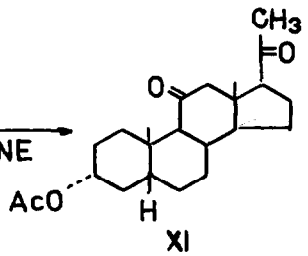
IX

1. PhMgBr
2. Ac_2O/AcOH



X

1. NBS
2. PYRIDINE
3. CrO_3



XI

We wish to point out the following interesting steps of our scheme.

II ⟶ IV. Methyl ester of desoxycholic acid II was treated with glacial acetic acid in presence of iodinemonobromide affording the monoacetate III; the reaction course was followed by TLC and interupted when all of starting ester II had reacted whereby only a small amount of diacetate was formed. The crude monoacetate III was further oxidized with chromic acid and the oxidation product crystallized from methanol. In this way, the crystalline ketone IV (m.p. 151°, $[\alpha]_D^{26^\circ} = +106^\circ$) (1) was obtained in an 81% yield. Mother liquor, which mainly consisted of the corresponding diacetate, could be saponified and desoxycholic acid easily recovered.

IV ⟶ VI. We found that when bromination of ketone IV, in glacial acetic acid in presence of HBr, was carried out at room temperature (48-72 hours) instead at 75°, pure crystalline equatorial 11α-bromo-derivative V was obtained almost quantitatively (m.p. 158°; NMR 3 H singlet δ (C-18) 1.05, 3 H singlet δ (C-19) 1.21, 3 H singlet δ (CH_3COO-) 2.0, 3 H singlet δ (-OCH_3) 3.66 and 1 H doublet centered at δ 5.0 $J_{H_{11}H_9}$ 10 cps). Upon alkaline treatment in an inert atmosphere,

this derivative was converted to "Marker - Lawson" acid VI in a yield averaging more than 70%.(2,3,4).

VII ⟶ VIII. Monoacetylation of ester VII was described to proceed in a poor yield (5). We found that this reaction may easily be effected with a yield of 80% by simply dissolving the ester VII in a fourfold excess (by weight) of acetic anhydride and by heating the resulting solution on a water bath for 45 minutes; usual work up and leaching of the product with methanol afforded the crystalline monoacetate VIII in an 80% yield (m.p. 114-116°; I.R. (KBr) : 3450, 1730, 1705, 1250 cm^{-1}).

VIII ⟶ X. The elimination of 12β-hydroxy group was performed according to Gallagher (6), and the crystalline 12β-bromo-derivative was obtained in a 70% yield. This derivative was further treated with 10 moles of PhMgBr to give, by reductive elimination and subsequent dehydration of the intermediate carbinol which had not been isolated, the first side chain degradation product X in a 90% yield (m.p. 169°; $[\alpha]_D^{26°}$ = +85°(7)).

Further side chain degradation was performed by allylic bromination by means of NBS, dehydrobromination and subsequent oxidation of the crude product by conventional methods (7,8), and pure 3α-acetoxy-11,20-diketo-(5β)-pregnane XI was obtained in a more than 50% yield, based on X (m.p. 133-135°; $[\alpha]_D^{26°}$ = +130°).

We believe that this is one of the simplest synthetic approaches to 11-oxygenated corticosteroid intermediates recently published.

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