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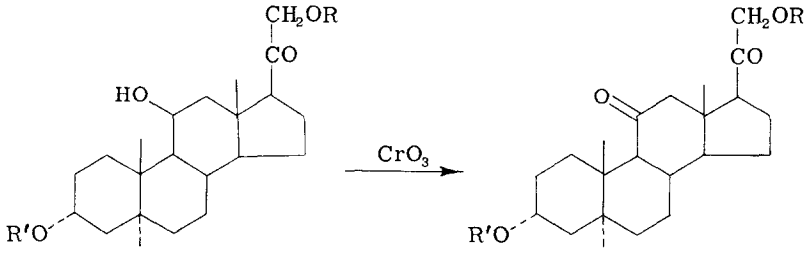
Synthesis of Allotetrahydro Compound A (allo-THA)

A recent publication by Starnes and Partlow (1) concerns the preparation of a urinary metabolite, allo-THA (structure Ia), on a microgram scale, for use in paper chromatographic studies of urinary metabolites. This was carried out by direct chromic acid oxidation of allo-THB (allo-THB = 3α,11β,21-trihydroxy-5α-pregnane-20-one, structure IIa) or oxidation of its 3,21-diacetate (IIb) followed by a stepwise hydrolysis of the diacetate (Ib).



IIa, R = R′ = H
b, R = R′ = Ac
c, R = Ac; R′ = HCO

Ia, R = R′ = H
b, R = R′ = Ac
c, R = Ac; R′ = HCO

We now wish to record our method for a facile synthesis of macro quantities of allo-THA. Allo-THB 3-formate 21-acetate (IIc) (2) was oxidized with chromic acid to furnish the 11-keto derivative (Ic) in 76% yield. Mild treatment with potassium bicarbonate yielded allo-THA in 55% yield.

3α,21-Dihydroxy-5α-pregnane-11,20-dione 3-formate 21-acetate (structure Ic). A solution of 360 mg of 3α,11β,21-trihydroxy-5α-pregnane-20-one 3-formate 21-acetate (IIc) (2) in 5 ml of acetic acid was treated at 0° with 7 ml of 5% chromic acid solution in 90% acetic acid. After keeping for 1 hr in the ice bath it was diluted with 50 ml of water and extracted 3 times with a total of 150 ml of chloroform. The organic phase was washed with water and dilute bicarbonate solution and evaporated. The residue was crystallized from acetone-petroleum ether and afforded 222 mg, m.p. 208.5–211°, and 51 mg, m.p. 204.5–207°. The analytical sample melted at 209–211°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.81; H, 8.01. $(\alpha)_D^{24}$ 155° (chloroform). R_f (thin-layer chromatography on silica gel G using ethyl acetate-cyclohexane 1:1):0.51.

3α,21-Dihydroxy-5α-pregnane-11,20-dione (structure Ia). A solution of 277 mg of compound (Ic) in 60 ml of methanol was treated with a solution of 700 mg of potassium bicarbonate in 7 ml of water. At first gentle warming may be necessary to keep the solid in solution. After standing for 48 hr the solvents were removed *in vacuo* at room temperature and the residue was diluted with water and extracted with ethyl acetate. Evaporation of solvent gave a solid, m.p. 161–170°, which was recrystallized from acetone-petroleum ether. The granular product, obtained in two crops, weighed 128 mg and melted at 167–170°. Further recrystallization from the same solvents furnished leaflets of allo-THA melting at 163–173°, obviously a mixture of different crystalline forms.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.61; H, 9.02. $(\alpha)_D^{24}$ 99° (methanol). R_f (TLC as above using benzene-acetone 1:1): 0.66.

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