A New Synthesis of Progesterone(1)

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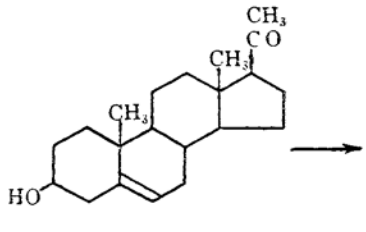
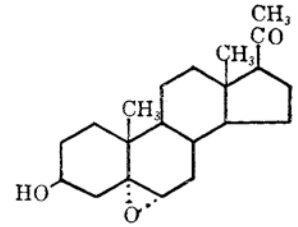
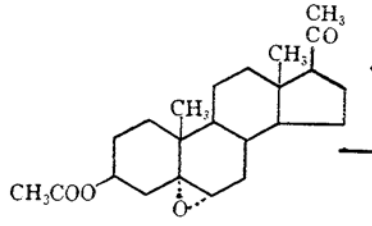
The principle used in this synthesis originates in the reduction of cholesterol oxides(2) and is the same as used in the new synthesis of testosterone,(3) consisting essentially of catalytic reduction of a 3β-hydroxy-5, 6α-epoxy-steroid to a 3β, 5α-dihydroxy-compound followed by oxidation to a 5α-hydroxy-3-ketone and dehydration to a Δ^4-3-ketone. The 5, 6α-oxido steroid gives always a 5α-hydroxy-compound on catalytic reduction, and this change can be taken as an evidence for an α-oxido structure. With an oxide possessing a carbonyl group a little complication may possibly arise, because at the same time the carbonyl group may be reduced ot either epimeric alcoholic group. In the case of the synthesis of testosterone, α-dehydroisoandrosterone oxide acetate gave fortunately the



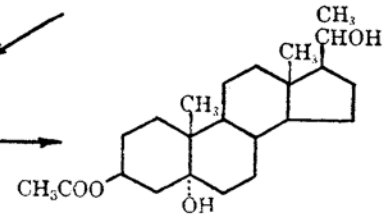
(I) Pregnenolone



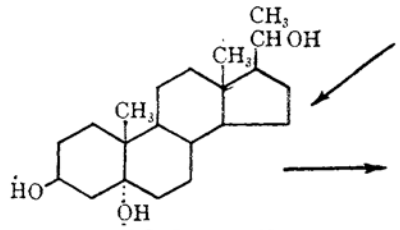
(II) Pregnenolone oxide



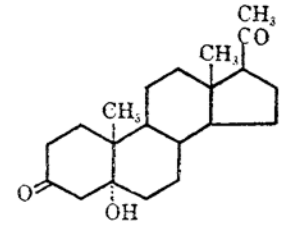
(III) Pregnenone oxide acetate



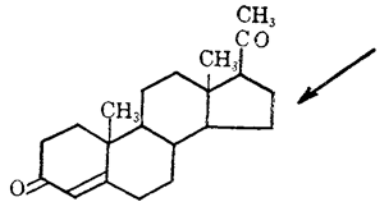
(IV) Allopregnane-triol-(3β, 5α, 20) 3-acetate



(V) Allopregnane-triol-(3β, 2α, 20)



(VI) 5α-Hydroxy-allopregnanane-dione-(3, 20)



(VII) Progesterone

(1) Japanese Patent applied for on July 1st, 1948, and entered as No. 184914 on October 20 th. 1950.

(2) Y. Urushibara and M. Chuman, This Bulletin, **22**, 70 (1949).

(3) Y. Urushibara and M. Chuman, This Bulletin, **22**, 1 (1949).

desired androstane-triol-(3β, 5α, 17β)[4] 3-acetate on catalytic reduction, as reported. Later experiments, however, yielded sometimes mixtures of epimeric triols.[5] The synthesis of progesterone starts from pregnenolone (I), and reduction of the carbonyl group at carbon atom 20 might cause a similar problem. But, such a complication, if any, can be eliminated in this case, because the carbon atom in question is oxidized again to a carbonyl group in the final product, progesterone.

The present synthesis cannot claim a method swifter or simpler than any of the known starting from pregnenolone, if the number of the steps of reactions involved be considered, but it proved notwithstanding a new method worth studying, because it afforded a proof for the α-oxido configuration of the pregnenolone oxide (II) and gave a satisfactory over-all yield.

Pregnenolone oxide (II) was prepared by the action of perbenzoic acid on pregnenolone (I) (65 mg.), and recrystallized from ethyl acetate. It melts at 185—187°, and is soluble in ethyl acetate, ethanol, methanol, and acetone, difficultly soluble in ether, and insoluble in petroleum ether. Yield about 90% of the theory (60 mg.).

Pregnenolone oxide acetate (III) was obtained by acetylation of the above oxide (II) (140 mg.) with acetic anhydride and pyridine, and recrystallized from acetone. It melts at 165—166°. Yield about 90% (130 mg.). M. Ehrenstein and M. T. Decker[6] treated pregnenolone acetate with potassium permanganate and obtained an oxide melting at 163—165°. Although a direct identification is lacking, the present authors believe that they obtained the same substance.

The above acetate (III) (50 mg.) was dissolved in glacial acetic acid and shaken with hydrogen and platinum oxide. About two mols of hydrogen were absorbed. The reduction product (IV) was then hydrolyzed with methanolic potassium hydroxide, and the hydrolyzate, perhaps an epimeric mixture of allopregnane-triols-(3β, 5α, 20) (V), was oxidized without purification with chromic acid in glacial acetic acid. The oxidation product was recrystallized from a mixture of ethanol and ethyl acetate. 5α-Hydroxy-allopregnane-dione-(3,20) (VI) thus obtained forms small plates melting at 264—266° and difficultly soluble in most organic solvents. Yield about 80% (35 mg.).

Dehydration of the above 5α-hydroxy-allopregnane-dione (VI) (20 mg.) with dry hydrogen chloride in chloroform gave progesterone (VII) in prisms melting at 125° after recrystallization from methanol. Yield about 80% (15 mg.). The substance showed a perfect physiological activity characteristic of progesterone.

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(4) The triol 3-acetate gave finally testosterone through succeeding processes and was designated as 17α in conformity with the configuration of testosterone assigned at that time. Later it has been known that the configuration of testosterone was corrected to 17β, and in consequence the triol is undoubtedly the androstanetriol-(3β, 5α, 17β).

(5) Compare L. Ruzicka and A. C. Muhr, *Chem. Abst.*, **38**, 6294 (1944).

(6) *J. Org. Chem.*, **5**, 544 (1940).