A New Synthesis of Testosterone[1].

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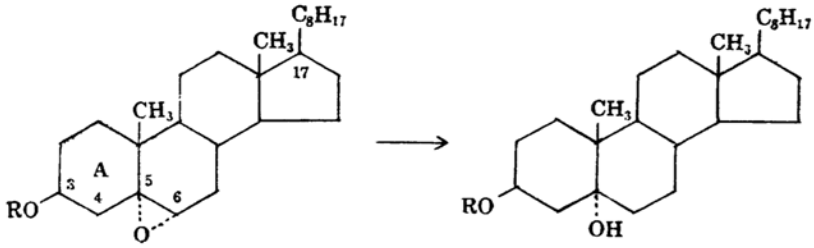
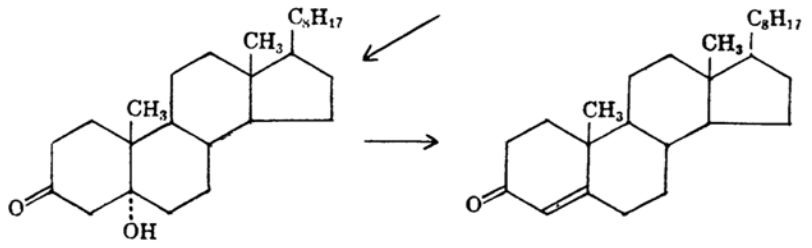
The scission reactions of α- and β-cholesterol oxides and their acetates have been studied in this laboratory[2] since the configurations of these stereo-isomeric oxido compounds were inferred from known informations.[3] A configuration of 5,6-epoxy-cholestanol-(3β) (I) (α-oxido structure) was assigned to α-cholesterol oxide. Its acetate (I′) gave cholestane-diol-(3β,5α) 3-acetate (II′) on catalytic reduction. It was hydrolysed to the free diol (II), and oxidation to 5-hydroxy-cholestanone-(3) (III) followed by dehydration yielded Δ^4-cholestenone (IV).[2]



(I) R = H: α-Cholesterol oxide
(I′) R = CH_3CO: The acetate of I
(II) R = H: Cholestane-diol-(3β, 5α)
(II′) R = CH_3CO: The 3-acetate of II



(III) 5-Hydroxy-cholestanone-(3)
(IV) Δ^4-Cholestenone

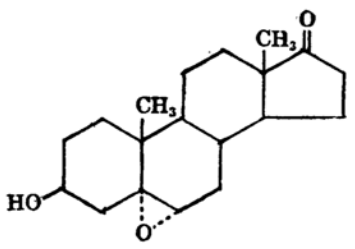
A similar course of reactions starting from α-dehydro-isoandrosterone oxide led successfully to a new synthesis of testosterone, a steroid hormone with ring A of the same structure as cholestenone. Two isomeric dehydro-isoandrosterone oxide acetates have been prepared, the higher melting isomeride (m. p. 221~222.5°) being designated as α and the lower melting (m. p. 188~190°) as β on the basis of the results of their acetolysis

(1) Abstract from the doctor thesis by M. Chuman. Read before the 68th annual meeting of the Chemical Society of Japan, on October 18th, 1946. Japanese Patent applied for on August 7th, 1946, and entered as No. 175210 on October 27th, 1947.

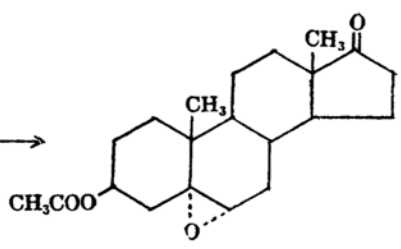
(2) M. Chuman, *J. Chem. Soc. Japan*, **64** (1943), 1369, 1486.

(3) Y. Urushibara, *this Bulletin*, **16** (1941), 182.

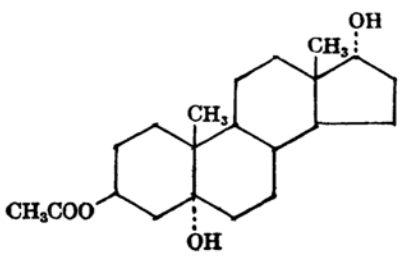
compared with those obtained with cholesterol oxide acetates[4]. Their configurations, however, had not yet been determined inasmuch as the designations α and β had been arbitrary in cholesterol oxides. α-Dehydro-isoandrosterone oxide acetate gave the changes corresponding to those of α-cholesterol oxide acetate, as described below, and thus was found to



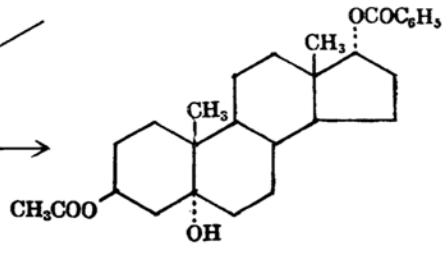
(V) α-Dehydro-isoandrosterone oxide



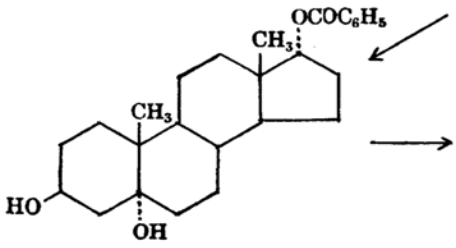
(VI) The acetate of V



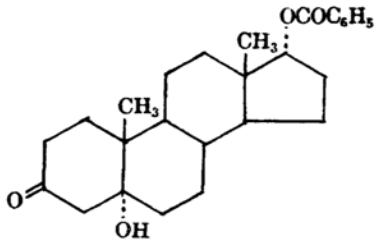
(VII) Androstane-triol-(3β, 5α, 17α) 3-acetate



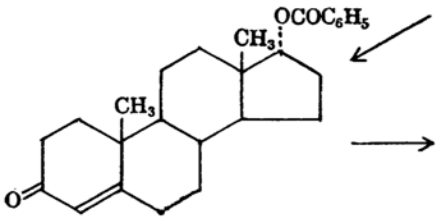
(VIII) The triol 3-acetate-17-benzoate



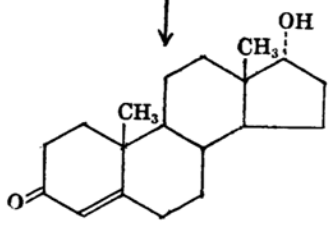
(IX) The triol 17-benzoate



(X) 5α-Hydroxy-17α-benzoxy-androstanone-(3)



(XI) Testosterone benzoate



(XII) Testosterone

(4) M. Ehrenstein, *J. Org. Chem.*, **6** (1941), 626. For earlier literature cf. *loc. cit.*

possess the same α-oxido structure (VI) as the latter, the configuration of which had been determined by one of the authors as mentioned above.

Catalytic reduction of α-dehydro-isoandrosterone oxide acetate (VI) (m. p. 220~221°), prepared from α-dehydro-isoandrosterone oxide (V) (m. p. 224~225°) with acetic anhydride and pyridine, with platinum oxide in glacial acetic acid gave androstane-triol-(3β,5α,17α) 3-acetate (VII), plates melting at 200~202° from acetone or ethyl acetate. On the reduction the oxido ring was splitted at the side of carbon atom 6 as in α-cholesterol oxide acetate[5] and the carbonyl group at carbon atom 17 was reduced to a hydroxyl group at the same time. The α- or trans-configuration of this hydroxyl group was determined because the triol finally gave (trans-)testosterone as described below.

The triol 3-acetate was benzoylated with benzoyl chloride and pyridine to androstane-triol-(3β,5α,17α) 3-acetate-17-benzoate (VIII), prisms melting at 232~234° from alcohol or ethyl acetate. Partial saponification with a calculated amount of methanol potash in two portions at the room temperature gave then androstane-triol-(3β,5α,17α) 17-benzoate (IX), flat needles or plates melting at 254~256° from acetone. Oxidation of the latter with chromic acid in glacial acetic acid at the room temperature yielded 5α-hydroxy-17α-benzoxy-androstanone-(3) (X), scales melting at 230~232° from alcohol, which was dehydrated with thionyl chloride and pyridine or better with hydrogen chloride in chloroform to testosterone benzoate (XI) melting at 180~182°. Saponification of the benzoate with methanol potash gave testosterone (XII) melting at 152~153°. The substance thus obtained was identified with an authentic specimen in the free state and in the form of acetate.

The action of dilute methanol potash on 5α-hydroxy-17α-benzoxy-androstanone-(3) effected saponification and dehydration to testosterone in one procedure.[6]

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(5) By a similar catalytic reduction the oxido ring in β-cholesterol oxide acetate is splitted at the side of carbon atom 5 and cholestane-diol-(3β, 6β) 3-acetate (but none of coprostane derivatives) is formed.

(6) Japanese Patent applied for on March 20th, 1947. This improvement was not reported in the paper read before the annual meeting mentioned above but included in the doctor thesis by M. Chuman.