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THE TOTAL SYNTHESIS OF 8-ISOTESTOSTERONE

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IN 1956, we reported the stereospecific syntheses of the benzohydrindanes (Ia and Ib) and dl-equilenin methyl ether,[1] with the expressed intention of converting Ia and Ib, *via* Birch reduction, to steroids, obviously, by the addition of ring A.[2] Recently Velluz and his coworkers have published a series of papers, wherein they have described the conversion of Ia and one of its optical antipodes to 19-nortestosterone,[3a] cortisone,[3b] and oestradiol[3c] by the method broadly indicated by us, the starting material having been prepared by our method.[1a] In view of these publications,[3] we wish to report the completion of one part of our work in this field, *viz.* the total synthesis of 8-isotestosterone starting from Ib.

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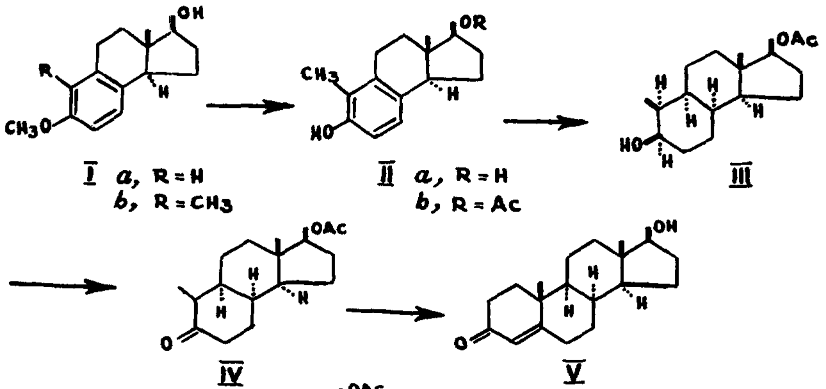
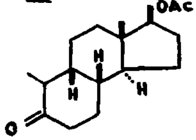
[1] a. D.K.Banerjee, S.Chatterjee, C.N.Pillai and M.V.Bhatt, *J.Amer.Chem.Soc.* **78**, 3769 (1956); b. D.K.Banerjee and S.K.Balasubramanian, *J.Org.Chem.* **23**, 105 (1958).

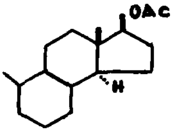
[2] *cf.* G.Stork, H.J.E.Loewenthal and P.C.Mukharji, *J.Amer.Chem.Soc.* **78**, 501 (1956).

[3] a. L.Velluz, G.Nomine, J.Mathieu, E.Toromanoff, D.Bertin, J.Tessier and A.Pierdet, *Compt.rend.* **250**, 1084 (1960); b. L.Velluz, G.Nomine, J.Mathieu, E.Toromanoff, D.Bertin, R.Bucourt and J.Tessier, *Compt.rend.* **250**, 1293 (1960); c. L.Velluz, G.Nomine, J.Mathieu, E.Toromanoff, D.Bertin, M.Vignau and J.Tessier, *Compt.rend.* **250**, 1510 (1960).





VI



VII

Demethylation of (Ib) with methyl magnesium iodide[4] at 175° gave the hydroxy phenol (IIa), m.p. 199-200°, in 79% yield. Partial acetylation of the hydroxy phenol (IIa) by refluxing with acetic acid and a catalytic amount of p-toluenesulphonic acid[5] gave the acetoxy phenol (IIb), m.p. 147°, in 42% yield. Hydrogenation of IIb in alcohol in the presence of 5% ruthenium-on-carbon catalyst[6] under 300 atm. pressure and at 100-110° gave a mixture

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[4] a. A.L.Wilds and W.B.McCormack, J.Amer.Chem.Soc. 70, 4127 (1948); b. W.S.Johnson, E.R.Rogier and J.Ackermann, J.Amer.Chem.Soc. 78, 6322 (1956).

[5] C.Chen, Private communication; cf. Tetrahedron 3, 43 (1958).

[6] We are indebted to Baker & Co. for a gift of this catalyst.

which on chromatography over alumina yielded the hydroxy acetate (III) as the major product, m.p. 87-88°; 95°, besides small quantities of the hydrogenolysed material (VII), m.p.75°, and a gum. Oxidation of III by chromic acid in sulphuric acid and acetone[7] furnished the acetoxy ketone (IV), m.p. 144-145°; 152-153°. The gum on oxidation by the same method[7] gave mainly the above acetoxy ketone (IV) and a small amount of a stereoisomeric ketone (VI). The major product of the hydrogenation - oxidation sequence is assigned the configuration (IV) on the basis of Linstead's hypothesis of catalyst hindrance.[8] The axially oriented β-methyl group in IIb is likely to hinder the β-approach of the catalyst. The configuration (VI) of the isomeric oxidation product is based on analogy with the work of Robinson[9] and of Chen.[10] The addition of vinyl methyl ketone to the acetoxy ketone (IV) in presence of "Triton-B" under nitrogen proceeded in a completely stereospecific fashion to give the tetracyclic ketone (V), m.p. 172.5-173.5°. The alkylation is very likely to take place from the convex side (α) of the <u>cis</u>-decalin system (IV). All our stereochemical deductions were confirmed by establishing the identity of our synthetic

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[7] C.Djerassi, E.R.Engle and A.Bowers, <u>J.Org.Chem.</u> <u>21</u>, 1547 (1956).

[8] R.P.Linstead, W.E.Doering, S.B.Davis, P.Levine and R.R.Whetstone, <u>J.Amer.Chem.Soc.</u> <u>64</u>, 1985 (1942).

[9] a. J.W.Cornforth, O.Kauder, J.E.Pike and R.Robinson, <u>J.Chem.Soc.</u> 3348 (1955); b. W.B.Renfrow and J.W.Cornforth, <u>J.Amer.Chem.Soc.</u> <u>75</u>, 1347 (1953).

[10] C.Chen, see reference 5; Dr.Chen kindly informed us that the oestrane isomer to which he had earlier[5] assigned the 5α,10β configuration was actually 5β,10β.

material with 8-isotestosterone obtained by Djerassi[11] from diosgenin by a comparison of their I.R. spectra.[12]

Works are in progress on the conversion of 8-isotestosterone to testosterone via 6,7-dehydro-8-isotestosterone and also on the preparation of 9-iso, 10-iso- testosterone from the isomeric acetoxy ketone (VI).

All compounds reported in this communication gave correct elementary analyses and infra-red and ultra-violet spectra.

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[11] C.Djerassi, A.J.Manson and H.Bendas, Tetrahedron **1**, 22 (1957).

[12] We are greatly indebted to Prof.C.Djerassi for a copy of the I.R. spectrum of the authentic 8-isotestosterone.