

SYNTHESES* OF 8-ISO-19-NORANTHRATESTOSTERONE**
AND 8-ISO-10-ISO-19-NORTESTOSTERONE

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(Received in UK 6 February 1968; accepted for publication 11 March 1968)

In continuation of our reported (1) synthesis of dl-8-isotestosterone (VIIb) and its anthracene analogue (Vb), the investigation on the synthesis of the corresponding 19-nor analogues was undertaken.

Demethylation of dl-trans-1 β -hydroxy-8-methyl-4,5-(4'-methoxybenzo)-hydrindane (Ia) (2) afforded the hydroxy phenol (Ib), m.p. 152-153°. The acetoxy phenol (Ic), m.p. 133-134°, was obtained in an overall yield of 86% from (Ib) by selective saponification of the diacetate (Id), m.p. 82-83°. Hydrogenation of (Ic) furnished the hydroxy acetate (IIa), m.p. 96-97°; 108-111°, (major product) and a very small quantity of its isomer (III), m.p. 92-93°, together with the diol (IIB), m.p. 152-153°, and a gum. Oxidation of the isomeric hydroxy acetates, (IIa) and (III), with Jones' reagent yielded the identical keto acetate (IVb), m.p. 136°. The gum also, on oxidation, yielded a small quantity of (IVb). The hydroxymethylene derivative of the keto acetate (IVb) was methylated and treated with alcoholic hydrochloric acid. The resulting product on acetylation furnished a methylated keto acetate, m.p. 117-117.5°, in which the methyl group should be equatorial. This compound was found to be different from the previously reported (1) dl-1 β ,2 α -(3'-acetoxy-cyclopentano)-2 β ,5 β -dimethyl-6-keto-1 α ,2,3,4 $\alpha\alpha$,5 α ,6,7,8,8 $\alpha\alpha$ -decahydronaphthalene (IVa), m.p. 159-160°, in which the methyl group was proved to be equatorial by equilibration experiment. Therefore, the methylated keto acetate should be represented by (IVc) and the hydroxymethylene group attached to the 7-position. The

* Presented at the Joint Convention of the Chemical Research Committee, C.S.I.R., and the Indian Chemical Society held in December 25-29, 1965 at Aligarh, India.

** This work formed a part of the thesis submitted by Dr. B. Sugavanam in 1965 in partial fulfilment of the Ph.D. Degree of the Indian Institute of Science.

hydroxymethylene derivative was next condensed with methyl vinyl ketone to give dl-8-iso-19-noranthraterosterone (Va), m.p. 151-153°.

At this stage, Velluz *et al.* (3) reported the total synthesis of d-8-iso-19-nortestosterone (VIIa) (4) and its ethylenic isomer (VI) by direct condensation of methyl vinyl ketone with d-keto acetate (IVb), the latter being prepared from d-(Ia) following identical steps described by us (1) for the synthesis of dl-8-isotestosterone (VIIb). Later, they claimed (5) the preparation of d- and l-forms of (VIIa), 8-iso-10-iso-19-nortestosterone (VIII) and the β,γ -isomer (VI).

These results prompted us to prepare (VI) and (VIII) by the following unambiguous method. dl-Dihydroequilenin (IXa), m.p. 225°, was hydrogenated (6,7) to furnish, along with the neutral material, dl-8-isooestradiol, m.p. 185-186°, in 21% yield. Birch reduction of dl-8-isooestradiol methyl ether, m.p. 101.5-102°, followed by hydrolysis with oxalic acid furnished dl-8-iso-17 β -hydroxy-19-norandrost-5(10)-en-3-one (VI), m.p. 159-160°. Treatment of (VI) with methanolic hydrochloric acid under nitrogen gave a mixture of β,γ - (major product) and α,β -unsaturated keto alcohols, which were separated by "Inverted Dry Column Chromatography" (8). The IR (CHCl₃) of the β,γ -isomer was identical with that of the sample obtained from Dr. Velluz. The IR (nujol) of the α,β -isomer, m.p. 148.5-152°, was different from that of the α,β -unsaturated keto alcohol (Va) and their mixture m.p. was depressed. Although Djerassi (9) suggested a boat conformation of the B-ring in 8-isotestosterone (VIIb) on the basis of the ORD data, yet the possibility of enolization of the C-10 hydrogen of the corresponding 19-nor compound under the equilibrating conditions employed for isomerization of the β,γ -isomer (VI) led us to assign α -configuration to it with the preferred all chair arrangement. To prepare the d-19-nor-compound, whose ORD data should prove the configuration, the ethylene ketal of d-equilenin (IXb), m.p. 175-176.5°, was hydrogenated. The phenolic fraction obtained after removal of the ethylenedioxy group consisted of d-8-isooestrone (major product) and d-9-isooestrone. d-8-Isooestrone methyl ether, m.p. 81-82°, was converted to the β,γ - and α,β -unsaturated keto alcohols, (VI)

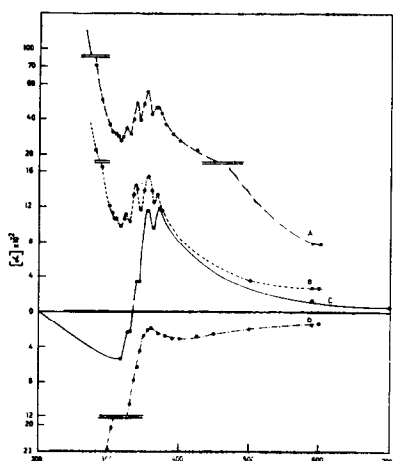
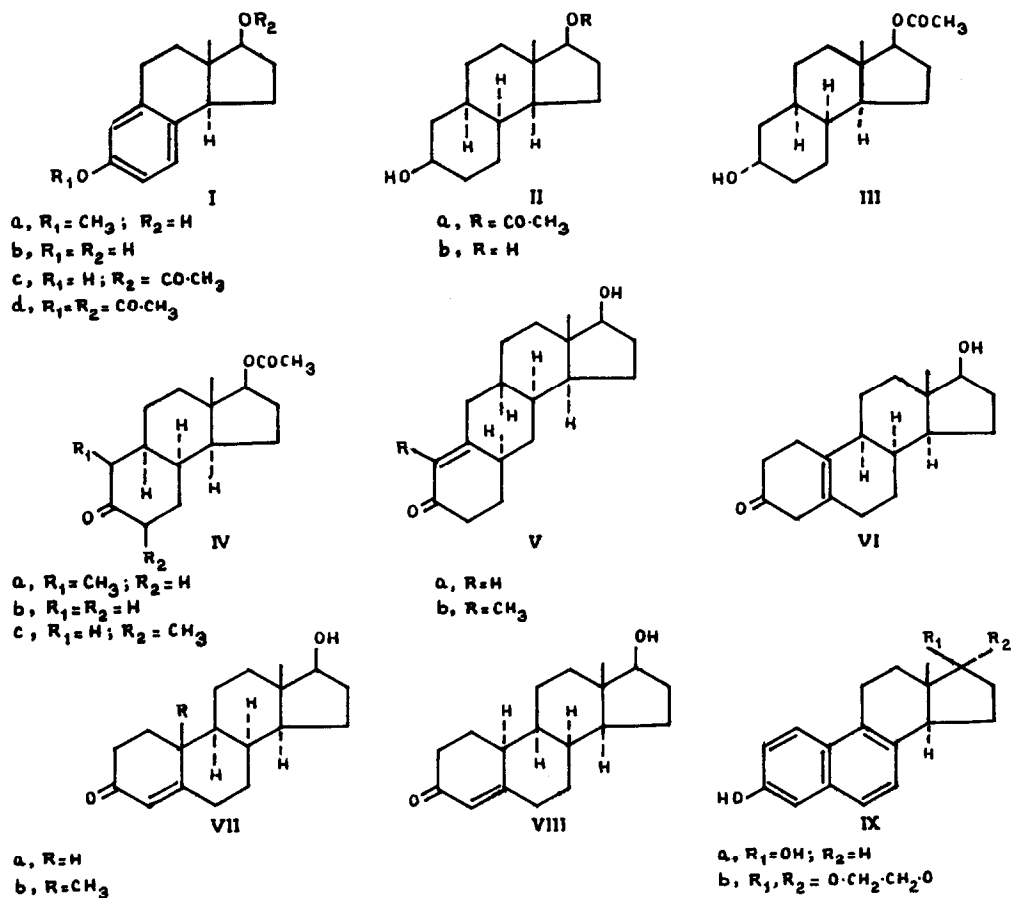


Fig.1

ORD Curves

- A. Authentic d-8-iso-10-iso-19-nortestosterone (VIII).
- B. d-8-Iso-10-iso-19-nortestosterone, supplied by Dr.R.Bucourt and Dr.G.Nomine.
- C. d-8-Iso-testosterone (9).
- D. d-8-Iso-19-nortestosterone, supplied by Dr.R.Bucourt and Dr.G.Nomine.

and (VIII). Mixture m.p. determination and the IR spectra (nujol) of Velluz's sample and our authentic \underline{d} -(VI), m.p. 187-190°, proved their identity. The shapes of the ORD curves (Fig.1) of the \underline{d} - α,β -isomer, m.p. 167-170°, and \underline{d} -8-isotestosterone (9) were different, proving the α -configuration of the C-10 hydrogen of the former (VIII). The ORD curve (Fig.1) of the sample of \underline{d} -8-iso-10-iso-19-nortestosterone, furnished by Dr. Nomine and Dr. Bucourt, was identical with that of our authentic compound (VIII); the mixture m.p. was also not depressed. Torgov *et al.* (10) claimed the preparation of \underline{d} 1-8-iso-19-nortestosterone (VIIa). Later, Smith (11) carried out the same experiment and suggested the possibility of the presence of the 10 α -compound (VIII) in the mixture he obtained. On the basis of the present work, Torgov's compound should be \underline{d} 1-8-iso-10-iso-19-nortestosterone (VIII).

The ORD curve (Fig.1) with the negative Cotton effect of the sample supplied by Dr. Nomine and Dr. Bucourt as 3-oxo-17 β -hydroxy-8 α -oestra-4-ene (VIIa), m.p. 138° (12), was entirely different from the positive ORD curve of \underline{d} -8-iso-testosterone (VIb). Therefore, this compound is definitely not 8-iso-19-nortestosterone.

Elemental analyses, IR and UV spectra were in agreement with the structures assigned to the compounds described in this communication. All m.p. are uncorrected.

Acknowledgement: Our grateful thanks are due to Professor W. S. Johnson, Stanford University, for ORD data and a few IR spectra, to Dr. B. Vithal Shetty, Strassenburgh Laboratories, for a gift of \underline{d} -equilenin, to Dr. L. Velluz and Dr. P. Poirier, Roussel-Uclaf, for their sample of 8-iso-19-nor- $\Delta^{5(10)}$ -androst-17 β -ol-3-one, to Dr. G. Nomine and Dr. R. Bucourt, Roussel-Uclaf, for their samples of 3-oxo-17 β -hydroxy-8 α ,10 α -oestra-4-ene and 3-oxo-17 β -hydroxy-8 α -oestra-4-ene. Our thanks are also due to the C.S.I.R., India, for financial help and a J.R.F. to B.S. and to the U.G.C., India, for a J.R.F. to G. N.

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