Tetrahedron Letters No.49, pp. 5093-5096, 1968. Pergamon Press. Printed in Great Britain.

TOTAL SYNTHESIS OF 8-ISO 19-NOR TESTOSTERONE AND 8-ISO 10-ISO 19-NOR TESTOSTERONE

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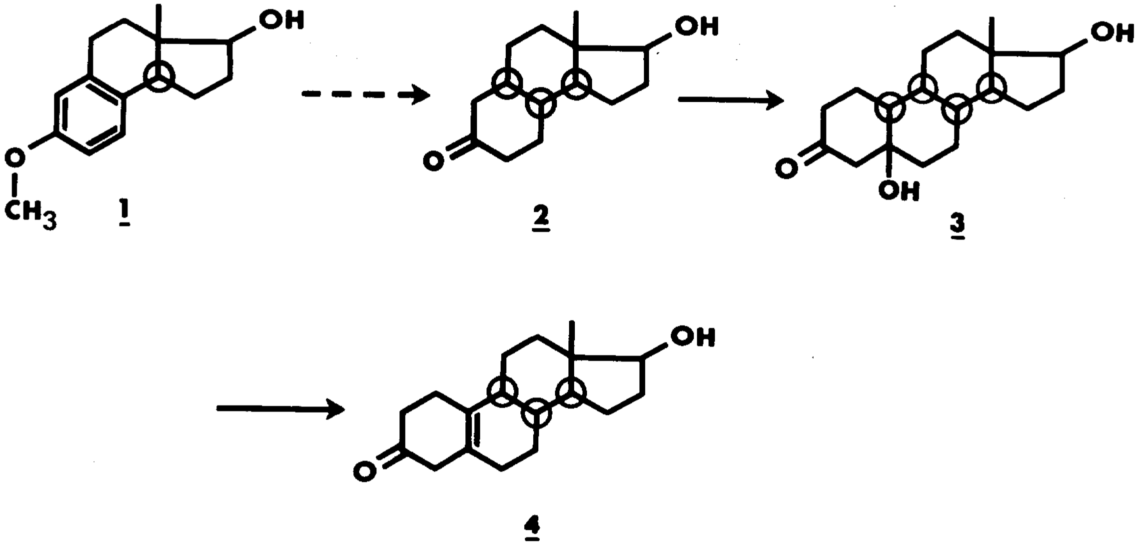
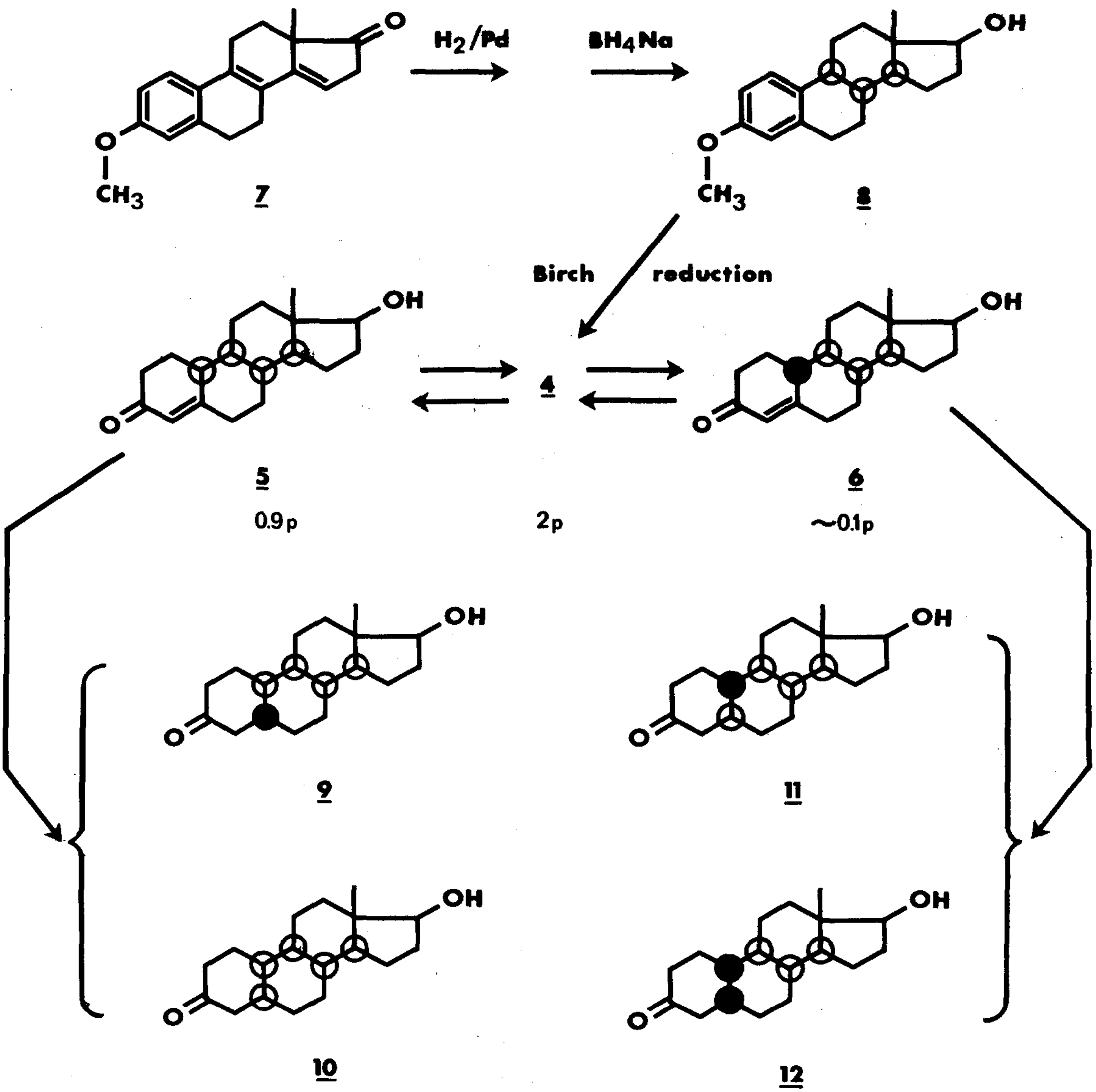
(Received in France 2 August 1968; received in UK for publication 6 September 1968)

In a previous paper (1) we reported the following route :



for the total synthesis of 8-iso 19-nor steroid compounds, starting from the optically active key intermediate 1. The A-ring elements of the steroid nucleus were added to the tricyclic ketoalcohol, 2, by means of Michael condensation of methylvinyl ketone. The aldol so obtained, 3, when treated with zinc chloride at 100°C, gave a mixture of the non-conjugated ketone 4 and its conjugated isomer (m. p. 176°, $[\alpha]_D$ + 123°). As we mentioned in our early



At first, the much greater stability of the 176° compound relative to the 138° one, reflected by the ratio of roughly 9 : 1 of the two compounds at equilibrium, suggested the choice of formula 5 for the 176° compound and the formula 6 for the 138° compound. A conformational analysis indeed revealed that the B ring of 5 may exist in a chair form while publication (ref. 1, formula IV, note 3), the stereochemistry at C_{10} of the conjugated ketone, m. p. 176°, remained unestablished at this stage of our work.

Since then, we have ascertained the configuration α of the C_{10} center of the conjugated ketone m. p. 176°, 5. Further, a third substance, m. p. 138°, which was isolated in very low quantity beside the compounds 4 and 5, proved to be the C_{10} epimer, 6, of the predominant conjugated compound 5.

In a recent issue of this periodical (2), Banerjee, to whom we sent, at his request, samples of our compounds for identification purposes, formulated erroneous criticisms, particularly about the authenticity of the conjugated ketone m. p. 138°. On the basis of the shape of the O. R. D. curve of this compound, different from that of 8-iso testosterone, the author wrote that our product "is definitely not 8-iso 19-nor testosterone". This prompts us to disclose the proofs of our structural assignments.

Taking advantage of a convenient asymmetric synthesis of the dienestrone 7 that was developed in our laboratory (3), the non-conjugated compound 4 is now more easily attainable by three successive reductions of 7 *via* the 8-iso derivative 8 following procedures previously described (4). This different approach confirms the point of attachment at C_{10} of the four carbon chain by the afore-mentioned Michael condensation (2 → 3).

On treatment with aqueous methanolic hydrochloric acid for 30 mn at room temperature, the non conjugated compound 4 underwent an isomerisation to give an approximately 2 : 0. 9 : 0. 1 mixture of the starting material 4 and two conjugated ketones m. p. 176° and m. p. 138° respectively. The two latter products, m. p. 176° and m. p. 138°, when separately submitted to the same acid treatment were also converted into the same equilibrium mixture of the same three substances. These observations led us to conclude that the only structural difference between the two conjugated ketones must be the configuration at C_{10}, one of these being 5 and the other 6.

this ring in the structure 6 must assume a twisted boat conformation increasing strongly the energy of 6 over that of 5.

This proposal was further substantiated by a study of the circular dichroism (C. D.) spectra of the four saturated ketones obtained from 5 and 6 by the following reactions. Reduction of the conjugated compound 5 (m. p. 176°) with lithium in liquid ammonia afforded as main product the ketone 9 (m. p. 216°) with a negative C. D. ($\Delta\varepsilon_{290} = - 1,36$), while the catalytic hydrogenation over palladium gave predominantly the ketone 10 (m. p. 130°) with a positive C. D. ($\Delta\varepsilon_{290} = + 1,53$). In a similar fashion the conjugated ketone 6 (m. p. 138°) yielded the ketone 11 (m. p. 137°) with a positive C. D. ($\Delta\varepsilon_{290} = + 1,69$), when chemically reduced, and the ketone 12 (m. p. 203°) having also a positive C. D. ($\Delta\varepsilon_{293} = + 0,11$) when catalytically hydrogenated. Octant projections of the four saturated ketones lead to the prediction of the following C. D. signs : - for 9, + for 10, + for 11 and + for 12. The correlation between the observed and the predicted signs of C. D. confirms that the conjugated ketone m. p. 176° is the 8-iso 10-iso 19-nor testosterone, 5, and the conjugated ketone m. p. 138° the 8-iso 19-nor testosterone, 6.

The deduction made by Banerjee (2) on the basis of O. R.D. comparison is therefore invalided. That α, β -unsaturated ketones of the same cyclic stereochemistry , but differently substituted, may exhibit unlike shapes of C. D. (or O.R. D.) curves has already been emphasized by a japanese research group (5). These authors reached the conclusion that "much caution should be exercised when correlating the Cotton effects of α, β -unsaturated ketones with their structure". The details of our study will be published elsewhere.

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