

### A ROUTE TO 8-AZAESTRONE

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(Received 19 June 1963; in revised form 26 July 1963)

MOST of the reported<sup>1,2</sup> preparations of azasteroids were partial syntheses utilizing natural steroids as starting materials. No azasteroids have been reported in which the nitrogen atom is common to two rings. We wish now to report the total synthesis of such a compound.

The condensation of 2-methyl-2-( $\beta$ -carboxyethyl)-cyclopentane-1,3-dione with m-methoxyphenethylamine affords a 35% yield of lactam I as a viscous oil. ( $\nu$ , 1748, 1668, 1628  $\text{cm}^{-1}$ ). Catalytic hydrogenation of this product proceeds stereospecifically to give in high yield a single saturated lactam, IIa, as an oil ( $\nu$ , 1740, 1640 1610  $\text{cm}^{-1}$ ). The same compound is formed in one step by reductive condensation of the diketo acid and the amine in the presence of 10% palladium on carbon catalyst. A second product formed during the course of the

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<sup>1</sup> T.L. Jacobs and R.B. Brownfield, J. Am. Chem. Soc. **82** 4033 (1960) and references cited therein.

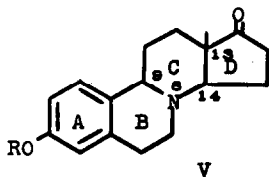
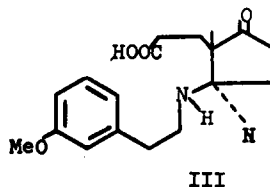
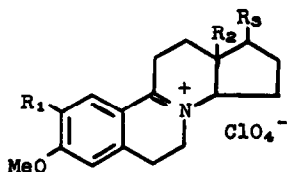
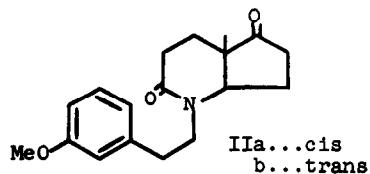
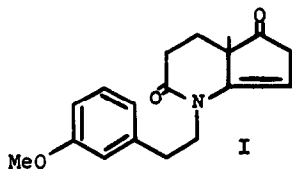
<sup>2</sup> J.H. Burckhalter and H. Watanabe, Abstracts 142nd. American Chemical Society Meeting, Cincinnati, Ohio, Biochem. No. 23, p. 14a, January, 1963.

reductive condensation is a crystalline amino acid (III), m.p.  $144^{\circ}$  from isopropanol ( $\nu$ , 1740, 1630, 1610,  $1560\text{ cm}^{-1}$ ). This amino acid is converted at its melting point to lactam IIB, m.p.  $82^{\circ}$  from cyclohexane. Stereochemical assignments to these 2 products are made on the basis of the widely differing ease of lactam formation, such behavior being consistent with the expected ease of ring closure based on examination of molecular models.

Treatment of lactams IIA and IIB with phosphorus oxychloride in benzene brings about cyclization to two isomeric quaternary salts, isolated as the crystalline perchlorates; cis perchlorate, IVA, m.p.  $159^{\circ}$  from methanol ( $\nu$ , 1740, 1630,  $1610\text{ cm}^{-1}$ ), trans perchlorate IVb, m.p.  $218^{\circ}$  from methanol ( $\nu$ , 1745,  $1610\text{ cm}^{-1}$ ). These salts are assigned the structures of para rather than ortho ring closure on the basis of the well-established preference of Bischler-Napieralski reactions for an available para position.<sup>3</sup> NMR spectra support this conclusion, since the aromatic region of these curves are typical of a 1,2,4- rather than a 1,2,3-tri-substituted benzene. Chemical proof of the direction of ring closure was obtained for the related salt IVc, prepared by the same route, by the standard procedure of oxidation to 3,4-dimethoxyphthalic anhydride and comparison of its N-methyl imide with authentic material.

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<sup>3</sup> W.M. Whaley and T.R. Govindachari, Organic Reactions, Vol. VI, p. 74. John Wiley and Sons, Inc. New York, (1951).



- Va...syn-cis\*...R=Me  
b...anti-cis\*...R=Me  
c...anti-trans\*...R=Me  
d...syn-cis\*...R=H  
e...anti-cis\*...R=H  
f...anti-trans\*...R=H

\* Prefixes syn-anti refer to the C-9; C-13 relationship. cis-trans refers to the C-D ring junction.

Catalytic reduction (platinum in ethanol) of the cis perchlorate IVa leads to a mixture of two bases, Va and Vb, in a ratio of 1 to 1.6, separable by fractional crystallization of the hydrobromide salts. Base Va, m.p. 125°, from aqueous acetone gives a white hydrobromide salt, needles from methanol m.p. 278.5-80°. Base Vb, m.p. 122° from aqueous acetone, gives

an off-white hydrobromide salt, plates from ethanol, m.p. 243-4°.

Reduction of perchlorate IVb gives a single saturated base, Vc, needles from acetone, m.p. 171-2°; hydrobromide, needles from ethanol, m.p. 246-8°.

Treatment of Va, Vb and Vc with 48% hydrobromic acid results in formation of three diastereomeric forms of 8-azaestrone, Vd, Ve and Vf respectively. Base Vd, m.p. 226-9° from aqueous acetone, forms a white crystalline hydrobromide, m.p. 286-8° from methanol. Base Ve, m.p. 191-3° from acetone, forms a white crystalline hydrobromide, m.p. 275-7° from methanol-ether. Base Vf forms a white crystalline hydrobromide, m.p. 282-285° from methanol-ether. This product is D,L-8-azaestrone.

The configurational assignments for the above saturated bases are made by consideration of the reduction product ratios formed under various conditions, molecular models of both the saturated and unsaturated compounds, epimerization studies, infrared absorption spectra, and by the relative rates of reoxidation of the saturated bases back to the quaternary salts by mercuric acetate. The data obtained in these studies and the arguments based on these data applied to the question of the configurations of the C-9 hydrogens, will be discussed at length in our full paper.

For all products, correct elemental analyses were obtained. Isomeric purities were determined by thin-layer chromatography.