

THE SYNTHESIS AND ITS ORD AND CD STUDY OF NEW STEROIDAL HETEROCYCLES
WITH A 4-OXOPERHYDROPYRIDAZINE SYSTEM FUSED TO RING D

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Much stereochemical interest has recently been shown on the reactions of steroid 2,4- and 5,7-dienes with esters of azodicarboxylic acid (1-3). The reactions have been found to be non-stereospecific giving both 1,4-adducts and addition-abstraction adducts (4) in different ratios.

We now wish to report in the present communication the first example of the Diels-Alder reaction of 3β -benzoyloxy-20-acetoxypregna-5,16,20-triene (I) with diethyl azodicarboxylate (II) leading to the epimeric (at C-16) 1,4-adducts* in high yield, and of the synthesis of new steroidal heterocycles with a 4-oxoperhydropyridazine system fused to ring D. The communication further provides a new information on ORD and CD that the Octant rule (9) can be applied to structural elucidation of the dissymmetric 4-oxoperhydropyridazine system (V).

The triene (I), prepared from 3β -benzoyloxy-20-acetoxypregna-5,16-dien-20-one (10) according to the procedure of Moffett and Weisblat (11), as colorless needles, m.p. 138-139°, ** *** $[\alpha]_D^{27} -32^\circ$ (c 0.79), reacted readily with

* Diels-Alder reactions of steroid 16,20-dienes (1-3, 5-8) have been reported to give the 1,4-adduct with α -configuration at C-16 as the only isolable product.

** All new crystalline compounds gave correct analyses.

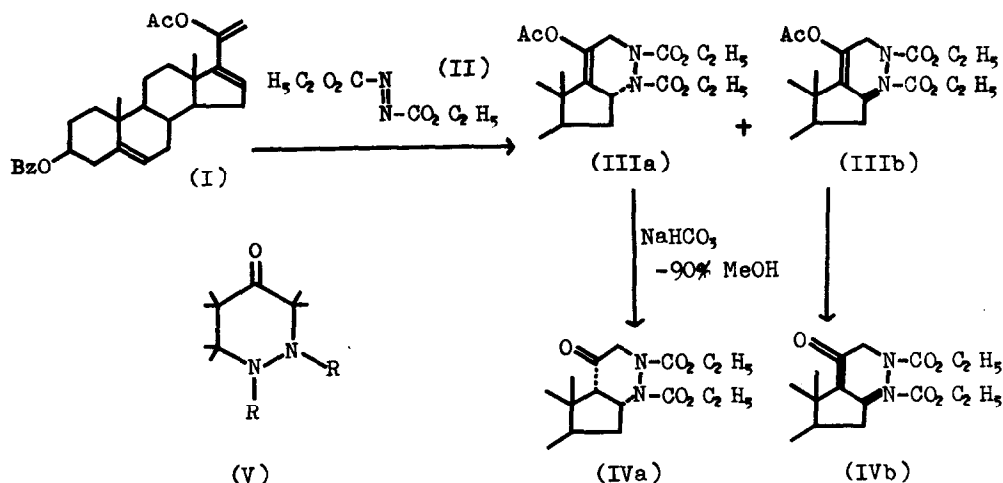
*** Optical rotations refer to chloroform, IR spectra to nujol, and NMR spectra (taken at 60 m.c. on a Varian Associates A-60 NMR spectrometer) to deuteriochloroform. The ORD and CD curves were run on a Japan Spectroscopic Co. ORD/UV-5 automatic recording spectrometer.

a slightly excess azo-ester (II) in refluxing benzene (6 hr) affording, on chromatography over silica gel, a mixture of epimeric (at C-16) 1,4-adducts, 3 β -benzoyloxy-20-acetoxy-16 α ,21-(N₁,N₂-bis(ethoxycarbonyl)hydrazo]pregna-5,17(20)-diene (IIIa) and its 16 β -epimer (IIIb), as a colorless semi-solid, $[\alpha]_D^{25} -50^\circ$ (c 1.25); $\nu_{\max} \text{ cm}^{-1}$: no NH absorption but 1757 (s) (20-OCOCH₃), 1738 (s), 1720 (s), 1712 (s) (N-CO₂C₂H₅, 3 β -OCOC₆H₅), in 76% yield. Formation of any addition-abstraction adduct was not observed.

That the product (III) is an epimeric mixture at C-16 was proved from the fact that rechromatography of III over silica gel (optical rotation and IR analyses) succeeded in separation of a small amount of a less polar component as a colorless semi-solid with the optical rotation of positive sign, $[\alpha]_D^{17} +2^\circ$ (c 0.98), and a more polar component as a colorless semi-solid with the rotation of negative sign, $[\alpha]_D^{17} \sim -69^\circ$ (c 0.07), in the ratio of 1:18. The minor (less polar) component was characterized to consist of 16 β -IIIb and the major (more polar) component was characterized as 16 α -IIIa, as, on mild alkaline hydrolysis (one eq. NaHCO₃, -90% methanol, reflux for 1^h min), the minor component afforded 3 β -benzoyloxy-16 β ,21-(N₁,N₂-bis(ethoxycarbonyl)hydrazo]pregn-5-en-20-one (IVb) as colorless needles, m.p. 174-175°, $[\alpha]_D^{24} -22^\circ$ (c 1.45), and the major component afforded 3 β -benzoyloxy-16 α ,21-(N₁,N₂-bis(ethoxycarbonyl)hydrazo]-17 α -pregn-5-en-20-one (IVa) as colorless needles, m.p. 153-154°, $[\alpha]_D^{23} +10^\circ$ (c 0.96), in 75% and 67% yields respectively. Further evidence for the epimeric character of III was provided that alkaline hydrolysis (NaHCO₃, -90% methanol) of III itself afforded directly those 20-keto derivatives, 16 α -IVa and 16 β -IVb, in 74% and 12% yields respectively.

Assignment of α -configuration at C-16 for the major product, IIIa, and its 20-keto derivative, IVa, and of β -configuration at C-16 for the minor product, IIIb, and its 20-keto derivative, IVb, was based on the mechanistic consideration that the general mode of attack to steroidal centers of unsaturation is from the α or less hindered side.

Assignment of cis ring juncture at C-16 and -17 of both IVa and IVb was based on the stereochemical consideration that trans ring juncture of six-membered ring on ring D appears to be very strained (7), whereas cis



ring juncture is not so. The more stable cis ring juncture is very likely to have been produced in the ketonization at C-20 of III to IV.

For these assignments, NMR informations were of further useful clue. The 18-methyl signal of IVa appears at τ 9.07 which is 0.10 p.p.m. lower than that of IVb, τ 9.17. Examination of possible conformations of VIa and VIb, which may exhibit the preferred stereochemistry around ring D of IVa and IVb respectively, suggests that while the 18-methyl group in the 17α -isomer lies in the area where the 20-keto group brings about a downfield shift, the 18-methyl group in the 17β -isomer lies about within the shielding cone of the 20-keto group. This agrees with the assignment of α -configuration at C-17 (and then at C-16) in IVa and of β -configuration at C-17 (and then at C-16) in IVb.

In relation to the structures and configurations of the isomeric 20-keto compounds, IVa and IVb, their ORD and CD analyses were proved to be very suggestive. As is shown in Fig. 1 and 2, IVa and IVb show symmetrical cotton effects with opposite sign. These data can well be understood if one applies the Octant rule to the 4-oxoperhydroimidazole system in IVa and IVb. The relation of configurations and signs in ORD and CD of the compounds is summarized in the Octant projection formulae VIIa for IVa and VIIb for IVb.

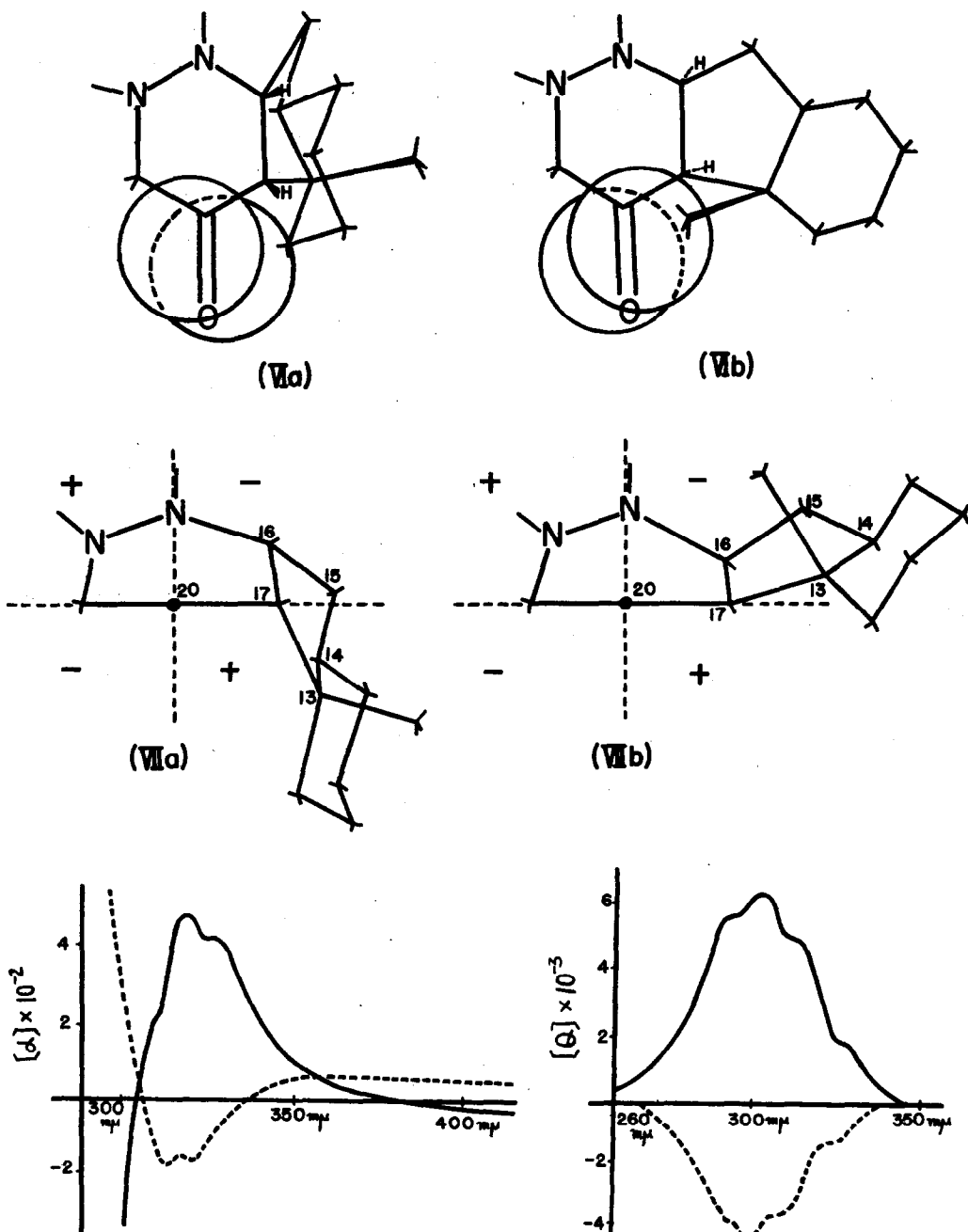


Fig.1 ORD Curves of Va (—) and Vb (---)

Fig.2 CD Curves of Va (—) and Vb (---)

The Diels-Alder reaction presented above has been successfully extended, for instance, to 3 β ,20-diacetoxypregna-5,16,20-triene, 3 β ,20-diacetoxy-11-oxo- α -pregna-16,20-diene and its 3 α -acetoxy- β -isomer as diene, and azodicarbonyl diamide as dienophile. The data will be published as a full paper elsewhere.

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