

Stereochemistry of 19-Hydroxy-19a-methyl-steroids

By E. CASPI and J. WICHA

(Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545)

WE present evidence for the 19-*S*-stereochemistry of the product (II) resulting from the reaction of methyl-lithium with 3 β ,17 β -diacetoxyandrost-5-en-19-al.¹ In addition, the rearrangement of the 19-acetate (IV) to the acyl derivative (VIII) is described.

The aldehyde (I) with methyl-lithium gave the triol (IIa) (90% yield). The triacetate (IIb) was selectively saponified to the monoacetate (IIc). Hydrogenation of (IIc) yielded (III) which was oxidized² to the diketone (IV). The 5 α -configuration of (III) and (IV) is based on a consideration of the stereochemistry of hydrogenation,³ on the o.r.d. data⁴ of (IV), and the formation of (VIb) and (VII) (see below⁵). The diketone (IV) gave the diketal (Va) (*ca.* 60%). Reduction of (Va) with lithium aluminium hydride yielded (Vb) and upon removal of the ketal groups the hydroxy-diketone (VI) was obtained. In the solid state (spectrum in KBr), the product existed, at least in part, as (VIa), as evidenced by bands at 3400, 1740, and 1712 cm.⁻¹ In chloroform solution, however,

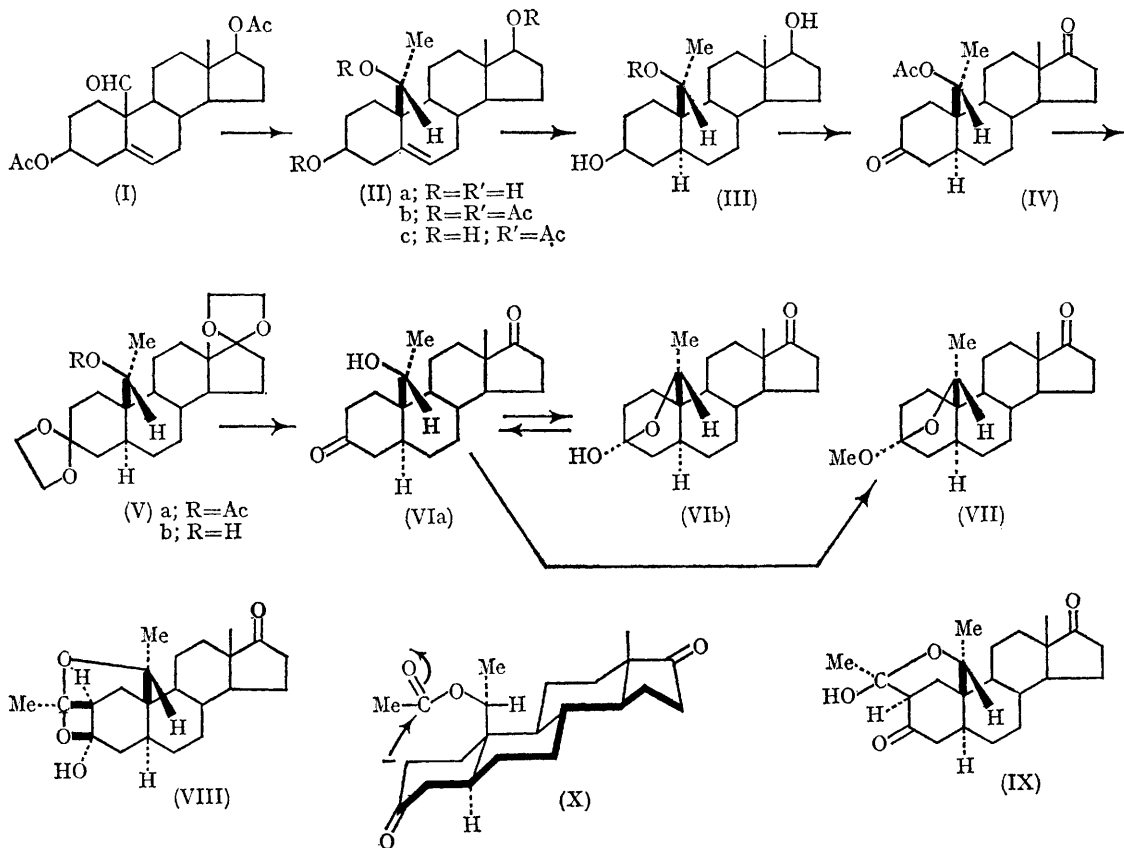
the hemiketal form (VIb) predominates (single band at 1730 cm.⁻¹). Conversion of (VI) into the methoxy-ketal (VII) provides support for the *trans* A/B junction.⁵

Inspection of models indicates that the rotation of the 19,19a-moiety around the C-10-C-19 bond is severely restricted and that the 19a-methyl will be located between carbons 1, 9, and 11 towards the rear of the molecule. Hence, the hydroxyl in (II) can be oriented either towards ring A giving the *S*-stereochemistry on C-19 or towards ring B giving the *R*-stereochemistry on C-19.

The spectrum of (VI) (in CHCl₃) and formation of (VII) provide evidence for the *S*-stereochemistry on C-19. Confirmation of the assignment was derived from the observed rearrangement involving the 19-acetate in diketone (IV). On attempted saponification of (IV) two products (VIII) and (IX) were isolated. Compound (VIII) was epimeric with the acetate (IV) and its structure was established by n.m.r. spectroscopy. Among

others, a singlet at 83.0 c./sec. equivalent to three protons was observed. The intensity and chemical shift of this resonance are consistent for a methyl on a carbon bearing two oxygens.⁶ The spectral

carbonyl⁷ of the 19-acetate as shown in (X). Since enolization of (IV) towards C-2 is more probable, we tentatively propose the structures (VIII) and (IX) for the products. The alternative



data for compound (IX) were in full agreement with the proposed structure. Moreover, it underwent easy conversion into (VIII) upon attempted recrystallization, heating under reduced pressure, sublimation, or treatment with acetic anhydride-pyridine.

It seems reasonable that rearrangement of (IV) proceeds *via* an intramolecular anion attack on the

structures with the acetyl attached at C-4 rather than C-2, though less probable, cannot be excluded on the basis of the present evidence. In any event, for the rearrangement to take place, the A/B junction must be *trans* and the acetate moiety at C-19 must be oriented towards ring A, hence the stereochemistry is 19-S.

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³ L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, 1959, p. 271.

⁴ C. Djerassi, "Optical Rotatory Dispersion", McGraw-Hill, New York, 1960, p. 49.

⁵ L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbé, E. Velarde, and J. A. Edwards, *J. Org. Chem.*, 1965, **30**, 2198.

⁶ E. Caspi, P. K. Grover, D. M. Piatak, and Y. Shimizu, *J. Chem. Soc.*, 1965, 3052.

⁷ For other examples of similar reactions, see A. Cross, U.S. Pat. 3,167,548 (*Chem. Abs.*, 1965, **62**, 11,876b); B. J. Magerlein and J. A. Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 2220; N. Tanabe, J. W. Chamberlin, and P. Nishiuta, *Tetrahedron Letters*, 1961, 601.