

The Conformation of Westphalen's
Diol Diacetate*

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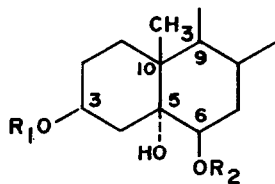
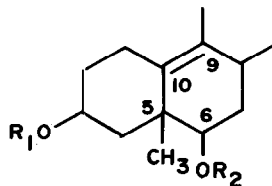
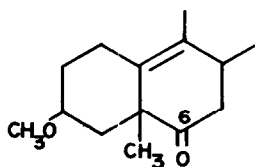
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In an attempt to acetylate the tertiary hydroxyl group of cholestane-3 β , 5 α , 6 β -triol, 3,6-diacetate (I), Westphalen¹ in 1915 treated the compound with acetic anhydride and sulphuric acid, but obtained in fact a re-arranged product whose correct structure was recognised as (II) after several decades². Since then considerable amount of work has been done on the environments necessary^{3a} for, and the mechanism^{3b} of, this reaction, but both of which are not yet quite clear^{3c}.

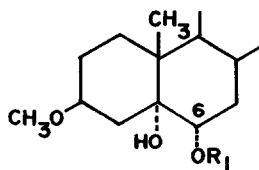
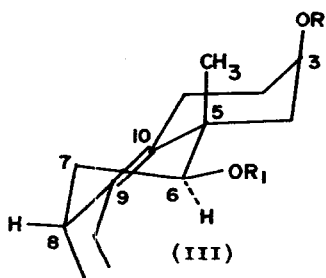
As the conformation of the starting material (I) is well known⁴, knowledge of the conformation of the re-arranged product (II) will not only be a useful additional information about it, but will also be of help in the other studies mentioned above. Compound (II) can exist in conformation (III), (A/B trans, B/C cis, C/D trans) or (IV), (A/B cis, B/C trans, C/D trans) or as a mixture of (III) and (IV), assuming the more stable all chair conformation for the molecule.

By an elegant series of experiments Jones and Summers recently concluded⁵ that (V) exists in conformation (IV). After hydrolysing (II) to a C₃-hydroxyl derivative, they methylated it to get (VI) which was hydrolysed to the C₆-hydroxy compound (VII), m.p. 107°, (α)_D²⁰ +118.5° which in turn was oxidised to the known ketone (VIII). Reduction of (VIII) with sodium and ethanol (or with LAH)

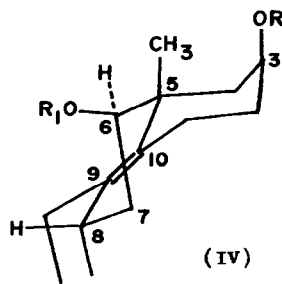
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(I) $R_1 = R_2 = \text{Ac}$ (IX) $R_1 = \text{CH}_3$; $R_2 = \text{Ac}$ (II) $R_1 = R_2 = \text{Ac}$ (V) $R_1 = R_2 = \text{H}$ (VI) $R_1 = \text{CH}_3$; $R_2 = \text{Ac}$ (VII) $R_1 = \text{CH}_3$; $R_2 = \text{H}$ 

(VIII)

(X) $R_1 = \text{Ac}$ (XI) $R_1 = \text{H}$ 

(III)



(IV)

$$R = \text{H} \quad \text{or} \quad \text{CH}_3 \quad \text{or} \quad \text{Ac}; \quad R_1 = \text{H} \quad \text{or} \quad \text{Ac}$$

Drawing of (III) is from the mirror image of Westphalen's compounds and the terms cis and trans are used for their A/B and B/C rings in the sense of quasi cis and quasi trans.

gave an oily 6α -alcohol $(\alpha)_D +22^\circ$. Grob and coworkers had earlier found⁶ that under vigorous conditions of acid catalysed equilibration, derivatives of Westphalen's diol gave a compound in which the double bond is isomerised to the 9,11-position when ring A probably became cis fused with the 5β -Me and a 10β -H. From these results Jones and Summers concluded that conformation (III) may be excluded for Westphalen's diol (V) and that it may be represented by conformation (IV).

However, from the unprecedentedly large M_D difference of over 400° between the 6β and the 6α -steroid alcohols, we suspected that the change that has taken place is more than the mere epimerization of the C_6 -alcohol. The problem was therefore reinvestigated. With the help of model compounds Westphalen's compounds were studied spectroscopically, as that would give more direct evidence.

Infrared spectra in carbon disulphide solution of cholestane 3β , 5α , 6β -triol, 3-methyl ether, 6-acetate (IX), which has a C_6 -axial acetate shows three strong bands at 1263, 1242 and 1227 cm^{-1} , whereas cholestane 3β , 5α , 6α triol, 3-methyl ether, 6-acetate (X) [m.p. 140° , $(\alpha)_D +42^\circ$, obtained by acetylating the corresponding $C_6\alpha$ -alcohol (XI) m.p. 172° , $(\alpha)_D +18^\circ$, prepared by treating cholesteryl methyl ether with osmium tetroxide], which has a C_6 -equatorial acetate shows only a single strong band at 1235 cm^{-1} due to the C-O-C stretching vibrations, as expected⁷. The IR spectrum of Westphalen's compound (VI) shows the C-O-C stretching band as a strong singlet at 1239 cm^{-1} . PMR spectrum of (IX) shows the $C_6\alpha$ -equatorial proton as a narrow triplet centred at $\tau 5.4$, $J \sim 3$ cps, whereas that of (X) shows the $C_6\beta$ -axial proton as a quartet centred at $\tau 5.1$, $J \sim 10$ and 5 cps as would be expected⁸ from the couplings of the axial and equatorial protons at C_7 with the C_6 -proton concerned. In the Westphalen's compound (VI), the $C_6\alpha$ -proton appears as a quartet centred at $\tau 5.2$, $J \sim 10$ and 5 cps. In the

diaacetate (II) also, the $C_6\alpha$ -H appears separate from the $C_3\alpha$ -H and as a quartet centred at τ 5.35; J \sim 10 and 5 cps. These clearly indicate that the $C_6\beta$ -acetate is equatorial and the $C_6\alpha$ -H axial, in the Westphalen's compounds (II) and (VI) and hence the conformation of the molecule should be represented by (III), and not by (IV) nor by a mixture of (III) and (IV).

The results of Jones and Summers could, however, be rationalised by assuming that the conformation of the molecule has flipped partly or wholly on oxidation of the alcohol (VII) to the ketone (VIII) (which is not unlikely since the 6β -substituent that probably stabilises (III) against (IV) is now removed) so that the alcohol they obtained on reduction may be partly or wholly the $C_6\alpha$ -equatorial alcohol⁹ with the rings in conformation (IV). That strong acid catalysed equilibration has isomerised $\Delta^9(10)$ to $\Delta^9(11)$, thereby making the A ring probably 5β , 10β , cis fused, does not necessarily mean that the A,B rings were in conformation (IV) and not in (III), when the double bond was present at C_9 , C_{10} .

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