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CONFORMATIONAL MOBILITY OF THE B RING IN SOME STEROIDS[*]

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The B ring being trans-fused to the C-ring at C_8, C_9, on one side, and fused to the A-ring at C_5, C_{10}, on the other side, is very rigid in the usual steroids and is generally taken as an example for the rigid chair form of the cyclohexane ring. However, when a double bond is introduced between C_9 and C_{10}, the possibility arises for the cyclohexene formed by the B ring to exist in two alternate half chair conformations, due to the flexibility at the carbon atoms C_6 and C_7. These two conformations in Westphalen's diacetate and corresponding compounds (I) to (V) can be represented by (VI) and (VII).

Models show that in (VI) where the C_6 β-substituent is axial, there is considerable crowding and consequent non-bonded interactions at the β-face of the molecule,due to the adjacent C_5-CH_3, C_3-axial substituent, C_8β-H and C_{13}-CH_3. This crowding is partly relieved in (VII), wherein the C_6β-substituent, which occupies a middle position, becomes equatorial (1). In agreement with this, it has been found that in (I), (II) (1) and (IV) (2), which in spite of having different substituents at C_3 and C_6 exist in conformation (VII).

However, when (III), (IV) or (V) is oxidised to the C_6-ketone, as in (VIII) to (X), this preference is no more applicable, and the B ring would be free to exist in

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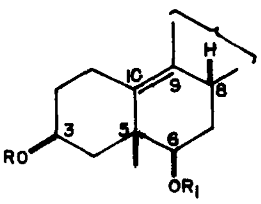
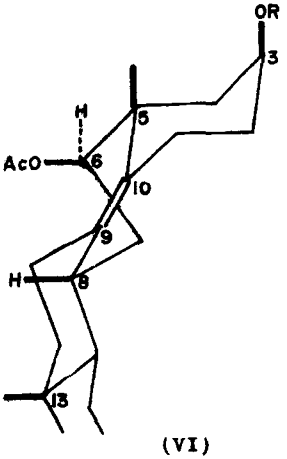
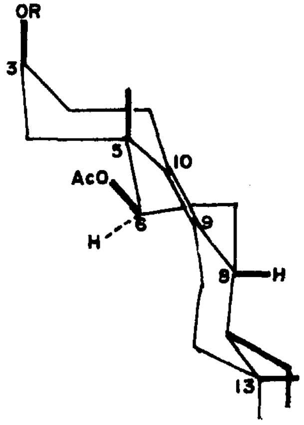


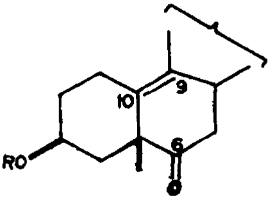
(I) R = R$_1$ = Ac
(II) R = CH$_3$; R$_1$ = Ac
(III) R = CH$_3$; R$_1$ = H
(IV) R = Ac, R$_1$ = H
(V) R = R$_1$ = H



(VI)



(VII)



(VIII) R = CH$_3$
(IX) R = Ac
(X) R = H

either of the two conformations (1). The ketone (VIII) obtained by oxidising (III) with chromium trioxide and pyridine (3) shows the expected IR and NMR spectra. Its UV absorption at λ_{max} 295 mμ shows a normal ε_{max} of 55, indicating thereby that there is no appreciable overlap between the C_9 double bond and the C_6-carbonyl (4). Models show that the ketone in conformation (VII) should give a positive Cotton effect, whereas in (VI), a strongly negative Cotton effect. The ORD curve of (VIII) (in methanol) shows a strongly negative Cotton effect at 310 mμ ($\Delta\varepsilon$ = -6.6); the CD curves of (IX) and (X) (in dioxane) also show strongly negative Cotton effects (5) at 297 mμ ($\Delta\varepsilon$ = -2.98) and at 296 mμ ($\Delta\varepsilon$ = -2.8) respectively. Therefore ketones (VIII) to (X) should be existing in conformation (VI) or as a mixture of conformations (VI) and (VII), but not in conformation (VII) alone. Hence reduction of the ketones with sodium and alcohol should be expected to give (6) the $C_6\alpha$-equatorial alcohol[from (VI)]or a mixture of both equatorial alcohols [from (VI) and (VII)].

Ketone (VIII) on reduction with sodium and ethanol gives an oil in 60% yield, which no more gives the IR or UV absorption for a ketone and instead gives a hydroxy band at 3400 cm^{-1}. The product on acetylation gives two overlapping spots on thin layer chromatography. Separation of the two by preparative thin layer chromatography by repeated development with benzene, 5% petroleum ether gives (II) as one of the products and a new compound, $(\alpha)_D$ +30°. It could not be resolved into further components by all solvent mixtures tried and hence should be considered chromatographically pure. Its IR spectrum in carbon disulphide solution differs from that of (II) and shows sharp peaks at 1730 and 1239 cm^{-1} showing thereby that it is the C_6 α-equatorial acetate (7). This is fully confirmed by its PMR spectrum, which gives a sharp quartet centred at δ 4.56 J = 11 and 4 cps, due to the axial $C_6\beta$-H, coupling with the axial and equatorial protons at C_7. Hydrolysis of the acetate gives the corresponding alcohol $(\alpha)_D$ +15°. These are thus quite different from the $C_6\beta$-acetate $(\alpha)_D$ +84°, C_6 α-H, δ 4.67 J = 10 and 5 cps and the C_6 β-alcohol, $(\alpha)_D$ +120° (8). The negative value of the $[M]_D$ difference between the alcohol and its acetate in the case of the α-alcohol, and the positive value in the case of the β-alcohol is in agreement with the rotational changes of the corresponding coprostane-6ols (9).

Thus, this is a very rare instance in the steroids, wherein, the B ring flips from one half chair conformation to another by a change of configuration of the C_6-substituent.

In Westphalen's compounds (I) to (V) with the C_9, C_{10}-double bond, the 1α and 11α hydrogen atoms are too close ($\backsim$1.5Å as per Drieding models), which considerably destabilise the molecule. In Δ^5, 10β, 9α,8β normal steroids (or in the saturated A/B trans ones) the distance between the 1β-H and 11α-H is only about 2Å or less. Although bonds could be twisted to increase this distance in the actual molecule, that will also involve strain. These facts would thus largely explain, why (i) the C_9, C_{10}-double bond is easily isomerized to the 9,11-position, making the A/B rings <u>cis</u> (10,2), (wherein the distance between the corresponding hydrogen atoms at C_1 and C_{11} goes beyond 3Å), (ii) all attempts to reverse Westphalen's rearrangement were unsuccessful (10) and (iii), even 5-cholestene appears to undergo Westphalen's rearrangement and the subsequent isomerization of the double bond to the 9,11-position (11,10).

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