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THE STEREOCHEMISTRY OF WOODWARD CIS-HYDROXYLATION IN SOME STEROIDAL OLEFINS

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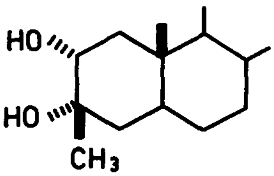
As a part of a study on the reaction of trisubstituted cyclic olefins with iodine and silver salts (1), the Prévost reaction of 3-methyl-5α-cholest-2-ene (I) and 2-methyl-5α-cholest-2-ene (II) was previously reported (2) to give no diols, the former leading to 3β-methyl-5α-cholestan-2-one (III) and a mixture of allylic alcohols [3-methyl-5α-cholest-2-en-4β-ol (IV), 3-methyl-5α-cholest-2-en-4α-ol (V), 3-methylen-5α-cholestan-2β-ol (VI), 3-methylen-5α-cholestan-2α-ol (VII), 3-methyl-5α-cholest-3-en-2β-ol (VIII), 3-methyl-5α-cholest-3-en-2α-ol (IX), 3-hydroxymethyl-5α-cholest-2-ene (X)], and the latter only to allylic alcohols [2-methyl-5α-cholest-2-en-1α-ol (XI), 2-methylen-5α-cholestan-3α-ol (XII), 2-methylen-5α-cholestan-3β-ol (XIII), 2-methyl-5α-cholest-1-en-3α-ol (XIV), 2-methyl-5α-cholest-1-en-3β-ol (XV) and 2-hydroxymethyl-5α-cholest-2-ene (XVI)].

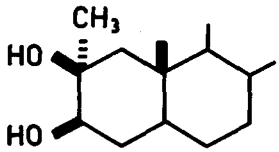
We have now found that in the Woodward conditions [reaction with iodine and silver acetate in moist acetic acid at room temperature (3) for 12 hours followed by alkaline hydrolysis] olefin (I) surprisingly gave cis-diol (XVII) (4) (m.p. 186-188°, $[\alpha]_D$ +27°, 22%) (5) with α-oriented hydroxyls, besides ketone (III) (17%) and alcohols (IV) (3%), (V) (2%), (VIII) (24%), (IX) (1%), (X) (<1%). On the other hand cis-diol (XVIII) (m.p. 171-172°, $[\alpha]_D$ +28°, 33%) (5) obtained from isomeric olefin (II), besides alcohols (XI) (5%), (XII) (3%), (XIV) (7%), (XV) (5%), (XVI) (3%) and 2α-methyl-5α-cholestan-3-one (XIX) (1%) (6), has the expected opposite ββ configuration (7).

As an explanation of this striking behaviour we suggest that in both olefins the addition of electrophilic iodine occours preponderantly, but not at all exclusively, from the α side of the molecule (8).

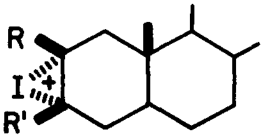
Thus olefin (I) gives apart from the α-iodonium ion (XXa), a minor but significant amount of the β-isomer (XXIa) which, besides competitive elimination to allylic iodide (9) as suggested for Prévost reaction (1), undergo transdiaxial opening respectively to iodoesters (XXIIa) and (XXIIIa). The reaction of (XXIIIa) with silver acetate then yields ion (XXIVa) from which αα-diol (XVII) is obtained, by hydrolysis. On the other hand, iodoester (XXIIa) fails to yield dioxolenium ion (XXVa) which would be destabilized by 1,3 interactions between 3α-methyl (10)



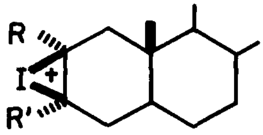
XVII



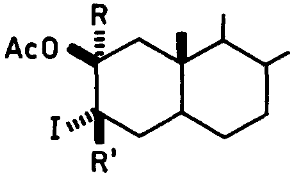
XVIII



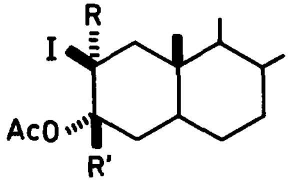
XX



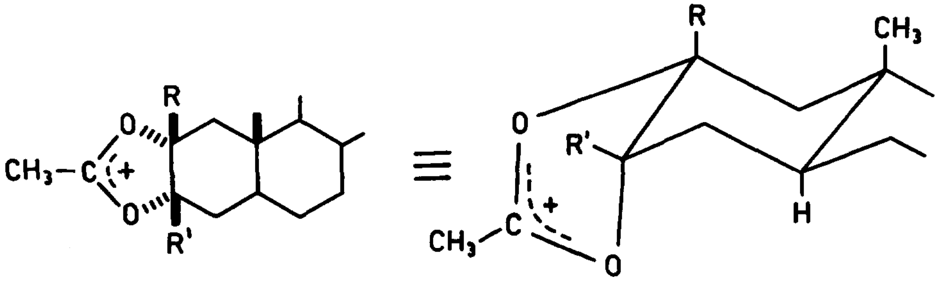
XXI



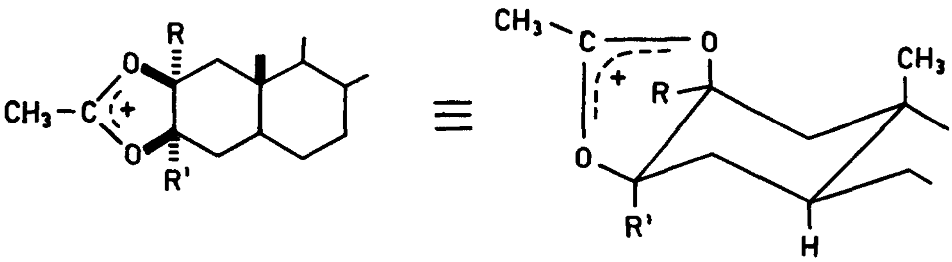
XXII



XXIII



XXIV



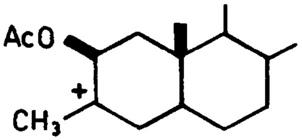
XXV

a R= H; R'= CH_3

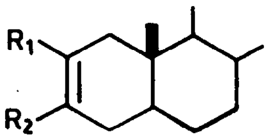
b R= CH_3: R'= H

and axial 1α- and 5α-hydrogens. The tertiary open carbocation (XXVI) (3-methyl on a trigonal carbon) is formed instead, which by elimination leads to enolacetate (XXVIIb) and (VIII)-acetate. Hydrolysis of these then yields ketone (III) and alcohol (VIII).

In a similar way, α-iodonium ion (XXb) from olefin (II) gives dioxolenium ion (XXVb) via trans-iodoacetate (XXIIb) and then the corresponding ββ-diol (XVIII). On the other hand, iodoester (XXIIIb) leads to tertiary carbocation (XXVIII), instead of the cyclic ion (XXIVb) because of the interactions of 2β-methyl (10) with angular methyl and 4β-hydrogen existing in this latter. Hydrolysis of enolacetate (XXVIIa), (XII)-acetate and (XIV)-acetate derived from (XXVIII) by elimination then gives (XIX), (XII) and (XIV) (11).

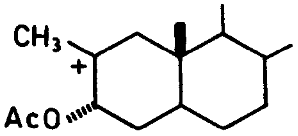


XXVI



XXVII

a $R_1 = CH_3$; $R_2 = OAc$
b $R_1 = OAc$; $R_2 = CH_3$



XXVIII

It is noteworthy that the behaviour of cholest-5-ene, which has been recently reported to give 5α,6α-diol (16% yield) in the Woodward conditions (14), may be analogously rationalized. Attack of electrophilic iodine from the less-favoured β side leads to αα-dioxolenium ion and then to observed cis-diol. The alternative, and more favoured, addition from the opposite α side fails to give ββ-dioxolenium ion because of the interactions between the heterocyclic ring and angular methyl, the tertiary carbocation being formed instead. This then gives the unidentified side-products (allylic alcohols?). Cholest-4-ene, however, which may give a ββ-dioxolenium ion where such interactions are not present, yields the expected 4β,5β-diol (14).

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REFERENCES AND FOOTNOTES

1. F.D. Gunstone, *Advances in Organic Chemistry*, *1*, 117 (1960).
2. L. Mangoni e V. Dovinola, *Gazz. Chim. It.*, *99*, 176 (1969); V. Dovinola e L. Mangoni, *ibid*, *99*, 195 (1969).
3. P.S. Ellington, D.G. Hey and G.D. Meakins, *J. Chem. Soc*. (C), 1327 (1966).
4. Satisfactory analyses were obtained for all compounds reported. Melting points were determined on a Kofler block and have not been corrected. Specific rotations were determined on chloroform solutions at room temperature.
5. Identified by comparison with an authentic sample (V. Dovinola, M. Adinolfi e L. Mangoni, *Gazz. Chim. It*., in press).
6. Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc*., *80*, 5220 (1958).
7. The Woodward cis-hydroxylation of olefins with a disubstituted double bond is known to give diols with hydroxyls on the more hindered side of the molecule (F.D. Gunstone, loc. cit.).
8. The α side is the less hindered one in both (I) and (II) as epoxidation [D.H.R. Barton et al., *J. Chem. Soc*., 3500 (1956); C. Djerassi et al., *J. Am. Chem. Soc*., *82*, 5488 (1958)] and cis-hydroxylation with osmium tetroxide (V. Dovinola, M. Adinolfi e L. Mangoni, loc. cit.) occurs predominantly from the α side.
9. The intermediacy of allylic iodides has been proposed in order to rationalize the formation of allylic alcohols (IV)-(X) (L. Mangoni e V. Dovinola, loc. cit.).
10. The orientation of 3α-methyl (and 2β-methyl, see below) is not rigorously axial as the ring of the dioxolenium ion is probably flattened by resonance [E.L. Eliel, N.L. Allinger, S.G. Angyal and G.A. Morrison, *Conformational Analysis*, Interscience, New York (1967)].
11. The isolation in very low yields of both 3β-methyl-5α-cholestan-2α,3α-epoxide (12) and 3α-methyl-5α-cholestan-2β,3β-epoxide (m.p. 107-108°, $[\alpha]_D$ +52°), obviously originated from unreacted iodoesters (XXIIIa) and (XXIIa) during final alkaline hydrolysis, supports the attack of electrophilic iodine on both sides of olefin (I). From olefin (II) a small amount of 2β-methyl-5α-cholestan-2α,3α-epoxide (13) and 2α-methyl-5α-cholestan-2β,3β-epoxide (m.p. 111-113°, $[\alpha]_D$ +52°) is analogously obtained.
12. D.H.R. Barton et al., loc. cit. .
13. C. Djerassi et al., loc. cit. .
14. C.W. Davey et al., *J. Chem. Soc*. (C), 2674 (1968).