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STEREOSELECTIVITY IN THE HYDROLYSIS OF ACYLOXONIUM IONS AND ORTHO ESTERS FUSED TO RIGID SIX-MEMBERED RINGS

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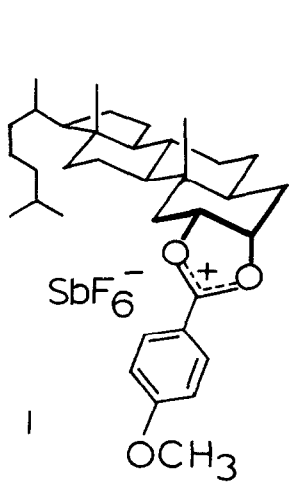
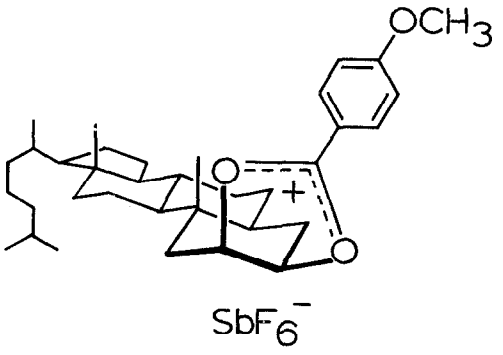
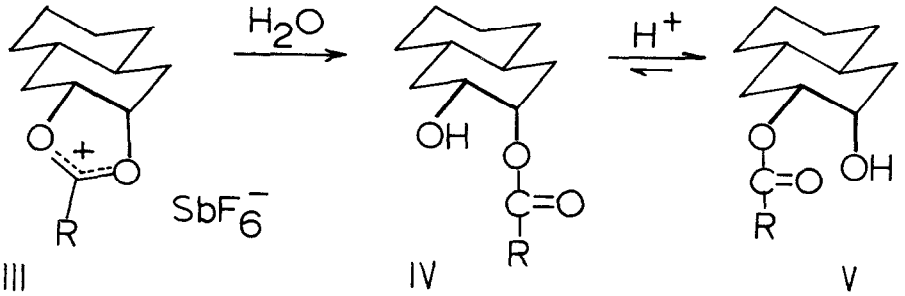
We have recently prepared acyloxonium (dioxolenium) salts I-IIIa, in which the five-membered ring is fused to a trans-decalin system, and have noted (1) that their S_N2 reaction with bromide ions normally yields predominantly the diaxial bromohydrin ester. In continuing our study of the stereochemistry of the reactions of acyloxonium ions, we have found that simple hydrolysis of these compounds to the cis-hydroxyester shows remarkable stereoselectivity. Treatment of IIIa in methylene chloride solution with aqueous acetic acid at room temperature, gave almost exclusively IVa, the compound in which the acyloxy group is axial and the hydroxyl equatorial. Thin layer chromatography shows a trace of the equatorial ester (Va), estimated to be less than 0.5% of the amount of IVa. The equatorial ester (Va) is readily obtained by acid-catalyzed rearrangement of IVa. Treatment of either pure IVa or Va with camphor-10-sulfonic acid gives an apparent equilibrium mixture containing roughly twice as much Va as IVa, clearly showing that the formation of IVa from IIIa is the result of kinetic control.



I



II



III IV V

a) R = CH_3O–C$_6$H$_4$–

b) R = CH_3CH_2–

c) R = CH_3–

d) R = C$_6$H$_5$–

e) R = H–

Exactly analogous results were obtained from I and II, each giving the corresponding axial ester (respectively, 5α-cholestan-2α-ol-3α-yl anisate (VI), and 5α-cholestan-3β-ol-2β-yl anisate (VII)), each of which in turn could be rearranged to the appropriate equatorial ester. The structures of VI and VII were demonstrated by (i) hydrolysis to the respective cis-glycols, and (ii) oxidation of VI and VII to the corresponding α-keto anisate followed by reduction with zinc and acetic acid; this gave 5α-cholestan-2-one as the only cholestanone from VI, and 5α-cholestan-3-one as the only cholestanone from VII. The n.m.r. spectra of the four steroid monoesters were in excellent agreement with expectation, and in turn served as a basis upon which to make secure assignments for the structures of the monoesters IVa and Va.

Dialkoxycarbonium ions (such as I-III) are currently believed (2) to be intermediates in the hydrolysis of ortho esters. The partial hydrolysis of ortho esters, therefore, if carried out under sufficiently similar conditions, would be expected to show the same stereoselectivity in ring opening. Accordingly the ethyl orthopropionate VIIIa and the ethyl orthoacetate VIIIb were found to give on mild acidic hydrolysis the respective axial esters (IVb and IVc), with only a trace of Vb or Vc detectable on thin layer chromatography.

Since the ortho esters VIIIa and VIIIb were prepared from the decalin diol, the above sequence is, in effect, a stereoselective partial esterification from a vicinal cis-glycol exclusively to the axial ester equatorial alcohol. For synthetic purposes isolation of the ortho ester is not necessary. Reaction of 9β,10α-decahydronaphthalene-2β,3β-diol with methyl orthobenzoate plus a trace of camphor-10-

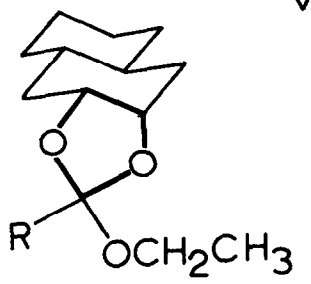
sulfonic acid, followed by mild hydrolysis of the crude reaction product, gave some recovered starting material (18%) and the axial benzoate half ester (IVd) (90%, based on unrecovered glycol). By contrast, direct esterification of the glycol with one equivalent of benzoyl chloride in pyridine gave (in addition to about 25% of recovered diol) the equatorial ester (Vd) (93%, based on unrecovered glycol) with only a trace of the axial ester (IVd).

Consideration of the phenomena responsible for the observed stereoselectivity reveals two factors which could be of significance. One is a possible difference in basicity between the two ring oxygens deriving from differences in stereochemistry. By analogy with amines (3), it would be expected that an equatorial oxygen would be slightly more basic than an axial oxygen. If this remains the case in the present system, and if all other effects cancel, then one would expect a faster rate of formation of the axial ester (IV).

What seems to be the much more significant factor, however, is the energy of the repulsive non-bonding interactions that arise on opening the ring to form the equatorial ester (V). As may be seen in IXa and IXb, the transition state leading to the equatorial ester (V) develops a strong non-bonding interaction between the nearest cis-axial hydrogen and the incipient carbonyl oxygen (in IXa) or the R group (in IXb). In the formation of the axial ester the corresponding interaction is very much smaller, as may be seen from structures Xa and Xb.

If R were H, and the reaction could proceed via IXb, the extra energy in the transition state leading to the equatorial ester would be expected to be much less, owing to the smaller size of hydrogen. In excellent agreement with this reasoning,

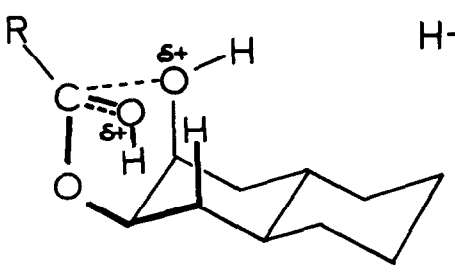
No.1



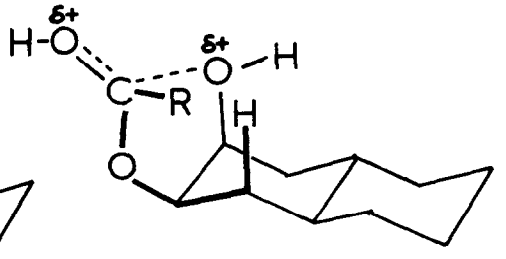
VIII a) R = CH_3CH_2-

b) R = CH_3-

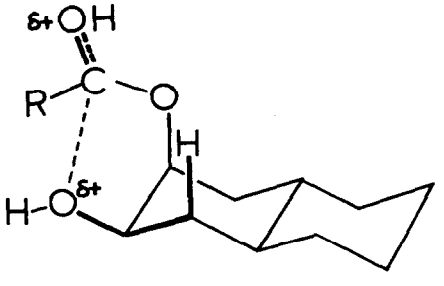
c) R = H−



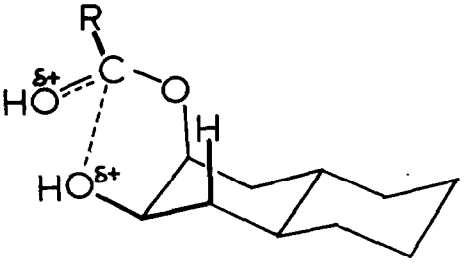
IXa



IXb



Xa



Xb

hydrolysis of the ethyl orthoformate VIIIc gave a mixture of notably different composition from those obtained in the other experiments, consisting of about three parts of the axial ester (IVe) to two parts of the equatorial compound (Ve).

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