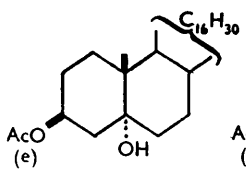
377. *Aspects of Stereochemistry. Part II.* Intramolecular Electrophilic Assistance of Displacement Reactions.*

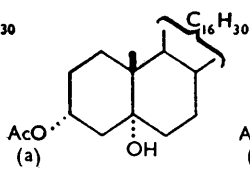
By H. B. Henbest and (Miss) B. J. Lovell.

If, in a monoester of a 1 : 3-diol, the hydroxyl and ester groups are held close together by their molecular environment, hydrogen bonding to the *alcohol* oxygen of the ester occurs. Such hydrogen bonding facilitates hydrolysis of the ester, and in *cyclo*hexane compounds the usual rule whereby equatorial esters are more easily hydrolysed than axial esters can be reversed. The rôle of the neighbouring hydroxyl group in these reactions may be regarded as that of an intramolecular electrophil.

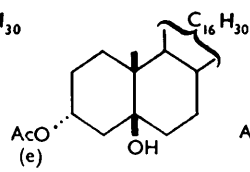
With the intention of finding suitable conditions for selective hydrolyses of 3-acetoxy-5-hydroxy-steroids, aqueous potassium hydrogen carbonate was studied, and conditions were thereby found under which a *cis*-diaxial hydroxy-ester was largely hydrolysed whereas non-hydroxylated esters were unchanged. The four 3-acetoxy-5-alcohols of the



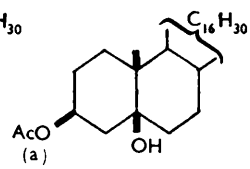
(I ; 18%)



(II ; 70%)



(III ; 13%)



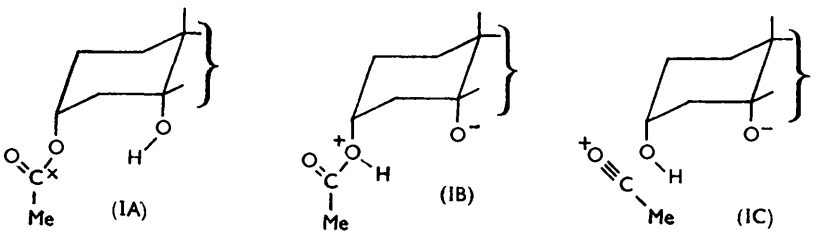
(IV ; 78%)

cholestane and coprostane series were therefore treated with potassium hydrogen carbonate solution under identical conditions—the percentage hydrolysis of each is shown below the formulæ (I)—(IV). The facilitating effect of a hydroxyl group *cis* to an ester group

* Part I, preceding paper.

results in the axial esters' being more rapidly hydrolysed than the equatorial esters, the usual rule [1] being reversed. 3α-Acetoxycholestane, the 5α-hydrogen analogue of ester (II), was recovered almost quantitatively after identical treatment.

These results are explicable in terms of hydrogen bonding of the 5-hydroxyl group to the alcoholic oxygen of the axial ester, a *quasi*-six-membered ring then being formed, *e.g.*,



Such an intramolecular hydrogen bond would cause a small increment of positive charge on alcoholic oxygen and on carbonyl oxygen through the extreme forms represented by (IB) and (IC). Production of forms (IB) and (IC) opposes and reduces the usual mesomeric donation of electronic charge from alcohol to carbonyl oxygen in the ester. Thus the carbonyl bond and the C^{x}O bond would be expected to move to higher and to lower orders, respectively (supporting infrared evidence below), and for the former this increase in bond order is reflected in a greater reactivity towards the nucleophilic reagent employed in the hydrolyses.

The infrared absorption spectra of the acetoxy-alcohols (I)—(IV) have confirmed and amplified these suggestions. From the results (Table) it may be seen that the directions of the shifts observed with diaxial compounds conform to the presence of the postulated hydrogen bonding (C=O stretching frequency raised, C–O stretching frequency lowered). Such hydrogen bonding to the *alcoholic* oxygen of an ester is apparently unprecedented, only bonding to the *carbonyl* oxygen having been observed previously. Thus, in mixed solutions of alcohols and esters shifts of the carbonyl stretching band to lower frequencies occur, corresponding to intramolecular hydrogen bonding to carbonyl oxygen.[2] Even larger decreases in carbonyl frequency take place in salicylic esters [3] where the bonding to the carbonyl group is apparently strengthened by interactions with the aromatic ring.

The unusual occurrence of hydrogen bonding to alcoholic oxygen in esters (II) and (IV) is probably due to the formation of a *quasi*-six-membered ring in preference to a *quasi*-eight-membered ring, the atoms comprising the smaller ring being held close together in their diaxial conformation. In this connection the strength of the intramolecular bonding to alcoholic oxygen appears to be diminished in the monoesters of more flexible, *e.g.*, acyclic, 1 : 3-diols (it is hoped to amplify these observations for subsequent publication).[4] In the more complicated 17-hydroxy-20-oxo-21-acetate cortical side-chain, hydrogen bonding to alcoholic oxygen cannot be discerned.[5]

The hydroxy-esters (I)—(IV) also show regular differences in the O–H stretching region, the *trans*-compounds giving double peaks (relative intensities varying on dilution), and the *cis*-compounds giving higher-intensity single peaks. No conclusions could be drawn from an examination of the bands just above 1000 cm.$^{-1}$ where both hydroxyl and acetate absorb, except that the axial–equatorial band correlations [6] were indistinct.

[1] Barton, *Experientia*, 1950, **6**, 316.
[2] Searles, Tamres, and Barrow, *J. Amer. Chem. Soc.*, 1953, **75**, 71.
[3] Gordy, *J. Chem. Phys.*, 1940, **8**, 516; Duncanson, Grove, and Zeally, *J.*, 1953, 1331. Our own data are given in the Table, positions of the C–O bands near 1250 cm.$^{-1}$ being given apparently for the first time.
[4] With the stronger bonding occurring between two hydroxyl groups, *cyclo*hexane-*cis*-1 : 3-diol shows evidence of intramolecular bonding in the normally less favourable diaxial conformation (Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; 1954, **76**, 4323).
[5] R. N. Jones, Humphries, Herling, and Dobriner, *ibid.*, 1951, **73**, 3215.
[6] Page, *J.*, 1955, 2017, where earlier references are also given.

In more general terms the effect of hydrogen bonding on ester reactivity may be considered to have some electronic analogy with the acid anhydride–ester relation, the

Infrared absorption bands of esters (in cm.$^{-1}$)

Compound	OH stretch.	C=O stretch.	C–O stretch.	Solv.
No hydrogen bonding				
3β-Acetoxycholestane	—	1732	1236	CCl_4
3β-Acetoxycholestan-5α-ol (I)	3590, 3430	1731	1236	CCl_4
3β : 6β-Diacetoxycholestan-5α-ol	3600, 3470	1732	1240	CCl_4
3α-Acetoxycholestane	—	1733	1234 †	CCl_4
3α-Acetoxy-coprostan-5β-ol (III)	3590, 3430	1734	1237	CCl_4
Hydrogen bonding to alcohol oxygen				
3α-Acetoxycholestan-5α-ol (II)	3570	1744	1224	CCl_4
3β-Acetoxycoprostan-5-ol (IV)	3570	1745	1223	CCl_4
3β : 6β-Diacetoxycoprostan-5β-ol [b]	3580	1740 *	1230 *	CCl_4
Hydrogen bonding to carbonyl oxygen				
Methyl salicylate	3180	1677	1310, 1258, 1217	CS_2
(Cf. Methyl benzoate)	—	1721	1281	CS_2
Methyl propionate and methanol [2]	not given	1740	not given	CS_2
(Cf. Methyl propionate) [2]	—	1748	not given	CS_2

* Broad.
† Most intense band of complex peak (cf. ref. 5); the other steroid acetates gave single peaks.

Infrared absorption bands of methyl ethers (in cm.$^{-1}$)

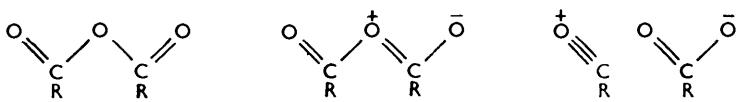
Compound	OH stretch.	C–O stretch.	Solv.
3β-Methoxycholestane [a]	—	1100	CS_2
3β-Methoxycholestan-5α-ol [b]	3580	1098	CS_2
3α-Methoxycholestane [a]	—	1086	CS_2
3α-Methoxycholestan-5α-ol [c]	3490	1080	CS_2
3α-*tert.*-Butoxycholestan-5α-ol [c]	3460	1080	CS_2

Infrared absorption of chloro-compounds (in cm.$^{-1}$)

Compound	OH stretch.	C–Cl stretch.	Solv.
3β-Chlorocholestane [d]	—	755, 710	CS_2
3β-Chlorocholestan-5α-ol [c]	3600	758, 711	CS_2
3α-Chlorocholestane [d]	—	735, 707	CS_2
3α-Chlorocholestan-5α-ol [c]	3590	732, 722, 686	CS_2

[a] Reference 6. [b] Henbest and Wilson, preceding paper. [c] Clayton, Henbest, and Smith, *J.*, 1957, 1982. [d] Barton, Page, and Shoppee, *J.*, 1956, 2017.

former being more reactive towards nucleophils due to the contribution to the ground state of forms such as (VB) and (VC) [analogous in electronic shifts to (IB) and (IC)].



(VA) (VB) (VC)

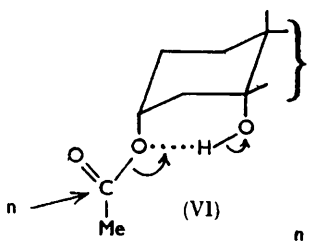
With the very reactive acyl halides the triple-bonded structure presumably provides an even larger contribution. In the infrared spectrum, these compounds also show progressive shifts of carbonyl frequency to higher values (*e.g.*, Me·CO·OMe, 1740 cm.$^{-1}$; Me·CO·O·COMe, 1824 and 1748 cm.$^{-1}$; Me·COCl, 1802 cm.$^{-1}$).

Marked hydrogen bonding occurs also with other 3α-substituted-5α-hydroxy-steroids. Thus 3α-methoxycholestan-5α-ol gives in the hydroxyl stretching region a more intense peak at somewhat lower frequency than that given by 3β-methoxycholestan-5α-ol; the peak near 1100 cm.$^{-1}$ is also shifted slightly. The 3α-methoxy-5α-alcohol is also eluted

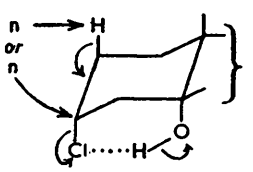
from alumina very much more easily than its *trans*-isomer, similar ease of elution being observed with the *cis*-acetate-alcohols (II) and (IV).

Alkyl halides are not usually considered to form hydrogen bonds very effectively with alcohols, but the juxtaposition of chlorine and hydroxyl in 3α-chlorocholestan-5α-ol causes appreciable bonding: the *cis*-compound again gave a more intense hydroxyl peak at a lower frequency than the *trans* isomer. Introduction of a 5α-hydroxyl group into 3α-chlorocholestane causes marked alterations in the positions and intensities of the carbon–chlorine stretching bands in the 750—650 cm.$^{-1}$ region: no appreciable changes were observed in the 3β-chloro-5α-series.

Facilitation of ester hydrolysis by a neighbouring hydroxyl group is explicable in terms similar to the termolecular (push-pull) concept of many S_N reactions in solution, *i.e.*, the 5-hydroxyl group provides the necessary electrophilic component for the displacement



(VI)



(VII)

(VIII)

n = nucleophil

at the carbonyl carbon atom, its adjacent position and partial bonding to the alcoholic oxygen atom assisting the development of the transition state as the nucleophil approaches (VI). With the 3α-chloro-5α-alcohol, reactions involving displacement of chlorine (as chloride) from $C_{(3)}$ should be similarly assisted (cf. VII). Preliminary observations have shown that hydrogen chloride is eliminated by pyridine much more rapidly from the *cis*-chloro-alcohol than from the corresponding 5-hydrogen compound. The reaction of the chloro-alcohol with pyrrolidine is also faster.

By contrast to intramolecular nucleophilic facilitation processes, assistance of S_N reactions by neighbouring electrophils has received little attention. A more complex example is the elimination of glycollic acid from strychninolic acid, which depends [7] on the appropriate configuration of a nearby hydroxyl group. Hydrogen bonding has been suggested [8] to account for the greater reactivity of *cis*- than of *trans*-2-hydroxy*cyclo*hexanecarboxylic acid derivatives. The more rapid hydrolysis of the *cis*-acetoxy-*p*-toluidide (VIII) being taken as example, it can be surmised that hydrogen bonding is more effective with the *cis*-compound, a quasi-*cis*-bicyclic structure being formed more easily. The preference for ring formation in such *cis*-structures where oxygen substituents (axial to the *cyclo*hexane ring) are involved is of course supported by a number of observations concerned with the formation of stable cyclic derivatives (lactones, *iso*propylidene derivatives, etc.).

Since publication of our preliminary report [9] on the ester hydrolysis Kupchan and Johnson have suggested [10] that the configuration of the $C_{(16)}$ hydroxyl group in cevine should be reversed (axial instead of equatorial), the ready hydrolysis of the $C_{(16)}$-esters being assisted by the nearby axial $C_{(20)}$ hydroxyl group.

[*Added, March 4th*, 1957.—The fact that the acid-catalysed dehydration of a steroid 8α-hydroxyl group takes place more readily when a 5α-hydroxyl group is also present than with the 5α-hydrogen analogue appears to provide another example of the phenomenon (Hallsworth and Henbest, unpublished work). Dr. R. C. Cookson has

[7] Woodward quoted by Holmes in "The Alkaloids," Academic Press Inc., New York, 1952, Vol. II, p. 517.
[8] Pascual, Sistaré, and Regás, *J.*, 1949, 1943.
[9] Henbest and Lovell, *Chem. and Ind.*, 1956, 278.
[10] Kupchan and Johnson, *J. Amer. Chem. Soc.*, 1956, **78**, 3864.

drawn our attention to the observations of Bartlett and Greene (*J. Amer. Chem. Soc.*, 1954, **76**, 1088), who found that the rate of alkaline hydrolysis of methyl triptoate is accelerated markedly on introduction of a 2α-hydroxyl group.]

Experimental

Hydrolysis of the Acetoxy-alcohols (I—IV).—The steroid (60 mg.) in benzene (1 c.c.) and methanol (4 c.c.) was treated with a solution of potassium hydrogen carbonate (7 mg.) in water (0·5 c.c.), the clear solution being kept at 20° for 65 hr. The product from each reaction was chromatographed on deactivated alumina: the m. p. of each crude product and the yield of each diol obtained on chromatography are tabulated.

Acetoxy-alcohol	M. p.	Crude product, m. p.	Pure diol, m. p.	Diol yield
(I)	184—186°	182—186°	220—223°	18%
(II)	136—138	191—198	197—220	70
(III)	145—148	139—148	184—189	13
(IV)	79—81	78—125	144—146	78

In a similar experiment, 3α-acetoxycholestane (100 mg.) (m. p. 97—98°) in benzene (3 c.c.) and methanol (15 c.c.) was treated with potassium hydrogen carbonate (25 mg.) in water (2 c.c.). Isolation of the product after 65 hr. gave unchanged material (98 mg.), m. p. 95—99°.

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The University, Manchester, 13.
Present address (H. B. H.):
King's College, Strand, London, W.C.2.

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