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INTRAMOLECULAR CATALYSIS. FACILITATION OF ALKALINE HYDROLYSIS OF ALICYCLIC 1,2-DIOL MONOESTERS*

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IT is well-established that the hydrolysis of alicyclic axial acetates is accelerated by the presence of an axial hydroxyl group at the 3-position. Earlier work in these laboratories has demonstrated the facilitation in strophanthidin 3-acetate[1,2] and in derivatives of cevine,[1,2] germine,[3] and protoverine.[4] Henbest and Lovell[5] independently showed that the same effect prevailed in some steroid 3,5-diol monoacetates when the acetoxy and hydroxy groups have a 1,3-diaxial relationship. The latter authors attributed the facilitation to hydrogen bonding between the hydroxyl group

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* Parts I and II in the series are references 1 and 2 respectively.

1 S. M. Kupchan and W. S. Johnson, J. Amer. Chem. Soc. 78, 3864 (1956).

2 S. M. Kupchan, W. S. Johnson and S. Rajagopalan, Tetrahedron 7, 47 (1959).

3 S. M. Kupchan and C. R. Narayanan, J. Amer. Chem. Soc. 81, 1913 (1959).

4 S. M. Kupchan, C. I. Ayres, M. Neeman, R. H. Hensler, T. Masamune and S. Rajagopalan, ibid. 82, 2242 (1960).

5 H. B. Henbest and B. J. Lovell, Chemistry and Industry 278 (1956); J. Chem. Soc. 1965 (1957).

and the ether oxygen of the ester, for which they advanced some infrared evidence.

We report herein that the base-catalyzed hydrolysis of some alicyclic acetates is accelerated by the presence of an adjacent hydroxyl group. Our first results were obtained with a steroid-5,6-diol monoacetate. When cholestane-5 α,6α-diol 6-monoacetate[6] was heated under reflux with potassium carbonate in aqueous methanol and benzene, 81% of the 5,6-diol was isolated after 1 h., and 93% after 2 h. The same treatment of cholestane-6α-ol acetate[6] led to formation of only 25% of cholestane 6α-ol after 2 h. Since variation of the 5α-substituent would have been difficult in this series, further studies were undertaken with various derivatives of cholestane-3β,4β-diol.

Subsequent hydrolyses were performed at 30° in aqueous dioxane containing sodium hydroxide. The amount of base consumed was measured by removing aliquots at intervals and titrating with standard hydrochloric acid. The compounds studied are listed in Table 1. There was some departure from strictly second order kinetics after the reactions had proceeded to some extent: when

Table 1. Second Order Rate Constants for Alkaline Hydrolysis in 20% Aqueous Dioxane at 30°

Compound	10^3k(l. mole^{-1} sec^{-1})
cholestane-3β-ol acetate	2.7
cholestane-3β,4β-diol 3-monoacetate[7]	22
cholestane-3β,4β-diol 4-monoacetate[8]	24
3β-methoxycholestane-4β-ol acetate[8]	1.3

[6] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, J. Chem. Soc. 2876 (1955).

this occurred. the approximate second order rate constants were calculated from the slopes of the initial portions of the kinetic plots. The constants thus obtained are probably accurate to within 10%.[10]

The hydrolysis of the 3-β-acetate is thus accelerated eight or nine-fold when a 4β-hydroxy group is introduced into the molecule. The greater extent of facilitation than that previously found for an aliphatic 1,2-diol monoester[11] is readily explicable in terms of a more effective interaction between the hydroxy and acetoxy groups in the rigidly fixed alicyclic case. In view of the migration of the acetate group from the 3 to the 4 position on slightly alkaline alumina,[8] alkaline hydrolysis of the 3β,4β-diol 3-acetate may proceed via intermediate formation of the 4-acetate.

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7 S. Liebermann and D. K. Fukushima, J. Amer. Chem. Soc. 72. 5211 (1950).

8 Prepared by treatment of cholestane-3β,4β-diol 3-acetate with slightly alkaline alumina (Woelm, "neutral", Activity I). The identity of the compound was proved by hydrolysis to the known cholestane 3β,4β-diol, and by oxidation to cholestane-3-one-4β-ol acetate (authentic specimen kindly supplied by Dr. K. L. Williamson; see K. L. Williamson, Ph.D. Dissertation, University of Wisconsin, 1960). Satisfactory analytical and spectral data were obtained for new compounds reported herein.

9 Prepared from the corresponding hydroxy-acetate by methylation with diazomethane in the presence of fluoroboric acid. Cf. M. Neeman, M. C. Caserio, J. D. Roberts and W. S. Johnson, Tetrahedron 6, 36 (1959).

10 We thank Professor T. Higuchi for valuable discussion of the kinetic data.

11 Ethylene glycol monoacetate has been shown to be hydrolyzed about 2 1/2 times faster than ethyl acetate in aqueous solution, M. H. Palomaa, Ann. Acad. Sci. Fennicae A 5, No. 4, 1 (1914), cf. Chem. Zentr. 89. I, 1143 (1918); H. Olsson, Z. physik. Chem. 133, 235 (1928).

In the case of the diol-4-monoacetate, it was found that replacement of the 3-hydroxy group by a methoxy group (with a very similar inductive effect) caused the rate of hydrolysis of the 4β-acetate to be retarded 19-fold. This strongly supports the view that the hydroxyl group plays an important role in the facilitation of hydrolysis noted in the hydroxy esters, probably through hydrogen bonding. Further studies on the nature of the facilitation are in progress.

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