is proposed for the formation of these compounds Formation of **6** would involve electrophilic attack at the 11a- rather than the 7-position.

Acknowledgment.—The authors are indebted to Professor E. J. Corey and to Professor G. Büchi for stimulating discussions concerning this work.

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GENERAL BASE-GENERAL ACID-CATALYSIS OF ESTER SOLVOLYSIS[1]

Sir:

Facilitation of the alkaline solvolysis of an alicyclic axial acetate by a hydroxyl group bearing a 1,3-diaxial juxtaposition to the acetate is a well-established fact.[2-5] Evidence is presented herewith for the argument that the solvolysis of 1,3-diaxial hydroxyacetates is subject to general base catalysis and that the reaction is therefore an instance of concerted general base-general acid-catalysis of ester solvolysis. Furthermore, in suitably constituted molecules, the solvolysis may be subject to general base and *bifunctional intramolecular* general acid-catalysis.[6]

Acetate esters were methanolyzed in solutions prepared by dissolving each compound in chloroform (10% of the total volume), adding buffer, and diluting to the required volume with 10% aqueous methanol. The rate of production of methyl acetate, the solvolysis product, was determined by direct gas chromatographic analysis of the reaction mixture, using a Wilkens Hy-Fi A600 Gas Chromatograph with a hydrogen flame detector.[7]

RATES OF ESTER SOLVOLYSIS AT IONIC STRENGTH 0.1 AND 3:1 TRIETHYLAMINE:TRIETHYLAMINE ACETATE BUFFER (0.21 *M*) AT 40°

Compound	k obs. (sec.$^{-1}$) (pseudo-first-order)	Ratio of rates
Coprostanol acetate (I)	3.0×10^{-8}	1
Coprostane-3β,5β-diol 3-monoacetate (II)	8.9×10^{-6}	300
Strophanthidin 3-acetate (III)	3.6×10^{-5}	1200
Strophanthidol 3-acetate (IV)	1.4×10^{-5}	470
Strophanthidinic acid methyl ester 3-acetate (V)	9.7×10^{-6}	320

(1) This is part VI of a series entitled "Intramolecular Catalysis"; part V, S. M. Kupchan and M. F. Saettone, *Tetrahedron*, in press.

(2) S. M. Kupchan and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 3864 (1956).

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

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

(5) S. M. Kupchan and C. R. Narayanan, *J. Am. Chem. Soc.*, **81**, 1913 (1959).

(6) *Cf.* the discussions in (a) S. M. Kupchan, P. Slade, R. J. Young and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962), and (b) B. M. Anderson, E. H. Cordes and W. P. Jencks, *J. Biol. Chem.*, **236**, 455 (1961).

(7) Identification of peaks and calibration of areas were carried out by injecting standard solutions of methyl acetate in the same solvent system. The chromatographic column consisted of 12.6 cm. of 10% Nujol on Fluoropak 80 and 1.5 m. of 20% glycerol on 60/80 mesh Gaschrom A. The column temperature was maintained at 50–55° and the over-all accuracy of the analytical procedure is estimated at ±5%.

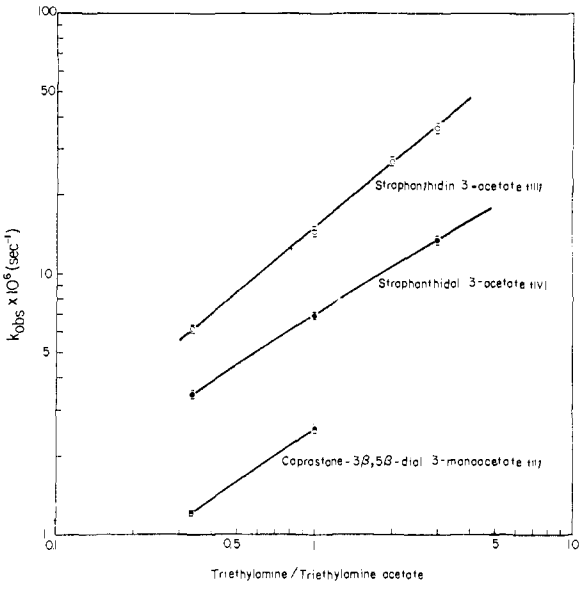
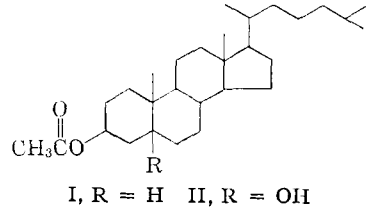
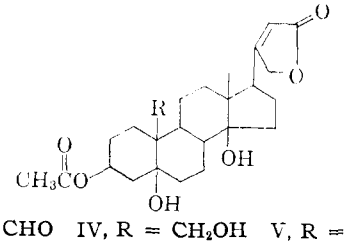


Fig. 1.—Plots of the observed pseudo-first-order rate constants (k_{obs}) for solvolysis at 40° (μ = 0.10 *M*) *vs.* buffer ratio.

The methanolysis reaction is base-catalyzed; a solution of II in the solvents described above in the absence of base shows no perceptible change for at least two months. The buffer ratio–rate profile (Fig. 1) confirmed the postulated basic catalysis of the pseudo-first-order solvolysis of II, III and IV. The basic catalysis of the solvolysis could have involved either general base-catalysis or specific base nucleophilic catalysis. The classic experiment for distinguishing general base catalysis from specific base nucleophilic catalysis involves determination of the reaction rate in a series of buffers of constant buffer ratio but varying absolute buffer concentration, and at constant ionic strength.[8,9] Figure 2 shows the variation of ob-



I, R = H II, R = OH



III, R = CHO IV, R = CH_2OH V, R = $COOCH_3$

served rates of methanolysis of coprostane-3β,5β-diol 3-monoacetate (II) and strophanthidin 3-acetate (III) with increasing concentrations of triethylamine–triethylamine acetate at constant

(8) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960).

(9) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

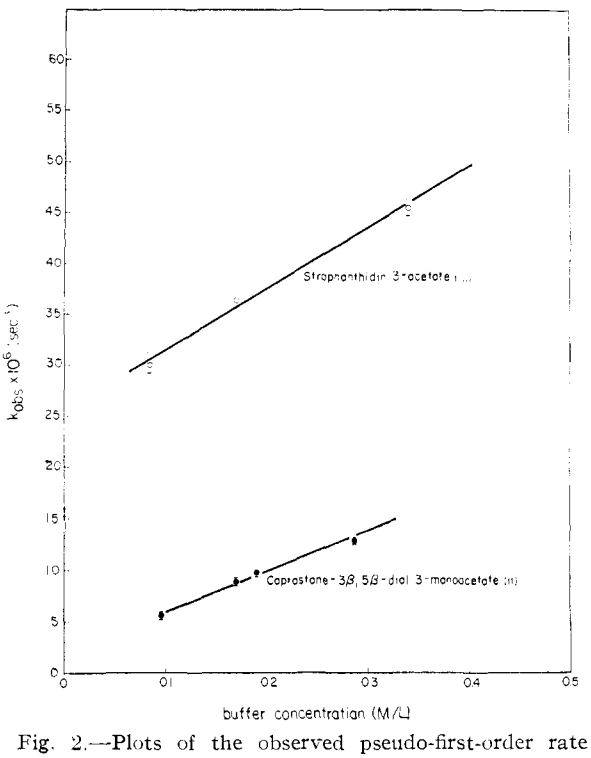
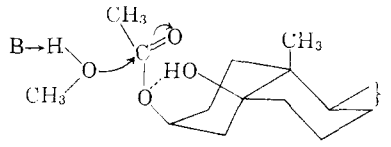


Fig. 2.—Plots of the observed pseudo-first-order rate constants (k_{obs}) for solvolysis at 40° (μ = 0.10 M), *vs.* concentration of triethylamine–triethylamine acetate at constant buffer ratio (3:1).

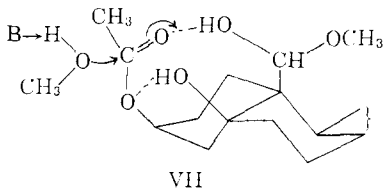
buffer ratio and constant ionic strength. The linear increase in rate conforms to the generally-accepted criterion for general base catalysis. To preclude the possibility of specific triethylamine catalysis, the solvolysis of II and III was repeated with another tertiary base of different base strength. The rates of solvolysis of II and III at constant buffer ratio and in the presence of varying concentrations of N-methylimidazole were found to be linear functions of the concentrations of base, strengthening the postulate that the solvolysis is indeed general base-catalyzed.

From the data in Table I, it is evident that introduction of a hydroxyl group at C-5 of coprostanol acetate (I), leading to the 1,3-diaxial hydroxyacetate (II), resulted in a 300-fold increase in the rate of solvolysis. The solvolysis of 1,3-diaxial hydroxyacetates, possibly to be regarded as in VI, appears to be the first recognized non-enzymatic example of general acid–general base-catalysis of ester solvolysis.[9,10,11]

Introduction of the 19-aldehyde group of strophanthidin 3-acetate (III) led to a four-fold increase in rate of solvolysis relative to II. Examination of molecular models reveals that the carbonyl group is too far from the acetoxy group to exert any direct facilitating effect. However, the model of the hemiacetal adduct (VII) shows that the acidic hemiacetal hydroxyl group is situated within hydrogen bonding distance of the carbonyl oxygen of the 3-acetate, as shown. The postulated hydrogen bonding shown would polarize the carbonyl group and facilitate attack of the nucleophile. In accordance with this view, the 19-alcohol, strophanthidol 3-acetate (IV) (with a less acidic 19-hydroxyl group), was found to be less labile toward solvolysis than strophanthidin 3-acetate (III), but more labile than coprostane-3β,5β-diol monoacetate (II). The rate of solvolysis of strophanthidinic acid methyl ester 3-acetate (V) was found to be the same as that of II, precluding an inductive effect by the C-10 substituent as an important factor in the facilitation.



VI



VII

Bruice, *et al.*, recently have studied the nature of neighboring hydroxyl group assistance in the alkaline hydrolysis of the ester bond in "systems of greater simplicity."[12] On the basis of kinetic isotope experiments (designed to test for possible general base-catalysis by the neighboring hydroxy group), the latter authors ruled out the possible involvement of general base-catalysis as the basis of the Henbest–Kupchan effect.[13] We suggest that the assumption that the nature of the hydroxyl-group assistance is the same in diverse systems is unwarranted. One is forced to conclude that the mechanism and magnitude of the rate enhancement of the solvolysis reaction will vary considerably with the detailed geometry and the conformational rigidity of hydroxy-acetates.[14]

We take pleasure in thanking Professor M. L. Bender for stimulating discussions.

(10) *Cf.* R. M. Krupka and K. J. Laidler, *J. Am. Chem. Soc.*, **83**, 1458 (1961).

(11) *Cf.* M. L. Bender, *ibid.*, **84**, 2582 (1962).

(12) See discussion following M. L. Bender, G. R. Schonbaum and G. A. Hamilton, *J. Polymer Sci.*, **49**, 75 (1961).

(13) T. C. Bruice and T. H. Fife, *J. Am. Chem. Soc.*, **84**, 1973 (1962).

(14) This work was supported in part by a research grant from the National Institutes of Health (H-2275).

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REVERSIBLE BLOCKING OF PROTEIN AMINO GROUPS BY THE ACETIMIDYL GROUP[1]

Sir:

The limited degradation of proteins to a few large peptides is a usual preliminary step in the determination of amino acid sequences.[2] In

(1) This research was supported by a grant from the Division of Medical Sciences of the National Institutes of Health and by a Predoctoral Fellowship (HF-7714-C2) granted to R. B. by the National Institutes of Health.

(2) F. Sanger, *Advances in Protein Chem.*, **7**, 1 (1952); C. B. Anfinsen and R. R. Redfield, *ibid.*, **11**, 2 (1956); B. Witkop, *ibid.*, **16**, 221 (1961).