(12.7 mmoles) of *t*-butyl α-bromomercuriphenylacetate was added, and the mixture was shaken to ensure dissolution of the alkylmercuric salt. Gaseous ammonia then was bubbled through the mixture for 30 min. The mixture then was centrifuged, and the mother liquor was decanted and evaporated to dryness on a rotary film evaporator. The residue was dissolved in $CHCl_3$ which was then evaporated to dryness. Crystallization of the residue from absolute ethanol gave 2.40 g (65%), m.p. 116–129°. Two further crystallizations raised the m.p. to 119.5–134°. The broad melting point is believed due to the presence of diastereoisomers. This is in agreement with the n.m.r. spectrum of this compound which is similar to that of the alkylmercuric salt excepting that the *t*-butyl and benzylic protons appear as doublets, the relative intensities of which change with crystallization.

This material slowly decomposes under the action of ammonia in chloroform to the hydrocarbon and an alkylmercuric salt. This side reaction has no effect on the kinetic determinations since (1) it is considerably slower than symmetrization and (2) the n.m.r. signal of the *t*-butyl protons of the decomposition products falls under that from the product *t*-butyl group.

Kinetic Method. A solution of NH_3 in $CHCl_3$ was prepared in an especially designed flask fitted with a side-arm buret and a Teflon valve. The concentration was determined by titration with HCl to the cresol red end point. Standard solutions were delivered into a 2-ml. volumetric flask fitted with a Teflon stopcock and a 3-mm. delivery tube. After mixing, about 1 ml. of the reaction solution was delivered into an n.m.r. tube. The space above the solution was filled with a piece of 4-mm. tubing. The tubes were then sealed and stored in an acetone–Dry Ice bath. For the kinetic runs, the tubes were placed in a bath at 31.4° until equilibrated. They were then placed in the n.m.r. probe and the rate was followed by appearance of the product *t*-butyl group. As the reaction proceeded, the formation of the ammonia–mercuric bromide precipitate caused broadening of the signal. Consequently, the tubes were removed from the probe and centrifuged periodically. The Varian Associates A-60 n.m.r. spectrometer was used for the analyses.

The Reaction of Diphenylmercury with Ethyl α-Bromomercuriphenylacetate. Standard solutions of the reactants in $CHCl_3$ were mixed in the proportions shown in Table II. A heavy precipitate formed immediately. After 2 min. the precipitate was filtered into a tared sintered-glass funnel and washed with a measured volume of cold $CHCl_3$. The identity of the precipitate was established by melting point, mixture melting point, and infrared spectrum.

Table II

Run	Ph_2Hg, mmole	mmole PhC(HgBr)-HCO_2Et	PhHgBr,[a] mmole	PhHgBr,[b] %
1	0.125	0.50	0.126	100
2	0.25	0.50	0.247	99
3	1.00	1.00	0.948	93
4	1.00	0.50	0.490	98

[a] Corrected for solubility of PhHgBr in $CHCl_3$ (0.0019 g./ml.). [b] Based on stoichiometry of eq. 10.

The n.m.r. spectrum of the mother liquor of run 3 (equimolar reactants) shows a triplet (three protons) at τ 8.75, a singlet (one proton) at 6.2, and a quartet (two protons) at 5.85. This splitting pattern is, of course, identical with that of di-α-(*t*-butyl phenylacetate)mercury. The two compounds are readily distinguished by their shifts in the n.m.r. spectrum. The peaks of the symmetrical compound are 1–5 c.p.s. upfield from those of the unsymmetrical dialkyl.

The fast step (eq. 10) is followed by a slow step which is represented by eq. 11. Run 2, for example, yielded after 1 week a second equivalent of phenylmercuric bromide and, within the limits of detection by n.m.r., pure di-α-(*t*-butyl phenylacetate)mercury. Run 3 yielded no phenylmercuric bromide after the initial fast reaction. The unsymmetrical dialkyl formed in run 3 slowly disproportionated into diphenyl mercury and di-α-(*t*-butyl phenylacetate)mercury. The ratio of the latter to the unsymmetrical material was approximately 2:1.

Intramolecular Catalysis. VIII.[1] General Base–General Acid Catalysis of Ester Solvolysis[2,3]

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Abstract: Evidence is presented for the argument that the solvolysis of 1,3-diaxial hydroxyacetates is an instance of concerted general base–general acid catalysis of ester solvolysis. Facilitation of the alkaline hydrolysis of an alicyclic axial acetate by a hydroxyl group bearing a 1,3-diaxial juxtaposition to the acetate had been established earlier. The buffer ratio–rate profile for the solvolyses of neogermitrine (I), strophanthidin 3-acetate (V), strophanthidol 3-acetate (VI), and coprostane-3β,5β-diol 3-monoacetate (X) indicated that the pseudo-first-order methanolysis of each is base catalyzed. The linear increase in rate with increasing buffer concentrations at constant buffer ratio and constant ionic strength support the view that the solvolyses of V and of X are catalyzed by a buffer component. Arguments for the view that the solvolysis is general base catalyzed are presented. Introduction of the 19-aldehyde group of strophanthidin 3-acetate (V) led to a fourfold increase of rate of solvolysis relative to X. The view is considered that the solvolyses of the acetate ester of V and of C-7 acetate esters in veratrum alkaloids such as I may be subject to general base and *bifunctional intramolecular* general acid catalysis.

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.[4–7] Evidence is presented herewith for the argument that the solvolysis of 1,3-diaxial hydroxy-acetates

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(2) The investigations which form the subject of this paper were first outlined in a preliminary communication: S. M. Kupchan, S. P. Eriksen, and M. Friedman, *ibid.*, **84**, 4159 (1962).

(3) This work was supported in part by Public Health Service Research Grant HE-02275, from the National Heart Institute.

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

(5) H. B. Henbest and B. J. Lovell, *Chem. Ind.* (London), 278 (1956); *J. Chem. Soc.*, 1965 (1957).

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

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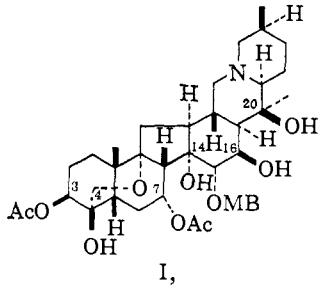
is also subject to general base catalysis and that the reaction is therefore an instance of concerted general base–general acid catalysis of ester solvolysis. Furthermore, in suitably constituted molecules, the solvolysis may be subject to general base and *bifunctional intramolecular* general acid catalysis.[8]

The background of this work stems from observations of very facile methanolyses of several acetate ester derivations in the course of our structural studies of the hypotensive veratrum alkaloids. Acetate esters in two different structural environments were found to be sensitive, and in each type, dissolution of the ester in aqueous methanol and allowing the solution to stand at room temperature overnight led to selective acetate cleavage at a specific position to afford a high yield of methanolysis product. The two types of facilitated solvolyses are exemplified by the selective methanolysis of the C-7 acetate of neogermitrine (I) to yield germidine (II),[9,10] and of the C-16 acetate of germine 3,4,7,-15,16-pentaacetate (III) to yield germine 3,4,7,15-tetraacetate (IV).[10]

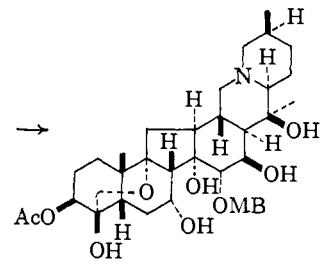
The unusual reactivity of the C-7 and C-16 acetate esters in the respective polyesters led us to postulate a facilitation of methanolysis by a neighboring hydroxyl group (at C-14 for the C-7 acetate and at C-20 for the C-16 acetate) bearing a *cis*-1,3-diaxial relationship to the ester group and thus juxtaposed for participation.[4,6] This hypothesis was tested by treatment of strophanthidin 3-acetate (V) with dilute methanol and cevine for 20 hr.; strophanthidin was isolated in 66% yield. Epiandrosterone 3-acetate (VIII) was recovered largely (75%) unchanged after similar treatment. Henbest and Lovell also have presented independently convincing demonstrations of this effect in the sterol series and have discussed mechanistic interpretations.[5,11]

Our early experiments and those of Henbest and Lovell were of a semiquantitative nature and did not allow the calculation of rate constants. Nevertheless, even from the first reports, there were indications that the methanolyses of veratrum C-7 and C-16 acetate esters and of strophanthidin 3-acetate were accelerated to a greater extent than simple steroidal 1,3-diaxial hydroxyacetates. The present report presents, in detail, our systematic studies of the methanolyses of strophanthidin acetate and of a veratrum C-7 acetate ester, neogermitrine.[2] The following paper will present the systematic studies of the methanolysis of veratrum C-16 acetate esters.[1,12]

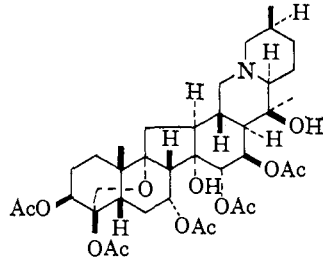
The acetate esters listed in Table I were methanolyzed in solutions prepared by dissolving each compound in chloroform (10% of the final volume), adding buffer, and diluting to the required volume with 9:1 methanol–water. The rate of production of methyl acetate, the solvolysis product, was determined by direct gas chromatographic analysis of the reaction mixture.



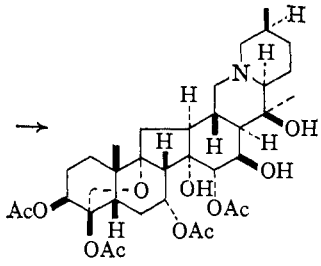
I,
MB(−)—α—methylbutyryl



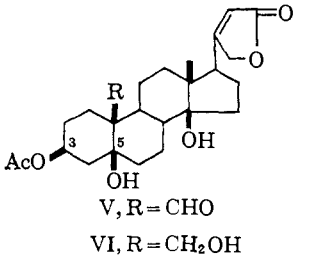
II,
MB(−)—α—methylbutyryl



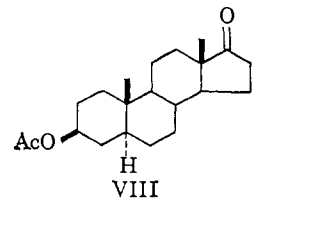
III



IV



V, R = CHO
VI, R = CH_2OH
VII, R = $COOCH_3$



VIII

Table I. Rates of Ester Solvolysis at Ionic Strength 3:1 Triethylamine–Triethylammonium Acetate Buffer 0.1 *M* and (0.21 *M*) at 40°

Compound	k_{obsd}, sec.$^{-1}$ (pseudo-first-order)	Ratio of rates
Coprostanol acetate (IX)	0.030×10^{-6}	1
Coprostane-3β,5β-diol 3-monoacetate (X)	9.0×10^{-6}	300
Strophanthidin 3-acetate (V)	37×10^{-6}	1200
Strophanthidol 3-acetate (VI)	13×10^{-6}	470
Strophanthidinic acid methyl ester 3-acetate (VII)	10×10^{-6}	320
Neogermitrine (I)	120×10^{-6}	4200
3-Keto-7,12-diacetoxy-cholanic acid methyl ester (XI)	$\leq 0.030 \times 10^{-6}$	≦1

The methanolysis reaction is base catalyzed; a solution of X in the solvents described above in the absence of base shows no perceptible change for at least 2 months. The buffer ratio–rate profile using triethylamine–triethylammonium acetate (Figure 1) confirmed the postulated basic catalysis of the pseudo-first-order solvolysis of I, V, VI, and X. The observed rate increase could have involved catalysis by either a buffer component or specific hydroxide (or methoxide) ion. That the rate increase was *not* caused by specific ion catalysis was demonstrated by determination of reac-

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

(9) J. Fried, P. Numerof, and N. H. Coy, *J. Am. Chem. Soc.*, **74**, 3041 (1952).

(10) S. M. Kupchan, *ibid.*, **81**, 1921 (1959).

(11) *Cf.* R. West, J. J. Korst, and W. S. Johnson, *J. Org. Chem.*, **25**, 1976 (1960); T. C. Bruice and T. H. Fife, *J. Am. Chem. Soc.*, **84**, 1973 (1962).

(12) S. M. Kupchan, S. P. Eriksen, and Y.-T. S. Liang, *ibid.*, **88**, 347 (1966).

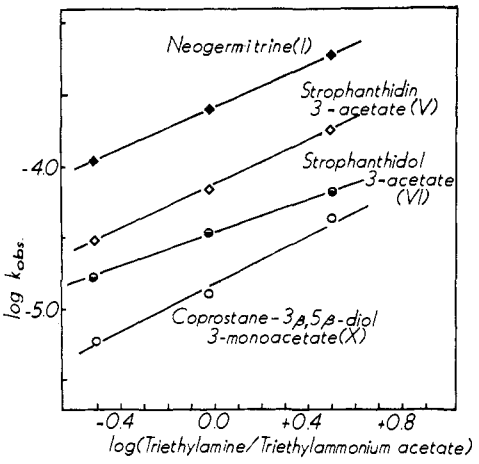


Figure 1. Plots of the logarithm of the observed pseudo-first-order rate constants (k_{obsd}) for solvolysis at 40° (μ = 0.10 *M*) *vs.* logarithm of the buffer ratio.

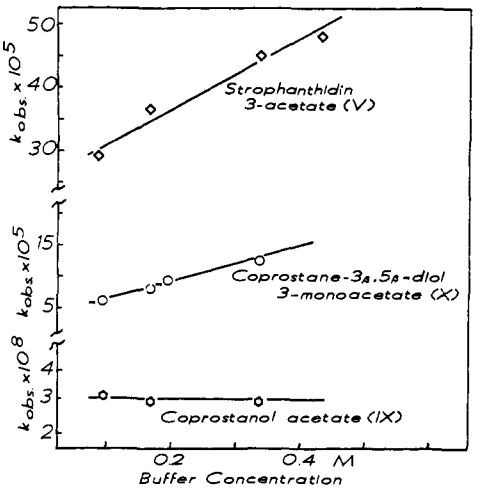


Figure 2. Plots of the observed pseudo-first-order rate constants (k_{obsd}) for solvolysis at 40° (μ = 0.10 *M*) *vs.* concentration of triethylamine–triethylammonium acetate at constant buffer ratio (3:1).

tion rate in a series of buffers of constant buffer ratio but varying absolute buffer concentration, and at constant ionic strength.[13] Figure 2 shows the variation of observed rate of methanolysis of coprostane-3β,5β-diol β-monoacetate (X) and strophanthidin 3-acetate (V) with increasing concentrations of triethylamine–triethylammonium acetate at constant buffer ratio and ionic strength. The linear increase in rate over the range of buffer concentrations used in the study indicates that the reaction is subject to either general base catalysis or to nucleophilic catalysis by the buffer. (In contrast, the corresponding data for coprostanol acetate (IX) indicate that the rate of solvolysis of the latter compound is not dependent upon buffer concentration. It is noteworthy that, in the one case studied in which neighboring group facilitation is not possible, no catalysis of solvolysis by a buffer component was observed.) Nucleophilic catalysis by triethylamine may be regarded as improbable on the basis of the demonstrated low nucleophilicity of triethylamine, presumably

(13) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, 82, 665 (1960); M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

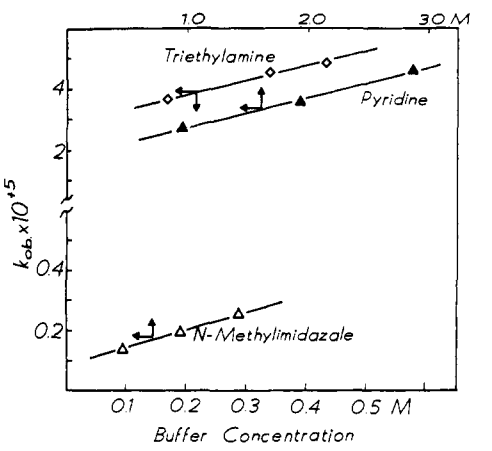
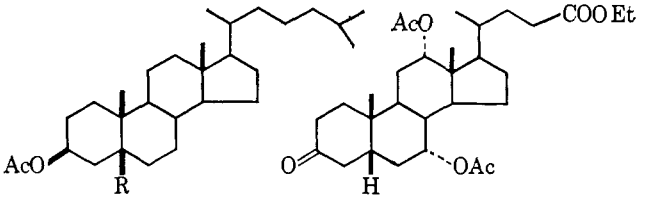


Figure 3. Plots of the observed pseudo-first-order rate constants (k_{obsd}) for solvolysis at 40° (μ = 0.10 *M*) of strophanthidin 3-acetate (V) *vs.* buffer concentration for three buffers (3:1 ratio of amine–ammonium acetate).

attributable to the interference of bulky groups near the reaction center.[14] Furthermore, the rates of solvolysis of V at constant buffer ratio and in the presence of varying concentrations of N-methylimidazole and pyridine were found to be linear functions of base also (Figure 3), strengthening the postulate that the solvolysis is general base catalyzed.[15] The N-methylimidazole-catalyzed solvolysis was some 20



IX, R=H
X, R=OH

XI

times slower than the triethylamine-catalyzed solvolysis, even when the N-methylimidazole buffer concentration was fivefold greater than that of the triethylamine buffer. The latter observation lends support to the view that the solvolysis is general base catalyzed, for N-methylimidazole has previously been shown to be many times more effective than a trialkylamine in nucleophilic catalysis of ester solvolysis.[16] The effectiveness of the pyridine buffer as a catalyst is noteworthy; no explanation is readily apparent.

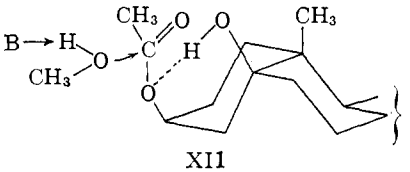
From the data in Table I, it is evident that introduction of a hydroxyl group at C-5 of coprostanol acetate (IX), leading to the 1,3-diaxial hydroxyacetate (X) resulted in a 300-fold increase in the rate of solvolysis. The solvolysis of 1,3-diaxial hydroxyacetates, possibly to be pictured as in XII, appears to be the first recognized nonenzymatic example of general acid–general base catalysis of ester solvolysis.[15,17,18]

Introduction of the 19-aldehyde group of strophanthidin 3-acetate (V) led to a fourfold increase in rate of

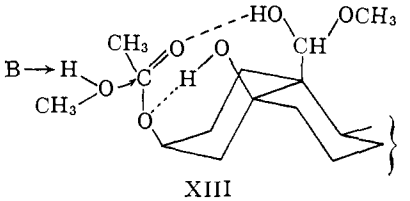
(14) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 82, 1778 (1960).
(15) *Cf.*, *e.g.*, T. C. Bruice and T. H. Fife, *ibid.*, **83**, 1124 (1961).
(16) *Cf.*, *e.g.*, M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1656 (1957).
(17) *Cf.* R. M. Krupka and K. J. Laidler, *ibid.*, **83**, 1458 (1961).
(18) *Cf.* M. L. Bender, *ibid.*, 84, 2582 (1962).

solvolysis relative to X. 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 (XIII) 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 (VI) (with a less acidic 19-hydroxyl group), was found to be less labile toward solvolysis than strophanthidin 3-acetate (V), but more labile than coprostane-3β,5β-diol monoacetate (X). The rate of solvolysis of strophanthidinic acid methyl ester 3-acetate (VII) was found to be the same as that of X, precluding an inductive effect by the C-10 substituent as an important factor in the facilitation.

A similar mechanism may be suggested for the solvolysis of other polyhydroxyacetates. Examination of the molecular model (XIV) of neogermitrine (I) shows that, in addition to the *cis*-1,3-hydroxyacetate

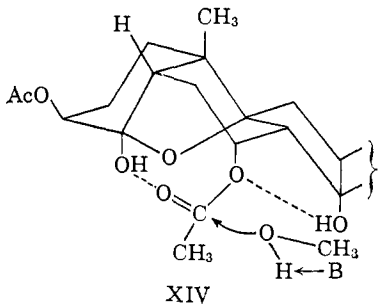


XII



XIII

interaction between the 7-α-(axial) acetoxy group and the 14-α-hydroxy group, the 4-(hemiketal)hydroxyl is situated within convenient hydrogen-bonding distance of the carbonyl oxygen of the acetoxy group. The marked enhancement in the rate of methanolysis of the 7-acetoxy group in I, as compared with, for instance, the 7-acetoxy group in XI, may be attributable to an intramolecular bifunctional general acid catalysis of ester solvolysis, involving assistance both by the hydroxyl group at C-14 and the hemiketal C-4 hydroxyl group. The apparent stability of the C-7 acetoxy group in germine 3,4,7,15,16-pentaacetate (III) is in good accord with the view that the C-4 hydroxyl group may be



XIV

important in the facilitation of solvolysis of the C-7 acetoxy group in neogermitrine and related compounds. It is likely that the low reactivity toward methanolysis of the C-7 acetoxy group in III is attributable also to steric hindrance by the C-4 acetoxy group.[7]

Experimental Section

Melting points are corrected for stem exposure.

Coprostanol Acetate (IX). This compound was prepared from coprostanol by treatment with acetic anhydride in pyridine, and was recrystallized from methanol as needles, m.p. 86–87°.

Coprostane-3β,5β-diol 3-Monoacetate (X). This compound was prepared as described by Plattner, *et al.*,[19] m.p. 79–81° (evacuated capillary).

Strophanthidin 3-Acetate (V). This compound was prepared as described by Reichstein and Rosenmund,[20] m.p. 248–250°.

Strophanthidol 3-Acetate (VI). This compound was prepared as described by Koechlin and Reichstein,[21] m.p. 234–237°.

Strophanthidinic Acid Methyl Ester 3-Acetate (VII). This compound was prepared as described by Koechlin and Reichstein,[21] m.p. 128–130°.

Neogermitrine (I). This alkaloid, m.p. 236–237° dec., was available from earlier studies of the alkaloids of *Zygadenus venenosus*.[22]

3-Keto-7,12-diacetoxycholanic Acid Methyl Ester (XI). This compound was prepared by the procedure of Jones, *et al.*,[23] m.p. 194–195°.

Kinetic Measurements. Acetate esters were methanolyzed in solutions prepared by dissolving each compound in the required volume of chloroform, adding the desired buffer and tetramethylammonium chloride solution in methanol–water (9:1) to adjust the ionic strength to 0.1 *M*, and diluting to the required volume with 9:1 methanol–water. The methanolyses were run in solutions in which chloroform constituted 10% of the final volume. The buffers were prepared by the general procedure exemplified by that used for triethylamine–triethylammonium acetate. Solutions of triethylamine (2.5 g.) in methanol–water (9:1, 50 ml.) and of acetic acid (1.484 g.) in methanol–water (9:1; 50 ml.) were prepared. To the triethylamine solution (5 ml.) was added the acetic acid solution in appropriate volumes to make the buffers expressed in terms of the ratio of triethylamine to triethylammonium acetate concentrations. It was found that at constant buffer ratio (3:1) the apparent pH of the solution (measured with a glass–aqueous calomel electrode pair and a Beckman Model G pH meter) was constant to better than ±0.04 units over the concentration range used. The reaction mixtures were equilibrated at 25° in a water bath. Aliquots were taken at intervals, and the 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. Identification of peaks and calibration of peak areas were carried out by injecting standard solutions of methyl acetate in the same solvent system. At least four datum points were obtained for each kinetic run and 4 half-lives was used as the infinite time interval. In the case of the extremely slow reactions, the weight of substrate was used as initial concentration. A suitable first-order plot was obtained in each case. The tabulated rate constant data were calculated from the slopes of the lines fitted visually to the assay points and represent the mean values of at least two runs. No acetic acid was detected in these systems. We suggest that there was little (if any) acetic acid formed, because the methyl acetate recovered usually approximated the theoretical expectation. The chromatographic column consisted of 5 in. of 10% Nujol on Fluoropak 80 and 5 ft. of 20% glycerine on 60–80 mesh Gaschrom A. The column temperature was maintained at 65–70° and the over-all accuracy of the analytical procedure is estimated at ±5%.

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

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(20) T. Reichstein and H. Rosenmund, *Pharm. Acta Helv.*, **15**, 150 (1940).
(21) H. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **30**, 1673 (1947).
(22) S. M. Kupchan and C. V. Deliwala, *J. Am. Chem. Soc.*, **76**, 5545 (1954).
(23) A. S. Jones, M. Webb, and F. Smith, *J. Chem. Soc.*, 2164 (1949).