Stereochemical Aspects of Ether Oxygen Participation. VII. The Dichotomous Solvolytic Behavior of 4- and 5-Oxocanyl Derivatives[1]

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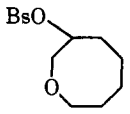
Abstract: The kinetics of acetolysis of oxocan-4-yl brosylate (**5**) have been measured and a sevenfold rate retardation relative to cyclooctyl brosylate (**1**) is observed. In striking contrast, oxocan-5-yl 3,5-dinitrobenzoate (**6**) hydrolyzes at a rate which, when appropriately normalized, reveals a 48,500-fold enhancement relative to **1**! These results are discussed in terms of inductive, steric, dipolar field, and anchimeric assistance effects of the ring ether oxygen. The kinetic behavior of **5** has been taken as evidence for the operation of adverse inductive and dipolar field effects which are, however, counterbalanced in part by a positive kinetic contribution arising from relief of nonbonded steric interactions in the ground state relative to **1**. The dramatic change in rate observed in the case of **6**, the highest level of neighboring group participation by a heteroatom on record, finds its origin in kinetically favorable R_2O-5 bonding. Product studies support the various conclusions.

Results stemming from acetolysis studies of eight-membered ring brosylates have shown that the rates of carbonium ion processes in such mesocycles are significantly affected by nonbonded interactions. For example, the appreciably enhanced (185-fold) solvolysis rate of cyclooctyl brosylate (**1**) relative to cyclohexyl brosylate is viewed to be the result of steric strain relief in the transition state for formation of a planar carbonium ion in **1**.[2] The rate constant for 4-cyclooctenyl brosylate (**2**) is some 60 times less than that of **1** due to the amelioration of strain in the ground state resulting from the presence of the double bond.[2] Replacement of a ring methylene group by ether oxygen as in **3** also



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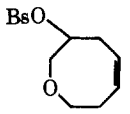

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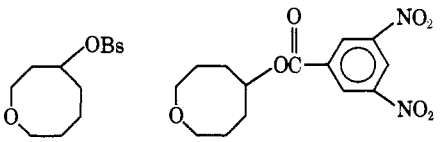
serves to remove a number of eclipsed hydrogen interactions.[3] Introduction of the heteroatom at this distance from the incipient ionizing center does, however, likewise alter appreciably other factors which affect the overall acetolysis rate. In **3**, for example, the oxygen substituent is certain to exert added inductive and transannular field effects; a further key factor is the propensity of ether oxygen to involve itself in R_2O-3 neighboring group participation.[4] As a result, total analysis of the rate retardation of 70 (relative to **1**) observed for **3** is complex.[5] Interestingly, R_2O-3 participation was found not to compete well with homoallylic participation in **4**, a conclusion derived chiefly from product studies.[5,6]

The purpose of the present investigation was to assess the steric and electronic contributions of divalent oxygen in the solvolysis of medium ring ethers **5** and **6**. In addition to the anticipated substantial diminution of inductive effect contributions from the heteroatom in these compounds, estimation (at least



5 **6**

semiquantitatively) of the dipolar field effect, or lack of it, was deemed possible.[7,8] Accordingly, an evaluation of R_2O-4 and R_2O-5 participation, reasonably uncomplicated by side issues, was considered feasible in these ring systems.

Results

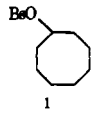
The requisite oxocan-4-ol was available from the companion study.[1] Its noncrystalline brosylate (**5**) was prepared in the customary manner. Lithium aluminum hydride reduction of oxocan-5-one[1] gave rise to the derived alcohol **14**. All attempts to convert **14** to its brosylate met with failure, presumably due to its high level of reactivity (*vide infra*). The crystalline and stable 3,5-dinitrobenzoate (**6**) was suitable for our intended purposes.

Solvolysis of brosylate **5** in sodium acetate buffered acetic acid was conducted at three different temperatures. The pertinent kinetic data are summarized in Table I; the rate constants for **1**, **3**, and **9** are included for comparison purposes. Table II lists the rate constants determined for the hydrolysis of **6** (and **13**) in 80:20 acetone–water. The values of the thermodynamic quantities $\Delta H^{\pm}$ and $\Delta S^{\pm}$ have also been included.

Plots of the disappearance of both **5** and **6** against time described negative curves, thus revealing the likely operation of internal return processes. Subsequently, the internal return products of each reaction, brosylate **9** and dinitrobenzoate **13**, respectively, were

(1) For part VI of this series, see L. A. Paquette and M. K. Scott, *J. Amer. Chem. Soc.*, **94**, 6751 (1972).
(2) A. C. Cope and P. E. Peterson, *ibid.*, **81**, 1643 (1959).
(3) L. A. Paquette and R. W. Begland, *J. Org. Chem.*, **32**, 2723 (1967).
(4) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).
(5) L. A. Paquette, R. W. Begland, and P. C. Storm, *J. Amer. Chem. Soc.*, **92**, 1971 (1970).
(6) Contrast the behavior of a somewhat related acyclic case: J. R. Hazen and D. S. Tarbell, *Tetrahedron Lett.*, 5927 (1968).
(7) D. S. Tarbell and J. R. Hazen, *J. Amer. Chem. Soc.*, **91**, 7657 (1969).
(8) (a) N. J. Leonard, T. W. Milligan, and T. L. Brown, *ibid.*, **82**, 4075 (1960); (b) L. A. Paquette and L. D. Wise, *ibid.*, **89**, 6659 (1967).

Table I. Acid Production and Rearrangement Rates Arising from Acetolysis of Oxocan-4-yl Brosylate (**5**) and Related Compounds

Compound	Rate constant designation	T, °C	$k \times 10^5$ sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
5	k_1	25.7	1.39	21.7 ± 0.4	−8 ± 1
		40.5	14.0		
		54.8	38.6		
		25.0	1.51[a]		
		70.0	215.0[a]		
	k_1	25.7	0.92		
		40.5	8.64		
		54.8	36.4		
	k_2	25.7	0.47		
		40.5	1.39		
		54.8	2.16		
	k_3	(see under **9**)			
3	k_1	25.0	5.03×10^{-2}[a,b]	26.7 ± 0.4	+2.3
		70.0	21.5[a,b]		
 1	k_1	25.0	12.2[c]	21.0 ± 0.4	−3.9
		70.0	1.48×10^{3}[c]		
9	k_1	85.4	0.416	24.7	−14.8
		100.5	1.77		
		115.8	6.69		
		25.7	3.44×10^{-4}[a]		
		40.5	2.56×10^{-4}[a]		
		54.8	1.50×10^{-2}[a]		

[a] Extrapolated values. [b] Taken from ref 5. [c] Taken from ref 2.

Table II. Acid Production and Rearrangement Rates Arising from Hydrolysis of Oxocan-5-yl 3,5-Dinitrobenzoate (**6**) and Its Internal Return Product **13** in 80:20 Acetone–Water

Compd	Rate constant designation	T, °C	$k \times 10^5$ sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
6	k_1	40.3	3.37	18.0 ± 0.4	−22.0 ± 1.4
		55.8	12.3		
		70.3	46.4		
		70.0	43.4[a]		
		100.0	394.0[a]		
	k_1	40.3	1.40		
		55.8	7.44		
		70.3	32.8		
	k_2	40.3	1.97		
		55.8	4.87		
		70.3	13.6		
	k_3	(see under **13**)			
13	k_1	101.1	2.39×10^{-2}	24.3	−1.5
		115.8	7.55×10^{-2}		
		130.1	27.2×10^{-2}		
		40.3	0.336×10^{-4}[a]		
		55.8	2.23×10^{-4}[a]		
		70.3	1.11×10^{-3}[a]		

[a] Extrapolated values.

shown independently to solvolyze at slower rates than the original substrates (Tables I and II). The gradual falling off of rate with time has been attributed to this causative factor. The general mechanistic profile of these processes (Scheme I) includes the first-order rate

Scheme I

$$\begin{array}{ccc} \text{ROX} & \xrightarrow[k_1]{\text{HOS}} & \text{ROS} + \text{HOX} \\ \downarrow{\scriptstyle k_2} & & \\ \text{R'OX} & \xrightarrow[k_3]{\text{HOS}} & \text{R'OX} + \text{HOX} \end{array}$$

constant k_1 for conversion of **5** or **6** (ROX) to the corresponding structurally unperturbed acetate or alcohol (ROS), k_2 for rearrangement of ROX to less reactive brosylate or 3,5-dinitrobenzoate (R'OX), and k_3 for the conversion of R'OX to its acetate or alcohol (R'OS). The sum of k_1 and k_2 is the rate constant k_i for total disappearance of the original substrate.

The best values of k_1, k_2, and k_3 were obtained by determining k_3 directly by experiment, estimating k_1 from a plot of the instantaneous rate constants plotted against time and extrapolated to zero time,[9] and evaluating k_2 with the aid of an appropriate iterative computer program.[10]

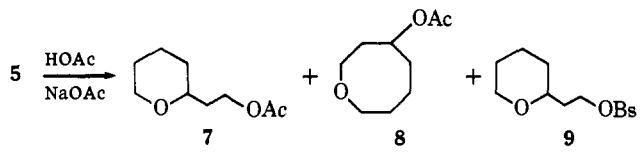
Preparative scale acetolysis of **5** at 65° for a time sufficient for complete solvolysis of the brosylate afforded a liquid fraction and a crystalline residue.

(9) W. G. Young, S. Winstein, and H. L. Goering, *J. Amer. Chem. Soc.*, 73, 1958 (1951).

(10) R. S. Macomber, *J. Org. Chem.*, 36, 2182 (1971). The actual program employed was a modification of that supplied by Professor Macomber whom we thank.

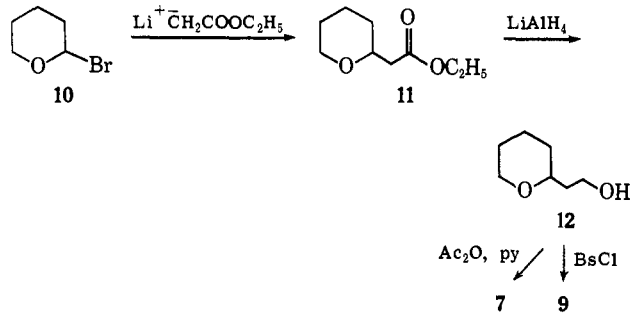
Vpc analysis of the volatile material showed it to be a mixture of acetates **7** (75%) and **8** (25%, Scheme II).

Scheme II



Nmr and ir studies gave evidence that the solid component was **9** and this conclusion was confirmed by independent synthesis (Scheme III). Treatment of

Scheme III

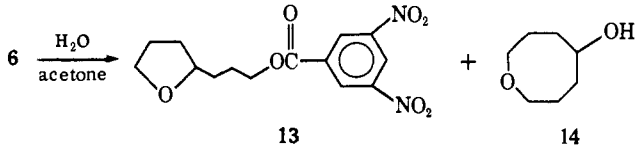


2-bromotetrahydropyran (**10**) with lithio ethyl acetate[11] gave ethyl (2-tetrahydropyranyl)acetate (**11**). Subsequent hydride reduction of this ester led to alcohol **12**, esterification of which with *p*-bromobenzenesulfonyl chloride or acetic anhydride in pyridine furnished **9** and **7**, respectively. Authentic **8** was prepared by acetylation of oxocan-4-ol.

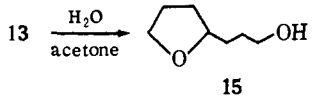
When a solution of brosylate **9**, an excess of sodium acetate, and anhydrous acetic acid was refluxed for 10 half-lives, acetate **7** (96%) was the only substance produced.

Hydrolysis of **6** in 80:20 acetone–water containing a twofold excess of 2,6-lutidine for 25 half-lives (based upon k_1) afforded 3-(2-tetrahydrofuranyl)propyl 3,5-dinitrobenzoate (**13**, 29%) and oxocan-5-ol (**14**, 71%, Scheme IV). Ester **13** was fully characterized by

Scheme IV

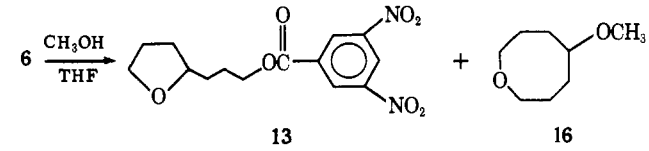


comparison with an authentic sample.[12] Submission of **13** to similar hydrolysis conditions led uniquely to alcohol **15**.



For the purpose of determining the extent, if any, of *O*-acyl cleavage in the 3,5-dinitrobenzoate group of **6**, a solution of **6** and a twofold excess of 2,6-lutidine in anhydrous methanol–tetrahydrofuran (3:1) was refluxed for 18.5 hr. From the reaction mixture there was isolated the dinitrobenzoate of internal return (**13**) in 62% yield and 38% of a liquid identified as 5-methoxyoxocane (**16**, Scheme V). Independent syn-

Scheme V

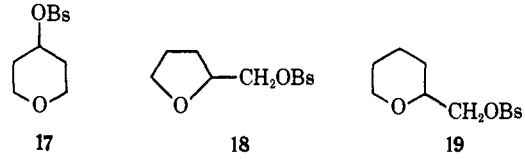


thesis of **16** was achieved by treating alcohol **14** with sodium hydride and methyl iodide. The absence of alcohol **14** and the presence of ether **16** serve to dismiss *O*-acyl cleavage in the hydrolysis of **6** and demonstrate that attack of the nucleophile occurs directly at C_5.

In contrast, methanolysis of **13** under identical conditions afforded alcohol **15** as the only product, thereby attesting to the operation of *O*-acyl cleavage in this instance.

Discussion

In a series of elegant papers,[13] Allred and Winstein have demonstrated that the rate constant for anchimerically assisted ionization of an ω-methoxy-substituted alkyl brosylate can be satisfactorily estimated by the Taft ($\rho^*\sigma^*$) treatment[14] of the inductive effect of the methoxyl substituent relative to the unsubstituted hydrocarbon counterpart. Unfortunately, this treatment cannot be employed with any anticipated degree of accuracy to gain mechanistic insight into the solvolytic behavior of oxygen heterocycles. This is because the oxygen substituent in an acyclic molecule exerts very little, if any, dipolar field effect on a time-averaged basis due to entropy considerations. In cyclic systems, the oxygen atom is constrained to reside significantly closer to the center of incipient positive charge such that destabilizing transannular dipole influences gain importance. The tenfold slower acetolysis rate of 4-tetrahydropyranyl brosylate (**17**)



relative to that estimated by Winstein's method clearly reflects the point at issue.[7] This rate decrease does not appear to be due to a sensitivity of the substituent constant to cyclic or acyclic character since the solvolytic behavior of **18** and **19** is correctly predictable on the basis of the normal rate-retarding inductive effect of the β oxygen atom.[15] Thus, transannular dipolar destabilization of solvolytic transition states can eventuate in substantial rate reduction.

The ease of ionization of a cyclic derivative containing a ring heteroatom can also be affected by alterations in the degree of transannular steric compression, particularly in medium-sized systems. It goes unquestioned that any structural changes which will result in strain relief at the transition state will result in enhanced solvolysis rates, and *vice versa*.

(11) M. W. Rathke, *J. Amer. Chem. Soc.*, 92, 3222 (1970).
(12) R. H. Bray and R. Adams, *ibid.*, 49, 2101 (1927).
(13) E. Allred and S. Winstein, *ibid.*, 89, 3991, 3998, 4008, 4012 (1967).
(14) (a) D. S. Noyce, B. R. Thomas, and B. N. Bastian, *ibid.*, 82, 885 (1960); (b) A. Streitwieser, *ibid.*, 78, 4935 (1956); (c) S. Winstein and E. Grunwald, *ibid.*, 70, 821 (1948).
(15) G. T. Kwiatkowski, S. J. Kavarnos, and W. D. Closson, *J. Heterocycl. Chem.*, 2, 11 (1965).

The third and final *a priori* consideration concerns transannular neighboring group participation and the effectiveness of such anchimeric assistance as a function of ring strain. The intervention of a given oxabicyclo[*m.n.o*]alkyloxonium ion will understandably be kinetically favored if the *m* and *n* bridges are of lengths sufficient to rule out strain influences. When the converse is true and ring-strain factors gain importance (as in R_2O-4 bonding), striking rate retardations will be in evidence.

Complications arise because these various factors can frequently counterbalance each other. The solvolytic behavior of oxocan-3-yl brosylate (**3**) is such a case. In the present study, oxocan-4-yl brosylate (**5**) has been found to experience ionization ten times faster than **3** (at 70°) but seven times slower than cyclooctyl brosylate (**1**). The faster rate of acetolysis of **5** compared to **3** may reasonably be interpreted as a manifestation of diminished inductive electron withdrawal by the γ-oxygen center. Data bearing on the possible transannular dipolar influence of the ether functionality in **5** were gained from a comparative examination of the infrared carbonyl stretching frequency of oxocan-4-one with those of several related compounds (Table III). Since the influence (if any)

Table III. Carbonyl Stretching Frequencies of Liquid Films[a]

Compound	$\nu_{C=O}$, cm^{-1}	Ref
	1692	*b*
	1713	*c*
	1700	*d*
	1696	*d, e*

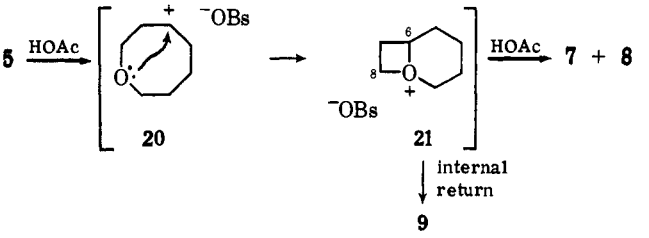
[a] The estimated accuracy of the data is ±1 cm^{-1}. [b] C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 214. [c] R. W. Begland, Ph.D. Thesis, The Ohio State University, 1968. [d] Reference 1. [e] Reference 8a.

of the ether dipole on the carbonyl group is to generate electrostatic repulsion such that partial feedback of negative charge from carbonyl oxygen to carbonyl carbon results (with an attendant increase in double bond character),[7,8a,16] the carbonyl stretching frequency will be raised relative to the parent ketone in direct proportion to the level of interaction.

The data of Table III reveal that the oxocanones are subject to intramolecular dipole–dipole interactions. Not unexpectedly, however, there is an appreciable lessening of the level of interaction with increasing distance between the two functional groups. To the extent that oxocan-4-one is subject to such dipolar factors, brosylate **5** is expected to experience rate retardation in its ionization. Although negative contributions to the rate of solvolysis of **5** from inductive and dipolar forces seem clear, an estimate of the exact magnitude of the rate deceleration remains difficult to assess. However, a rough estimate places the value somewhat lower than the sevenfold rate retardation observed (relative to **1**). Because past experience[4] and the experimentally determined acetolysis rate constant for **5** preclude *direct* R_2O-4 participation at the transition state, the small rate difference between **5** and **1** also likely reflects a positive kinetic contribution from relief of nonbonded interactions provided by the reduced steric requirements of ether oxygen relative to a methylene group.[3]

Although transannular oxygen participation is nonoperative at the transition state of the rate-determining ionization, indication of subsequent $O–C_4$ bond formation is derived from the acetolysis product composition. To account for the genesis of **7** and **9**, subsequent interception of initially produced secondary carbonium ion **20** is proposed (Scheme VI). Oxabicyclic oxonium ion

Scheme VI



21 then sustains attack at C_8 to give the observed 2-(2-tetrahydropyranyl)ethanol derivatives. Nucleophilic attack at C_6 gives rise to oxocan-4-yl acetate (**8**); this substance can also arise by direct interception of **20**.

Interestingly, the acetolysis of **9** led uniquely to **7**, thereby demonstrating a lack of proclivity on the part of this brosylate toward R_2O-4 involvement and regeneration of oxonium ion **21**.

Turning our attention now to **6**, we see that the k_i for its hydrolysis reflects a highly enhanced ionization rate. Using a conversion factor of 500 for solvolysis of 3,5-dinitrobenzoates in 60% aqueous acetone at 100° and tosylates in acetic acid at 25°[17] and a factor of 3.0 for solvolysis of both brosylates and tosylates in acetic acid,[18] the estimated k_i for the hypothetical 6-brosylate at 25° is 5.91, some 48,500 times greater than the acetolysis rate of **1**. If one considers that **6** must experience some rate retardation because of the steric advantages of the heteroatom and to some degree because of dipolar forces, it becomes necessary to conclude that transannular anchimeric assistance by the ether oxygen in the ionization of **6** is simply overwhelming.

The large negative entropy of activation observed for this reaction (−22.0 eu) also supports this conclusion, since a number of degrees of freedom associated with the eight-membered ring are lost in the transition state to oxabicyclic oxonium ion **22** (Scheme VII). Although *O*-acyl cleavages of 3,5-dinitrobenzoates generally show large entropy losses, *O*-alkyl heterolyses of such derivatives usually exhibit marginally negative entropy terms.[17a,19] That the entropy loss in the case

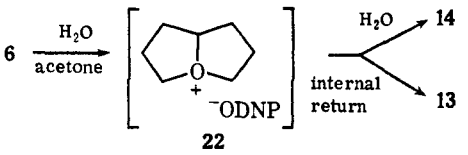
(16) S. S. Stradling and D. S. Tarbell, *J. Org. Chem.*, **29**, 1170 (1964), and references therein.

(17) (a) J. E. Baldwin and W. D. Foglesong, *J. Amer. Chem. Soc.*, **89**, 6372 (1967); (b) P. von R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966); (c) K. B. Wiberg and A. J. Ashe, III, *Tetrahedron Lett.*, 1553 (1965); (d) D. D. Roberts, *J. Org. Chem.*, **29**, 294 (1964).

(18) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956).

(19) O. Cox, Ph.D. Thesis, The Ohio State University, 1968.

Scheme VII



of **6** is not caused by *O*-acyl cleavage was demonstrated earlier by a suitable methanolysis experiment.

On scrutinizing the product distribution resulting from hydrolysis of **6**, it is seen that attack of water on **22** is highly regiospecific (C_5 only!). This preferential nucleophilic attack parallels quantitatively the relative reactivities of C_2 and C_5 toward carbonium ion formation and may therefore denote a higher percentage of positive charge at C_5 relative to C_2 (oxygen, of course, does bear most of the cationic burden). Such behavior suggests that **22** enjoys appreciable thermodynamic stability such that it survives long enough to exercise discrimination toward various nucleophiles. The origin of lesser amounts of internal return dinitrobenzoate **13** probably lies in the collapse of an intimate ion pair.

Summarizing briefly then, we find that the small structural change attending the interpolation of CH_2 and O groups between C_4 and C_5 of an eight-membered ring results in striking alterations of intrinsic chemical behavior. The solvolytic data relating to oxocan-5-yl 3,5-dinitrobenzoate (**6**) reveal the highest level of kinetic acceleration for intramolecular nucleophilic substitution by a heteroatom on record as known to us. Although there is obviously an expected heavy bias for the formation of oxonium ion **22**, a more in-depth analysis of the precise proximity requirements for effective heteroatomic neighboring group participation is warranted and we hope to provide information on this point at a later date.

Experimental Section

Melting points are corrected. Proton magnetic resonance spectra were obtained with a Varian A-60A spectrometer and apparent coupling constants are cited. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Oxocan-4-yl *p*-Bromobenzenesulfonate (5). A solution of 0.835 g (6.42 mmol) of oxocan-4-ol[1] in 5.0 ml of anhydrous pyridine at 0° was added to a solution of 3.30 g (12.87 mmol) of *p*-bromobenzenesulfonyl chloride in 10 ml of anhydrous pyridine at 0° and was allowed to stand for 36 hr at 5°. Ice was added to the solution, followed by treatment with 30 ml of ice water. The resulting mixture was extracted with two 30-ml portions of ether. The combined ether layers were washed with 15-ml portions of iced 1 *N* hydrochloric acid until acidic and then with 18 ml of 5% sodium carbonate solution. The ether solution was dried, filtered, and evaporated to furnish **5** as an oily brosylate (2.117 g, 89% yield, 93% pure, see infinity titer) which resisted crystallization: $\delta_{TMS}^{CDCl_3}$ 7.75 (s, 4, aryl), 4.82 (m, 1, >C*H*O), 3.61 (m, 4, CH_2O), 2.03 (m, 4), and 1.60 (m, 4).

Oxocan-5-ol (14) and Oxocan-5-yl 3,5-Dinitrobenzoate (6). A solution of 2.50 g (19.5 mmol) of oxocan-5-one[1] in 12.0 ml of ether was added dropwise to a slurry of 1.48 g (39.0 mmol) of lithium aluminium hydride in 50.0 ml of ether and the resulting mixture was stirred overnight. After adding 1.48 ml of water, 1.48 ml of 30% sodium hydroxide solution, 3.84 ml of water, and solid anhydrous magnesium sulfate, the mixture was filtered and the ether was evaporated. The residue was purified by preparative vpc[20] to give 2.35 g (92%) of **14** as a clear liquid: ν_{max}^{neat} 3400 and 1120 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.10 (m, 1, O*H*), 3.60 (m, 4, CH_2O), 3.45 (s, 1, >C*H*O), and 1.80 (m, 8, remaining methylenes).

The 3,5-dinitrobenzoate was prepared by adding a solution of 0.600 g (4.7 mmol) of **14** and 3.52 ml of anhydrous pyridine to a solution of 2.40 g (10.4 mmol) of 3,5-dinitrobenzoyl chloride in 7.5 ml of pyridine and warming the mixture until most of the 3,5-dinitrobenzoyl chloride had dissolved. After standing overnight at 0° the mixture was treated with 50 ml of ice water and filtered. The precipitate was washed with water and 5% sodium carbonate solution, and dissolved in chloroform. This solution was dried, filtered, and evaporated. The resulting solid was dissolved in 100 ml of ether, boiled until the volume was approximately 20 ml, and cooled. A white crystalline solid separated which was recrystallized three times from ether to give 1.172 g (79%) of **6**: mp 102–104°; $\nu_{max}^{CCl_4}$ 1728 and 1627 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 9.10 (s, 3, aryl), 5.56 (m, 1, >C*H*O), 3.66 (m, 4, CH_2O), and 1.90 (m, 8, remaining methylenes).

Anal. Calcd for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.85; H, 4.99; N, 8.51.

Preparative Scale Acetolysis of 5. A solution of 1.2164 g (3.49 mmol) of **5**, 0.219 g (2.09 mmol) of anhydrous sodium carbonate, and 15.0 ml of anhydrous acetic acid was heated at 60–65° for 1 hr 35 min (9 half-lives), cooled, poured into 40 ml of ice water, and extracted with three 25-ml portions of ether. The ether layers were washed with saturated sodium bicarbonate solution until neutral, dried, and evaporated. The liquid residue was distilled to give 0.296 g (50%, corresponding to 97.5% relative) of liquid, bp 57–59° (0.5 mm), which was separated into two components by preparative vpc.[20]

The component of least retention time (75%) was identified as 2-(2-tetrahydropyranyl)ethyl acetate (**7**) by comparison with an independently synthesized sample. The component of greater retention time (25%) was identified as oxocan-4-yl acetate (**8**) by comparison with an authentic sample.

The distillation residue was taken up in pentane and cooled to 0°. The crystalline solid (mp 77.5–79°, 0.0186 g, 1.5% corresponding to 2.5% relative) which deposited was identified as 2-tetrahydropyranylethyl brosylate (**9**) by comparison with an authentic sample. The mother liquor was evaporated to give an additional 0.0192 g of the acetate mixture.

Ethyl (2-Tetrahydropyranyl)acetate (11). A solution of 6.90 g (0.0427 mol) of hexamethyldisilazane in 13.2 ml of ether was treated with 25 ml of 1.6 *M* *n*-butyllithium during 2 min and the solution was refluxed for 0.5 hr. The ether was evaporated and the solid residue was dissolved in anhydrous tetrahydrofuran and cooled to −78°. Ethyl acetate (4.13 g, 0.088 mol) was introduced and the solution was stirred for 15 min. To this solution was added 6.47 g (0.039 mol) of 2-bromotetrahydropyran [**10**, prepared by bubbling hydrogen bromide gas through 3.30 g (0.039 mol) of dihydropyran until the theoretical amount of hydrogen bromide was consumed] and the resulting solution was stirred at −78° for 10 min. Hydrochloric acid (7.0 ml) and water (3.0 ml) were added and the mixture was allowed to warm to room temperature. The ether layer was separated and the aqueous layer was extracted with 25 ml of ether. The combined organic layers were dried, filtered, and evaporated. The residue was distilled to give 1.64 g (24%) of **11**; bp 88–90° (6.0 mm); ν_{max}^{neat} 1735 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.12 (q, $|J|$ = 6.5 Hz, 2, OCH_2), 3.78 (m, 3, CH_2OC*H*<), 2.42 (d of d, $|J|$ = 3.0 and 2.0 Hz, 2, CH_2COO), 1.52 (m, 6, remaining methylenes), and 1.25 (t, $|J|$ = 6.5 Hz, 3, CH_3).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.41; H, 9.47.

2-(2-Tetrahydropyranyl)ethanol (12). A solution of 1.40 g (8.15 mmol) of **11** in 10 ml of anhydrous ether was added dropwise to a slurry of 0.25 g (6.42 mmol) of lithium aluminum hydride in 90 ml of anhydrous ether and the resulting mixture was allowed to stir overnight. The flask was cooled in ice while 0.25 ml of water, 0.25 ml of 30% sodium hydroxide solution, and 0.80 ml of water were added slowly. The inorganic salts were removed by filtration, the filtrate was evaporated, and the residue was distilled to give **12**: bp 87–89° (7.0 mm); ν_{max}^{neat} 3395 and 1090 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.60 (m, 6, <C*H*O) and 1.55 (m, 8, remaining methylenes).

2-(2-Tetrahydropyranyl)ethyl Acetate (7). Acetic anhydride (0.400 g, 3.92 mmol) was added to 0.100 g (0.77 mmol) of **12** dissolved in 1.0 ml of anhydrous pyridine and the solution was refluxed for 10 min, cooled, poured into 3.0 ml of ice water, and extracted with two 10-ml portions of ether. The ether layers were combined and washed with 1 *N* hydrochloric acid until acidic, dried, filtered, and evaporated. Preparative vpc[21] of the residue afforded 0.10 g

(20) A 5.5 ft × 0.25 in. aluminum column packed with 10% FFAP on 60–80 mesh Chromosorb G was employed.

(21) A 6 ft × 0.25 in. aluminum column packed with 10% SE-30 on 60–80 mesh Chromosorb G was employed.

(82%) of pure **7**: ν_{max}^{neat} 1740 and 1240 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.18 (t, $|J|$ = 6.5 Hz, 2, CH_2O), 3.85 (br s, 1, >CHO), 3.40 (br m, 2, CH_2O), 2.03 (s, 3), and 1.68 (m, 8, remaining methylenes).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.48; H, 9.71.

2-(2-Tetrahydropyranyl)ethyl Brosylate (9). An ice-cold solution of 0.8215 g (6.32 mmol) of **12** in 5.0 ml of anhydrous pyridine was added to a solution of 3.30 g (12.85 mmol) of *p*-bromobenzenesulfonyl chloride in 10 ml of anhydrous pyridine at 0° and the resulting solution was allowed to stand 36 hr at 5°. Ice and then 30 ml of water were added to destroy excess sulfonyl chloride. The mixture was extracted with two 30-ml portions of ether. The combined ether layers were washed with 1 *N* hydrochloric acid until acidic and then 18 ml of 5% sodium carbonate solution, dried, filtered, and evaporated. The residue became crystalline after scratching with a glass rod and was subsequently recrystallized three times from ether to give 1.728 g (78%) of **9** as a white crystalline solid: mp 77.5–79.0°; $\delta_{TMS}^{CDCl_3}$ 7.72 (s, 4, aryl), 4.20 (t, $|J|$ = 6.0 Hz, 2, CH_2O), 3.50 (m, 3, CH_2OOCH<), and 1.50 (m, 8, remaining methylenes).

Anal. Calcd for $C_{13}H_{17}BrO_4S$: C, 44.71; H, 4.91; S, 9.18. Found: C, 44.64; H, 4.93; S, 9.17.

Oxocan-4-yl Acetate (8). Acetylation of 0.100 g (0.77 mmol) of oxocan-4-ol as above with 0.400 g (3.92 mmol) of acetic anhydride gave 0.090 g (68%) of vpc-purified **8**: ν_{max}^{neat} 1730 and 1245 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.00 (pent, J = 5.0 Hz, 1, >CHO), 3.70 (m, 4, CH_2O), 2.00 (s, 3, CH_3), and 1.80 (m, 8, remaining methylenes).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.41; H, 9.39.

Preparative Scale Solvolysis of 2-(2-Tetrahydropyranyl)ethyl Brosylate (9). A solution of 0.383 g (1.09 mmol) of brosylate **9**, 0.089 g (0.84 mmol) of anhydrous sodium carbonate, and 6.20 ml of anhydrous acetic acid was refluxed (118°) for 41.5 hr (17 half-lives), cooled, poured into 13.0 ml of ice water, and extracted with three 10-ml portions of ether. The ether layers were combined and washed with saturated sodium bicarbonate solution until neutral, dried, filtered, and evaporated to give 0.183 g (96%) of **7** which was shown to be pure by vpc.[20]

Preparative Scale Hydrolysis of 6 in 80:20 Acetone–Water. A solution of 0.502 g (1.59 mmol) of **6**, 0.382 g (3.57 mmol) of 2,6-lutidine, and 33 ml of 80:20 acetone–water was refluxed for 18 hr, and cooled, and the acetone evaporated. The aqueous residue was extracted with ether and the combined organic layers were dried, filtered, reduced in volume to about 2 ml, and cooled. A white solid precipitate (0.034 g), soluble in water and dilute base, was separated and discarded. The mother liquor was reduced to 1.0 ml and cooled to give 0.114 g (22% corresponding to 29% relative) of crystalline solid, mp 63–66°, identified as **13** on the basis of its nmr and ir spectra.

Additional processing of the mother liquor gave a liquid which was purified by vpc:[21] 0.112 g (54% corresponding to 71% relative). This substance was identified as oxocan-5-ol (**14**).

Preparative Scale Methanolysis of 6 in 75:25 Methanol–Tetrahydrofuran. A solution of 0.500 g (1.54 mmol) of **6**, 0.383 g (3.57 mmol) of 2,6-lutidine, and 33 ml of 75:25 anhydrous methanol–tetrahydrofuran was refluxed 18 hr and the solvents were evaporated at 65° (80 mm) to give a semisolid residue. This material was taken up in pentane and cooled to give 0.191 g of a water and dilute base-soluble solid, mp 127–129°, which was discarded.

The mother liquor was reduced in volume and cooled to give 0.162 g (33% corresponding to 62% relative) of **13**, mp 61.5–63.5°. Further evaporation of the mother liquor afforded a liquid which was purified by preparative vpc.[21] There was obtained 0.049 g (22% corresponding to 38% relative) of a colorless liquid identical in all respects with an authentic sample of 5-methoxyoxocane (**16**).

5-Methoxyoxocane (16). A solution of 42.0 mg (0.32 mmol) of **14** in 1.0 ml of benzene was treated with 14 mg of 57% sodium hydride in mineral oil. The mixture was stirred for 30 min until hydrogen evolution ceased and then 0.026 ml of methyl iodide was added. After stirring the reacton mixture overnight, vpc analysis indicated only 25% conversion. Therefore, the above sequence was repeated. The mixture was filtered and the benzene was evaporated at 50° (80 mm). The liquid residue was subjected to preparative vpc[21] to give 0.02 g of starting alcohol (**14**) and 0.02 g (50%) of methyl ether **16**: $\nu_{max}^{CCl_4}$ 1100 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.59 (m, 5, >CHO), 3.28 (s, 3, OCH_3), and 1.77 (m, 8, remaining methylenes).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.30; H, 11.23.

3-(2-Tetrahydrofuranyl)propyl 3,5-Dinitrobenzoate (13). Treatment of 6.00 g (46.0 mmol) of 3-(2-tetrahydrofuranyl)propanol (**15**) in 23 ml of anhydrous pyridine at 0° with 11.07 g (48.0 mmol) of 3,5-dinitrobenzoyl chloride according to the directions of Bray and Adams[12] afforded 6.18 g (41.5%) of **13**, mp 65.5–67°, from ether (lit.[12] mp 65–66°): $\nu_{max}^{CCl_4}$ 1734 and 1628 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 9.10 (s, 3, aryl), 4.54 (t, $|J|$ = 6.0 Hz 2, CH_2OCO), 3.80 (m, 3, >CHO), and 1.90 (m, 8, remaining methylenes).

Preparative Scale Solvolysis of 13 in 80:20 Acetone–Water. A solution of 0.303 g (0.933 mmol) of **13**, 0.230 g (2.15 mmol) of 2,6-lutidine, and 20 ml of 80:20 acetone–water was maintained at 160° for 138 hr in a thick-walled glass sealed tube. The vessel was cooled and the contents were evaporated to remove the acetone. The aqueous residue was extracted with ether, and the combined organic layers were dried, filtered, and cooled to deposit a crystalline solid which was collected to give 0.2280 (75%) of recovered **13**. The mother liquor was evaporated and the liquid so obtained was purified by preparative vpc[21] to give 0.030 g (25%) of a single component identified as 3-(2-tetrahydrofuranyl)propanol (**15**) on the basis of its nmr and ir spectra.

Preparative Scale Solvolysis of 13 in 75:25 Methanol–Tetrahydrofuran. A solution of 0.30 g (0.925 mmol) of **13**, 0.230 g (2.15 mmol) of 2,6-lutidine, and 20 ml of 75:25 methanol–tetrahydrofuran was maintained at 160° in a thick-walled sealed glass tube for 137 hr. The solvents were removed and the residue was taken up in pentane. The insoluble material was recrystallized from ether to give 0.153 g of methyl 3,5-dinitrobenzoate: mp 107–110° [lit.[22] mp 108°]; $\nu_{max}^{CCl_4}$ 1740 and 1628 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 9.18 (s, 3, aryl) and 4.12 (s, 3, OCH_3). The pentane solution was evaporated to give 0.099 g (82.5%) of **15** based on its nmr and ir spectra.

Kinetic Procedure for Acetolysis. A. Reagents. Anhydrous acetic acid was prepared by refluxing a solution of 2–2.5 l. of glacial acetic acid and 50 ml of acetic anhydride overnight with protection from atmospheric moisture and subsequent fractional distillation in a dry atmosphere. The perchloric acid solution (0.0154 *M*) was prepared by dissolving approximately 2.0 g of 74.39% aqueous perchloric acid in anhydrous acetic acid and diluting to 500 ml. This solution was then standardized against 0.04037 *M* potassium acid phthalate in acetic acid with Bromophenol Blue as indicator. The 0.30 *M* sodium acetate–acetic acid solution was prepared by dissolving anhydrous sodium carbonate (dried at 115° under vacuum for 12 hr) in anhydrous acetic acid and standardizing the resulting solution against the perchloric acid solution.

B. Kinetic Measurements. An accurately weighed amount of the brosylate was dissolved in 0.03 *M* sodium acetate solution and diluted to the mark in a 50-ml volumetric flask giving an approximately 0.02 *M* solution of brosylate. Aliquots of 2.2 ml were transferred to precleaned Pyrex test tubes which were cooled in ice water and sealed. The tubes were placed in a constant temperature oil bath and after 10 min a tube was withdrawn and cooled in ice water and an accurate timer was started. After 2 min, the tube was placed in water at room temperature for 3 min and opened. A 1.8983-ml aliquot of the contents was withdrawn and titrated with 0.01454 *M* perchloric acid solution using Bromophenol Blue as indicator. From this value the molarity of the sodium acetate $[NaOAc]_t$ at time t was calculated. Subtracting $[NaOAc]_t$ from $[NaOAc]_0$ gave the amount of *p*-bromobenzenesulfonic acid present at time t, $[BsOH]_t$. By subtracting $[BsOH]_t$ from the molarity of brosylate at time t, $[ROBs]_t$ was obtained. The log $[ROBs]_t$ was then plotted against t. Infinity titers of **5** were obtained by allowing a sample of the reaction mixture to solvolyze at 115° for a time (~10 hr) corresponding to 10 half-lives of rearranged brosylate **9** and then titrating.

Kinetic Procedure for Hydrolysis. A. Reagents. Reagent grade acetone was purified by distillation from potassium permanganate and pure 2,6-lutidine was obtained by careful fractional distillation of practical grade material. The water which was used was doubly distilled.

B. Kinetic Measurements. An approximately 0.02 *M* solution of the 3,5-dinitrobenzoate was prepared by dissolving an accurately weighed sample in 80:20 acetone–water and diluting to the mark in a 25-ml volumetric flask. Aliquots of approximately 2.2 ml of this solution were placed in constricted Pyrex tubes (made from 125 × 15 mm Pyrex test tubes), cooled in ice, and sealed. The tubes were simultaneously placed in a constant temperature oil bath and after 10 min the first tube was withdrawn and an accurate timer was started. The sample was cooled in ice for 2 min, brought to room temperature, and opened. A 1.9021-ml aliquot was

(22) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1956, p 212.

Table IV. Acetolysis Rate Calculation for **5** in Acetic Acid at 54.8° Containing 0.03057 *N* Sodium Acetate

Time, sec	ml of 0.01473 *M* $HClO_4$–HOAc	[HOBs], *M*	$[HOBs]_\infty - [HOBs]_t$, *M*	ln *X*	ln C[a]
550	3.478	0.00358	0.01301	0.24308	0.20246
1730	2.920	0.00791	0.00868	0.64778	0.62634
2657	2.572	0.01061	0.00598	1.02038	0.94594
4054	2.332	0.01247	0.00412	0.39295	1.39615
5314	2.170	0.01373	0.00286	1.75798	1.75873
6547	2.086	0.01438	0.00221	2.01581	2.06303
7805	2.012	0.01496	0.00163	2.32022	2.31522
∞	1.825[b]	0.01659			

[a] Computer-derived values. [b] Titrated with 0.01454 *M* $HClO_4$–HOAc.

Table V. Hydrolysis Rate Calculations for **6** in Acetone–Water (80:20) at 40.3° Containing 2,6-Lutidine

Time, sec	ml of 0.01015 *N* NaOH–H_2O	[HODNB], *M*	$[HODNB]_\infty - [HODNB]_t$, *M*	ln *X*	ln *C*
1275	0.062	0.00033	0.01835	0.01782	0.01770
3686	0.181	0.00097	0.01771	0.05332	0.05004
5673	0.255	0.00136	0.01732	0.07559	0.07559
7482	0.332	0.00177	0.01691	0.09955	0.09812
9677	0.395	0.00211	0.01657	0.11986	0.12410
11549	0.468	0.00250	0.01618	0.14368	0.14545
13621	0.541	0.00289	0.01579	0.16808	0.16811
∞	3.500	0.01868			

withdrawn and titrated potentiometrically with 0.01015 *N* sodium hydroxide solution using a Fisher "Accumet" Model 310 pH meter fitted with a Fisher Microprobe Combination Electrode. Additional samples were removed at different time intervals and from the titration the amount of liberated 3,5-dinitrobenzoic acid was determined. The various values were subtracted from the original amount of dinitrobenzoate (as obtained from the infinity titer) to give the concentration of dinitrobenzoate, which was plotted against time *t*. By maintaining a sample of the hydrolysis mixture of **6** at 160° for 10 half-lives (~85 hr) of rearranged 3,5-dinitrobenzoate **13**, the infinity titer of **6** was obtained.

Determination of Solvolytic Rate Constants. The specific first-order rate constant k_i for SN1 type solvolysis reactions is shown in eq 1. In the solvolyses of **5** and **6** the situation is complex since the

$$\ln\left(\frac{[HOX]_\infty - [HOX]_0}{[HOX]_\infty - [HOX]_t}\right) = k_i t \qquad (1)$$

substrate is rearranging to a less reactive compound in addition to solvolyzing (see Scheme I). Thus the observed titrimetric rate constant k_1 is a combination of rate constants k_1, k_2, and k_3. It has been shown that when $k_3 \ll k_2 \approx k_1$, the relationship between these rate constants, time *t*, and acid production is that shown in eq 2.[10]

$$\frac{d}{dt}\ln\left(\frac{[HOX]_\infty}{[HOX]_\infty - [HOX]_t}\right) = \frac{d}{dt}\ln\left[\frac{k_1 + k_2 + k_3}{k_2 e^{-k_3 t} + (k_1 - k_3)e^{-(k_1+k_2)t}}\right] \qquad (2)$$

The corresponding k_1, k_2, and k_3 for the solvolyses of **5** and **6** were evaluated from the experimental data using eq 2 in conjunction with an iterative Fortran IV computer program, written by R. S. Macomber and modified by M. J. Epstein. Insertion of experimentally determined values of $[HOX]_\infty$ (infinity titer) and $[HOX]_t$ afforded values of ln *X* (eq 3). The experimental data required to

$$\ln X = \ln\left(\frac{[HOX]_\infty}{[HOX]_\infty - [HOX]_t}\right) \qquad (3)$$

calculate ln *X* are shown in Tables IV and V for two typical runs. The estimated rate constants were varied over specific ranges and were used to calculate the computer equivalent of ln *X*, ln *C*. Those values of k_1, k_2, and k_3 which gave a minimum total absolute error between ln *X* and ln *C* were retained.

Since it was necessary to include a data card for $t = 0$ and ln $X = 0$, the absolute time of the data points had to be used. These time values were obtained by extrapolating the time *vs.* log [ROX] curves to log $[ROX]_0$ and adding the value of the time axis intercept (t_0) to the experimental time values. The value of t_0 was varied over a small range and the data were treated using the iterative program. The value of t_0 which was kept was that corresponding to the smallest total absolute error between ln *X* and ln *C*.

Initial values of k_1, k_2, and k_3 were obtained in various ways. A plot of the slopes (instantaneous rate constants)[9] of the experimental curves *vs.* time and extrapolated to zero time afforded an estimate of k_1. The value of k_2 was initially estimated to be roughly the same as k_1, although in some instances this had to be revised downward if the computed values were at the bottom of its variation range.

Rate constant k_3 was determined titrimetrically using authentic samples of brosylate **9** and 3,5-dinitrobenzoate **13**.

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