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THE EFFECT OF ETHER OXYGEN IN THE CHEMISTRY
OF MEDIUM-SIZED RINGS

DISSERTATION
Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By
Malcolm Keith Scott, B.S., M.S.

* * * * *

The Ohio State University
1971

Approved by

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DEDICATION

To Ann, Sarah, and Stephen with all my love.
ACKNOWLEDGMENT

The author wishes to thank Professor Leo A. Paquette for providing the opportunity to pursue basic research in organic chemistry. In addition, his guidance and moral support were deeply appreciated.

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Finally, the author acknowledges the care and support provided by his family and friends.
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PUBLICATIONS


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INTRODUCTION

An interesting phenomenon associated uniquely with the chemistry of medium-sized rings is that of transannular reactivity. One of the earlier examples of this process, studied by Prelog, was the acid-catalyzed rearrangement of cyclohexanediol 1 to ketone 2 via a 1,6-hydride shift. Later, it was discovered that heterocatoms such as nitrogen and sulfur were capable of perturbing and reacting with sites positioned diametrically across the medium-sized ring. Thus, Leonard's study of heterocyclic ketones 3 and 5 revealed the operational feasibility of interaction between the carbonyl group and the nitrogen and
sulfur atoms. This was shown by infrared studies of the carbonyl stretching frequency and by the conversion of ketones 3 and 5 to the corresponding bicyclic ammonium and sulfonium salts 4 and 6, respectively, upon treatment with perchloric acid. There is apparently a tendency for medium-sized rings to form bicyclic products, the driving force being the relief of strain from non-bonded interactions.

The reaction of ketone 7 with hydrochloric acid, however, did not afford a bicyclic oxonium salt but instead gave 1,7-dichloro-4-heptanone (8) as the only product. In addition, infrared studies of 7 revealed no perturbation of the carbonyl group by the ether oxygen. Thus, while there was some indication that weakly nucleophilic oxygen was capable of transannular participation, as in the case of 7, there remained the need for more conclusive proof.

In 1965, Paquette and Begland reported the first bona fide examples of transannular participation by ether oxygen in acid-catalyzed reactions of medium-sized rings. It was found that the reaction of
ketone 2 with hydrochloric acid led exclusively to tetrahydrofuranone 11 as the result of chloride ion attack on bicyclic oxonium ion 10, produced from transannular Michael type addition of the ether oxygen to the \( \alpha,\beta \)-unsaturated ketone group. Additionally, it was demonstrated that the carbonyl group was not necessary for this type of reaction to occur. Thus, when olefin 12 was treated with hydrochloric acid, there was obtained tetrahydrofuran 14. In this instance, transannular interception of the initially generated benzyl cation by ether oxygen was followed by attack of chloride ion on the resulting bicyclic oxonium ion (13).

Besides being capable of transannular reaction, ether oxygen can accelerate the rate of solvolysis of certain compounds by neighboring group participation. Examples of anchimeric assistance by methoxy groups are well known and the tetrahydrofuran group was shown to be twice as effective in neighboring group participation as the methoxy group. In addition, it was postulated that a result of anchimeric assistance of the tetrahydrofuran group in the acetolysis of 3-(2-tetrahydrofuran)propyl brosylate (15) would be the formation of a [3.3.0] bicyclic oxonium ion (16).
The presence of ether oxygen in cyclic compounds can also have an effect on their solvolysis rates. For example, the rate of acetolysis of 3-tetrahydropyranyl brosylate was assumed to be enhanced due to R₂O-3 participation by the ether oxygen, although no rearranged products were observed.

Interestingly enough, the acetolysis of oxocan-3-yl brosylate (17), which exhibits R₂O-3 participation leading to bicyclic oxonium ion 18 from which rearranged products 19-22 arise, is 70 times slower than its
carbocyclic analog $^{3,11}$ Analysis of the rate enhancement due to $R_2O_3$ participation in this case is complicated by the fact that there is an unknown amount of rate retardation due to relief of strain arising from the lesser steric demands of oxygen compared to those of a methylene group.

The present investigations were undertaken to evaluate further the role of ether oxygen in the chemistry of medium-sized oxygen containing heterocycles. Particular emphasis was placed on the study of reactions where a positive charge might be generated in the ring or where anchi-meric assistance by ether oxygen was possible. In Part I, the acid-promoted reactions of several bicyclic ethers containing cis-fused cyclopropane rings is described. In Part II, the first order kinetic rate constants and solvolysis products of the hydrolysis of oxocan-5-yl 3,5-dinitrobenzoate and the acetolysis of oxocan-4-yl brosylate were determined and are discussed.
PART I. Acid-Promoted Reactions of cis-[n.1.0] Medium-Sized Bicyclic Ethers

Introduction

The study of medium-sized [n.1.0] bicyclic compounds has shown that varying amounts of transannular hydride shifts occur, depending on the size of n. For cis-bicyclo[6.1.0]nonane (24, n=6) the extent of transannular reaction which occurred upon exposure to formic acid was 97%; in contrast, acetolysis of cis-bicyclo[5.1.0]octane (25, n=5) afforded 12% of products resulting from transannular hydride shift.

The marked difference in the amount of transannular reaction between

\[
\begin{align*}
\text{cis-bicyclo[6.1.0]nonane} & \xrightarrow{\text{HCOOH}} \text{cis-bicyclo[6.1.0]nonane} + \text{products} \\
\text{cis-bicyclo[5.1.0]octane} & \xrightarrow{\text{CH₃COOH}} \text{cis-bicyclo[5.1.0]octane} + \text{products}
\end{align*}
\]
is due to the ability of the larger ring, because of decreased non-bonded interactions relative to the smaller ring, to attain conformations which bring the ring hydrogens into close proximity with the incipient carbonium ion.

Since these bicyclo alkanes exhibit a tendency to undergo transannular reactions and because it had been demonstrated, in the case of monocyclic ethers 9 and 12, that the ether oxygen does participate in transannular fashion in carbonium ion processes, it was deemed of interest to investigate the acid-promoted reactions of a series of medium-sized bicyclic ethers of this type. With this goal in mind, 3-oxabicyclo[5.1.0]octane (26), 4-oxabicyclo[5.1.0]octane (27), and 4-oxabicyclo[6.1.0]nonane (28) were synthesized.

**Synthesis of the cis-[n.1.0]bicyclic Ethers**

3-Oxabicyclo[5.1.0]octane (26). The preparation of 26 was carried out as outlined in Scheme I. Benzyl alcohol was treated successively with sodium and chloroacetaldehyde dimethyl acetal to give acetal ether 30. Reductive cleavage of the benzyl group in 30 with sodium in liquid ammonia afforded glycolaldehyde dimethyl acetal (31). Subsequent treatment of 31 with sodium hydride and chloroacetaldehyde dimethyl acetal
**SCHEME I**

1. **29**

   \[
   \text{Ph-CH}_2\text{OH} \xrightarrow{1) \text{Na}} \text{Ph-CH}_2\text{OCH}_2\text{CH(OCH}_3)_2
   \]

2. **30**

   \[
   \text{Na, liq NH}_3
   \]

3. **31**

   \[
   \text{HOCH}_2\text{CH(OCH}_3)_2 \xrightarrow{1) \text{NaH}} \text{(CH}_3\text{O)}_2\text{CHCH}_2\text{OCH}_2\text{CH(OCH}_3)_2
   \]

4. **32**

   \[
   \text{CH}_3
   \]

5. **33**

   \[
   \text{1) HOAc/H}_2\text{O} \xrightarrow{2) \text{MeNH}_2\cdot\text{HCl}, \text{HOOC-C-COOH}}
   \]

6. **34**

   \[
   \text{1) LAH} \xrightarrow{2) \text{H}_2\text{SO}_4/\text{H}_2\text{O}}
   \]

7. **35**

   \[
   \text{1) CH}_3\text{I} \xrightarrow{2) \text{OH}^\text{+}, \text{TRA-400}} \xrightarrow{3) \Delta}
   \]

8. **36**

   \[
   \text{H}_2\text{O}^\text{+}
   \]

9. **37**

   \[
   \text{1) LAH} \xrightarrow{2) \text{BsCl, PY}}
   \]

10. **38**

    \[
    \text{LAH}
    \]

11. **26**

    \[
    \text{LAH}
    \]
furnished 32, conversion of which to its aldehyde followed by Robinson-Schöpf condensation with methylvamine hydrochloride and acetone dicarboxylic acid led to 9-methyl-3-oxagranatanin-7-one (33). Lithium aluminum hydride reduction of 33 and subsequent dehydration of the derived alcohol with aqueous sulfuric acid gave rise to 9-methyl-3-oxagranatoline (34) which was in turn quaternized with methyl iodide, converted to the corresponding hydroxide, and heated. The dienamine so produced (35) was heated at 150° for 10 minutes to achieve conversion to 7,8-dihydro-N,N-dimethyl-2H-oxocin-3-amine (36), hydrolysis of which with aqueous fluoroboric acid furnished 7,8-dihydro-2H-oxocin-3(4H)-one (37). Reduction of 37 with lithium aluminum hydride and functionalization of the derived alcohol with brosyl chloride afforded 3,4,7,8-tetrahydro-2H-oxocin-3-yl brosylate (38). Treatment of 38 with lithium aluminum hydride gave the desired bicyclic ether 26.

4-Oxabicyclo[5.1.0]octane (27). Synthesis of 27 was achieved by the route shown in Scheme II. Treatment of 3-butyln-1-ol (39) with tetrahydropyran gave acetylene 40 which was converted to 41 by means of lithium amide and ethylene oxide. Catalytic reduction of 41 to cis-olefin 42 followed by treatment with tosyl chloride and pyridine gave tosylate 43. Acid hydrolysis of 43 and subsequent treatment with sodium iodide led to iodo alcohol 45. The action of silver oxide on 45 gave cis-2,3,6,7-tetrahydrooxepin (46). Dichlorocarbene addition to 46 afforded cis-8,8-dichloro-4-oxabicyclo[5.1.0]octane (47) which was subsequently reduced to 27 with sodium in liquid ammonia.
SCHEME II

\[ \text{HO} \quad \text{H} \quad \text{32} \quad \text{40} \]

\[ \text{H}_2\text{Pd/C} \quad \text{41} \quad \text{42} \]

\[ \text{H}_3\text{O}^+ \quad \text{43} \quad \text{44} \]

\[ \text{Ag}_2\text{O} \quad \text{45} \quad \text{46} \]

\[ \text{Na} \quad \text{liq NH}_3 \quad \text{27} \]

\[ \text{TsCl} \quad \text{Py} \]

\[ \text{NaI} \]
cis-4-Oxabicyclo[6.1.0]nonane (28). The synthetic route to 28 is shown in Scheme III. Esterification of 1,3-butandiol (48) with acetyl

SCHEME III

\[
\begin{align*}
\text{OH} & \text{OH} \xrightarrow{\text{AcCl}} \text{AcOH} \xrightarrow{\text{CH}_3\text{O}} \text{OAc} \\
48 & \quad 49 \quad 50 \\
\rightleftharpoons & \quad \xrightarrow{\text{LAH}} \\
\text{OH} & \xrightarrow{\text{K}_2\text{Cr}_2\text{O}_7} \text{HHH} \\
51 & \quad 52 \quad 53 \\
\rightleftharpoons & \quad \xrightarrow{\text{nBuLi}} \quad \xrightarrow{\text{CCl}_3} \\
\text{Cl} & \xrightarrow{\text{Na, liq NH}_3} \text{O} \\
55 & \quad 28
\end{align*}
\]
chloride followed by treatment of diacetate \(^{49}\) with paraformaldehyde, acetic acid, and sulfuric acid gave 4-acetoxytetrahydropyran (50). Reduction of 50 to 4-hydroxytetrahydropyran (51) followed by oxidation afforded tetrahydro-4-pyrone (52) treatment of which with excess diazomethane gave oxocan-5-one (I). Conversion of I to tosylhydrazone 53 followed by reaction with n-butyllithium led to cis-3,6,7,8-tetrahydro-2H-oxocin (54). Reaction of 54 with dichlorocarbene gave cis-9,9-dichloro-4-oxabicyclo[6.1.0]nonane (55) which afforded 28 on reduction with sodium in liquid ammonia.

Results and Discussion

Formolysis of 3-oxabicyclo[5.1.0]octane (26). The reaction of 26 with formic acid at 50° afforded a mixture of three diformates consisting of 30.4% of 1,4-hept-6-enediol diformate (56), 19.5% of trans-2-(3-propanol)cyclobutanol diformate (57), and 45.4% of trans-1,7-hept-3-enediol diformate (58). Structures were assigned on the basis of ir and nmr spectroscopy and proven by independent synthesis. The authentication of 58 was carried out by catalytic reduction to its saturated
analog 59 and ultimate comparison to an authentic sample of the same material prepared from commercially available 1,7-heptanediol (60).

The structure of diformate 56 was elucidated by reducing it to 1,4-heptanediol diformate (61) for comparison purposes. The authentic sample of
was synthesized by treating 2-propyltetrahydrofuran (64) with formic acid and zinc chloride. Treatment of 3-(2-tetrahydrofuranyl)propanol (62) with thionyl chloride gave 3-(2-tetrahydrofuranyl)propyl chloride (62) which was reduced with sodium and liquid ammonia to yield the requisite 64.

The unequivocal synthesis of diformate 57 was achieved via the synthetic route shown in Scheme IV. The sequence began with cis-bicyclo[3.2.0]hept-6-en-2-one ethylene ketal (69), obtained by irradiation of a mixture of 2-cyclopentenone (65) and trans-1,2-dichloroethylene, ketalization of 67, and reduction with sodium in liquid ammonia. Hydrogenation of 69 afforded ketal 70 which was hydrolyzed to bicyclo[3.2.0]heptan-2-one (71). Baeyer-Villiger oxidation of 71 gave a mixture of lactones 72 and 73 which was reduced with lithium aluminum hydride to a mixture of diols 74 and 75. cis-2-(3-hydroxypropyl)cyclobutanol (74) was separated and allowed to react with acetyl chloride in pyridine to give monoacetate (76) which was subsequently oxidized to keto acetate 77. Lithium aluminum hydride reduction of 77 afforded trans-2-(3-hydroxypropyl)cyclobutanol (78) which was converted to diformate 57 with acetic-formic anhydride. The formation of diformates 56, 57, and 58 from the formic acid reaction of 26 might be explained by invoking a transannular participation mechanism where the ether oxygen assists the acid-promoted cyclopropane ring opening as shown in Scheme V to give a [3.3.0] bicyclic oxonium ion intermediate (16). Collapse of 16 as shown would afford the observed products via the oxygen-protonated forms of 54 and 79.
SCHEME IV

\[ \text{65} + \text{66} \xrightarrow{\text{hv}} \text{67} \]

\[ \text{68} \xrightarrow{\text{Na, liq NH}_3} \text{69} \xrightarrow{\text{H}_2/\text{Pd}} \text{70} \]

\[ \text{71} \xrightarrow{\text{H}_2\text{O}^+} \xrightarrow{\text{m-ClC}_6\text{CO}_3\text{H}} \text{72} + \text{73} \xrightarrow{\text{LAH}} \]

\[ \text{74} + \text{75} \xrightarrow{\text{AcCl/py}} \text{76} \]

\[ \text{77} \xrightarrow{\text{LAH}} \text{78} \xrightarrow{\text{HCOOCH}_3} \text{79} \]
SCHEME V

[Chemical structure equations and reactions]

[Diagrams and reactions]
This mechanism was shown not to be operative when olefin 54 afforded alcohol 62 and formate 81 under the reaction conditions. Based on the acid-promoted reaction of olefin 12, which proceeds through a bicyclic oxonium ion, olefin 54 forms a secondary carbonium ion which is intercepted in transannular fashion by the ether oxygen to give bicyclic oxonium ion 16 as shown in Scheme VI. Since the product array from the attack of solvent on 16 is different than that observed in the formolysis of bicyclic ether 26, transannular participation of ether oxygen in cyclopropane ring opening of 26 must not be occurring.

Further experimentation revealed that when diformates 56, 57, and 58 were subjected to the reaction conditions, 56 and 58 were recovered unchanged but diformate 57 afforded 56 exclusively. A mechanism which
is consistent with this observation and the observed product array involves initial 1,2-carbon oxygen bond cleavage of oxygen protonated 26 to give cyclopropylcarbinyl cation 82 as shown in Scheme VII. This

SCHEME VII

\[
\begin{align*}
&\text{26} \quad \rightarrow \quad 82 \\
&\quad \quad \left[ 83 \quad \rightarrow \quad 51 \right] \\
&\quad \quad \left[ 84 \quad \rightarrow \quad 56 \right]
\end{align*}
\]
species can become equilibrated with cyclobutyl cation \( \text{III} \) which is the precursor to diformate \( 77 \). Cyclopropylcarbinyl cation \( 82 \) also suffers solvent attack at the 3-position with subsequent internal bond cleavage and formation of diformate \( 56 \). Solvent attack at the primary cationic site in \( 82 \) gives cis-2-(3-hydroxypropyl)cyclopropyl methanol diformate (84) which could rearrange via a six center transition state to diformate \( 58 \). Some credence was lent this mechanistic proposal by the behavior of cis-2-(3-hydroxypropyl)cyclopropylmethanol (91), synthesized as shown in Scheme VIII, under the formolysis conditions. Diformates \( 56 \), \( 57 \), and \( 58 \) were all produced.

**SCHEME VIII**

\[ \text{HO} \overset{\equiv}{\longrightarrow} \text{H} \quad \overset{\text{H}^+}{\longrightarrow} \quad \text{HO} \overset{\equiv}{\longrightarrow} \text{H} \quad 85 \]

\[ 1) \text{LiNH}_2 \quad 2) \text{H}_3\text{O}^+ \quad 86 \quad \overset{\text{H}_2/\text{Pd-BaSO}_4}{\longrightarrow} \quad \text{HO} \overset{\equiv}{\longrightarrow} \text{OH} \quad 88 \]

\[ \text{HO} \overset{\equiv}{\longrightarrow} \text{OH} \quad \overset{\text{CH}_2\text{I}_2}{\longrightarrow} \quad \text{HO} \overset{\equiv}{\longrightarrow} \text{OH} \quad 90 \]

\[ \text{HO} \overset{\equiv}{\longrightarrow} \text{OH} \quad \overset{\text{Zn-Cu}}{\longrightarrow} \quad \text{HO} \overset{\equiv}{\longrightarrow} \text{OH} \quad 91 \]
Formolysis of cis-4-Oxabicyclo[5.1.0]octane (27). Formolysis of 27 in a sealed Pyrex tube at 50° gave a mixture of 81% trans-4-hydroxy-5-methyl-2,3,4,5,6,7-hexahydrooxepin formate (92) and 19% of oxocan-4-yl formate (93), the structures of which were assigned on the basis of ir and nmr spectra and proven by independent synthesis. An authentic sample of formate 92 was prepared by treating trans-4-hydroxy-5-methyl-2,3,4,5,6,7-hexahydrooxepin, available from methyllithium addition to 4,5-epoxy-2,3,4,5,6,7-hexahydrooxepin (94), with acetic-formic anhydride. The trans stereochemistry of formate 92 was assigned based on analogous nucleophilic epoxide ring openings in cyclic molecules which are recognized to afford alcohols of trans-diaxial stereochemistry.
The synthesis of formate 93 was carried out as outlined in Scheme IX. Treatment of olefin 46 with dibromocarbene afforded 8,8-dibromo-

\[
\text{SCHEME IX}
\]

\[
\begin{align*}
\text{46} & \xrightarrow{\text{CBr}_2} \text{96} \xrightarrow{\text{NaH, DMSO}} \text{97} \xrightarrow{\text{3OH}} \text{98} \\
\text{He/Pd-C} & \quad \text{OH} \\
\text{99} & \quad \text{100} \\
\end{align*}
\]

8,8-dibromo-

4-oxabicyclo[5.1.0]octane (96), reduction of which with sodium hydride and dimethylsulfoxide led to exo-8-bromo-4-oxabicyclo[5.1.0]octane (97). Basic hydrolysis of 97 gave trans-3,4,7,8-tetrahydrotetrahydro-2H-oxocin-4-ol (98), hydrogenation of which resulted in a 1:1 mixture of oxocan-4-ol 99, and oxocan-4-one (100). Complete conversion of this mixture to alcohol 92 with lithium aluminum hydride and subsequent reaction with acetic-formic anhydride gave formate 93.

The mechanistic rationale for the formolysis of bicyclic ether 27, on the basis of the observed products, involves acid-catalyzed stereoselective cyclopropane ring opening without participation of ether oxygen. If transannular participation of ether oxygen were occurring, either or both bicyclic oxonium ions 101 and 102 would result and formates 92 and 93 would result from solvent attack at the bridgehead.
positions. Formates 103-106 would probably also arise from solvent attack at the other available positions, but they are not observed. Furthermore, a reaction which does proceed through bicyclic oxonium ion 102, namely the acetolysis of oxocan-4-yl brosylate (107), affords
a product of solvent attack exclusively at the 8-position of ion 102 to
give 2-(2-tetrahydropyranyl)ethyl acetate (108). No corresponding
formate is isolated from the formolysis of bicyclic ether 27.

An examination of a model of 4-oxabicyclo[5.1.0]octane in its two
conformers, boat (A) and chair (B), shows that only the boat conformer
would be capable of transannular reaction between the oxygen atom and
the cyclopropane ring. As the oxygen would approach either the 1 or 7

position, eventually resulting in either bicyclic oxonium ions 101 or
102, severe strain due to bond bending would build up. Conceivably,
this strain could result in a high activation energy for this process,
making it kinetically unfavored.

A comparison of the formolysis products from bicyclic ether 27
with those of the acetolysis of cis-bicyclo[5.1.0]octane (25) indicates
that the formolysis of 27 proceeds in a stereoselective manner whereas
there is very little stereoselectivity in the acetolysis of 25. This
is due to the fact that in $^{25}$ nucleophilic approach to the backside of a protonated bent bond cannot be collinear because of the large steric requirements. Hence, the carbonium ion process and non-stereoselectivity predominate.

However, unlike its carbocyclic analog $^{25}$, bicyclic ether $^{27}$ can attain a conformation favorable to collinear nucleophilic attack on the protonated bent bond of its cyclopropane ring. Thus, the boat conformation of $^{27}$ allows relatively unhindered access of the nucleophile (solvent) to the bridgehead carbon atoms, either from the backside of the external cyclopropane bond (C) or the internal cyclopropane bond (D). Possibly, the ether oxygen in the boat conformer of $^{27}$ is capable of

```
\[ \text{H-O} \quad \text{H} \quad \text{C=O} \quad \text{H}^+ \]
\[ \text{C} \]

\[ \text{H}^+ \quad \text{O=O} \quad \text{H} \]
\[ \text{D} \]
```

"assisting" the nucleophile in its attack at the bridgehead carbon, as shown below, and would explain the product ratio of 80:20 in favor of formate $^{22}$. The increased amount of formate resulting from internal cyclopropane bond cleavage ($^{22}$), as compared to the carbocyclic case, could also perhaps be due to a direct hydride transfer from protonated oxygen to the internal bond in the boat form of $^{27}$. 
Formolysis of cis-4-Oxabicyclo[6.1.0]nonane (28). The only product of formolysis of 28 at 50\(^\circ\) in a sealed Pyrex tube was 3-(2-tetrahydro-pyranyl)propyl formate (109). Assignment of its structure was based on IR and NMR spectroscopy and the synthesis of an authentic sample as shown in Scheme X. The action of ethyl magnesium bromide and 2-chlorotetrahydropyran on acetylene (110) gave (111) which was reduced and converted to 3-(2-tetrahydropyranyl)propanol (112). This alcohol was subsequently treated with acetic-formic anhydride.

The formation of formate 109 in the formolysis of 28 points to a mechanism involving the formation of a secondary carbonium ion which is intercepted by the ether oxygen to give bicyclic oxonium ion 113.
or anchimeric assistance of the ether oxygen in acid promoted cyclo-
propane ring opening (Scheme XI). Bicyclic oxonium ion \( \text{113} \) then suffers
solvent attack at position 9.
In comparing the formolysis of the carbocyclic analog, bicycloalkane 24, with the formolysis of bicyclic ether 28, it may be seen that the product array obtained from 24 contains no formate resulting from internal cyclopropane bond cleavage whereas the product array from bicyclic ether 28 is the result of exclusive internal cyclopropane bond cleavage. This fact would support a cyclopropane ring opening mechanism where the ether oxygen perturbs the internal cyclopropane bond and attacks the bridgehead carbon in a concerted manner as the internal bond breaks.

The manifestation of a transannular reaction in bicyclic ether 28 is in direct contrast to the results of formolysis of 27, which exhibited no such reaction. From a study of a model of 28, it appears that the extra methylene group renders the molecule less rigid than 27, especially as the ether oxygen approaches bridgehead carbon 8. Decreased rigidity of the system, as regards this process, would be reflected in a lower activation energy for transannular participation of ether oxygen, thereby making it kinetically favorable.
PART II. Solvolysis of Oxocan-4-yl Brosylate and Oxocan-5-yl 3,5-Dinitrobenzoate

Introduction

It has been shown that the rates of carbonium ion processes in medium-sized rings can be significantly affected by the presence or absence of non-bonded interactions. For instance, the acetolysis of cyclooctyl brosylate (23) proceeds with an $185$-fold rate enhancement relative to that of cyclohexyl brosylate (113). Apparently such an increase is

\[
\begin{array}{c}
\text{Rel Rate} \\
185 \\
23 \quad \text{CH}_3\text{COOH} \\
1 \\
113 \\
2.9 \quad \text{CH}_3\text{COOH}
\end{array}
\]
Synthesis

Oxocan-4-yl Brosylate (107). Treatment of alcohol 99 with brosyl chloride in pyridine afforded brosylate 107 as a liquid which resisted crystallization. Infinity titers of the acetolysis reaction of 107 indicated a purity of 93.5%.

Oxocan-5-yl 3,5-Dinitrobenzoate (115). Various attempts to synthesize oxocan-5-yl brosylate (117) were unsuccessful. Lithium aluminum hydride reduction of ketone J gave oxocan-5-ol (116) which afforded 3,5-dinitrobenzoate 115 as a crystalline solid upon treatment with 3,5-dinitrobenzoyl chloride and pyridine.
Product Studies

Acetolysis of Oxocan-4-yl Brosylate. A solution of brosylate 107 and anhydrous acetic acid containing a small excess of sodium acetate was heated at 65°C for 10 half-lives. Workup of the reaction afforded a liquid which was separated by vpc into two components in the ratio 75:25. The major component (75%) was identified as 2-(2-tetrahydro-
pyranyl)ethyl acetate (108) on the basis of comparison with an authentic sample. Unequivocal synthesis of acetate 108 was carried out as shown in Scheme XII. Treatment of 2-bromotetrahydropyran (120) with

Scheme XII

\[ \text{Scheme XII} \]

\[
\begin{align*}
\text{120} & \xrightarrow{\text{Li, } CH_3COOEt} \text{121} & \xrightarrow{\text{LAH}} \text{122} \\
\text{120} & \xrightarrow{\text{CH_3COCCH_3, pyridine}} \text{108}
\end{align*}
\]

lithio ethyl acetate gave ethyl(2-tetrahydropyranyl)acetate (121) which, after conversion to 2-(2-tetrahydropyranyl)ethanol (122) with lithium aluminum hydride, afforded acetate 108 upon treatment with acetic anhydride and pyridine.

The remaining component (25%) was found to be oxocan-4-yl acetate (118) from comparison with an independently synthesized sample. Authentic acetate 118 was prepared from alcohol 99 and acetic anhydride in pyridine.
A small amount (2.5%) of crystalline 2-(2-tetrahydropyranyl)-
ethyl brosylate (119) was recovered from the distillation pot residue
and was synthesized independently by treating alcohol 120 with brosyl
chloride in pyridine. When a solution of brosylate 119, an excess of
sodium acetate, and anhydrous acetic acid was refluxed (118°C) for 10
half-lives, there was obtained as the only product, acetate 108 (96%).

**Hydrolysis of Oxocan-5-yl 3,5-Dinitrobenzoate.** A solution of 115 in
80:20 acetone-water containing a 2-fold excess of 2,6-lutidine as a
buffer was refluxed for 25 half-lives. Isolated from the reaction mix-
ture was 3-(2-tetrahydrofuranyl)propyl 3,5-dinitrobenzoate (123, 29%)
which was identified by comparison with an authentic sample, and 71% of
alcohol 116.
Submission of 3,5-dinitrobenzoate 123 to the hydrolysis conditions afforded alcohol 62 as the only product. Synthesis of 123 was carried out by treating alcohol 62 with 3,5-dinitrobenzoyl chloride in pyridine.

Methanolysis of Oxocan-5-yl 3,5-Dinitrobenzoate. In order to determine the extent, if any, of 0-acyl cleavage in the 3,5-dinitrobenzoate group of 115, a solution of 115 and a 2-fold excess of lutidine as a buffer in 75:25 anhydrous methanol-anhydrous tetrahydrofuran was refluxed for 18.5 hours. If 0-acyl cleavage were occurring, production of alcohol 116 should be observed as shown below. From the reaction mix-
ture there was isolated 62% of 3,5-dinitrobenzoate \textit{123} and 38% of a liquid which was identified as 5-methoxycyclohexane \textit{124}. Independent

synthesis of \textit{124} was achieved by treating alcohol \textit{116} with sodium hy-

\begin{equation}
\text{116} \xrightarrow{1) \text{NaH}} \text{124}
\end{equation}
dride and methyl iodide. The absence of alcohol 116 and the presence of ether 124 in the reaction mixture rules out 0-acyl cleavage in the hydrolysis of 115 and demonstrates that attack of the nucleophile (methanol or water) occurs directly at position 5. However, methanoly-

sis of 123 under identical conditions afforded alcohol 63 as the only product, thereby attesting to the operation of 0-acyl cleavage in this instance.

Rate Determination

Plots of the disappearance of brosylate 107 and 3,5-dinitrobenzoate 115 in their solvolysis reactions against time described negative curves which suggested the predominance of an internal return process. The internal return product of each reaction, brosylate 119 or 3,5-dinitro-

benzoate 123, solvolyzed at a slower rate than the original substrate, thereby causing the observed rate to diminish with time. The general mechanistic rationale which describes this process (Scheme XIII) in-

\[
\text{Scheme XIII}
\]

\[
\text{ROX} \xrightarrow{k_1} \text{ROS} + \text{HOX}
\]

\[
\text{R'OX} \xrightarrow{k_3} \text{R'OS} + \text{HOX}
\]
volves the first order rate constant $k_1$ for conversion of starting brosylate or 3,5-dinitrobenzoate (ROX) to their corresponding 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 corresponding acetate or alcohol (R'OS). The sum of $k_1$ and $k_2$ is the rate constant $k'_1$ 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 from experimental data, estimating $k_1$ from a plot of the instantaneous rate constants plotted against time and extrapolated to zero time, and evaluating $k_2$ with the aid of an appropriate iterative computer program. The resulting values, along with activation parameters, from the acetylsis of 107 and the hydrolysis of 115 are displayed in Table I.

Discussion of Results

Comparison of $k_1$ of brosylate 107 with those of its 3-isomer 17 and carbocyclic analog 23 shows 107 to undergo ionization 10 times faster than 17 but 7 times slower than 23. The rate increase of 107 compared to 17 is probably a manifestation of the diminished inductive and dipolar field effects of the ether oxygen on the 4-position relative to the 3-position. In a comparable structural situation, Tarbell and Hazen observed a 32-fold decrease in the rate of acetylsis of 4-tetrahydropyranyl brosylate (125) compared to cyclohexyl brosylate (113) due to the destabilizing effect of the ether oxygen dipole at
Table I. Solvolysis Data for the Acetolysis of 107 in Acetic Acid-Sodium Acetate and the Hydrolysis of 115 in 80:20 Acetone-Water

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rate Constant</th>
<th>T,°C</th>
<th>Rate Constant</th>
<th>ΔH⁺</th>
<th>ΔG⁺</th>
<th>ΔE⁺</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Designation</td>
<td></td>
<td>x 10⁵ sec⁻¹</td>
<td>kcal/mol</td>
<td>eu</td>
<td></td>
</tr>
<tr>
<td></td>
<td>k₁</td>
<td>25.7</td>
<td>1.39</td>
<td>21.7 (+ 0.4)</td>
<td>-8 (+ 1)</td>
<td></td>
</tr>
<tr>
<td>107</td>
<td>k₁</td>
<td>40.5</td>
<td>0.92</td>
<td>24.0 (+ 0.4)</td>
<td>-1 (+ 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>k₂</td>
<td>54.8</td>
<td>36.4</td>
<td>10.76 (+ 20)</td>
<td>-48 (+ 70)</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>k₁</td>
<td>40.3</td>
<td>3.37</td>
<td>18.0 (+ 0.4)</td>
<td>-22.0 (+ 1.4)</td>
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</table>
Table I (Continued)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rate Constant Designation</th>
<th>$T , ^\circ C$</th>
<th>Rate Constant $x \cdot 10^5 \text{ sec}^{-1}$</th>
<th>$\Delta H^{\ddagger}$ kcal/mol</th>
<th>$\Delta S^{\ddagger}$ eu</th>
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<tbody>
<tr>
<td>$k_1$</td>
<td></td>
<td>40.3</td>
<td>1.40</td>
<td>21.8 ($\pm 0.4$)</td>
<td>-11.2 ($\pm 1.4$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55.8</td>
<td>7.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>70.3</td>
<td>32.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_2$</td>
<td></td>
<td>40.3</td>
<td>1.97</td>
<td>13.8 ($\pm 2.6$)</td>
<td>-38.5 ($\pm 8.6$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55.8</td>
<td>4.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>70.3</td>
<td>13.6</td>
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<td></td>
</tr>
<tr>
<td>$k_3$</td>
<td></td>
<td>40.3</td>
<td>$3.36 \times 10^{-5}$</td>
<td>24.3 ($\pm 0.4$)</td>
<td>-24.3 ($\pm 1.4$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55.8</td>
<td>$2.23 \times 10^{-4}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>70.3</td>
<td>$1.11 \times 10^{-3}$</td>
<td></td>
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<tr>
<td>$k_4$</td>
<td></td>
<td>25.0</td>
<td>$5.03 \times 10^2$</td>
<td>26.7 $^b$ ($\pm 0.4$)</td>
<td>+2.30 $^b$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70.0</td>
<td>21.5</td>
<td></td>
<td></td>
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<tr>
<td>$k_1'$</td>
<td></td>
<td>25.0</td>
<td>12.2 $^c$</td>
<td>21.0 $^c$ ($\pm 0.4$)</td>
<td>-3.9 $^c$</td>
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<td></td>
<td></td>
<td>70.0</td>
<td>1480.0 $^c$</td>
<td></td>
<td></td>
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</table>

$^a$Extrapolated values. $^b$Values taken from ref 11. $^c$Values taken from ref 3. $^d$The deviation represents the difference between activation parameters calculated using the first two and last two temperatures and those calculated using all three temperatures.
the site of incipient carbonium ion formation. In addition, the rate enhancement factor due to R₂O-4 participation in the acetolysis of 107 can be considered small by analogy with the essentially unaffected rate of acetolysis of 3-methoxy-1-propyl brosylate 126 as compared to 1-butyl brosylate 127.

\[
\begin{align*}
\text{CH₃OCH₂CH₂CH₂OBS} & \quad \text{CH₃CH₂CH₂CH₂OBS} \\
126 & \quad 127
\end{align*}
\]

From a study of molecular models it appears that the ring oxygen is the same distance (through space) from the 4-position in both 107 and 126. Because of its flexibility, however, 107 could attain conformations where the negative end of the dipole is in proximity to the incipient cationic center thereby stabilizing any positive charge at the 4-position. Conversely in either conformation of 125, boat or chair, the positive end of the dipole would be oriented toward the 4-position. Thus, it would appear that the oxygen dipole effect might be more important in the less flexible molecule 125 than in the more highly conformationally mobile structure 107.

If it is assumed that the dipolar and inductive effects of the oxygen atom are small and the R₂O-4 rate enhancement is negligible, then the rate difference of 7 between 107 and 23 may be attributed
to the relief from non-bonded interactions (normally found in medium sized rings) provided by the reduced steric requirements of oxygen relative to a methylene group.

The solvolytic mechanism for brosylate 107 fits the general process shown in Scheme XIV based on product composition and rate data.

Scheme XIV

Thus brosylate 107 ionizes to a secondary carbonium ion which suffers transannular interception by ether oxygen to give bicyclic oxonium ion 102 or possibly sustains attack by acetate anion to give acetate 118. Solvent attack on 102 at the starred positions would afford acetate 108 and 118, while internal return of brosylate ion would give less reactive brosylate 119 and possibly original brosylate 107. The acetolysis of brosylate 119 produced only acetate 108 thereby demonstrating little or no tendency for 119 to proceed through ion 102 to
oxocan derivatives.

The comparable values for the activation parameters for the acetolysis of $^{107}$ (k$_1$), and of $^{17}$ and $^{23}$ where initial secondary carbonium ion formation has been reported to occur (see Table I), supports the conclusion that transannular participation of ether oxygen must be occurring after ionization of $^{107}$. As to whether this is the rate determining process in the rearrangement of $^{107}$ to $^{119}$ (k$_2$) is not clear because of the uncertainty of the activation parameters for k$_2$. If there were a relative large negative entropy of activation associated with the rearrangement of $^{107}$ to $^{119}$ (k$_2$), this would suggest direct transannular participation of ether oxygen in this step since some degrees of freedom are lost in the transition state leading from $^{107}$ to bicyclic oxonium ion $^{102}$.

In contrast to the small relative differences in k$_1$ for brosylates $^{23}$, $^{17}$, and $^{107}$, the k$_1$ for 3,5-dinitrobenzoate $^{115}$ reflects a highly enhanced ionization rate. Using a conversion factor of 500 for solvolysis of 3,5-dinitrobenzoate in 60% aqueous acetone at 100$^\circ$ and tosylates in acetic acid at 25$^\circ$ and a factor of 3.0 for solvolysis of both brosylates and tosylates in acetic acid, the calculated k$_1$ for the hypothetical 5-brosylate at 25$^\circ$ is 5.91, some 5x10$^4$ greater than k$_1$ for carbocyclic brosylate 23. Although $^{115}$ must experience rate retardation due to the steric effect of ether oxygen, this factor is overwhelmed by transannular anchimeric assistance of the ether oxygen in the ionization step.
The large negative entropy of activation ($\Delta S^\ddagger = -22.0$ eu) observed for this process also supports this conclusion, since a number of degrees of freedom associated with the eight-membered ring system are lost in the transition state to the bicyclic oxonium ion. That the entropy loss is not caused by O-acyl cleavage of the 3,5-dinitrobenzoate group was demonstrated by methanolysis of 115 (see above). Additionally, solvolysis reactions of 3,5-dinitrobenzoates, for example 128 and 129, usually show small entropy losses.

Mechanistically, the hydrolysis of 115 follows the process in Scheme XIV. Anchimeric assistance by the ether oxygen in the ionizing step affords bicyclic oxonium ion 16 which sustains attack by water at the 5-position and internal return at the 2-position (and
possibly also the 5-position) to give alcohol 116 and 3,5-dinitrobenzoate 123. It is possible that 115 becomes solvent separated quickly as the 3,5-dinitrobenzoate group is displaced by ether oxygen and a water molecule immediately attacks the vacated 5-position. This would explain the apparently selective formation of alcohol 116. Alternatively, internal return of the 3,5-dinitrobenzoate anion, in the intimate ion pair 16a, at the 2-position would be expected to be faster than attack by weakly nucleophilic water at the same position and would account for the formation of 123 rather than alcohol 62.
EXPERIMENTAL

PART I. Acid Promoted Reactions of cis[n.1.0] Medium Sized Bicyclic Ethers

9-Methyl-3-oxagranatanin-7-one (33).  

A. Sodium (141.0 g, 6.13 g-atoms) was added with stirring to 1200 g (11.1 moles) of benzyl alcohol (29) at a rate that maintained a gentle reflux. The mixture was cooled to approximately 75° and a solution of 672.0 g (5.41 moles) of chloroacetaldehyde dimethyl acetal in 700 ml of anhydrous toluene was added rapidly. The mixture was stirred at reflux for 18 hr, cooled in ice, filtered, and the filtrate was extracted with 600 ml of water. After drying with magnesium sulfate, the organic layer was evaporated and the residue was distilled to give 400 g (37%) of benzyloxyacetaldehyde dimethyl acetal (30), bp 114-120° (6 mm) [lit bp 134.5-135.5° (15 mm)].

B. To a solution of 513.0 g (2.62 moles) of 30 in approximately 2000 ml of liquid ammonia was added slowly 90.0 g (2.55 g-atoms) of sodium which resulted in the appearance of a dark blue color. The blue mixture was stirred for 45 minutes followed by treatment with 20 ml of absolute ethanol. After standing overnight, the reaction mixture was treated with 600 ml of water and the ether layer was separated and
washed with two 100-ml portions of water. The water layers were combined, saturated with carbon dioxide, and extracted with ether by means of a continuous extractor. The ether solution was dried over magnesium sulfate, filtered, and evaporated to give a crude yellow liquid. Distillation of the yellow liquid afforded 163.3 g (59%) of glycolaldehyde dimethyl acetal (31), bp 60-65° (10 mm) [lit bp 58-60° (12 mm)].

C. A solution of 319.0 g (3.0 moles) of 31 in 320 ml of anhydrous toluene was added to a mixture of 133.0 g (3.06 moles) of 56% sodium hydride in mineral oil and 3000 ml of anhydrous toluene. The mixture was refluxed for 1 hr, cooled, and 373.0 g (3.0 moles) of chloroacetaldehyde dimethyl acetal was added dropwise over 20 minutes. After refluxing overnight, the mixture was cooled, filtered, and evaporated to yield a dark brown liquid distillation of which gave 199.4 g (31%) of oxydiacetaldehyde bis(dimethyl acetal) (32), bp 83-89° (6.0 mm) [lit bp 103-107° (14 mm)].

D. A mixture of 60.0 g (0.31 mole) of 32, 28 ml of glacial acetic acid, and 84 ml of water was refluxed for two hours, cooled, and added to a solution of 25 g of monopotassium phosphate, 40 g of disodium phosphate, 47 g (0.69 mole) of methylamine hydrochloride, and 80 g (0.55 mole) of acetonedicarboxylic acid (prepared from 250 g of citric acid, 454 g of fuming sulfuric acid, and 500 g of ice) in 1050 ml of water. The solution was adjusted to pH 5 with 50% potassium hydroxide solution and stirred for 40 hr. Addition of excess base to the solution followed by extraction with ten 150-ml portions of methylene chloride.
afforded a dark viscous oil from which 10 g (21%) of crystalline solid was obtained by distillation, bp 85-100° (0.3 mm). Recrystallization of this material afforded white crystals of 9-methyl-3-oxagranatin-7-one (33), mp 74-77° [lit mp 77-79°].

7,8-Dihydro-3-N,N-dimethylamino-2H-oxocin (36). A. A solution of 40.6 g (0.26 mole) of 32 in 800 ml of anhydrous ether was added dropwise to a mixture of 16.4 g (0.43 mole) of lithium aluminum hydride in 1000 ml of anhydrous ether. The mixture was stirred overnight at reflux, cooled, and treated with 16.3 ml of water, 16.3 ml of 30% sodium hydroxide solution, and 50 ml of water. The resulting mixture was filtered and the residual solid was washed thoroughly with ether. After drying over magnesium sulfate, the ether solution was evaporated to give 39.0 g (95%) of 9-methyl-3-oxagranatin-7-ol as a white solid, mp 129-130° [lit mp 130-132°] which was not purified further.

B. Thirty nine g (0.25 mole) of 9-methyl-3-oxagranatin-7-ol was dissolved in 21.4 g of glacial acetic acid with efficient cooling. To this solution was added slowly with cooling 72.0 g of concentrated sulfuric acid; the syrupy solution turned very dark. After refluxing at 170° for 4 hr, the solution was cooled and 240 ml of water was added with cooling. The solution was rendered alkaline with 20% sodium hydroxide solution and filtered to remove a small amount of black
material. The filtrate was extracted with eight 100-ml portions of chloroform which were combined, dried over magnesium sulfate, and evaporated to give a light yellow liquid. Distillation afforded 25.1 g (72%) of 9-methyl-3-oxagranatoline (34), bp 83-85° (15 mm) [lit bp 85-87° (16 mm)].

C. A solution of 25.0 g (0.18 mole) of 34, 87.7 g (0.62 mole) of iodomethane and 248 ml of absolute ethanol was refluxed with stirring for 2 hr, cooled, and filtered to furnish 50.0 g (99%) of 9,9-dimethyl-3-oxa-9-azoniabicyclo[3.3.1]non-6-ene iodide, mp 303-306° [lit mp 305-307°].

D. An aqueous solution of 50.0 g (0.18 mole) of this methiodide was passed through a column of basic (OH-) Amberlite IRA-400 ion exchange resin. The eluate was evaporated to a thick syrup which was heated at 90-120° at 10 mm resulting in the elimination of water and the subsequent distillation of a yellow liquid. The liquid was taken up in 300 ml of ether and the solution was dried over magnesium sulfate and evaporated. The residue was heated at 150° at 80 mm for 10 minutes and then crudely distilled by gradually lowering the pressure. The distillate was redistilled to give 15.8 g (57%) of 7,8-dihydro-N,N-dimethylamino-2H-oxocin (36), bp 96-100° (10 mm), nD 1.5246 [lit bp 123° (20 mm) nD 1.5240].
3,4,7,8-Tetrahydro-2H-oxocin-3-yl Brosylate (38). A. A solution of 8.8 g (0.06 mole) of 36, 17.6 g of 50% fluoro boric acid and 43 ml of water was refluxed for 15 minutes, cooled, saturated with sodium bicarbonate, and extracted continuously for 6 hr with ether. The ether solution was dried over magnesium sulfate and evaporated; the liquid residue was distilled to afford 5.9 g (82%) of 7,8-dihydro-2H-oxocin-3(4H)-one (37), bp 90-93°C (20 mm), \( n_D^{24} 1.4881 \) [lit \( \text{bp } 85-87°C (15 \text{ mm}) \), \( n_D^{25} 1.4838 \)].

B. A solution of 10.0 g (0.08 mole) of 37 in 40 ml of anhydrous ether was added dropwise to a mixture of 5.9 g (0.15 mole) of lithium aluminum hydride in 107 ml of anhydrous ether. After refluxing for 4 hr, the mixture was cooled and 5.9 ml of water, 5.9 ml of 30% sodium hydroxide solution, and 17.7 ml of water were added sequentially. The mixture was filtered and the solids were washed thoroughly with ether. The ether fractions were combined, dried over magnesium sulfate, and evaporated to give a liquid, distillation of which yielded 8.2 g (81%) of 3,4,7,8-tetrahydro-2H-oxocin-3-ol, bp 95-115°C (10 mm) [lit \( ^{11} \text{bp } 94-96°C (18 \text{ mm}) \)].

C. A solution of 12.0 g (0.05 mole) of p-bromobenzenesulfonyl chloride and 40 ml of pyridine was prepared with cooling and then cooled in ice. To this solution was added dropwise an ice cold solution of 3.0 g (0.03 mole) of 3,4,7,8-tetrahydro-2H-oxocin-3-ol in 20 ml of
pyridine. The resulting dark solution was allowed to stand for 24 hr at 5° after which a few grams of ice were added followed by 100 ml of water. The mixture was extracted with two 100-ml portions of ether which were combined and extracted with 50 ml portions of iced 1 N hydrochloric acid until the washings were acidic. The ether layer was washed with 50 ml of 5% sodium bicarbonate solution, dried over magnesium sulfate, and evaporated. The resulting crystalline solid, mp 74-77° was recrystallized from petroleum ether (bp 30-60°) ether to afford 5.3 g (60%) of 3,4,7,8-tetrahydro-2H-oxocin-3-yl brosylate (38) as white crystals, mp 78-79.5° [lit 11 mp 79-80°].

3-Oxabicyclo[5.1.0]octane (26). A solution of 5.3 g (0.015 mole) of 38 in 20 ml of anhydrous ether was added dropwise to a stirred slurry of 1.4 g (0.037 mole) of lithium aluminum hydride in 55 ml of anhydrous ether and the resulting mixture was refluxed for 19 hr. The mixture was cooled, treated with 1.5 ml of water, 1.5 ml of 30% sodium hydroxide solution, and 6.0 ml of water, and filtered with the residue being washed thoroughly with ether. The combined ether solutions were dried over magnesium sulfate and evaporated at atmospheric pressure through a Vigreux column. The residue was distilled to give 1.2 g (70%) of 26, bp 79-83° (75 mm) [lit 17 bp 75-76° (60 mm)].
cis-6-(2-Tetrahydropyranloxy)-3-hexen-1-ol (42). A. A mixture of 75.0 g (0.89 mole) of 2,3-dihydropyran and 60.7 g (0.86 mole) of 3-butyln-1-ol (39) was prepared with cooling and treated with 0.8 g of concentrated hydrochloric acid with cooling. The mixture was stirred for 18 hr at room temperature, neutralized with powdered potassium hydroxide, and filtered. The filtrate was distilled to give 124.7 g (95%) of 4-(2-tetrahydropyranloxy)but-1-yne (40), bp 93-96° (18 mm) [lit bp 92-95° (18 mm)].

B. A solution of 49.5 g (0.32 mole) of 40 in 25 ml of anhydrous ether was added during 20 minutes to lithium amide in liquid ammonia [2.3 g (0.33 mole) of lithium in 1000 ml of liquid ammonia catalyzed by ferric nitrate] and the mixture was stirred for 30 minutes. Ethylene oxide (38.0 g, 0.86 mole) was added quickly and the mixture was stirred for 6 hr after which the ammonia was allowed to evaporate. To the residue was added 1000 ml of ether, 75 ml of saturated ammonium chloride solution, and 300 ml of water. The water layer was separated and extracted with three 100-ml portions of ether. The ether layers were combined, dried over magnesium sulfate, and evaporated. The residue was distilled to give 39.0 g (61%) of 6-(tetrahydro-2-pyranloxy)hex-3-yn-1-ol (41), bp 115-123° (0.5 mm) [lit bp 116° (0.4 mm)].

C. A mixture of 0.5 g Pd/carbon catalyst, 75.4 g (0.38 mole) of 41, and 300 ml of ethyl acetate was hydrogenated at atmospheric pressure
on a Brown hydrogenation apparatus (hydrogen uptake was 0.38 moles based on the amount of sodium borohydride used). The mixture was filtered and the filtrate was evaporated to give a liquid which afforded on distillation 65.7 g (86%) of \( \text{H}_2 \), bp 96-105\(^{\circ}\) (0.2 mm) [lit bp 103-106\(^{\circ}\) (0.5 mm)].

2,3,6,7-Tetrahydrooxepin (46). A. To a cooled solution of 71.5 g (0.37 mole) of p-toluenesulfonyl chloride in 33 ml of pyridine was added dropwise with cooling 65.7 g (0.33 mole) of \( \text{H}_2 \). The resulting mixture was stirred at 15\(^{\circ}\) for 1 hr and then at room temperature overnight. Water (90 ml) was added and the mixture was extracted with two 100-ml portions of ether. The ether layers were combined and extracted with two 75-ml portions of 10% sulfuric acid, two 75-ml portions of water, two 75-ml portions of saturated sodium bicarbonate solution, and finally with two 75-ml portions of water. The ether layer was dried over magnesium sulfate and evaporated to give 109.7 g (95%) of cis-6-(2-tetrahydropyanyloxy-3-hexenyl-p-tosylate (43) as a light yellow liquid. The infrared spectrum of this compound was identical with the spectrum of 43 described by Meinwald.

B. With cooling at 10\(^{\circ}\), a mixture of 87.0 g (0.25 mole) of 43, 306 ml of methanol, and 276 ml of water was treated with 27 ml of concentrated sulfuric acid and the resulting mixture was stirred overnight at room temperature. Sodium bicarbonate (75 g) was added in small por-
tions until the mixture was neutral. Enough water was added to dis- 
solve the solids which had formed and the methanol was evaporated on 
a rotary evaporator. The resulting mixture was extracted with three 
100-ml portions of methylene chloride which were combined and extracted 
with 100 ml of saturated sodium bicarbonate solution, water, and dried 
over magnesium sulfate. Evaporation of the methylene chloride afforded 
60.9 g (92%) of cis-6-hydroxy-3-hexen-1-yl p-tosylate (44) as a light 
yellow liquid. The infrared spectrum of this compound was identical to 
that reported in the literature.

C. A mixture of 60.5 g (0.22 mole) of 44, 33.6 g (0.22 mole) of 
sodium iodide, and 250 ml of dry acetone was stirred for 14 hr, re- 
fluxed for two hr, cooled, and filtered. The filtrate was evaporated 
to give an orange liquid which was treated with methylene chloride and 
water. The methylene chloride layer was extracted with 10% sodium 
thiosulfate solution, water, dried over magnesium sulfate, and evaporated 
to give a brown liquid distillation of which afforded 30.7 g of liquid, 
bp 71-80° (0.3 mm), and 9.3 g of liquid, bp 81-100° (0.3 mm) [lit 
bp 89-95° (1.0 mm)]. Gas chromatographic analysis of both fractions 
showed them to be essentially the same with a small amount of impurity 
in the lower boiling fraction. On this basis the fractions were com-
bined to give 40.0 g (80%) of cis-6-iodo-3-hexen-1-ol (45).

D. A solution of 40.0 g (0.18 mole) of 45 in 350 ml of anhydrous 
ether was added dropwise during 8 hr to a slurry of 85.5 g of freshly 
prepared silver oxide in 500 ml of anhydrous ether. The mixture was
refluxed for 18 hr, cooled, and filtered. Evaporation of the filtrate at 45° and atmospheric pressure using a Vigreux column left a clear liquid distillation of which afforded 3.6 g (21%) of 2,3,6,7-tetrahydro-oxepin (46), bp 38° (34 mm), \( n^2_D 1.4532 \) [lit bp 118-120°, \( n^2_D 1.455 \)].

8,8-Dichloro-4-oxabicyclo[5.1.0]octane (47). To a slurry of 40 ml of olefin-free petroleum ether (bp 30-60°), 3.90 g (0.072 mole) of freshly prepared sodium methoxide, and 2.0 g (0.2 mole) of 46 was added dropwise with stirring during 30 minutes 13.3 g (0.070 mole) of ethyl trichloroacetate. The mixture was stirred at 0° for 4 hours and then at room temperature for 24 hours. Sixty ml of water was added and the petroleum ether layer was separated. The water layer was washed with two 20-ml portions of ether and the organic layers were combined, dried over magnesium sulfate, and evaporated at atmospheric pressure through a Vigreux column. Distillation of the residue afforded 2.97 g (82%) of clear liquid, \( \frac{47}{47} \), bp 55-60° (0.9 mm); \( \nu_{\text{max}} \) neat 1100 (C-O), and 820 and 875 cm\(^{-1}\) (C-Cl); \( \delta_{\text{CDCl}_3} \) 4.10-3.10 (m, 4H, -CH\(_2\)-OCH\(_2\)-), and 2.50-1.50 (m, 6H, remaining methylene).

**Anal. Calcd for C\(_7\)H\(_{10}\)Cl\(_2\)O:** C, 46.43; H, 5.57. **Found:** C, 46.80; H, 5.78.
4-Oxabicyclo[5.1.0]octane (27). A solution of 2.85 g (0.158 mole) of \( \text{47} \) in 20 ml of anhydrous ether was added dropwise during 30 minutes to a solution of 2.45 g (0.107 mole) of sodium in liquid ammonia. The mixture was stirred for two hr and 20 ml of ether together with 2.0 ml of water were added slowly. After the ammonia had evaporated, the ether layer was separated, dried over magnesium sulfate, and evaporated to give a residue, distillation of which afforded 0.55 g (30%) of a clear liquid, \( \text{27} \), bp 80-85° (75 mm); \( \text{CDCl}_3 \) 3.75 (m, 4H, \(-\text{CH}_2-0-\text{CH}_2-\)) and 2.50-0.00 (br, m, 8H).

**Anal.** Calcd for \( \text{C}_7\text{H}_{12}\text{O} \): C, 74.95; H, 10.78. Found: C, 74.72; H, 10.67.

4-Hydroxytetrahydropyran (51). A. To a solution of 200 g (2.22 moles) of 1,3-butanediol (48), 356 g (4.5 moles) of pyridine, and 1000 ml of chloroform was added dropwise with stirring 356 g (4.55 moles) of acetyl chloride. The solution was refluxed for 2 hr, cooled in ice, and filtered. The filtrate was washed with water, 10% sodium bicarbonate solution, dried, filtered, and evaporated. The residual liquid which was distilled to give 231 g of butanediol-1,3-diacetate (49), bp 85-90° (10 mm) \[ \text{lit. bp 92-94° (13 mm)} \].
B. A solution of 154 g (0.89 mole) of 49 and 7.7 g of p-toluenesulfonic acid was distilled to give 145.5 g of a liquid, bp 100-130°, which was added to a mixture (which had been previously heated to 110° and cooled to 40°) of 41.0 g (0.51 mole) of paraformaldehyde, 105 ml of acetic acid and 3.9 ml of sulfuric acid at 40°. The resulting solution was heated carefully until (approx. 80-90°) it appeared to become exothermic at which point the heat was removed. The temperature was observed to rise slowly to 110-120°. After the exotherm subsided, the reaction mixture was heated to reflux for 2 hr, cooled, and treated with 7.0 g of anhydrous sodium carbonate to neutralize the sulfuric acid. From this mixture was distilled 110 ml of liquid, bp 104-128°. The remainder of the mixture was distilled at reduced pressure to give 70 ml of liquid, bp 40-90° (9.0 mm) which was dissolved in ether and treated with saturated sodium bicarbonate solution until the evolution of gas ceased. The ether layer was dried, filtered, and evaporated at atmospheric pressure. The residue was distilled to give 13.75 g (11%) of 4-acetoxy-tetrahydropyran (50), bp 72-76° (9.0 mm) [lit bp 71.5° (9.0 mm)].

C. A solution of 13.75 g (0.095 mole) of 50 and 25 ml of ether was added dropwise to a mixture of 2.5 g (0.065 mole) of lithium aluminum hydride in 75 ml of ether and the mixture was stirred at room temperature overnight. After the addition of 2.5 ml of water, 2.5 ml of 30% sodium hydroxide solution, and 7.5 ml of water, the mixture was treated with magnesium sulfate and filtered. The inorganic salts were washed with
boiling chloroform and the organic layers were combined and evaporated. Distillation of the residue afforded 7.1 g (75%) of a liquid, 4-hydroxy-tetrahydropyran (51), bp 86° (12 mm) [lit bp 88.5° (13 mm)], ν neat 3275 (-OH) and 1080 cm⁻¹ (C-O). The infrared spectrum of 51 was identical with the published spectrum.

Tetrahydرو-4-pyrone (52). To a solution of 82.0 g (0.803 mole) of 51

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in 300.0 ml of water was added drop-wise with stirring a cold solution of 101.5 g (0.341 mole) of sodium dichromate, 82.0 ml of sulfuric acid and 113.0 ml of water. The temperature of the reaction was kept below 30° by intermittent cooling with an ice bath. After standing overnight, the solution was neutralized with solid sodium carbonate and extracted with four 200-ml portions of ether. The combined ether layers were dried, filtered, and evaporated at atmospheric pressure. Distillation of the residue afforded 52.0 g (63%) of liquid, tetrahydرو-4-pyrone (52), bp 62-75° (13 mm) [lit bp 57-59° (11 mm)]. The infrared spectrum of this material was identical to that reported except for a small hydroxyl impurity.

Oxocan-5-one (7). To a room temperature solution of diazomethane,

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prepared from 22.5 g (0.223 mole) of N-nitroso-N-methylurea, 200 ml of ether, and 68 ml of 50% potassium hydroxide solution, was added in two portions during 15 min a solution
of 5.0 g (0.5 mole) of 52 in 95 ml of methanol. After standing overnight the solvents were evaporated to give 5.5 g of yellow liquid which was shown to contain large amounts of presumed epoxides (79%), a small amount of oxocan-4-one (100) (5%), and 16% of oxocan-5-one 7. A total of 35 g of a mixture of ketones and epoxides was amassed and distilled through a spinning band column to give 5.00 g (11%) of 7, bp 119-121° (19 mm), the ir and nmr spectra of which were identical with those of an authentic sample; \( \nu_{\text{max}} \) \( 1699 \text{ cm}^{-1} \) (C=O) and 1100 cm\(^{-1}\) (C-O); \( \delta \) \( ^{1} \text{H} \) \( 3.60 \) (t, \( J = 5.0 \text{ Hz} \), 4H, \(-\text{CH}_2-\text{O-CH}_2-\)), \( 2.38 \) (m, 4H, \(-\text{CH}_2-\text{C-CH}_2-\)), and \( 2.05 \) (m, 4H).

1-Oxacyclooctan-5-tosylhydrazone (53). To a hot solution of 1.80 g (9.6 mmoles) of p-toluenesulfonylhydrazide in 30 ml of alcohol was added 0.964 g (7.55 mmoles) of oxocan-5-one 7. The solution was distilled until the volume was reduced to 10 ml and then it was cooled. White crystals formed which were collected and dried to give 2.15 g (96%) of 53, mp 170-171.5° dec after two recrystallizations; \( \delta \) \( ^{1} \text{H} \) \( 7.50 \) (q, \( J = 8.0 \text{ Hz} \), 4H, aromatic), \( 3.42 \) (s, 4H, \(-\text{CH}_2-\text{O-CH}_2-\)), \( 2.33 \) (s, 3H, \( \text{CH}_3-\)), \( 2.25 \) (m, 4H, \( \text{-N-CHaCCHg-}\)), and \( 1.80 \) (m, 4H, remaining methylene).

cis-3,6,7,8-Tetrahydro-2H-oxacin (54). To a slurry of 2.00 g (6.75 mmoles) of tosylhydrazone 53 and 30 ml of anhydrous ether was added slowly (2-3 min). 15 ml of 1.6 M $\mu$-butyl lithium in pentane at $0^\circ$. The resulting mixture was stirred at $0^\circ$ for 7.5 hr and allowed to stand overnight at room temperature. Water (5.0 ml) was added and the ether layer was separated, dried over magnesium sulfate, filtered, and evaporated at atmospheric pressure to afford a liquid which by vpc analysis was shown to be approximately 30% ether, 10% toluene, and 60% olefin, corresponding to 0.62 g (83%) of 54. A pure sample of 54 was obtained by preparative vpc; $\nu_{\text{max}}$ (CDCl$_3$) 1100 cm$^{-1}$ (C=O); $\delta$$_{\text{TMS}}$ (CDCl$_3$) 2.25 (m, 4H, allylic), 1.62 (m, 2H, remaining methylene).

The vinyl proton signals of cis-cyclooctene, which appear at 5.60 $\delta$, have the same pattern as the vinyl protons shown above, whereas the pattern for those of trans-cyclooctene are different. On this basis, cis-stereochemistry is assigned to the olefinic portion of 55.

Anal. Calcd for C$_7$H$_{12}$O: C, 74.95; H, 10.78. Found: C, 75.13; H, 10.84.

9,9-Dichloro-4-oxabicyclo[6.1.0]nonane (55). To a mixture of 0.3 g (2.68 mole) of 55, 0.97 g (18.0 mmoles) of freshly prepared sodium methoxide and 7.0 ml of dry olefin free petroleum ether (bp 30-60°)
cooled was added 2.0 g (10.5 mmoles) of ethyl trichloroacetate during 0.5 hr. After stirring the mixture overnight at room temperature, water was added and the organic layer was separated. The aqueous layer was extracted several times with ether and the ether layers were combined, dried, and evaporated at atmospheric pressure. Preparative vpc of the residue afforded a pure sample of 55; \( \nu_{\text{max}}^{\text{neat}} \) 1150 cm\(^{-1}\) (C=O); \( \delta^{\text{CDCl}_3}_{\text{TMS}} \) 3.69 (m, 4H, -CH\(_2\)-O-CH\(_2\)-), and 2.20-1.00 (m, 8H, remaining methylene).

Anal. Calcd for C\(_8\)H\(_{12}\)Cl\(_2\)O: C, 49.25; H, 6.20; Cl, 36.35. Found: C, 49.31; H, 6.42; Cl, 35.73.

4-Oxabicyclo[6.1.0]nonane (28). To a solution of 0.5 g of sodium in 20 ml of liquid ammonia was added 0.300 g (1.5 mmoles) of 55 in 3.0 ml of anhydrous ether. The mixture was stirred for 8 hr, water and ether were added slowly, and the ammonia was allowed to evaporate. The ether layer was separated and the aqueous layer was washed twice with 10-ml portions of ether. The ether layers were combined, dried, and evaporated at atmospheric pressure to give a liquid residue which was purified by preparative vpc to give 11 mg (6%) of 28; \( \nu_{\text{max}}^{\text{CCl}_4} \) 1120 cm\(^{-1}\) (C=O); \( \delta^{\text{CDCl}_3}_{\text{TMS}} \) 3.70 (m, 4H, -CH\(_2\)-O-CH\(_2\)-), 2.40-0.60 (complex m, 9H), and -0.20 (m, 1H, cyclopropyl).

Formolysis of 3-Oxabicyclo[5.1.0]octane. Following the procedure of Cope, 0.30 g (2.68 mmoles) of 26 was dissolved in 1.50 ml of 97-100% formic acid and this solution was sealed in a Pyrex tube and maintained at 50° for 123 hr in an oil bath. The tube was cooled in ice, opened, and the contents were dissolved in 40.0 ml of ether. The ether solution was washed with three 30-ml portions of saturated sodium bicarbonate solution and the aqueous layers were back extracted with 20 ml of ether. Drying of the combined organic layers over magnesium sulfate, filtering, and careful evaporation of the ether through a Vigreux column at atmospheric pressure afforded a liquid residue. Analysis of this material by vpc revealed the presence of six components: A (1.56%), B (2.14%), C (1.08%), D (30.35%), E (19.48%), and F (45.39%) in order of retention time.

This product mixture and that of another identical (0.20 g, 1.79 mmoles) run were combined to give 0.54 g of material from which was obtained by preparative vpc pure D, 1,4-hept-6-enediol diformate (56); ν\textsubscript{CDCl₃}\textsuperscript{max} 1720 (C=O), 1180 (C-O), 1645 (C=C), 1420, and 995 cm\textsuperscript{-1}; δ\textsubscript{CDCl₃}\textsuperscript{TMS} 8.10 (s, 2H, -C-H), 5.70 (m, 1H, olefinic), 5.25 (m, 2H, olefinic), 5.05 (m, 1H, H\textsuperscript{2}C-OCH), 4.20 (m, 2H, H\textsuperscript{2}C-OCH), 2.40 (t, J\textsubscript{HH}/= 5.0 Hz, 2H, allylic), and 1.8 (q. J\textsubscript{HH}/=0.6 Hz, 4H, remaining methylene).

Anal. Calcd for C₉H₁₄O₄: C, 58.05; H, 7.58. Found: C, 58.05; H, 7.63.
The major component of medium retention time E, trans-2(3-hydroxy-propylcyclobutanol diformate (57), was also obtained by preparative vpc; ν\text{max}\text{CHCl}_3 1720 (C=O), 1180 (C-O), and 820 cm\(^{-1}\); δ\text{CDCl}_3 8.10 and 8.00 (two s, 2H, O-C-H), 4.80 (q, /J/=6.5Hz, 1H, H-C-0CH), 4.20 (m, 2H, H\text{H}_2-C-OCH), and 2.60-1.00 (br m, 9H, remaining methylene).


Similarly, the component of greatest retention time, F, was trans-1,7-hept-3-enediol diformate (58); ν\text{max}\text{CHCl}_3 1720 (C=O) and 1180 cm\(^{-1}\) (C-O); δ\text{CDCl}_3 8.10 (s, 2H, O-C-H), 5.55 (p, /J/=0.6Hz, 2H, olefinic), 4.20 (t, /J/=6.5Hz, 4H, -CH\(_2\)-0-), and 2.10 (m, 6H, remaining methylene). The olefinic proton region of 58 exhibits a multiplicity-pattern quite similar to that of trans-3-hexene but different from that of cis-3-hexene. Accordingly, trans stereochemistry has been assigned to this diformate.

Anal. Calcd for C\(_9\)H\(_{14}\)O\(_4\): C, 58.05; H, 7.58. Found: C, 58.09; H, 7.53.

Reduction of 1,7-Hept-3-enediol Diformate (58). Olefinic diformate 58 was dissolved in 20 ml of hexane and hydrogenated at atmospheric pressure over 5% Pd-C as catalyst. The mixture was filtered and the hexane was removed at atmospheric pressure. The residue was purified by means of preparative vpc to give a pure liquid. The infrared curve, nmr spectrum, and glc retention
time of this compound were identical with those of 1,7-heptanediol diformate (59).

1,7-Heptanediol Diformate (59). One and one tenth grams (0.008 mole) of 60 and 6.0 ml of 97-100% formic acid were mixed and allowed to react in a sealed tube at 50° for two days. The resulting clear solution was dissolved in 50 ml of ether and treated with 180 ml of saturated sodium bicarbonate solution. The ether layer was separated, dried, and evaporated. The residue was distilled to give 0.8 g (39%) of clear liquid, 59, bp 141-144° (10.0 mm); \( \nu_{\text{max}} \) 1725 (C=O), and 1190 cm\(^{-1}\) (C-O); \( \delta_{\text{CDCl}_3} \) 8.10 (s, 2H, formyl), 4.20 (t, J=6.0Hz, 4H, -CH\(_2\)-OC-), and 2.00-1.10 (m, 10H, remaining methylene).

Gas chromatographic analysis\(^{47a}\) of 59 revealed no impurities.

2-Propyltetrahydrofuran (61b). A solution of 50 ml of dry benzene and 13.0 g (0.1 mole) of 2-tetrahydrofuranpropanol (62) was brought to reflux and 11.9 g (0.1 mole) of thionyl chloride was added dropwise. The mixture which became very dark was refluxed for 20 min. The benzene was evaporated on a rotary evaporator and the residue was distilled to give 5.8 g (40%) of a clear liquid, \( \sim \), bp 67-72° (6.0 mm) [lit \( \sim \) bp 75° (4.0 mm)].
The chloride \( \text{CHCl}_3 \) was dissolved in 20 ml of ether and added dropwise to a solution of 1.50 g (0.065 g atom) of sodium in liquid ammonia. After two hr, 50 ml of ether and 10.0 ml of water (added slowly) were added to the mixture and the ammonia was allowed to evaporate. The ether layer was separated, dried, and evaporated at atmospheric pressure to give a residue distillation of which afforded 1.01 g (87%) of \( \text{CHCl}_3 \) as a clear liquid, bp 70-72° (100 mm) \([\text{lit} \ bp 70° (100 \text{ mm})]\).

1,4-Hept-6-enediol Diformate (61). To a solution of 7.0 ml of 99% formic acid and 0.24 g of zinc chloride was added 1.0 g of 2-propyltetrahydrofuran (64) and the resulting solution was refluxed under anhydrous conditions for 4 days. The solution was dissolved in ether and treated with saturated sodium bicarbonate solution until all acid was neutralized. The ether layer was separated, dried, filtered, and evaporated at room temperature. The residue was separated into its two major components by preparative gas chromatography. The component of shorter retention time (43%) was identical with the hydrogenation product of (56); \( \nu_{\text{max}} \) neat 1725 (C=O), and 1185 cm\(^{-1} \) (C-O); \( \delta_{\text{CDCl}_3} \) 8.10 and 8.18 (two s, 2H, formyl), 5.10 (m, 1H, H-C-O-), 4.20 (m, 2H, -CH\(_2\)-O-), 1.1-1.90 (m, 6H), and 0.90 (m, 3H, methyl).

Hydrogenation of 1,4-Hept-6-enediol Diformate (56). The same procedure was used as that described for the hydrogenation of diformate 58. The
pure reduced material was isolated by preparative vpc and had the same ir and nmr spectra and vpc retention time as authentic 61.

Bicyclo[3.2.0]heptan-2-one (71). A. A solution of 12.5 g (0.153 mole) of 2-cyclopentenone (65) and 72.0 g (0.75 mole) of trans-1,2-dichloroethylene 66 in 250 ml of pentane was photolyzed (450W Hanovia Lamp, Pyrex filter) for 6 hr. The pentane was evaporated to give 18.1 g of a yellow liquid which was refluxed overnight in 150 ml of benzene containing 6.3 g (0.102 mole) of ethylene glycol and 5 mg of p-toluenesulfonic acid. The solution was extracted with two 20-ml portions of 5% sodium bicarbonate solution, dried, and evaporated to give 18.0 g (89%) of liquid (68) which contained no ketone or hydroxyl absorptions in its ir spectrum.

B. A solution of 18.0 g (0.081 mole) of 68 in 150 ml of ether was added to 360 ml of liquid ammonia. To the stirred solution was added 4.45 g (0.195 g atom) of sodium and the resulting dark blue solution was stirred for two hr. Ammonium chloride was added to dispel the blue color and the ammonia was allowed to evaporate overnight. Water was added and the ether layer was dried and evaporated to a yellow liquid, distillation of which gave 6.85 g (56%) of ketal (58) as a clear liquid, bp 53-55° (3.0 mm); \( n_D^{25} 1.4810; \nu_{\text{max}}^{\text{neat}} 1100 \text{ cm}^{-1} \) (C-O); \( \delta_{\text{CDCl}_3}^{\text{TMS}} 6.00 \text{ (s, 2H, olefinic), 3.82 (s, 4H, -O-CH}_2\text{CH}_2\text{-O-), 3.20 (m, 1H, one allylic), 2.90 (m, 1H, other allylic), 2.50-1.30 (br m, 4H).} \)
C. A solution of 6.83 g (0.045 mole) of 63 in 30 ml of ethanol was hydrogenated at 30 psig in the presence of 0.7 g of platinum oxide on a Paar apparatus. The mixture was filtered through Celite and evaporated at atmospheric pressure. The resulting liquid residue was distilled to give 6.2 g (91%) of 70 as a clear liquid; bp 56-58° (2.7 mm); \( n^D \) 1.4742, \( \nu_{\text{max}}^{\text{neat}} \) 1100 cm\(^{-1}\) (C-O); \( \delta_{\text{TMS}}^{\text{CDCl}_3} \) 3.80 (m, 4H, -OCH\text{CH}_3\text{CH}_2-), and 3.00-1.20 (br m, 10H).

D. A mixture of 6.0 g (0.039 mole) of ketal 70, 13 ml of 3 N hydrochloric acid and 26 ml of ether was stirred at room temperature for 3 hr. The ether layer was separated, dried, and evaporated to give a liquid residue which was distilled to give 3.58 g (84%) of bicyclo-[3.2.0]heptan-2-one (74), bp 71-80° (18 mm); \( \nu_{\text{max}}^{\text{neat}} \) 1730 cm\(^{-1}\) (C=O); \( \delta_{\text{TMS}}^{\text{CDCl}_3} \) 3.30-1.50 (br m).

cis-2(3-Hydroxypropyl)cyclobutanol (74). To a solution of 1.10 g (0.01 mole) of 74 in 30 ml of ether at 0° was added 15.1 ml of ethereal 0.704 N monoperphthalic acid solution. After stirring at room temperature for 24 hr, a white precipitate had formed. The mixture was filtered and the precipitate was washed with chloroform and combined with the ethereal filtrate. Evaporation of the solvents afforded a semisolid which was washed several times with chloroform. The chloroform washings were evaporated to give a liquid which was distilled to afford 1.1 g of liquid, bp
115-120° (5.0 mm), a mixture of lactones \( \tau_2 \) and \( \tau_3 \).

A solution of 0.47 g (3.73 mmole) of this liquid in 5.0 ml of ether was added slowly to a mixture of 0.15 g (3.95 mmole) of lithium aluminum hydride in 30 ml of ether. The mixture was stirred overnight at room temperature and after the usual work-up there was obtained 0.38 g (74%) of crude liquid. Purification of this material by preparative \( \text{vpc}^{47b} \) gave \( \tau_4 \) as a pure colorless liquid; \( \nu_{\text{max}} \) neat \( 3220 \text{ cm}^{-1} \) (O-H); \( \delta_{\text{TMS}} \) \( 4.35 \text{ m, } 4\text{H, } -\text{CH}_2-\text{O- and } H-C-\text{O-} \), 3.60 (m, 2H, -OH), and 1.80 (m, 9H, remaining methylene).

**Anal.** Calculd for C\( _7 \)H\( _{14} \)O\(_2\): C, 64.58; H, 10.84. Found: C, 64.62; H, 10.92.

Unequivocal Synthesis of trans-2(3-Hydroxypropyl)cyclobutanol Diformate

A. To a solution of 0.249 g (1.92 mmole) of \( \tau_4 \) in 1.25 ml of chloroform and 0.14 ml of pyridine at 0° was added 0.14 ml of acetyl chloride during 30 min. The solution was stirred for 3 hr at room temperature, washed with two 2.0-ml portions of water, dried, and evaporated to give a liquid residue. Preparative \( \text{vpc}^{47b} \) afforded 0.084 g (26%) of \( \tau_6 \); \( \nu_{\text{max}} \) neat \( 3300 \text{ (O-H) and } 1725 \text{ cm}^{-1} \) (C=O).

B. Chromium trioxide (0.13 g) was added slowly to 1.25 ml of pyridine at 0° during 1 hr. The resulting yellow-orange suspension was treated with 0.084 g (0.49 mmole) of \( \tau_6 \) and the mixture was stirred at room temperature for 48 hr. The mixture was poured into 10 ml of ice
cold water and was extracted with four 10-ml portions of ether. The ether layers were combined, dried, and evaporated to provide a liquid residue. Pure 2-(acetoxypropyl)cyclobutanone (II), 0.042 g (32%) was isolated by preparative vpc, \( \nu_{\text{max}}^{\text{neat}} = 1738 \text{ and } 1779 \text{ cm}^{-1} \) (C=0).

C. After reduction of 0.042 g (0.244 mmole) of ketone II with lithium aluminum hydride, the crude trans-diol 78 was treated with 0.05 ml (0.57 mmole) of acetic-formic anhydride and was allowed to react overnight. The reaction mixture was dissolved in ether and washed with saturated sodium bicarbonate solution until neutral. After drying and careful evaporation of the ether solution, the residue was separated into three components by preparative vpc. 47b The component of least retention time had nmr and ir spectra identical to those of 57; \( \nu_{\text{max}}^{\text{neat}} = 1720 \text{ (C=0) and } 1180 \text{ cm}^{-1} \) (C-0); \( \delta_{\text{CDCl}_3}^{\text{TMS}} = 8.10 \text{ and } 8.05 \text{ (two s, } 2\text{H, formyl}), 4.80 \text{ (q, } J=6.5 \text{ Hz, } 1\text{H, HCOOCH}), 4.20 \text{ (m, } 2\text{H, HCOOCH}_2^-), \text{ and } 2.60-1.00 \text{ (m, } 9\text{H, remaining methylene}).

Attempted Formolysis of trans-1,7-Hept-3-enediol Diformate (58). A solution of 0.1864 g (0.1 mmole) of 59 in 1.5 ml of formic acid was sealed in a tube and heated at 50° for 120 hr. The tube was opened and the contents were worked up as in the previously described form to give a liquid which had infrared and nmr spectra identical with those of the starting material.
Attempted Formolysis of 1,6-Hept-6-enediol Diformate (56). A solution of 0.0890 (0.04 mmole) of 57 in 0.75 ml of formic acid was subjected to the same conditions as above and afforded upon work-up, a liquid identical to the starting material (infrared and nmr spectral comparisons).

Formolysis of trans-2-(3-Hydroxypropyl)cyclobutanol Diformate (57). A solution of 0.0413 g (0.22 mmole) of 56 in 0.1 ml of 97% formic acid was placed in a sealed tube and heated at 50° for 71 hr. The contents were dissolved in ether and extracted with 5% sodium bicarbonate solution. After drying, the ether solution was evaporated and the liquid residue was separated into its two components by preparative vpc. By comparison of nmr and infrared spectra, the components were found to be diformates 56 and 57.

Formolysis of cis-3,6,7,8-Tetrahydro-2H-oxocin (54). A solution of 0.065 g (0.58 mmole) of 54 in 0.25 ml of 97% formic acid was heated at 50° for 115 hr. The contents were dissolved in ether and extracted with 5% sodium bicarbonate solution. After drying, the ether solution was evaporated and the residue was separated into its three components by preparative vpc. The components were identified, in the order of their retention time, as starting material (54) (33.44%), 3-(2-tetrahydrofuranyl)propyl formate (81) (48.76%), and 3-(2-tetrahydrofuranyl)-propanol (62) (17.79%) by comparison of their nmr and ir spectra with those of the known compounds.
3-(2-Tetrahydrofuranyl)propyl Formate (81). To 1.4 g (0.0159 mole) of formic-acetic anhydride at 0-10°C was added dropwise 1.37 g (0.0105 mole) of 2-tetrahydrofuranpropanol. After standing overnight at room temperature, the mixture was taken up in ether, washed with saturated sodium bicarbonate solution until neutral, dried, filtered, and evaporated to give 1.00 (66%) g of liquid. Preparative vpc of this material afforded pure formate (81); neat 47\textsuperscript{a}

\[
\text{CDCl}_3 8.08 (s, 1H, -OC\text{\textsubscript{H}}), 4.20 (t, J=6.0Hz, 2H, -CH}_2\text{OCCH}_3), 3.78 (m, 3H, -CH}_2\text{OCH}, \text{and 2.30-1.20 (m, 8H, remaining methylenes).}
\]

Anal. Calcd for C\textsubscript{18}H\textsubscript{30}O\textsubscript{3}: C, 60.74; H, 8.92. Found: C, 60.34; H, 9.20.

Tetrahydropyranyl Derivative of Propargyl Alcohol (86). A solution of 41.7 g (0.745 mole) of propargyl alcohol (85), 25.0 g (0.30 mole) of dihydropyran, 1.3 g of p-toluenesulfonic acid, and 100 ml of ether at 0°C was stirred for 0.5 hr and then refluxed overnight. Anhydrous sodium acetate (1.3 g) was added and the mixture was refluxed for 0.5 hr, cooled, and filtered. The filtrate was extracted with 10% sodium carbonate solution, dried, filtered, and evaporated. The liquid residue was distilled to give 30.5 g (73%) of 86, bp 80-82°C (18 mm) [lit \textsuperscript{48} bp 78-82°C (18 mm)].
Tetrahydropyranyl Derivative of 1-Bromopropanol (87). To 5.15 g (0.037 mole) of 3-bromopropanol at 0° was added 3.1 g (0.037 mole) of dihydropyran, followed by three drops of concentrated hydrochloric acid. After stirring at room temperature for three hr, the mixture was dissolved in ether and extracted with 10% sodium hydroxide solution. The organic phase was dried and evaporated and the resulting oil was distilled to give 5.95 g (72%) of 87, bp 110-115° (12 mm) [lit. bp 111-112° (12 mm)].

Hex-2-yne-1,6-diol (89). A. A mixture of 1.58 g (0.228 g atom) of lithium wire, 900 ml of liquid ammonia, and a catalytic amount of ferric nitrate was allowed to react until gray colored. Acetylene 86 was added during 10 min after which the reaction was stirred for 45 min. A solution of 59.5 g (0.267 m) of 87 was added and the mixture was stirred 6 hr and allowed to evaporate overnight. To the residue was added 45 ml of saturated ammonium chloride solution, 180 ml of water and 225 ml of ether. The aqueous layer was extracted twice with ether and the combined organic layers were dried and evaporated. Distillation of the residual liquid afforded 36.3 g (57%) of the bis-tetrahydropyranyl derivative of hex-2-yne-1,6-diol (89), bp 157-165° (0.4 mm); ν max 1050 cm⁻¹ (C=O); 6 (CDCl₃) 4.75 (m, 2H, -O-CH₂-C≡C-), 4.20 (m, 2H, -O-CH-O), 3.65 (m, 6H, -CH₂-O-),
2.30 (m, 2H, -C=O-CH₂⁻), and 1.60 (m, 14H, remaining methylene).

B. To a solution of 36.3 g (0.129 mole) of 88, 70 ml of water, and 210 ml of methanol at 0° was added dropwise with stirring 16.8 ml of concentrated sulfuric acid. After stirring overnight at room temperature, the mixture was neutralized with 31.5 g of sodium carbonate. The solution was evaporated to a sludge which was extracted with methylene chloride and chloroform. The organic layers were combined, dried, and evaporated to a clear liquid residue which was distilled to give 6.48 g (44%) of hex-2-yne-1,6-diol (89), bp 105° (0.3 mm) [lit bp 145-147° (4.0 mm)].

cis-Hex-2-ene-1,6-diol (90). Hydrogenation of 3.42 g (0.03 mole) of 89 in 60 ml of ethyl acetate with the atmospheric hydrogenator in the presence of Lindlar's Catalyst (5% Pd/BaSO₄) afforded 2.3 g (67%) of 90: bp 96° (0.3 mm); νmax 3340 (0-H), and 1090 cm⁻¹ (C=O); δCDCl₃ 5.60 (m, 2H, olefinic), 4.42 (s, 2H, -O-CH₂-C=O⁻), 4.18 (d, /J/=5.0 Hz, 2H, -O-H), 3.60 (t, /J/=6.0 Hz, 2H, -O-CH₂-), 2.20 (m, 2H, -CH₂-OC⁻), and 1.60 (m, 2H, remaining methylene).

The diacetate of diol 90 was prepared and a pure sample was obtained by preparative vpc for analysis: νmax 1740 cm⁻¹ (C=O); δCDCl₃ 5.65 (m, 2H, olefinic), 4.65 (d, /J/=5.0 Hz, 2H, -OCH₂-C=O⁻), 4.10 (t, /J/=6.0 Hz, 2H, -CH₂-OC⁻), 2.00 (s, 6H, CH₃C⁻), and 2.40-1.20 (br m, 4H, remaining methylene).
Anal. Calcd for C_{10}H_{16}O_4: C, 59.98; H, 8.05. Found: C, 59.59; H, 8.00.

cis-2(3-Hydroxypropyl)cyclopropanemethanol (91). To zinc-copper couple prepared by LeGoff's method using 3.5 g (0.054 g-atom) of powdered zinc was added 15.0 ml of anhydrous ether followed by a few drops of methylene iodide. The mixture was heated to initiate the reaction and the remainder (9.4 g, 0.035 mole) of the methylene iodide was added during twenty min with stirring. A mixture of 2.01 g (0.017 mole) of 90 and 10 ml of ether was added slowly causing a slight exothermic reaction to take place. After refluxing the mixture overnight, 10% sodium hydroxide solution was added, the ether layer was separated, and the aqueous layer was extracted with ether and chloroform. The organic layers were combined, dried, and evaporated. The residual oil was distilled to afford 0.7 g of liquid, bp 95-100° (0.3 mm). Preparative vpc of this material gave olefin 90 and 91: \( \delta^{CDCl_3} \) 4.21 (s, 2H, -O-H), 3.65 (m, 4H, -CH_2-OH), 1.25 (m, 6H), and -0.05 (m, 2H, cyclopropyl).

The diacetate of diol 91 was prepared in the same way as that of 90 and purified by vpc: \( \delta^{CDCl_3} \) 4.08 (m, 4H, -CH_2-OC-), 2.00 (s, 6H, CH_3C-), 2.10-0.80 (br m, 7H), and 0.00 (m, 1H, cyclopropyl).
Reaction of \textsuperscript{91} with Formic Acid. A solution of 0.1 g (0.77 mmole) of 90 in 0.3 ml of formic acid was heated at 50° in a sealed tube for 99 hr and worked up in the previously described manner. Preparative vpc of the reaction mixture afforded three diformates: A (23.69%), B (23.50%), and C (52.81%) in the order of their retention times. From their nmr spectra, A was identified as 57, B as 58, and C as 59.

Formolysis of 4-Oxabicyclo[5.1.0]octane (27). A solution of 0.5584 g (4.96 mmoles) of 27 and 1.0 ml of 99% formic acid was maintained at 50° in a sealed Pyrex tube for 115.5 hr, cooled, dissolved in ether, and washed with saturated sodium bicarbonate solution until neutral. The ether solution was dried, filtered, and evaporated to give 0.9500 g of liquid which was separated into five components by preparative vpc: A (1.63%), B (3.50%), C (30.86%), D (51.54%), and E (12.45%).

Component C was identified as bicyclic ether 27.

Component D was found to be the formate of trans-4-hydroxy-5-methyl-2,3,4,5,6,7-hexahydrooxepin (22) on the basis of comparison with an authentic sample.

\textbf{Anal.} Calcd for C\textsubscript{6}H\textsubscript{14}O\textsubscript{3}: C, 60.74; H, 8.92. Found: C, 60.60; H, 8.84.

Component E was identified as oxocan-4-yl formate (23) by comparison with an authentic sample.

\textbf{Anal.} Calcd for C\textsubscript{6}H\textsubscript{14}O\textsubscript{3}: C, 60.74; H, 8.92. Found: C, 60.54; H, 8.90.
4,5-Epoxy-2,3,4,5,6,7-hexahydrooxepin (94). A solution of 7.4 g (0.0382 mole) of 89.5% m-chloro-perbenzoic acid in 150 ml of chloroform was added slowly with cooling to a solution of 2.5 g (0.0255 mole) of 46 in 10.0 ml of chloroform. After standing for three days, the solution was extracted with 10% sodium bicarbonate solution and dried. Evaporation of the solvent afforded a liquid which was distilled to give 1.52 g (52%) of 9h, bp 77-80° (30 mm); \[\text{lit } \text{bp 77.5-78° (30 mm)}\]; \[\text{CDCl}_3 \ 4.00-3.00 \ (m, 6H, -\text{CH}_2-0-\text{CH}_2-, \ -\text{CH}_2-0-\text{CH}_2-, \ -\text{CH}_2-0-\text{CH}_2-, \ \text{H}_2\text{C}^{\text{C-}}\text{C}<\text{H}^\text{a}\)], and 2.19 (m, 4H, remaining methylene).

Formate of 4-Hydroxy-5-methyl-2,3,4,5,6,7-hexahydrooxepin (92). To 1.14 g (0.01 mole) of 94 under nitrogen was added slowly with stirring 5.43 ml (0.01 mole) of a 5.26% solution of methyllithium in ether. After the slight exothermic reaction had subsided the mixture was stirred for 48 hr at room temperature. The mixture was poured into 50 ml of ice and the aqueous layer was extracted with three 20-ml portions of ether and three 20-ml portions of chloroform. The organic layers were combined, dried, and evaporated. Preparative vpc \[\text{of the resulting yellow liquid afforded as a single peak two inseparable components. This material was treated with 0.15 ml of acetic-formic anhydride and after standing overnight the reaction was worked up in the usual manner. The liquid which was} \]
isolated was now readily separable into two components by preparative vpc. One of the components was identified as formate 92; \( \nu_{\text{max}} \) 1725 (C=O) and 1190 cm\(^{-1}\) (C-O); \( \delta_{\text{TMS}} \) 8.10 (s, 1H, H-C-), 4.90 (q, /J/=6.5Hz, 1H, \( \gamma \)CH-0-), 3.75 (m, 4H, -CH2-0-CH2-), 2.00 (m, 6H), and 1.00 (d, /J/=6.5Hz, 3H, -CH3).

The other component was identified as the formate of 3-hydroxy-2,3,4,7-tetrahydrooxepin: \( \nu_{\text{max}} \) 1720 (C=O), and 1180 cm\(^{-1}\) (C-O); \( \delta_{\text{TMS}} \) 8.10 (s, 1H, H-C-), 5.78 (s, 3H, -CHCH=CH-), 4.20 (m, 2H, -OCH3CH=), 3.90 (t, /J/=5.5Hz, 2H, -OCH2-), and 2.19 (q, /J/=5.5Hz, 2H, methylene).

No attempt was made to obtain analysis for this compound.

8,8-Dibromo-4-oxabicyclo[5.1.0]octane (96). To a stirred mixture of 3.0 g of potassium t-butoxide, 2.0 g (0.02 mole) of 46 and 18 ml of pentane at 0° was added 4.95 g (0.0196 mole) of bromoform during 1 hr. The mixture was stirred for 3 hr at 0° and then overnight at room temperature. Water was added dropwise and the mixture was extracted with ether, dried, and evaporated. Distillation of the liquid residue afforded 1.1 g of 46 and 1.53 g (28%) of 96, bp 87° (0.4 mm); \( \nu_{\text{max}} \) 1120 cm\(^{-1}\) (C-O); \( \delta_{\text{TMS}} \) 4.20-3.20 (m, 4H, -CH2-0-CH2-), and 2.70-1.30 (m, 6H).

exo-8-Bromo-4-oxabicyclo[5.1.0]octane (97). To 11.1 ml of dry distilled dimethyl sulfoxide under nitrogen was added 0.555 g of 57% sodium hydride which had been washed three times with pentane. The mixture was stirred at 75° for 45 min, cooled to 15-20°, and 96 was added during two min. After stirring for 6 hr at room temperature and standing overnight, 37 ml of water was added while keeping the temperature at 20° with an ice bath. The mixture was extracted with ether and the combined ether layers were extracted with water and saturated sodium chloride solution. After drying, the ether solution was evaporated and the orange brown liquid was molecularly distilled to give 0.465 g (44%) of 97, bp 95° (20 mm); $\nu_{max}$ neat 1120 cm$^{-1}$ (C=O); $\delta_{CDCl_3}$ 3.60 (m, 4H, -C(CH$_2$-O-CH$_2$-), 2.85 (m, 1H, -CHBr-), 2.50-1.90 (m, 2H), and 1.54 (m, 4H).

Anal. Calcd for C$_7$H$_{11}$BrO: C, 44.00; H, 5.80. Found: C, 44.01; H, 5.94.

trans-3,4,7,8-Tetrahydro-2H-oxocin-4-ol (98). A solution of 0.465 g (2.44 mmoles) of 97, 0.2 g of sodium bicarbonate, 11.1 ml of dioxane, and 5.7 ml of water was refluxed 20 hr, cooled, and distilled at 90° (pot temperature) and 35 mm. The liquid residue was dissolved in 5 ml of water and extracted with ether. The ether solution was dried and evaporated to give 0.14 g
of crude liquid. Preparative vpc of this liquid afforded two minor components and a major component identified as \( \text{v}_{\text{neat}} \) 3450 (0-H) and 1040 cm\(^{-1}\) (C-O); \( \delta_{\text{TMS}}^{\text{CDCl}_3} \) 5.65 (m, 2H, olefinic), 4.60-3.50 (m, 4H, \(-\text{CH}_2-0-\text{CH}_2\)-), 3.40-2.50 (m, 2H, \(\text{CH} \cdot \text{CH}\)), and 2.40-1.40 (m, 4H, \(-\text{CH}_2\)-, and \(-\text{CH}_2-\text{CH}_2\)-).

The corresponding 3,5-dinitrobenzoiate was prepared from 3,5-dinitrobenzoyl chloride and pyridine.

Anal. Calcd for C\(_{14}\)N\(_{14}\)N\(_{2}\)O\(_7\): C, 52.17; H, 4.38; N, 8.69. Found: C, 52.47; H, 4.54; N, 8.42.

**Oxocan-4-ol (99).** A solution of 0.12 g (0.94 mmole) of 98 in 7 ml of ethyl acetate was hydrogenated over 10% Pd on carbon at atmospheric pressure. The solution was filtered and the filtrate was evaporated. Preparative vpc of the residue afforded two components in the ratio of 1:1. The component of least retention time was ketone 100; \( \text{v}_{\text{neat}} \) 1600 (C=O) and 1090 cm\(^{-1}\) (C-O); \( \delta_{\text{TMS}}^{\text{CDCl}_3} \) 3.70 (d of t, J\(\text{J}=6.0\text{Hz}\) and 18 Hz, \(\text{hH}, \text{-CH}_2-0-\text{CH}_2\)-), 2.52 (m, \(\text{hH}, \text{-CH}_2\)-, \(-\text{CH}_2-\text{CH}_2\)-), and 1.82 (m, \(\text{hH}\)).

Alcohol 22 was found to be the component of greater retention time: \( \text{v}_{\text{neat}} \) 3350 (0-H) and 1105 cm\(^{-1}\) (C-O); \( \delta_{\text{TMS}}^{\text{CDCl}_3} \) 3.58 (m, 5H, \(-\text{CH}-0\)-and \(-\text{CH}_2-0-\text{CH}_2\)-), 3.20 (m, 1H, \(-0-\text{H}\)), and 1.72 (m, 8H, remaining methylenes).

One and three tenth g (0.01 mole) of a mixture of the ketone and alcohol was reduced with 0.735 g (0.02 mole) of lithium aluminum hy-
dride. The usual workup afforded 1.100 g (85%) of alcohol 92.

**Anal.** Calcd for C₇H₁₄O₂: C, 64.58; H, 10.84. Found: C, 64.20; H, 10.81.

**Oxocan-4-yl Formate (93).** A mixture of 0.03 g (2.3 mmoles) of 92 and 0.35 ml of acetic-formic anhydride were allowed to stand overnight. The solution was dissolved in ether, extracted with 5% sodium bicarbonate solution, dried, and evaporated.

Preparative vpc of the residual oil afforded a colorless liquid, formate 93, $\nu_{\text{max}}^{\text{neat}}$ 1725 (C=O) and 1190 cm⁻¹ (C-O); $\delta$CDCl₃ 8.10 (s, 1H, $^\text{TMS}$), 5.20 (m, 1H, $^\text{CH}$O), 3.70 (m, 4H, $^\text{CH}_2$O-$\text{CH}_2$), and 2.30-1.10 (m, 8H, remaining methylene).

**Formolysis of h-Oxabicyclo[6.1.0]nonane (28).** A solution of 5.5 mg (0.044 mole) of 28 in 0.032 ml of 99% formic acid in a sealed tube was heated at 50° for 167 hr, dissolved in ether and treated with saturated sodium bicarbonate solution until neutral. The ether was evaporated at atmospheric pressure and the residue was separated into three components by preparative vpc. The component of least retention time (13.85%) had the same retention time as an impurity seen in the precursor 28. The second component (86.15%) was identified as the formate of 3-(2-tetrahydropyranyl)propanol (103); $\nu_{\text{max}}^{\text{CCL}_4}$ 1725 (C=O) and
1175 cm\(^{-1}\) (C=O); \(\delta\)\(^{\text{TMS}}\)\(^{\text{CDCl}_3}\) 8.09 (s, 1H, HCO\(^{\text{H}}\)), 4.20 (t, \(\mathcal{J}/=7.0\) Hz, 2H, -CH\(_2\text{-O}^\text{-}\)), 3.90 (m, 1H, CH\(_{\text{H}-}\)), 3.34 (m, 2H, -CH\(_{\text{H}-}\)) and 1.54 (m, 10H, remaining methylene).


3-(2-Tetrahydropyranyl)propanol (112). A solution of 7.0 g (0.05 mole) of 110 in 12.5 ml of THF was added slowly to a solution of ethyl magnesium bromide (from 8.17 g ethyl bromide and 1.82 g magnesium turnings) in 38 ml of anhydrous tetrahydrofuran. Gas was evolved. The mixture was stirred at reflux for 1 hr and then treated with 11.7 g (0.075 mole) of 2-chlorotetrahydropyran made from anhydrous HCl and tetrahydropyran. After stirring of this solution overnight, 100 ml of saturated ammonium chloride was added. The aqueous layer was extracted with ether and all the organic layers were combined, dried, and evaporated. Distillation of the residue at 117-122\(^{\circ}\) (0.4 mm) afforded 5.0 g of liquid. This material (1.4 g) was hydrogenated at atmospheric pressure over 5\% Pd-C as catalyst in ethyl acetate. After removal of the solvent, the oily residue was refluxed overnight in a solution of 6.0 ml of methanol, 6.0 ml of water, and 0.55 ml of concentrated sulfuric acid. The mixture was neutralized with sodium carbonate, evaporated, and extracted with dichloromethane. After drying and evaporation of the dichloromethane solution, a liquid residue was isolated which was purified by prepara-
tive vpc to give 0.1 g (1.5%) of 112; \( \nu_{\text{max}} \) 3325 (0-H), and 1090 cm\(^{-1}\) (C-O); \( \delta_{\text{TMS}}^{\text{CDCl}_3} \) 4.25-3.10 (m, 5H, -CH\(_2\)-CH and -CH\(_2\)-O-), 2.90 (s, 1H, OH), 1.60 (m, 10H, remaining methylenes).

3-(2-Tetrahydropyranyl)propyl Formate (109). Alcohol 112 (0.10 g, 0.69 mmole) was treated with 0.60 g (0.69 mmole) of acetic formic anhydride and allowed to stand overnight. The solution was taken up in ether and treated with 5% sodium bicarbonate solution until neutral. Drying of the ether layer with magnesium sulfate and evaporation afforded a liquid residue which was purified by preparative vpc to give formate 109; \( \nu_{\text{max}} \) CCl\(_4\) 1725 (C=O) and 1175 cm\(^{-1}\) (C-O); \( \delta_{\text{TMS}}^{\text{CDCl}_3} \) 8.09 (s, 1H, H\(_B\)-), 4.20 (t, /\(J/=6.5\) Hz, 2H, -CH\(_2\)-OCH\(_2\)-), 3.90 (m, 1H, CH-0-), 3.34 (m, 2H, -CH\(_2\)-O-), and 1.54 (m, 10H, remaining methylene).

PART II. Solvolysis of Oxocan-4-yl Brosylate and Oxocan-5-yl 3,5-Dinitrobenzoate

Oxocan-4-yl p-Bromobenzenesulfonate (107). A solution of 0.835 g (6.42 mmoles) of alcohol 29 in 5.0 ml of anhydrous pyridine at 0° was added to a solution of 3.30 g (12.87 mmoles) 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 to destroy excess brosyl chloride, 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 a liquid brosylate, 107, 2.1169 g (89% yield, 93% pure, see infinity titer), which resisted crystallization; ν max 1575 cm⁻¹ (arom C-H); δCDCl₃ 7.75 (s, 4H, aryl), 4.82 (m, 1H, CH-O-), 3.61 (m, 4H, -CH₂-O-CH₂-), 2.03 (m, 4H, remaining methylene), and 1.60 (m, 4H, -CH₂-CH₂-).

Infinity titers obtained from the acetolysis of this material showed it to be 93.50% pure.
Oxocan-5-ol (116). A solution of 2.50 g (19.5 mmole) of ketone \( I \) in 12.0 ml of ether was added dropwise to a slurry of 1.48 g (39.0 mmole) of lithium aluminum 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 to give 2.35 g (92%) of clear liquid, alcohol 116; \( \nu_{\text{max}} \) 3400 (O-H), and 1120 cm\(^{-1}\) (C=O); \( \delta_{\text{TMS}}^{\text{CDCl}_3} \) 4.10 (m, 1H, -O-H), 3.60 (m, 4H, -CH\(_2\)-O-CH\(_2\)-), 3.45 (s, 1H, >CH-O-), and 1.80 (m, 8H, remaining methylene).

The 3,5-dinitrobenzoate of alcohol 116 was prepared by adding a solution of 0.6000 g (4.7 mmole) of the alcohol and 3.52 ml of anhydrous pyridine to a solution of 2.400 g (10.4 mmole) of 3,5-dinitrobenzoyl chloride in 7.50 ml of pyridine and warming the mixture until most of the 3,5-dinitrobenzoyl chloride had dissolved. After standing overnight at 0\(^{\circ}\) 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 1.1720 g (79%) 3,5-dinitrobenzoate 115: mp 102-104\(^{\circ}\).
$^{13}C\text{Cl}_{4}$ 1728 (C=O) and 1627 cm$^{-1}$ (arom C-H); $^6_{\text{CDCl}_3}$ 9.10 (s, 3H, aryl), 5.56 (m, 1H, $\text{CH-O}$), 3.66 (m, 4H, -CH$_2$-O-CH$_2$), and 1.90 (m, 8H, remaining methylenes).

Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.85; H, 4.99; N, 8.51.

Preparative Scale Acetolysis of Oxocan-4-yl Broxylate (107). A solution of 1.2164 g (3.49 mmoles) of oxocan-4-yl broxylate, 0.219 g (2.09 mmoles) of anhydrous sodium carbonate, and 15.0 ml of anhydrous acetic acid was heated at 60-65° for 1 hr and 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.

The component of least retention time (75%) was identified as 2-(2-tetrahydropyranyl)ethyl acetate (108) by comparison with an independently synthesized sample.

The component of greater retention time (25%) was identified as oxocan-4-yl acetate (118) by comparison with an authentic sample.

The distillation residue was taken up in pentane and cooled to 0°. A crystalline solid, 0.0186 g (1.5% corresponding to 2.5% relative) mp 77.5-79°, which deposited was identified as 2-tetrahydropyranethyl
brosylate (119) 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 (121).** A solution of 6.90 g (0.0427 mole) of hexamethyldisilazane (Aldrich Chemical Co.) in 13.2 ml of ether was treated with 25 ml of 1.6 M n-butyllithium during two 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 mole) was introduced and the solution was stirred for 15 min. To this solution was added 6.47 g (0.039 mole) of 2-bromo-tetrahydropyran [120, prepared by bubbling hydrogen bromide gas through 3.30 g (0.039 mole) 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 liquid 121, bp 88-90° (6.0 mm); \( \nu_{\text{max}} \) neat 1735 cm\(^{-1}\) (C=O); \( \delta_{\text{TMS}}^{\text{CDCl}_3} \) 4.12 (q, J=6.5 Hz, 2H, -O-CH\(_2\)CH\(_3\)), 3.78 (m, 3H, -CH\(_2\)-O-CH\(_3\)), 2.42 (dd, J=3.0Hz and 2.0 Hz, 2H, -CH\(_2\)COO-), 1.52 (m, 6H, remaining methylenes), and 1.25 (t, J=6.5Hz, 3H, -O-CH\(_2\)CH\(_3\)).

2-(2-Tetrahydropyranyl)ethanol (122). A solution of 1.40 g (8.15 mmoles) of ethyl (2-tetrahydropyranyl)acetate (121) in 10.0 ml of anhydrous ether was added dropwise to a slurry of 0.25 g (6.42 mmoles) of lithium aluminum hydride in 90 ml of anhydrous ether and the resulting mixture was allowed to stir overnight. The reaction was cooled in ice and 0.25 ml of water, 0.25 ml of 30% sodium hydroxide solution, and 0.80 ml of water were added slowly, followed by anhydrous magnesium sulfate and the inorganic salts were removed by filtration. The filtrate was evaporated and the residue was distilled to give a liquid, alcohol 122, bp 87-89° (7.0 mm); νₚₑᵃᵗₚₑₙₚₑ₅ 3395 (O-H) and 1090 cm⁻¹ (C-O); δCDCl₃ 3.60 (m, 6H, -CH₂-O-CH₂), and 1.55 (m, 8H, remaining methylenes).

2-(2-Tetrahydropyranyl)ethyl Acetate (108). Acetic anhydride (0.400 g, 3.92 mmoles) was added to a solution of 0.100 g (0.77 mmole) of alcohol 122 in 1.0 ml of anhydrous pyridine.
acidic, dried, filtered, and evaporated. Preparative vpc of the residue afforded 0.10 g (82%) of pure acetate \(108\): \(v_{\text{max}}\) neat 1740 (C=O) and 1240 cm\(^{-1}\) (C-O); \(\delta^1\text{CDCl}_3\) 4.18 (t, /J/=6.5Hz, 2H, -\(\text{CH}_2\)-O-), 3.85 (br s, 1H, \(\text{CH}\)-O-), 3.40 (br m, 2H, -\(\text{CH}_2\)-O-), 2.03 (s, 3H, CH C-), and 1.68 (m, 8H, remaining methylenes).


\(2-(2-\text{Tetrahydropyranyl})\text{ethyl Brosylate (119).}\) An ice-cold solution of 0.8215 g (6.32 mmoles) of \(2-(2-\text{tetrahydropyranyl})\text{ethanol (121) in 5.0 ml of anhydrous pyridine was added to a solution of 3.30 g (12.85 mmoles) of p-bromobenzene-sulfonyl 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 white crystalline solid, \(119\): mp 77.5-79.0°; \(v_{\text{max}}^\text{CCl}_4\) 1577 (arom C-H); \(\delta^1\text{CDCl}_3\) 7.72 (s, 4H, aryl), 4.20 (t, /J/=6.0Hz, 2H, -\(\text{CH}_2\)-SO\(_3\)Ar), 3.50 (m, 3H, -\(\text{CH}_2\)-O-\(\text{CH}\)), and 1.50 (m, 8H, remaining methylenes).
Anal. Calcd for \( \text{C}_{13}\text{H}_{17}\text{BrO}_4\text{S} \): C, 44.71; H, 4.91; S, 9.18. Found: C, 44.64; H, 4.93; S, 9.17.

Oxocan-4-yl Acetate \((\text{II8})\). Using the same procedure described for the preparation of acetate \(\text{I08}\), 0.100 g (0.77 mmole) of oxocan-4-ol was treated with 0.400 g (3.92 mmoles) of acetic anhydride to give 0.090 g (68%) of vpc purified acetate \(\text{I18}\);

\[ \text{v}_{\text{max}}^{\text{neat}} 1730 \text{ (C=O) and } 1245 \text{ cm}^{-1} \text{ (C-O); } \delta_{\text{CDCl3}}^{\text{TMS}} 5.00 \text{ (p, } /J/=5.0\text{ Hz, 1H, } \text{CH-0}\text{-}), 3.70 \text{ (m, 4H, } -\text{CH}_2\text{-0-CH}_2\text{-}), 2.00 \text{ (s, 3H, } \text{CH}_3\text{-}), \text{ and } 1.80 \text{ (m, 8H, remaining methylene)}. \]


Preparative Scale Solvolysis of 2-(2-Tetrahydropyranyl)ethyl Brosylate \((\text{II9})\). A solution of 0.3833 g (1.092 mmole) of brosylate \(\text{I19}\), 0.0887 g (0.840 mmole) of anhydrous sodium carbonate, and 6.20 ml of anhydrous acetic acid was refluxed \(\text{I18}^\circ\) 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 0.1830 g (96%) of liquid which was shown to be pure by vpc. A pure sample was ob-
tained by preparative vpc\textsuperscript{47b} and found to be identical with an authentic sample of acetate \textsuperscript{108}.

Preparative Scale Hydrolysis of Oxocan-5-yl 3,5-Dinitrobenzoate (115) in 80:20 Acetone-Water. A solution of 0.5017 g (1.59 mmoles) of oxocan-5-yl 3,5-dinitrobenzoate (115), 0.382 g (3.57 mmoles) of 2,6-lutidine, and 33 ml of 80:20 acetone water was refluxed for 18 hr (25 half-lives), cooled, and the acetone was evaporated. The aqueous residue was extracted with ether and the ether layer was dried, filtered, reduced in volume to about 2 ml, and cooled. A white solid precipitate, soluble in water and dilute base, was collected 0.0342 g, mp 130-133°. The nmr and ir of this material showed it to be an aromatic acid. The mother liquor was reduced to 1.0 ml and cooled to give 0.114 g (22\% corresponding to 23\% relative) of crystalline solid, mp 63-66°, identified as 3,5-dinitrobenzoate \textsuperscript{123} on the basis of its nmr and ir spectra.

Additional processing of the mother liquor gave a liquid which was purified by vpc\textsuperscript{47a} 0.1122 g (54\% corresponding to 71\% relative). This substance was identified as oxocan-5-ol (116).
Preparative Scale Methanolysis of Oxocan-5-yl 3,5-Dinitrobenzoate (115) in 75:25 Methanol-Tetrahydrofuran. A solution of 0.500 g (1.54 mmoles) of 3,5-dinitrobenzoate 115, 0.383 g (3.57 mmoles) of 2,6-lutidine and 33 ml of 75:25 anhydrous methanol-tetrahydrofuran was refluxed 18 hr and the solvents were evaporated at 65° and 80 mm to give a semisolid residue. This material was taken up in pentane and cooled to give 0.1914 g of a solid, mp 127-129°, which proved soluble in water and dilute base.

The mother liquor was reduced in volume and cooled to give 0.1624 g (33% corresponding to 62% relative) of a crystalline solid, mp 61.5-63.5°, identical with 3,5-dinitrobenzoate 123 on the basis of nmr and ir spectra.

Further evaporation of the mother liquor afforded a liquid which was purified by preparative vpc. There was obtained 0.0485 g (22% corresponding to 38% relative) of a colorless liquid which was identical with an authentic sample of 5-methoxyoxocane (124).

5-Methoxyoxocane (124). A solution of 42.0 mg (0.32 mmole) of alcohol 116 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 reaction mixture over-
night, vpc analysis indicated only 25% conversion. Therefore, the above sequence was repeated. The mixture was filtered and the benzene was evaporated at $50^\circ$ and 80 mm. The liquid residue was subjected to preparative vpc to give 0.02 g of starting alcohol and 0.02 g (50%) of methyl ether $\text{CCl}_4$, $\nu_{\text{max}}$ $1110 \text{ cm}^{-1}$ (C=O); $\delta_{\text{TMS}}$ $3.59$ (m, 5H, -CH$_2$-O-CH$_3$- and CH-0-), $3.28$ (s, 3H, -O-CH$_3$), and $1.77$ (m, 8H, remaining ethylene).

**Anal.** Calcd for C$_8$H$_{16}$O$_2$: C, 66.63; H, 11.18. Found: C, 66.30; H, 11.23.

3-(2-Tetrahydrofuryl)propyl 3,5-Dinitrobenzoate (123). To a solution of 6.00 g (46.0 mmoles) of 3-(2-tetrahydrofuryl)propanol (62) in 23 ml of anhydrous pyridine at $0^\circ$ was added 11.07 g (48.0 mmoles) of 3,5-dinitrobenzoyl chloride. The mixture was stirred 2 hr at room temperature and poured into 60 ml of ice water. The resulting solid was filtered, washed with water and 5% sodium carbonate solution, taken up in ether, and dried. Filtration of the ethereal solution followed by evaporation, afforded a solid which, after three recrystallizations from ether, gave 6.18 g (41.5%) of a white crystalline solid (123): mp 65.5-67$^\circ$ (lit$^{41}$ mp 65-66$^\circ$); $\nu_{\text{max}}$ $1734$ (C=O) and $1628 \text{ cm}^{-1}$ (arom C-H); $\delta_{\text{TMS}}$ $9.10$ (s, 3H, aryl), 4.54 (t, $/J$/=6.0Hz, 2H, -CH$_2$OOC-Ar), $3.80$ (m, 3H, CH-0-), and $1.90$ (m, 8H, remaining methylene).
Preparative Scale Solvolysis of 3-(2-Tetrahydrofuranyl)propyl Dinitrobenzoate (123) in 80:20 Acetone-Water. A solution of 0.3029 g (0.933 mmole) of 3-(2-tetrahydrofuranyl)-propyl 3,5-dinitrobenzoate, 0.230 g (2.15 mmoles) of 2,6-lutididine, and 20 ml of 80:20 acetone-water was maintained at 160° for 138 hr in a thick wall 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 123. The mother liquor was evaporated and the liquid so obtained was purified by preparative vpc to give 0.0295 g (25%) of a liquid which was identified as 3-(2-tetrahydrofuranyl)propanol (62) on the basis of its nmr and ir spectra.

Preparative Scale Solvolysis of 3-(2-Tetrahydrofuranyl)propyl 3,5-Dinitrobenzoate (123) in 75:25 Methanol-Tetrahydrofuran. A solution of 0.30 g (0.925 mmole) of 3,5-dinitrobenzoate 123, 0.230 g (2.15 mmoles) of 2,6-lutididine, and 20 ml of 75:25 methanol-tetrahydrofuran was maintained at 160° in a thick wall sealed glass tube for 137 hr. The solvents were removed and the residue was taken up in pentane. The insoluble material was recryst-
stallized from ether to give 0.1534 g of solid, mp 107-110°, which was evidently methyl 3,5-dinitrobenzoate [lit mp 108°]; \( \nu_{\text{max}}^{\text{CCl}_4} \) 1740 (C=O str) and 1628 cm\(^{-1} \) (arom C-H str); \( \delta^{\text{CDCl}_3}_\text{TMS} \) 9.18 (s, 3H, aryl) and 4.12 (s, 3H, -O-CH\(_3\)).

The pentane solution was evaporated to give 0.0994 g (82.5%) of 3-(2-tetrahydrofuranyl)propanol (62) based on its nmr and ir spectra.
Kinetics of the Acetolysis of Oxocan-4-yl Brosylate and 2-(2-Tetrahydro-pyranyl)ethyl Brosylate

Reagents

Anhydrous acetic acid was prepared by refluxing a solution of 2-2.5 l glacial acetic acid and 50 ml of acetic anhydride overnight with protection from the atmosphere and distilling, discarding the first 10% and last 10% of material.

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 using bromophenol blue as indicator (yellow to clear color change). The 0.03 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.

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 the solvolysis 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 two 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 bromphenol blue as indicator. From this value the molarity of the sodium acetate \([\text{NaOAc}]_t\) as time \(t\) was calculated. Subtracting \([\text{NaOAc}]_t\) from \([\text{NaOAc}]\) gave the amount of P-bromobenzensulfonic acid present at time \(t\), \([\text{BsOH}]_t\). By subtracting \([\text{BsOH}]_t\) from the molarity of brosylate at time \(t\) \([\text{ROBs}]_t\) was obtained. The log \([\text{ROBs}]\) was then plotted against \(t\). Infinity titers of 107 were obtained by allowing a sample of the reaction mixture to solvolyze at 115° for a time (~10 hr) corresponding to 10 half-lives for rearranged brosylate and then titrating.

**Kinetics of the Hydrolysis of Oxocan-5-yl 3,5-Dinitrobenzoate and 3-(2-tetrahydrofuranyl)propanyl 3,5-Dinitrobenzoate**

**Reagents**

Reagent grade acetone was purified by distillation from potassium permanganate and pure 2,6-lutidine was obtained by distillation from practical grade material. The water which was used was doubly distilled.

**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 125x15 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 two min, brought to room temperature, and opened. A 1.9021 ml aliquot was withdrawn and titrated potentiometrically with 0.01015 N sodium hydroxide solution using a Fisher "Accumet" Model 310 pH meter fitted with a Fisher Micro-probe 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 \( 115 \) at 160\(^\circ\) for 10 half-lives (\(~85\) hr) of rearranged 3,5-dinitrobenzoate (23), the infinity titer of 115 was obtained.

**Determination of Solvolytic Rate Constants**

The specific first order rate constant \( k_i \) for SnI type solvolysis reactions is shown in equation (1) where SOH is solvent, ROX is sub-

\[
\begin{align*}
\text{ROX} & \xrightarrow{\text{SOH}} \text{ROS} + \text{HOX} \\
-\frac{d[\text{ROX}]}{dt} &= \frac{d[\text{HOX}]}{dt} = k_i[\text{ROX}] \\
\ln \left( \frac{[\text{HOX}]_\infty - [\text{HOX}]_0}{[\text{HOX}]_\infty - [\text{HOX}]_t} \right) &= k_i t 
\end{align*}
\]

(1)
strate, \([\text{HOX}]_\text{as}\) as is the concentration of acid liberated at infinite time, \([\text{HOX}]_0\) is acid concentration at zero time, and \([\text{HOX}]_t\) is acid concentration at time \(t\). For \(S_N1\) processes a plot of \(\ln \left( \frac{[\text{HOX}]_\infty - [\text{HOX}]_0}{[\text{HOX}]_\infty - [\text{HOX}]_t} \right)\) versus time gives a straight line of slope \(k\).

In the solvolyses of 107 and 115 the situation is complex since the substrate is rearranging to a less reactive compound in addition to solvolyzing (see Scheme XIII). 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 equation (2). \(^{43}\)

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

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

The corresponding \(k_1, k_2,\) and \(k_3\) for the solvolyses of 107 and 115 were evaluated from the experimental data using equation (2) in conjunction with an iterative Fortran IV computer program, written by R. S. Macomber and modified by M. J. Epstein, the listing of which is shown in Figure 1. Insertion of experimentally determined values of \([\text{HOX}]_\infty\) (infinity titer) and \([\text{HOX}]_t\) afforded values of \(\ln X\). The experimental data required to calculate \(\ln X\) is shown in Table II for a typical run.

THE DATA CARDS SHOULD FOLLOW THE //SYSIN GO CARD.
DATA CARD #1. THE NUMBER OF DATA SETS (RUNS), M; THIS INTEGER MUST END IN COLUMN 2.

LET N BE THE NUMBER OF ONE RUN (N <= M).
DATA CARD #N+1. A TITLE FOR THE RUN MAY BE TYPED ANYWHERE IN COLUMNS 1-68.


THE INTEGER VALUE OF PTS may be up to 3 DIGITS long and must end in COLUMN 39.


DATA CARD #N+3. HERE IS SPECIFIED THE NUMBER OF VALUES TO BE TRIED FOR EACH K. EACH NUMBER MAY BE UP TO 3 DIGITS LONG AND MUST END IN COLUMNS 3, 6, 9. THESE ARE NUM1, NUM2, NUM3. TYPICAL VALUES FOR THEM ARE 0.5, 0.5, 0.5.

DATA CARD #N+4. HERE IS SPECIFIED THE FRACTIONS (FRAC'S) BY WHICH THE K'S ARE TO BE VARIED. FOR EXAMPLE, K1 IS VARIED FROM K1 TO K1 - K1*FRAC1. TYPICAL VALUES ARE 0.01 FOR EACH. FRAC1, FRAC2, AND FRAC3 SHOULD BE PUNCHED ACCORDING TO E OR F FORMAT, AND MUST END IN COLUMNS 12, 24, 36, RESPECTIVELY.

//FORKSYSIN DD = integer TL(17), Pts
KEAL k1, k2, k3, T(20), LNC(20), LNX(20), SLNC(20)
READ (5, 1) M
1 FORMAT (12)
DO J = 1, M
READ (5, 2) (TL(I), I = 1, 17)
2 FORMAT (17A4)
WRITE (6, 3) (TL(I), I = 1, 17)
3 FORMAT (12) /////////////10X, 17A4)
READ (5, 4) UK1, UK2, UK3, Pts
4 FORMAT (3E10.5, 13)
READ (5, 21) NUM1, NUM2, NUM3
21 FORMAT (13)
READ (5, 22) FRAC1, FRAC2, FRAC3
22 FORMAT (3E12.6)
KANGE1 = UK1 - FRAC1*NUM1
KANGE2 = UK2 - FRAC2*NUM2
KANGE3 = UK3 - FRAC3*NUM3
WRITE (5, 98) UK1, KANGE1, NUM1, OK1, RANGE1, NUM1, OK1, RANGE1, NUM1
98 FORMAT (10, 1X), 'THE TESTED RANGES OF THE K'S ARE:',
1* 'K1 FROM ', 'E12.5', ' TO ', 'E12.5', ' IN ', 'E12.5', ' STEPS', '1',
2* 'K2 FROM ', 'E12.5', ' TO ', 'E12.5', ' IN ', 'E12.5', ' STEPS', '1',
3* 'K3 FROM ', 'E12.5', ' TO ', 'E12.5', ' IN ', 'E12.5', ' STEPS', '1',

FIGURE 1. LISTING OF ITERATIVE PROGRAM FOR CALCULATION OF K1, K2, AND K3.
K1 = UK1
K2 = UK2
K3 = UK3
DELK1 = FhAC1 * K1
DELK2 = FhAC2 * K2
DELK3 = FhAC3 * K3
DO 5 I = 1, P15
5 READ (5, 6) T(I), LNX(I)
6 FORMAT (2F10.5)
   SAVER = 1000.0
   DO 15 N = 1, NUM1
      K1 = K1 - DELK1
      K2 = K2
      DO 15 K = 1, NUM2
         K2 = K2 - DELK2
      K3 = UK3
      DO 15 L = 1, NUM3
         K3 = K3 - DELK3
      SUMER = 0.0
      DO 7 I = 1, P15
         LNC(I) = ALOG((K1 + K2 - K3)/(K2 * EXP(-K3 * T(I)) + (K1 - K3) * EXP(-K1 - K2) * T - I)))
      7 SUMER = SUMER + ABS(LNC(I) - LNX(I))
      IF (SUMER .GT. SAVER) GO TO 15
      SAVER = SUMER
      SK1 = K1
      SK2 = K2
      SK3 = K3
      DO 8 I = 1, P15
8      SLNC(I) = LNC(I)
      15 CONTINUE
      WRITE (6, 9) SK1, SK2, SK3
      9 FORMAT (I0, ' THE BEST FIT WAS FOUND WITH K1 = ', E13.5, ', K2 = ',
               '-E13.5', ' AND K3 = ', 'E13.5')
      WRITE (6, 10)
      10 FORMAT (1HO, ' TIME LNX LNC DELTA')
      DO 11 I = 1, P15
      11 EE = SLNC(I) - LNX(I)
      WRITE (6, 12) T(I), LNX(I), SLNC(I), EE
      12 FORMAT (1HO, 'TIME LNX LNC DELTA')
      WRITE (6, 13) SAVEx
      13 FORMAT (1HO, 'TOTAL ABSOLUTE ERROR (LNC-\tLNX) = ', F10.5)
C THE FOLLOWING CARDS ARE FOR PLOTTING SOMEWHERE ELSE. GRAPH1 MUST BE CHANGED
C BEFORE WE CAN USE IT. SO THESE CALL STATEMENTS ARE DEACTIVATED.
C 16 CALL GRAPPL(T, SLNC, P13, SK1, SK2, SK3, LNX)
C CALL ENPLT
16 CONTINUE
STOP
END

FIGURE 1. CONTINUED
TABLE II. Acetolysis of $\text{IO}_7$ in Acetic Acid at $54.8^\circ$ Containing $0.03057$ N Sodium Acetate

<table>
<thead>
<tr>
<th>Time in seconds</th>
<th>ml of $0.01473$ M HClO$_4$</th>
<th>$[\text{NaOAc}]$</th>
<th>$[\text{ BsOH}]$</th>
<th>$[\text{ BsOH}]_\infty - [\text{ BsOH}]_t$</th>
<th>lnX</th>
</tr>
</thead>
<tbody>
<tr>
<td>550</td>
<td>3.478</td>
<td>0.02699</td>
<td>0.00358</td>
<td>0.01301</td>
<td>0.24308</td>
</tr>
<tr>
<td>1730</td>
<td>2.920</td>
<td>0.02266</td>
<td>0.00791</td>
<td>0.00868</td>
<td>0.64778</td>
</tr>
<tr>
<td>2657</td>
<td>2.572</td>
<td>0.01996</td>
<td>0.01061</td>
<td>0.00598</td>
<td>1.0204</td>
</tr>
<tr>
<td>4054</td>
<td>2.332</td>
<td>0.01810</td>
<td>0.01247</td>
<td>0.00412</td>
<td>1.39295</td>
</tr>
<tr>
<td>5314</td>
<td>2.170</td>
<td>0.01684</td>
<td>0.01373</td>
<td>0.00286</td>
<td>1.75798</td>
</tr>
<tr>
<td>6547</td>
<td>2.086</td>
<td>0.01619</td>
<td>0.01438</td>
<td>0.00221</td>
<td>2.01581</td>
</tr>
<tr>
<td>7805</td>
<td>2.012</td>
<td>0.01561</td>
<td>0.01496</td>
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<td>0.01398</td>
<td>0.01659</td>
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$^a$Titrated with $0.01454$ M HClO$_4$ in acetic acid.
The estimated rate constants were varied over specified ranges and were used to calculate the computer equivalent of \( \ln X \) (see eq. 2), \( \ln C \). 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 versus \( \log[ROX] \) 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 \( \ln C \).

Displayed in Figures 2-7 is the computerized data for duplicate runs (No. 1, No. 2) at three temperatures for the solvolysis of brosylate \( 107 \) (4-OBx) and 3,5-dinitrobenzoate \( 115 \) (5-ODNB). Figures 8 and 9 are plots of \( \ln X \) and \( \ln C \) versus time for \( 107 \) and \( 115 \) respectively. Listed are the ranges over which the rate constants were varied, time, \( \ln X, \ln C, \) Delta (difference between \( \ln X \) and \( \ln C \)), and the total absolute error. In the case of \( k_1 \) and \( k_2 \) the highest value of the range is 25% above the estimated value whereas that for \( k_3 \) is 5% above the estimated value. Also \( k_1 \) and \( k_2 \) were varied over fifty one percent increments and \( k_3 \) was varied ten percent increments. Thus, because \( k_3 \) was accurately determined, its variation range was much narrower.

Initial values of \( k_1, k_2, \) and \( k_3 \) were obtained in various ways. A plot of the slopes (instantaneous rate constants) of the experimental curves versus time and extrapolated to zero time afforded an estimate
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<td>25.37</td>
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<td>0.9922</td>
<td>0.0419</td>
</tr>
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**FIGURE 2.** COMPUTER OUTPUT FOR ACETYLATION OF 207 AT 25.7°C.
ACETOLYSIS OF 4-ORS AT 40.5°C NO 1

THE TESTED RANGES OF THE K'S ARE

K1 FROM 0.1066E-03 TO 0.5330E-04 IN 50 STEPS.
K2 FROM 0.8524E-04 TO 0.42620E-04 IN 50 STEPS.
K3 FROM 0.2469E-07 TO 0.24210E-07 IN 10 STEPS.

THE BEST FIT WAS FOUND WITH K1 = 0.85280E-04 K2 = 0.47734E-04 AND K3 = 0.26362E-07

TIME LNX LNC DELTA
0.0 0.0 7.0 0.0
160.0 0.01405 0.01359 -0.00046
1139.0 0.10497 0.09478 0.00021
2537.0 0.20749 0.19729 -0.01020
3415.0 0.29463 0.28424 -0.01039
5267.0 0.38486 0.37402 0.01084
6674.0 0.43559 0.42736 0.00823
7811.0 0.57644 0.55494 -0.02150

TOTAL ABSOLUTE ERROR (LNC-LNX) = 0.05245

ACETOLYSIS OF 4-ORS AT 40.5°C NO 2

THE TESTED RANGES OF THE K'S ARE

K1 FROM 0.9933E-04 TO 0.49405E-04 IN 50 STEPS.
K2 FROM 0.67206E-04 TO 0.33604E-04 IN 50 STEPS.
K3 FROM 0.2690E-07 TO 0.24210E-07 IN 10 STEPS.

THE BEST FIT WAS FOUND WITH K1 = 0.87410E-04 K2 = 0.65184E-04 AND K3 = 0.25824E-07

TIME LNX LNC DELTA
0.0 0.0 0.0 0.0
160.0 0.04765 0.01391 -0.03374
1139.0 0.13557 0.11615 -0.01942
2537.0 0.21309 0.20232 0.01077
3415.0 0.27926 0.26119 0.01807
5267.0 0.38692 0.38242 -0.00450
6674.0 0.45573 0.45566 -0.00007
7811.0 0.50471 0.50494 0.00023

TOTAL ABSOLUTE ERROR (LNC-LNX) = 0.00064

FIGURE 3. COMPUTER OUTPUT FOR ACETOLYSIS OF 407 AT 40.5°C.
### Table 1: Acetolysis of 4-UBS at 54.8 °C

<table>
<thead>
<tr>
<th>TIME</th>
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<th>DELTA</th>
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<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
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**TOTAL ABSOLUTE ERROR (LNC-LNX) = 0.19266**

### Table 2: Acetolysis of 4-UBS at 54.8 °C

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**TOTAL ABSOLUTE ERROR (LNC-LNX) = 0.21262**

---

**Figure 4:** Computer output for acetolysis of 4-UBS at 54.8 °C.
HYDROLYSIS OF 5-BDNB AT 40.3°C NO 1

The tested ranges of the K's are:

- **K1**: From 0.2036E-04 to 0.1010E-04 in 50 steps.
- **K2**: From 0.2036E-04 to 0.1010E-04 in 50 steps.
- **K3**: From 0.3523E-09 to 0.1170E-09 in 10 steps.

The least square fits were found with K1 = 0.1840E-04, K2 = 0.1832E-04, and K3 = 0.3311E-09.

<table>
<thead>
<tr>
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<td>0.0</td>
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<td>9677.0</td>
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<td>11549.0</td>
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<tr>
<td>13621.0</td>
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Total absolute error (LNC-LNX) = 0.01086

HYDROLYSIS OF 5-BDNB AT 40.3°C NO 2

The tested ranges of the K's are:

- **K1**: From 0.2115E-04 to 0.1059E-04 in 50 steps.
- **K2**: From 0.2115E-04 to 0.1059E-04 in 50 steps.
- **K3**: From 0.3527E-09 to 0.1170E-09 in 10 steps.

The least square fits were found with K1 = 0.1398E-04, K2 = 0.2097E-04, and K3 = 0.3205E-09.

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<tr>
<td>3693.0</td>
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<td>7492.0</td>
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<td>13621.0</td>
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Total absolute error (LNC-LNX) = 0.01684

**Figure 5.** Computer output for hydrolysis of 5-BDNB at 40.3°C.
### HYDROLYSIS OF 5-ODNB AT 55.8°C NO 1

- **The Tested Ranges of the K's Are**
  - $K_1$ from $0.9915E-04$ to $0.4957E-04$ in 50 steps.
  - $K_2$ from $0.6440E-04$ to $0.3200E-04$ in 50 steps.
  - $K_3$ from $0.2338E-09$ to $0.2142E-08$ in 10 steps.

- **The Best Fit Was Found With** $K_1 = 0.7337E-04$, $K_2 = 0.4480E-04$, and $K_3 = 0.2151E-08$.

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**Total Absolute Error (LNC-LNX) = 0.03240**

### HYDROLYSIS OF 5-ODNB AT 55.8°C NO 2

- **The Tested Ranges of the K's Are**
  - $K_1$ from $0.9915E-04$ to $0.4957E-04$ in 50 steps.
  - $K_2$ from $0.6440E-04$ to $0.3200E-04$ in 50 steps.
  - $K_3$ from $0.2338E-09$ to $0.2142E-08$ in 10 steps.

- **The Best Fit Was Found With** $K_1 = 0.7535E-04$, $K_2 = 0.5248E-04$, and $K_3 = 0.2314E-08$.

<table>
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**Total Absolute Error (LNC-LNX) = 0.02422**

**Figure 6. Computer Output for Hydrolysis of 5-ODNB at 55.8°C.**
HYDROLYSIS OF 5-CDNA AT 70.3°C NO 1

THE TESTED RANGES OF THE K'S ARE

K1 FROM 0.373ACCE-03 TO 0.18690E-03 IN 50 STEPS.
K2 FROM 0.14909E-03 TO 0.70009E-04 IN 50 STEPS.
K3 FROM 0.11960E-07 TO 0.10671E-07 IN 10 STEPS.

THE BEST FIT WAS FOUND WITH K1 = 0.32147E-03 K2 = 0.12460E-03 AND K3 = 0.11078E-07

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TOTAL ABSOLUTE ERROR (LNC-LNX) = 0.15532

HYDROLYSIS OF 5-UONU AT 70.3°C NO 2

THE TESTED RANGES OF THE K'S ARE

K1 FROM 0.35660E-03 TO 0.17830E-03 IN 50 STEPS.
K2 FROM 0.23542E-03 TO 0.70009E-03 IN 50 STEPS.
K3 FROM 0.11190E-07 TO 0.10671E-07 IN 10 STEPS.

THE BEST FIT WAS FOUND WITH K1 = 0.33520E-03 K2 = 0.14720E-03 AND K3 = 0.10966E-07

<table>
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</tbody>
</table>

TOTAL ABSOLUTE ERROR (LNC-LNX) = 0.12020

FIGURE 7. COMPUTER OUTPUT FOR HYDROLYSIS OF 5-CDNA AT 70.3°C.
Figure 8. Plot of ln X and ln C versus Time for the Acetolysis of 107 in Acetic Acid-.03057 N Sodium Acetate at 25.7°C.
Figure 9. Plot of ln X and ln C versus Time for the Hydrolysis of \( \text{115} \) in 80:20 Acetone-Water at 55.8\(^\circ\).
of $k_1$. Table III shows values of $k_1$ obtained in this way for 107 and 115. The value of $k_2$ was estimated to be 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 119 and 3,5-dinitrobenzoate 123. The experimental data was evaluated by means of a sequence of computer programs designed to solve equation (3),

$$\ln X_t = -kt + \ln X$$

where $X_t$ is the concentration of substrate at time $t$, $X_0$ is the concentration of substrate at time zero, and $k$ is the first order rate constant. The first program, First Order Kinetics-1 (FOK-1), calculated $X_t$ and converted it, into a dummy variable, $Y_t$ suitable for least squares analysis. Values of time $t$ and $Y_t$ were fed into a second program, STAT-6, which performed a least squares regression on a form of equation (3), equation (4) where

$$y = mx + b$$

$$m = \frac{n\Sigma(xy) - \Sigma x \Sigma y}{n\Sigma x^2 - (\Sigma x)^2} = -1000 \ k$$

$$b = \frac{\Sigma x \Sigma y}{n\Sigma x^2 - (\Sigma x)^2} = 6 + \ln X_0$$

$$y = 6 + \ln X_t$$

$$X = \text{time (seconds/thousand)}$$
TABLE III. Rate Constant $k_1$ for 107 and 115 Estimated by the Method of Instantaneous Rate Constants

<table>
<thead>
<tr>
<th>Compound</th>
<th>T°, C</th>
<th>Run</th>
<th>$k_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBs</td>
<td>25.7</td>
<td>1</td>
<td>9.35x10^{-8}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>9.42x10^{-8}</td>
</tr>
<tr>
<td>NO₂</td>
<td>40.5</td>
<td>1</td>
<td>8.52x10^{-5}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>7.47x10^{-5}</td>
</tr>
<tr>
<td>107</td>
<td>54.8</td>
<td>1</td>
<td>3.75x10^{-4}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>3.72x10^{-4}</td>
</tr>
<tr>
<td>NO₂</td>
<td>40.3</td>
<td>1</td>
<td>1.63x10^{-5}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>1.70x10^{-5}</td>
</tr>
<tr>
<td>NO₂</td>
<td>55.8</td>
<td>1</td>
<td>7.93x10^{-5}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>7.90x10^{-5}</td>
</tr>
<tr>
<td>115</td>
<td>70.3</td>
<td>1</td>
<td>2.99x10^{-4}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>2.85x10^{-4}</td>
</tr>
</tbody>
</table>

\(^{a}\)Reference 42.
and generated values of m, b, and \( \sigma \). Treatment of these values with a third program, First Order Kinetics-2 (FOK-2) afforded values for \( x_{t}^{\text{calc}} \), \( x_{o}^{\text{calc}} \), and first order rate constant \( k \). Values of experimental \( k_{3} \) for the acetolysis of brosylate \( 119 \) and hydrolysis of 3,5-dinitrobenzoate \( 123 \) are displayed in Table IV. Programs FOK-1, FOK-2, and STAT-6 were designed by M. J. Epstein for use in conjunction with a Wang Electronic Calculator.

**Calculation of Activation Parameters**

Equation (5) describes the relation between rate constant \( k \), temperature \( T \), and activation parameters, \( \Delta H^{\pm} \) and \( \Delta S^{\pm} \).

\[
k = \frac{k^{'}T}{h} e^{-\Delta H^{\pm}/RT} e^{\Delta S^{\pm}/R}
\]  

(5)

where \( k = \) specific rate constant

\[
k' = \text{Boltzmann's constant} = (1.3805 \pm 0.0001) \times 10^{-16} \text{ erg/deg}
\]

\[
h = \text{Planck's constant} = (6.6266 \pm 0.0005) \times 10^{-27} \text{ erg/sec}
\]

\[
T = \text{Temperature} \text{ } ^{\circ}K
\]

\[
R = \text{gas constant} = 1.9872 \pm 0.0001 \text{ cal mole}^{-1} \text{ deg}^{-1}
\]

Taking the logarithm of both sides of equation (5) and substituting in the values given above affords equation (6) which is of the form of equation (4).

\[
\log \frac{k}{T} = 10.3188 - \frac{\Delta \Delta H^{\pm}}{4.576 (T)} + \frac{\Delta S^{\pm}}{4.576}
\]  

(6)

\[y = mx + b\]
<table>
<thead>
<tr>
<th>Compound</th>
<th>T°,C</th>
<th>Rate Constant $^a$ x10^5 sec$^{-1}$</th>
<th>$\Delta H^\ddagger$ kcal/mol</th>
<th>$\Delta S^\ddagger$ eu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>85.4</td>
<td>0.416</td>
<td>24.7</td>
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<tr>
<td>119</td>
<td>100.5</td>
<td>1.77</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>115.8</td>
<td>6.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.7</td>
<td>3.44x10$^{-4}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40.5</td>
<td>2.56x10$^{-4}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54.8</td>
<td>1.50x10$^{-2}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>101.1</td>
<td>2.39x10$^{-2}$</td>
<td>24.3</td>
<td>-24.3</td>
</tr>
<tr>
<td>123</td>
<td>115.8</td>
<td>7.55x10$^{-2}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>130.1</td>
<td>27.2x10$^{-2}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40.3</td>
<td>0.336x10$^{-4}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55.8</td>
<td>2.23x10$^{-4}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70.3</td>
<td>1.11x10$^{-3}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Corresponding to experimental $k_3$. $^b$ Calculated.
where \( y = \log \left( \frac{k}{t} \right) \)

\[
x = \frac{1}{T}
\]

\[
m = -\frac{\Delta H^\pm}{4.576}
\]

\[
b = \frac{\Delta S^\pm}{4.576} + 10.3188
\]

The errors in the enthalpy and entropy of activation for all rate constants in this study were calculated using equations (7) and (8)

\[
\delta = R \frac{T'T}{T'-T} \ln \frac{H_\alpha}{1-\alpha}
\]

(7)

\[
\sigma = \delta \left( \frac{1}{T} \right) + R \ln (1+\alpha)
\]

(8)

where \( \delta \) is the error in \( \Delta H^\pm \), \( \sigma \) is the error in \( \Delta S^\pm \), \( T \) and \( T' \) are the extremes of the temperature range, and \( \alpha \) is the maximum fractional error in the rate constant \( k \).

By means of a computer program for activation parameters (AP-1) \( k_T \) and \( T \) were transformed into dummy variables for least squares analysis and were submitted to the STAT-6 program. The values of \( m \) and \( b \) which were obtained were fed into another activation parameters program (AP-2) affording values of the specific rate constant \( k_1 \), at any temperature, \( \Delta H^\pm \) and \( \Delta S^\pm \). Both programs AP-1 and AP-2 were designed by M. J. Epstein and used with a Wang Electronic Calculator.
BIBLIOGRAPHY

24. Chemical Samples Co., Columbus, Ohio.


47. (a) A 6 ft x ½ in aluminum column packed with 10% SE-30 on 80/80 Chromosorb G used with an Aerograph A-700 gas chromatograph.
   (b) A 5.5 ft x ½ in aluminum column packed with 10% FFAP on 80/80 Chromosorb G. (c) A 6 ft x ½ in aluminum column packed with 10% carbowax on 80/80 Chromosorb G.


