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THE SYNTHESIS AND CHARACTERIZATION OF COMPOUNDS DESIGNED TO EXHIBIT MACROCYCLIC RING-CHAIN TAUTOMERISM

JOHN ELTON DEWHURST

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THE SYNTHESIS AND CHARACTERIZATION OF
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by

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THIS THESIS IS DEDICATED TO MY WIFE JUDE
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ABSTRACT

THE SYNTHESIS AND CHARACTERIZATION OF COMPOUNDS DESIGNED TO EXHIBIT MACROCYCLIC RING-CHAIN TAUTOMERISM

by

J. ELTON DEWHURST

A series of ortho- and meta- \( \omega \)-hydroxyalkoxybenzaldehydes have been synthesized and examined by ir, nmr and uv spectroscopy for ring-chain tautomerism. The compounds were prepared by alkylation of the corresponding phenolic aldehydes with a series of \( \omega \)-bromoalkanols.

No unequivocal evidence for the existence of a dynamic equilibrium between cyclohemiacetal and free aldehyde forms was obtained.

The reaction of picolinaldehyde with \( \omega \)-haloalkanols was explored. From 2-bromoethanol and 3-bromopropanol hemiacetal quaternary pyridinium salts are formed, presumably via an intramolecular Menschutkin reaction. From 4-chlorobutanol, a highly deliquescent, bright orange uncharacterized material was formed, and for longer chain bromohydrins no quaternization could be achieved.
HISTORICAL

A chemical compound which exists as an equilibrium mixture of cyclic and acyclic forms is said to exhibit ring-chain tautomerism if the cyclization occurs with concomitant migration of an atom or group from one atom in the open-chain form to another in the ring form. For example, the $\omega$-hydroxyalkanals can exist as a mixture of the free aldehyde and the cyclohemiacetal, with a hydrogen atom as the migrating entity. This is shown in Figure I.

![Figure I](image1)

This behavior must be distinguished from three related phenomena; valence tautomerism, reversible isomerism, and irreversible isomerism.

If the two isomers interconvert with no $\sigma$-bond breaking, and therefore with no migration of an atom or group, then they are exhibiting valence tautomerism, of which an example is shown in Figure II.

![Figure II](image2)

$R = C_6H_5, \, p-CH_3C_6H_4$

Figure II
If the two isomers can both be isolated and either can be cleanly converted to the other by such means as acid, base or heat, then reversible isomerism is observed.\(^2\) On the other hand, it is a case of irreversible isomerism if the transformation can be made in one direction only.\(^2\) Then, as stated before, the two criteria for identifying ring-chain tautomerism are the detection of a dynamic equilibrium between the tautomers and the migration of an atom or group as part of the transformation.

The energy diagrams in Figure III illustrate the difference between ring-chain tautomerism and both reversible and irreversible isomerism. If the barrier to interconversion is small, then tautomerism is observed, and the position of the equilibrium is dependent on the relative energies of the two forms. If the barrier is large, then isomerism is the case and this will be reversible only if the barrier from one form to the other is roughly equal from both directions.

![Energy Diagrams](image)

**Figure III**

Jones has described two types of ring-chain tautomerism, nucleophilic and electrophilic, based on the nature of the migrating group.\(^1\) In
Figure IV, Y is more electronegative than A, as would be the oxygen of a carbonyl or the nitrogen of an imino or cyano group. The terminus, B, is the migrating group, and its nucleophilicity or electrophilicity determines the atom, A or Y, to which it is bonded in the cyclic tautomer.

- Nucleophilic
  - $X \quad Y$
  - $A \quad B$

- Open-chain Form
  - $X \quad B$
  - $A \quad Y$

- Electrophilic
  - $X \quad A \quad Y \quad B$

Ring closures can be further classified by the nature and position of the atoms which bond to close the ring. In a study of rules for ring closure, Baldwin has defined the general mechanisms shown in Figure V. In this scheme, n stands for the ring size, exo refers to Y remaining outside the ring, endo to Y becoming a ring atom, tet denotes tetrahedral geometry about A, trig for trigonal and dig for digonal.

It should be noted that an exo-tet ring closure involves the splitting off of a leaving group. Thus, this cannot apply to a tautomeric
n-exo-tet:  \( (\text{CH}_2)^{n-2} \xrightarrow{\text{X:}} y \xrightarrow{\text{A}} (\text{CH}_2)^{n-2} \xrightarrow{\text{X}} y + \text{A} : \)

n-endo-tet:  \( (\text{CH}_2)^{n-3} \xrightarrow{\text{X:}} y \xrightarrow{\text{A}} (\text{CH}_2)^{n-3} \xrightarrow{\text{X}} y : \)

n-exo-trig:  \( (\text{CH}_2)^{n-2} \xrightarrow{\text{X:}} y \xrightarrow{\text{A}} (\text{CH}_2)^{n-2} \xrightarrow{\text{X}} y : \)

n-endo-trig:  \( (\text{CH}_2)^{n-3} \xrightarrow{\text{X:}} y \xrightarrow{\text{A}} (\text{CH}_2)^{n-3} \xrightarrow{\text{X}} y : \)

n-exo-dig:  \( (\text{CH}_2)^{n-2} \xrightarrow{\text{X:}} y \xrightarrow{\text{A}} (\text{CH}_2)^{n-2} \xrightarrow{\text{X}} y : \)

n-endo-dig:  \( (\text{CH}_2)^{n-3} \xrightarrow{\text{X:}} y \xrightarrow{\text{A}} (\text{CH}_2)^{n-3} \xrightarrow{\text{X}} y : \)

Figure V
system. An endo-tet system is not a ring closure, but rather a re-arrangement. This is also excluded. The ring-chain tautomerism exhibited by \( \omega \)-hydroxyalkanals (see Figure I) can be classified as electrophilic-exo-trig.

Besides the simple equilibrium between a ring and a chain form, two special cases of ring-chain tautomerism have been observed which are worth noting. The first of these constitutes one of the best-known examples of ring-chain tautomerism and is found in the chemistry of carbohydrates. The mutarotation of sugars such as glucose is a direct observation of the consequences of this phenomenon.\(^7\)-\(^8\)

At 20° C, at equilibrium, D-glucose consists of a mixture of about 33% \( \alpha \)-D-glucose and 67% \( \beta \)-D-glucose, with a specific rotation of \([\alpha] = +52.7^\circ\) for the mixture.\(^7\) In this case the \( \alpha \) and \( \beta \) forms are diastereomeric ring tautomers of a common chain tautomer.\(^8\)

![diagram](image)

\( \alpha \)-D-glucose \quad \text{Chain tautomer} \quad \beta \)-D-glucose

Figure VI

While the equilibrium appears to be between the two epimeric ring forms, the transformation is visualized as taking place through the open-chain structure.

The second case is illustrated by the work of Griot and Frey in
In 1963, in this case the large ring tautomer is obtained from the open-chain-like structure through the bicyclic form.

![Figure VII](image)

This particular system is very sensitive to ring size. Unless the large-ring tautomer is at least ten-membered, and unless both rings of the bicyclic form are at least six-membered, the large ring tautomer is not seen.  

Other examples of ring-chain tautomerism involving bicyclic forms are shown in Figure VIII. In these cases, an oxygen atom bridges the two smaller rings.  

![Figure VIII](image)
For any given ring-chain tautomeric system, several factors may govern the position of the equilibrium. Most of these can be described as part of the nature of the medium. These include the polarity and solvating properties of the solvent, the pH, where applicable, the temperature, and the concentration. The remaining factor to be considered is the ring size.

In 1971, Whiting and Edward established that for 5-hydroxy-2-pentanone and 6-hydroxy-2-hexanone, increasing solvent polarity favors the open-chain forms. Indeed, they were unable to detect any ring tautomer in aqueous media. In addition, it has been noted that increased temperatures also favor open-chain forms. This temperature effect is in accord with the work of Hurd and Saunders on the \( \omega \)-hydroxyalkanals. Both of these systems are classified as electrophilic-exo-trig.

The particular reaction of aldehydes with alcohols to form acetals and hemiacetals is catalyzed by acids. Therefore, it can be expected that acid may catalyze the ring-chain tautomerism of the \( \omega \)-hydroxyalkanals. Indeed, trace amounts of acids catalyze the mutarotation of glucose. It should be emphasized that catalysis does not change the value of equilibrium constants, only the rate of approach to equilibrium. Thus, for a particular system, acid catalysis can change the energy profile from one of isomerism to one of tautomerism (see Figure III).

A change in pH can effect a change in polarity of the medium, however, and this factor may come into play. The conventional mechanism of acid-catalyzed hemiacetal formation is shown in Figure IX.
The reaction which competes with ring-chain tautomerism is dimerization, shown in Figure X.

\[
\begin{align*}
\text{OH} & \quad \overset{k_1}{\rightleftarrows} \quad \text{HO(CH}_2\text{)_nC}_n^\text{H} \quad \overset{k_2}{\rightleftarrows} \quad \text{HO(CH}_2\text{)_nC}_n^\text{O} \\
\text{HO(CH}_2\text{)_nC}_n^\text{H} & \quad \overset{k_1}{\rightleftarrows} \quad \text{(CH}_2\text{)_nCH - OH}
\end{align*}
\]

Figure X

The effect of concentration on the position of equilibrium is manifested by a decrease in dimerization with decreasing concentration. This is illustrated by the following equations. If \([C]\) is very small, then \([C]^2\) is smaller yet and the effect of \(k_1[C]\) swamps out that of \(k_2[C]^2\).

\[
-d[C]/dt = k_1[C] + k_2[C]^2 - k_{-1}[R] - k_{-2}[D]
\]
The effect which is related to concentration and the relative importance of dimerization is the ease of ring closure. Baldwin's rules for ring closure specify that some types of closures are disfavored because of stereochemical requirements of the transition state. If a ring closure is disfavored, then dimerization becomes a probable alternative. Baldwin's rules are applicable only up to seven-membered rings.

In macrocyclic rings an additional factor comes into play. As the number of atoms between the ends of the chain increases, the number of possible conformations of the molecule increases. There is, therefore, an entropy effect to be overcome in bringing the two reactive ends of the molecule together. High dilution of such molecules assures that one reactive end of a chain will meet the other end of the same molecule more often than it will the other end of another molecule.

A third consideration is the thermodynamic stability of the ring itself as a function of ring size. If a particular ring size is subject to strain, then the transition state leading to that ring may be strained. Flory, Suter, and Mutter have stated that closure of a ring is dependent on three conditions. These are that the atoms which bond to close the ring must be able to come within a bond's length of each other, that acceptable bond angles must result and that the torsional strain in the rest of the chain must be within tolerable limits.

The consequences of this were observed in Borgen's studies of the synthesis of macrocyclic ketals. A series of \( \alpha, \omega \)-alkanediols were allowed to react with acetone under acid catalysis and with the azeotropic removal of water. It was found that if the resultant monomeric cyclic ketal was six- or seven-membered, it was the major product. If the monomeric cyclic ketal was nine-membered, ten- or eleven-membered, then
the dimeric cyclic ketals were formed. These were 18-, 20-, and 22-
membered, respectively. The structures of these compounds are shown in Figure XI.

Methods are available, however, for the synthesis of strained, medium-sized acetics.\textsuperscript{20}

The effect of ring size versus stability is seen in cyclic hemiacetals as well. Glycolaldehyde is the first member of the homologous series of \( \omega \)-hydroxyalkanals. The monomeric cyclohemiacetal, which would be its simplest ring tautomer, would be three-membered. These rings are highly strained, and as expected, none of this tautomer is observed in solution. What has been observed by Collins and George is shown in Figure XII.\textsuperscript{21}

\[ \text{I:II:III:IV} \]
4:9:17:70\% in water
4:36:60:0\% in dimethyl sulfoxide

\textbf{Figure XII}
Both the symmetrical cyclic dimer, II, and the asymmetrical cyclic dimer, III, come from the acyclic dimer, as shown in Figure XIII.

![Figure XIII](image)

The next member of the series, hydracrylaldehyde, when isolated by distillation, spontaneously dimerizes, as shown in Figure XIV.\(^{22}\)

![Figure XIV](image)

In this case, the less-strained six-membered ring of the asymmetric dimer is formed.

The remaining members of the series of homologous $\omega$-hydroxy-alkanals have been examined by two groups in order to determine the effect of ring size on the position of the equilibrium. Their results are
summarized in Table I.\textsuperscript{11,23} Included is a measure of ring strain in terms of heats of combustion per methylene group for the corresponding cycloalkanes.\textsuperscript{24}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Ring Size} & \textbf{\% Free Aldehyde in 75\% Dioxane}\textsuperscript{11} & \textbf{\% Free Aldehyde in Toluene at}\textsuperscript{23} & \textbf{Heat of Combustion per Methylene (Kcal)}\textsuperscript{24} \\
\hline
\textbf{25\textdegree C} & \textbf{35\textdegree C} & \textbf{70\textdegree C} & \\
\hline
5 & 11.4 & 13.4 & - & 158.7 \\
6 & 6.1 & 6.8 & 10 & 157.4 \\
7 & 85 & 89 & 85 & 158.3 \\
8 & - & - & 84 & 158.6 \\
9 & 80 & 80 & 70 & 158.8 \\
10 & 91 & 91 & 84 & 158.6 \\
11 & - & - & 59 & 158.4 \\
12 & - & - & 68 & 157.8 \\
13 & - & - & - & 157.7 \\
14 & - & - & 75 & 157.4 \\
15 & - & - & - & 157.5 \\
16 & - & - & 65 & 157.5 \\
\hline
\end{tabular}
\caption{\% Aldehyde in Solutions of \textit{\omega}-Hydroxyalkanals}
\end{table}

There seems to be no clear-cut relationship between percent open-chain form and ring size. It may not be strictly valid to emphasize comparisons with the cycloalkanes; but, for example, there would appear to be more ring for the nine-membered ring than for either of the less-strained eight- or ten-membered rings. In addition, although the seven-membered ring is slightly less strained than the five-membered ring, there would appear to be much more five-membered ring tautomer in solution than seven-membered, despite the fact that Baldwin classifies both 5-exo-trig and 7-exo-trig ring closures as favored.\textsuperscript{6}

One of the compounds which is missing from the Table is tetra-
decanal-14-ol, which has been reported as a solid melting at 55°-56°C. It undergoes a transformation, upon standing for one month at room temperature, to a solid melting at 64°-65°C which has no carbonyl peak in its ir spectrum. These authors attributed this change to polymerization.

In no case to date has evidence been presented which would allow one to distinguish between ring tautomer formation and polymerization for these higher homologs. The lack of correlation of ring size with the percent free aldehyde (open-chain form) seems to argue in favor of either polymerization or complex equilibria involving acyclic, asymmetric cyclic, and symmetric cyclic dimers.

In designing a system with which to study ring-chain tautomerism, two synthetic schemes can be followed. The first of these is to direct the synthesis toward the open-chain form and look for ring closure in the product under conditions which should favor equilibration. This approach was pursued by Jones, Saltzman and Panicci. The electrophilic-exo-trig systems shown in Figure XV were studied. In each case the ring tautomers would be para-bridged ansa compounds which could be easily detected by nmr. In none of the cases was there rigorous evidence for ring tautomer.

![Figure XV](image-url)
A more fruitful example is by Fuson, who has reported that ozonolysis of the alkenes shown in Figure XVI yields cycloheximacetals as the products.\textsuperscript{29}

\[
\begin{align*}
\text{Mes} & \quad \text{CHOH} \\
\text{CH}_2(\text{CH}_2)\text{CH}=\text{CH}_2 & \quad \rightarrow \quad \text{CH}_2(\text{CH}_2)_n
\end{align*}
\]

Mes = Mesityl; n = 2 or 3

Figure XVI

The second scheme is to synthesize the ring compound and try to induce ring opening. Several examples of this approach are known.

Lactones have been reduced to hydroxyaldehydes with lithium aluminum hydride by Arth.\textsuperscript{30}

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{CH}_3\text{C} & \quad \rightarrow \quad \text{H}_3\text{C} \quad \text{OH} \\
\text{O} & \quad \text{CHO} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Figure XVII

Lithium tri-tert-butoxyaluminum hydride has also been used to reduce lactones.\textsuperscript{31}
Oxidations have also been used to generate cyclohemiacetals, as shown in Figure XIX.\textsuperscript{32,33}

In cases where a benzene ring is annulated to the ring, the analogy to cycloalkanes no longer holds. It is known that oxygen atoms in the place of methylenes, or rigid groups such as cis double bonds enhance the ease of ring closure over that in cycloalkane systems.\textsuperscript{34} In a recent study of ring strain energies of cyclic hydrocarbons, the cis cycloalkenes showed less of a destabilization for the medium-sized rings than did the cycloalkanes.\textsuperscript{35} In both cases, however, the six-membered ring was the most stable.

An attempt to discern the effect of oxygen as a ring atom on ring closures has been reported by Illuminati \textit{et al.}\textsuperscript{36,37} The kinetics of ring closures for the ortho-(ω-bromoalkoxy)-phenols were compared with the kinetics for the same reaction with the analogous ortho-(ω-bromoalkyl)-phenols. The reactions are shown in Figure XX.
The reaction which competes with these ring closures most often is intramolecular $\beta$-elimination to give the terminal alkene.

In one case, however, 3.4% dimer was obtained, which is pictured in Figure XXII.
For the ortho-($\omega$-bromoalkyl)-phenols the entropy of activation decreases linearly with increasing chain length.\textsuperscript{37} Table II shows a comparison of kinetic yields of the cyclic products for both series.

Table II

<table>
<thead>
<tr>
<th>Ring Size</th>
<th>Spectrophotometric Data ($293 \text{ nm}$)</th>
<th>Data From gc Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$X=\text{CH}_2$</td>
<td>$X=\text{O}$</td>
</tr>
<tr>
<td>5</td>
<td>96</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>78</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>85</td>
<td>95</td>
</tr>
</tbody>
</table>

It can be seen that there is no dramatic decrease in yield for the medium-sized rings in the series with the two oxygen heteroatoms, the diethers, as there is where there is only one oxygen heteroatom. Table III shows the rate ratios for the ring closures versus ring size. In the medium-sized rings the diethers close much faster.

Table III

<table>
<thead>
<tr>
<th>Ring Size</th>
<th>$K(\text{Diether})/K(\text{Monoether})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.81</td>
</tr>
<tr>
<td>7</td>
<td>0.42</td>
</tr>
<tr>
<td>8</td>
<td>6.54</td>
</tr>
<tr>
<td>9</td>
<td>7.55</td>
</tr>
<tr>
<td>10</td>
<td>4.16</td>
</tr>
</tbody>
</table>

With this kind of information at hand, it was decided that a study
of a homologous series of \( \omega \)-hydroxyaldehydes with an ortho-disubstituted aromatic ring in the chain might prove interesting. The commercial availability of salicylaldehyde, the ease of alkylation of its phenolic oxygen\(^3\)\(^8\),\(^3\)\(^9\) and the ease of preparation of the bromohydrins\(^4\)\(^0\) made the system shown in Figure XXIII an appealing choice. In this series the ring tautomer contains two oxygen heteroatoms.

![Figure XXIII]

The first two members of the series, \((n=2 \text{ and } 3)\), have previously been reported as heat-sensitive materials.\(^4\)\(^1\),\(^4\)\(^2\) No detailed studies have been done on possible equilibria involving cyclic tautomers.

If dimerization is allowed to compete with the formation of monomeric cyclic tautomerism, and if the acyclic dimers tautomerize to cyclic dimers, the resulting compounds are structurally similar to crown ethers. For example, if 2-(2-hydroxyethoxy)-benzaldehyde forms a symmetrical cyclo-dimer, a dibenzo-14-crown-4 compound results, as shown in Figure XXIV.

![Figure XXIV]
It may be possible to induce dimerization by providing an alkali metal ion in solution with the open-chain monomer and taking advantage of the template effect. A similar dibenzo-14-crown-4 has been shown to form complexes with lithium ions. The structure of this macrocycle is shown in Figure XXV.

![Figure XXV](image)

A convenient method of detecting the ability of a crown ether to form complexes with metal ions is to allow a solution of the crown ether in a water-immiscible solvent to come in contact with an aqueous solution of an alkali metal hydroxide with some added picrate. If the metal binds to the macrocycle, the resulting complex will be more soluble in the organic phase and will carry the colored picrate ion with it. Without the presence of the crown ether, the yellow picrate color remains in the aqueous phase.

A related system, aimed toward synthesis of the ring tautomer directly, involves the quaternization of picolinaldehyde. The scheme shown in Figure XXVI illustrates the possible courses of the reaction between picolinaldehyde and an \( \omega \)-bromoalkanol.
It has been established that picolinaldehyde forms hemiacetal spontaneously in the presence of any alcohol without acid catalysis. If picolinaldehyde is quaternized with methyl iodide in acetone, the result is the quaternized aldehyde. If this material is dissolved in methanol, or if the quaternization is run in methanol, the product is the quaternized methyl hemiacetal. This is shown in Figure XXVII.
From this evidence, it is predicted that the reaction in Figure XXVI goes via Pathway B. An opposing view has been expressed by Newkome, who argues that the ketalization of di-2-pyridylketone in base occurs by the mechanism in Figure XXVIII, which involves quaternization prior to hemiacetal formation.
An examination of molecular models supports the mechanism shown in Figure XXIX, however.
Intramolecular quaternization of pyridine compounds leading to cyclic salts has been seen to occur in several systems. As pointed out before, dimerization becomes important if the ring sizes resulting from monomeric cyclization involve high strain energies, despite the fact that this means the formation of doubly charged ions. Sorm and Sedivy synthesized a dimer from 2-bromomethylpyridine as Boekelheide and Feely did from 2-(2-bromoethyl)-pyridine: these are shown in Figure XXX.
Attempts to synthesize the dimer shown in Figure XXXI were unsuccessful, however.\textsuperscript{51}
Monomeric cyclic salts have been obtained which are five- and six-membered. Winterfeld and Muller obtained the five-membered salt\(^{52}\) while Bohlmann, Ottawa, and Keller obtained the six-membered salt\(^{53}\) shown in Figure XXXII.

![Figure XXXII](image)

Cyclic ketones have also been obtained by intramolecular quaternization, as shown in Figure XXXIII.\(^{54,55}\)

![Figure XXXIII](image)
Boekelheide and Gall obtained the six-membered cyclic alcohol shown in Figure XXXIV. 56

![Chemical structure](image)

Figure XXXIV

Boekelheide and Feely were able to effect intramolecular alkylation of an N-oxide oxygen to close five- and six-membered rings, as shown in Figure XXXV. 50

![Chemical structures](image)

Figure XXXV
The intramolecular acylation of a pyridine nitrogen has been reported by Bradsher and Lohr.\textsuperscript{57} This is shown in Figure XXXVI.

\begin{center}
\begin{tikzpicture}
  \node[anchor=west] (a) at (0,0) {\includegraphics[width=0.5\textwidth]{figure36.png}};
\end{tikzpicture}
\end{center}

\textbf{Figure XXXVI}

Zimmer and Pampalone were able to alkylate both the nitrogen and the sulfur of 2-mercaptopyridine\textsuperscript{58} as shown in Figure XXXVII.

\begin{center}
\begin{tikzpicture}
  \node[anchor=west] (a) at (0,0) {\includegraphics[width=0.5\textwidth]{figure37.png}};
\end{tikzpicture}
\end{center}

\textbf{Figure XXXVII}

Some novel sulfur heterocycles have been obtained by Undheim, et al., as shown in Figure XXXVIII.\textsuperscript{59,60}
In an interesting separate experiment, these workers brominated the allyl sulfide shown in Figure XXXVI. Theoretically, the resultant bromonium ion should have yielded a mixture of five- and six-membered rings, but only the five-membered cyclic salt was formed.60
A second nitrogen atom can be introduced into the new ring, as shown in Figure XL.

Such heterocycles have also resulted from ring-chain tautomerism. The product of the reaction shown in Figure XLI shows no IR peak in the carbonyl region (1660-1800 cm\(^{-1}\))\(^{62}\), evidence for the ring tautomer.

It is possible that several compounds which have been reported in the literature as open-chain forms could actually be ring forms. In most of the cases considered below, no spectral information was given which could
allow one to distinguish between tautomers.

N-(3-hydroxypropyl)-2-acetylpuridinium bromide undergoes phosphorylation to a solid melting at 138-140° C. As shown in Figure XLII, this could exist in equilibrium with a ring tautomer which would be a cyclohexim-ketal. It was not established unequivocally whether the phosphorylated product was cyclic or acyclic, but it was assumed to be acyclic.

Two interesting and related compounds which have been reported are N-(2-hydroxyethyl)-3-acetylpuridinium bromide and N-(4-hydroxybutyl)-3-acetylpuridinium chloride. While ring closure is not expected for these compounds, they may be useful as model compounds for open-chain tautomers, although they may undergo polymerization.

The synthesis of the latter compound is interesting in that it involves the acid-catalyzed hydrolysis of an acetate ester which bears a full positive charge at the pyridinium moiety.
The oximes of \( N-(2\text{-hydroxyethyl})-2\text{-formylpyridinium bromide} \) and \( N-(3\text{-hydroxypropyl})-2\text{-formylpyridinium bromide} \) have been reported and tested for anti-nerve gas activity.\(^{66,67}\) They show reduced activity over that of the prototype drug 2-PAM. One explanation for the reduced activity of these compounds toward reactivating nerve gas-deactivated enzymes is the possibility of ring-chain tautomerism for these structures, as shown in Figure XLIV.

\[ \begin{align*}
\text{Br}^- & + \left( \text{CH}_2\right)_n \text{OH}^+ & \rightarrow & \left( \text{CH}_2\right)_n^0 \text{Br}^- \n \text{N} \quad \text{CH=NH} & + & \text{CH-} & \text{NH-} & \text{OH} \\
\end{align*} \]

\[ n = 2 \text{ or } 3 \]
In addition, long-chain pyridinium salts are of interest because of their antibacterial and antifungal activity. Quaternized pyridine aldehyde acetals have been patented as additives to skin creams and lotions to promote increased circulation of the blood near the surface of skin. A unique series of macrocyclic bisquaternary diquinolinium salts have been patented by Stark for their activity against Gram positive bacteria, Gram negative bacteria, and some pathologically important fungi. The general structure of these salts is shown in Figure XLV. It should be noted that this work indicates that it is possible to close macrocyclic rings via the quaternization of a heterocyclic amine, and in some cases, ones with a 2-substituent on the pyridine ring.

![Figure XLV](image.png)

\[ R = H, CH_3, CH_2CH_3; R' = H, CH_3; X = Cl, Br, I; \]
\[ n = m = 4 \text{ or } 10 \text{ } \text{71-74}; n = m = 4-12 \text{ } \text{75} \]

Figure XLV
Therefore a study of ring-chain tautomerism of a homologous series of \( \omega \)-hydroxyaldehydes with ortho-disubstituted benzene and/or pyridine linkages in the chain has been undertaken.
EXPERIMENTAL

Many basic starting materials were obtained commercially, and these are noted in each appropriate section below.

Nuclear magnetic resonance (nmr) spectra were determined on a Jeol JMN-MH-100 spectrometer in solvents stated for each compound, and chemical shifts are reported relative to the internal standard, tetramethylsilane. The singlet for the standard was set at 0 ppm and chemical shifts are reported downfield from this. Infrared (ir) spectra were obtained as films or KBr pellets on a Perkin-Elmer 337 grating spectrophotometer. Ultraviolet (uv) spectra were obtained on a Bausch and Lomb Spectronic 505. Literature spectra cited are published by Sadtler. All spectra obtained at UNH are on file in the Department of Chemistry. Unless otherwise noted, UNH spectra available published spectra.

Thin-layer chromatography was done on 10 x 20 cm HF silica gel plates developed with 1:3 (V/V) ethyl acetate-hexane. Spots were visualized under both long and short wavelength ultraviolet lamps. High-pressure liquid chromatography was performed by Mr. Michael Pazdon with a Waters Associates' PrepLC/System 500 through two PrepPAK-500/SILICA columns. The solvent system used was ethyl acetate-hexane in proportions reported for each compound.

All melting points were measured on a Thomas-Hoover 6406-H melting point apparatus and are corrected. Elemental analyses were done by Ms. Deanna Cardin with an F and M Model 185 analyzer at UNH.
I. Aliphatic Compounds

2-Chloroethanol was a colorless oil from Eastman and was used without further purification. 2-Bromoethanol and 3-Bromopropan-1-ol (46°C/2.6 mm) were obtained from Aldrich as yellow oils and were vacuum distilled before use. Sadtler spectra are available for all of these compounds.

2-Chloroethanol: ir, prism: 73

2-Bromoethanol: ir, prism: 4724

3-Bromopropan-1-ol: ir, prism: 44907

4-Bromobutyl Acetate: This was prepared by the method of Cloke and Pilgrim. To 24 g (0.333 mol) of anhydrous tetrahydrofuran (Aldrich) at 0°C was added one crystal of anhydrous zinc chloride with stirring, followed by dropwise addition of 45 g (0.366 mol) of acetyl bromide (Eastman). Once all the acetyl bromide was added, the mixture was allowed to warm up to room temperature. The solution was then refluxed for fifteen minutes, during which the solution turned black. After one hour of refluxing the mixture was cooled, diluted with 150 ml of chloroform, washed with two 100-ml portions of 5% sodium bicarbonate and two 100-ml portions of water. The combined aqueous layers were extracted with three 50-ml portions of chloroform, and the combined chloroform layers were dried over anhydrous sodium sulfate. The chloroform was filtered and evaporated to yield 58.8 g of a dark, red, fruity-smelling oil. The oil was distilled at 89°C/7.5 mm(lit 89.5-92°C/15 mm) to yield 40.3 g (62% yield) of colorless product; nmr (CCl₄) 4.16.
(t, 2, $J = 6$ Hz, OCH$_{2}$), 3.55 (t, 2, $J = 8$ Hz, CH$_{2}$-Br), 2.08 (s, CH$_{3}$C O, 1.90 (m, 4, -CH$_{2}$-CH$_{2}$-).

Sadtler spectrum: ir, prism: 4701
UNH spectrum: ir: 21257
nmr: 4031

4-Chlorobutan-1-ol was supplied by Dr. John Marshall, who synthesized it from tetrahydrofuran and HCl, by the method of Starr and Hixon. In the Sadler nmr, which was run in CDCl$_{4}$, the OH proton signal appears at 2.53, whereas, in the UNH spectrum run in CCl$_{4}$, the OH peak appears at 6.92.

Sadtler spectra: ir, prism: 4891
nmr: 241

UNH spectra: ir: 22827
nmr: 5681

5-Bromopentyl Acetate: This was prepared from tetrahydrofuran and acetyl bromide in the same manner as 4-bromobutyl acetate. In this case, 28 g (0.333 mol) of tetrahydrofuran (Aldrich) were treated with 45 g (0.366 mol) of acetyl bromide in the presence of a catalytic amount of anhydrous zinc chloride to yield an oil which was distilled at 82° C./2.3 mm (lit 112-113°/17 mm). The yield was 52 g (75%).

Sadtler spectra: ir, prism: 6639
nmr: 10956

UNH spectra: ir: 22835
nmr: 5680

6-Bromohexan-1-ol: A solution of 30 g (0.254 mol) of 1,6-hexane-diol (Aldrich) in 110 ml of 48% HBr was placed in a continuous liquid-liquid extractor and was heated to 60° C. by means of a water bath. The mixture was then extracted with benzene until the level of aqueous phase
remained unchanged. The benzene was cooled, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The resultant oil was heated in vacuo until no benzene odor could be detected and finally vacuum distilled at 88°/1.4 mm (lit 105-106°/5mm) to yield 35.9 g (78.0%) of product; IR (neat) 3340 cm⁻¹ (OH).

Sadtler spectrum: nmr: 23873
UNH spectra: ir: 22818

nmr: 5673

8-Bromooctan-1-ol: A solution of 30 g (0.206 mol) of 1,8-octanediol (Aldrich) in 100 ml of 48% HBr was placed in a continuous liquid-liquid extractor and was heated to 60° C. by means of a water bath. The mixture was then extracted with benzene until the level of the aqueous layer remained unchanged. The benzene solution was cooled, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The resultant oil was heated in vacuo until the benzene odor could no longer be detected and finally vacuum distilled at 108°/1.1 mm to yield 31.2 (72.5%) of product; IR (neat) 3330 (OH) cm⁻¹; nmr (CCl₄) 4.40 (s, 1, OH), 3.25 (m, 4, Br-CH₂- and -CH₂-OH), 1.80 (m, 2, -CH₂-CH₂-OH), 1.32 (m, 10, methylene envelope). Although this is a known compound, no literature boiling point could be found. In a separate experiment, Mr. Guy Tetreau observed a boiling point of 119°/1.9 mm. No Sadtler spectra are available.

UNH spectra: ir: 22817

nmr: 5674

9-Bromononan-1-ol: A solution of 25 g (0.156 mol) of 1,9-nonanediol (Aldrich) in 100 ml of 48% HBr placed in a continuous liquid-liquid extractor and heated to 60° C. by means of a water bath. The mixture, once heated, was extracted with benzene until the level of the aqueous
layer remained unchanged. The benzene layer was cooled, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The resultant oil was heated in vacuo until the benzene odor was no longer detected and finally vacuum distilled at 109°/0.1 mm (lit 97-100°/.06 mm) to yield 14.3 g (41%) of product. Care must be taken not to allow the material to solidify in the condenser during the vacuum distillation. This soon solidifies to a crystalline mass melting at 30° C (lit 31.5-33° C.); ir (neat) 3330 cm⁻¹ (OH); nmr (CCl₄) 4.44(s, 1, OH), 3.25 (m, 4, Br-CH₂- and -CH₂-OH), 1.82 (m, 2, -CH₂-CH₂OH), 1.33 (m, 12, methylene envelope). No Sadtler spectra are published.

UNH spectra: ir: 22816

nmr: 5675

10-Bromodecan-1-ol: Thirty g (0.172 mol) of 1,10-decanediol (Aldrich) was dissolved in 100 ml of 48% HBr. This required slight heating. The solution was placed in a continuous liquid-liquid extractor, heated to 60° C. by means of a water bath, and was extracted with benzene. Three layers developed in the extractor. The bottom layer was aqueous; the middle layer, which was dark brown, was presumably a mixture of the bromohydrin and diol, and the top, colorless layer was benzene. After 24 hours the middle layer had disappeared. At this point, the benzene solution was cooled, whereupon a solid crystallized from solution. This was collected and found to be the diol (9.1 g). The benzene was then dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to yield an oil which was heated in vacuo until the benzene odor could no longer be detected. The oil was vacuum distilled at 140°/2.1 mm (lit 166-169°/10 mm) to yield 23.8 g (79.8%) of product, based on 20.9 g of diol; ir (neat) 3330 cm⁻¹ (OH); nmr (CCl₄) 4.00 (s, 1, OH), 3.32 (m, 4, Br-CH₂- and -CH₂-OH), 1.80 (m, 2, -CH₂-CH₂OH), 1.30 (m, 14, methylene envelope)
No Sadtlter spectra were available.

UNH spectra: ir: 22815

nmr: 5672

II. Benzaldehyde Derivatives

General Procedure for Phenolic Alkylation. To a solution of 6.1 g (0.05 mol) of salicylaldehyde or m-hydroxybenzaldehyde in 300 ml of acetonitrile was added 0.055 mol of the appropriate bromohydrin and 7 g of anhydrous potassium carbonate. A magnetic stirring bar was placed in the flask and the mixture was heated to reflux with stirring. A yellow color rapidly developed which eventually faded as the phenol was depleted. When tlc indicated the absence of starting phenol, in usually about two days, the mixture was allowed to cool and was filtered. The solid was washed with additional acetonitrile and the combined acetonitrile fractions were evaporated under reduced pressure to yield crude product.

General Procedure for Purification by Bisulfite Addition Compounds. This is the procedure of Vogel,85 which was employed by Blackadder and Hinschelwood to obtain bisulfite addition compounds of several o-alkoxybenzaldehydes.86 To a solution of 25 g of sodium bisulfite in 40 ml of water was added 35 ml of absolute ethanol. The mixture was stirred until some solid precipitate formed. Enough water to dissolve this precipitate (about 25 ml) was added. At this point 0.15 mol of the crude alkoxybenzaldehyde was added with stirring. After an hour the solid bisulfite addition compound was collected by suction filtration, washed with absolute ethanol and then washed with anhydrous ether. The aldehyde was regenerated by dissolving the solid in 50 ml of 10% aqueous sodium hydroxide. The resulting solution was extracted with ether. The ether was dried over anhydrous
sodium sulfate, filtered, and evaporated under reduced pressure to yield the aldehyde.

2-(2-Hydroxyethoxy)-benzaldehyde: The General Procedure could not be used for this compound. This is the method of Baldwin. To 40 g (1 mol) of sodium hydroxide in 1000 ml water is added 122 g (1 mol) of salicylaldehyde dropwise with stirring. When the addition is complete, 80.5 g (1 mol) of 2-chloroethanol is added dropwise followed by heating the mixture to reflux for eight hours. The mixture is cooled in an ice bath and made strongly basic by the addition of 40 g of sodium hydroxide. The basic solution is extracted with four 500-ml portions of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to yield 58 g (35%) of a brown oil. The oil solidified to a brown waxy mass upon storage in the freezer.

The bisulfite addition procedure was used to purify 25 g of the crude product. All of the aldehyde dissolved in the saturated bisulfite solution with the evolution of heat. Storage in the refrigerator was required to precipitate the addition compound. Decomposition of one addition compound gave an oil which contained ethanol. Removal of the ethanol in vacuo left 14 g (52%) of a light yellow solid: mp 36-37°C (lit. 37°C); uv max (CH$_3$CN) 251 mu (e offscales), 315 mu (e 40,000); ir (neat) 1680 (C=O), 3400 (OH); nmr (CDCl$_3$) $^6$10.22 (s, 1, CHO), $^6$7.60(m, 1, aromatic), $^6$7.35 (m, 1, aromatic), $^6$6.85 (m, 2, aromatic), $^6$4.05, $^6$3.95 (m, 5, -OCH$_2$-CH$_2$-OH). UNH spectra: ir 22872, uv JED-3, nmr 5715 (CDCl$_3$), 5716 (CDCl$_3$ + HCl), 5718 (DMSO), 5719 (CH$_3$CN) and 5720 (acetone + NaI).

The semicarbazone of 2-(2-Hydroxyethoxy)-benzaldehyde: This was prepared by the method of Shriner and Fuson. One gram of the crude alde-
hyde was dissolved in 10 ml of ethanol. Water was added dropwise until the solution turned cloudy. To this solution 1 g of semicarbazide hydrochloride and 1.5 g of sodium acetate were added and dissolved. The solution was heated on a steam bath for 15 minutes, followed by slow cooling to room temperature and finally cooling via an ice bath. The solid which precipitated was recrystallized from 50% aqueous ethanol to yield 0.8 g (57%) of product: mp 169-170°C. A mixed melting point of this compound with an analytical sample previously prepared showed no depression.

2-(3-Hydroxypropyloxy)-benzaldehyde: The General Procedure for phenolic alkylations in acetonitrile was followed using 6.1 g (0.05 mol) of salicylaldehyde and 7.65 g (0.055 mol) of 3-bromopropan-1-ol. The theoretical yield based on 0.05 mol of product and 0.005 mol of residual bromohydrin was 9.6 g and 8.8 g of an oil was obtained: ir (neat) 1685 (C=O) 1740 (impurity), 3400 cm⁻¹ (OH); nmr (CDCl₃) δ10.55 (s, impurity), δ10.5 (s, CHO), δ7.00-7.80 (m, aromatic protons), δ3.40-4.20 (m, -OCH₂-CH₂OH- plus impurities), δ2.00 (m, CH₂-CH₂-OH); UNH spectra ir 22306, nmr 5733. Attempted purification via the bisulfite addition compound failed because no precipitate formed, even after being stored at 0°C overnight. An attempted distillation of the crude oil resulted in the formation of a hard, transparent glass. A semicarbazone was obtained from the crude oil by the method of Shriner and Fuson which gave no melting point depression with an analytical sample previously prepared, mp 146-147°C.

2-(4-Hydroxybutyloxy)-benzaldehyde: The General Procedure could not be used. The method of Baldwin which was used to prepare 2-(2-hydroxyethyloxy)-benzaldehyde was employed. To 40 g (1 mol) of sodium hydroxide in 1000 ml of water, was added 122 g (1 mol) of salicylaldehyde dropwise with stirring. The mixture was heated to reflux for eight hours. The mixture was cooled in an ice bath and made strongly basic by the addition of
40 g (1 mol) of sodium hydroxide. The basic solution was extracted with four 500 ml-portions of chloroform. The combined chloroform fractions were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to yield 31 g (16%) of a yellow oil. High-pressure liquid chromatography was performed on a 2 g sample. The fraction with a retention volume of 4445 ml (1:1 (V/V) ethyl acetate-hexane) was collected. Evaporation of solvent yielded 0.8 g of a yellow oil: ir (neat) 1680 (C=O), 3400 cm\(^{-1}\) (OH); nmr (CDCl\(_3\)) \(\delta\) 10.64 (s, 0.67, CHO), \(\delta\) 7.00-8.00 (m, 4, aromatic protons), \(\delta\) 4.10 (m, 4, \(-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}–\)), \(\delta\) 3.60 (m, impurity), \(\delta\) 1.80 (m, \(-\text{CH} \text{CH} – \text{ plus impurity}\); UNH spectra: ir 22241, 22317; nmr 5741.

**Anal.** Calcd for \(\text{C}_{11}\text{H}_{14}\text{O}_3\): C, 65.92; H, 7.74. Found: C, 68.51; H, 7.98.

**2-(4-Acetoxybutyloxy)-benzaldehyde:** The General Procedure was followed using 6.1 g (0.05 mol) of salicylaldehyde, 10.7 g (0.055 mol) of 4-bromobutyl acetate, 300 ml of acetonitrile, and 7 g of potassium carbonate. The theoretical yield based on 0.05 mol of product and 0.005 mol of residual 4-bromobutyl acetate was 12.2 g and 11.7 g of product was obtained as an oil: ir (neat) 1680 (C=O), 1720 (ester C=O), 3400 cm\(^{-1}\) (impurity); nmr (CDCl\(_3\)) \(\delta\) 10.45 (bs CHO), \(\delta\) 10.30 (aldehyde impurity), \(\delta\) 6.90-7.80 (m, aromatic protons), \(\delta\) 3.50-4.40 (m, \(-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}–\)), \(\delta\) 2.05 (s, CO\(_2\text{CH}_3\)), \(\delta\) 1.50-2.30 (m, \(-\text{CH}_2\text{CH}_2\text{–}\) in product and impurity). The impurity was believed to be the corresponding alcohol. A spot on tlc at \(R_f = 0.2\) (1:3 (V/V) ethyl acetate-hexane) corresponded to the major spot from the previously prepared alcohol. The other major spot (\(R_f = 0.75\)) was believed to be the ester. Saponification of 1 g of the crude ester resulted in obtaining 0.03 g of an oil having no spot at \(R_f = 0.75\).

**2-(5-Acetoxypentyloxy)-benzaldehyde:** The General Procedure was followed using 6.1 g (0.05 mol) of salicylaldehyde, 11.5 g (0.055 mol)
of 5-bromopentyl acetate, 300 ml of acetonitrile and 7 g of potassium carbonate. The theoretical yield based on .05 mol of product and .005 mol of residual 5-bromopentyl acetate was 13.5 g and 14.9 g of crude product was obtained as an oil: ir (neat) 1680 (C=O), 1725 cm\(^{-1}\) (ester C=O); nmr (CDCl\(_3\)) \(\delta10.20\) (s, 1, CHO), \(\delta6.60-7.60\) (m, 4, aromatic protons), \(\delta3.90\) (t, 4, \(-O-CH_2CH_2CH_2CH_2O-\)), \(\delta1.88\) (s, 3, \(\_CH_3\)), \(\delta1.40-2.00\) (m, 6, \(-CH_2CH_2CH_2-\)). UNH spectra: ir 22875; nmr 5676.

**2-(5-Hydroxypentyl oxy)-benzaldehyde:** Five g (0.02 mol) of 2-(5-acetoxypentyl oxy)-benzaldehyde was added to 50 ml of 10% aqueous sodium hydroxide with stirring. It did not dissolve. The mixture was heated on a steam bath for 30 minutes and allowed to cool to room temperature with stirring overnight. It was then extracted with three 100-ml portions of chloroform. The combined chloroform fraction was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to yield 2.9 g (69%) of a yellow oil. The absence of a tlc spot at \(R_f = 0.70\) indicated that the ester was completely hydrolyzed. High-pressure liquid chromatography on 2 g of crude oil yielded .8 gram of oil with a retention volume at 3640 ml (1:1 (V/V) ethyl acetate-hexane): ir (neat) 1680 (C=O), 3400 cm\(^{-1}\) (OH); nmr (CDCl\(_3\)) \(\delta10.65\) (s, 0.59, CHO), \(\delta6.9-7.9\) (m, 4, aromatic protons), \(\delta5.84\) (s, 0.15,?), \(\delta4.10\) (m, 2, \(-OCH_2-\)), \(\delta3.60\) (m, 2, \(-O-CH_2-\)), \(\delta1.0-62.0\) (m, 6, \(-CH_2CH_2CH_2-\)); UNH spectra: ir 22880; nmr 5736.

**Anal.** Calcd for C\(_{12}\)H\(_{16}\)O\(_2\): C, 69.21; H, 7.74 Found: C,70.13; H,8.16.

**2-(6-Hydroxyhexyl oxy)-benzaldehyde:** The General Procedure was followed using 6.1 g (0.09 mol) salicylaldehyde, 12.2 g (0.055 mol) of 6-bromohexan-1-ol, 300 ml of acetonitrile and 7 g of potassium carbonate. The theoretical yield based on .05 mol of product plus .005 mol of residual 6-bromohexan-1-ol is 12.2 g and 11.0 g of crude product was obtained as an oil. High-pressure liquid chromatography was performed on 2 g of the crude
product. The fraction with a retention volume of 2879 ml (1:1 (V/V) ethyl acetate-hexane) was collected. After evaporation of solvent at reduced pressure, .9 g of light yellow oil was obtained: ir (neat) 1680 (C=O), 3400 cm\(^{-1}\) (OH); uv max (cyclohexane) 313 \(\mu_{\text{m}}\) (\(\varepsilon 2,480\)), 255 \(\mu_{\text{m}}\) (shoulder), 249 \(\mu_{\text{m}}\) (\(\varepsilon 3,630\)); nmr (CDCl\(_3\)) 610.75 (s, 0.62, CHO), 67.0-8.0 (m, 4, aromatic protons), 65.85 (s, .23, ?), 64.10 (m, 2, OCH\(_2\)), 63.69 (m, 2, OCH\(_2\)), 61.2-2.0 (m, 8, \(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\)). UNH Spectra: ir 22871; uv JED-5, nmr (CDCl\(_3\)) 5742, (CDCl\(_3\) + HCl) 5743.


2-(8-Hydroxyoctyloxy)-benzaldehyde: The General Procedure was followed using 6.1 g (0.05 mol) of salicylaldehyde, 12.0 g (0.055 mol) of 8-bromoOctan-1-ol, 300 ml of acetonitrile and 7 g of potassium carbonate. The theoretical yield based on 0.05 mol of product plus 0.005 mol of residual 8-bromooctan-1-ol was 13.6 g and 13.1 of a viscous oil was obtained. High-pressure liquid chromatography was performed on 2 g of crude oil and the fraction with a retention volume of 2205 ml (1:1 (V/V) ethyl acetate-hexane) was collected. After evaporation of the solvent, .8 g of yellow oil was obtained: ir (neat) 1680 (C=O), 3400 cm\(^{-1}\) (OH); uv max (cyclohexane) 313 \(\mu_{\text{m}}\) (\(\varepsilon 8,240\)), 253 \(\mu_{\text{m}}\) (shoulder), 249 \(\mu_{\text{m}}\) (\(\varepsilon 17,700\)); nmr (CDCl\(_3\)) 610.29 (s, 0.8, CHO), 66.70-7.60 (m, 4, aromatic protons), 63.90 (t, 2, O-CH\(_2\)), 63.50 (m, 3, OH + -OCH\(_2\)), 61.0-1.9 (m, 12, methylene envelope). UNH Spectra: ir 22862; uv JED-4, nmr (CDCl\(_3\)) 5726, (CDCl\(_3\) + HCl) 5727.

Anal. Calcd for C\(_{15}\)H\(_{22}\)O\(_3\): C, 71.97; H, 8.86. Found: C, 71.88; H, 8.92.

2-(9-Hydroxynonyloxy)-benzaldehyde: The General Procedure was followed using 6.1 g (0.05 mol) of salicylaldehyde, 12.3 g (0.055 mol) of 9-bromononan-1-ol, 300 ml of acetonitrile and 7 g of potassium carbonate.
The theoretical yield based on 0.05 mol of product plus 0.005 mol of residual 9-bromononan-1-ol was 14.3 g and 13.7 g of a viscous oil was obtained. High-pressure liquid chromatography was performed on 2 g of crude oil and the fraction with the retention volume of 2345 ml (1:1 (V/V) ethyl acetate-hexane) was collected. After evaporation of solvent under reduced pressure, 0.9 g of a yellow oil was obtained: \( \text{ir (neat) } 1680 \text{ (C=O), } 3400 \text{ cm}^{-1} \text{ (OH); uv max (cyclohexane) } 312 \text{ m}\mu (\epsilon 2,840), 254 \text{ m}\mu (\text{shoulder), } 248 \text{ m}\mu (\epsilon 5,850); \text{nmr (CDCl}_3) 610.40 (s, 0.46, CHO), 66.80-7.80 (m, 4, aromatic protons), 64.00 (t, 2, -OCH}_2-, 63.60 (t, 2, OCH}_2), 62.90 (bs, 1, OH), 1.00-1.80 (m, 14, methylene envelope). UNH Spectra: \text{ir } 22860, \text{uv JED-6, nmr (CDCl}_3) 5732, (CDCl}_3 + \text{HCl) } 5733. \)

**Anal.** Calcd for C_{16}H_{24}O_3: C, 72.69; H, 9.15. Found: C, 72.52; H, 9.27.

2-(10-Hydroxydecyloxy)-benzaldehyde: The General Procedure was followed using 6.1 g (0.05 mol) of salicylaldehyde, 13.1 g (0.055 mol) of 10-bromodecan-1-ol, 300 ml of acetonitrile and 7 g of potassium carbonate. The theoretical yield on 0.05 mol of product and 0.005 mol of 10-bromodecan-1-ol was 15.1 g and 14.5 g of viscous oil was obtained. High-pressure liquid chromatography was performed on 2 g of the crude product and the fraction with a retention volume of 1960 ml (1:1 (V/V) ethyl acetate-hexane) was collected. After evaporation of solvent under reduced pressure, 0.7 g of a light yellow oil was obtained: \( \text{ir (neat) } 1680 \text{ (C=O), } 3400 \text{ cm}^{-1} \text{ (OH); uv max (cyclohexane) } 313 \text{ m}\mu (\epsilon 1420), 255 \text{ m}\mu (\text{shoulder), } 249 \text{ m}\mu (\epsilon 2920), \text{nmr (CDCl}_3) 610.20 (s, 0.46, CHO), 66.6-7.6 (m, 4, aromatic protons), 65.6 (s, 0.15, ?), 63.90 (t, 2, OCH}_2), 63.50 (t, 2, OCH}_2), 63.2 (s, 1, OH), 61.10-1.90 (m, 16, methylene envelope). UNH Spectra: \text{ir } 22858, \text{uv JED-7, nmr (CDCl}_3) 5722, (CDCl}_3 + \text{HCl) } 5723. \)

**Anal.** Calcd for C_{17}H_{26}O_3: C, 73.35; H, 9.41. Found: C, 73.29;
3-(6-Hydroxyhexyloxy)-benzaldehyde: The General Procedure was followed using 6.1 g (0.05 mol) of 3-hydroxybenzaldehyde, 12.2 g (0.055 mol) of 6-bromohexan-1-ol, 300 ml of acetonitrile and 7 g of potassium carbonate. The theoretical yield based on 0.05 mol of product and 0.005 mol of 6-bromohexan-1-ol was 12 g and 11 g of a viscous oil was obtained. High-pressure liquid chromatography was performed on 2 g of crude product and the fraction with a retention volume of 2765 ml (1:1 (V/V) ethyl acetate-hexane) was collected. After evaporation of solvent under reduced pressure, 0.7 g of a yellow oil was obtained: \( \text{ir (neat) 1690 (C=O), 3400 cm}^{-1} (\text{OH}); \text{uv max (cyclohexane) 313 \text{mu} (\epsilon 6150), 253 \text{mu} (\text{shoulder}), 249 \text{mu} (\epsilon 17,700)}; \text{nmr (CDCl}_3) 6.10.10 (s, 0.7, \text{CHO}), 6.7.0-7.6 (m, 4, aromatic protons), 6.5.5 (s, 0.2, ?), 6.4.05 (t, 2, OCH}_2, 6.3.6 (m, 3, \text{OH + OCH}_2, 6.1.1-1.9 (m, 8, methylene envelope), \text{UNH spectra: ir 22878; uv JED-8; nmr (CDCl}_3) 5734, (CDCl}_3 + \text{HCl) 5735.} \)

\text{Anal. Calcd for C}_{15}H_{18}O_3: \ C, 70.24; \ H, 8.16. \text{ Found: C, 70.00; H, 8.23.} \)

3-(8-Hydroxyoctyloxy)-benzaldehyde: The General Procedure was followed using 6.1 g (0.05 mol) of 3-hydroxybenzaldehyde, 11.5 g (0.055 mol) of 8-bromooctan-1-ol, 300 ml of acetonitrile and 7 g of potassium carbonate. The theoretical yield based on 0.05 mol of product plus 0.005 mol of 8-bromooctan-1-ol was 13.6 g and 12.8 g of product as an oil was obtained. High-pressure liquid chromatography was performed on 2 g of the crude product and the fraction with a retention volume of 2310 ml (1:1 (V/V) ethyl acetate-hexane) was collected. Upon evaporation of the solvent under reduced pressure, 0.8 g of a thick yellow oil was obtained: \( \text{ir (neat) 1690 (C=O), 3400 cm}^{-1} (\text{OH}); \text{uv max (cyclohexane) 309 \text{mu} (\epsilon 7000), 253 \text{mu} (\text{shoulder}), 248 \text{mu} (\epsilon 20000); nmr (CDCl}_3) 6.9.64 (s, 0.91, \text{CHO}, 6.6.80-7.20 (m, 4,} \)
aromatic protons), 63.80 (t, 2, -OCH<sub>2</sub>-), 63.44 (t, 2, -OCH<sub>2</sub>-), 62.50 (s, 1, OH), 61.20-1.80 (m, 12, methylene envelope), UNH spectra: ir 22861; uv JED-9; nmr (CDCl<sub>3</sub>) 5730, (CDCl<sub>3</sub> + HCl) 5731.

**Anal.** Calcd for C<sub>15</sub>H<sub>22</sub>0<sub>3</sub>: C, 71.97; H, 8.86. Found: C, 71.69, H, 8.98.

3-(9-Hydroxynonyloxy)-benzaldehyde: The General Procedure was followed using 6.1 g (0.05 mol) of 3-hydroxybenzaldehyde, 12.3 g (0.055 mol) of 9-bromononan-1-ol, 300 ml of acetonitrile and 7 g of potassium carbonate. The theoretical yield based on 0.05 mol of product and 0.005 mol of residual 9-bromononan-1-ol was 14.3 g, and 13.9 g of product was obtained as an oil. High-pressure liquid chromatography was performed on 2 g of the crude material, and the fraction with a retention volume of 6000 ml (1:3 (V/V) ethyl acetate-hexane) was collected. After evaporation of the solvent under reduced pressure, 0.9 g of a yellow oil was obtained: ir (neat) 1690 (C=O), 3400 cm<sup>-1</sup> (OH); uv max (cyclohexane) 309 µm (ε 8220), 253 µm (shoulder), 248 µm (ε 25,400); nmr (CDCl<sub>3</sub>) δ9.60 (s, 0.6, CHO), δ6.90-7.20 (m, 4, aromatic protons), δ5.24 (s, 0.24, ?), δ3.84 (t, 2, -OCH<sub>2</sub>-), δ3.44 (m, 3, OCH<sub>2</sub> + impurity), δ2.64 (s, 1, OH), δ1.00-1.80 (m, 14, methylene envelope), δ0.84 (m, 2, impurity), UNH spectra: ir 22842; uv JED-10; nmr (CDCl<sub>3</sub>) 5728, (CDCl<sub>3</sub> + HCl) 5729.

**Anal.** Calcd for C<sub>16</sub>H<sub>24</sub>0<sub>3</sub>: C, 72.69; H, 9.15. Found: C, 72.93; H, 9.13.

3-(10-Hydroxydecyloxy)-benzaldehyde: The General Procedure was followed using 6.1 g (0.05 mol) of 3-hydroxybenzaldehyde, 13.0 g (0.055 mol) of 10-bromodecan-1-ol, 300 ml of acetonitrile and 7 g of potassium carbonate. The theoretical yield based on 0.05 mol of product plus 0.005 mol of 10-bromodecan-1-ol was 15.1 g and 14.4 g of a viscous oil was obtained. High-pressure liquid chromatography was performed on 2 g of the crude material
and the fraction with a retention volume of 1995 ml (1:1 (V/V) ethyl acetate-hexane) was collected. Upon evaporation of the solvent under reduced pressure, .8 g of yellow oil was obtained: ir (neat) 1690 (C=O), 3400 cm⁻¹ (OH); uv max (cyclohexane) 309 mu (ε 2,720), 253 mu (shoulder), 248 mu (ε 77,000); nmr (CDCl₃) δ9.64 (s, 0.72, CHO), δ6.90-7.30 (m, 4, aromatic protons), δ3.84 (t, 2, -OCH₂), δ3.50 (t, 2, -OCH₂-), δ3.20 (s, 1, OH), δ1.10-1.80 (m, 16, methylene envelope), UNH spectra: ir 22859; uv JED-2; nmr (CDCl₃) 5724, (CDCl₃ + HCl) 5725.


III. Pyridine Derivatives

Picolinaldehyde Dimethyl Acetal: A solution of 5 g (.047 mol) of picolinaldehyde (Aldrich) in 250 ml of anhydrous methanol was brought to reflux. Dry hydrogen chloride gas was bubbled into the refluxing solution for one hour. The mixture was refluxed for an additional hour, cooled to 0°C and neutralized by the addition of saturated aqueous potassium carbonate. The mixture was extracted with three 200-ml-portions of chloroform. The combined chloroform layers were dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure. The resultant oil was vacuum distilled at 80°C/9 mm (lit 88-89°C/12 mm) to yield 1.4 g (20%) of a mobile liquid with an odor reminiscent of fresh cucumber: nmr (CDCl₃) δ7.00-8.35 (m, 4, aromatic protons), δ5.20 (s, 1, (CH₃O)₂CH-), δ3.24 (s, 6, CH₃), UNH nmr 2539.

2-(1,3-Dioxolan-2-yl)-pyridine: A mixture of 5 g (0.047 mol) of picolinaldehyde, 4.3 g (0.069 mol) of ethylene glycol and 150 ml of benzene was brought to reflux in a flask fitted with a Dean-Stark trap. Dry,
gaseous hydrogen chloride was bubbled into the refluxing mixture for one hour. Water began to be azeotropically distilled into the Dean-Stark trap. The mixture was allowed to cool when 0.9 ml of water was collected. The mixture consisted of a yellow benzene layer on the top and a red ethylene glycol layer on the bottom. The entire mixture was washed with three 150-ml portions of ice-cold, saturated aqueous potassium carbonate solution. The benzene layer was separated, dried over anhydrous potassium carbonate, filtered, and evaporated under reduced pressure. The resultant oil was vacuum distilled at 130° C/10 mm (lit 122° C/4 mm) to yield 4.3 g (62%) of a colorless, odorless oil: nmr (CDCl₃) no aldehyde band; δ7.00-8.40 (m, 4, aromatic protons), δ5.80 (s, 1, acetal methinyl proton), δ3.90 (m, 4, CH₂-CH₂), UNH nmr 3165.

The Cyclic Tautomer of N-(2-Hydroxyethyl)-2-Formylpyridinium Bromide: A mixture of 1.07 g (0.01 mol) of picolinaldehyde and 1.25 g (0.01 mol) of 2-bromoethanol was allowed to stand in a beaker in a desiccator flushed with nitrogen. Within four days, the solution solidified to a yellow, waxy solid. The material was pulverized under anhydrous ethyl ether to leach out unchanged starting material. Recrystallization from acetonitrile resulted in obtaining 1.5 g (65%) of nearly colorless crystals: mp 138-139° C; ir (KBr) 3100 cm⁻¹ (OH); nmr (DMSO) δ8.30-9.40 (m, 5, OH plus aromatic protons), δ6.40 (s, 1, hemiacetal methinyl proton), δ4.90 (m, 2, N-CH₂), δ4.50 (m, 2, O-CH₂), UNH spectra: ir 22877; nmr 5739.

Anal. Calcd for C₈H₁₀NO₂Br: C, 41.40; H, 4.34; N, 6.07. Found: C, 41.94; H, 4.54; N, 6.55. (C, 41.59; H, 4.56; N, 5.87; Br, 34.63)*

The Cyclic Tautomer of N-(3-Hydroxypropyl)-2-Formylpyridinium Bromide: A mixture of 1.07 g (0.01 mol) of picolinaldehyde and 1.39 g (0.01 mol) of 3-bromopropan-1-ol was allowed to stand in a beaker in a

*Analysis by Galbraith Laboratories, Inc.
desiccator until, after two weeks, the mixture had darkened. The addition of acetone caused the immediate precipitation of an orange solid. The acetone was decanted and the solid was washed repeatedly with anhydrous ethyl ether until the odor of picolinaldehyde was gone. Recrystallization from acetonitrile was accompanied by extensive loss of material, but provided 0.75 g (30%) of product: mp 161-163° C; ir (KBr) 3100 cm\(^{-1}\) (OH); nmr (DMSO) \(\delta 8.30-9.50\) (m, 4, aromatic protons), \(\delta 6.50\) (s, 1, hemiacetal methinyl), \(\delta 5.30\) (m, 2, N-CH\(_2\)), \(\delta 4.24\) (m, 2, O-CH\(_2\)), the remaining protons were obscured by the solvent signal (see Appendix), UNH spectra: ir 22879; nmr 5744.

**Anal.** Calcd for C\(_9\)H\(_{12}\)NO\(_2\)Br: C, 43.92; H, 4.91; N, 5.69. Found C, 43.83; H, 4.87; N, 5.89.

**The Reaction of Picolinaldehyde with 4-Chlorobutan-1-ol:** A mixture of 1.07 g (0.01 mol) of picolinaldehyde and 1.09 g (0.01 mol) of 4-chlorobutan-1-ol was allowed to stand in a beaker in a desiccator under nitrogen. After three weeks the mixture had darkened considerably. The addition of anhydrous ethyl ether caused the formation of a flocculent, bright orange powder. This was washed repeatedly with anhydrous ether until no picolinaldehyde odor could be detected. It was necessary to centrifuge the solid between washings to avoid mechanical loss. The solid could be stored under ether at 0° C without visible decomposition, but exposure to air for a few seconds caused the solid to become a dark, brown tar. No spectra were obtained from this material.
Results and Discussion
Benzaldehyde Derivatives

The purpose of this investigation was to synthesize compounds which might exhibit ring-chain tautomerism where the ring size is somewhat larger than six or seven, and, if possible, to document evidence for the existence and observation of this phenomenon. Previous studies of the position of the ring-chain tautomeric equilibrium as a function of ring size have focused on electrophilic-exo-trig systems. Since previous workers in this laboratory have had no success in detecting ring tautomer for para-disubstituted benzenes which were electrophilic-exo-trig, a study of ortho and meta compounds of this type was undertaken.

The general scheme which was followed involved joining two bifunctional molecules to create a new molecule whose remaining terminal functionalities could interact to form a ring. The linking method chosen was alkylation, and the reacting termini were a primary alcohol and a formyl group. Thus, a major portion of the research was directed toward synthesizing precursors to the compounds of interest and toward alkylating substrates with these precursors. The synthetic aspects of this work will be discussed first.

The necessary bromohydrins leading to potential macrocyclic ring tautomers are either not commercially available or are prohibitively expensive. 2-Bromoethanol and 3-bromopropanol could be purchased, but the ring sizes (seven and eight) resulting from use of these alkylating agents are smaller than macrocyclic. The lower homologs serve as model compounds for studying the potential macrocycles.

4-Chlorobutanol can be obtained synthetically, but it is a poor alkylating agent in some applications. By comparison, alkyl bromides are
generally better than alkyl chlorides, and, in addition, 4-bromobutyl acetate can be obtained from the reaction of tetrahydrofuran and acetyl bromide, and this compound does not present the problems encountered by the chlorohydrin. By an analogous reaction, 5-bromopentyl acetate can be obtained, and it is also a satisfactory alkylating agent. Once these esters have been used in an alkylation, the acetate protecting group is easily removed by treatment with warm 10% aqueous sodium hydroxide.

The bromohydrins with six or more carbons in the chain can be obtained by the reaction of the corresponding diol with 48% HBr under continuous extraction with hydrocarbon solvents. Aliphatic solvents such as hexane tend to extract the bromohydrin too slowly, allowing a large portion of the bromohydrin to react further to yield the dibromide, an undesirable side-product. Use of benzene as the extracting solvent eliminates this problem. Benzene extracts both the diol and the bromohydrin, and the diol usually crystallizes upon cooling. Thus, dibromide is not formed, and starting material is recovered. Any diol which does not crystallize is easily removed by vacuum distillation. A notable exception is 9-bromononan-1-ol, which, in contrast to its neighboring higher and lower homologs, is a low-melting, waxy solid. This problem led to extensive mechanical loss during its preparation which severely lowered the isolated yield.

The alkylation of the phenolic oxygen of salicylaldehyde and meta-hydroxybenzaldehyde proceeds smoothly in acetonitrile. This solvent has the advantage of being relatively low-boiling compared to other polar, aprotic solvents such as dimethylformamide and dimethyl sulfoxide. Previous workers employed dimethylformamide as the solvent in the alkylation of salicylic acid, salicylate esters, thiosalicylic acid and thiosalicylate esters, and salicylaldehyde. The work-up procedures employed were either air evaporation of the dimethylformamide over a period of two weeks
or washing with water. Initial experiments using this solvent with water extraction as the work-up afforded products containing substantial amounts of the solvent as a contaminant. Since the 2-(ω-hydroxyalkoxy)-benzaldehydes cannot be distilled, this presented problems. Dimethyl sulfoxide was tried, and it was found that this solvent could be effectively washed out with water; however, extensive decomposition of the starting material and/or products was encountered. This was presumably oxidation, inasmuch as dimethyl sulfide was also a major contaminant. Acetonitrile was tried next with success. This solvent can be removed under reduced pressure easily.

It was also discovered that, unless the alkylating agent in this reaction is kept in slight excess, the mixtures darken considerably. If the alkylating agent decomposes in base, as is the case with 4-chlorobutanol, the reaction mixture will darken even if the alkylating agent is in excess, and the yield will be poor. The product will also contain a considerable amount of starting phenol. Of those alkylating agents used in this study, 2-bromoethanol and 4-chlorobutanol proved to be unsuitable for the reaction in acetonitrile for these reasons. In addition, it has been found that primary tosylates do not seem to work well as alkylating agents under these conditions. Furthermore, substituted benzoic acids can be esterified by primary alkyl bromides in acetonitrile and potassium carbonate. The alkylation of the phenolic oxygen of salicylate esters, the sulfur of thiosalicylate esters and the nitrogen of anthranilate esters has been accomplished with primary alkyl bromides in dimethyl sulfoxide and potassium carbonate. These reactions have not been tried in acetonitrile.
A major difficulty was encountered with the purification of the \( \omega \)-hydroxyalkoxybenzaldehydes. With the exception of \( \omega -(2\text{-hydroxyethoxy}) \)-benzaldehyde, all of the crude compounds were obtained as viscous oils, after evaporation of acetonitrile under reduced pressure. It should be noted that the two esters were somewhat more mobile than the alcohols. An attempted vacuum distillation of \( \omega -(3\text{-hydroxypropyloxy}) \)-benzaldehyde resulted in the formation of a hard, transparent glass rather than a distillate. The bisulfite addition compound procedure worked for the one compound that was not an oil initially, \( \omega -(2\text{-hydroxyethoxy}) \)-benzaldehyde. For the next two higher homologs, no bisulfite addition compound precipitated even though some warming of the solution was noted. When the procedure was tried on \( \omega -(8\text{-hydroxyoctyloxy}) \)-benzaldehyde, a precipitate was formed. Despite repeated washing of this solid with ethanol and ethyl ether, however, the oil obtained upon decomposition of the addition compound with aqueous base displayed an identical array of spots on tlc plates as did the crude material.

Several small-scale attempts to form N-aryl imines with the aldehydes and some substituted anilines also yielded oils. It was hoped that crystalline anils could be obtained, recrystallized, and used in this study, but this route was abandoned. The ring and chain tautomers of such compounds are shown in Figure XLVI.

\[
\begin{align*}
\text{O(CH}_2\text{)}_n\text{OH} & \quad \text{O(CH}_2\text{)}_n\text{OH} \\
\text{CH} & \quad \text{CH} \\
\text{N} & \quad \text{N} \\
\text{X} & \quad \text{X} \\
\end{align*}
\]

\( X = \text{Br, OCH}_3, \text{OH, NO}_2, \text{COOH} \)

Figure XLVI
Finally, high-pressure liquid chromatography was employed as the method of obtaining pure samples. Even this met with only partial success. Initially, the solvent used was 1:3 (V/V) ethyl acetate-hexane and the whole gaussian peak corresponding to the major product was collected. The elemental analysis of samples thus obtained were, for the most part, unacceptable. Next, a 1:1 mixture of these solvents was tried and because of the appearance of a shoulder in the leading half of the gaussian, only the second half was collected. In this manner, most of the samples emerged as oils whose analyses were within 0.3\% in carbon and hydrogen.

Although infrared spectra were obtained for all the compounds examined, the usefulness of this technique in determining the amount of cyclic tautomer is very limited. If the carbonyl band is absent, then one can assume that the compound exists entirely as the cyclohemiacetal of polyhemiacetal. The ir spectrum of an equilibrium mixture of hydroxyaldehyde and cyclohemiacetal will contain both OH and carbonyl bands, and the relative amounts of each can only be approximated.

Specific bands have been identified as diagnostic for acetals and ketals. For both acetals and ketals four bands due to various combinations of C-O stretchings are seen, within the following ranges: 1038-1056 cm\(^{-1}\); 1063-1098 cm\(^{-1}\); 1124-1143 cm\(^{-1}\); and 1158-1190 cm\(^{-1}\).\(^{93}\) While these bands occur in the spectra of acetals and ketals, an additional band occurs at 1110 cm\(^{-1}\) in the spectra of acetals which does not appear in the spectra of ketals.\(^{93}\)

Bands in the general area of these diagnostic bands in the published Sadtler Spectra of three compounds structurally related to those prepared in this study are listed in Table IV.
### Table IV

| Diagnostic Bands for Acetals and Ketals & Selective Bands in Model Compounds |
|---------------------------------|-----------------|-----------------|-----------------|
| **Diagnostic Bands**            | **Compounds**   |
| for Acetals and Ketals          | I               | II              | III             |
| 1038-1056                       | 1040            | 1050            | 1045            |
| 1063-1098                       | -               | 1080            | 1080            |
| 1110 (Acetals)                  | -               | -               | 1110            |
| 1124-1143                       | -               | -               | -               |
| 1158-1190                       | 1160            | 1160            | 1160            |
|                                 | 1190            | 1180            |                 |

* Values in cm\(^{-1}\)

** I = o-Ethoxybenzaldehyde
II = 2-Phenoxyethanol
III = p-(2-Hydroxyethoxy)-benzaldehyde

In the case of o-ethoxybenzaldehyde it is impossible for there to be any hemiacetal in a pure sample. While there can be no cyclohemiacetal derived from p-(2-hydroxyethoxy)-benzaldehyde, there can be intermolecular hemiacetal formation, and this is most likely in the pure state. Both of the Sadtler Spectra were obtained on the pure materials. The bands at 1045 cm\(^{-1}\), 1080 cm\(^{-1}\), 1110 cm\(^{-1}\), and 1160 cm\(^{-1}\) in the spectrum of the latter compound are all in the diagnostic region for acetals. However, there is no band in the range between 1124-1143 cm\(^{-1}\) in the spectrum of this aldehyde. It may be the case that a band in this region is diagnostic for acetals and ketals but not for hemiacetals or hemiketals. The appearance of bands at 1040 cm\(^{-1}\), 1160 cm\(^{-1}\), and 1190 cm\(^{-1}\) in the spectrum of o-ethoxybenzaldehyde and bands at 1050 cm\(^{-1}\), 1080 cm\(^{-1}\), 1160 cm\(^{-1}\), and 1180 cm\(^{-1}\) in the spectrum of 2-phenoxyethanol casts doubt on the utility of these diagnostic bands as well. Taking these facts into account, it is still
difficult to assess the possibility of intermolecular interaction, however even though there is a band at 1110 cm\(^{-1}\), which is diagnostic for acetals and not ketals, in the spectrum of \(\text{p-}(2\text{-hydroxyethoxy})\text{-}\text{benzaldehyde}\). Furthermore, there is virtually no difference in the intensity or position of the C=O band in the spectra of these two compounds from that in the spectrum of \(\text{p-ethoxybenzaldehyde}\) (Sadtler ir 43089), nor any difference in the intensity, position or general shape of the OH stretching band in the ir spectrum of 2-phenoxyethanol from that of \(\text{p-}(2\text{-hydroxyethoxy})\text{-}\text{benzaldehyde}\).

Quantitative, high-dilution ir spectroscopy has been used to measure the amount of cyclohemiketal in equilibrium with \(\omega\)-hydroxy methyl ketones, but the technique required calibration of the C=O peak intensity relative to that in the corresponding ethyl ethers as standards.\(^{12}\)

Hullar and Failla reported that there is no C=O band in the ir spectrum of pure, solid 2-(2-hydroxyethoxy)-3,5-dichlorobenzaldehyde (measured as a KBr pellet), and this was explained by proposing the cyclohemiacetal structure shown in Figure XLVII.\(^{94}\) In contrast, there is a C=O band in the solution spectrum of the same compound (in tetrahydrofuran) at 1695 cm\(^{-1}\).\(^{94}\)

\[\text{Cl} \quad \text{OCH}_2\text{CH}_2\text{OH} \quad \text{Cl} \quad \text{CHO} \quad \text{Cl} \quad \text{O} \quad \text{Cl} \quad \text{OH}\]

Figure XLVII
The differences to be expected in the nmr spectra of the ring and chain forms center on the shift of the aldehydic proton of the chain form versus the shift of the hemiacetal methinyl proton of the ring form.

Cottier and Descote reported that they were able to obtain values for percent ring tautomer for the ω-hydroxyalkanals by integrating the aldehyde singlet and the hemiacetal methinyl singlet (see Table I), however, they failed to report the shifts of these peaks. The concentration of their solutions (in deuterated toluene) was likewise not reported. For this reason, the possibility of intermolecular hemiacetal formation could not be ruled out in the interpretation of their data.

By definition, all hemiacetals contain a chiral center, and, therefore in principle, all the pairs of methylene protons in the series of compounds shown in Figure XLVIII are diastereotropic. It might be expected, then, that some differences in the appearance of these signals could be observed in the spectrum. The closer a pair of methylene protons is to the chiral center, the better are the chances that non-equivalence of these protons will be observed. With this in mind, one might predict that the α-methylene, the one next to the ether oxygen of the hemiacetal function, would be the most likely candidate. The ω-methylene, attached to the phenolic ether oxygen, even though not directly bonded, is reasonably close and may also be measurably affected.

![Figure XLVIII](image)
The third signal to examine for differences in the two forms is that of the hydroxyl proton. Chapman and King have reported that in dimethyl sulfoxide, the exchange of hydroxy protons is slowed down to such an extent that coupling is observed between the hydroxyl proton and any protons on the carbon bound to that oxygen. Thus, the OH signal of a primary alcohol shows up as a triplet, that in a secondary alcohol as a doublet, and that in a tertiary alcohol as a singlet. In the open-chain tautomer the OH signal should show up as a triplet if the spectrum is measured in dimethyl sulfoxide, whereas, the same proton in the ring form should occur as a doublet. Furthermore, Chapman and King remark that the shift of hemiacetal hydroxyl protons lies farther downfield (δ 5.0-8.0) than that of normal aliphatic alcohols (δ4.0-5.0). A serious problem in using this solvent is that in highly polar solvents, open-chain form is usually predominant. Nevertheless, Hullar and Failla were able to observe both ring and chain tautomers in the nmr spectrum of 2-(2-hydroxyethoxy)-3,5-dichlorobenzaldehyde determined in dimethyl sulfoxide. At 60°C, they observed an aldehyde proton peak at δ10.57 and a hemiacetal methinyl proton peak at δ5.93. The ratio of ring to chain form was 1.0/0.4.

Ultraviolet absorption spectroscopy has the advantage over ir and nmr in that high dilution is required for obtaining good spectra. Furthermore, there is precedent in the literature for employing this technique to measure the extent of hemiacetal and acetal formation in similar systems.

The uv spectra of both ortho and meta-methoxybenzaldehyde have been reported by Deardon and Forbes in cyclohexane and in ethanol. Their results are summarized in Table V.
Table V

Ultraviolet Spectra of Methoxybenzaldehydes

In Cyclohexane and Ethanol

<table>
<thead>
<tr>
<th></th>
<th>B-band</th>
<th></th>
<th>C-band</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\lambda_{\text{max}}$</td>
<td>$\varepsilon_{\text{max}}$</td>
<td>$\lambda_{\text{max}}$</td>
</tr>
<tr>
<td><strong>ortho</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclohexane</td>
<td>246</td>
<td>10,500</td>
<td>306</td>
</tr>
<tr>
<td>ethanol</td>
<td>253</td>
<td>8,500</td>
<td>314</td>
</tr>
<tr>
<td><strong>meta</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclohexane</td>
<td>247</td>
<td>6,800</td>
<td>304</td>
</tr>
<tr>
<td>ethanol</td>
<td>251</td>
<td>6,500</td>
<td>313</td>
</tr>
</tbody>
</table>

Melchior has published the uv spectra of o-methoxybenzaldehyde in methanol and acidified (HCl) methanol. Crowell, Powell and Varsel extended this work to a great many more aldehydes, including m-methoxybenzaldehyde. These workers reported the wavelength maxima in millimicrons and the peak intensities as ratios relative to the strongest peak in the spectrum of the free aldehyde. Their results are summarized in Table VI.

Table VI

Ultraviolet spectra of methoxybenzaldehydes

in Methanol and acidified ($H_2SO_4$) Methanol

<table>
<thead>
<tr>
<th></th>
<th>Methanol $\lambda_{\text{max}}$ (ratio)</th>
<th>Acidified Methanol $\lambda_{\text{max}}$ (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ortho</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>319</td>
<td>(0.45)</td>
<td>280 (0.25)</td>
</tr>
<tr>
<td>253</td>
<td>(1.00)</td>
<td>273 (0.27)</td>
</tr>
<tr>
<td><strong>meta</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>312</td>
<td>(0.19)</td>
<td>288 (0.14)</td>
</tr>
<tr>
<td>253</td>
<td>(0.59)</td>
<td>275 (0.15)</td>
</tr>
<tr>
<td>223</td>
<td>(1.00)</td>
<td>220 (0.50)</td>
</tr>
</tbody>
</table>
These workers concluded that the spectra obtained in acidified methanol represent 100% hemiacetal, and they made the comment that the ortho and para alkoxy compounds should exhibit less tendency to form hemiacetal than the meta. This is in accord with the fact that for the methoxybenzaldehyde diethyl acetals, the para isomer is hydrolyzed much more rapidly than the meta isomer.

Hurd and Saunders employed uv spectroscopy to measure the ring-chain tautomeric equilibrium constants for the ω-hydroxyalkanals, as did Whiting and Edward with the ω-hydroxy methyl ketones. In both of these studies, the extinction coefficient of the corresponding aldehyde with an alkoxy instead of a hydroxy group was taken as the standard assumed to be 100% carbonyl compound. Whiting and Edward demonstrated that a mixed cyclic acetal had no uv bands in the region of interest. Thus, the intensity of the carbonyl band could be taken as proportional to the amount of open-chain tautomer.

In an effort to obtain evidence for or against ring-chain tautomerism in the compounds synthesized in this study, ir, nmr, and uv spectra were recorded. In the tables of spectral data below, the following codes are used for the new compounds. Those derived from salicylaldehyde are "S" compounds, and those derived from m-hydroxybenzaldehyde are "M" compounds; the numbers following these letters indicate the number of carbons in the bromohydrin used to alkylate the phenol. Thus, for example, the product of alkylation of salicylaldehyde with 2-bromoethanol is called S-2.

Infrared spectra of all liquid samples were obtained from neat films. The spectra of all the salicylaldehyde derivatives include an aromatic substitution band at 750 cm⁻¹, whereas the m-hydroxybenzaldehydes display an aromatic substitution pattern of two broad bands at 780 cm⁻¹ and 880 cm⁻¹.

A potassium bromide pellet of the solid o-(hydroxyethoxy)-benzaldehyde (S-2) could not be made because of its low melting point. Hullar
and Pailla reported no C=O band in the IR spectra of a KBr pellet of the higher-melting 3,5-dichloro derivative. The spectrum of the unsubstituted compound was obtained from a melt of the waxy solid. Compared with the other compounds tested, it has a C=O band of lower absorbance relative to the OH band. Table VII contains a list of the relative absorbance of the C=O band versus the OH bands for the S and M aldehydes.

Table VII

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative Absorbance (C=O/OH)</th>
<th>C, H Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-2</td>
<td>0.69</td>
<td>Not obtained</td>
</tr>
<tr>
<td>S-3</td>
<td>1.37</td>
<td>Not obtained</td>
</tr>
<tr>
<td>S-4</td>
<td>1.33</td>
<td>Not satisfactory</td>
</tr>
<tr>
<td>S-5</td>
<td>2.66</td>
<td>Not satisfactory</td>
</tr>
<tr>
<td>S-6</td>
<td>1.66</td>
<td>Not satisfactory</td>
</tr>
<tr>
<td>S-8</td>
<td>1.22</td>
<td>Within 0.3%</td>
</tr>
<tr>
<td>S-9</td>
<td>1.42</td>
<td>Within 0.3%</td>
</tr>
<tr>
<td>S-10</td>
<td>1.54</td>
<td>Within 0.3%</td>
</tr>
<tr>
<td>M-6</td>
<td>1.37</td>
<td>Within 0.3%</td>
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<tr>
<td>M-8</td>
<td>1.76</td>
<td>Within 0.3%</td>
</tr>
<tr>
<td>M-9</td>
<td>1.61</td>
<td>Within 0.3%</td>
</tr>
<tr>
<td>M-10</td>
<td>1.99</td>
<td>Within 0.3%</td>
</tr>
</tbody>
</table>

Because this is a qualitative technique, the only significant value is probably the low value for S-2. From these spectra, determined from the neat oils, intermolecular hemiacetal formation cannot be ruled out, however. The radically different value for S-2 may indicate the existence of some ring form in the pure, undiluted state. The unusually high value for S-5 may indicate that there is very little, if any, ring form for this compound, and therefore, at least some ring form for the others. The ring size of the cyclic tautomer of S-5 is ten. This is within the range of the relatively strained medium-sized rings (see Table I.)
The C=O band region, 1000-1250 cm\(^{-1}\), in the S series is nearly identical for all the compounds. The most consistent and striking features are the two bands at 1150 and 1170 cm\(^{-1}\). In view of the aforementioned ambiguities involved in the interpretation of bands in this region, it is felt that no conclusions can be drawn from them. In the M series, the consistent pattern in this region is a pair of bands at 1140 and 1160 cm\(^{-1}\).

The nmr spectrum of S-2 was determined in deuteriochloroform, acidified deuteriochloroform (dry HCl in CCL\(_4\)), dimethyl sulfoxide, acetonitrile and acetone saturated with NaI. Hullar and Failla reported that the equilibrium constant in dimethyl sulfoxide for the 3,5-dichloro derivative corresponds to 2.5 times more cyclic than acyclic form.\(^94\) The nmr spectrum of S-2 determined in dimethyl sulfoxide in this laboratory displayed no evidence of a methinyl proton; expected for the ring tautomer; and, furthermore, the OH band appeared as a triplet as predicted for the primary alcohol in the chain form.\(^95\) Only in deuteriochloroform containing a drop of acid did a small peak appear at about \(\delta 5.5\) in the spectrum of S-2. Small peaks in this region (between \(\delta 5.00 - \delta 6.00\)) occurred in some, but not all, of the spectra in the S and M series. In Table VIII are listed the ratios of the integration of the aldehyde proton to the aromatic protons (which should for chain tautomers be 0.25) and the ratio of the sum of aldehyde and presumed methinyl peaks to aromatic protons for the S and M aldehydes. S-3 is omitted from Table VIII because its aldehyde proton signal appeared as a multiplet, this being an indication of impurities. It should be noted that there is more than one C=O peak in the ir spectrum of S-3 as well.
### Table VIII

Ratios of Aldehyde to Aromatic Protons in the ω-Hydroxyalkoxybenzaldehyde NMR Spectra

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aldehyde/Aromatic</th>
<th>(Aldehyde + Extra Peak)/Aromatic</th>
</tr>
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<tbody>
<tr>
<td>S-2</td>
<td>0.24</td>
<td>-</td>
</tr>
<tr>
<td>S-4</td>
<td>0.16</td>
<td>-</td>
</tr>
<tr>
<td>S-5</td>
<td>0.16</td>
<td>-</td>
</tr>
<tr>
<td>S-6</td>
<td>0.15</td>
<td>0.21</td>
</tr>
<tr>
<td>S-8</td>
<td>0.20</td>
<td>-</td>
</tr>
<tr>
<td>S-9</td>
<td>0.20</td>
<td>-</td>
</tr>
<tr>
<td>S-10</td>
<td>0.19</td>
<td>0.23</td>
</tr>
<tr>
<td>M-6</td>
<td>0.18</td>
<td>0.20</td>
</tr>
<tr>
<td>M-8</td>
<td>0.23</td>
<td>-</td>
</tr>
<tr>
<td>M-9</td>
<td>0.16</td>
<td>0.23</td>
</tr>
<tr>
<td>M-10</td>
<td>0.21</td>
<td>-</td>
</tr>
</tbody>
</table>

It is tempting to speculate that for those compounds with a peak between 65.0 and 66.0 there is ring tautomer in solution, however, at the concentrations necessary to acquire reasonable spectra, however, (about 50% (V/V) in CDCl₃), intermolecular hemiacetal formation would be enhanced as well. No change, other than the sharpening of the OH signal, was observed upon addition of acid (dry HCl in CCl₄) to the deuteriochloroform solutions of any of the compounds in Table VIII. It should be noted that catalysis can not alter equilibrium constants, however.¹⁶

The methylene triplets for the α and ω methylene protons (see Figure XLVIII) do not appear as well defined triplets for any of these compounds. It is conceivable that this would be the case of the compound existed as a mixture of tautomers. There is no correlation between the relative absorbances of the C=O and OH ir bands (see Table VII) and the ratios of the nmr aldehyde/aromatic proton signal intensity ratios recorded in Table VIII.

The uv spectra were determined for the ω-hydroxyalkoxybenzaldehydes in cyclohexane and in cyclohexane + HCl, with the exception of S-2, which is
insoluble in this solvent, was determined in acetonitrile. This is a high-dilution technique ideally suited for promoting intramolecular interactions. In every case, the uv spectra displayed the bands described in the literature for the o-alkoxy- and m-alkoxybenzaldehyde chromophores. Furthermore, in no case did the addition of acid change the spectrum significantly.

The sensitivity of this technique is open to question for the alkoxybenzaldehydes. The relative intensity of the uv bands for the acetics versus the free aldehydes is quite small (see Table VI). For example, if a member of the S series existed in solution as 10% cyclohemiacetal, the ratio of the most intense peaks in the respective spectra of the two forms would be .03 for the cyclohemiacetal peak at 273 nm vs the aldehyde peak at 253 nm. The situation is even more dramatic for the meta- compounds, where the most intense peak in the acetal spectrum is at 220 nm compared to the most intense peak in the spectrum of the aldehyde at 223 nm. Therefore, unless a rather significant amount of cyclohemiacetal is present, peaks indicating its presence may not be observed.

Ultraviolet absorption spectroscopy was used as a qualitative technique in this study even if it may not be reliable as a quantitative method. Although the maxima were closely similar in each series, the extinction coefficients varied widely from spectrum to spectrum.

The basic premise of this investigation was the unlikelihood of hemiacetal in compounds which would have strained ring tautomers and the likelihood of hemiacetal in those which would have macrocyclic (relatively unstrained) ring tautomers. Had this been the case, and if a high dilution technique such as uv could have been used to demonstrate this, a strong argument could have been made for the existence of macrocyclic ring-chain
tautomerism in these series. However, it was not possible to obtain S-4, S-5 and S-6 analytically pure. Consequently no models for compounds which are unlikely to cyclize were obtained.

Some representative ir, uv, and nmr spectra of compounds in the S and M series are included in the Appendix.
Picolinaldehyde Derivatives

Quaternizations of picolinaldehyde and derivatives of picolin-aldehyde have been accomplished under a variety of conditions. The aldehyde itself has been alkylated with methyl iodide\(^\text{47,99}\) and with benzylic bromides\(^\text{100-104}\) but attempted alkylation with \(\alpha\)-haloketones failed.\(^\text{105}\) Various acetals have been alkylated with benzylic bromides\(^\text{92-106}\) and with \(\alpha\)-haloketones.\(^\text{105}\) Quaternized hemiacetals can be obtained by allowing the aldehyde to react with alkylating agents in alcohols\(^\text{47,107-8}\) or by dissolving the alkylated aldehyde in an alcohol.\(^\text{47}\)

Besides allowing the pyridine compound to react with the alkyl halide without any solvent,\(^\text{99,100,102,105}\) alkylation has been conducted in acetone,\(^\text{47}\) sulfolane,\(^\text{92}\) dimethylformamide\(^\text{101,106}\) and acetonitrile\(^\text{103}\) with success.

It was reasoned that since it is possible to alkylate the nitrogen of picolinaldehyde, the alkylation with an \(\omega\)-bromoalkanol would yield an \(\omega\)-hydroxyaldehyde whose carbonyl group is highly activated toward nucleophilic attack. Also, since picolinaldehyde forms substantial amounts of hemiacetal in the presence of alcohols, intramolecular quaternization of the hemiacetal from picolinaldehyde and an \(\omega\)-bromoalkanol would yield a cyclohemiacetal directly.

It was found that after standing for two or three days, an equimolar mixture of picolinaldehyde and 2-bromoethanol solidifies to a waxy, ether-insoluble mass. Pulverizing this mass under ether leaches out un-reacted starting material. Finally, recrystallization from acetonitrile resulted in isolation of a compound which exhibits no C=O band in the ir spectrum and no aldehyde proton peak in the nmr spectrum. The C, H, N analysis was within 0.5% of the calculated values for a one-to-one addition
product of picolinaldehyde and 2-bromoethanol. The two structures which are consistent with these facts are shown in Figure XLIX.

![Structures](image)

*Figure XLIX*

When equimolar portions of picolinaldehyde and 3-bromopropan-1-ol were combined and allowed to stand, no solid was formed. After two or three weeks, when the mixture had darkened considerably, acetone was added and a precipitate immediately developed. This was washed repeatedly with ether and finally recrystallized with much difficulty and loss of material from acetonitrile. The resulting crystalline solid displayed no C=O band in its ir spectrum and no aldehyde proton signal in its nmr spectrum. The C, H, N analysis was within 0.3% of the calculated percentages for a one-to-one adduct of the two starting materials.

When this reaction is carried out with 4-chlorobutanol, a bright orange, powdery solid is obtained which must be stored under dry ether in the freezer. Exposure to the air for even a few seconds caused rapid conversion of the powder to a dark brown tar. For this reason, no spectra were obtained.
When this procedure was carried out with 6-bromohexan-1-ol, 8-
bromooctan-1-ol, 9-bromononan-1-ol or 10-bromodecan-1-ol, no quaternization
occurred. These reaction mixtures were allowed to stand for two to three
weeks in a desiccator under nitrogen. Under these conditions quaterni-
ization readily occurs with the shorter chain halohydrins. For this reason,
it is believed that the reaction products from 2-bromoethanol and 3-bromo-
propan-1-ol with picolinaldehyde are cyclic and not polymeric.

Two acetals of picolinaldehyde were made as model compounds. These
were dimethyl acetal and the cyclic dimethylene acetal. The acetal
methinyl proton singlet occurs at 65.20 and 65.78 respectively for these
two compounds. The aromatic proton pattern is shifted upfield relative to
the aromatic proton pattern in the aldehyde but the general patterns are
remarkably similar. This same pattern can be seen in the spectra of the
two quaternary pyridinium salts prepared in this laboratory (see Appendix).
The hemiacetal methinyl singlets appear in the spectra of these salts at
66.4 and 66.5 for the six- and seven-membered ring compounds respectively.
However, the difference in the shifts between the hemiacetal methinyls and
the aromatic ring proton signals is almost identical to the same shift dif-
ference in the spectrum of the dimethyl acetal of picolinaldehyde. This
shift difference is not the same in the five-membered cyclic dimethylene
acetal of picolinaldehyde, suggesting that the five-membered ring is not a
good model for the salts which contain six- and seven-membered rings.

The powdery orange solid which is obtained from the reaction of 4-
chlorobutan-1-ol with picolinaldehyde could be one of several possible com-
ounds. If it is cyclic, the ring is eight-membered, and this may account
for its instability. If it is the free aldehyde, sensitivity to moisture
could be due to hydrate formation. It seems unlikely that it is a polymer
however, since the same type of material was not formed from the longer chain bromohydrins.
Suggestions for Further Work

Research in the area of macrocyclic ring-chain tautomerism can take many directions. An attempt has been made here to identify evidence for the existence of the large ring tautomers in dilute solutions under equilibrating conditions. A step beyond this approach would be the trapping of such ring forms by isolating products which are derived from them. To this end two schemes come to mind.

Formation of the mixed cycloacetal shown in Figure L is attractive because gc yields could be used to determine the percent ring closure versus ring size data. This requires isolation, identification and purification of both acetals for any given chain length and cataloging gc retention times. Since only the acyclic acetal has a free OH, this could be used as a handle in the chromatographic separation of the two products.

This approach suffers from the complication that the cycloacetal could arise from a cyclic or an acyclic hemiacetal, however.
A second method of trapping the cyclohemiacetal is acylation. The results in this case could be regarded as less equivocal if one could establish that the two esters themselves do not exhibit an electrophilic-exo-trig equilibrium with each other where the migrating electrophile is an acylium ion.

Related to trapping the cyclic tautomer is directing the synthesis
toward the ring form. The best methods for this approach may involve systems such as those shown in Figure LIII.

\[ \text{hv} \quad \text{O(CH}_2\text{)}_n \quad \text{NBS/CCl}_4 \quad \text{O(CH}_2\text{)}_n \]

Figure LIII

Since the possibility of ring closure leading to both ortho- and meta-bridged cyclohemiacetals has been explored, experiments designed to observe the effects of competition between such ring closures may prove interesting. A model system for such a study is shown below.

\[ \text{HO} \quad \text{O(CH}_2\text{)}_n \quad \text{CHO} \quad \text{O(CH}_2\text{)}_n \quad \text{OH} \quad \text{CHO} \]

Figure LIV

One obvious variation that can be made on the systems that have
been studied is to increase the chain length, or ring size, beyond those previously examined. However, a more interesting effect to study may be the effect of gem-dimethyl groups on the position of the equilibrium. It has been reported that for macrocyclic acetals derived from α,ω-alkanediols, gem-dimethyl groups generally increased yields because of increased stability of the rings. In this way, the equilibrium may be shifted toward more ring tautomer by stabilizing the ring itself.

An alternative to stabilizing the ring through gem-dimethyl groups is the strategy of destabilizing the aldehyde moiety relative to the hemiacetal moiety. This could be accomplished by either electron-withdrawing substituents on the aromatic ring or by changing the nature of the linking functionality which is employed in joining the alcohol portion of the molecule to the aldehydic part. Compounds which may show more ring tautomer because of this effect are shown in Figure LV.

Other possible areas to explore involve changing the nature of the ring closure itself. Nucleophilic ring-chain tautomerism, such as is shown below, could be studied.
Endo ring closures could be studied if the double bond were that of an imino group.

In this particular system, the reactivity of the double bond could be modified by X, and the basic starting materials would include the readily available para-substituted benzaldehydes.

Varying the type of catalyst needed for ring closure opens up another area of study. Ring tautomers patterned after crown ethers may be interesting if catalysis is specific to selected metals.
Two areas in which such compounds might prove useful are medicinal and analytical chemistry. One could envision, for example, developing medicinals which are activated only in the presence of certain metal ions, or analytical reagents, specific for selective non-uv absorbing metal ions, whose chromophore in the cyclic form is greatly different from that of the open-chain form. One medicinal which exhibits a special type of macrocyclic ring-chain tautomerism is the natural product, pimaricin, an antifungal, macrocyclic polyene antibiotic which contains a cyclohemiketal moiety as a partial structure. In this case, the six-membered cyclohemiketal ring is bridged by a macrocyclic ring. 110
BIBLIOGRAPHY


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88. Jones, P. R., Unpublished Data.
89. Jones, P. R. and Rellas, S., Unpublished Results.
2-(2-Hydroxyethoxy)-benzaldehyde

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The image contains a graph with a spectral analysis of a substance. The x-axis represents frequency (cm⁻¹) ranging from 3000 to 3500, and the y-axis represents absorbance ranging from 0.0 to 1.0. The graph shows multiple peaks across different frequency ranges.

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<td>9/1/77</td>
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<td>REMARKS</td>
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The absorbance peaks at various frequencies are indicated, suggesting the presence of specific chemical bonds or functional groups within the substance being analyzed.
2-(2-Hydroxyethoxy)-benzaldehyde

SAMPLE

ORIGIN

SOLVENT

CURVE NO.

CONC.

CELL PATH

REFERENCE
2-[(9-Hydroxy)xyloxy]-benzaldehyde

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CURVE NO.: 22860
CONC.
ORIGIN: synthetic
CELL PATH
SOLVENT: neat
REFERENCE
**Aldehyde**

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Aldehyde

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SLIT

DATE 4/24/77

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<th>CONC.</th>
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<th>CELL PATH</th>
<th>REFERENCE</th>
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<tr>
<td>kΘr</td>
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N-(3-Hydroxypropyl)-2-Formylpyridinium Bromide

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<th>SAMPLE</th>
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<td>$\beta$-3-Br</td>
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<tbody>
<tr>
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<td>$\alpha$Ic</td>
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</tbody>
</table>
2-(8-Hydroxyoctyloxy)-benzaldehyde
2-(8-Hydroxyoctyloxy)-benzaldehyde (CDCl₃ + HCl)
3-(10-Hydroxydecyloxy)-benzaldehyde
N-(2-Hydroxyethyl)-2-Formylpyridinium Bromide
N-(3-Hydroxypropyl)-2-Formylpyridinium Bromide
2-(9-Hydroxynonyloxy)-benzaldehyde
3-\{6-\text{hydroxyhexyloxy}\}-benzaldehyde