Summer 1967

INVESTIGATIONS INTO THE SYNTHESIS OF POTENTIAL MACROCYCLIC RING-CHAIN TAUTOMERS AND MODEL COMPOUNDS

RONALD JOHN PANICCI

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INVESTIGATIONS INTO THE SYNTHESIS OF
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TAUTOMERS AND MODEL COMPOUNDS

by

RONALD JOHN PANICCI

B. S., Holy Cross College, 1963

A THESIS

Submitted to the University of New Hampshire
In Partial Fulfillment of
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Doctor of Philosophy

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Department of Chemistry
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This thesis has been examined and approved.

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The author also wishes to express his thanks to Dr. J. John Uebel for his help in operating the Varian A-60 Nmr Spectrometer; to Mr. Harold T. McKone for his help in operating the Cary 15 Ultraviolet Spectrophotometer; and to the Chemistry Department of the University of New Hampshire for their constant encouragement and aid and for the opportunity to conduct this work under an NDEA grant.

Lastly, but certainly not least, the author wishes to express his most sincere thanks to his parents whose aid and unceasing encouragement allowed him to attain this goal.

[Signature]

Ronald J. Panissi
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INVESTIGATIONS INTO THE SYNTHESIS OF POTENTIAL MACROCYCLIC RING-CHAIN TAUTOMERS AND MODEL COMPOUNDS

by

RONALD JOHN PANICCI

A series of \( \omega \)-acyl alcohols and acids and their derivatives were prepared in order to examine them for ring-chain tautomerism. The ring tautomer, if formed, would contain at least sixteen members and contain a para-phenylene bridge. The phenyl group was incorporated into the structure in order to aid in the detection of the ring tautomer.

A model compound, 9-(\(\beta\)-hydroxymethylbenzoyl)-nonanoic acid lactone (15) was prepared and examined for unusual chemical and spectral behavior. The nmr spectrum of 15 exhibited a shift of the methylene protons to higher field than in any of the open chain analogues. This was attributed to the methylenes lying over the ring and therefore in the shielding cone of the ring. This phenomenon was then used as a probe for the existence of ring tautomers in equilibrium with the chain tautomers synthesized.

An attempt was thus made to prepare 9-(p-hydroxy-methylbenzoyl)-nonanoic acid (29), 9-(p-acetoxy-methylbenzoyl)-nonanal (33), 10-(p-hydroxy-methylbenzoyl)-2-decanone (31) and 9-(p-formylbenzoyl)-nonanoic acid (36) and some of their derivatives, all of which are capable of engaging in ring-chain tautomerism. The synthesis of a few of these compounds

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was accompanied by reaction at another functional group, and thus their isolation was impossible. The acetoxy aliphatic aldehyde 33, for example, always underwent oxidation to the aliphatic acid when it was subjected to saponification or Fischer esterification conditions.

The ring-chain equilibrium was examined by nmr spectroscopy on these compounds and on their products under Fischer esterification conditions. In no case was a cyclic tautomer detected in the nmr spectra of these compounds.

Since ring closure to form the lactone 15 had to be carried out under high dilution, it is thought that the entropy of ring closure to form cyclic tautomer under nmr or Fischer concentrations is probably unfavorable. Specialized nmr equipment which can detect protons at very low concentrations would be useful to examine these compounds in concentrations conducive to ring tautomer formation.
INTRODUCTION

Ring-chain tautomerism, involving the formation of five- or six-membered rings, has been the object of many papers since Meyer and Jacobson first discussed the possibility of such a phenomenon.\(^1\) Both Newman and Jones have examined the tautomerism of $\beta$-acyl acids by chemical means involving, primarily, Fischer esterification experiments and by physical means involving infrared, ultraviolet and nmr spectroscopy.\(^2\) The examples cited of ring tautomers of more than seven members, however, are quite rare. Indeed the actual synthesis of cyclic structures involving seven or more atoms becomes increasingly difficult as the number of atoms increases. The stability of these rings, while low for eight to fifteen members, increases remarkably for sixteen- or more-membered rings.

It is the object of the present work to prepare a series of $\omega$-acyl acids and alcohols and to examine such compounds for ring-chain tautomerism by Fischer esterification experiments and by infrared, ultraviolet and nmr spectroscopy. Since it has been noted that para-substituted methylenes in ansa\(^3\) compounds exhibit unusual properties, especially in the nmr spectra, such $\omega$-acyl acids and alcohols will be designed such that the ring tautomers will consist of sixteen members and will contain a para-substituted phenyl function.

An attempt will be made to synthesize, as a model compound, an $\omega$-hydroxy acid lactone consisting of sixteen members and containing a para-substituted phenyl ring (1).
Such a structure will be examined for unusual chemical and physical properties, which may be used for identification of the ring tautomers from \( \omega \)-acyl acids and alcohols.
HISTORICAL

Ring-Chain Tautomerism

The mobile equilibrium between two isomers involving ring closure can be termed ring-chain tautomerism. The general requirement for such an equilibrium is that the chain tautomer possesses two functional groups, one of which is a multiple bond and the other capable of effecting an additive reaction at the multiple bond.

Two main types of ring-chain tautomerism can be considered.

If X is electron deficient then ring tautomer 3, where A adds to Y and X to Z, will be formed. This is termed electrophilic tautomerism.

If X is electron rich then ring tautomer 4, where A adds to Z and X to Y, will be formed. This is termed nucleophilic tautomerism.

The number of examples cited of nucleophilic tautomerism is by far in the minority. The most numerous examples occur
when X is halogen and YZ is CO. For example, two forms of phthaloyl chloride are known.

![Phthaloyl chloride tautomerism](image)

Instances of electrophilic tautomerism, on the other hand, are preponderant. Newman has examined a series of o-benzoylbenzoic acids, by both chemical and physical means in order to determine the mechanism of esterification in the Fischer procedure. By examining both the kinetic product after fifteen minutes and the thermodynamic product after six hours, he was able to postulate the existence of a ring-chain equilibrium in the Fischer esterification of these acids. These are shown in steps B₂ and C₂ in Scheme 1 below. In several cases he showed the existence of the tautomerism prior to the esterification by ultraviolet spectroscopy, as shown in step D₁ of the esterification mechanism.

Jones and Desio have also examined a series of o-acylbenzoic acids, by chemical and physical methods.
SCHEME 1

\[
\begin{align*}
\text{A1} & : \quad \text{C}_6\text{H}_5\text{COOH} + \text{CH}_3\text{OH} \rightleftharpoons \text{C}_6\text{H}_5\text{COOCH}_3 + \text{H}_2\text{O} \\
\text{B1} & : \quad \text{CH}_3\text{OH} + \text{C}_6\text{H}_5\text{COOCH}_3 \rightleftharpoons \text{C}_6\text{H}_5\text{COOH} + \text{CH}_3\text{OH} \\
\text{B2} & : \quad \text{CH}_3\text{OH} + \text{C}_6\text{H}_5\text{COOH} \rightleftharpoons \text{C}_6\text{H}_5\text{COOCH}_3 + \text{H}_2\text{O} \\
\text{B3} & : \quad \text{CH}_3\text{OH} + \text{C}_6\text{H}_5\text{COOCH}_3 \rightleftharpoons \text{C}_6\text{H}_5\text{COOH} + \text{H}_2\text{O} \\
\text{A2} & : \quad \text{C}_6\text{H}_5\text{COOH} \rightleftharpoons \text{C}_6\text{H}_5\text{COOCH}_3 \\
\text{C1} & : \quad \text{C}_6\text{H}_5\text{COOCH}_3 \rightleftharpoons \text{CH}_3\text{OH} \\
\text{C2} & : \quad \text{CH}_3\text{OH} \rightleftharpoons \text{C}_6\text{H}_5\text{COOCH}_3 \\
\text{D1} & : \quad \text{C}_6\text{H}_5\text{COOH} \rightleftharpoons \text{C}_6\text{H}_5\text{C}=\text{O} + \text{H}_2\text{O} \\
\text{D2} & : \quad \text{C}_6\text{H}_5\text{C}=\text{O} \rightleftharpoons \text{C}_6\text{H}_5\text{COOH} + \text{CH}_3\text{OH} \\
\text{D3} & : \quad \text{C}_6\text{H}_5\text{COOCH}_3 \rightleftharpoons \text{C}_6\text{H}_5\text{C}=\text{O} + \text{H}_2\text{O} \\
\end{align*}
\]
The aim was to examine both steric and electronic effects on the equilibrium and to correlate the evidence for tautomerism by chemical means (Fischer esterification) with that of the physical evidence based primarily on nmr spectroscopy. This correlation was shown in a great majority of cases. It was also shown that the \( R_5 \)-substituent exerted a stabilizing effect on the ring tautomer, while the \( R_2 \)-substituent had little or no effect on the position of the equilibrium.

Another area of great interest in ring-chain tautomerism lies in the carbohydrate series, specifically the monosaccharides. The polyhydroxy aldehyde, glucose (7 and 8) and the polyhydroxy ketone, fructose, were shown to exist primarily in the ring form 7.
However, since glucose does give some typical aldehyde reactions such as Tollens and Fehlings tests, it does exist to a small extent in the chain form in the presence of reagent (probably less than 0.5%).

**Macrocycles**

H. C. Brown has classified ring systems into four categories: small rings (3-4), common rings (5-7), medium rings (8-11), and large or "macro" rings (12 and higher). These macro rings can range in complexity from the simple carbocyclic series and their substituted derivatives up through the heterocyclic and bicyclic series and their substituted derivatives. In general the ease of synthesis can be said, therefore, to depend on the complexity of the molecule.

The simple cyclic hydrocarbons can be made from the cyclic ketones by reduction or from the cyclic alcohols by elimination followed by reduction. The alcohol, in turn, can be synthesized by reduction of the ketone. It can be seen, therefore, that numerous other derivatives can also be made from any of these.

\[\text{C}=\text{O} \xrightarrow{\text{Clemmenson}} \text{CH}_2 \xrightarrow{\text{H}_2\text{, Ni}} \text{CHOH}\]

The synthesis of the cyclic ketone, however, seems to be the key to a great variety of macrocyclic compounds.

Ruzicka has carried out pyrolytic decarboxylation of thorium, yttrium and cerium salts of several aliphatic \(\alpha,\omega\)-dicarboxylic acids to obtain cyclic ketones and their dimers.
It is not surprising that Ruzicka noted a marked increase in the ratio of dimer or polymer to monomer as \( n \) increased. Ziegler\textsuperscript{12} utilized a high dilution technique in the treatment of \( \alpha,\omega \)-dicyano alkanes with lithium N-ethylanilide.

The Hunsdiecker procedure\textsuperscript{13} involves an intramolecular condensation of an \( \omega \)-haloacylacetec ester followed by hydrolysis and decarboxylation.
Leonard\textsuperscript{14} has utilized the similar Dieckmann Condensation to give comparable results.

Rodd\textsuperscript{15} claims the acyloin condensation "is the method par excellence for obtaining macrocyclic compounds." Both Stoll\textsuperscript{16} and Prelog\textsuperscript{16} showed independently that, when one heats a well stirred solution of an \(\alpha,\omega\)-dicarboxylic ester in xylene and molten sodium, one obtains the acyloin\textsuperscript{12} in excellent yields.
While the other methods give cyclic products with sixteen members and above in fair yield and medium ring compounds in negligible amounts, the acyloin method gives 40\% yields for the C_9 - C_{13} acyloins and up to 96\% for the C_{21} acyloin.\textsuperscript{15}

Huisgen has incorporated the benzene nucleus into the macrocyclic series by use of an intramolecular Friedel-Crafts acylation\textsuperscript{17}, to give the \([n]\) paracyclophanes or \textit{ansa} compounds.

\[
\begin{array}{c}
\text{C}_{\text{H}_2} \quad \text{Cl} \\
\text{C} = \text{O} \\
\text{A}_{12} \quad \text{Cl} \\
\text{A}_{14} \quad \text{Br}^3 \\
n = 13, 15, 18, 20
\end{array}
\]

Cram\textsuperscript{18} has synthesized similar compounds utilizing an acyloin condensation.

The same methods can of course be used in the synthesis of the metacyclophanes\textsuperscript{19} and orthocyclophanes\textsuperscript{20} from compounds of the appropriate chain lengths.

Winberg\textsuperscript{21} has incorporated two benzene nuclei into the macrocyclic system to give the \([m,n]\) paracyclophanes.
Macrocyclic compounds, like the small and common ring systems, need not be confined to simple carbocycles. A wide variety of hetero-macrocycles are known. Huisgen has developed a variety of syntheses of macrocycles containing nitrogen.

\[
\text{CH}_3 - \text{C} - \text{CH}_2\text{Br} + \text{Me}_3\text{N} \xrightarrow{\text{Hg}_2\text{O}} \text{CH}_3 - \text{C} - \text{CH}_2\text{NMe}_3\text{OH}^-
\]

Macroyclic compounds, like the small and common ring systems, need not be confined to simple carbocycles. A wide variety of hetero-macrocycles are known. Huisgen has developed a variety of syntheses of macrocycles containing nitrogen.
Macrocyclic lactones can also be synthesized by a variety of methods, including the action of persulfuric acid on a macrocyclic ketone and the depolymerization of a polyester. Upon treatment of ω-bromo aliphatic acids with excess potassium carbonate in methyl ethyl ketone under high dilution conditions, Hunsdiecker obtained the ten- to eighteen-membered lactones.

\[
\text{Br(CH}_2\text{)}^n\text{COOH} \xrightarrow{\text{K}_2\text{CO}_3/\text{MEK, High Dilution}} \text{(CH}_2\text{)}^n\text{O}
\]

\[n = 8-16\]

In a similar manner, when the lithium, potassium, or silver salts of ω-bromo aliphatic acids are treated under suitable conditions, the macrolactones are produced.

The stability of a ring can be considered from a kinetic or a thermodynamic point of view. The kinetic stability of the ring is nothing more than a measure of the ease of ring closure or the facility with which the reactive chain termini can approach each other. The fourteen-membered ansa-compound, p-decamethylenebenzene is the lowest homolog that could be synthesized in the p-methylenebenzene series. Thus,
in the thirteen-membered ring compound, the reactive ends of the chain cannot come close enough to each other to react; and this ring would be considered kinetically unstable.

The kinetic criterion for measuring the stability of a ring, however, is far from satisfactory. A better method for determining ring stability would be the thermodynamic data as measured by the heats of combustion. The heats of combustion per methylene group for a series of cycloalkanes are given below.

<table>
<thead>
<tr>
<th>n</th>
<th>( \frac{H_c}{n} )</th>
<th>( \frac{H_c}{n} - 157.4 )</th>
<th>n</th>
<th>( H_c )</th>
<th>( \frac{H_c}{n} - 157.4 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>166.6</td>
<td>9.2</td>
<td>9</td>
<td>158.8</td>
<td>1.4</td>
</tr>
<tr>
<td>4</td>
<td>163.95</td>
<td>6.55</td>
<td>10</td>
<td>158.6</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>158.7</td>
<td>1.3</td>
<td>11</td>
<td>158.4</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>157.4</td>
<td>0.0</td>
<td>12</td>
<td>157.7</td>
<td>0.3</td>
</tr>
<tr>
<td>7</td>
<td>158.3</td>
<td>0.9</td>
<td>13</td>
<td>157.8</td>
<td>0.4</td>
</tr>
<tr>
<td>8</td>
<td>158.6</td>
<td>1.2</td>
<td>14</td>
<td>157.4</td>
<td>0.0</td>
</tr>
<tr>
<td>15</td>
<td>157.5</td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>16</td>
<td>157.5</td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>17</td>
<td>157.2</td>
<td>-0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>157.4</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If one plots \( \frac{H_c}{n} - 157.4 \) against the ring size, one obtains the following graph. The heat of combustion (157.4) for the strain-free cyclohexane is considered the standard, and any deviation from this (\( \frac{H_c}{n} - 157.4 \)) would be a measure of the ring stability.
Thus we can see that the smallest of the large rings with sufficient stability to be isolated is probably the fourteen-membered ring system. It is assumed that the same treatment with comparable results could be obtained in any of the other more complicated macrocyclic series.

The spectroscopic properties of the different macrocycles are, with several notable exceptions, very similar to the open chain analogs. In the \([n,n]\) paracyclophane series one notes both a bathochromic and a hypochromic shift in the ultraviolet spectrum for the case of \(n<4\). Bolkelheide has also noted some drastic shifts in the nmr spectra in a series of metacyclophanes. This would, in part, be due to ring currents
In order to test this theory, Waugh and Fessenden have examined a series of \([n]\) paracyclophanes and have noted a dramatic shift of the aliphatic protons toward higher field in the nmr spectra. This would suggest that the methylenes are located in the shielding cone of the ring.

Thus, in the infrared, ultraviolet and nmr spectra, most macrocycles exhibit the same characteristics as their open chain analogs. On the other hand, the spectral peculiarities exhibited by some macrocycles can be utilized to distinguish between these cyclic compounds and their acyclic counterparts.
EXPERIMENTAL

The infrared spectra were determined with a Perkin-Elmer Model 337 grating spectrophotometer unless otherwise stated. Spectra determined with a Perkin-Elmer Model 21 spectrophotometer are indicated by the number "21" before the spectrum number. Double mulls were run with halocarbon for the region 4000-1300 cm⁻¹ and Nujol for the region 1300-650 cm⁻¹.

Nuclear magnetic resonance spectra were determined with a Varian A-60 spectrophotometer. Ultraviolet spectra were taken on a Perkin-Elmer Model 4000 spectrophotometer (indicated by the number "4000" before the spectrum number) or a Cary 14 or 15 spectrophotometer (indicated by the number "14" or "15" before the spectrum number).

The combustion analyses were performed by Galbraith Laboratories of Knoxville, Tennessee. Melting points are uncorrected.

Unless otherwise stated, thin layer chromatography was carried out on silica plates (G. Merck, Type G, GF, H, or HF); thickness varied from 300 to 500 microns. Chloroform was used as eluent unless otherwise stated. Thick layer chromatography was carried out in the same manner on 20 x 20 cm glass plates with 24 g silica gel GF.
Preparation of PhenylNitromethane. - To a stirred solution of 60 ml dimethylformamide, 3.6 g (0.052 mole) sodium nitrite, 4 g urea and 2 g phloroglucinol maintained at -15 to -20°C, was added 5.13 g (0.03 mole) of benzyl bromide. After 5 hr the mixture was poured into a mixture of 150 ml ice water and 25 ml ethyl ether. After separation, the aqueous layer was extracted five times with 20-ml portions of ether and the ether extracts were combined. The ethereal solution was then washed three times with 10-ml portions of 10% sodium thiosulfate, twice with 20-ml portions of water, dried over anhydrous magnesium sulfate, filtered and concentrated. The remaining liquid was distilled at 0.5 mm:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>bp</th>
<th>color</th>
<th>$n^\text{D}_{25}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>28°</td>
<td>light yellow</td>
<td>1.5033</td>
</tr>
<tr>
<td>B</td>
<td>30-75°</td>
<td>light blue</td>
<td>1.5418</td>
</tr>
<tr>
<td>C</td>
<td>75-85°</td>
<td>colorless</td>
<td>1.5312</td>
</tr>
</tbody>
</table>

Refractive index shows fraction C is the phenylNitromethane, while A is probably benzyl nitrite; (lit. $n^\text{D}_{20}$ 1.5006 (benzyl nitrite), $n^\text{D}_{20}$ 1.5315 (phenylNitromethane).

Effect of Aluminum Chloride on PhenylNitromethane. - To 2 ml phenylNitromethane was added 0.35 g aluminum chloride at room temperature. After several hours the mixture was washed several times with dilute hydrochloric acid and extracted with ether. After the ether was evaporated, the remaining oil was distilled at 10-15 mm and a clear, yellowish liquid, bp 120-130°C, was collected. The phenylNitromethane was recovered quantitatively; $n^\text{D}_{25}$ 1.5304, infrared spectrum (2-No.6163,film).
Attempted Preparation of p-(Nitromethyl)-acetophenone. --

Method A. - A mixture of 8 g (0.058 mole) phenyl nitromethane and 6.15 g (0.787 mole) acetyl chloride was dissolved in 50 ml of carbon disulfide. To this stirred solution was added 21 g of aluminum chloride in small portions. As hydrogen chloride was evolved, a black tarry solid formed in the flask. When the reaction was completed (as shown by the termination of gas evolution), 100 ml of a 50% hydrochloric acid-water mixture and 25 ml of carbon disulfide were added. The mixture was filtered and the organic and aqueous layers separated. The aqueous layer and the solid were washed repeatedly with ether and the separate ether and carbon disulfide layers washed repeatedly with 10% sodium hydroxide and water. The two organic layers were then combined and concentrated to yield approximately 10 mg of a waxy solid. An infrared spectrum (21 No.6196, film) exhibited very weak ketone carbonyl absorption at 1675 cm\(^{-1}\) and nitro bands at 1555 and 1375 cm\(^{-1}\).

Method B. - The above reaction was modified in several ways. The amount of carbon disulfide was increased to 75 ml and the system fitted with a reflux condenser to minimize the loss of solvent. The reaction was allowed to proceed for 6 hr. An oily, waxy solid (0.14 g) was obtained. An infrared spectrum (21 No.6196, film) again showed the ketone carbonyl and the nitro group to be present.

To the 0.14 g of the above product were added 0.3 g sodium dichromate, 1 ml of concentrated sulfuric acid and 3 ml of water. The mixture was warmed gently for 3 hr. It was then extracted with ether and the ether layer concentrated. A greenish-yellow solid was obtained. An infrared spectrum (21 No.6112, film) showed no strong acid bands. The solid was treated a second time with dichromate solution at reflux for 3 hr. Ether extraction
yielded a greenish, semi-waxy solid, mp 95-105 (softening, 60-95°). An infrared spectrum (21 No.6213, CHCl₃) was identical to a spectrum of benzoic acid (21 No.6218, CHCl₃).

Preparation of Methyl Hydrogen Sebacate. 37 (19). - Barium hydroxide octahydrate (55 g, 0.175 mole) was added slowly to a constantly stirred mixture of 104 g (0.35 mole) benzene, 371 g (1.16 moles) methanol and 80.9 g (0.35 mole) dimethyl sebacate. A white precipitate began to form immediately. Stirring was allowed to continue for 24 hr after completion of addition. The fine, waxy precipitate was collected by suction and washed several times with methanol. Dissolution of the salt in 25% HCl liberated the free acid, which was extracted with ether several times. The ethereal extracts were washed several times with water and dried over anhydrous sodium sulfate. Concentration of the ether gave a white, soapy solid (27 g, 72%). Absence of a greenish-yellow flame on ignition indicated that no barium ion was present. A neutralization equivalent (171) indicated the presence of some sebacic acid.

An infrared spectrum (No.6090, melt) compared favorably with one previously reported. 38

In subsequent preparations anhydrous barium hydroxide was used and yields of 70-90% methyl hydrogen sebacate were achieved.

Preparation of 9-Carbomethoxynonanoylchloride. (20). - Method A. - A 250-ml flask fitted with a condenser and a mechanical stirrer was charged with 15 g (0.065 mole) methyl hydrogen sebacate and 125 g dry ligroin. The solution was heated to 70° and 31 g (0.26 mole) unpurified thionyl chloride was added in small portions. After the solution had been stirred at 70-75° for 7 hr, the excess thionyl chloride was distilled at atmospheric pressure. The remaining dark brown,
viscous liquid was distilled at 0.5-0.25 mm and 10 g (45%) of a clear liquid collected at 119-125°. An infrared spectrum (21 No.6227, film) was identical to one of an authentic sample.

**Method B.** - A 1-l flask fitted with a reflux condenser was charged with 200 ml freshly purified thionyl chloride and 125 g (0.58 mole) methyl hydrogen sebacate. The solution was stirred for 36 hr and then refluxed for 1 hr. The excess thionyl chloride was removed at atmospheric pressure and the last traces at reduced pressure. The product was used without further purification.

**Preparation of Methyl 9-Benzoylnonanoate.** (21). - A 500-ml flask fitted with a condenser, mechanical stirrer and solid addition apparatus was charged with 10 g (0.042 mole) of 9-carbethoxynonanoyl chloride and 40 ml of benzene. The solution was cooled to 3° and 11.5 g of anhydrous aluminum chloride added slowly, with stirring. The mixture was stirred for 1 hr at 5-10° upon completion of addition, then warmed on the steam bath for 8 hr. The reaction mixture was decomposed with 100 ml of a 1:1 ice-hydrochloric acid mixture and the organic and aqueous layers separated. The aqueous layer was washed with ether and this was combined with the organic layer. This was then steam distilled; the residue was taken up in ether, washed with sodium bicarbonate and water, dried over anhydrous sodium sulfate and concentrated.

The yellow, waxy solid obtained, 7 g (57.5%), showed ketone and ester absorption respectively at 1680 and 1730 cm⁻¹ (21 No. 6232, film).

**Preparation of 9-Benzoylnonanoic Acid.** (22). - The crude methyl 9-benzoylnonanoate (10 g) was heated with aqueous sodium hydroxide for 2 hr. After ether extraction, acidification of
the basic layer gave a yellow solid, mp 72-78°. Recrystal-
lization from ether-pentane gave a white solid, mp 78-79°;
lit. mp 78-79°. Infrared spectra (No. 1265, 21 NO.6317,
double mull) showed the typical broad -OH at 3000 cm⁻¹.

Anal. Calcd for C₁₆H₂₂O₃: C, 73.25; H, 8.45.
Found: C, 73.26; H, 8.60.

Preparation of 10-Phenyldecanoic Acid (23). - A 250-ml flask
fitted with a reflux condenser was charged with 7 g crude
methyl 9-benzoylnonanoate, 5.61 g potassium hydroxide, 5 ml
hydrazine hydrate and 80 ml diethylene glycol and allowed to
reflux for 1.5 hr. The condenser was removed and the tempera-
ture of the solution allowed to rise to 195°. Reflux was then
allowed to continue for 4 hr.

After cooling to room temperature, 80 ml of water and
50 ml of concentrated hydrochloric acid were added. The
organic and aqueous layers were separated and the former washed
several times with saturated sodium bicarbonate. The basic
washings were acidified and washed several times with ether.
The ethereal layer was washed several times with water, dried
over anhydrous magnesium sulfate and concentrated. An amber
oil (3.4 g, 60% based on 7 g of crude starting material) was
obtained and an infrared spectrum (21 No.6262, film) gave an
acid carbonyl absorption at 1705 cm⁻¹. The acid was then con-
verted to the ester for further characterization.

The organic layer remaining after washing with satu-
rated sodium bicarbonate was concentrated and 1.8 g of an
amber oil (infrared 21 No.6263, film) obtained.

Preparation of Methyl 10-Phenyldecanoate (24). - A solution of
5 g of potassium hydroxide, 8 ml of water and 25 ml of 95%
ethanol was placed in a 300-ml flask fitted with a dropping
funnel and a condenser set for distillation. The condenser was
connected to two flasks in series, the second of which contained 30 ml of ether. The inlet to the second receiving flask was placed below the level of the ether and both receiving flasks cooled to 0°.

The ethanolic solution was heated in a water bath to 65° and a solution of 21.5 g (0.1 mole) of "Diazald" (Aldrich Chemical Co.) was added through the dropping funnel over a period of 25 min. The rate of addition was regulated so as to equal the rate of distillation. More ether was added through the dropping funnel and the distillation continued until the distillate was colorless.

To the ethereal distillate was added 3.4 g of crude 10-phenyldecanoic acid dissolved in ether. The resulting solution was washed with dilute sodium hydroxide and water, concentrated and yielded 2.5 g (75%) of an amber oil. Fractional distillation of a larger sample prepared in exactly the same manner gave an amber oil, bp 172-178 (1 mm). A small amount of this oil (1 g) was chromatographed on neutral alumina (eluent: 3:1 benzene-ether (v:v)). A colorless oil, bp 150° (0.5 mm), was obtained. An infrared spectrum (No.1367, film) showed ester absorption at 1745 cm⁻¹.

**Anal.** Calcd for C_{17}H_{26}O_2: C, 77.82; H, 9.99. Found: C, 78.00; H, 9.83.

**Attempted Preparation of Methyl 10-(p-Chloromethylphenyl)-decanoate (25). Method A.** - A 500-ml flask fitted with a reflux condenser, to which was attached a sodium hydroxide trap, gas inlet tube and mechanical stirrer, was charged with 13.37 g (0.051 mole) methyl 10-phenyldecanoate, 5 g (0.166 mole) paraformaldehyde, 7.2 g (0.053 mole) anhydrous zinc chloride and 200 ml sym-tetrachloroethane. The mixture was heated to 60° with stirring and a rapid stream of hydrogen chloride gas
allowed to bubble in for 20 min.

The organic layer was removed, washed with water and
dilute sodium bicarbonate, dried over calcium chloride and
fractionally distilled. An infrared spectrum (No.1414, film)
taken on the fraction (7.44 g) boiling at 165-167° (0.7 mm),
showed no \( \rho \)-disubstitution at 850 cm\(^{-1} \) but did exhibit mono­
substitution bands at 700 and 750 cm\(^{-1} \). Thin layer chroma­
tography showed only one component to be present. A negative
Beilstein test indicated the absence of chlorine. Alcoholic
silver nitrate gave a white precipitate, but it also gave a
yellow precipitate with methyl 10-phenyl decanoate. Acetone
and sodium iodide also gave a negative chloride test. Sodium
fusion and subsequent testing with aqueous silver nitrate
gave no precipitate.

The basic layer (from the sodium bicarbonate wash)
was acidified and extracted with ether. An infrared spectrum
(No.1491, film) of the residual oil showed a broad acid band
at 3000 cm\(^{-1} \) as well as an ester band at 1730 cm\(^{-1} \), with a
large shoulder at 1650-1700 cm\(^{-1} \). Absorption also appeared
at 800-830 cm\(^{-1} \), 750 and 710 cm\(^{-1} \).

Thin layer chromatography showed evidence of two com­
pounds. The mixture was washed with 5% sodium bicarbonate.
The ethereal layer was concentrated and gave a yellow oil.
This was distilled (150° at 15 mm).

**Anal.** Calcd for \( \text{C}_{17}\text{H}_{24}\text{O}_{2} \) (lactone): C, 78.42; H, 9.29.
Found: C, 76.40; H, 9.57.

An infrared spectrum (No.1575, film) showed ester
absorption at 1740 cm\(^{-1} \) and monosubstitution absorption at
700 and 750 cm\(^{-1} \).

The basic layer was acidified, extracted with ether
and concentrated to give white crystals (mp, 48-70°). An in­
frared spectrum (No.1580, double mull) showed broad acid
absorption at 3000 cm\(^{-1}\), carbonyl absorption at 1700 cm\(^{-1}\) and a band at 720 cm\(^{-1}\) but no absorption at 750 cm\(^{-1}\).

Tetrahydrofuran was used as the solvent in place of the tetrachloroethane in the chloromethylation of methyl 10-phenyldecanoate. Nmr spectroscopy (No.574, CCl\(_4\)) indicated the absence of the chloromethyl group.

**Method B.** - To a stirred mixture of 5 g (0.019 mole) of methyl 10-phenyldecanoate, 1.5 g (0.02 mole) chloromethyl methyl ether and 40 ml chloroform was added 3.2 g (0.02 mole) stannic chloride dissolved in 10 ml of chloroform. The solution was kept in an ice bath during the addition, and upon completion of addition 50 ml of water was added. The organic layer was separated, washed with water, dried over calcium chloride and concentrated. Infrared spectra (No.2092, film) of the product and the starting material were identical.

The reaction was repeated with 18.24 g (0.07 mole) stannic chloride which was added rapidly. After separation, washing and concentration of the organic layer, an oil remained. Its infrared spectrum (No.2093, film) contained a rather strong band at 750 cm\(^{-1}\) with a weaker one at 670 cm\(^{-1}\). A broad, weak band appeared at 800-850 cm\(^{-1}\).

**Attempted Preparation of \(\alpha\)-Dichloromethyl Ether.** - A suspension of 30 g of paraformaldehyde in 40 g concentrated sulfuric acid was cooled to 0\(^\circ\). Chlorosulfonic acid (175 g) was added slowly while the temperature was kept below 10\(^\circ\). In three attempts the product failed to separate as reported.\(^{42}\)

**Attempted Preparations of \(p\)-Chloromethyltoluene.** - Various unsuccessful chloromethylations of toluene in different solvents were attempted as outlined in the following table.
<table>
<thead>
<tr>
<th>Method</th>
<th>Amt. Toluene(g)</th>
<th>Reagents (Amt.)</th>
<th>Solvent</th>
<th>Infrared Spectrum No. of Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>ZnCl₂ (0.6g)</td>
<td>Cl₂CHCHCl₂</td>
<td>Polymer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CH₂O) x HCl₂ (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>ZnCl₂ (15 g)</td>
<td>Tetrahydrofuran</td>
<td>1818</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CH₂O) x HCl₂ (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td>ZnCl₂ (15 g)</td>
<td>CHCl₃</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CH₂O) x HCl₂ (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>40% CH₂O (aq) (30 ml)</td>
<td>Petroleum Ether</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>conc HCl (30 ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>10</td>
<td>40% CH₂O (aq) (30 ml)</td>
<td>Petroleum Ether</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>conc HCl (30 ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZnCl₂ (15g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>10</td>
<td>Cl₁CH₂OCH₃ (8.9g)</td>
<td>Cl₁CH₂OCH₃</td>
<td>2035</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SnCl₄ (28.67g)</td>
<td></td>
<td>2036</td>
</tr>
<tr>
<td>G</td>
<td>10</td>
<td>Cl₁CH₂OCH₃ (8.9g)</td>
<td>CHCl₃</td>
<td>2041</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SnCl₄ (28.67g)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In methods A-E the mixtures were placed in a three-neck flask fitted with a reflux condenser and gas inlet tube. Dry hydrogen chloride gas was allowed to bubble into the refluxing, stirred solution. The organic layer was then removed, washed successively with water and dilute sodium bicarbonate, dried over calcium chloride and concentrated. Where possible, the resulting solutions were examined by infrared spectroscopy.

Method B was attempted twice. The first time a yellow liquid was obtained and fractionated. Seven fractions were collected.

<table>
<thead>
<tr>
<th>Fraction</th>
<th>bp (mm)</th>
<th>Infrared Spectrum No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98-100 (760)</td>
<td>1861</td>
</tr>
<tr>
<td>2</td>
<td>140-152 (760)</td>
<td>1862</td>
</tr>
<tr>
<td>3</td>
<td>152-160 (760)</td>
<td>1863</td>
</tr>
<tr>
<td>4</td>
<td>160-195 (760)</td>
<td>1864</td>
</tr>
<tr>
<td>5</td>
<td>95-164 (0.5)</td>
<td>1871</td>
</tr>
<tr>
<td>6</td>
<td>164-180 (0.5)</td>
<td>1872</td>
</tr>
<tr>
<td>7</td>
<td>180-185 (0.5)</td>
<td>1873</td>
</tr>
</tbody>
</table>

Only fraction 3 gave a positive silver nitrate test for halogen.

**Anal.** Calcd for C₈H₇Cl: C, 67.83; H, 7.07; Cl, 25.10. Found: C, 45.87; H, 7.85; Cl, 31.18.

Thin layer chromatography showed the existence of at least three components.

The reaction was repeated according to Method B except that all quantities were doubled. The mixture was again distilled and the fraction boiling at 150-155 (760 mm) (infrared spectrum No.1931, film) was chromatographed on neutral alumina. The eluent consisted of the following solvents or the binary mixtures combined successively: petroleum ether, benzene, chloroform, ether, methanol. Three fractions were collected.
An infrared spectrum (No.1946, film) indicated the presence of alcohol in Fraction 2. The other fractions appeared to be hydrocarbons (No.1946, film).

Methods F and G were carried out at ice-bath temperature. The toluene and chloromethyl methyl ether were mixed with the appropriate solvent and the stannic chloride added dropwise. In both cases a dark red solution resulted upon completion of addition.

In Method F the solution was concentrated. The remaining black, tarry residue was extracted first with petroleum ether and then with ethyl ether. An infrared spectrum (No.2036, film) of the residual oil from the ethyl ether layer exhibited a broad peak centered at 3400 cm\(^{-1}\) but no strong bands at 3000 or 700-800 cm\(^{-1}\). The oil became progressively darker on standing.

By concentration of the petroleum ether layer an oil was obtained, whose infrared spectrum (No.2036) showed bands at 700 and 750 as well as at 800 cm\(^{-1}\).

In Method G, 50 ml of water was added after completion of addition of the stannic chloride. After the organic layer had been dried over calcium chloride and concentrated, a greenish oil remained. Its infrared spectrum (No.2041, film) gave bands at 825 and 760 cm\(^{-1}\). Further attempts at purification led to polymerization.

Preparation of 9-(p-Toluyl)-nonanoic Acid (16). - A 2-1 flask fitted with a mechanical stirrer, reflux condenser and a solid addition apparatus was charged with the 9-carbomethoxynonanoyl chloride prepared in the experiment above and with 500 ml of dry toluene. The reaction flask was kept in an ice bath while 200 g of anhydrous aluminum chloride was added with stirring over a period of 6 hr. The mixture was allowed to come to room
temperature, then heated for 12 hr on a steam bath. Upon cooling 300 ml of an ice-dilute HCl mixture was added and the aqueous and organic layers separated. The aqueous layer was washed several times with ether and the organic layers combined.

The organic layer was heated at reflux for 10 hr with a solution of 300 ml of water and 100 g of sodium hydroxide. The emulsion which formed was broken by the addition of both ether and water. The aqueous layer was acidified and extracted with ether. The amber ether solution was concentrated and tetrahydrofuran added. Refluxing for 4 hr with decolorizing charcoal failed to remove the amber coloration. A water wash again gave an emulsion which could be broken by the addition of a small amount of acetone. The solution was concentrated to give an amber solid. Recrystallization from ether-pentane gave a grayish solid, (125 g, 40% from dimethyl sebacate), mp 92-93. An infrared spectrum (No.2182 m double mull) showed phenyl absorption at 3050 cm$^{-1}$ and ketone and acid carbonyls at 1695 and 1720 cm$^{-1}$, respectively. An nmr spectrum (636, CCl$_4$) showed a quartet centering at 7.44; two triplets at 2.8 and 2.28; a singlet at 2.38; and a broad multiplet at 1-2.

An ultraviolet spectrum (14 No.202, 9.06 x 10$^{-6}$ M in methanol) showed a $\lambda_{\text{max}}$ at 252.3 m$\mu$, f = 38,300. In further attempts the 9-(p-tolyl)-nonanoic acid was obtained in 20-50% yield.

Wolff-Kishner Reduction of 9-p-Toluylnonanoic Acid. - A mixture of 20 g (0.073 mole) 9-(p-tolyl)-nonanoic acid, 11.8 g potassium hydroxide, 12 ml of 85% hydrazine hydrate and 400 ml of $\beta,\beta'$ dimethoxyethyl ether was allowed to reflux for 1.5 hr. The condenser was drained and the temperature of the solution allowed to rise to 195°. Refluxing was continued for 4 hr. The

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solution was then cooled, acidified, concentrated and the residue recrystallized from ether-pentane.

An infrared spectrum (No. 2130, double mull) of the yellowish solid (10 g, 50%) showed the presence of the acid carbonyl at 1695 cm\(^{-1}\) but absence of the ketone carbonyl at 1720 cm\(^{-1}\).

Preparation of 9-(p-Bromomethylbenzoyl)-nonanoic Acid (17). - To 5 g (0.018 mole) of 9-(p-toluyl)-nonanoic acid in 100 ml carbon tetrachloride was added a few crystals of "Vazo" (azobisisobutyronitrile, Dupont) and the amounts of N-bromo-succinimide shown in Table (1). In each reaction the mixture was allowed to reflux for 2 hr, filtered hot and then cooled. A precipitate was obtained upon cooling in each case. Recrystallization from ether-pentane gave two fractions each in reactions A and C and one in reaction B (cf. Table 1). The nmr spectra of these various fractions (cf. p. 59) seemed to show that the 1:1 reaction gave only benzyl bromination. Thus the bromination was repeated with a 1:1 molar ratio of 9-(p-toluyl)-nonanoic acid and NBS. A solid (mp 92-94) was obtained whose nmr spectrum (No. 775, CDCl\(_3\)) gave an identical spectrum as before with the exception of the appearance of a strong singlet at 7.3.

When the reaction was run again and the solid recrystallized several times from benzene-pentane (mp 103-104), nmr spectroscopy showed the singlet at 7.3 had shifted to 7.8.

Anal. Calcd for C\(_{17}\)H\(_{23}\)O\(_3\)Br: C, 57.47; H, 6.52; Br, 22.50. Found: C, 57.70; H, 6.64; Br, 22.60.

When a small amount of hydrogen bromide gas was passed into the sample, an nmr spectrum of the solution (No. 995, CDCl\(_3\)) again gave the singlet at 7.8. Recrystallization of the solid from acetone-water gave a white solid, (mp 105-106°), whose nmr
TABLE 1

Bromination of 9-(p-Toluyl)-nonanoic Acid with NBS

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Ratio of substrate to NBS</th>
<th>g NBS</th>
<th>Fractions obtained (g)</th>
<th>mp</th>
<th>Infrared Spectrum No.</th>
<th>Nmr Spectrum No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1:1</td>
<td>3.23</td>
<td>1.0</td>
<td>104-106</td>
<td>2166</td>
<td>736</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
<td>77-87</td>
<td>2167</td>
<td>751</td>
</tr>
<tr>
<td>B</td>
<td>1:2</td>
<td>6.46</td>
<td>2.0</td>
<td>102-104</td>
<td>2168</td>
<td>752</td>
</tr>
<tr>
<td>C</td>
<td>1:3</td>
<td>9.69</td>
<td>1.5</td>
<td>84-86</td>
<td>2169</td>
<td>753</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.75</td>
<td>71-74</td>
<td>2170</td>
<td>754</td>
</tr>
<tr>
<td>D</td>
<td>1:1</td>
<td></td>
<td></td>
<td>92-94</td>
<td></td>
<td>775</td>
</tr>
<tr>
<td>E</td>
<td>1:1</td>
<td></td>
<td></td>
<td>103-104(^a)</td>
<td>948</td>
<td>1002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>105-106(^b)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Recrystallized from benzene-pentane.

\(^b\) Recrystallized from acetone-water.
spectrum (No.1002, CDCl₃) exhibited no singlet previously appearing at 7.3 or 7.8.

**Anal.** Calcd for C₁₇H₂₃O₃Br: C, 57.47; H, 6.52; Br, 22.50. Found: C, 57.65; H, 6.45; Br, 22.29.

Yields of the bromination reaction ranged from 30-70%.

**Preparation of 9-(p-Hydroxymethylbenzoyl)-nonanoic Acid Lactone (15).** - A 5-l flask charged with 2 l of tetrahydrofuran was fitted with two reflux condensers, each of which was fitted with a dropping funnel. One funnel was charged with a solution of 0.5 g of 9-(p-bromomethylbenzoyl)-nonanoic acid in 250 ml of tetrahydrofuran; the other with a solution of 0.08 g of potassium hydroxide, 25 ml of water and 100 ml of tetrahydrofuran. Both solutions were added dropwise to the stirred, refluxing solvent over a period of 6 hr. A white solid which formed was separated by decantation. The solution was concentrated to an oily solid. An nmr spectrum (No.1039, CDCl₃) of the crude material gave a singlet at 5.13 and broad peaks at 1.1-1.8 and at 0.6-0.8. An infrared spectrum (No.2918, film) showed absorption at 1690 and 1735 cm⁻¹. Attempted separation by gas chromatography failed to give any positive results. Micro thin layer chromatography (eluent: 50% benzene in chloroform) showed two major spots as well as two minor ones.

The mixture was then dissolved in a minimum amount of chloroform and several thick layer chromatograms were prepared with the same eluent system. The two major bands were collected and extracted with ether. A white solid was obtained in both cases. The solid from the lower band showed only aliphatic carbon and hydrogen in the infrared (νₐₐ 3065B, double mull). The white solid from the upper band, mp 78-79.5, showed both ketone and ester carbonyls at 1685 and 1720 cm⁻¹, respectively, in the infrared (No.3085, CDCl₃). An nmr spectrum of this
upper band (No. 1148, CDCl₃) showed multiplets at 0.6-1.1 and 1.1-1.7, triplets at 2.2 and 2.8, a doublet at 7.7 and a singlet at 5.2

The ultraviolet spectrum (4000 No. 350, 1.1 x 10⁻⁴ M in ethanol) exhibited a λ max at 246 mμ, Φ = 13,800. The mass spectrum contained peaks at m/e 274 (molecular ion), 256, 228, 216, 189, 134, 118, and 90, with metastable peaks at about 239, 204 and 191.

Anal. Calcd for C₁₇H₂₂O₃: C, 74.42; H, 8.08. Found: C, 74.25; H, 8.11.

Attempted Preparation of 10-(p-Hydroxymethylphenyl)-decanoic Acid.

Method A. - A 1-l flask fitted with a reflux condenser was charged with 25 g (0.1 mole) of 9-(p-acetoxymethylbenzoyl)-nonanoic acid, 16.2 g (0.3 mole) of potassium hydroxide, 20 ml of hydrazine hydrate and 500 ml of diglyme. After a reflux period of 1.5 hr, the condenser was removed and the temperature of the solution allowed to rise to 195°. Refluxing was then continued for 12 hr.

The solution was concentrated and water and ether added. The aqueous layer was washed several times with ether and the ether layer concentrated until a yellow solid remained. The infrared spectrum (No. 4437, CHCl₃) and the nmr spectrum (No. 1851, CHCl₃) were identical to those of the starting material.

When the reaction was repeated in the same manner, a black oily material was isolated. Its infrared spectrum (No. 4512, film) showed no ketone carbonyl at 1685 cm⁻¹. An nmr spectrum (No. 1892, CHCl₃) contained no benzylic methylene singlet but a singlet at 2.3 (ArCH₃). The triplet at 2.9, characteristic of the starting material, was also missing.

Method B. - A mixture of 17 g (0.053 mole) of 9-(p-acetoxymethylbenzoyl)-nonanoic acid, 3.25 ml (0.53 mole) of hydrazine hydrate
and 50 ml of ethanol was heated for 15 min, then concentrated to a yellow oil. An infrared spectrum (No.4668, film) showed strong acetate and acid carbonyls and a weak aromatic ketone. An nmr spectrum (No.1952, CHCl₃) contained singlets at 2.1 (-OCOCH₃), 5.2 and 6.6 (shifted on dilution), triplets at 3.1 (ArCOCH₂⁻) and 2.2 (-CH₂COO⁻) and a broad multiplet at 1.0-2.0 (-CH₂⁻).

The yellow oil was taken up in 30 ml of dry DMSO and added to a red solution of 18 g (0.16 mole) of anhydrous potassium t-butoxide in 150 ml of dry DMSO. The red solution turned black on addition of the oil, and a gas was evolved over a period of several hours. The black solution was then acidified, diluted with water and extracted six times with methylene chloride. The combined methylene chloride fractions were then washed with water, dried over anhydrous magnesium sulfate and concentrated to give a dark amber, waxy solid. An infrared spectrum (No.4668A, film) showed broad absorption at 1680-1760 cm⁻¹, indicating the presence of at least some aromatic ketone. An nmr spectrum (No.1962, CHCl₃) showed a singlet at 4.75 (-CH₂O⁻) and triplets at 3.0 and 2.3 with relative intensities of 1:2. Thin layer chromatography showed the presence of starting material as well as two other major components and three minor ones.

Preparation of Oxalyl Chloride. - A 1-l flask fitted with a reflux condenser, gas inlet tube and solid addition apparatus, was charged with 90 g of oxalic acid. The flask was cooled in an ice bath and a positive pressure of nitrogen maintained while 390 g of powdered phosphorus pentachloride was added over a period of 12 hr. Within 48 hr the solid material began to liquefy. After one week at room temperature the liquid was distilled at atmospheric pressure, the fraction at 60-100°.
being collected. By redistillation through a column packed with helices, two fractions were separated: oxalyl chloride, 32.1 g (25%), bp 60-62, and phosphorus oxychloride, bp 100-105.

In subsequent preparations oxalyl chloride was obtained in yields up to 50%.

Preparation of 9-(\(p\)-Acetoxymethylbenzoyl)-nonanoic Acid (28).—A mixture of 2.2 g (6.2 x 10^{-3} mole) of 9-(\(p\)-bromomethylbenzoyl)-nonanoic acid, 2.2 g of anhydrous sodium acetate and 50 ml glacial acetic acid was refluxed 10 hr with stirring. The solution was then concentrated and the resulting solid washed with water. The remaining solid (1.18 g, 56%, mp 77-80) was air dried, and an infrared spectrum (No.3647, double mull) showed both ketone and acid carbonyls at 1690 and 1710 cm\(^{-1}\), respectively, as well as an ester carbonyl at 1750 cm\(^{-1}\). An nmr spectrum (No.1464, CHCl\(_3\)) showed singlets at 2.15 and 5.16; broad triplets at 3.0 and 2.31; and a broad multiplet at 1.34-1.7. Recrystallization from ether-pentane gave a white solid, mp 80-81.

An ultraviolet spectrum (No.304, 1.14 x 10^{-5} M in methanol gave a \(\lambda_{\text{max}}\) at 247 m\(\mu\), \(f\) = 58,400.

Fischer Esterification of 9-(\(p\)-Acetoxymethylbenzoyl)-nonanoic Acid. - A 250-ml flask was charged with 2 g (0.006 mole) of 9-(\(p\)-acetoxymethylbenzoyl)-nonanoic acid and 100 ml of dry methanol and the contents saturated with hydrogen chloride gas. The mixture was allowed to reflux for 6 hr and then poured into 250 ml of water. A white solid precipitated. This was extracted several times with ether; the ether layers were combined, washed several times with sodium bicarbonate and water, dried over anhydrous magnesium sulfate and concentrated.
An infrared spectrum (No. 5728, double mull) on the resulting white solid showed hydroxyl absorption at 3400 cm\(^{-1}\) and two carbonyls at 1695 and 1750 cm\(^{-1}\). An nmr spectrum (No. 2852, CDCl\(_3\)) contained singlets at 4.8 and 3.68. Thin layer chromatography (eluent: 5% methanol-chloroform) showed the presence of two major components, which were subsequently separated by thick layer chromatography. Both strips were extracted with ether and concentrated; the bottom layer containing most of the material (about 0.7 g). This solid was recrystallized from ether-hexane to give a white crystalline solid, mp 69.5-70.5°. An infrared spectrum (no. 5795, double mull) and an nmr spectrum (No. 2921, CDCl\(_3\)) were both consistent for methyl 9-(\(\alpha\)-hydroxymethylbenzoyl)-nonanoate. The nmr spectrum showed singlets at 4.76 and 3.57; triplets at 2.3 and 2.9, a quartet at 7.7 and a broad multiplet at 1-2. An ultraviolet spectrum (14 No. 207, 1.22 x 10\(^{-5}\) M in methanol) showed a \(\lambda_{\text{max}}\) at 250 m\(\mu\), \(\varepsilon = 54,000\).

**Anal.** Calcd for C\(_{18}\)H\(_{26}\)O\(_4\): C, 70.56; H, 8.55. Found: C, 70.38; H, 8.43.

**Examination of Side Products in the Fischer Esterification of 9-(\(\alpha\)-Acetoxymethylbenzoyl)-nonanoic Acid.** - Thick layer chromatography of the product of the Fischer esterification of 9-(\(\alpha\)-acetoxymethylbenzoyl)-nonanoic acid, using 5% methanol-chloroform as the eluent, produced two major components. An nmr spectrum (No. 3048, CDCl\(_3\)) of the lower component showed it to be the expected 9-(\(\alpha\)-hydroxymethylbenzoyl)-nonanoic acid.

An nmr (No. 3042, CDCl\(_3\)) of the upper component on the thick layer plate showed small aromatic absorption at 7-8; a strong singlet at 3.68; a weak triplet at 2.9 and a strong one at 2.4; strong methylene protons at 1-2 and a weak signal at 0.8-1. An infrared spectrum (21 No. 6614, CDCl\(_3\)) showed strong
carbonyl absorption at 1740 with a shoulder at 1685 cm\(^{-1}\).

Thin layer chromatography of this top band, using 100 ml of 1:1 hexane: chloroform with 10 drops methanol as the eluent, gave two major spots and one minor spot between them. Thick layer chromatography using the same eluent gave two bands.

An infrared spectrum (No.5908, film) of the upper component (an oil) and an nmr spectrum (No.3107, CDCl\(_3\)) proved to be identical to those of dimethyl sebacate (IR No. 5911, film; nmr No.1191, neat).

An infrared spectrum (No.5907, CHCl\(_3\)) of the lower component (a yellow, waxy solid) showed three carbonyl bands at 1695, 1725 and 1740 cm\(^{-1}\). An nmr spectrum (No.3105, CDCl\(_3\)) showed triplets at 2.3 and 2.9; phenyl protons at 8.0-8.12 (closely resolved doublet); methylenes at 1-2 (strong) and 0.8-1.0 (weak); a strong singlet at 3.67 and a weak singlet at 3.96.

More of this component was separated by thick layer chromatography and a more concentrated nmr (No.3289, CDCl\(_3\)) showed all the same peaks as above plus an aldehyde proton at 10.

The appearance of the singlet at 10 ppm and the absence of any PhCH\(_2\)X absorption indicate that this group has been oxidized to the benzaldehyde.

**Preparation of 9-(p-Hydroxymethylbenzoyl)-nonanoic Acid (29).**

**Method A.** A 100-ml flask fitted with a condenser was charged with 50 mg of 9-(p-hydroxymethylbenzoyl)-nonanoic acid lactone, 50 ml of 50% aqueous potassium hydroxide and 50 ml of ether. The stirred solution was refluxed for 6 hr. The ether layer was washed several times with water and the aqueous layers combined. The aqueous phase was then washed twice with ether, acidified with dilute hydrochloric acid, extracted with ether.
and the ether extracts concentrated. The residue, mp 90-92, was a white-yellow solid whose spectrum (No. 1266, CDCl$_3$) contained a sharp singlet at 5.2 and a broad weaker one at 5.7. Heating the solution (increasing the solubility) caused a shift in the latter peak to 5.85. A broad triplet also appeared at 2.9 as well as one at 2.25, with the methylene absorption at 1.2-1.6.

An infrared spectrum (No. 3168, halocarbon mull) showed a broad peak at 3250 cm$^{-1}$ and one at 3300-2500 cm$^{-1}$. A sharp peak appeared at 1670 with a shoulder at 1700 cm$^{-1}$. An ultraviolet spectrum (4000 No. 351, 3.42 x 10$^{-5}$ M in CHCl$_3$) exhibited a λ$_{\text{max}}$ at 251 mμ, $\varepsilon$ = 20,450; lit.$^1$ 251 mμ, $\varepsilon$ = 20,500.

**Anal.** Calcd for C$_{17}$H$_{24}$O$_4$: C, 69.84; H, 8.27. Found: C, 64.06; H, 7.86.

**Method B.** A mixture of one gram (0.003 mole) of 9-(p-bromo-methylbenzoyl)-nonanoic acid, 2 g of potassium hydroxide and 100 ml of 50% aqueous methanol was refluxed for 3 hr. After acidification, the solution was concentrated, extracted with ether and the ether extract concentrated to give a yellow-orange, oily solid. Attempted recrystallization from ether-pentane solution gave 15 mg of an orange solid, mp 45-51°. Repeated recrystallization elevated the melting point to 90-91°. The nmr spectrum (No. 1355, CHCl$_3$) showed a multiplet at 1-2 (-CH$_2$-), triplets at 2.2 (-CH$_2$COOH), 2.9 (ArCOCH$_2$-) and a singlet at 4.7 (ArCH$_2$O-). Infrared spectra (No. 3319, 3320, double mull) showed -OH absorption at about 3400 cm$^{-1}$.

An ultraviolet spectrum (14 No. 203, 1.71 x 10$^{-5}$ M in methanol) showed a λ$_{\text{max}}$ at 250.3 mμ, $\varepsilon$ = 49,100.

**Anal.** Calcd for C$_{17}$H$_{24}$O$_4$: C, 69.84; H, 8.27. Found: C, 69.64; H, 8.29.
Fischer Esterification of 9-(p-Hydroxymethylbenzoyl)-nonanoic Acid. - A 250-ml flask fitted with a reflux condenser was charged with 2.6 g (0.009 mole) of 9-(p-hydroxymethylbenzoyl)-nonanoic acid and 100 ml of dry methanol and saturated with hydrogen chloride gas. The solution was then refluxed for 14 hr and poured into 250 ml of ice water. The aqueous layer was extracted several times with ether; the ether layers were combined, washed successively with sodium bicarbonate and water, dried over anhydrous magnesium sulfate and concentrated. The oily solid obtained was recrystallized from ether-hexane to give a yellow-white solid.

The solid was separated into fractions by thick layer chromatography (eluent: 5% methanol-chloroform). The top band was extracted with chloroform and concentrated to give a white, crystalline material, mp 70-70.5. A mixture melting point with known methyl 9-(p-hydroxymethylbenzoyl)-nonanoate characterized in a previous experiment (p. 35) showed no depression, 69-70°.

An infrared spectrum (No.5805, double mull) and an nmr spectrum (No.2991, CDCl$_3$) were identical to those of the hydroxy ester.

An nmr spectrum (No.3010, CDCl$_3$) at -70 and -75° showed no shifts to higher or lower field.

Attempted Preparation of 10-(p-Hydroxymethylbenzoyl)-2-decanone (31). Part A. Preparation of 9-(p-Acetoxymethylbenzoyl)-nonanoyl Chloride (30). - A 50-ml flask fitted with a magnetic stirring apparatus and a reflux condenser was charged with 4 g (0.012 mole) of 9-(p-acetoxymethylbenzoyl)-nonanoic acid and 3 ml (0.035 mole) of oxalyl chloride, and stirring was maintained for 4 hr at room temperature. The solid gradually dissolved in the oxalyl chloride with the evolution of a
gas. An nmr spectrum of the solution (No.3018, COCl\(_2\)) gave a quartet at 7.6; a strong triplet at 2.9; singlets at 5.1 and 2.05; and a broad multiplet at 1-2.

To the clear amber liquid was added 5 ml dry benzene, and distillation allowed to proceed until the temperature exceeded 65°.

**Part B. Preparation of Methylcadmium Reagent.** - A solution of 10 g (0.105 mole) of methyl bromide in 100 ml of dry ether was added dropwise, with stirring, to a mixture of 2.5 g (0.103 mole) of magnesium turnings in 25 ml of dry ether. Upon completion of reaction 20 g (0.1 mole) of anhydrous cadmium chloride was added and the mixture allowed to reflux for 2 hr. A Gilman test for the Grignard reagent was negative.

**Part C. Reaction of 9-((p-Acetoxymethylbenzoyl))-nonanoyl Chloride with Methylcadmium Chloride.** - An ethereal solution of all the 9-((p-acetoxymethylbenzoyl))-nonanoyl chloride (Part A) was added over a period of 2 hr to all the methylcadmium chloride (Part B) at such a rate that spontaneous refluxing was maintained. Then refluxing was allowed to continue for 12 hr.

After the ethereal solution had been added to 100 ml of dilute hydrochloric acid, three liquid layers separated. The mixture was reduced to two phases upon addition of 25 ml each of water and ether.

The aqueous layer was washed several times with ether and the ether layers combined. The ether solution was then washed with water, dilute sodium hydroxide and again with water, dried over anhydrous magnesium sulfate and concentrated, to give an amber oil containing a waxy solid.

Addition of ether or acetone to this mixture forced a solid out of solution, the solid being soluble in chloroform.
Thus the whole mixture was dissolved in a minimum amount of chloroform. Its nmr spectrum (No.1710, CHCl$_3$) showed a doublet centered at 5.12; singlets at 4.74, 4.64 (weak), 3.6 (shifts on dilution), 2.1 (very strong, possibly a doublet); triplets at 2.9 and 2.35; and a broad multiplet at 1.0-1.8 with a small shoulder at 0.8-1.0. Expansion of the peak at 2.1 showed the possibility of a triplet on which is superimposed a singlet.

An infrared spectrum (No.4150, CHCl$_3$) showed broad absorption at 3500 cm$^{-1}$, as well as carbonyl absorption at 1745, 1702 and 1680 cm$^{-1}$ but no broad acid absorption below 3000 cm$^{-1}$.

Thin layer chromatography indicated the presence of five components, one being a major constituent.

A concentrated chloroform solution of the mixture was separated on a Florisil column in the usual manner into two main fractions.

Nmr (No.1754, CDCl$_3$) and infrared (No.4233, double mull) spectra indicated the first fraction, mp 42.5-43.5, was the 10-(p-acetoxymethylbenzoyl)-2-decanone.

Anal. Calcd for C$_{20}$H$_{28}$O$_4$: C, 72.26; H, 8.49. Found: C, 73.15; H, 9.68.

Nmr (No.1753, CDCl$_3$) and infrared (No.4234, double mull) spectra indicated the second fraction, mp 67.5-68.5, to be the 10-(p-hydroxymethylbenzoyl)-2-decanone.

Anal. Calcd for C$_{18}$H$_{26}$O$_3$: C, 74.45; H, 9.02. Found: C, 72.08; H, 8.70.

Further attempts at synthesis resulted in very low yields, usually not enough to allow recrystallization for an analytical sample.
Attempted Preparation of 11- (p-Hydroxymethylphenyl)-11-hydroxydodecan-2-one (32). - A 1-1 flask was charged with 500 ml of dry ether and 1 g of lithium metal, and methyl bromide gas was bubbled into the stirred suspension until almost all the lithium was consumed. To this stirred solution maintained at ice-bath temperature was added over a period of 1 hr a solution of 3.5 g (0.01 mole) of 9-(2-acetoxymethylbenzoyl)-nonanoic acid in 200 ml of dry ether. The solution was then hydrolyzed with an ice-dilute hydrochloric acid mixture and extracted several times with ether. The ether extracts were combined, dried over magnesium sulfate, and concentrated to give a waxy solid. An nmr spectrum (No.3332, CDCl₃) exhibited phenyl protons at 7.3-8.1; singlets at 5.18, 4.78, 4.7 and 2.1 (strong); triplets at 3.0 and 2.4; and a multiplet at 1-2. A strong singlet \((\mathrm{CH}_3)_3\mathrm{OH}) was also seen at 1.28. An infrared spectrum (No.6835, CHCl₃) indicated the presence of acid. An iodoform test was positive.

The solid was dried at 68° (0.3 mm) to remove any residual t-butyl alcohol, taken up in ether, washed several times with base and then water, dried over magnesium sulfate and concentrated to give a yellow, waxy solid. An infrared spectrum (No.6903, CHCl₃) showed sharp absorption at 3610 cm⁻¹ (nonbonded -OH) and broad absorption at 3300-3600 cm⁻¹ (bonded -OH), a strong carbonyl at 1720 cm and a weak carbonyl at 1695 cm⁻¹ (ArCO⁻).

An nmr spectrum (No.3422, CDCl₃) showed phenyl absorption at 7.3-7.5; broad, weak singlets at 5.17, 5.12, 4.64, 2.1 and 1.52; broad multiplets at 2.6-3.0 (weak), 2.2-2.5 (weak), 1.1-2.0 (strong) and 0.7-1.1 (weak). The nmr spectrum (No.3422, 3431, CDCl₃), at varying temperatures (-46.5°, -30°, -11.5°, +3°, 30°, 35°, 42°, 49°, 55°) showed no shift in the position
of the peaks.

The basic washings were combined, acidified, and extracted with ether. The ether layer was dried over magnesium sulfate, then added over a period of 1 hr to 60 ml of a solution of 2.1 M commercial methyllithium in ether. Stirring was then allowed to continue for 6 hr and finally the solution was hydrolyzed. This was then extracted with ether and the dried extracts concentrated to give a yellow oil.

An infrared spectrum (No. 6918, film) showed no \(-OH\) or carbonyl absorption.

An nmr spectrum (No. 3451, CDCl\(_3\)) showed a broad multiplet at 0.4-2 and a weak singlet at 4.7.

**Preparation of 9-(\(p\)-Acetoxymethylbenzoyl)-nonanal (33).** - A 250-ml flask, fitted with a low temperature thermometer, stirrer assembly, addition funnel and gas inlet and outlet tubes, was charged with the acid chloride prepared as in Part A of the previous experiment dissolved in 50 ml of dry diglyme. The flask was immersed in a dry ice-acetone bath and a mixture of 7.6 g (0.03 mole) of lithium aluminum \(t\)-butoxyhydride in 50 ml of dry diglyme was added to the stirred mixture over the period of 1 hr. The bath was then removed and the solution allowed to come to room temperature over a period of 2 hr. The solution was then poured into 100 g of ice and dilute hydrochloric acid. The aqueous mixture was washed several times with ether; the ether layers were combined, washed successively with dilute sodium hydroxide and water, dried over anhydrous magnesium sulfate and concentrated.

The resulting yellow, waxy solid was recrystallized six times from ether-hexane to give a white solid, mp 110-112.
An infrared spectrum (No.4855, double mull) showed no acid or hydroxyl -OH absorption but contained two strong carbonyl bands at 1680 and 1760 cm$^{-1}$, with a shoulder at 1720 cm$^{-1}$. The nmr spectrum (No.2021, CHCl$_3$) showed singlets at 5.18, 9.88 and 2.13; a triplet at 3.0; and a broad multiplet at 1.2-2.0.

An ultraviolet spectrum (14 No.205) gave a $\lambda_{\text{max}}$ at 247.2 nm.

A Bordwell test for aldehydes was positive.

**Anal. Calcd for C$_{19}$H$_{26}$O$_4$:** C, 71.67; H, 8.23. **Found:** C, 71.46; H, 8.05.

Subsequent attempts at synthesizing the aldehyde with tetrahydrofuran as the solvent led to a cleaner product in higher yields. After the reaction was complete the solvent was evaporated, ether added and the work-up carried out in the same manner.

**Attempted Saponification of 9-(p-Acetoxymethylbenzoyl)-nonanal.**

A solution of 200 ml of tetrahydrofuran, 100 ml of 10% sodium hydroxide and 1 g of 9-(p-acetoxymethylbenzoyl)-nonanal was stirred for 30 hr at room temperature. To this mixture was added 100 ml of water and the solution was extracted repeatedly with ether. Acidification of the basic aqueous layer and extraction with ether gave a solid, the infrared spectrum of which (No.5155, double mull) was identical to that of 9-(p-hydroxy-methylbenzoyl)-nonanoic acid. No material was recovered from the original ether extracts.

The hydrolysis was again attempted with 1% sodium hydroxide in a nitrogen atmosphere. The neutral fraction consisted of dark amber oil containing a small amount of a white solid. An infrared spectrum (No.5290, film) of the white solid showed strong aliphatic absorption at 2900 cm$^{-1}$ but very weak
carbonyl absorption. The infrared spectrum of the amber oil (No. 5288, film) showed strong carbonyl absorption at 1700-1750 cm$^{-1}$. The oil was chromatographed on a Florisil column, and a thin layer chromatogram of the resulting fractions showed four major components. Similar components were combined into Fractions 1-4.

An nmr spectrum (No. 2184, CHCl$_3$) of Fraction 3 indicated the presence of hydroxy aldehyde. Further examination of this fraction by thin layer chromatography showed it to be a mixture of four components. Thick layer chromatography gave one major crystalline material, mp 47-47.5, and several minor oily fractions. An infrared spectrum (No. 5305, film) of the solid showed hydroxyl absorption at 3100-3450 cm$^{-1}$ and carbonyl absorption at 1750 and 1685 cm$^{-1}$. An nmr spectrum (No. 2185, CDCl$_3$) was consistent with either the aldehyde or acid structure. Further attempts at the hydrolysis of the acetoxy aldehyde gave, in very poor yields, a mixture which appeared to contain mostly hydroxy acid.

The Behavior of 9-(p-Acetoxymethylbenzoyl)-nonanal under Fischer Esterification Conditions. - A 250-ml flask, fitted with a reflux condenser, gas inlet tube and magnetic stirring apparatus, was charged with 100 ml dry methanol, 0.3 g 9-(p-acetoxymethylbenzoyl)-nonanal and the solution saturated with hydrogen chloride gas. After the solution had been allowed to reflux under nitrogen for 10 hr, it was poured into 500 ml of an ice-water mixture. Filtration yielded a white solid.

An infrared spectrum (No. 6044, double mull) and an nmr spectrum (No. 3183, CDCl$_3$) were identical with the spectra of methyl 9-(p-hydroxymethylbenzoyl)-nonanoate previously reported.
Preparation of 10-(p-Hydroxymethylphenyl)-1,10-decandiol (37). - A 250-ml flask fitted with a reflux condenser, addition funnel and magnetic stirring apparatus was charged with 1.6 g of lithium aluminum hydride in 70 ml of anhydrous ether. To this stirred solution was added, over a period of 2 hr, 2 g of 9-(p-acetoxymethylbenzoyl)-nonanoic acid. Refluxing was allowed to continue for 4 hr. The mixture was decomposed by the drop-wise addition first of water and then of a dilute hydrochloric acid-ice mixture. The ether layer was separated, dried over anhydrous magnesium sulfate and concentrated to give a mixture of a white crystalline material and a yellow oil. This mixture was dissolved in ether; the ether layer was washed with sodium bicarbonate and then with water, dried over anhydrous magnesium sulfate and concentrated to give 1.36 g of a mixture consisting of a white, waxy solid and an oil. The infrared spectrum of both the solid and the oil (No. 5354, 5355, film) were identical, both showing strong hydroxyl absorption. When the mixture was again taken up in ether and the ether allowed to evaporate at room temperature, a white powder was the only material formed.

Recrystallization from ether-hexane gave 1.67 g (97.5%) of white crystals, mp 88-90°. An infrared spectrum (No.5358, double mull) showed strong alcohol and aliphatic absorption with no carbonyl absorption.

Anal. Calcd for C₁₇H₂₈O₃: C, 72.82; H, 10.06. Found: C, 72.8, 73.5; H, 10.3, 10.1. The molecular ion peak in the mass spectrum was at 280 m/e.

Preparation of Manganese Dioxide "B". - A porcelain dish was covered with 200 g manganese carbonate and heated for 24 hr at 280°. The resultant black powder was cooled, mixed with 400 ml of a 15% aqueous nitric acid solution, filtered and washed with distilled water until the washings tested for a pH of 4-5. The black powder was then heated for 12 hr at 250°.
Attempted Preparation of 9-(p-Formylbenzoyl)-1-nonanol (34)
with Manganese Dioxide "B". - A 1-l flask fitted with a magnetic stirring assembly was charged with 5 g (0.018 mole) of 10-(p-hydroxymethylphenyl)-1,10-decanediol, 50 g of manganese dioxide "B" and 500 ml of dry ether, and the mixture was stirred for five days. It was then filtered and the solid washed with ether and acetone, the washings being combined with the filtrate. The filtrate was concentrated to give 2 g of a yellow, oily solid. Upon addition of acetone this was converted into a white powder and a yellow solution, which were separated by filtration.

An infrared spectrum (No.5660, double mull) of the white powder (mp 108-1; 151-153) contained only one sharp carbonyl band at 1690 cm\(^{-1}\). The filtrate was concentrated to an amber oil. An infrared spectrum (No.5659, film) showed strong -OH absorption at 3200-3700 cm\(^{-1}\) and a broad, strong carbonyl band centered at 1710 cm\(^{-1}\). A thin layer chromatogram showed it to be a mixture of at least five components.

Attempted Preparation of 9-(p-Formylbenzoyl)-nonanoic Acid (36) with Dimethyl Sulfoxide. - A 1-l flask fitted with a reflux condenser was charged with 3 g (0.011 mole) of 9-(p-hydroxymethylbenzoyl)-nonanoic acid and 50 ml of dry dimethyl sulfoxide. A stream of air was passed through the refluxing mixture for 24 hr. Then it was cooled, poured into 200 ml of water and extracted with ether.

An nmr spectrum (No.2941, CHCl\(_3\)) of the resulting solid showed a singlet at 4.78 (ArCH\(_2\)O-), indicating oxidation had not taken place. Successive attempts gave the same results.
Attempted Preparation of 9-(p-Formylbenzoyl)-nonanoic Acid (36) by the Action of Nitric Acid on the Benzyl Bromide.  

A 100-ml flask fitted with a reflux condenser was charged with 2.5 g (0.007 mole) of 9-(p-bromomethylbenzoyl)-nonanoic acid and 34.4 ml of 10% nitric acid. After a reflux period of 15 hr, the mixture was cooled and filtered to give a white solid (mp 123-127). An infrared spectrum (No.5852, double mull) contained a large, broad carbonyl between 1700-1800 cm\(^{-1}\) as well as broad acid absorption at 3300-2000 cm\(^{-1}\). It was insoluble in chloroform and only partially soluble in acetone. After recrystallization from acetone-water, its melting point was 126.5-128°.

**Anal.** Calcd for C\(_{17}H_{22}O_4\): C, 70.32; H, 7.64; N.E. 290.

**Found:** C, 57.37; H, 8.25; N.E. 131.

Use of a 20% nitric solution produced the same results.

Attempted Preparation of 9-(p-Formylbenzoyl)-nonanoic Acid (36) with Cromyl Chloride.  

A 500-ml flask fitted with a thermometer, mechanical stirrer and addition funnel was charged with 5 g of 9-(p-toluyl)-nonanoic acid and 100 ml of chloroform and cooled to ice-bath temperature. To the stirred solution was added, over a period of 1 hr, 3.2 ml of chromyl chloride dissolved in 100 ml of chloroform. The temperature remained below 5° during the addition. Then 50 ml of chloroform was added and the solution allowed to come to room temperature with stirring over a period of several hours. When it was poured into 2-3 l of ice water with constant stirring, an emulsion resulted. The chloroform was removed under vacuum and ether was added to give two distinct layers. The ether layer was dried over magnesium sulfate and concentrated to give a small amount of an oily solid. This was taken up in a minimum
amount of boiling ether, and hexane was added to the point of cloudiness. When cooled, the mixture deposited a yellow powder (0.3 g). The filtrate was concentrated to 50 ml, and a light yellow solid precipitated. Infrared spectra (No. 5754, 5756, double mull) and nmr spectra (No. 2907, 2908, CHCl₃) of the two solids were identical. The nmr spectrum contained a sharp singlet at 2.4, indicating the tolyl methyl group had not been oxidized.

**Attempted Preparation of 9-(p-Formylbenzoyl)-nonanoic Acid (36) by the Action of DMSO on the Benzyl Tosylate.**

A 250-ml flask was charged with 7 g (0.02 mole) of 9-(p-bromo-methylbenzoyl)-nonanoic acid, 5.6 g (0.02 mole) of silver p-toluenesulfonate and 100 ml acetonitrile. The mixture was stirred for 2 hr in the dark in an ice bath and then allowed to come to room temperature in the dark over a period of 10 hr. It was then poured into an ice-water mixture, extracted with ether and the ether extractions dried over anhydrous magnesium sulfate and concentrated to give 5 g of a white solid, mp 79-88°. An nmr spectrum (No. 3176, CDCl₃) showed singlets at 5.15, 4.5 and 2.43, indicating the presence of unchanged benzyl bromide along with benzyl tosylate.

The white solid was returned to the flask with 4 g of silver tosylate and 100 ml acetonitrile. Stirring was maintained in the dark for 48 hr. The clear solution was worked up in the same manner as before to give a white solid, mp 98.0-98.5° after two recrystallizations from an ether-hexane mixture. An nmr spectrum (No. 3177, CDCl₃) showed the strong singlet at 5.15 but no absorption at 4.5.

**Anal. Calcd for C₂₄H₃₀O₆S: C, 64.55; H, 6.77; S, 7.18. Found: C, 64.23; H, 7.02; S, 7.35.**
To a stirred solution of 120 ml DMSO and 5 g sodium bicarbonate maintained at 100° was added 2 g of the benzyl tosylate prepared above. After stirring for 5 min the solution was cooled rapidly to room temperature and then poured onto 500 g of ice. Filtration gave an off white solid which proved to be insoluble in ether. Suspension in dilute hydrochloric acid followed by filtration still gave an ether insoluble solid. An infrared spectrum (No. 6082, double mull) showed carbonyl adsorption at 1690 and 1750 cm⁻¹ but no acid -OH at 3000 cm⁻¹.

The aqueous DMSO filtrate was acidified and extracted with ether; the ether layer was dried over magnesium sulfate and concentrated to give 0.36 g of a white solid. An infrared spectrum (No. 6117, double mull) showed at least two, and possibly three, carbonyl peaks between 1690 and 1710 cm⁻¹. An nmr spectrum (No. 3204, CDCl₃) showed a small singlet at 10.13 but also showed phenyl protons similar to the benzyl tosylate or to p-toluenesulfonic acid itself. The mass spectrum gave no molecular ion peak (m/e 290).

Thin layer chromatography indicated the solid to be a mixture of the hydroxy acid (formed by hydrolysis of the benzyl tosylate) and several other components.

Preparation of 9-(p-Formylbenzoyl)-nonanoic Acid (36) from the gem-Diacetate 39. - Method A. - A 250-ml flask, fitted with a mechanical stirrer and a long immersion thermometer, was charged with 50 ml of glacial acetic acid, 50 ml of acetic anhydride and 3 g (0.011 mole) of 9-(p-toluyl)-nonanoic acid. The flask was immersed in an ice-salt bath; and when the temperature of the solution was less than 5°, 3 ml of concentrated sulfuric acid was added.

When the solution had again cooled below 5°, 4 g (0.04 mole) of chromic anhydride was added at such a rate so as to
keep the temperature below 5°. The solution was stirred for 10 min after completion of addition of the \( \text{CrO}_3 \); then it was poured into 2 l of ice and 1 l of water. A brown, waxy solid was obtained by filtration.

An infrared spectrum (No. 5242, film) showed characteristic gem-diacetate absorption at 1770 cm\(^{-1}\). An nmr spectrum (No. 3137, CDCl\(_3\)) showed a quartet at 7.5-8; singlets at 7.75 (ArCH(OAc)\(_2\)), 2.21 (-OCOCH\(_3\)) and 10.1 (-CHO); triplets at 2.9 and 2.3; and a broad multiplet at 1-2.

The entire sample was taken up in 200 ml of a 2% sodium carbonate solution and stirred for 1 hr at room temperature. The solution was then acidified with dilute acid; the solid was collected and dried in vacuo. An nmr spectrum (No. 3138, CDCl\(_3\)) showed the presence of the acetate methyl at 2.21, indicating incomplete hydrolysis. When the hydrolysis was attempted over a period of 24 hr, an nmr spectrum (No. 3146, CDCl\(_3\)) of the yellow solid product still showed the presence of some acetate. Several attempts at purifying this solid (including recrystallization and thick layer chromatography) always resulted in a material whose nmr spectrum contained the singlet at 2.21.

**Method B** - The diacetate was again synthesized and then some hydrolyzed with 5% sodium hydroxide. After acidification, a yellow powder was obtained, mp 167-180°, after three recrystallizations from ether-hexane. The powder was soluble only in large volumes of the common solvents. Attempted recrystallizations from a variety of other solvents, such as chloroform and ethanol, always gave the same yellow powder.

**Method C** - Freshly prepared diacetate (2 g, crude) was dissolved in 10 ml of ethanol, 10 ml of water and 1 ml of concentrated sulfuric acid; and the solution was refluxed for 40 min. The mixture was then filtered hot, and the filtrate
allowed to cool to give a yellow precipitate. An infrared spectrum (No.7041, double mull) showed broad -OH absorption at 3000 cm\(^{-1}\) and carbonyl absorption at 1690-1720 and 1750 cm\(^{-1}\). A Bordwell test for aldehydes\(^\text{46}\) gave an immediate greenish-blue precipitate. A 2,4-dinitrophenylhydrazine test gave a red solid, mp 160\(^\circ\). The yellow solid was recrystallized twice from ethanol to give a white crystalline material, mp 122.5-123.5\(^\circ\).

**Anal.** Calcd for C\(_{17}H_{22}O_4^+\): C, 70.32; H, 7.64. Found: C, 67.84; H, 7.73.

An infrared spectrum (No.7055, double mull) on this purified material showed broad -OH at 3000 cm\(^{-1}\) and carbonyl absorption at 1740, 1705 and 1690 cm\(^{-1}\). An nmr spectrum (No. 3502, CDCl\(_3\)) showed quartets at 8.13 and 4.14; triplets at 3 and 2.3; a broad multiplet (with several sharp peaks superimposed on it) at 1-2; and a singlet at 7.28 (relative intensities 4:2:2:2:15:1, respectively). The nmr spectrum was measured again after the material had been dried at 80\(^\circ\) (0.3 mm) for 4 hr; it was unchanged. Since the nmr spectrum indicated the presence of ethanol, the analysis was recalculated on the basis of the benzaldehydic acid with one ethanol of crystallization.

**Anal.** Calcd for C\(_{19}H_{28}O_5^+\): C, 67.83; H, 8.39. Found: C, 67.84; H, 7.73.

An ultraviolet spectrum (14 No.222, CH\(_3\)OH) showed \(\lambda_{\text{max}}\) at 249.3 m\(\mu\) and 289.4 m\(\mu\).

**Fischer Esterifications of the Products Obtained from the Basic and Acidic Hydrolysis of 9-(p-Diacetoxymethylbenzoyl)-nonanoic Acid.** - **A. Esterification of Product from Basic Hydrolysis.** - One gram of the product from Method B in the previous experiment was dissolved in 50 ml of dry methanol. The solution was saturated with hydrogen chloride gas and refluxed for 6 hr.
The solid obtained after pouring the solution into 1 l of ice water was dried and recrystallized several times from ethanol to give white crystals, mp 92.5-94.

\textit{Anal.} Calcd for C_{18}H_{24}O_4: C, 71.03; H, 7.95. Found: C, 69.24; H, 8.12.

An infrared spectrum (No. 6811, double mull) of this purified product showed carbonyl absorption at 1740, 1730 and 1690 cm\(^{-1}\). An nmr spectrum (No. 3488, CDCl\(_3\)) showed a broad multiplet at 1.2-2, triplets at 2.3 and 2.9, singlets at 3.68 and 3.97; and a closely resolved doublet at 8.07 (relative intensities 12:2:2:3:3:4, respectively).

Since all the evidence seems to point to the existence of an ester methoxy and an acetal methoxy, the analysis was recalculated for an acetal dimer of the aldehyde minus one methoxyl group.

\textit{Anal.} Calcd for C_{38}H_{54}O_9: C, 69.70; H, 8.31. Found: C, 69.24; H, 8.12.

\textbf{B. Esterification of Product from Acidic Hydrolysis.}

One gram of 9-([p-formylbenzoyl])-nonanoic acid with one ethanol of crystallization was dissolved in 50 ml of methanol. The solution was saturated with hydrogen chloride gas and refluxed for 5 hr. A yellow solid was obtained after pouring the solution into 1 l of ice. Filtration and recrystallization from ethanol gave a white solid, mp 90.5-91°, whose infrared spectrum (No. 7146, CDCl\(_3\)) and nmr spectrum (No. 3526, CDCl\(_3\)) were essentially the same as those of the product obtained in Part A. A mixture melting point of this product and that obtained in Part A showed no depression, mmmp 91.5-92°. An ultraviolet spectrum showed a \(\lambda_{\text{max}}\) at 251 mp with a shoulder at 291 mp.

\textit{Anal.} Calcd for C_{38}H_{54}O_9: C, 69.70; H, 8.31. Found: C, 70.57; H, 8.44.
Fischer Esterification Experiment with 9-[p-(Diacetoxymethyl)-benzoyl]-nonanoic Acid. - A 250-ml flask was charged with 0.9 g of 9-[p-(diacetoxymethyl)-benzoyl]-nonanoic acid, 100 ml dry methanol and saturated with hydrogen chloride gas and allowed to reflux for 7 hr. The contents were then poured into an ice-water mixture and the product was extracted several times with ether. The ether extracts were combined, dried over magnesium sulfate and concentrated.

An infrared spectrum (No.5984, film) was identical to the suspected oxidation product in the Fischer esterification of 9-(p-acetoxymethylbenzoyl)-nonanoic acid (No.6190, CHCl₃) (see p.34). An nmr spectrum (No.3161, CDCl₃) contained singlets at 3.95, 3.68, 3.32, and 10; a closely resolved doublet at 8.1; triplets at 2.9 and 2.3; and broad multiplets at 1-2 and 0.8-1 ppm. This nmr spectrum was also identical to that (No.3289, CDCl₃) of the possible oxidation product described above.
RESULTS AND DISCUSSION

In order to examine the various long chain ω-acyl acids and alcohols for ring-chain tautomerism, a model cyclic compound first had to be synthesized. Abnormal spectral properties of such a macrocyclic compound could then be utilized in the identification of a ring tautomer. It was therefore decided to attempt the preparation of one of the macrocyclic ansa lactones 14 or 15.

\[
\begin{align*}
14 & \quad \text{CH}_2\text{O} \quad \text{C=O} \\
& \quad \text{O} \quad \text{(CH}_2\text{)}_9 \quad \text{C=O} \\
15 & \quad \text{CH}_2\text{O} \\
& \quad \text{O} \quad \text{C} \quad \text{(CH}_2\text{)}_8 \\
\end{align*}
\]

The presence of the ketone function at this time appeared immaterial.

The preparation of lactone 15 had previously been attempted by way of bromination of p-toluylnonanoic acid (16) to give 9-(p-bromomethylbenzoyl)-nonanoic acid (17).

\[
\begin{align*}
16 & \quad \text{CH}_3 \\
& \quad \text{O} \quad \text{C} \quad \text{(CH}_2\text{)}_8 \text{COOH} \\
17 & \quad \text{CH}_2\text{Br} \\
& \quad \text{O} \quad \text{C} \quad \text{(CH}_2\text{)}_8 \text{COOH} \\
\end{align*}
\]

However, at the time, no method of positive structure proof
of 17 was available. Thus it was initially decided to place another "handle" in the ring at the position para to the long chain acid.

The first "handle" chosen was the phenylnitro group. Phenylnitromethane was synthesized according to the method of Kornblum. 36 The action of aluminum chloride on this compound was then tested. After several hours contact with Lewis acid, phenylnitromethane was recovered quantitatively. Thus it was assumed that this compound would undergo Friedel-Crafts acylation without serious complications involving the nitro group. However, one consideration was the activation or deactivation of the ring by the nitromethyl group. If it served to de-activate the ring, acylation would be impeded. 56 This was shown to be the case. The dichromate oxidation product of the reaction mixture from phenylnitromethane and acetyl chloride under Friedel-Crafts conditions proved to be benzoic acid, rather than terephthalic acid.

Another "handle" which might be attached to an ω-phenyl acid was thought to be the chloromethyl group. The procedure for the attempted synthesis of 9-(p-chloromethyl-phenyl)-decanoic acid (25) is outlined in Scheme 1.

\[
\begin{align*}
\text{CH}_3\text{OOC-}(\text{CH}_2)_8\text{COOCH}_3 & \rightarrow \text{18} \\
\text{18} & \rightarrow \text{19} \\
\text{SOCl}_2 & \rightarrow \text{CH}_3\text{OOC-}(\text{CH}_2)_8\text{COCl} \\
\text{CH}_3\text{OOC-}(\text{CH}_2)_8\text{COCl} & \rightarrow \text{20} \\
\text{C}_6\text{H}_6 & \rightarrow \\
\text{C}_6\text{H}_6 & \rightarrow \text{AlCl}_3
\end{align*}
\]
When barium hydroxide is added slowly to a methanol-benzene solution of dimethyl sebacate, an immediate hydrolysis of one of the ester functions takes place with precipitation of the half ester-half barium salt of the acid. Acidification of this salt then allows one to isolate the half acid-ester, methyl hydrogen sebacate. Since it is possible that both ester groups in any one molecule might be hydrolyzed, thus resulting in sebacic acid after hydrolysis, a distillation of the crude acidification product is advantageous.

Treatment of methyl hydrogen sebacate with thionyl chloride to give the half acid chloride-ester and treatment of this with benzene under Friedel-Crafts acylation conditions, followed by complete hydrolysis, gives 9-benzoylnonanoic acid. The hydrolysis step is necessary since partial hydrolysis occurs in the Friedel-Crafts reaction.

Treatment of 9-benzoylnonanoic acid with hydrazine hydrate and potassium hydroxide under Wolff-Kischner conditions followed by re-esterification of the intermediate acid leads to methyl 10-phenyl-decanoate. However, when the product was subjected to chloro-
methylation under a variety of conditions, the only product was starting material.

An investigation was made into the chloromethylation of toluene by varying the chloromethylating reagent, catalyst and solvent. In none of these attempts was p-chloromethyl-toluene formed.

It was therefore decided to re-examine the bromination of 9-toluylnonanoic acid $16$. The acid was prepared$^1$ from $18$ by way of 9-carbomethoxynonanoyl chloride (20), which was treated with toluene under Friedel-Crafts acylating conditions, as seen in Scheme 2.

**SCHEME 2**

$$\text{CH}_3\text{OOC-(CH}_2\text{)}_8\text{COOCH}_3 \xrightarrow{\text{Ba(OH)}_2, \text{H}^+} \xrightarrow{\text{SOCI}_2} \text{CH}_3\text{OOC-(CH}_2\text{)}_8\text{COCl}$$

$$\text{C}_6\text{H}_5\text{CH}_3 \xrightarrow{\text{AlCl}_3, \text{NaOH}, \text{H}^+} \text{O=C-(CH}_2\text{)}_8\text{COOH}$$

The acid $16$ has three potentially reactive sites for reaction with a free radical reagent such as N-bromosuccinimide (NBS). Bromination could take place at the methyl group or at either methylene alpha to the carbonyl or the carboxy group. Thus it was decided to examine the bromination carried out with varying
amounts of reagent. Experiments were carried out where the NSB:16 ratio was 1:1, 2:1 and 3:1. The nmr spectrum of 16 shows a sharp singlet at 2.3 due to the methyl group and broad triplets at 2.2 and 2.9 due, respectively, to the methylenes alpha to the acid and ketone functions. Thus bromination of the methyl group should be accompanied by the disappearance of the singlet at 2.3 and the appearance of a singlet at 4-5.57

If the methylenes are substituted, then one should observe the corresponding shifts of the broad triplets at 2.2 and 2.9 to broad triplets at 4-5.5. Examination of the spectra (Figures 4 and 5) shows conclusively that the reaction does take place and only at the methyl group when a 1:1 ratio of NBS:p-toluylnonanoic acid (16) is used. A mixture of bromination products resulted from the use of larger amounts of NBS.

\[
\text{(1 mole)} \quad \begin{array}{c}
\text{CH}_3 \\
0=\text{C-(CH}_2\text{)}_8\text{COOH}
\end{array} \quad \xrightarrow{(1 \text{ mole}) \text{NBS}} \quad \begin{array}{c}
\text{CH}_2\text{Br} \\
0=\text{C-(CH}_2\text{)}_8\text{COOH}
\end{array}
\]

16 \quad 17

The necessary functional groups being present, the compound was now set up for cyclization.
Figure 4

Nmr Spectrum of 16 (CDCl₃)

CH₃-\(\text{O-CH}_2\text{(CH}_2\text{)}_6\text{-CH}_2\text{COOH}\)

(a) (b) (c) (d) (e)

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Figure 5

Nmr Spectra of Bromination Products of 16 (CDCl₃)

NBS:16 (1:1)

NBS:16 (2:1)

NBS:16 (3:1)

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A competing reaction with cyclization is that of polymerization.

\[
\begin{align*}
\text{CH}_2\text{Br} & \quad \text{CH}_2\text{O} \\
\text{O} = \text{C-(CH}_2\text{)}_8\text{COOH} & \quad \text{O} = \text{C-(CH}_2\text{)}_8\text{COH} \\
\end{align*}
\]

17 15

or

\[
\text{OCH}_2\text{--}[\text{O} = \text{C-(CH}_2\text{)}_8\text{C}]_x
\]

26

In order to keep the ratio of monomer to polymer at a minimum, a high-dilution technique was employed. Very dilute THF solutions of the bromo acid 17 and potassium hydroxide were added simultaneously and separately over a long period of time to a large volume of a vigorously stirred, refluxing solution of THF. The final maximum concentration of 17 was \(6 \times 10^{-3}\) M. Because of this dilution and the reaction conditions, the acid-base reaction would occur at a much faster rate than the hydrolysis of the bromide. The carboxylate group could then displace a bromide ion, forming monomeric lactone 15 or polymeric ester 26. The lactone, formed intramolecularly, should be favored over the intermolecular polymeric product because of the dilution.

Waugh and Fessenden\(^3\) have shown that protons influenced by the shielding cone of an aromatic ring exhibit a dramatic shift to higher field in the nmr spectrum. Should the lactone 15 be formed from 17, this upfield shift should be observed since at least some of the methylene protons should be situated...
"over" the ring (Figure 6).

Figure 6

Shielding Effects in 15

\[ [1 + m + n] = 8 \]

A comparison of the nmr spectra of bromo acid 17 (Figure 7) and the product of the high-dilution reaction with base (Figure 8) shows this shift to higher field and thus indicates the structure as lactone rather than polymer.
Figure 7

Nmr Spectrum of 17 (CDCl₃)

(b)

O=C-(CH₂)₆-CH₂-COOH

(c) (d) (e)

Figure 8

Nmr Spectrum of 15 (CDCl₃)

(f)

O=C-(CH₂)-(CH₂)₆

(e) (c&d)

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A shift of the singlet at 4.5 (ArCH₂Br) to 5.2 (ArCH₂O⁻CO⁻)³ is also consistent with the lactone structure. Another notable change is that of the phenyl protons from a quartet at 7.6 to a closely resolved apparent doublet at 7.9.

An ultraviolet spectrum of toluyl acid 16 showed a λₘ₉ at 252 mμ; that of the lactone 15 shows a λₘ₉ at 246 mμ. It was first thought that such a shift was due to a distortion in the chromophore brought about by lactone formation. However, an ultraviolet spectrum of 9-(p-acetoxyethylbenzoyl)-nonanoic acid 28 also shows a λₘ₉ at 247 mμ.

Thus without further investigation of similar compounds of varying ring size, one cannot attribute such a shift in the ultraviolet spectrum to any property of the ring.

In any case the model compound had been prepared, and the predicted unusual properties in the nmr spectrum were noted. These properties, specifically the shift to higher field, could be used to check for the existence of ring formation in the tautomerism of ω-acyl acids and alcohols.
The ω-acyl acids and esters investigated along with the ring-chain equilibria expected are shown in Scheme 3.

**SCHEME 3**

\[
\begin{align*}
\text{CH}_2\text{OAc} & \quad \leftrightarrow \quad \text{CH}_2\text{O} - \text{OAc} \\
\text{O} = \text{C} - (\text{CH}_2)^8\text{COOH} & \quad \text{or} \quad \text{O} = \text{C} - (\text{CH}_2)^8\text{COOH} \\
\text{CH}_2\text{OH} & \quad \leftrightarrow \quad \text{CH}_2\text{O} - \text{OH} \\
\text{O} = \text{C} - (\text{CH}_2)^8\text{COOH} & \quad \text{or} \quad \text{O} = \text{C} - (\text{CH}_2)^8\text{COOH} \\
\text{CH}_2\text{OAc} & \quad \leftrightarrow \quad \text{CH}_2\text{O} - \text{Cl} \\
\text{O} = \text{C} - (\text{CH}_2)^8\text{COCl} & \quad \text{or} \quad \text{O} = \text{C} - (\text{CH}_2)^8\text{COCl} \\
\end{align*}
\]
31 \quad 31a

32 \quad 32a

33 \quad 33a

34 \quad 34a

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The possibility of tautomerism was examined in all cases by nmr analysis and, where appropriate, by Fischer esterification and nmr analysis of these products.

Of the \( \omega \)-acyl acids and alcohols prepared, there are some which can be considered better candidates for ring-chain tautomerism than others. One of the poorer ones was the acetoxy acid 28. The cyclic tautomer 28a or 28b, which might be formed if the tautomerism were to take place, would be a monoacetylated, monoesterified ortho acid. However, since 28 was an intermediate in the preparation of better candidates for the tautomerism, it was decided to examine its behavior.

The acetoxy acid 28 was prepared by the displacement
of bromide ion with acetate ion.

\[
\begin{align*}
\text{CH}_2\text{Br} & \quad \xrightarrow{\text{NaOAc}} \quad \text{CH}_2\text{OAc} \\
\text{O=-(CH}_2\text{)}_8\text{COOH} & \quad \xrightarrow{\text{HOAc}} \quad \text{O=-(CH}_2\text{)}_8\text{COOH}
\end{align*}
\]

An nmr analysis of 28 showed no high field protons indicative of cyclic structure but was consistent with the normal acetoxy acid structure (Figure 9).

Figure 9

Nmr Spectrum of 28 (CDCl$_3$)

\[
\begin{align*}
\text{CH}_3\text{COOCH}_2\text{-} & \quad \text{CO-CH}_2\text{-} \quad (\text{CH}_2\text{)}_6\text{CH}_2\text{COOH} \\
\text{(a)} & \quad \text{(b)} & \quad \text{(c)} & \quad \text{(d)} & \quad \text{(e)} & \quad \text{(f)}
\end{align*}
\]

It is, of course, entirely possible that a ring tautomer would be present to an extent too small to be detected by the nmr method. Because all of the potential chain tautomers were of high molecular weight (>250), it was difficult to obtain a concentrated solution for nmr analysis. Thus
the presence of ring tautomer to the extent of a few percent might easily be undetectable in the nmr spectrum.

The acetoxy acid 28 and many of the other chain tautomers were therefore subjected to the Fischer esterification conditions in an attempt to "trap" a cyclic tautomer. Such a tautomer might be the result of an equilibration of products or it might be one component of a mixture of chain and ring tautomers.

Thus for 28, one might predict the formation of the cyclic compound F29b from the following equilibria.2

\[
\text{CH}_2\text{OAc} \rightleftharpoons \text{CH}_2\text{O-} \text{OAc} \quad \text{O=C-(CH}_2)_8\text{COOH} \rightleftharpoons \text{O=C-(CH}_2)_8\text{OH}
\]

\[
\text{CH}_2\text{OH} \rightleftharpoons \text{CH}_2\text{O-} \text{OH} \quad \text{H}^+ \quad \text{CH}_2\text{OH} \rightleftharpoons \text{CH}_2\text{O-} \text{OAc} \quad \text{H}^+ \quad \text{CH}_2\text{OH} \rightleftharpoons \text{CH}_2\text{O-} \text{OCH}_3 \quad \text{H}^+
\]

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Compound F29b, an ortho ester, should be more stable than the ring compound 28a or 28b. During the reaction hydrolysis of the benzyl acetate to the benzyl alcohol was observed. Hence the equilibrium between 28 and F29 involving loss of the acetate ion is included in Scheme 4. An nmr analysis of this Fischer product, purified by thick layer chromatography, showed only the hydroxy ester to be present (Figure 10).

The nmr spectrum (Figure 11) of the remaining product (after thick layer chromatography of the Fischer product of 28) was quite different. It showed the absence of the benzyl methylene (ArCH2O-), the appearance of singlets at 10 (characteristic of an aldehyde proton) and 3.96 and — most noteworthy — the appearance of a weak multiplet at 0.7-1.0. Apparently the acetoxy or hydroxymethyl group had undergone oxidation with formation of the aldehyde F36. The appearance of the multiplet at 0.7-1.0 (possibly caused by -CH2- shielded by the ring) and the singlet at 3.96 (caused by the methinyl proton) indicates
the presence of a cyclic structure such as F36a (cf Scheme 5).

Figure 11
Nmr Spectrum of F36, (CDCl₃)

This ring tautomer could result either before or after esterification of 36.
Thus the synthesis of the benzaldehyde acid 36 and its Fischer esterification would be of great interest. This synthesis and nmr analysis will be discussed later.

Another candidate similar to 28 in its ability to undergo ring-chain tautomerism is the hydroxy acid 29, whose cyclic tautomer 29a would probably be less stable than 28a or 28b. The acid 29 was prepared by basic hydrolysis of the bromo acid 17.
An nmr analysis of purified 29, however, showed no cyclic structure to be present, at least not to an extent that could be detected in the nmr spectrum. In an attempt to "trap" a cyclic structure under Fischer conditions, as was attempted in the case of the acetoxy acid 28, the hydroxy acid 29 was similarly treated. An nmr analysis, however, even at several different temperatures, failed to show any cyclic structure such as F29b. In fact the Fischer esterification of 29 gave the same products as those from 28: hydroxy ester F29 and benaldehyde ester F36.

\[
\begin{align*}
\text{F29b} \\
\text{CH}_2\text{O} & \quad \text{C} & \quad \text{OCH}_3 \\
\text{O}=\text{C}\text{-(CH}_2\text{)}_8\text{COOH} & \quad \text{O}=\text{C}\text{-(CH}_2\text{)}_8\text{COOCH}_3 \\
\end{align*}
\]

The formation of a cyclic tautomer of an \( \omega \)-hydroxy acid such as 29 is not particularly favorable, however. The cyclic tautomer of an \( \omega \)-hydroxy aldehyde or ketone should be more stable since it is a hemiacetal; and its Fischer esterification product would be an acetal. Thus it was decided to attempt the synthesis of the \( \omega \)-hydroxymethyl ketone 31 by
the reaction of methylcadmium reagent with the acid chloride 30.

\[
\begin{align*}
\text{CH}_2\text{OAc} & \quad \text{(COCl)}_2 \quad \text{CH}_2\text{OAc} \\
\text{O} &= \text{C-} - \text{(CH}_2\text{)}_8\text{COOH} & \quad \text{O} &= \text{C-} - \text{(CH}_2\text{)}_8\text{COCl} \\
\end{align*}
\]

\(\text{28}\) \quad \text{CH}_3\text{CdCl} \quad \text{H}_2\text{O} - \text{C} - \text{(CH}_3\text{)} - \text{(CH}_2\text{)}_8\text{COCH}_3

\[\text{31b}\]

A mixture of products, obtained in small yield, seemed to contain 31 and 31b. Although repeated attempts failed to produce either methyl ketone in sufficient yield to be isolated in pure form, an nmr spectrum of the crude mixture showed no evidence of any cyclic tautomer.

A second method of preparing an \(\omega\)-hydroxymethyl ketone such as 31 is the reaction of methyllithium with an \(\omega\)-acetoxy acid such as 28. Although the tertiary alcohol 32 would be the expected product, the loss of the original

\[
\begin{align*}
\text{CH}_2\text{OAc} & \quad \text{CH}_2\text{OH} \\
\text{O} &= \text{C-} - \text{(CH}_2\text{)}_8\text{COOH} & \quad \text{HO} - \text{C} - \text{(CH}_3\text{)} - \text{(CH}_2\text{)}_8\text{COCH}_3 \\
\end{align*}
\]

\(\text{28}\) \quad \text{32}\]
The product from 28 and methyllithium after one hour, obtained in very low yield, appeared to contain a methyl ketone. However, no evidence for a cyclic structure such as 32a was observed.

When the reaction was allowed to proceed for six hours, the only product obtained showed neither carbonyl absorption in the infrared nor phenyl protons in the nmr spectrum. It appeared to be a hydrocarbon. Apparently chain cleavage and further reaction of the acid function with methyllithium had occurred. This would explain the poor yield, even in the one-hour reaction.

Since the acid chloride 30 was prepared as an intermediate and is a candidate for ring-chain tautomerism, its nmr spectrum was also analyzed (Figure 12).

Figure 12
Nmr Spectrum of 30 [(COCl)₂]
As can be seen in Figure 12, no evidence for cyclic tautomer such as 30a or 30b was observed.

Another potentially good candidate for the tautomerism is the ω-acetoxy or ω-hydroxy aldehyde 33 or 34. Thus the acid chloride 30 was treated with lithium aluminum tri-(t-butoxy)-hydride, the aliphatic aldehyde 33 being obtained in fair yields.

\[
\begin{align*}
\text{CH}_2\text{OAc} & \quad \text{LiAl(O-t-Bu)}_3\text{H} & \quad \text{CH}_2\text{OAc} \\
\circ & \quad \xrightarrow{\quad} & \quad \circ \\
\text{O=C-(CH}_2)_6\text{COCl} & \quad & \text{O=C-(CH}_2)_6\text{CHO} \\
30 & \quad & 33
\end{align*}
\]

Nmr analysis of 33 failed to show any cyclic tautomer such as 33a.

The aldehyde 33 was then subjected to Fischer esterification conditions for two reasons. It had been noted that the Fischer conditions brought about hydrolysis of the benzyl acetate in the case of 28. Thus from 33 one should expect the ω-hydroxy aldehyde 34. Should 34 participate in ring-chain tautomerism, thus giving the hemiacetal cyclic tautomer 34a, one might be able to "trap" the more stable acetal cyclic tautomer F34a as shown in Scheme 6.
However, despite precautions to exclude oxygen the only product isolated was that of oxidation of the aldehyde to the hydroxy ester F29.

In fact, any attempt at hydrolysis (basic or acidic) of the aldehydo acetate 33 resulted in oxidation of the aldehyde.
Up to this point all attempts had been directed toward the synthesis of aliphatic acyl compounds. Aromatic acyl compounds, such as 35 or 36, would be equally good candidates for tautomerism. Thus it was decided to attempt the synthesis of the benzaldehydo aliphatic alcohol 35 according to the sequence outlined in Scheme 7.

SCHEME 7

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Again, the production of the tertiary alcohol 35b would be of no consequence in observing the possible tautomerism. Both 35 and 35b should lead to cyclic tautomers similar to 34a.

The triol 37 was produced quantitatively by the action of lithium aluminum hydride on the acetoxy acid 28. Attempts at the selective oxidation of the triol with specially prepared manganese dioxide failed because the product could not be separated from the catalyst.

The side product in the Fischer esterification of the acetoxy acid 213 did appear to be an aldehyde. Also the benzaldehydo aliphatic acid 36 may be just as good a candidate for ring-chain tautomerism as the benzaldehydo aliphatic alcohol 35. The macrocyclic tautomer 36a resembles many cyclic tautomers which are known to exist in the normal ring series.

\[
\begin{align*}
\text{COOH} & \quad \text{COR} \\
\text{COOH} & \quad \text{HO-C-(CH}_2\text{)}_8\text{COO} \\
\text{CHO} & \quad \text{HO-C-(CH}_2\text{)}_8\text{COO} \\
\text{36} & \quad \text{36a}
\end{align*}
\]

For these reasons it was decided to attempt the synthesis of 36. An outline of some of the methods used to attempt the preparation of 36 is shown in Scheme 8.
**SCHEME 8**

1. 
   \[
   \text{CH}_2\text{OH} \quad \xrightarrow{\text{DMSO} \Delta \text{(O}_2)} \quad \text{CH}_2\text{Br} \quad \xrightarrow{10\% \ HNO}_3 \text{ or } 20\% \ HNO}_3 \n   \]

2. 
   \[
   \text{CH}_2\text{OTos} \quad \xrightarrow{\text{DMSO} \ NaHCO}_3 \ 100^\circ \text{ (10 min)}} \n   \]

3. 
   \[
   \text{CH}_3 \quad \xrightarrow{\text{CrO}_2\text{Cl}_2} \n   \]

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When the hydroxy acid 29 was refluxed with DMSO and a stream of air passed through the solution, only starting material was recovered. Treatment of the bromo acid 17 with refluxing nitric acid at several different concentrations produced an insoluble material that appeared to be a cleavage product. Regardless of its structure, it was not the expected product 36.

Kornblum\(^{52}\) had reported the reaction of benzyl tosylate with DMSO and sodium bicarbonate to give benzaldehyde. Thus the tosylate acid 38 was prepared from the bromo acid 17 and silver tosylate.

\[
\begin{align*}
\text{CH}_2\text{Br} & \quad \text{AgOTos} \\
\text{O=C-} \left(\text{CH}_2\right)_8\text{COOH} & \quad \text{CH}_2\text{CN} & \quad \text{O=C-} \left(\text{CH}_2\right)_8\text{COOH}
\end{align*}
\]

17 38

Treatment of 38 with DMSO and sodium bicarbonate for ten minutes at 100° gave several products, including the hydroxy acid 29 and a possible cleavage product, but no aldehyde. Treatment of the toluyl acid 16 with chromyl chloride failed to yield any isolable product.

Treatment of 16 with chromic anhydride\(^{53}\) gave the gem-diacetate 39.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CrO}_3 \\
\text{O=C-} \left(\text{CH}_2\right)_8\text{COOH} & \quad \text{HOAc} & \quad \text{Ac}_2\text{O} \\
0 & \quad \text{CH(OOCCH}_3\text{)}_2 \\
\text{O=C-} \left(\text{CH}_2\right)_8\text{COOH} & \quad 0
\end{align*}
\]

16 39

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Hydrolysis of $39$ under both basic and acidic conditions was used in order to prepare the aldehydo acid $36$. The product of the basic hydrolysis was a solid $40$, showing a marked insolubility in the common solvents such as acetone, chloroform and ether, as well as the aqueous base itself (Scheme 9). However, when acidic hydrolysis was attempted, $36$, containing one ethanol of crystallization, was isolated. The structure was proved by infrared and nmr spectroscopy, as well as by elemental analysis.

SCHEME 9

\[ \begin{align*}
5\% \text{NaOH} & \quad \text{NaOH} \\
39 & \quad \text{H}_2\text{SO}_4 \quad \text{EtOH} \quad \text{H}_2\text{O} \\
& \quad \text{CHO} \\
& \quad \overset{\cdot}{\text{C}_2\text{H}_5\text{OH}} \\
& \quad 0=\overset{-}{\text{C}}-(\text{CH}_2)_8\text{COOH} \\
36 & \end{align*} \]
The nmr spectrum (Figure 13) showed no evidence for cyclic tautomer 36a.

Figure 13
Nmr Spectrum of 36 (CDCl₃)

Again, in an effort to "trap" a cyclic tautomer such as F36a, both 40 and 36 were treated under Fischer esterification conditions.
The products of both Fischer esterifications were identical. Their nmr spectra (Figure 14) showed singlets at 7.31, 3.97 and 3.68. From this spectrum, other spectral data, an analysis, and from a consideration of the reaction conditions, a dimeric acetal structure 41 of the aldehyde 36 was theorized.

\[
\begin{align*}
\text{CH}_3\text{OH} & \xrightarrow{\text{H}^+} \text{CH}_3\text{O}-(\text{CH}_2)_{n}\text{COOCH} \\
\text{CH}_3\text{OH} & \xrightarrow{\text{H}^+} \text{CH}_3\text{O}-(\text{CH}_2)_{n}\text{C}0=0
\end{align*}
\]

\[
\begin{align*}
\text{O=C-(CH}_2)_8\text{COOCH} & \\
\text{CH}_3\text{O}-(\text{CH}_2)_{n}\text{C}0=0 & \\
\end{align*}
\]

Figure 14

Nmr Spectrum of 41 (CDCl₃)

(a) (b) (c) (d) (e) (f) (g)

In any case the nmr showed no evidence of cyclic tautomer such as F36a.

In general, a serious problem in synthesizing compounds capable of ring-chain tautomerism was the accumulation of pure products in large enough quantity to perform the necessary experiments. The compounds were sufficiently complex.
to allow for many side reactions, and the molar concentrations low enough to give poor yields.

In order to detect a ring tautomer of this size, it must be present to an extent of several per cent. Although a ring of sixteen or more members once formed is probably stable, the entropy of cyclization is not favorable. The best conditions for such macrocycle formation would be those at high dilution. However, at such low concentrations ring tautomers could not be observed with the present nmr instrumentation. Although the use of specialized equipment to obtain spectra at such concentrations might be possible, it was impractical in the present investigation.

In conclusion it would be worthwhile to attempt the synthesis and nmr analysis of compounds possessing as few functional groups as possible. If nmr instrumentation were available for use at low concentrations, it would be highly recommended.
BIBLIOGRAPHY


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12. K. Ziegler et. al., Ann., 504, 94 (1933); 512, 164 (1934); 513, 14 (1934); 528, 114 (1937); Ber., 67A, 139 (1934).


22. R. Huisgen et. al., Chem. Ber., 90, 1844 (1957); 93, 1496 (1960).


38. R. M. Stimson, (21 No.1979), University of New Hampshire.


43. We are grateful to Dr. Kenneth L. Rinehart, Jr., and associates, University of Illinois, Urbana, for determination of the mass spectrum.


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47. Analysis was obtained on the F & M Analyzer, University of New Hampshire, Durham, New Hampshire.


