THE CHEMISTRY AND STEREOCHEMISTRY
OF BICYCLO (6.2.1) UNDECANES

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TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>ii</td>
</tr>
<tr>
<td>LIST OF TABLES.</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>vi</td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>I.  INTRODUCTION.</td>
<td>1</td>
</tr>
<tr>
<td>Conformation in Cyclic Systems</td>
<td>1</td>
</tr>
<tr>
<td>The Synthesis of Medium Rings</td>
<td>9</td>
</tr>
<tr>
<td>Stereoisomerism in the Bicyclo[6.2.1]-undecane System</td>
<td>13</td>
</tr>
<tr>
<td>Statement of the Problem</td>
<td>15</td>
</tr>
<tr>
<td>II. RESULTS AND DISCUSSION.</td>
<td>18</td>
</tr>
<tr>
<td>Synthesis of the cis- and trans-1,3-Cyclopentanedicarboxylic Acids.</td>
<td>18</td>
</tr>
<tr>
<td>The Acyloin Reaction of Dimethyl trans-1,3-Cyclopentanedicarboxylate</td>
<td>28</td>
</tr>
<tr>
<td>The cis-Bicyclo[6.2.1]undecane System</td>
<td>44</td>
</tr>
<tr>
<td>III. EXPERIMENTARY</td>
<td>69</td>
</tr>
<tr>
<td>General</td>
<td>69</td>
</tr>
<tr>
<td>Characterization and Preparation of Starting Materials</td>
<td>70</td>
</tr>
<tr>
<td>Acyloin Reactions in Xylene</td>
<td>90</td>
</tr>
<tr>
<td>Acyloin Reactions in Dioxane</td>
<td>99</td>
</tr>
<tr>
<td>Chapter</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Preparation and Reactions of cis-Bicyclo[6.2.1]undecane Derivatives</td>
<td>123</td>
</tr>
<tr>
<td>IV. SUMMARY</td>
<td>135</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>138</td>
</tr>
<tr>
<td>BIOGRAPHICAL SKETCH</td>
<td>143</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table                                      Page
1. Physical Constants of Preliminary Compounds  27
2. NMR Resonance Peaks of cis-Bicyclic Products  68
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cyclodecane (11) conformation</td>
<td>8</td>
</tr>
<tr>
<td>2.</td>
<td>Cyclononane (12) conformation</td>
<td>8</td>
</tr>
<tr>
<td>3.</td>
<td>Characterization of trans products.</td>
<td>36</td>
</tr>
<tr>
<td>4.</td>
<td>Possible acyloin products</td>
<td>43</td>
</tr>
<tr>
<td>5.</td>
<td>Mechanism of the decomposition of the cis-acyloin-diketone mixture.</td>
<td>52</td>
</tr>
<tr>
<td>6.</td>
<td>Cyclodecane-based conformation of cis-bicyclo[6.2.1]undecane (33)</td>
<td>57</td>
</tr>
<tr>
<td>7.</td>
<td>Cyclodecane-based conformation of cis-bicyclo[6.2.1]undecan-4,5-dione (75)</td>
<td>57</td>
</tr>
<tr>
<td>10.</td>
<td>Cyclononane-based conformation B of cis-bicyclo[6.2.1]undecane (33)</td>
<td>60</td>
</tr>
<tr>
<td>11.</td>
<td>Cyclononane-based conformation B of cis-bicyclo[6.2.1]undecan-4,5-dione (75)</td>
<td>60</td>
</tr>
<tr>
<td>13.</td>
<td>Unsymmetrical conformation of cis-bicyclo[6.2.1]undecan-4,5-semidione (123)</td>
<td>62</td>
</tr>
<tr>
<td>14.</td>
<td>EPR spectrum of cis-bicyclo[6.2.1]-undecan-4,5-semidione (123)</td>
<td>63</td>
</tr>
</tbody>
</table>
CHAPTER I

INTRODUCTION

Conformation in Cyclic Systems

Monocyclic systems can be conveniently divided into four groups according to the number of ring atoms: small rings of three or four atoms, normal rings of five to seven atoms, medium rings of eight to twelve atoms, large rings of more than twelve atoms.¹ That this designation is not arbitrary is evidenced by the considerable differences in chemical and physical properties exhibited by the four groups.

Differences in stability of rings of different sizes was first explained by Baeyer.² It was proposed, assuming that all rings are planar, that the differences in stability are due to deviation of the internal bond angles from the normal carbon tetrahedral angle of 109° 28'. The small rings, with a large deviation from the normal tetrahedral angle, are more unstable than cyclopentane and cyclohexane in which the bond angles are more nearly tetrahedral.

It was pointed out by Sachse³ that rings of six or more carbon atoms are not necessarily planar and that
normal tetrahedral angles can be attained in these cases by not having all of the atoms in the same plane. The classic example is cyclohexane which can assume the chair (1) and boat (2) forms in which the angles are tetrahedral and free from Baeyer strain. Such forms, differing in spatial arrangement of atoms and produced by rotation about single bonds in a molecule, are known as conformational isomers. Considering only Baeyer strain, the chair and boat conformations of cyclohexane should be of equal energy; however, other sources of strain must be taken into consideration.

Prior to 1936, rotation about carbon–carbon single bonds was considered to be completely free. In 1936 calculation of the thermodynamic properties of ethane by means of statistical mechanics was attempted. It was found that the calculated values were in agreement with the experimental values only if a 3 kcal./mole barrier to free rotation were assumed. It was postulated that this barrier to rotation arises from a repulsion, similar to van der Waals repulsion, of electrons in the carbon–hydrogen bonds.
Rotation of one of the methyl groups in ethane with respect to the other gives rise to a sinusoidal energy curve as a function of the angle of rotation. Minima on the energy curve occur when the hydrogens are staggered as in the Newman projection (3), while maxima occur when the hydrogens are eclipsed (4).

Rotation about the 2-3 carbon-carbon bond in butane gives two eclipsed energy maxima (6 and 8) and two energy minima (5 and 7). The conformations are, in order of increasing severity of interaction and increasing energy: 5, 7, 6, 8.
If the methyl groups of the gauche orientation are replaced by a four-carbon bridge, the projection obtained is that which would be seen by looking down any carbon-carbon bond of the chair conformation of cyclohexane (1). Examination of the boat conformation of cyclohexane (2) reveals that two of the skew orientations of the chair conformation (1) are replaced by eclipsed orientations. Looking down the 2-3 and 5-6 carbon-carbon bonds of 2, the situation is that of eclipsed-butane conformation 6 in which the methyl groups have been replaced by a four-carbon bridge. The chair conformation of cyclohexane (1) can, therefore, be considered to be composed of six skew-butane interactions, while the boat conformation is composed of four skew-butane and two eclipsed-butane interactions.\(^\text{10}\) Since the eclipsed interactions are of higher energy than the skew interactions, the boat conformation is less favorable energetically than the chair conformation of cyclohexane. This difference in energy resulting from repulsion of bonds to adjacent atoms has been termed Pitzer strain.\(^\text{11}\)

A third type of strain energy which must be considered in cyclic systems arises from van der Waals repulsion of non-bonded atoms. An example of this type of interaction is present in the boat conformation of cyclohexane (2). The hydrogen atoms pointed toward each other on the 1 and 4 carbon atoms of 2 are closer together than the sum of
their individual van der Waals radii.\textsuperscript{12} This non-bonded repulsion adds to the total strain energy of 2 and makes it even less energetically favorable with respect to the chair conformation (1). This type of strain is more important in medium rings because of the characteristic proximity of atoms across the ring and has been termed transannular strain.\textsuperscript{10}

The bond angles of planar cyclopentane (108°) are nearly tetrahedral, and the molecule has little Baeyer strain. Considering Pitzer strain, however, all of the carbon-hydrogen bonds around the ring are eclipsed, giving rise to five interactions of the eclipsed-butane type (g) in which the methyls are replaced by a three-carbon bridge. Calculation of the thermodynamic functions of cyclopentane\textsuperscript{13} indicate that the potential energy is actually a maximum in the planar conformation. The molecule exists in a puckered conformation in which the Pitzer strain is partially relieved at the expense of Baeyer strain.

In medium ring systems the situation is much more complex since the number of possible conformations and interactions increases rapidly with ring size. Systematic investigation of models of the medium rings\textsuperscript{14} has shown that all of the possible conformations in this range contain unfavorable contributions from one or more of the types of strain discussed above, particularly from
transannular strain. A balance exists between the various types of strain, and, without quantitative knowledge of each, it is impossible to predict the conformation in a given system which corresponds to an energy minimum. In rings of more than twelve atoms it is again possible to construct models which are free from unfavorable eclipsed interactions and which have sufficient flexibility to permit relief of transannular strain.\textsuperscript{14} The physical and chemical properties of medium rings reflect their high energy content. The density and index of refraction of a homologous series of cycloalkanes and their derivatives increase rapidly in the medium-ring range,\textsuperscript{15,16} in contrast to the steady increase observed for a homologous series of acyclic compounds. Measurement of the heats of combustion of a series of cycloalkanes\textsuperscript{17} has revealed the presence of strain in medium rings relative to cyclohexane. The effect of ring size on the equilibrium constants for the reaction of a series of cycloalkanones with hydrogen cyanide\textsuperscript{18,19} and for the dissociation of polymethylene imines\textsuperscript{20} affords evidence for the unique properties of medium rings. In addition, Brown and co-workers have shown that the rates of solvolysis of cycloalkanyl tosylates\textsuperscript{21} and the rates of reduction of cycloalkanones with sodium borohydride\textsuperscript{22} are markedly dependent on ring size.

Various techniques have been utilized in the study
of medium-ring conformations. In 1959 Chiurdoglu and co-workers\textsuperscript{23,24} concluded from a careful study of the scissoring vibrational mode of the methylene group in the infrared spectra of a series of cycloalkanes and cycloalkanones that cyclodecane and cyclononane exist exclusively in the conformations \textsuperscript{9} and \textsuperscript{10}. In disagreement with these results, Dunitz and Prelog\textsuperscript{25} obtained the conformations \textsuperscript{11} and \textsuperscript{12}, shown in Figures 1 and 2, by X-ray crystallography of cyclodecyl and cyclononyl amine salts. Hendrickson\textsuperscript{26} employing basic equations defining the various types of ring strain, calculated the total strain energy of possible conformations of the medium rings. A single minimum energy conformation, identical to that (Figure 1) observed experimentally by Dunitz and Prelog, was calculated for cyclodecane. The two following conformations (\textsuperscript{13} and \textsuperscript{14}), with an energy separation of 1.1 kcal./mole, were calculated for cyclononane:
Figure 1. Cyclodecane (11) conformation\textsuperscript{25}

Figure 2. Cyclononane (12) conformation\textsuperscript{25}
The higher energy form \( \text{I}^4 \) is identical to the conformation of Figure 2, observed by Dunitz and Prelog for cyclo­nonane using X-ray crystallography. The experimental observation of the higher energy form was attributed to the effect of intermolecular forces within the crystal.\(^{26}\) Lown\(^{27}\) has recently obtained evidence from electron paramagnetic resonance (EPR) studies on cyclononanone ketyl for the existence of two conformations of cyclononanone having a small energy separation, in agreement with the work of Hendrickson.

The Synthesis of Medium Rings

The unique character of medium rings is also reflected in the difficulties encountered in their synthesis. Ring-closure reactions which are commonly applied to the synthesis of normal and small rings are unsuccessful in the medium-ring range. In a study of the synthesis of a series of cycloalkanones by the pyrolysis of rare-earth salts of dicarboxylic acids, Ruzicka and co-workers\(^{28,29}\) found that the yield of cyclic product decreases markedly in the medium-ring range to a minimum of less than 1 per cent for

\[
\begin{align*}
\text{(CH}_2\text{)}_n\text{CO}_2^- + M^{+2} & \xrightarrow{\Delta} (\text{CH}_2\text{)}_n\text{O} = O + M\text{CO}_3^- \\
\end{align*}
\]
the formation of cyclodecanone (15; n=9). The yields were found to improve somewhat in the large-ring molecules. Ziegler and co-workers\textsuperscript{30,31} developed a cyclization technique involving the reaction of a dinitrile (16) with lithium ethylanilide to give a ketimino nitrile (17). Using a high-dilution technique (P. Ruggli\textsuperscript{32}), excellent yields of normal and large-ring ketones are attainable; however, yields in the medium-ring range are negligible.

\[ \text{LiN(ET)}_2 \xrightarrow{\text{CH}_2\text{C}=\text{N}} \text{CH}_2\text{N}=\text{C} \xrightarrow{\text{H}^+} \text{CH}_2\text{N}=\text{C}=\text{O} \]

16 \hspace{1cm} 17

The investigation of medium rings was hampered by the lack of a suitable synthetic method before the introduction of the acyloin condensation,\textsuperscript{33,34} which gives good yields of cyclic products, even in the medium-ring range. In this reaction a diester (18) is added to a dispersion of metallic sodium in an inert solvent to give an \( \alpha \)-hydroxy ketone (19).

\[ \text{CH}_2\text{C}=\text{O} \xrightarrow{1) \text{Na}} \text{CH}_2\text{C}=\text{O} \]

18 \hspace{1cm} 19
The failure of ordinary condensation reactions to give significant yields of cyclic products in the medium-ring range has been attributed to the higher strain energy of the product and to the large entropy of activation to be overcome in bringing the ends of a long chain together.\(^{35}\) In the postulated mechanism of the acyloin condensation,\(^ {34}\) the electrophilic ester groups are absorbed initially onto the electron-rich surface of the sodium. Movement of the ester groups over the surface of the metal requires less energy than desorption, and when they approach closely enough, reaction occurs. The product, being less electrophilic than the ester groups, no longer adheres to the surface of the metal. Most of the entropy of activation is overcome by absorption onto the surface of the sodium, and cyclization is accomplished with less expenditure of energy than that required in a homogeneous reaction.

Van Heyningen\(^ {36}\) has shown that the acyloin reaction probably proceeds via a free radical mechanism. The following mechanistic scheme, involving initial formation of the sodium ketyl \(21\), was proposed for the acyloin condensation of 1-phenyl-1-carbethoxy cyclopentane (20):

\[
\begin{align*}
\text{ONa} & \\
\text{Na} & \\
\text{20} & \xrightarrow{\text{COET}} \xrightarrow{\text{21}} \xrightarrow{\text{22}} \xrightarrow{\text{NaCOET}}
\end{align*}
\]
Of the possible products shown above, the products of disproportionation (24 and 25) of the radical 22 and those of radical coupling (23, 26, and 27) were isolated. Neither the diketone 28, the aldehyde 29, nor its reduction product were isolated; however the yellow color of the product indicated the presence of 28.
Stereoisomerism in the Bicyclo[6.2.1]-undecane System

It is known that the number of stereoisomers of a molecule having \( n \) asymmetric centers is \( 2^n \). The actual number of stereoisomers observed in normal-ring, bridged bicyclic systems such as camphor (30) is one-half of the number theoretically predicted; therefore, camphor exists as one \( \text{dl} \) pair instead of two. This has been attributed to the fact that the bridge must be \( \text{cis} \), and the two asymmetric centers are not independent.\(^{37}\) In larger bicyclic systems, in which the rings are more flexible, the possibility of \( \text{trans} \) bridgehead bonding cannot be discounted. Dauben and Westman\(^{38}\) have shown that both \( \text{cis} \) and \( \text{trans} \) bridgehead bonding are present in the more flexible bicyclo[4.4.1]undecan-1-ols (31 and 32).

30 \hspace{1cm} 31 \text{cis} \hspace{1cm} 32 \text{trans}

The possibility of \( \text{cis-trans} \) bridgehead bonding in the bicyclo[6.2.1]undecane system has some interesting consequences. The bridgehead carbon atoms are asymmetric and identically substituted. Examination of the Newman projection along the 10-1 and 9-8 carbon-carbon bonds reveals...
two possible geometric isomers for the molecule with cis bridgehead bonding (33). In one isomer the six-carbon bridge is bonded to the cyclopentane ring pseudo-diaxially

(33), and in the other the bonding is pseudo-diequatorial (35). Because of the restriction imposed by the six-carbon bridge, the bonding is probably pseudo-diaxial. The two asymmetric carbons are of opposite absolute configuration, and the molecule as a whole is an optically inactive meso form. The trans-bonded bicyclo[6.2.1]undecane (36) also has two identically substituted bridgehead carbon atoms, but of the same absolute configuration. There is

only one geometric isomer since the bonding of the six-carbon bridge to the cyclopentane ring is pseudo-axial-
equatorial. There are, examining the Newman projections, two possible isomers of the trans molecule (37 and 38) which are mirror images, and the trans molecule should be optically active as the result of bridgehead bonding. Unsymmetrical derivatives of 36, such as the trans-acyloin 42 (R' = H, -OH), no longer have identically substituted bridgehead carbon atoms, and two dl pairs should be possible as the result of bridgehead asymmetry. In addition, the trans-acyloin 42 (R' = H, -OH) has another asymmetric center at the hydroxy carbon, and a total of eight isomers (2^3), four dl pairs, is possible. In symmetrical derivatives of 36, such as the trans-diketone 42 (R' = O), the situation with regard to stereochemistry is the same as in 36, and only one dl pair is possible. Resolution of a symmetrical derivative of 36 would constitute the first demonstration of optical activity resulting exclusively from bridgehead bonding.

Statement of the Problem

Although the chemistry and stereochemistry of bridged bicyclic systems containing normal rings have been extensively investigated, there is a lack of such information regarding the more inaccessible medium-ring, bridged bicyclic systems. The acyloin condensation has been used to prepare a variety of fused-ring and bridged-aromatic,
bicyclic systems. A considerable amount of work has been done on the effect of aliphatic substituents and the incorporation of heteroatoms, triple bonds, and double bonds on the formation of medium rings by the acyloin condensation; however, there apparently is no information available regarding the effect on the reaction of a bridging aliphatic chain, as encountered in the formation of a bridged bicyclic molecule. Also, the acyloin condensation has apparently not been explored previously as a method for synthesizing bridged-aliphatic, bicyclic systems. The bicyclo[6.2.1]undecanes are of interest both from the standpoint of their possible synthesis by means of the acyloin condensation and because of their stereochemistry.

It was, therefore, the goal of this research to investigate the acyloin condensation of the esters 39 and 41 (R=CH₃ or -CH₂CH₃) of the cis- and trans-1,3-cyclopentane-dipropionic acids to the corresponding cis- (40) and trans-bicyclo[6.2.1]undecane (42) derivatives (R'=H, -OH; =O) and to obtain information regarding the chemistry and stereochemistry of 40 and 42. The dipropionic esters 39 and 41 were chosen since it was believed that the side chains might be of sufficient length to allow cyclization of both cis and trans isomers.

In the course of this investigation it was necessary to characterize the previously unknown, isomeric cis- (39)
and trans-1,3-cyclopentanediisopropionic (41) acids (R=H) and to develop large-scale syntheses for these compounds.
CHAPTER II

RESULTS AND DISCUSSION

Synthesis of the cis- and trans-1,3-Cyclopentane-
dipropionic Acids

Since the cis- and trans-1,3-cyclopentanedipropionic acids were unreported, it was necessary to characterize the compounds unequivocally with regard to their stereochemistry and to develop convenient stereospecific synthetic routes starting with readily available reagents. cis-1,3-Cyclopentanedicarboxylic acid (44), obtained by the oxidation of norbornylene (43) with potassium permanganate, was epimerized to a mixture of the cis- (44) and trans-dicarboxylic (45) acids by treatment with concentrated hydrochloric acid according to the procedure of Pospischill. The mixture of isomeric acids was then separated by the method of Perkin and Scarborough.
Reaction of a mixture of the two isomeric acids with an excess of acetyl chloride gives a product containing unreacted 45 and the cis-anhydride 46. This mixture may be separated simply by extraction with ether, in which 45 is soluble but 46 insoluble. Recrystallization of 44 and 45 afforded the pure compounds, the melting points of which were in agreement with the reported values\textsuperscript{41} for the pure stereoisomers.

In considering various methods for the homologation of 44 and 45 to the corresponding isomeric cyclopentane-dipropionic acids, it was necessary to choose one in which the stereochemistry of the starting acids is preserved. The Arndt-Eistert synthesis\textsuperscript{43,44} was chosen because of its simplicity and because of its demonstrated stereospecificity.\textsuperscript{45} In the Arndt-Eistert synthesis, illustrated below for 44, a carboxylic acid is converted to its acid chloride 47 which is then treated with an excess of diazomethane. The resulting diazoketone 48 undergoes silver-
catalyzed rearrangement in the presence of base to give an intermediate ketene which reacts with water to give the expanded acid, in this case cis-1,3-cyclopentanedicarboxylic acid (50). Arndt-Eistert expansion of the two

dicarboxylic acids 44 and 45 afforded two isomeric acids which gave the correct analyses for the cis- (50) and trans-1,3-cyclopentanedicarboxylic (51) acids. Further homologation of the diacetic acids afforded pure cis-1,3-cyclopentanedi-1-propionic acid (52), m.p. 100-101°C., and trans-1,3-cyclopentanedi-1-propionic acid (53), m.p. 101-102°C.
The dipropionic acids 52 and 53 gave correct elemental analyses, the infrared spectra were different, and the mixture melting point of 52 with 53 was depressed by about 15°. Although the Arndt-Eistert synthesis is an excellent route to small quantities of pure acids, the problems involved in handling diazomethane prevented its use for the synthesis of quantities of 52 and 53 larger than a few grams.

In 1954 Stork and co-workers\textsuperscript{46,47} introduced a synthetic method for conveniently preparing $\alpha$-substituted ketones. The reaction involves addition of one or two moles of an electrophilic reagent such as an acyl halide or an $\alpha,\beta$-unsaturated ester or nitrile to the pyrrolidine or piperidine enamine of the ketone, followed by acid hydrolysis of the resulting enamine to the substituted ketone. Using the enamine synthesis, Westman and Paredes\textsuperscript{48} successfully added two moles of ethyl acrylate to the pyrrolidine enamine of cyclohexanone (54). Hydrolysis of the resulting enamine 55 afforded diethyl 2,6-cyclohexanone-dipropionate (56) in good yield.

\[ \text{[Diagram]} \]
Acrylonitrile was found to add readily to the pyrrolidine enamine of cyclopentanone (57) in an analogous fashion to give a 27 per cent yield of 2,5-cyclopentanone-dipropionitrile (58) and a small amount of a highly insoluble solid, m.p. 178-179°C., which was not identified. It was found that the yield of 58 could be increased to 66 per cent without formation of the unidentified by-product. This was accomplished by adding the piperidine enamine of cyclopentanone, instead of 57, to an excess of acrylonitrile (reversal of the usual order of addition). The
ketodinitrile $58$ was characterized by elemental analysis and by hydrolysis to the known $49$ cyclopentanonedipropionic acid ($59$).

Wolff-Kishner reduction (Huang-Minlon modification $50$) of $58$ afforded an acid, the melting point of which was several degrees below that of the pure trans-dipropionic acid $53$. The infrared spectrum of this material appeared to be identical to that of $53$, and the mixture melting point with $53$ was undepressed. Subjection of the ethyl ester of the acid to gas-liquid chromatographic (GLC) analysis on several different columns revealed only one peak. Based on these results, it was concluded that the acid obtained by Wolff-Kishner reduction of $58$ was a reasonably pure sample of the desired trans-dipropionic acid $53$.

The formation of predominantly trans-1,3-cyclohexane-dipropionic acid ($62$) by the Wolff-Kishner reduction of $56$ has also been observed. $48$ In this case it was postulated that under the strongly basic conditions of the reaction an equilibrium exists between the cis and trans isomers $56$ and $60$. The trans isomer $60$ preferentially forms the intermediate hydrazone $61$ because of steric interference by a "2-alkyl ketone" effect $51$ rather than the cis-hydrazone. The trans-hydrazone $61$ then undergoes decomposition to the trans-dipropionic acid $62$. A similar explanation could apply in the preferential formation of $53$ by
Wolff-Kishner reduction of 58; however, examination of models indicates that eclipsing of the α-equatorial bonds in cyclopentanone with the carbonyl group is not as severe as eclipsing of the α-equatorial bonds in cyclohexanone.

The following reaction sequence was considered as a synthetic route to the cis-dipropionic acid 52:
The first two steps of the synthesis led to the formation of the diethyl 2,5-cyclopentanoldipropionate (64) in good yield; however, considerable difficulty was encountered in dehydrating 64 to the diethyl 1,3-cyclopent-1-enedipropionate (65). Attempted dehydrations using sulfuric acid or phosphorus pentoxide were unsuccessful, but 65 was finally obtained in low yield by azeotropic removal of water using p-toluenesulfonic acid as a catalyst. Dehydration in this manner produced a large amount of the lactone 67; a similar result was observed by Paredes in attempts to dehydrate the corresponding cyclohexanol derivative. The unsaturated diester 65 was readily separated from 67 by column chromatography, and 65 was hydrolyzed to 1,3-cyclopent-1-enedipropionic acid (66).
The unsaturated acid 66 was characterized by infrared spectral analysis and by elemental analysis.

It was anticipated that catalytic hydrogenation of 66 would result predominantly or exclusively in the formation of the cis-dipropionic acid 52 because of sterically favored absorption onto the catalyst surface from the side of the molecule opposite the side chain. Hydrogenation of 66 in acetic acid using 5 per cent rhodium on alumina catalyst afforded a saturated acid in good yield. The infrared spectrum of the hydrogenation product was identical to that of the authentic sample of 52 prepared by the Arndt-Eistert route, and the mixture melting point with 52 was undepressed.

The cis- and trans-dipropionic acids 52 and 53 were converted to their methyl and ethyl esters for use in the acyloin condensations. Physical data for these and other compounds are listed in Table 1.
TABLE 1

PHYSICAL CONSTANTS OF PRELIMINARY COMPOUNDS

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Melting Point or Boiling Point</th>
<th>( n^20_D )</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{cis}-1,3-cyclopentane-diacetic acid (50)</td>
<td>m.p. 141-142°C.</td>
<td></td>
</tr>
<tr>
<td>\textit{trans}-1,3-cyclopentane-diacetic acid (51)</td>
<td>m.p. 152-153°C.</td>
<td></td>
</tr>
<tr>
<td>\textit{cis}-1,3-cyclopentane-dipropionic acid (52)</td>
<td>m.p. 100-101°C.</td>
<td></td>
</tr>
<tr>
<td>dimethyl \textit{cis}-1,3-cyclopentanedi-propionate (71)</td>
<td></td>
<td>1.4568</td>
</tr>
<tr>
<td>diethyl \textit{cis}-1,3-cyclopentanedi- propionate (69)</td>
<td>b.p. 121-123°C./ 0.25 mm.</td>
<td>1.4505</td>
</tr>
<tr>
<td>\textit{trans}-1,3-cyclopentane-di- propionic acid (53)</td>
<td>m.p. 101-102°C.</td>
<td></td>
</tr>
<tr>
<td>dimethyl \textit{trans}-1,3-cyclo- pentanedi-propionate (70)</td>
<td></td>
<td>1.4572</td>
</tr>
<tr>
<td>diethyl \textit{trans}-1,3-cyclo- pentanedi-propionate (68)</td>
<td>b.p. 121-123°C./ 0.15 mm.</td>
<td>1.4509</td>
</tr>
<tr>
<td>2,5-cyclopentanone-dipropionitrile (58)</td>
<td>m.p. 66-67°C.</td>
<td></td>
</tr>
<tr>
<td>diethyl 2,5-cyclopentanoldipropionate (64)</td>
<td>b.p. 175-176°C./ 0.55 mm.</td>
<td>1.4686</td>
</tr>
<tr>
<td>1,3-cyclopent-1-ene-dipropionic acid (66)</td>
<td>m.p. 81-82°C.</td>
<td></td>
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The Acyloin Reaction of Dimethyl trans-1,3-Cyclopentanedi propionate

Preliminary examination of models of cis-(73) and trans-bicyclo[6.2.1]undecan-4-ol-5-one (72) indicated that the latter compound would be more difficult to cyclize. However, since the trans-dipropionic acid 53 is more accessible synthetically and since it was anticipated that some starting material would be lost in developing technique initially, it was decided to use the trans esters 68 and 70 in preliminary cyclization studies.

Several reactions were run on diethyl trans- (68) and dimethyl trans-1,3-cyclopentanedi propionate (70) using the apparatus and procedure described by Prelog and co-workers.
without modification. In each case distillation of the product afforded a residue, the infrared spectrum of which was identical to that of the starting diester. No appreciable amount of anything but starting material was detected by GLC analysis of the residue. A small amount of material was isolated by column chromatography, but infrared analysis showed this to be an acid rather than the desired acyloin product 72.

In order to test the experimental procedure being used at this point, a condensation was run on the cis-dipropionic ester 69. The apparatus and experimental procedure of Prelog and co-workers was used again except that glacial acetic acid rather than methanol was used to destroy excess sodium at the end of the reaction. Distillation of solvent from the crude product followed by column chromatography afforded a 10 per cent yield of the cis-acyloin 73. The product 73 reacted with Fehling's reagent at room temperature, showed the expected infrared absorption bands at 3400 cm. (O-H) and 1690 cm. (C=O), and was characterized by elemental analysis of its p-nitrobenzoate derivative 74. The cis-acyloin 73 was oxidized with chromium trioxide in acetone to cis-bicyclo[6.2.1]undecan-4,5-dione (75), and the 2,4-dinitrophenyllosazone derivative 76 was prepared. The derivative 76 proved to be quite difficult to purify, and the elemental analysis was somewhat in
error. This successful condensation of 69 indicated that the proper experimental conditions were being attained; however, judging from the low yield of 73, it was apparent that refinement of the technique was necessary if cyclization of the trans-isomer to the more highly strained trans-acyloin 72 was to be accomplished.

In the several subsequent attempts to cyclize 70, the apparatus and experimental procedure employed by Cram and Steinberg\textsuperscript{53} in their synthesis of the highly strained paracyclophanes was used. This method differs from that of Prelog and co-workers in a longer reaction time and in the use of a more efficient high-speed stirrer, which affords a better sodium dispersion. In a typical run, 200 mg. of
material other than starting diester 70 was isolated by column chromatography from the reaction product of 26 g. of 70. This material had infrared absorption bands at 3500 cm.\(^{-1}\), 1700-1750 cm.\(^{-1}\), and 1060 cm.\(^{-1}\), but was not the desired acyloin product 72, as evidenced by its failure to react with Fehling's reagent, even upon heating. Attempts to prepare the \(\text{p}\)-nitrobenzoate derivative of this material were unsuccessful. Changes in the reaction time and workup procedure did not result in any observable acyloin product.

By this time, the reaction equipment and procedure had been refined to the point that it seemed unlikely that either one was the source of difficulty. Accordingly, the literature was searched to determine what solvents besides xylene had been used previously in acyloin condensations. Apparently, only toluene, xylene, and ether had been used previously; nevertheless, it was decided to attempt a reaction in dioxane. Dioxane was chosen since its boiling point is high enough to permit preparation of a sodium dispersion. In addition, the product may be isolated by pouring the reaction mixture into water and extracting with ether, thus eliminating the necessity of removing a large volume of high-boiling solvent by distillation. It was reasoned that this would be advantageous in the event that the trans-acyloin 72 decomposed upon heating.
The first attempted condensation of the trans-dimethyl ester 70 in dioxane afforded several products. Two fractions besides 70 were isolated by column chromatography of the crude product from 19 g. of 70. Acyloin fraction A (1.6 g.), eluted with benzene, reacted with Fehling's reagent at room temperature, and the infrared spectrum was essentially identical to that of the cis-acyloin 73 obtained previously. Acyloin fraction B, eluted with ether, gave a weak Fehling's test upon heating (probably incomplete separation from A), and the infrared spectrum was very similar to that of material isolated from previous trans reactions in xylene. Oxidation of fraction A with bismuth trioxide in glacial acetic acid55 gave the cis-diketone 75, which was identified by comparison of its 2,4-dinitrophenylosazone derivative with the authentic sample of 76. The infrared spectra proved to be identical, and the mixture melting point with 76 was undepressed. Two products were isolated by bismuth trioxide oxidation in glacial acetic acid of acyloin fraction B, followed by column chromatography. One product (77) had infrared absorption bands at 1740 cm.\(^{-1}\), 1240 cm.\(^{-1}\), and 1040 cm.\(^{-1}\), and the other product (78) had the same absorption bands plus an additional one at 3400 cm.\(^{-1}\).

The obvious explanation for the isolation of cis-acyloin 73 from the reaction of trans-dimethyl ester 70
is that the starting acid \( 53 \) obtained by Wolff-Kishner reduction of the ketodinitrile \( 58 \) was contaminated with an appreciable amount of the cis-dipropionic acid \( 52 \). The infrared spectrum of pure \( 52 \), obtained from the Arndt-Eistert synthesis, was compared with that of the pure trans-dipropionic acid \( 53 \) to determine if infrared spectral data could be used qualitatively as an indication of the purity of \( 53 \). An absorption band at 1240 cm.\(^{-1}\), present in the infrared spectrum of \( 52 \) but not in that of \( 53 \), was chosen for this purpose. The infrared spectrum of the trans-dipropionic acid \( 53 \), obtained by Wolff-Kishner reduction of \( 58 \) and recrystallized several times from water-acetic acid to m.p. 96-97°C., had a small absorption band at 1240 cm.\(^{-1}\) due to contaminating \( 52 \). Repeated recrystallization from a variety of solvents neither raised the melting point nor reduced the intensity of the infrared band at 1240 cm.\(^{-1}\). The infrared band at 1240 cm.\(^{-1}\), characteristic of contaminating \( 52 \), was successfully removed by recrystallization of \( 53 \) several times from tetrahydrofuran-hexane-acetic acid solvent. The trans-dipropionic acid \( 52 \) purified in this manner, had a melting point of 100 - 101°C.

The fact that the small amount of cis isomer \( 71 \) present in the trans-dimethyl ester \( 70 \) did not yield a detectable quantity of cis-acyloin \( 73 \) in xylene, but did in
dioxane, was taken as evidence for the superiority of the latter solvent. Dioxane was used, therefore, for the solvent in the remaining acyloin reactions rather than xylene.

Another condensation in dioxane using 20 g. of the purified trans-dimethyl ester 70 afforded the same amount of fraction B obtained with unpurified 70 (ca. 2 g.), but a substantial reduction was noted in the amount of fraction A isolated. The infrared spectrum of fraction A indicated incomplete separation from starting 70, and less than 100 mg. of cis-diketone 75 was isolated by column chromatography of the bismuth trioxide oxidation product of fraction A. The cis-diketone 75 was identified as before by comparison of the 2,4-dinitrophenylhydrazone derivative with an authentic sample of 76. No trans-acyloin products were isolated.

Acyloin fraction B, obtained from purified 70, was distilled in order to obtain a pure sample for characterization. The distillate had infrared absorption bands at 3400 cm.\(^{-1}\) and 1060 cm.\(^{-1}\), and the spectrum was identical to that of a sample of trans-1,3-cyclopentanedi(propanol (79) obtained by the lithium aluminum hydride reduction of 53. A sample of the same dialcohol 79 was isolated by column chromatography of acyloin fraction B on silica gel and was converted to the \(\text{p}\)-nitrobenzoate derivative 80. The infrared spectrum of the derivative was identical to
that of an analytical sample of \( \text{trans-1,3-cyclopentane-dipropanol-bis-p-nitrobenzoate (80)} \) prepared from an authentic sample of 79. Treatment of the known \( \text{trans-dipropanol 79} \) with bismuth trioxide in glacial acetic acid, followed by column chromatography, afforded the same two products (77 and 78) observed previously upon similar treatment of acyloin fraction B. Reaction of 79 with acetic anhydride, followed by column chromatography, also gave 77 and 78. It was concluded that 77 is the diacetate derivative of the \( \text{trans-dipropanol 79} \) and that 78 is the monoacetate of 79.

Acidic material recovered from the sodium bicarbonate wash of the crude acyloin reaction product was also examined. Infrared analysis of the distillate from this material revealed absorption bands at 2500-2700 cm\(^{-1}\), (CO\(_2\)H), 1740 cm\(^{-1}\) (ester C=O), 1705 cm\(^{-1}\) (acid C=O), and 1100-1300 cm\(^{-1}\). The elemental analysis was correct for \( \text{trans-3(\beta-carbomethoxyethyl)-cyclopentylpropionic acid (81)} \).

Two products were obtained by chromium trioxide-acetone oxidation of acyloin fraction B. The major product,
Figure 3. Characterization of trans products
m.p. 101-102°C., was identified as the trans-dipropionic acid \( \text{53} \) by comparison of its infrared spectrum with that of an authentic sample of \( \text{53} \) and by an undepressed mixture melting point with \( \text{53} \). The infrared spectrum of the minor component was identical to that of the trans-acid-ester \( \text{81} \). It was postulated that \( \text{53} \) came from oxidation of \( \text{79} \) present in acyloin fraction B and that \( \text{81} \) was produced by oxidation of the trans-alcohol-ester \( \text{82} \) present in fraction B. The acyloin reaction products of the trans-dimethyl ester \( \text{70} \) are summarized in Figure 3.

Thin-layer chromatography (TLC) and gas-liquid chromatography (GLC) were used in the final two trans acyloin reactions in an attempt to detect the presence of any trans-acyloin \( \text{72} \). TLC examination of acyloin fraction A showed at least five components to be present. Several pure components of the mixture were isolated by following the course of a column chromatography on silica gel with diagnostic TLC. The presence of ester groups in each component was indicated by an intense absorption band at 1150-1300 cm.\(^{-1}\) in the infrared spectrum. None of the components isolated could be identified as \( \text{72} \), and again only cis-acyloin \( \text{73} \) was isolated from the reaction mixture.

In the final attempt to obtain \( \text{72} \), only trans-dimethyl ester \( \text{70} \) which had been reclaimed from previous reactions was used. It was reasoned that nearly all of the contaminating cis isomer \( \text{71} \) should have been removed in previous
reactions and that the product would be enriched in the trans-acyloin 72, if it were present at all. GLC examination of the reaction products revealed the presence of a number of components in agreement with the TLC results. It was estimated that the reaction of 9.7 g. of 70 afforded 0.7 g. of acidic material, 1.7 g. of volatile products (retention time of less than three minutes at the GLC conditions used), and several major components with retention times of over five minutes. The major components were identified as 75 (110 mg.) and 79 (275 mg., 4 per cent yield); the remainder was unreacted 70.

Since the acyloin condensation of 70 was unsuccessful, several attempts were made to effect ring closure of the expanded ester dimethyl trans-1,3-cyclopentanedicarbonylrate (86) to trans-bicyclo[8.2.1]tridecan-5-ol-6-one (87). Reclaimed 70 was homologated as follows:

\[
\begin{align*}
70 & \xrightarrow{\text{LiAlH}_4} 79 & 79 & \xrightarrow{\text{PBr}_3} & \text{83} \\
& & & & \\
\text{84} & \xrightarrow{\text{H}_2\text{O}^+} & \text{85} & \xrightarrow{\text{MeOH}} & \text{85}
\end{align*}
\]
The reaction of 86 with sodium in dioxane is apparently analogous to the reaction of 70, since the only product isolated (7 per cent) was \textit{trans}-1,3-cyclopentanedibutanol (88). The \textit{trans}-dialcohol 88 was characterized by the similarity of its infrared spectrum to that of 79 and by elemental analysis of its \textit{p}-nitrobenzoate derivative.

It is interesting to compare previous studies regarding the effect of ring size in various systems on cyclization by the acyloin condensation with the results obtained here. The effects of ring strain and entropy, already discussed, apparently reach an unfavorable maximum even for the formation of an unsubstituted nine-membered ring, as evidenced by the minimum yield (40 per cent) observed in this case. The incorporation of four methyl substituents \(\alpha\) to the ester groups and in other positions has been shown to reduce the yield of medium-ring acyloins. Substitution of four methyls \(\beta\) to the ester functions has,
however, resulted in an increased yield. The effect of a bridging carbon chain has apparently not been reported.

Studies have been reported on the lower limits of cyclization by the acyloin reaction of rings containing triple bonds. Cram and co-workers have shown that acyloin condensation of the alkyne to takes place when \( m = n = 4 \) (73 per cent yield) but not all when \( m = n = 3 \) or when \( m = 3 \) and \( n = 4 \). A triple bond has, however, been introduced into a preformed ring of as few as eight carbon atoms. Similarly, the fact that neither the trans-bicyclo[6.2.1]undecane nor the system with two more carbons, the trans-bicyclo[8.2.1]tridecane, can be synthesized by the acyloin condensation is not sufficient evidence that these systems are incapable of existence. It is more reasonable to postulate, particularly in the case of 87, that a large entropy barrier to cyclization in addition to inherent product instability may be the reasons for the failure of the trans-diesters 70 and 86 to cyclize.
There are few reported studies regarding the nature of by-products in the acyloin condensation. The most complete analysis is that reported by Machtinger\textsuperscript{62} for the acyloin condensation of diethyl sebacate. The following products were isolated from the reaction of diethyl sebacate with sodium in refluxing xylene: 14 per cent cyclononanone (91) and cyclodecanediole (92), 3 per cent 1,10-decanediol (93), 0.5 per cent cycloeicosanediol dioxide (94), 15 per cent cyclononadecanol-1-dione-2,11 (95), 17 per cent sebacic acid, 49 per cent polymeric acid. The acyloin product analysis and free radical mechanism reported by Van Heyningen\textsuperscript{36} have already been mentioned.

It is interesting to note that fewer major products were isolated in this work than were observed by Machtinger and Van Heyningen. This may be explained by consideration
of the reaction mechanism and comparison of the reaction conditions. By analogy with the mechanism proposed by Van Heyningen, the sodium ketylts 97 and 98 are probably formed initially. The sodium ketylts 97 and 98 may then decompose to form radicals such as 99, and a variety of reaction products can result from intra- and intermolecular reactions. Some of the possible reactions of these radicals are indicated in Figure 4. A number of other reaction products are possible; however, compounds analogous to all of those listed in Figure 4, with the exception of 82, 109, and 110, have been observed previously.

The initially formed radicals apparently follow three major reaction pathways: (i) intramolecular reaction leading to cyclic products, (ii) intermolecular reaction leading to linear dimeric products, (iii) reaction with sodium or solvent. In previous work no effort was made to use a high-dilution technique to minimize intermolecular reactions and, in addition, the formation of intramolecular products was not particularly unfavorable; consequently, a number of products arising from both
Figure 4. Possible acyloin products
intramolecular and intermolecular reactions of the initial radicals were observed. In the present work, however, the entropy barrier to cyclization makes intramolecular reactions unfavorable, while the use of a high-dilution technique renders intermolecular reactions unfavorable; therefore, the only products observed are those which result from reaction of the initially formed radicals with sodium and solvent.

The cis-Bicyclo[6.2.1]undecane System

Dimethyl cis-1,3-cyclopentanedicarboxylate (Z1) was cyclized in good yield by reaction with sodium in dioxane at 50°C. GLC analysis of the fractions obtained by column chromatography of the product on florex revealed the presence of only two major components, cis-bicyclo[6.2.1]undecan-4-ol-5-one (Z3) and cis-bicyclo[6.2.1]undecan-4,5-dione (Z5). Infrared analysis of a sample of the larger component, collected by GLC, revealed major absorption bands at 3400 cm\(^{-1}\) (O-H), and 1690 cm\(^{-1}\) (C=O), and comparison of the spectrum with that of an authentic sample of the cis-acyloin (Z3) obtained previously showed them to be identical. The product contained 83 per cent cis-acyloin Z3 and 17 per cent cis-diketone Z5. The total yield of Z3 was at least 47 per cent, and the yield of Z5 was 10 per cent. The yield of cyclic product (57 per cent total) obtained in this case
was a marked improvement over that of the same reaction run in xylene, from which a total of only 10 per cent cyclic product was isolated. No appreciable amount of either cis-1,3-cyclopentanediipropanol or starting cis-diester 71 was present in the product as evidenced by the small amount of non-ketonic material isolated using Girard's T reagent.

The crude acyloin-diketone (73 and 75) mixture was reduced readily with zinc and hydrochloric acid\textsuperscript{3,4} to a mixture of cis-diketone 75 and cis-bicyclo[6.2.1]undecan-4-one (111; 28 per cent yield). A sample of the monoketone (111), purified by column chromatography and distillation,

\[
\begin{array}{c}
\text{Zn/HCl} \\
73 + 75 \\
\rightarrow \\
\text{111}
\end{array}
\]

gave the correct elemental analysis and showed the following infrared absorption bands: 1700 cm.\textsuperscript{-1} (C=O), 1170 cm.\textsuperscript{-1}, 1110 cm.\textsuperscript{-1}, 995 cm.\textsuperscript{-1}.

Upon standing in a refrigerator for several days, the acyloin-diketone (73 and 75) mixture began to solidify. Reëxamination of the infrared spectrum of this material revealed the presence of a broad absorption band at 2500-2700 cm.\textsuperscript{-1} characteristic of carboxylic acids. The
compound causing this absorption was isolated by extraction with sodium bicarbonate solution and found to be the cis-dipropionic acid \(^{52}\). Similar decomposition of cyclo-decanedione (92) to sebacic acid has been reported by Machtinger.\(^{62}\) It was found that the decomposition of 92 could be retarded by dissolution in pentane or by addition of phosphorus pentoxide to the neat material. Because of the retardation by added phosphorus pentoxide, it was concluded that the decomposition of 92 is caused by reaction with water.

The decomposition of three identical samples of the freshly prepared acyloin-diketone (73 and 75) mixture was examined under different conditions in order to study the mechanism of this reaction. A small quantity of hydroquinone was added to sample A, and the sample was left open to the atmosphere. Sample B was left open to the atmosphere and untreated, and sample C was left untreated in a vacuum desiccator. After standing for two weeks at room temperature, the infrared spectra of the samples were compared to that of the original sample. The spectrum of sample A was essentially identical to that of the original material, and sample C had partially decomposed, as evidenced by broadening of the carbonyl absorption and by the appearance of absorption in the 2500–2700 cm.\(^{-1}\) region (no solid had formed in the sample). The untreated sample B
had undergone extensive decomposition, as evidenced by solidification to an oily solid, carbonyl broadening, and the appearance of an intense infrared absorption band at 2500-2700 cm\(^{-1}\), and a weak band at 1780 cm\(^{-1}\). The observed inhibition of the decomposition by hydroquinone indicates that a free radical mechanism may be involved, and the partial decomposition of sample C in the vacuum desiccator indicates that water may not be required.

α-Hydroxyketones are known to undergo cleavage to acids upon treatment with base in the presence of oxygen. The following mechanism has been proposed by Weissberger\(^{63}\) to account for the cleavage of benzoin (112) to benzoic acid (116):

\[
\begin{align*}
\text{112} & \xrightarrow{\text{base}} \text{113} \xrightarrow{\text{O}_2} \text{114} \xrightarrow{\text{H}_2\text{O}^+} \text{115} \\
\text{115} + \text{H}_2\text{O}^+ & \rightarrow 2 \text{116}
\end{align*}
\]

In this mechanism, 112 reacts with base to give the anion 113, which is in equilibrium with its enol form 114. The
enol-anion $114$ reacts with oxygen to form benzil ($115$) and the hydroperoxide anion, which can then attack benzil (not benzoin) to give benzoic acid ($116$).

A mechanism analogous to the one above can be written for the decomposition of the acyloin-diketone mixture as follows:

The reaction of $75$ with the hydroperoxide ion may take the following course, analogous to the reaction of peracids with ketones.$^{64}$
The presence of the anhydride \textit{118} could account for the observed absorption band at 1780 cm\textsuperscript{-1} in the infrared spectrum of the decomposition product.

The above mechanism can probably be discounted on the basis of the following arguments. GLC analysis of a freshly prepared sample of the acyloin-diketone mixture revealed a ratio of \textit{73} to \textit{75} of 3.7 to 1. This sample was dissolved in ether and extracted with 20 per cent aqueous potassium hydroxide. GLC analysis of the residue from the ethereal solution revealed a ratio of \textit{73} to \textit{75} of 7.2 to 1. If the above mechanism were operating in this case, the ratio of acyloin \textit{73} to diketone \textit{75} should have decreased since only enough hydroperoxide ion is formed to react with \textit{75} arising from the reaction of \textit{117} with oxygen. The amount of \textit{73} present in the final mixture would have been reduced, while the amount of \textit{75} would have remained constant. A decrease in the ratio of \textit{73} to \textit{75} would have been observed, even if the reaction of \textit{75} with oxygen proceeded quantitatively.

Infrared analysis of samples B and C showed that the predominant decomposition product of the acyloin-diketone mixture is the \textit{cis}-dipropionic acid \textit{52} rather than the anhydride \textit{118}. If the foregoing mechanism were operating here, \textit{118} should have been the predominant product because of the anhydrous conditions, particularly
in the case of sample C which was stored in a vacuum desiccator.

Russell and co-workers\textsuperscript{65} have recently shown that aliphatic \(\alpha\)-diketones (119) in the presence of enediol dianions (120) readily undergo reduction to semidiones (121) in an electronic disproportionation as follows:

\[
\begin{array}{c}
\text{C-C-R} \\
\text{119}
\end{array}
+ \begin{array}{c}
\text{C=O-R} \\
\text{120}
\end{array} \rightarrow \begin{array}{c}
\text{2 C=O-R} \\
\text{121}
\end{array}
\]

Application of this observation to the present problem leads to postulation of the mechanism shown in Figure 5 for the decomposition of the acyloin-diketone mixture. In this mechanism 73 reacts with a small amount of base present initially in the sample to give the enediol anion 122. The dianion 122 undergoes electronic disproportionation with a molecule of 75 to give two molecules of the semidione 123 which reacts with oxygen to give the radical 124. By rearrangement 124 affords the radical 125 which can abstract a hydrogen atom from 73 to give 127 and another semidione radical, thus continuing the process. The anion 127 undergoes ring-opening to the aldehyde-peracid anion 128 which can act as a base to initiate formation of more semidione 123 by removal of a proton from 73. The aldehyde-peracid anion 128, or the
corresponding aldehyde-peracid, is easily converted to the cis-dipropionic acid \( 52 \), probably by intermolecular reaction with another molecule of \( 128 \).

The above mechanism seems to explain satisfactorily the experimental observations. When a mixture containing more cis-acyloin \( 73 \) than diketone \( 75 \) is treated with an excess of base, equal amounts of \( 73 \) and \( 75 \) are consumed in forming the semidione \( 123 \). Since a large excess of base is present, the amount of \( 73 \) consumed by reaction with the radical \( 125 \) is probably small compared to the amount consumed by base. The disappearance of \( 73 \) and \( 75 \) by reaction with excess base would be approximately equal, and the ratio of \( 73 \) to \( 75 \) is observed to increase. In the neat material only a trace of base is required to initiate formation of a small concentration of the semidione \( 123 \). Once a small quantity of the radical \( 125 \) is formed by the reaction of \( 123 \) with oxygen, the process can be sustained by reaction of \( 125 \) with \( 73 \) to afford additional semidione \( 123 \). The observed inhibition\(^62\) of the decomposition of cyclodecadione \( (92) \) by solution in pentane or by addition of phosphorus pentoxide to the neat material can probably be attributed to interference with the first step of the reaction. The acidic phosphorus pentoxide reacts preferentially with any base present initially, preventing its reaction with \( 73 \), and pentane, being a poor ionizing
Figure 5. Mechanism of the decomposition of the cis-acyloan-diketone mixture
solvent, makes the first ionization step unfavorable. Added hydroquinone probably inhibits the reaction by inter­rupting the propagation step involving reaction of the radical $1_{25}$ with $7_3$.

The presence of a small amount of unreacted aldehyde-peracid $1_{28}$ in the final product could account for the small absorption band at $1780 \text{ cm}^{-1}$ in the infrared spectrum; performic and perbutyric acids have been found to exhibit carbonyl absorption in the vapor phase at $1750 \text{ cm}^{-1}$.

The original cis-acyloin-diketone ($7_3$ and $7_5$) mixture was converted to the more stable cis-diketone $7_5$ by reaction with bismuth trioxide. It was found that pure $7_5$ could be isolated readily through the use of Girard's T reagent $1_{29}$. Reaction of $7_5$ with two moles of $1_{29}$ gives the water-soluble derivative $1_{30}$ which, after removal of unreacted, water-insoluble impurities by extraction with ether, can readily be decomposed to pure $7_5$.

$$7_5 + 2\left[\left(\text{CH}_3\right)_3\text{NCH}_2\text{C-NNH}_2\right]^+ \text{OH}^{-} \rightarrow 1_{29}$$

The cis-diketone $7_5$ purified in this manner (65 per cent recovery from crude $7_5$) proved to be 99+ per cent pure, as
evidenced by GLC analysis. This material gave the correct elemental analysis, and the 2,4-dinitrophenylosazone derivative 76 was identical to the samples obtained from previous reactions. Oxidation of a pure sample of 75 with chromium trioxide-acetone afforded pure cis-dipropionic acid 52, thus confirming the assigned stereochemistry.

The reactions of both 73 and 75 with Fehling's reagent were studied. The acyloin was found to react readily at room temperature, reducing the reagent to cuprous oxide, but 75 failed to produce any cuprous oxide, even after heating for several hours. The same reaction product, an acid m.p. 118.5-119.5°C., was isolated from both reactions. This material had a neutralization equivalent of 200, and infrared analysis revealed absorption bands at 3460 cm.⁻¹ (O-H), 2500-2700 cm.⁻¹ (CO₂H), 1730 cm.⁻¹ (C=O), and 1060 cm.⁻¹ (O-H). The nuclear magnetic resonance (NMR) spectrum showed a broad singlet at δ3.9(2H) and a complex multiplet at δ7.5-8.6 (16 H). The elemental analysis was correct for 4-hydroxy-cis-bicyclo[5.2.1]-decan-4-carboxylic acid (131). This product most likely results from a benzilic acid type of rearrangement of 75 in the basic reagent as follows:

\[
75 \xrightarrow{\text{HO}^-} \text{O}^{\text{−}} \xrightarrow{\text{O}} \text{OH} \xrightarrow{\text{CO}_2\text{H}} 131
\]
In the case of \( 73 \), oxidation by Fehling's reagent to \( 75 \) probably takes place first, followed by benzilic acid rearrangement to \( 13 \).

The bicyclo[6.2.1]undecanes can be considered to be derivatives of cyclononane (12) or cyclodecane (11) having, respectively, an added 1,3-ethylene or 1,4-methylene bridge. The problem of the conformation of cis-bicyclo[6.2.1]undecane derivatives was investigated qualitatively by examining models of the known \( 25,26 \) conformations of 11 and 12 (Figures 1 and 2) to determine how the additional carbon bridges could be incorporated with a minimum of added strain.

Examination of a model of cyclodecane (Figure 1) reveals that existing carbon-hydrogen bonds are suitably oriented for replacement by a methylene bridge across the 1-4, 4-7, 2-9, or 6-9 positions. When this substitution is made across any of these positions, the cis-bicyclo[6.2.1]undecane (33) conformation of Figure 6 results. Some bond-angle deformation appears to be necessary to add the methylene, and the resulting conformation still has, as seen in Figure 6, the original trans-annular non-bonded interactions between the 3, 6, and 9 hydrogen atoms and an additional severe interaction between the 4-11 hydrogens. A possible conformation of the cis-diketone 75 can be derived from Figure 6 by
replacement of the 4 and 5 carbon atoms with carbonyl groups. The 4-oxygen, 11-hydrogen interaction resulting from this substitution can be relieved by twisting the carbonyl groups into coplanarity, giving the symmetrical conformation of 75 shown in Figure 7.

Additional conformations of 33 and 75 can be derived by using the known conformation (Figure 2) of cyclo-nonane (12) as a starting point. Examination of a model of 12 reveals that there are four possible sites where carbon-hydrogen bonds are suitably oriented for replacement by a 1,3-ethylene bridge without disrupting the conformation. Substitution across either the 1-3 or 2-9 carbon atoms of 12 (Figure 2) leads to the conformation type A shown in Figure 8. The substitution can be made with little or no changes in bond angles; however, the original transannular non-bonded interactions between the 1-7 and 3-7 or 2-5 and 5-9 hydrogens in Figure 2 are replaced by two carbon-hydrogen interactions of the ethylene carbon atoms with the opposing hydrogen atom. In Figure 8 this is seen as the interaction between the 5-hydrogen and the 9 and 10 carbon atoms. Further replacement of the 4-5 carbons with carbonyl groups affords the possible cis-diketone 75 conformation of type A shown in Figure 9. Although the carbon-hydrogen interactions of the hydrocarbon 32 are removed, they are replaced by a
Figure 6. Cyclodecane-based conformation of cis-bicyclo[6.2.1]undecane (33)

Figure 7. Cyclodecane-based conformation of cis-bicyclo[6.2.1]undecan-4,5-dione (75)
Figure 8. Cyclononane-based conformation A of \textit{cis}-bicyclo[6.2.1]undecane (33)

Figure 9. Cyclononane-based conformation A of \textit{cis}-bicyclo[6.2.1]undecan-4,5-dione (75)
non-bonded interaction between the 5-carbonyl oxygen and 9-hydrogen atoms. An attempt to twist the carbonyl groups into \textit{cis}-coplanarity increases the 5-9 oxygen-carbon interaction and introduces interaction between the 4-oxygen and 10-hydrogen. Also, the carbonyls cannot become \textit{trans}-coplanar because of increased 3-11 hydrogen-hydrogen and 5-oxygen and 10-hydrogen interactions. In the most favorable conformation the carbonyl groups are nearly perpendicular.

A second set of possible conformations of 33 and 75 can be derived from cyclononane (Figure 2) by substitution of an ethylene bridge across either the 4-6 or 6-8 positions, leading to the type B conformation of 33 shown in Figure 10. It appears that this substitution can be made without introducing any strain factors not already present in 12. In addition, an envelope cyclopentane ring is automatically formed by addition of the ethylene bridge. Replacement of the 4 and 5 carbon atoms by carbonyl groups affords the conformation of 75 indicated in Figure 11. This replacement can also be accomplished without introduction of any additional strain factors, and the transannular non-bonded interactions between the 4-6-11 and 2-5-7 hydrogens of the hydrocarbon 33 (Figure 10) are actually eliminated. The carbonyl groups can be twisted into coplanarity to give the symmetrical
Figure 10. Cyclononane-based conformation B of cis-bicyclo[6.2.1]undecane (33)

Figure 11. Cyclononane-based conformation B of cis-bicyclo[6.2.1]undecan-4,5-dione (75)
conformation of Figure 12, but only with increased 3-6-11 non-bonded hydrogen interactions and with eclipsing of the α-β carbon-hydrogen bonds.

The semidione 122 of the freshly purified cis-diketone 75 was prepared in dimethyl sulfoxide-t-butanol by the procedure of Russell and Strom,\textsuperscript{68} and the electron paramagnetic resonance (EPR) spectrum measured in order to obtain experimental information regarding the actual conformation of 75. The observed 48-line spectrum (Figure 14) is a triplet having 16 equally spaced lines under each peak. The large triplet hyperfine splitting constant is about 7.5 gauss, and the small splitting between each peak is about 0.5 gauss. Although a complete analysis was not possible by inspection, several of the possible conformations of 75 proposed above can be eliminated on the basis of the EPR spectrum.

The magnitude of the hyperfine splitting constant $a^H$ of the electron in the semidione 122 with the α-hydrogen atoms is determined by the Heller-McConnell equation,

$$a^H = \rho_c B \cos^2 \theta + B' \rho_c$$

where $B' \sim 0$, $\rho_c$ is the spin density of the carbonyl carbon atom, $B$ is a constant between 40 and 60 gauss, and $\theta$ is the dihedral angle between the carbonyl $p_z$ orbital and the carbon-hydrogen bond.\textsuperscript{65,69} Examination of models of the symmetrical conformations (Figures 7 and 12) of
Figure 12. Cyclononane-based conformation of cis-bicyclo[6.2.1]undecan-4,5-dione (75)

Figure 13. Unsymmetrical conformation of cis-bicyclo[6.2.1]undecan-4,5-semidione (123)
Figure 14. EPR spectrum of cis-bicyclo[6.2.1]-
undecan-4,5-semidione (123)
It reveals that the angle $\Theta$ in the Heller-McConnell equation is the same for both pairs of $\alpha$-hydrogens (one pair above and one below the plane of the carbonyl system) in these conformations. In the conformation of Figure 10 all of the $\alpha$-hydrogens are equivalent and the observed spectrum should be a symmetrical pentet, possibly with smaller splitting by coupling with the $\beta$-hydrogens. In the conformation of Figure 7 the value of the angle $\Theta$ is different for the two pairs of $\alpha$-hydrogens above and below the carbonyl plane, and the observed spectrum would be expected to be a triplet of triplets split further by coupling to the $\beta$-hydrogens. Assuming that all of the possible lines are observed in the EPR spectrum of Figure 14, it is impossible to obtain a 48-line spectrum of the correct relative peak intensities by using only triplet splitting. In addition, it is interesting to examine the large hyperfine splitting constant of 7.5 gauss in light of the Heller-McConnell equation. For normal 9-, 10-, and 12-membered monocyclic semidiones, Russell and co-workers have found the carbonyl-carbon spin density $\rho_c$ to vary between 0.18 and 0.33. Substituting the observed hyperfine splitting constant of 7.5 gauss into the Heller-McConnell equation using 0.18 ($B = 58.5$) and 0.33 ($B = 40$) for the limits of $\rho_c$, the values of the dihedral angle $\Theta$ associated with this splitting are calculated to
be 32° and 41° respectively. Since the dihedral angle of the other pair of α-hydrogen atoms in the symmetrical conformations must be 60° - θ, the necessary hyperfine splitting constant can be calculated by substituting the values of θ = 60° - 32° = 28° and θ = 60° - 41° = 19° into the Heller-McConnell equation using the same limits of 0.18 and 0.33 for ρc. When this is done, values of 8.2 gauss or 11.8 gauss are calculated for the hyperfine splitting constant of the pair of α-hydrogens on the same carbon atoms as those causing the observed splitting of 7.5 gauss. This is obviously not in agreement with the observed spectrum, and the symmetrical conformations of 25 (Figures 7 and 12) can be eliminated.

If, on the other hand, the two equivalent hydrogen atoms causing the observed triplet splitting are located on the same α-carbon atom, the dihedral angle of both carbon-hydrogen bonds must be 30° since their sum must be 60°. Calculation by means of the Heller-McConnell equation of ρc using a value of θ = 30° and the observed hyperfine splitting constant of 7.5 gauss gives a range of spin density of 0.17 to 0.25, in good agreement with values of spin density found by Russell and co-workers for 9-, 10-, and 12-membered monocyclic semidiones.

An unsymmetrical semidione conformation which appears to fit the spectral requirements can be derived from the
cis-diketone 75 conformation of Figure 9 by rotation about the 5-6 carbon-carbon bond. This rotation brings the carbonyl groups into coplanarity, a requirement for resonance stabilization of the semidione 123, and at the same time raises the cyclopentane ring over the plane of the carbonyl system. The resulting conformation, shown in Figure 13, has two equivalent $\alpha$-hydrogen atoms ($\Theta = 30^\circ$) on the 3-carbon and two non-equivalent $\alpha$-hydrogens on the 6-carbon.

The NMR spectrum of the quinoxaline derivative 132 of the cis-diketone 75 affords additional evidence for the conformation of Figure 13. The aromatic quinoxaline ring can be incorporated into the unsymmetrical semidione of Figure 13 across the 4-5 positions without changing the conformation. In the resulting quinoxaline 132, one of the hydrogens on the 11-carbon atom is located above and close to the plane of the aromatic rings. The NMR spectrum of 132 shows an aromatic multiplet in the $\tau 1.8 - 2.6$ region (four hydrogens), a broad multiplet from $\tau 6.2 - 8.8$ (15 hydrogens), and a doublet of triplets centered
at τ9.5 (one proton; \( J = 12 \) cps, 3 cps). The peaks at τ9.5 were assigned to the 11-hydrogen held above the aromatic ring. The larger coupling constant is of the order of magnitude of that observed for geminal protons\(^70\) and may be attributed to coupling with the other 11-hydrogen atom. The smaller triplet coupling constant of 3 cps may be assigned to coupling with the two bridgehead protons. The observed shift of the 11-hydrogen to about 1 ppm. higher field than the normal methylene position may be attributed to shielding by the aromatic system of the type observed by Waugh and Fessenden\(^71\) for decamethylene benzene 133. The ε-hydrogens in 132 experience long-range shielding by the aromatic nucleus and appear at 0.7 ppm. higher field than the normal methylene position. The NMR spectra of cis products are summarized in Table 2.

Based on the above arguments, the most reasonable conformation for the cis-diketone 25 seems to be that of Figures 9 or 13. It should be noted, however, that the conformation of the semidione 123 and the quinoxaline 132 may differ somewhat from that of 25 in which the carbonyl groups are not restricted to coplanarity.
### TABLE 2

NMR RESONANCE PEAKS OF CIS-BICYCLIC PRODUCTS

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Peak Positions τ</th>
<th>Peak Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-bicyclo[6.2.1]undecan-4,5-dione (25)</td>
<td>7.3-8.8 M. a</td>
<td></td>
</tr>
<tr>
<td>cis-bicyclo[6.2.1]undecan-4-one (31)</td>
<td>7.0-8.9 M.</td>
<td></td>
</tr>
<tr>
<td>4-hydroxy-cis-bicyclo[5.2.1]decan-4-carboxylic acid (31)</td>
<td>7.5-8.6 M.</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>1.8-2.6 M.</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>6.2-7.2 M.</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>7.3-8.8 M.</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>9.5 b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.9 c</td>
<td>2</td>
</tr>
</tbody>
</table>

aM. = multiplet

bDoublet of triplets (J = 12, 3cps)

cBroad singlet
CHAPTER III

EXPERIMENTAL

General

Sodium dispersions were made using a Lab-Line Stir-O-Vac high-speed stirrer (No. 1285) coupled to a Premier Dispersator made by Premier Mill Corporation of Geneva, New York.

All melting and boiling points are uncorrected and reported in degrees centigrade. Melting points were obtained with a Laboratory Devices Mel-Temp Capillary Melting Point Apparatus. Pressures are expressed in millimeters of mercury.

Refractive indices were obtained with a Bausch and Lomb Abbe 34 Refractometer equipped with an acromatic compensating prism.

Gas-liquid chromatographic (GLC) analyses were made with an Aerograph A-90-P Gas Chromatograph using a Leeds and Northrup Speedomax-H Model S Recorder. GLC analyses were made on an 8 ft. by 1/4 in. column packed with 20 per cent Silicone GE SF-96 on firebrick. The analyses were made at a column temperature of 235°C. using helium
for the eluent gas.

Infrared spectra were obtained with a Perkin-Elmer Infracord Double-beam Infrared Recording Spectrophotometer or a Beckman Model IR-10 Double-beam Infrared Recording Spectrophotometer.

Nuclear magnetic resonance (NMR) spectra were obtained with a Varian A-60-A High Resolution Nuclear Magnetic Resonance Spectrometer.

Electron paramagnetic resonance (EPR) spectra were obtained with a Varian V-4502-14 Electron Paramagnetic Resonance Spectrometer.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Pure cis-1,3-cyclopentanedicarboxylic acid (44), m.p. 120-122°C., was obtained from Humble Oil and Refining Company.

Characterization and Preparation of Starting Materials

Homologation of the cyclopentanedicarboxylic acids by the Arndt-Eistert synthesis

cis-1,3-Cyclopentanedicarboxylic acid (50).—Following the procedure of Bachmann, Cole, and Wilds,72 the acid chloride (47) of cis-1,3-cyclopentanedicarboxylic acid
(44) was prepared and reacted with an excess of diazomethane in ether. The crude bis-diazoketone 48 obtained was then subjected to a modification of the Wolff rearrangement developed by Newman and Beal. To 40 ml. of dry benzene at 0°C. in a 125-ml. filter flask was added 1 ml. of dry pyridine and 15 ml. of thionyl chloride. To the cold solution was added 4.0 g. (0.026 mole) of 44 in powder form. The mixture was allowed to warm to room temperature and stand until the evolution of gas ceased (about 1 hour). The solvent was removed at reduced pressure at room temperature. Benzene (20 ml.) was added, and the solution was evaporated again to remove traces of excess thionyl chloride. The residual acid chloride 47 was dissolved in 100 ml. of dry benzene and decanted through a plug of glass wool in the side arm of the flask to remove a small amount of solid. The benzene solution of 47 was then added dropwise to a stirred solution of diazomethane in ether at 0°C. The ethereal solution of diazomethane was prepared from 43.0 g. of N-methyl-N-nitroso-p-toluenesulfonamide (Diazald) by the method of de Boer and Backer. The reaction mixture was allowed to stand overnight at room temperature and then filtered to remove solid polymeric material. The solvent was removed at reduced pressure (room temperature), and the residual bis-diazoketone 48 (4.0 g., 0.02 mole) was
dissolved in 55 ml. of absolute methanol and placed in a three-necked flask equipped with dropping funnel, reflux condenser, and drying tube. A solution of 1.0 g. (0.004 mole) of dry silver benzoate in 12.5 ml. (9.1 g.) of triethylamine was added dropwise with stirring to the solution of 48 at room temperature. The silver benzoate solution was added in small portions at intervals until the evolution of nitrogen ceased (about 1 hour). After this time the reaction mixture was refluxed for a few minutes with decolorizing carbon and filtered. Removal of the solvent afforded a yellow oil which was dissolved in ether, washed successively with dilute hydrochloric acid and sodium bicarbonate solutions, and dried over anhydrous magnesium sulfate. To the crude dimethyl ester of 50, obtained upon removal of the solvent, was added 75 ml. of a 10 per cent solution of potassium hydroxide in methanol. After refluxing for 2 hours the solution was evaporated to dryness at reduced pressure, and the residue was dissolved in 50 ml. of water and acidified with 6 N hydrochloric acid. The acidified mixture was cooled and extracted with several portions of ether. The combined ethereal extracts were washed once with water and dried over anhydrous magnesium sulfate. The solvent was removed, leaving a residual oil which solidified upon standing. The solid was washed thoroughly with hexane and
recrystallized from benzene. One more recrystallization from water using decolorizing carbon afforded 1.1 g. (23 per cent yield based on 44) of cis-1,3-cyclopentanedicarboxylic acid (50), m.p. 140-141°C. An analytical sample of 50, m.p. 141-142°C., was obtained by two additional recrystallizations from water.

Anal. Calcd. for C9H14O4: C, 58.05; H, 7.58. Found: C, 58.06; H, 7.60.

cis-1.5-Cyclopentanedipropionic acid (53).-Using the same procedure as employed in the expansion of 44, 1.0 g. (0.0054 mole) of the cis-diacetic acid 50 was treated with 4 ml. of thionyl chloride and 5 drops of pyridine in 10 ml. of anhydrous benzene. The crude acid chloride was reacted with an excess of diazomethane in ether (prepared from 11.0 g. of Diazald 74), and the resultant bis-diazoketone was rearranged using a solution of silver benzoate in triethylamine. Hydrolysis of the crude cis-dimethyl ester 71 as before, followed by two recrystallizations of the product from water, gave 0.30 g. (26 per cent yield based on 50) of cis-1,3-cyclopentanedicarboxylic acid (52), m.p. 98-99°C. One additional recrystallization from water afforded an analytical sample of 52, m.p. 100-101°C.


trans-1.3-Cyclopentanedicarboxylic acid (51).-The trans-
diacetic acid 51 was prepared from 4.0 g. (0.026 mole) of the trans-dicarboxylic acid 45 by the same procedure used to prepare the cis-diacetic acid 50. In the case of the trans isomer, however, the ethereal diazomethane solution which was used was prepared from 20.0 g. of N,N'-dinitroso-N,N'-dimethylterephthalamide (28.4 g. of Du Pont EXR-101) according to the procedure of Arndt. 75 The crude trans-dimethyl ester of 51 obtained from the Wolff rearrangement was hydrolyzed as before, and the product was recrystallized once from acetone-hexane and twice from water to give 1.88 g. (40 per cent yield based on 45) of trans-1,3-cyclopentanedicarboxylic acid (51), m.p. 151-152°C. An analytical sample of 51, m.p. 152-153°C., was obtained by two more recrystallizations from water.

**Anal.** Calcd. for C₉H₁₄O₄: C, 58.05; H, 7.58. Found: C, 58.36; H, 7.84.

**trans-1,3-Cyclopentanedicarboxylic acid (53).** One gram (0.0054 mole) of the trans-diacetic acid (51) was reacted with 4 ml. of thionyl chloride and 5 drops of pyridine in 10 ml. of dry benzene using the same procedure as that employed in the preparation of the cis-dipropionic acid 52. The crude acid chloride was treated with an excess of diazomethane in ether prepared from 7.1 g. of EXR-101. 75 Rearrangement and hydrolysis in the usual manner, followed by recrystallization of the acid from
water, gave 0.35 g. (30 per cent yield based on 51) of trans-1,3-cyclopentanedicarboxylic acid (53), m.p. 97-98°C. An analytical sample of 52, m.p. 101-102°C., was prepared by two additional recrystallizations from water.

Anal. Calcd. for C_{11}H_{18}O_{4}: C, 61.66; H, 8.47
Found: C, 61.86; H, 8.55.

Large-scale syntheses of the cis- and trans-1,3-cyclopentanedicarboxylic acids

2,5-Cyclopentanone-2,5-dicarboxylic acid (58). Procedure A.- Acrylonitrile was added to the pyrrolidine enamine of cyclopentanone 57 prepared by the method of Stork and co-workers. 47 Cyclopentanone (252 g., 3.0 moles), 320 g. (4.5 moles) of pyrrolidine, and 1 l. of benzene were refluxed in a 3-l. flask equipped with a reflux condenser and a Dean-Stark water separator and protected by a Drierite drying tube. Refluxing was continued overnight until no more water separated, then the solvent was removed at 80°C./30 mm. The crude enamine 57 was dissolved in 1 l. of absolute ethanol, the solution was cooled in an ice bath, and 500 ml. (400 g., 7.5 moles) of acrylonitrile was added dropwise with stirring in 1 hour. After the addition was complete, the mixture was warmed to room temperature and then refluxed for 4 hours, after which time 250 ml. of water was added, and refluxing was
continued for an additional hour. The solvent and other volatile materials were removed by distillation at 100°C./30 mm. A solid which formed during the initial reflux period was removed from the residue by vacuum filtration and washed with chloroform. The chloroform wash and an additional 500 ml. of chloroform were added to the residual oil, and the resulting solution was washed with three 200-ml. portions of 3 N hydrochloric acid, followed by water. After drying the chloroform solution over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to yield a dark, viscous oil which deposited 106 g. of the crystalline ketodinitrile 58 upon standing in a refrigerator for several days. This first crop of crystals was separated by vacuum filtration, and the filtrate was further concentrated by distillation up to 180°C./0.3 mm. Upon standing overnight in a refrigerator, the concentrated filtrate deposited an additional 47 g. of the ketodinitrile 58. The combined yield of 58 was 153 g. (27 per cent based on cyclopentanone), m.p. 63-65°C., after washing the crystalline material several times with 50 per cent ethanol, followed by drying in a vacuum desiccator. An analytical sample of 2,5-cyclopentanonedipropionitrile (58), m.p. 66-67°C., was obtained by two recrystallizations from 95 per cent ethanol. The following absorption bands were observed in the infrared spectrum.
of 2250 cm.\(^{-1}\) (C=N), 1725 cm.\(^{-1}\) (O=O).

**Anal. Calcd. for C\textsubscript{11}H\textsubscript{14}ON\textsubscript{2}:** C, 69.44; H, 7.42; N, 14.73. **Found:** C, 69.23; H, 7.36; N, 14.56.

**2,5-Cyclopentanonedipropionitrile (58). Procedure B.** In this procedure the crude piperidine enamine of cyclopentanone, prepared by the method of Stork and coworkers\(^{47}\), was added to an excess of acrylonitrile in absolute ethanol. Cyclopentanone (252 g., 3.0 moles), 383 g. (4.5 moles) of piperidine, 1.0 g. of \(p\)-toluenesulfonic acid, and 1 l. of benzene were refluxed for 28 hours, and the crude enamine was isolated as in Procedure A. A 3-l. flask was equipped with a reflux condenser, a magnetic stirrer, and a 500-ml. dropping funnel. The flask was protected from moisture with a Drierite drying tube and immersed in an ice bath. Acrylonitrile (398 g., 7.5 moles) and 750 ml. of absolute ethanol were placed in the flask, and the stirrer was started. The crude cyclopentanone-piperidine enamine was dissolved in 250 ml. of absolute ethanol and added dropwise to the cold, stirred acrylonitrile solution. The addition was complete in 1 hour, and the reaction mixture was stirred for an additional 30 minutes at room temperature. The magnetic stirrer was then replaced by a heating mantel, and the reaction mixture was refluxed for 4 hours, after which time 250 ml. of water was added, and refluxing was
continued for an additional hour. Solvent (about 1100 ml.) was removed by distillation at atmospheric pressure, and the residual liquid was then further concentrated by distillation at 80°C./30 mm. The final dark oil was poured into a beaker and allowed to stand in a refrigerator for several days. The crystalline mass which formed during this time was crushed and separated by vacuum filtration. The crystals were triturated thoroughly with two 400-ml. portions of 50 per cent ethanol and refiltered. This technique afforded 376 g. (66 per cent yield based on cyclopentanone) of 2,5-cyclopentanonedipropionitrile (58), m.p. 63-65°C., which was identical to the sample of 58 prepared and characterized in Procedure A.

2,5-Cyclopentanonedipropionic acid (59).—The keto-dinitrile 58 (47 g., 0.25 mole) was refluxed for 3 hours with 500 ml. of concentrated hydrochloric acid. The reaction mixture was then evaporated to dryness at reduced pressure on a steam bath. The solid residue was triturated with several portions of ethanol, and the insoluble ammonium chloride was removed by filtration. Evaporation of the combined ethanol filtrates afforded crude 59. The residue was recrystallized twice from dioxane-hexane to give 48 g. (85 per cent yield) of pure 2,5-cyclopentanone-dipropionic acid (59), m.p. 121-122.5°C.; lit. 49 m.p. 122°C.
trans-1,3-Cyclopentanedicarboxylic acid (53) via Wolff-Kishner reduction of 58. The modified Wolff-Kishner reduction described by Huang-Minlon was employed. The ketodinitrile 58 (57 g., 0.3 mole) was mixed with a solution of 84 g. (1.5 moles) of potassium hydroxide in 600 ml. of diethylene glycol. Hydrazine hydrate (42 ml. of 85 per cent, 1.2 moles) was added, and the mixture was refluxed for 1.5 hours (about 135-140°C.). After this time the reflux condenser was removed, and the mixture was maintained at 200-220°C. for about 4 hours until the evolution of nitrogen ceased and the mixture began to darken. The reaction mixture was cooled, 600 ml. of water was added, and the basic solution was extracted once with ether to remove unreacted 58. The basic solution was then acidified by the addition of 600 ml. of 6 N hydrochloric acid and extracted with five 200-ml. portions of ether. The combined ethereal extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave 55.0 g. (86 per cent yield) of trans-1,3-cyclopentanedicarboxylic acid (53), m.p. 96-97°C., after one recrystallization from water-acetic acid. A mixture melting point of the acid with the trans-dipropionic acid 53 (m.p. 101-102°C.), previously prepared via the Arndt-Eistert synthesis, was 98-100°C. A mixture melting point of 53 with the cis-dipropionic acid 52
(m.p. 100-101°C.) was 88-94°C. The infrared spectra of the two samples of the trans-dipropionic acid 53 were identical except for absorption band intensities.

**Diethyl 2,5-cyclopentanonedipropionate (63).**-The ketodinitrile 58 (140 g., 0.74 mole) was mixed with 170 ml. (3 moles) of absolute ethanol and 300 ml. of dry benzene. Concentrated sulfuric acid (289 g., 3.0 moles) was added cautiously, and the mixture was refluxed for 12 hours after the initial spontaneous reaction subsided. After cooling to room temperature, the reaction product was poured into 800 ml. of ice and water, and the benzene layer was separated. The aqueous layer was then extracted with several portions of ether. The combined ethereal extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed to give 181 g. (87 per cent yield) of crude 63. Distillation of this material afforded pure diethyl 2,5-cyclopentanonedipropionate (63), b.p. 170-171°C./0.55 mm., \( n_D^{20} 1.4612; \) lit.76 b.p. 161-162°C./0.4 mm., \( n_D^{20} 1.4633. \)

**Diethyl 2,5-cyclopentanoldipropionate (64).**-The ketodiester 63 was reduced with sodium borohydride in ethanol according to the procedure of Leonard, Conrow, and Fulmer.77 To a solution of 48 g. (0.17 mole) of 63 in 400 ml. of absolute ethanol cooled in an ice bath, was
added 4.0 g. (0.1 mole) of sodium borohydride in portions, with continuous stirring, over a 15-minute period. After stirring for 2 hours after the addition was complete, the mixture was poured into 800 ml. of ice and water, and the product was isolated by extraction with several portions of chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate. Removal of solvent gave an oil which, upon vacuum distillation, afforded 39 g. (81 per cent yield) of pure diethyl 2,5-cyclopentanoldi-propionate (64), b.p. 175-176°C./0.55 mm., nD 1.4686. Infrared analysis revealed the following absorption bands: 3500 cm.⁻¹ (O-H), 1740 cm.⁻¹ (C=O), 1125-1300 cm.⁻¹ (ester). This material (64) could not be isolated sufficiently pure for analysis by distillation, and attempts to make solid derivatives were unsuccessful.

1,3-Cyclopent-l-enedipropionic acid (66).—Crude alcohol-diester 64 (10.0 g., 0.035 mole) was dissolved in 50 ml. of dry benzene. One gram of p-toluenesulfonic acid was added, and the mixture was refluxed overnight under a Dean-Stark water separator until no more water was formed. The resulting benzene solution was washed with dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The residual oil obtained by evaporation of solvent was eluted from a column of florex with pentane. Evaporation of the pentane eluate afforded
3.2 g. (34 per cent yield) of diethyl 1,3-cyclopent-1-enedipropionate (65). The unsaturated ester 65 (3.2 g., 0.012 mole) was added to a solution of 2.5 g. of potassium hydroxide in 25 ml. of methanol, and the mixture was refluxed with stirring for 3 hours. The solvent was then evaporated to dryness, and the residue was dissolved in a small amount of water. The basic, aqueous solution was washed once with ether and acidified with 6 N hydrochloric acid. The product was isolated by extraction of the acidified mixture with several portions of ether. The combined ethereal extracts were washed once with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave 2.0 g. (77 per cent yield) of 1,3-cyclopent-1-enedipropionic acid (66). An analytical sample of 66, m.p. 81-82°C., was obtained by three recrystallizations from water. Infrared analysis of 66 revealed the following absorption bands: 2500-2700 cm.⁻¹ (O-H, broad), 1725 cm.⁻¹ (C=O), 1660 cm.⁻¹ (C=C), 840 cm.⁻¹ (C=C).


cis-1,3-Cyclopentanedipropionic acid (52) via hydrogenation of 66.—The crude unsaturated acid 66 (20.0 g., 0.094 mole) was dissolved in 200 ml. of glacial acetic acid, and 1.5 g. of 5 per cent rhodium on alumina catalyst was added. The hydrogenation was performed using a
modified Paar apparatus at an initial pressure of 30 p.s.i.; hydrogen uptake was complete in 3 hours. The solution of product was filtered into 500 ml. of water, and the aqueous solution was extracted with several portions of ether. The combined ethereal extracts were washed several times with water then dried over anhydrous magnesium sulfate. Removal of the solvent yielded 52 containing a small amount of acetic acid which was removed by azeotropic distillation at reduced pressure with several portions of heptane. Pure cis-dipropionic acid 52 (17.3 g., 86 per cent yield), m.p. 98-99°C., was obtained after one recrystallization from water-acetic acid. The mixture melting point of 52 with an authentic sample of cis-1,3-cyclopentanedicarboxylic acid (m.p. 100-101°C.), previously obtained via the Arndt-Eistert synthesis, was 98-99°C. A mixture melting point of 52 with the trans-dipropionic acid 53 (m.p. 101-102°C.) was 87-92°C. The infrared spectra of the two samples of 52 were identical except for absorption band intensities.

Diethyl trans-1,3-cyclopentanedicarboxylate (68).—Pure trans-dipropionic acid 53 was converted to the diethyl ester by the method of Vogel.78 The trans-dipropionic acid 53 (14 g., 0.065 mole) was mixed with 12.0 g. (0.26 mole) of absolute ethanol, 25 ml. of dry benzene, and 4.0 g. (2.2 ml.) of concentrated sulfuric acid and
refluxed overnight. The reaction mixture was then poured into 50 ml. of ice and water, and the benzene layer was separated. The aqueous layer was extracted with several portions of ether, and the combined benzene-ether extracts were washed with dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the solvent and vacuum distillation of the residue gave 15.0 g. (85 per cent yield) of diethyl trans-1,3-cyclopentane-dipropionate (68), b.p. 121-123°C./0.15 mm., nD 1.4509.

Diethyl cis-1,3-cyclopentane-dipropionate (69).- Pure cis-dipropionic acid 52 (17.1 g., 0.08 mole) was reacted according to the procedure of Vogel78 with 14.7 g. (0.32 mole) of absolute ethanol and 4.7 g. (2.6 ml.) of concentrated sulfuric acid in 30 ml. of dry benzene. Work-up in the usual manner, followed by vacuum distillation of the crude product, gave 17.2 g. (80 per cent yield) of diethyl cis-1,3-cyclopentane-dipropionate (69), b.p. 121-123°C./0.25 mm., nD 1.4505.

Dimethyl trans-1,3-cyclopentane-dipropionate (70).- Pure trans-dipropionic acid 53 was esterified by the method of Vogel.78 In a typical run, 31.0 g. (0.15 mole) of 53 was mixed with 19.2 g. (0.60 mole) of reagent grade methanol, 60 ml. of reagent benzene, and 7.2 g. (4 ml.) of concentrated sulfuric acid and refluxed for 8 hours.
The product was poured into 150 ml. of ice water. The benzene layer was separated, and the aqueous layer was extracted with additional benzene. The combined benzene extracts were washed with dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The residue obtained upon removal of the solvent at reduced pressure was dissolved in 100 ml. of petroleum ether (b.p. 20-40°C.) and filtered through a column of 50 g. of activity grade I alumina. Elution was continued with the same solvent until no residue was obtained upon evaporation of the eluate. Removal of the solvent at reduced pressure gave 31.8 g. (91 per cent yield) of dimethyl trans-1,3-cyclopentanedicarboxylate (70), nD^20 1.4572.

**Dimethyl cis-1,3-cyclopentanedicarboxylate (71).**

Following the same procedure as described for the preparation and purification of the trans-dimethyl ester 70, 29.0 g. (0.136 mole) of pure cis-dipropionic acid 52 was refluxed for 8 hours with 17.5 g. (0.55 mole) of reagent grade methanol and 7.2 g. (4 ml.) of concentrated sulfuric acid in 60 ml. of benzene. Evaporation of the petroleum ether eluate afforded 29.3 g. (90 per cent yield) of dimethyl cis-1,3-cyclopentanedicarboxylate (71), nD^20 1.4558.

**trans-1,3-Cyclopentanedicarboxylic Acid (79). Procedure A.**
The trans-dipropionic acid 22 was reduced to the trans-dialcohol 79 with lithium aluminum hydride by the method of Nystrom and Brown. To a 2-l., three-necked flask equipped with a Hershberg stirrer, dropping funnel, and reflux condenser with attached drying tube was added 600 ml. of anhydrous ether and 12.0 g. (0.31 mole) of lithium aluminum hydride. To the stirred hydride slurry was added 26.9 g. (0.125 mole) of fused 22 in 500 ml. of anhydrous ether at a rate such as to produce gentle reflux. Fifteen minutes after the addition was complete, water was added cautiously with continued stirring to decompose excess lithium aluminum hydride. During the addition of water it was necessary to add a 200-ml. portion of ether and to moderate the reaction by intermittent cooling of the reaction flask in an ice bath. Sufficient 10 per cent sulfuric acid was then added with cooling to dissolve the hydroxide precipitate and give a clear solution. The contents of the flask were transferred to a separatory funnel, and the ether layer was removed. The aqueous layer was then extracted with several portions of ether. The combined ethereal extracts were washed with dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the solvent gave 20.6 g. (88 per cent yield) of crude trans-1,3-cyclopentanedi-panol (79), \( n^D_{20} 1.4767 \). The following absorption bands
were observed in the infrared spectrum of 79: 3400 cm.\(^{-1}\) (O-H), 1060 cm.\(^{-1}\) (O-H). The \(p\)-nitrobenzoate derivative 80 of 79 was prepared and purified by recrystallization. An analytical sample of 80, m.p. 87-88\(^\circ\)C., was obtained by four recrystallizations from 95 per cent ethanol.


**trans-1,3-Cyclopentanedipropanol (79). Procedure B.**

The procedure developed by Nystrom and Brown\(^{80}\) was employed to reduce dimethyl \(\text{trans-1,3-cyclopentanedi}\)propionate (70) to the \(\text{trans-dip}\)ropanol 79. To a solution of 6.1 g. (0.16 mole) of lithium aluminum hydride in a 1-l., three-necked flask equipped with a Hershberg stirrer, dropping funnel, and reflux condenser was added a solution of 9.7 g. (0.04 mole) of 70 in 100 ml. of anhydrous ether. The solution of 70 was added at a rate such as to produce gentle reflux (about 1 hour). After 2 hours of additional stirring, 50 ml. of water was added drop-wise with intermittent cooling in an ice bath to decompose excess lithium aluminum hydride. During the addition of water it was necessary to add two 200-ml. portions of ether to replace lost solvent. Enough 10 per cent sulfuric acid was then added to dissolve the hydroxide precipitate and give a clear solution. Isolation of the product as in Procedure A gave 7.0 g.
(94 per cent yield) of crude trans-1,3-cyclopentanediopropanol (79). The infrared spectrum of this material was identical to that of 79 obtained by Procedure A.

**trans-1,3-Cyclopentanedi-\(\gamma\)-bromopropane (83).** The trans-dibromide 83 was prepared by the method of Cloke and co-workers. A 300-ml., three-necked flask was equipped with a dropping funnel, a mechanical stirrer, and a reflux condenser with attached drying tube. Phosphorus tribromide (27.1 g., 0.1 mole) was placed in the flask, which was immersed in an ice bath. The stirrer was started, and 18.6 g. (0.1 mole) of the crude trans-dipropanol 79 was added dropwise over a period of 2 hours. The mixture was allowed to warm to room temperature overnight then heated with continued stirring on a steam bath for several hours. Ice and water (150 ml.) was added to the cooled reaction mixture, and the product was extracted with several portions of chloroform. The chloroform extract was washed several times with concentrated sulfuric acid, followed by water and dilute sodium bicarbonate solution. Removal of the solvent after drying the solution over anhydrous magnesium sulfate gave 25.4 g. (82 per cent yield) of trans-1,3-cyclopentanedi-\(\gamma\)-bromopropane (83), \(n_\text{D}^\text{20} 1.5094\).

**trans-1,3-Cyclopentanedi dibutynitrile (84).** Following the procedure of Allen, 25.0 g. (0.08 mole) of the
trans-dibromide 83 was reacted with 13.7 g. (0.2 mole) of potassium cyanide in ethanol-water solvent. The crude trans-dibutyronitrile 84 was purified by chromatography on a column of florex (60 g.). Upon evaporation of the ether eluate, 15.7 g. (96 per cent yield) of trans-1,3-cyclopentanenedibutyronitrile (84), nD 1.4698, was obtained. A sample of 84 was further purified by preparative gas liquid chromatography (GLC) at 280°C. on an SE 30 Silicone column. The pure sample of trans-1,3-cyclopentanenedibutyronitrile (84) which was collected had nD 1.4708, and infrared analysis revealed the expected absorption band at 2250 cm.⁻¹ (C=N).

trans-1,3-Cyclopentanenedibutyric Acid (85). - Six grams (0.03 mole) of the trans-dibutyronitrile 84 was heated with 30 ml. of 75 per cent sulfuric acid at 90°C. for 3 hours. The reaction mixture was cooled and poured into 150 ml. of ice and water. The product was isolated by extraction with several portions of ether, and the combined ethereal extracts were washed once with water then extracted with 100 ml. of 10 per cent potassium hydroxide. The basic, aqueous extract was boiled to remove dissolved ether, filtered using Celite, then cooled and added slowly to a cold, stirred solution of 20 ml. of concentrated hydrochloric acid in 50 ml. of water. The precipitate was suction filtered and dried to give 5.8 g.
(82 per cent yield) of crude trans-1,3-cyclopentanedi-
butyric acid (85). An analytical sample of 85, m.p. 118-
120°C., was prepared by three recrystallizations from a
large volume (250 ml./g.) of 5 per cent acetic acid.

Anal. Calcd. for C_{13}H_{22}O_{4}: C, 64.44; H, 9.15.
Found: C, 64.26; H, 9.23.

**Dimethyl trans-1,3-cyclopentanedicarboxylate (86).**

Crude trans-dibutyric acid 85 (5.6 g., 0.23 mole) was rea-
acted with 3.2 g. (0.1 mole) of reagent grade methanol and
1.4 g. (0.8 ml.) of concentrated sulfuric acid in 12 ml.
of benzene. Workup in the usual manner and purification
of the product by chromatography on activity I alumina
gave 4.4 g. (70 per cent yield) of pure dimethyl trans-1,3-
cyclopentanedicarboxylate (86), n_{D}^{20} 1.4579.

**Acyloin Reactions in Xylene**

I. Acyloin condensation of diethyl cis-1,3-cyclopentane-
di-propionate (69)

**cis-Bicyclo[6.2.1]undecan-4-ol-5-one (73).** - The
apparatus described by Prelog and co-workers was em-
ployed, and the workup procedure was that of Cram and
Steinberg. A 250-ml., three-necked flask was equipped
with a high-speed stirring motor (20,000 RPM) connected
to a glass stirrer shaft. The stirrer shaft was fitted with a Hershberg stirrer and a water-cooled bearing. In one of the outer necks of the flask was placed a Claissen adapter. A West condenser was placed in the arm of the adapter directly over the flask, and a Hershberg dropping funnel was placed in the outer arm. This arrangement afforded additional dilution by refluxing solvent of the material entering the flask. In the other neck of the reaction flask was placed a second Claissen adapter, the inner arm of which was stoppered and the outer arm of which held a gas-inlet stopcock. A gas-outlet stopcock attached to a mercury bubbler with a small head of mercury was fitted into the top of the reflux condenser.

Xylene (125 ml.), dried over sodium, was placed in the reaction flask, and to remove traces of moisture, a small portion of the solvent was distilled through the condenser temporarily placed in distilling position. During the distillation the air in the flask was replaced by argon. The condenser was replaced in reflux position, and 4.9 g. (0.21 g. at.) of freshly cut sodium metal was added through the top of the reflux condenser under a continuing flow of argon. After reheating the xylene to reflux, the stirrer was set in motion, and the molten sodium was dispersed by stirring at an estimated 2,000 RPM for 15 minutes. Addition of a solution of 13.9 g.
(0.052 mole) of 69 in 25 ml. of dry xylene to the sodium dispersion was completed in 45 hours. The reaction mixture was heated with continued stirring for an additional 3 hours. After cooling in an ice bath, 14 g. (0.24 mole) of glacial acetic acid was added dropwise to decompose excess sodium. During the addition of acetic acid it was necessary to add 50 ml. more xylene to suspend the sodium acetate formed. The sodium acetate was removed by vacuum filtration and returned to the reaction flask with a 50-ml. portion of fresh xylene. After stirring vigorously for several minutes, the solid was again filtered, and the xylene filtrates were combined. The xylene solution was then washed with water and dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The xylene was removed by distillation through a 10 cm. Vigreaux column. Additional product was recovered by dissolving the sodium acetate in 200 ml. of water and extracting with ether several times. The washed, dried ethereal extract afforded a residue upon evaporation of the solvent, the infrared spectrum of which was identical to that of the residue from the xylene distillation. The two samples were combined (4.1 g. total) and chromatographed on a 14 x 1.5 cm. column of activity V Woelm neutral alumina. Evaporation of the benzene eluate gave 0.9 g (10 per cent yield) of cis-bicyclo[6.2.1]undecan-
4-ol-5-one (73). Continued elution with increasingly polar solvents afforded no additional products. Infrared analysis of 73 revealed absorption bands at 3400 cm.$^{-1}$ (O-H) and 1690 cm.$^{-1}$(C=O). The sample of 73 was rechromatographed on a column of activity I Woelm neutral alumina in order to obtain a pure sample for characterization. After washing the column with solvents through ether, a small amount of pure 73 was eluted from the column with methanol. The residue from the methanol eluate (about 100 mg.) was converted to the p-nitrobenzoate derivative 74. A pure sample of 74 m.p. 140-141°C., was obtained by recrystallization of the crude material from acetone-water and two sublimations at 179°C./0.4 mm.


cis-Bicyclo[6.2.1]undecan-4,5-dione (75).—The cis-acyloin 73 was oxidized to the cis-diketone 75 by the method of Bowden and co-workers.$^{54}$ A solution of 0.6 g. (0.006 mole) of chromium trioxide in 2 ml. of water and 0.8 g. of concentrated sulfuric acid was added dropwise to a cold, stirred solution (0°C.) of 0.9 g. (0.005 mole) of 73 in 2 ml. of acetone. The addition was completed in 1.5 hours, and stirring was continued for 30 minutes longer. Water (20 ml.) was added to the reaction
mixture at the end of this time, and the aqueous solution was extracted with several portions of ether. The combined ethereal extracts were washed with water and dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the ether gave 0.4 g. (67 per cent yield) of cis-bicyclo[6.2.1]undecan-4,5-dione (75) as a viscous, yellow oil. The cis-diketone 75 was characterized as its 2,4-dinitrophenylhydrazone derivative 76. The derivative 76 was prepared and recrystallized four times from a mixture of chloroform and 95 per cent ethanol to give an analytical sample of cis-bicyclo[6.2.1]undecan-4,5-dione 2,4-dinitrophenylhydrazone (76), m.p. 236-237°C. (dec.).

Anal. Calcd. for C_{23}H_{24}N_{8}O_{8}: C, 51.11; H, 4.48; N, 20.74. Found. C, 49.07; H, 4.31; N, 19.70.

II. Acyloin reaction of diethyl trans-1,3-cyclopentanedi-propionate (68)

Experimental procedure.-The apparatus and experimental procedure employed was essentially the same as that used in acyloin condensation I of the cis-diethyl ester 69 except that a 500 ml. flask was used for a reaction vessel. The trans-diethyl ester 68 (27.0 g., 0.1 mole) was dissolved in 100 ml. of xylene and dried over sodium. This solution was added in 48 hours to a dispersion of 9.2 g.
(0.4 g. at.) of sodium in 250 ml. of dry xylene. Stirring was continued for 48 hours at reflux temperature after the addition of 68 was complete. The reaction mixture was then cooled in an ice bath, and 27 g. (0.45 mole) of glacial acetic acid was added dropwise to decompose excess sodium. The neutral xylene solution obtained from workup as before was distilled at reduced pressure (30 mm.). The infrared spectrum of the distillation residue was essentially identical to that of the starting trans-diethyl ester 68. No other neutral products were isolated at that time.

III. Acyloin reaction of dimethyl trans-1,3-cyclopentane-dipropionate (70)

Experimental procedure and GLC analysis.-The cyclization procedure of Prelog and co-workers34 was followed, using the apparatus described for the acyloin condensation I of the cis-diethyl ester 69. A 1-l. reaction flask was used. The trans-dimethyl ester 70 (50.0 g., 0.21 mole) in 100 ml. of xylene was added to a dispersion of 19.6 g. (0.85 g. at.) of sodium metal in 500 ml. of dry xylene over a period of 50 hours. After addition the flask was immediately cooled in an ice bath, and 40 ml. of methanol was added dropwise to decompose the excess sodium. The mixture was poured into 500 ml. of ice water and acidified
with dilute sulfuric acid, and the xylene layer was separated. The aqueous layer was extracted again with ether, and the combined xylene-ether extracts were washed with water and dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Distillation of the solvents through a Vigreaux column afforded a residue, the infrared spectrum of which was identical to that of the starting trans-dimethyl ester 70. Analysis of the residue by GLC revealed the presence of a small amount of xylene, 70, and possibly a third component with a retention time slightly greater than that of 70. The third component detected by GLC was isolated by column chromatography on florex.

Column chromatography of products from acyloin reactions II and III.—The combined residues from acyloin reactions II and III were placed on a 2 x 25 cm. column of florex in petroleum ether (b.p. 20-40°C.). Elution with this solvent was continued until no residue was obtained upon evaporation of the eluate. The column was then stripped with ether, and the solvent was removed to give 1.26 g. of a yellow oil. This material was oxidized with chromium trioxide by the method of Bowden and co-workers.54 Reaction of the compound in 3 ml. of acetone with a solution of 0.8 g. (0.008 mole) of chromium trioxide and 1 g. of sulfuric acid in 3 ml. of water gave
0.7 g. of product. The following absorption bands were observed in the infrared spectrum of this material: 2500-2700 cm.\(^{-1}\) (O-H, broad band), 1700-1760 cm.\(^{-1}\) (C=O), 1125-1300 cm.\(^{-1}\) (ester). The oxidation product was not identified at the time, but comparison of the infrared spectrum with that of an analytical sample of trans-3-(3-carbomethoxyethyl)-cyclopentylpropionic acid (81), isolated from acyloin reaction VIII, showed them to be essentially identical.

IV. Acyloin reaction of dimethyl trans-1,3-cyclopentane-dipropionate (70)

Apparatus and experimental procedure.—The experimental procedure described by Cram and Steinberg\(^{53}\) was used with some modification. The apparatus used was the same as that described in acyloin condensation I of the cis-diethyl ester 69 except that a 1-1. Morton flask and a high-speed, stainless steel stirrer were used. Reagent grade xylene was dried and purified by refluxing over sodium for 8 hours and distillation directly from the sodium through a spinning-band column. Before use the apparatus was heated with a flame while flushing with argon to remove traces of moisture. In a typical run, 400 ml. of dry xylene was placed in the Morton flask and stirring and heating were begun. About 20 ml. of xylene was
distilled while passing argon through the system. The flask was then cooled, and 10.0 g. (0.44 g. at.) of freshly cut sodium was introduced into the flask through the top of the reflux condenser, replaced in reflux position. The sodium was dispersed by stirring at an estimated 8,000 RPM or higher for 30 minutes. Twenty-six grams (0.11 mole) of the trans-dimethyl ester ZQ, purified by filtration through a column of activity I alumina, was dissolved in 200 ml. of dry xylene and dried over 4 A molecular sieve. The dried solution of ZQ was added to the refluxing sodium dispersion in 30 hours with continued stirring at about 6,000 RPM. After stirring for an additional 7 hours, 27.0 g. (0.45 mole) of glacial acetic acid was added to the reaction mixture cooled in an ice bath. The resulting suspension was vacuum filtered to remove solids. The filter cake was returned to the reaction flask and stirred for several minutes at high-speed with 200 ml. of ether and filtered again. Removal of the ether gave 1.6 g. of an oil, the infrared spectrum of which was identical to that of ZQ. The xylene solution was filtered through 50 g. of activity I Woelm neutral alumina, and the xylene and unreacted ZQ were removed by washing with a large volume of petroleum ether. The column was then stripped with methanol to give 200 mg. of an oil upon removal of the
solvent. Infrared analysis of the oil revealed the following absorption bands: 3500 cm$^{-1}$(O-H), 1700-1750 cm$^{-1}$(C=O), 1060 cm$^{-1}$(O-H). An attempt to prepare a p-nitrobenzoate derivative of this material was unsuccessful. In several subsequent attempts to cyclize the trans-dimethyl ester changes were made in the reaction time and workup technique. In none of these attempts was a trans-acyloin product or derivative isolated. Dioxane was used for a reaction solvent in the remaining condensations.

**Acyloin Reactions in Dioxane**

V. Acyloin reaction of dimethyl trans-1,3-cyclopentane-dipropionate (70) at 100°C.

**Apparatus and reagents.** The apparatus described by Cram and Steinberg$^{53}$ was used with some modification. All glassware was dried overnight in an oven at 120°C and protected by drying tubes during assembly. A 1-l. Morton flask was equipped with a high-speed, stainless steel stirrer and a high-speed (20,000 RPM) stirrer motor. In one of the necks of the flask was placed a Claissen adapter holding a West condenser directly over the flask and a 250-ml. Hershberg dropping funnel in the outer arm. In the other neck of the flask was placed a second Claissen adapter, one arm of which was stoppered and
one arm of which held a gas-inlet stopcock. A gas-outlet stopcock attached to a U-tube having a small head of mercury was placed in the top of the reflux condenser. The Claissen adapters were wired securely to the necks of the Morton flask. In order to remove the last traces of moisture, the entire system was heated with a flame while flushing with argon. Reagent grade dioxane was further purified by refluxing over sodium metal for 12 hours under argon. The dry dioxane was then distilled under argon directly onto 4 A molecular sieve in an oven-dried bottle. Ester used in the remaining condensations was purified by filtration through activity I alumina in petroleum ether. After removal of the petroleum ether, the ester was dissolved in pure, dry dioxane and stored over 4 A molecular sieve for several days before use.

Experimental procedure.—Pure, dry dioxane (400 ml.) was siphoned into the Morton flask under argon. Crust-free sodium metal (7.2 g., 0.31 mole) was added to the reaction flask through the top of the reflux condenser, and after heating the dioxane to reflux, the molten sodium was dispersed by stirring at an estimated 8,000-9,000 RPM for 15 minutes. A solution of 19.0 g. (0.078 mole) of the trans-dimethyl ester 70, prepared from trans-dipropionic acid 52 of m.p. 96-97°C., in 200 ml. of
Dioxane was siphoned into the Hershberg dropping funnel under argon. Addition of the diester solution was completed in 36 hours at a somewhat reduced rate of stirring. Stirring was continued for 10 hours at reflux temperature (100°C.) with no observable change in the color of the reaction mixture. The reaction mixture was cooled to about 50°C. (the ambient temperature produced by stirring) and stirred for an additional 48 hours, during which time the reaction mixture changed to a dark yellow color. The reaction mixture was finally cooled in an ice bath, and 20 g. (0.34 mole) of glacial acetic acid was added dropwise with continued stirring. When it was certain that the sodium had been completely destroyed, the reaction mixture was carefully poured into 1 l. of ice and water, and the product was extracted with several portions of ether. Some solid, polymeric material separated at this time and was removed by filtration. The ether filtrate was washed several times with water and dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the solvent afforded 7.3 g. of a residue which gave a positive Fehling's test at room temperature, indicating the possible presence of acyloin product. The sodium bicarbonate solution was acidified and extracted with several portions of ether. The dried ethereal extract gave 1.3 g. of acidic material upon
removal of the solvent. A sample (1.2 g.) of the neutral residue was placed on a column of 25 g. of activity IV Woelm neutral alumina. The column was washed with 75 ml. of petroleum ether then eluted with 150 ml. of benzene and 100 ml. of ether. Removal of solvent from the benzene eluate gave 200 mg. of an oil, the infrared spectrum of which was essentially identical to that of the cis-acyloin 73 isolated in the same manner from acyloin condensation I of the cis-diethyl ester 69. Removal of the solvent from the ether eluate gave 100 mg. of an oil. This material was not identified at the time, but investigation of a similar fraction from later trans reactions showed it to consist largely of the trans-dipropanol 79. Because of the low recovery from alumina, a more careful chromatography of the crude acyloin product on a less polar column was attempted. A sample of the neutral condensation residue (750 mg.) was placed on a 1.5 x 15 cm. column of florex. Careful elution with increasingly polar solvents through 1:1 petroleum ether:benzene gave only trace amounts of material. Elution with 150 ml. of benzene gave 125 mg. of cis-acyloin (73) upon removal of the solvent. Elution with 100 ml. of ether gave 185 mg. of material. Attempts to make the p-nitrobenzoate derivatives of the two fractions by standard techniques were unsuccessful, probably because of the impurity
of the samples. It was found that distillation of the neutral condensation residue at reduced pressure (micro-Hickman still) afforded a sample of material which, by infrared analysis, was identical to that obtained from the benzene eluate; however, the recovery was low. The remainder of the crude reaction product (4.5 g.) was placed on a 2.2 x 25 cm. column of florex. The column was washed with 200 ml. of petroleum ether then eluted with 400 ml. of benzene and 300 ml. of ether. The benzene eluate, acyloin fraction A, gave 1.0 g. (11 per cent total yield) of crude cis-bicyclo[6.2.1]undecan-4-ol-5-one (73) upon removal of the solvent. Removal of the solvent from the ether eluate, acyloin fraction B, gave 1.6 g. (total yield 18 per cent based on the trans-dipropanol 79) of material.

Oxidation of the cis-acyloin 73 with chromium trioxide-pyridine. - The crude cis-acyloin 73 was oxidized with chromium trioxide-pyridine according to the procedure of Cope and co-workers.83 Acyloin fraction A (180 mg.) was dissolved in 4 ml. of dry pyridine and added to a solution of 0.8 g. of the preformed chromium trioxide-pyridine complex (Eastman bis(pyridine)chromium oxide) in 8 ml. of dry pyridine. After stirring for 4 hours, the reaction mixture was poured into 100 ml. of water and extracted with
several portions of ether. The combined ethereal extracts were carefully washed with water, 3 N hydrochloric acid, and dilute sodium bicarbonate solution. Removal of the solvent after drying over anhydrous magnesium sulfate gave 100 mg. of crude oxidation product. Elution of the crude product from a 1.5 x 15 cm. column of florex with benzene gave 77 mg. (51 per cent yield) of the cis-diketone 75, as evidenced by comparison of the infrared spectrum with that of the authentic sample of 75 obtained in acyloin condensation I. The 2,4-dinitrophenylosazone derivative was prepared and recrystallized once from chloroform-ethanol and three times from dioxane-water to m.p. 236-236.5°C. (dec.). The infrared spectrum of the derivative was identical to that of the cis-diketone 2,4-dinitrophenylosazone 76, m.p. 236-237°C. (dec.), obtained in acyloin condensation I, and the mixture melting point of the two samples was undepressed. The starting trans-dipropionic acid 53 was purified more carefully before attempting additional condensation reactions in order to eliminate, or at least minimize, contamination of the product by the cis isomer.

Purification of the trans-dipropionic acid 53 from Wolff-Kishner reduction of the ketodinitrile 58

Crude trans-dipropionic acid 53 (50 g.), from the
Wolff-Kishner reduction of 58, was dissolved in 1500 ml. of boiling water. Decolorizing carbon was added, and the solution was boiled for a few minutes and rapidly vacuum filtered with the aid of Celite. The resulting oily filtrate was reheated, and 200 ml. of glacial acetic acid was added to afford a clear solution. The crystals obtained upon cooling the solution were filtered, washed with water, and dried to give 52 of m.p. 96–97°C. Repeated recrystallization by the same technique did not alter the melting point. Careful examination of the infrared spectrum of 52, purified in this manner, revealed the presence of contaminating cis-dipropionic acid 52, as evidenced by a small peak at 1240 cm\(^{-1}\). This absorption band is of medium intensity in the infrared spectrum of 52, but it is absent in the spectrum of the pure 53 obtained from the Arndt-Eistert homologation. The thoroughly dried 53 was dissolved in a minimum amount of tetrahydrofuran at room temperature. This solution was heated to boiling, and sufficient hexane was added to cloud the hot solution. Enough glacial acetic acid was then added to restore clarity, and the solution was filtered rapidly and allowed to cool slowly to room temperature. The crystals which formed were separated and recrystallized two more times in the same manner. This procedure afforded 19.0 g. of the pure trans-1,3-cyclopentanedipropionic acid (53), m.p.
106

100-101°C., and the absorption band at 1240 cm.⁻¹, characteristic of the cis-dipropionic acid 52, was absent.

VI. Acyloin reaction of dimethyl trans-1,3-cyclopentane-dipropionate (70) at 50°C.

Apparatus and experimental procedure. - The reaction was carried out in the apparatus described for acyloin reaction V with some modification of the experimental procedure. The trans-dimethyl ester 70 (19.0 g., 0.078 mole), prepared from purified trans-dipropionic acid, was dissolved in 175 ml. of pure, dry dioxane and placed over 4 A molecular sieve. A dispersion of 7.2 g. (0.31 g. at.) of sodium in 400 ml. of dioxane was prepared as before by stirring at 8,000-9,000 RPM for 15 minutes. The dioxane solution of 70 was added slowly to the refluxing dispersion for 1 hour. The heating was then stopped, and the rate of stirring was decreased somewhat. Addition of the solution of 70 was completed in 40 hours, and stirring was continued for an additional 48 hours. After this time the sodium was decomposed at 0°C. by the addition of 20.0 g. (0.34 mole) of glacial acetic acid, and the crude product (13.8 g.) was isolated in the usual manner. Chromatography of the crude product on florex, as described in acyloin reaction V, afforded a petroleum ether fraction (7.2 g.), a benzene fraction (2.6 g., acyloin
fraction A), and an ether fraction (1.6 g., acyloin fraction B).

Oxidation of acyloin fraction A.-Acyloin fraction A was oxidized with bismuth trioxide according to the procedure of Blomquist and Buck. One gram of acyloin fraction A (5.5 mmole based on bicyclic acyloin) and 1 g. of bismuth trioxide (2.2 mmole) were refluxed in 5 ml. of glacial acetic acid for 30 minutes with stirring. The hot acetic acid solution was filtered to remove metallic bismuth and poured into 15 ml. of cold water. The product was extracted with several portions of benzene, and the combined benzene extracts were washed with water and dilute sodium bicarbonate solution. The benzene solution was dried over anhydrous magnesium sulfate and evaporated to give 0.8 g. of a bright yellow oil. Infrared analysis of this oil revealed absorption bands at 1700-1750 cm.$^{-1}$(C=O) and 1100-1300 cm.$^{-1}$ (probably trans-dimethyl ester Z0), and the infrared spectrum was essentially identical to that of acyloin fraction A except for the absence of an absorption band at 3500 cm.$^{-1}$(O-H). The product was obviously impure, probably being contaminated with starting trans-dimethyl ester Z0, and an attempt was made to isolate any diketone present by chromatography on florex. The crude oxidation product was distilled when no separation was achieved by chromatography. Distillation
of the crude material in a micro-Hickman still (130°C./
0.25 mm.) afforded a small amount of a pale yellow dis-
tillate. The distillate was apparently still contaminated
with 70 as evidenced by the presence in the infrared spec-
trum of the broad absorption band at 1100-1300 cm.\(^{-1}\),
characteristic of the starting diesters. The distillate
was, however, considerably enriched in another component
showing a carbonyl absorption band in the infrared spec-
trum at 1700 cm.\(^{-1}\), so the initial distillate was redistil-
led carefully in an attempt to isolate a pure sample of
this material. The first fraction collected (105-110°C./
0.25 mm.) deposited a small amount of a yellow solid
(m.p. 99-104°C. after washing with ether). Infrared anal-
ysis of this solid revealed a sharp absorption band at
1700 cm.\(^{-1}\)(C=O) and other absorption bands at 1040 cm.\(^{-1}\)
and 920 cm.\(^{-1}\). Insufficient material was obtained for
complete characterization. The second fraction obtained
by redistillation (125-130°C./0.25 mm.) had an infrared
spectrum identical to that of the starting trans-dimethyl
ester 70.

**Investigation of acyloin fraction B.** One gram of
acyloin fraction B was oxidized with bismuth trioxide in
acetic acid by the same procedure used to oxidize acyloin
fraction A. Comparison of the infrared spectrum of the
oxidation product with that of the starting material revealed little or no change in the major absorption bands at 3400 cm.\(^{-1}\) and 1040-1060 cm.\(^{-1}\) present in the starting material, but a significant increase in the intensity of the carbonyl absorption at 1700-1725 cm.\(^{-1}\). In addition, an intense absorption band appeared at 1240 cm.\(^{-1}\) in the spectrum of the oxidation product. Chromatography of the crude oxidation product on florex afforded two fractions. The infrared spectrum of the first fraction, eluted with 1:1 petroleum ether:benzene, had infrared absorption bands at 1740 cm.\(^{-1}\), 1240 cm.\(^{-1}\), and 1040 cm.\(^{-1}\). The second fraction, eluted with benzene, had infrared absorption bands at 3500 cm.\(^{-1}\), 1740 cm.\(^{-1}\), 1240 cm.\(^{-1}\), and 1040-1060 cm.\(^{-1}\). The two compounds were not completely characterized; however, subsequent investigations indicated that the first fraction was the diacetate derivative \(^{22}\) of trans-1,3-cyclopentanedipropanol (\(^{20}\)) and that the second fraction was the monoacetate derivative \(^{22}\).

VII. Acyloin reaction of dimethyl trans-1,3-cyclopentanedicarboxylate (\(^{20}\))

Apparatus and experimental procedure. Using the same apparatus and experimental procedure described in acyloin reaction VI, a solution of 20.0 g. (0.082 mole) of pure \(^{20}\) in 200 ml. of dioxane was added to a dispersion of 7.6 g.
(0.332 g. at.) of sodium in 400 ml. of dioxane in 40 hours. After stirring for 48 hours longer, 22.0 g. (0.37 mole) of glacial acetic acid was added to decompose sodium. Workup in the usual manner gave 16.0 g. of crude acyloin product. The crude acyloin product was placed on a column of 200 g. of florex and washed with 2 l. of petroleum ether, followed by 250 ml. of benzene. Evaporation of the eluates and examination of their infrared spectra showed the residues to be identical samples of unreacted trans-dimethyl ester 70 (7.2 g. total). Continued elution with benzene afforded 0.6 g. of acyloin fraction A upon removal of the solvent. Elution with ether gave 2.5 g. of acyloin fraction B.

Oxidation of acyloin fraction A. - Acyloin fraction A (0.6 g.) was oxidized with bismuth trioxide by the method of Blomquist and Buck,55 as described in acyloin reaction VI. The crude oxidation product (0.5 g.) was placed on a 1.5 x 15 cm. column of silica gel (Fisher S-662). Elution of the column with 5:1 petroleum ether:chloroform afforded a small amount (50 mg.) of an oil upon removal of the solvent. The infrared spectrum of this material was quite similar to that of the pure cis-diketone 75 obtained in acyloin condensation I of the cis-diethyl ester 69. The 2,4-dinitrophenylhydrazone derivative of
this material had m.p. 233-234°C. (dec.) after two recrystal-
lizations from chloroform-ethanol solvent. Comparison
of the infrared spectrum of the derivative with that of an
authentic sample of cis-bicyclo[6.2.1]undecan-4,5-dione
2,4-dinitrophenyllosazine (76) showed them to be identical.
Additional fractions eluted from the silica gel column
with solvents of increasing polarity contained increasing-
ly greater amounts of unreacted starting trans-dimethyl
ester 70. Distillation (105°C./0.25 mm.) of the residue
obtained by stripping the column with ether afforded a
distillate, the infrared spectrum of which was identical
to that of the material obtained by distillation of
acyloin fraction A in reaction VI.

Isolation of trans-1,3-cyclopentanediopropanol (79)
from acyloin fraction B.-Acyloin fraction B was distilled
in an attempt to obtain a pure compound for characteriza-
tion. Distillation in a micro-Hickman still at 100°C./
0.25 mm. gave a small quantity of a colorless oil, infra-
red analysis of which revealed major absorption bands at
3400 cm.\(^{-1}\) (O-H) and 1060 cm.\(^{-1}\) (O-H). Comparison of the
infrared spectrum of this material with that of an authen-
tic sample of the trans-dipropanol 79 showed them to be
identical. Insufficient pure material was obtained by
distillation for the preparation of a solid derivative.
Reaction of the trans-dipropanol 79 with bismuth trioxide.—A sample of 79 was treated with bismuth trioxide in glacial acetic acid to determine if the products obtained by oxidation of acyloin fraction B in condensation VI could be accounted for. The trans-dipropanol 79 (100 mg.), prepared by lithium aluminum hydride reduction of the trans-dipropionic acid 53, was stirred with 100 mg. of bismuth trioxide in 3 ml. of refluxing glacial acetic acid for 30 minutes. Workup as before yielded 90 mg. of a colorless oil. The infrared spectra of this material and the fractions obtained by chromatography on florex were identical to those of the corresponding fractions isolated from the reaction with bismuth trioxide of acyloin fraction B in acyloin reaction VI. Treatment of 79 with acetic anhydride also afforded the same two compounds, and it was concluded that the two compounds were the mono and diacetates of the trans-dipropanol 79.

Oxidation of acyloin fraction B with chromium trioxide-acetone.—Acyloin fraction B (350 mg.) was dissolved in 7 ml. of acetone. To this solution was added 700 mg. of chromium trioxide and 1.5 ml. of concentrated sulfuric acid in 7 ml. of water. After stirring for 22 hours at room temperature, the mixture was poured into 20 ml. of water and extracted with four portions of ether. The combined ethereal extracts were washed with water and
dilute sodium bicarbonate solution. The basic, aqueous extract was acidified with concentrated hydrochloric acid and extracted with several portions of ether. Removal of the solvent from the dried, ethereal extract gave 260 mg. of solid which had m.p. 101-102°C. after two recrystallizations from acetonitrile. This material had a mixture melting point of 101-102°C. with pure trans-dipropionic acid 53. Evaporation of the original, base-washed ether solution afforded 95 mg. of an oil. The infrared spectrum of this material was identical to that of a sample of trans-3(6-carboxymethoxyethyl)-cyclopentylpropionic acid (81) isolated from acyloin reaction VIII. It was postulated that 81 resulted from oxidation of trans-3(6-carboxymethoxyethyl)-cyclopentylpropanol (82) present in fraction B.

VIII. Acyloin reaction of dimethyl trans-1,3-cyclopentane-dipropionate (70)

Apparatus and experimental procedure.-The apparatus and procedure used was the same as that described for acyloin reaction VI. Pure 70 (18.0 g., 0.075 mole) in 180 ml. of dioxane was reacted with 6.9 g. (0.30 g. at.) of sodium dispersed in 400 ml. of dioxane. Workup in the usual manner afforded 15.9 g. of crude product. The crude product was placed on a 2.2 x 25 cm. column of florex and
eluted with 600 ml. of petroleum ether, 850 ml. of benzene, and 400 ml. of ether. Evaporation of the petroleum ether eluate gave 7.7 g. of material. Evaporation of the benzene eluate gave 3.0 g. of acyloin fraction A, and 1.4 g. of acyloin fraction B was recovered from the ether eluate. The sodium bicarbonate wash of the original ether extract afforded 1.1 g. of acidic material upon acidification and extraction with ether.

Investigation of acyloin products by thin-layer chromatography (TLC).—The petroleum ether residue and acyloin fraction A were dissolved in benzene and spotted on diagnostic TLC plates coated with a 0.25 mm. layer of unactivated silica gel (Research Specialties Silica Gel G). The plates were eluted with 3:1 cyclohexane:ethyl acetate, air dried, and developed with iodine vapor. The petroleum ether residue contained starting trans-dimethyl ester 70 plus a second component, and acyloin fraction A contained at least five components. Attempts to separate acyloin fraction A into its components on a 2.0 mm. preparative plate were unsuccessful. It was found that as little as 25 mg. of material severely overloaded a 20 x 20 cm. plate, resulting in no distinct separation of bands, so this method was abandoned. TLC examination of the bismuth trioxide oxidation product of acyloin
fraction A showed it to contain the same five components (same $R_f$ values) as the unoxidized material plus an additional component of higher $R_f$ value. Attempts to obtain a pure sample of this component by preparative TLC were also unsuccessful. The bismuth trioxide oxidation product of acyloin fraction A was placed on a column of silica gel and eluted with 3:1 cyclohexane:ethyl acetate. Ten ml. fractions of the eluate were evaporated and examined on diagnostic TLC plates as before. In this manner several small fractions were isolated which appeared to contain only one component. Insufficient quantities for characterization of the pure components were obtained by this technique, and only trans-dimethyl ester 70 was identified from its infrared spectrum. The infrared spectra of the other pure components isolated showed evidence of ester absorption at about 1200 cm.$^{-1}$, although they were not contaminated with 70 as evidenced by the TLC analyses. None of the components exhibited infrared absorption characteristic of bicyclic acyloin or diketone.

**Investigation of the petroleum ether eluate.**—The residue (7.7 g.) from the petroleum ether eluate was redissolved in 50 ml. of petroleum ether and filtered through a column of 50 g. of activity I Woelm neutral alumina. The column was washed with additional petroleum
ether until evaporation of the eluate left no residue. The column was then eluted with acetone, followed by methanol. The first portion of the acetone eluate was mostly trans-dimethyl ester 70, but continued elution with acetone gave fractions containing an increasing amount of acyloin material, as revealed by infrared analysis. Fractions eluted with methanol showed very strong contributions from acyloin material in the infrared spectra (3400 cm.$^{-1}$ and 1690 cm.$^{-1}$), but contaminating 70 was still present. The later fractions, containing a large proportion of acyloin material, were combined and reacted with 2,4-dinitrophenylhydrazine reagent. The amorphous solid which precipitated was placed on a 1.5 x 15 cm. column of activity I Woelm neutral alumina in a small amount of chloroform. The orange oil obtained upon evaporation of the chloroform eluate was recrystallized from dioxane-water several times to give an analytical sample, m.p. 231-232°C. (dec.). The infrared spectrum of this material was identical to that of an analytical sample of cis-bicyclo[6.2.1]undecan-4,5-dione 2,4-dinitrophenylosazone (76) isolated in acyloin condensation I. No trans derivative could be identified among the remaining fractions obtained by continued elution of the column.

**Anal.** Calcd. for C$_{25}$H$_{24}$N$_8$O$_8$: C, 51.11; H, 4.48; N, 20.74. Found: C, 51.38; H, 4.60; N, 21.00.
Isolation and characterization of the trans-diprop-panol 29 from acyloin fraction B.-Acyloin fraction B (200 mg.) was placed on a 1.5 x 15 cm. column of silica gel and eluted with 1:1 benzene:acetone. Infrared analysis revealed that the initial fractions were contaminated with a large proportion of material having absorption bands at 1700-1750 cm\(^{-1}\) (C=O) and 1100-1300 cm\(^{-1}\). Continued elution with the same solvent afforded several fractions in which the carbonyl absorption was negligible and which had major infrared absorption bands only at 3400 cm\(^{-1}\) (O-H) and 1060 cm\(^{-1}\) (O-H). This material was identified as the trans-dipropanol 29 by comparison of the spectrum with that of a known sample and by preparation of the p-nitrobenzoate derivative. The p-nitrobenzoate derivative had m.p. 86-87°C after two recrystallizations from 95 per cent ethanol. The mixture melting point with an authentic sample of the p-nitrobenzoate derivative 80 (m.p. 87-88°C.) of the trans-dipropanol 29 was undepressed, and the infrared spectra of the two samples were identical.

Isolation and characterization of trans-3(3-carbo-methoxyethyl)-cyclopentylpropionic acid (81).-The acidic material from the bicarbonate wash was placed on a 1.5 x 15 cm. column of florex after removal of a solid (trans-dipropionic acid 53) which had crystallized upon standing.
The column was washed with 60 ml. of benzene then eluted with ether. Infrared analysis of the residue obtained by removal of the solvent from the ether eluate revealed a broad absorption band at 2500-3500 cm.\(^{-1}\), characteristic of carboxylic acids, as well as a broad band at 1100-1300 cm.\(^{-1}\), characteristic of esters. The carbonyl absorption appeared at 1740 cm.\(^{-1}\) (ester) and 1705 cm.\(^{-1}\) (acid). Distillation of this material in a micro-Hickman still at 175°C./0.15 mm. afforded an analytical sample, \(n_D^{20}\) 1.4680, of trans-3(3-carboxmethoxyethyl)-cyclopentylpropionic acid.

**Anal. Calcd. for \(C_{12}H_{20}O_4\):** C, 63.13; H, 8.83.
**Found:** C, 62.98; H, 8.97.

**IX. Acyloin reaction of reclaimed trans-dimethyl ester 70.**

**Apparatus and procedure.** In order to minimize contamination of the starting material by the cis isomer, the trans-dimethyl ester 70 used in this reaction was recovered from previous condensation attempts. Recovered 70 was purified by filtration through activity I alumina in petroleum ether. The pure trans-dimethyl ester 70 (9.7 g., 0.04 mole) in 100 ml. of dioxane was reacted with 3.7 g. (0.16 g. at.) of sodium dispersed in 200 ml. of dioxane following the procedure described in condensation VI. Workup in the usual manner afforded 10.0 g. of crude product. The crude product was placed on a 2.2 x 25 cm.
column of florex, and the following fractions were collected: 5.0 g. of fraction A (500 ml. of petroleum ether), 285 mg. of fraction B (200 ml. of benzene), 77 mg. of fraction C (100 ml. of benzene), 57 mg. of fraction D (100 ml. of benzene), 29 mg. of fraction E (100 ml. of benzene), 102 mg. of fraction F (300 ml. of ether).

Analysis of acyloin products by GLC. - GLC analysis of acyloin fractions A through E was performed at a column temperature of 235°C. to determine the distribution of products in the various fractions and to get some estimate of the yields. The per cent composition of each fraction was obtained from the relative areas under the chromatogram peaks and was only an approximation, since the extent of decomposition of the components under the analysis conditions could not be determined. Each of the fractions B through F had as many as seven minor components with retention times of less than 3 minutes. No attempt was made to isolate or obtain the yields of these compounds. Starting trans-dimethyl ester 2Q. was found to give a single peak comprising 98+ per cent of the sample and appearing at a retention time of 10 minutes. A known sample of the trans-dipropanol 2Q. had a retention time of 8 minutes. Two major components other than 2Q. or 2Q. were detected in the GLC analyses. Component A appeared
at a retention time of 6.5 minutes and was identified as the cis-diketone 25 by collection of a small sample and comparison of its infrared spectrum and 2,4-dinitrophenyl-hydrazone derivative with those of an authentic sample of 25. Component B, appearing at a retention time of 5.5 minutes, was present in too small an amount to be isolated and identified. The total yield of the cis-diketone 25 from all of the fractions was 110 mg., and the total yield of the trans-dipropanol 79 was 275 mg. Volatile minor components accounted for 1.7 g. of the acyloin product, and the remaining material was unreacted 70.

X. Acyloin reaction of dimethyl trans-1,3-cyclopentane-dibutyrate (86)

Apparatus and experimental procedure. - In order to minimize the possibility of contamination by the cis isomer, the trans-dibutyrlic ester 86 used in this reaction was obtained by expansion of trans-dipropionic ester 70 which had been recovered from previous condensation attempts. Pure 86 (4.4 g., 0.016 mole) in 70 ml. of dioxane was reacted with 1.5 g. (0.065 g. at.) of sodium metal dispersed in 150 ml. of dioxane according to the procedure described for acyloin reaction V. The ester addition was completed in 20 hours, and after an additional 24 hours of stirring, the reaction mixture was
yellow. The same color change had been noted previously in the attempted condensation of the trans-dipropionic ester 70 (reaction V). Workup in the usual manner, using 5 g. of glacial acetic acid to decompose the excess sodium, afforded 500 mg. of neutral material. Acidification of the bicarbonate wash and extraction with ether gave 1.7 g. of crude acidic material. The neutral product was placed on a 1.5 x 15 cm. column of florex and eluted, as before, with petroleum ether, benzene, and ether. Evaporation of the benzene eluate afforded 50 mg. of acyloin fraction A; 400 mg. of acyloin fraction B was recovered from the ether eluate. Removal of solvent from the petroleum ether eluate gave only a trace of material. Infrared analysis of the two fractions A and B showed them to be essentially the same (absorption bands at 3400 cm.\(^{-1}\), 1700-1725 cm.\(^{-1}\), and 1040-1060 cm.\(^{-1}\)). The infrared spectra of fractions A and B were very similar to the spectrum of the ether acyloin fraction isolated in reaction V, shown to consist largely of the trans-dipropanol 79.

**Isolation and characterization of trans-1,3-cyclopentanedi-butanol (88) from acyloin fraction B.** The crude acyloin fraction B was separated into ketonic and non-ketonic material with Girard's T reagent\(^{67}\) using the procedure described in acyloin condensation XI for the
isolation of the cis-diketone 75. Acyloin fraction B (400 mg.) was reacted with 660 mg. (4.0 mmole) of Girard's T reagent (129) in 15 ml. of 10 per cent acetic acid in ethanol. After refluxing for 1.5 hours, the reaction mixture was poured into 90 ml. of water containing 860 mg. of sodium carbonate. Workup as in condensation XI afforded 25 mg. of ketonic material and 250 mg. of non-ketonic material. An attempt to make a 2,4-dinitrophenyl-hydrazone derivative of the ketonic material yielded an oil which was not investigated further. The infrared spectrum of the non-ketonic material was very similar to that of a sample of the trans-dipropanol 79, having major absorption bands at 3400 cm.\(^{-1}\) and 1060 cm.\(^{-1}\). The sample of crude trans-dibutanol 88 (250 mg.; about 7 per cent yield) was further purified by distillation at 120°C./0.2 mm. in a micro-Hickman still. The distillate, \(n_D^{20}\) 1.4798, was converted to its p-nitrobenzoate derivative. An analytical sample of the p-nitrobenzoate derivative of 88, m.p. 83.5-84.5°C., was prepared by elution of the sample from a column of florex with benzene, followed by three recrystallizations from 95 per cent ethanol.

Anal. Calcd. for \(C_{27}H_{32}O_8N_2\): C, 63.27; H, 6.29; N, 5.47. Found: C, 63.41; H, 6.10; N, 5.31.
Preparation and Reactions of cis-Bicyclo[6.2.1]-undecane Derivatives

XI. Acyloin condensation of dimethyl cis-1,3-cyclopentane-dipropionate (71)

Apparatus and experimental procedure. - The apparatus and experimental procedure used was the same as that employed in acyloin reaction VI. The pure cis-dimethyl ester 71 (15.0 g., 0.062 mole) was dissolved in 150 ml. of dioxane and added to a dispersion of 5.7 g. (0.25 g. at.) of sodium in 300 ml. of dioxane. Workup in the usual manner afforded 15.1 g. of crude acyloin product. The crude acyloin product was placed on a 2.2 x 25 cm. column of florex and eluted with petroleum ether, benzene, and ether. Removal of the solvents gave 3.0 g. of acyloin fraction A from the petroleum ether, 3.2 g. of acyloin fraction B from the benzene, and 1.1 g. of acyloin fraction C from the ether.

GLC analysis of cis products. - The analyses were performed as before at a column temperature of 235°C. Analysis of the starting cis-dimethyl ester 71 revealed a single peak appearing at a retention time of 9.5 minutes. Injection of a sample of acyloin fraction A revealed, in addition to a small amount of volatile material at a
retention time of less than 2 minutes, two major peaks at retention times of 6.5 and 8 minutes in the ratio of 1:3.7. Analysis of acyloin fraction B showed that the sample was essentially free from volatile material and contained the same two major components as fraction A in the ratio of 1:5.7 (6.5 min.:8 min.). From previous results, the material at retention time 6.5 minutes was identified as the cis-diketone 75 (total yield 10 per cent). A sample of the component of retention time 8 minutes was collected. Infrared analysis of this material revealed the following absorption bands: 3400 cm.\(^{-1}\), 1690 cm.\(^{-1}\), 1080 cm.\(^{-1}\), 1030-1050 cm.\(^{-1}\), 990 cm.\(^{-1}\).

This material was identified as the cis-acyloin 73 (total yield 47 per cent) by comparison of the infrared spectrum with that of 73 obtained in acyloin condensation I. GLC analysis of acyloin fraction C revealed the same two components, but this fraction was considerably enriched in 75, 73 and 75 being present in approximately equal amounts. No appreciable amount of any other product was observed in GLC analysis.

**Attempted separation of the cis-acyloin-diketone mixture.**—It was found that the proportion of 75 in the acyloin fractions could be reduced by treatment of the cis-acyloin-diketone mixture with dilute sodium bisulfite solution. The ether solution was dried over
anhydrous magnesium sulfate, and the solvent was removed. GLC analysis of the purified material showed it to contain 91 per cent of the cis-acyloin \( \text{Z3} \) as compared to 79 per cent in the untreated acyloin fraction A. Further attempts to purify \( \text{Z3} \) for characterization were abandoned when it was discovered that \( \text{Z3} \) was unstable. Upon standing at room temperature for several days, acyloin fractions A and B began to solidify. Infrared analysis of this material revealed absorption bands at 2500-2700 cm\(^{-1}\) not present in the freshly prepared acyloin fractions. Acyloin fractions A and B were combined, dissolved in ether, and washed with several portions of dilute sodium bicarbonate solution. The basic extract was acidified and extracted with several portions of ether. Removal of the solvent from the dried ethereal extract afforded 300 mg. of crude material which had m.p. 97.5-99°C. after two recrystallizations from water-acetic acid. The mixture melting point with a sample of the pure cis-dipropionic acid \( \text{Z2} \) (m.p. 98-99.5°C.) was undepressed, and the infrared spectra were identical. Because of the instability of \( \text{Z3} \) the entire sample was oxidized to the more stable cis-diketone \( \text{Z5} \).

Preparation of cis-bicyclo[6.2.1]undecan-4,5-dione (75) and isolation using Girard's T reagent. The combined acyloin fractions A and B (2.6 g., 1.4 mmoles) were dissolved in 20 ml. of glacial acetic acid and reacted with
2.6 g. (5.6 mmoles) of bismuth trioxide by the procedure of Blomquist and Buck\textsuperscript{55} as described in reaction VI. The crude cis-diketone \textsuperscript{75} (2.14 g.) obtained was purified by reaction with Girard's T reagent (129) according to the procedure of Girard and Sandulesco.\textsuperscript{67} The crude cis-diketone (2.14 g., 12.0 mmoles) was dissolved in 75 ml. of a solution of exactly 10 per cent by weight of acetic acid in absolute ethanol. Girard's T reagent (4.0 g., 12.0 mmoles) was added, and the mixture was refluxed for 1.5 hours. The reaction mixture was cooled and poured into 450 ml. of ice water containing 4.31 g. of sodium carbonate (final pH 5-6). The aqueous solution was extracted repeatedly with ether to remove unreacted, non-ketonic material, adding enough extra ethanol when necessary to break the emulsions formed. The final aqueous layer was filtered to remove a small amount of suspended material, and the volume of the clear, aqueous solution was measured. Enough concentrated hydrochloric acid was added to give a 0.8 N solution, and the solution was allowed to stand at room temperature to regenerate \textsuperscript{75}. After standing for 1.5 hours, the cloudy, aqueous solution was again extracted repeatedly with ether. The combined ethereal extracts of \textsuperscript{75} were washed with several portions each of water and dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate.
Removal of the solvent afforded 1.7 g. (65 per cent yield based on the crude acyloin) of the cis-diketone 25. GLC analysis of the sample under the usual conditions revealed a single peak at retention time 6.5 minutes comprising 99+ per cent of the sample. Infrared analysis revealed the following absorption bands: 1700 cm.\(^{-1}\) (C=O), 1050 cm.\(^{-1}\), 1020 cm.\(^{-1}\), 985 cm.\(^{-1}\), 885 cm.\(^{-1}\), 855 cm.\(^{-1}\). In addition, weak absorption bands at 3400 cm.\(^{-1}\) (O-H) and 760 cm.\(^{-1}\) (C=C) were observed. An analytical sample of cis-bicyclo[6.2.1]undecan-4,5-dione (75) distilled in a micro-Hickman still at 110°C/0.5 mm., had \(n_D^{20}\) 1.5011.

**Anal.** Calcd. for C\(_{11}\)H\(_{16}\)O\(_2\): C, 73.30; H, 8.95. Found: C, 73.34; H, 9.03.

The 2,4-dinitrophenyllosazone derivative was prepared. An analytical sample, m.p. 238-239°C. (dec.), was obtained by elution of the derivative 26 from a column of activity I Woelm neutral alumina with chloroform, followed by several recrystallizations from dioxane-water.

**Anal.** Calcd. for C\(_{23}\)H\(_{24}\)N\(_8\)O\(_8\): C, 51.11; H, 4.48; N, 20.74. Found: C, 50.98; H, 4.52; N, 20.56.

Oxidative cleavage of the cis-diketone 75.-A sample of pure 75 was cleaved to the starting cis-dipropionic acid 52 to confirm the assigned stereochemistry. cis-Diketone 75 (180 mg., 1.0 mmole), purified using Girard's
T reagent, was dissolved in 4 ml. of acetone. An excess of chromium trioxide (400 mg., 4.0 mmoles) dissolved in a solution of 1.5 ml. of concentrated sulfuric acid in 4 ml. of acetone was added, and the mixture was stirred overnight at room temperature. The acetone was removed at reduced pressure, and the aqueous mixture was transferred to a separatory funnel using 5 ml. of water to rinse the reaction flask. The aqueous solution was extracted with several portions of ether, and the combined ethereal extracts were washed with a small amount of water and dried over anhydrous magnesium sulfate. Removal of the ether gave 202 mg. of the crude cis-dipropionic acid 52 (95 per cent yield). The crude solid was dissolved in 6 ml. of hot water, treated with decolorizing carbon, and filtered. The acid was redissolved, then 0.7 ml. of glacial acetic acid was added, and the solution was cooled slowly. Another recrystallization from water-acetic acid afforded 96 mg. of cis-1,3-cyclopentanedicarboxylic acid (52), m.p. 98-100°C. The mixture melting point of this acid with an authentic sample of 52 (m.p. 98-100°C.) was undepressed, and the infrared spectra of the two samples were identical.

Reaction of the cis-acyloin 73 and the cis-diketone 75 with Fehling's reagent.—Acyloin fraction A (300 mg.) was stirred with an excess (30 ml.) of Fehling's reagent
for 6 hours at room temperature. The resulting basic, aqueous solution was filtered to remove precipitated cuprous oxide and washed with several portions of ether. The basic solution was acidified and extracted with several portions of ether. The combined ethereal extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave 220 mg. (67 per cent yield) of crude 4-hydroxy-\textit{cis}-bicyclo[5.2.1]decan-4-carboxylic acid (131). The crude acid was dissolved in sodium bicarbonate solution, treated with decolorizing carbon, and acidified in the cold with concentrated hydrochloric acid. The precipitated acid was recrystallized once from water-acetic acid to m.p. 117-118°C. Infrared analysis of this acid revealed the following absorption bands: 3460 cm.\(^{-1}\)(O-H), 2500-2700 cm.\(^{-1}\)(CO\(_2\)H), 1730 cm.\(^{-1}\)(C=O), 1060 cm.\(^{-1}\). A sample of the pure \textit{cis}-diketone 25 (200 mg.) was heated with 20 ml. of Fehling's solution on a steam bath for 2 hours. Workup as before, followed by two recrystallizations of the crude product from water-acetic acid, gave plates with m.p. 117-118°C. The mixture melting point of this material with the acid from acyloin fraction A was undepressed, and the infrared spectra of the two samples were identical. An analytical sample of the hydroxy acid 131, prepared by an additional recrystallization from
water-acetic acid, had a neutralization equivalent of 200 (theory: 198).

Anal. Calcd. for C\textsubscript{11}H\textsubscript{18}O\textsubscript{3}: C, 66.64; H, 9.15.
Found: C, 66.06; H, 9.01.

cis-Bicyclo[6.2.1]undecano(4,5-b)quinoxaline (132). -
The quinoxaline derivative 132 of the cis-diketone 75 was prepared by a modification of the procedure of Leonard and Mader. A sample of pure 75 (180 mg., 1.0 mmole) was refluxed for 45 minutes with 162 mg. (1.5 mmole) of \(\alpha\)-phenylenediamine in 3 ml. of glacial acetic acid. The product was poured into 15 ml. of water and extracted with several portions of ether. The combined ethereal extracts were washed with dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the solvent left a solid residue which was extracted with several portions of hot hexane. Evaporation of the hexane gave 120 mg. (48 per cent yield) of the crude quinoxaline derivative 132. An analytical sample of cis-bicyclo [6.2.1]undecano(4,5-b)quinoxaline (132), m.p. 106-107°C., was obtained by recrystallization of the crude material from acetonitrile several times.

Anal. Calcd. for C\textsubscript{17}H\textsubscript{20}N\textsubscript{2}: C, 80.91; H, 7.99; N, 11.10. Found: C, 81.08; H, 7.99; N, 10.99.
XII. Acyloin condensation of dimethyl cis-1,3-cyclopentanetanedi­
propionate (71)

Apparatus and experimental procedure. - The apparatus
and experimental procedure employed was the same as that
described in acyloin reaction VI. Pure \( \text{Z}_1 \) (13.0 g.,
0.054 mole), dissolved in 130 ml. of dioxane, was added
to a dispersion of 5.3 g. of sodium (0.23 g. at.) in 230
ml. of dioxane. The crude acyloin product (10.8 g.) was
placed on a 2.2 x 25 cm. column of florex and eluted with
petroleum ether and benzene. The residues obtained upon
removal of the solvents had identical infrared spectra
and were combined to give 4.2 g. (43 per cent yield) of
material containing about 85 per cent \( \text{cis-acyloin Z}_2 \) and
10 per cent \( \text{cis-diketone Z}_5 \) by GLC analysis.

cis-Bicyclo[6.2.1]undecan-4-one (111).—The crude
\( \text{cis-acyloin Z}_2 \) was reduced to the monoketone \( \text{lll} \) by the
procedure of Cope, Barthel, and Smith. The freshly
prepared \( \text{cis-acyloin Z}_2 \) (910 mg., 5 mmoles) was mixed with
2 ml. of glacial acetic acid and 810 mg. (12.4 mg. at.)
of zinc powder. Three 1.8 ml. portions of concentrated
hydrochloric acid were added to the stirred mixture main­
tained at 50–60°C. in an oil bath. Workup afforded 720 mg.
of crude reduction product which was purified using
Girard's T reagent. The crude material (720 mg., 4.34
mnoles based on \textit{III}) was refluxed with 756 mg. (4.5 
mnoles) of Girard's T reagent in 25 ml. of 10 per cent 
acetic acid in absolute ethanol for 1.5 hours. The re-
action product was poured into 150 ml. of ice water 
containing 1.44 g. of sodium carbonate. Workup in the 
usual manner gave 270 mg. of ketonic material. GLC analy-
sis of the ketonic fraction at a column temperature of 
235°C. showed it to contain about 85 per cent of the \textit{cis-}
ketone \textit{III}, which had a retention time of 6 minutes, and 
15 per cent of the \textit{cis}-diketone \textit{75}, which had a retention 
time of 6.5 minutes. The yield of \textit{cis}-ketone \textit{III} was 28 
per cent based on the starting \textit{cis}-acyloin \textit{73}. The mix-
ture of \textit{III} and \textit{75} was separated by chromatography on 
florex. The mixture was placed on a 1.5 x 15 cm. column 
of florex and eluted with 1:1 petroleum ether:benzene. 
Removal of the solvent from the first few fractions afford-
ed 110 mg. of the \textit{cis}-ketone \textit{III} which was essentially 
free from contaminating \textit{75}. Continued elution with the 
same solvent gave eluates containing increasing amounts 
of the \textit{cis}-diketone \textit{75}. An analytical sample of \textit{cis-}
bicyclo[5.2.1]undecan-4-one \textit{III}, m.p. 34-36.5°C., was 
prepared by distillation of the initial chromatography 
residue at 60-70°C./0.4 mm. in a micro-Hickman still. 
Infrared analysis of the analytical sample of \textit{III} revealed 
the following absorption bands: 1700 cm.$^{-1}$(C=O),
The 2,4-dinitrophenyl-hydrazone derivative crystallized as orange needles, m.p. 142.5-143.5°C., from 95 per cent ethanol.

Anal. Calcd. for C$_{11}$H$_{18}$O: C, 79.46; H, 10.91. Found: C, 79.62, H, 11.05.

Attempted preparation of 4-diazo-cis-bicyclo[6.2.1]-undecan-5-one (134).—An attempt was made to prepare the diazo-ketone 134 by the method of Meinwald and Crandall. The cis-diketone 75 (243 mg., 1.35 mmoles), freshly prepared and purified, was dissolved in 1.5 ml. of reagent grade chloroform, and 100 mg. of anhydrous magnesium sulfate was added. The mixture was cooled in an ice bath, and tosylhydrazine (250 mg., 1.35 mmoles) was added in small portions. The mixture was allowed to stand in the cold for several hours then placed on a 2 x 2.5 cm. column (7.5 g.) of basic alumina (Merck 71707) and eluted with chloroform. The initial eluate (10 ml.) gave a small amount of yellow oil, the infrared spectrum of which had absorption bands at 2100 cm.$^{-1}$(N≡N) and 1700 cm.$^{-1}$(C=O). Continued elution with 50 ml. of chloroform gave 162 mg. of a pale yellow solid, m.p. 102-106°C. The solid had m.p. 106.5-108.5°C. after one recrystallization from benzene and was identified as unreacted tosylhydrazine on the basis of its infrared spectrum and an undepressed
mixture melting point with a known sample of tosylhydrazone. Continued elution with a large volume of chloroform and methanol afforded no additional material which could be identified as the desired diazoketone.

Preparation of cis-Bicyclo[6.2.1]undecan-4,5-semidione (123). Samples containing the semidione were prepared for electron paramagnetic resonance (EPR) examination by the method of Russell and Strom. A 0.1 M solution of potassium t-butoxide in 80 per cent dimethyl sulfoxide (dried over calcium hydride)-20 per cent t-butanol was prepared. A 0.05 M solution of the freshly purified cis-acyloin or cis-diketone in the same solvent was mixed with an equal volume of the basic solution immediately before measurement of the EPR spectrum. No special care was taken to exclude oxygen during the preparation of the samples.
Pure cis- (52) and trans-1,3-cyclopentanedicarboxylic (45) acids were prepared by stereospecific Arndt-Eistert homologation of the known cis- (44) and trans-1,3-cyclopentanedicarboxylic (45) acids, and large-scale, stereoselective synthetic routes to the isomeric dipropionic acids (52 and 53) were developed. The acyloin reactions at high dilution of dimethyl cis- (71) and trans-1,3-cyclopentanedicarboxylic (70) were investigated as possible methods for the synthesis of derivatives of the cis- (33) and trans-bicyclo[6.2.1]undecane (36) systems respectively.

In xylene or dioxane, dimethyl trans-1,3-cyclopentanedicarboxylic (70) was observed to undergo only abnormal reactions of the isolated ester functions with sodium, leading to the formation of several acidic and neutral products. The major acidic product was the starting trans-dipropionic acid 53, while the major neutral product was trans-1,3-cyclopentanediol (79), formed in 4 per cent yield. The acyloin reaction of dimethyl
trans-1,3-cyclopentanedicarboxylate (86) in dioxane similarly afforded, as the major products, trans-1,3-cyclopentanedicarboxylic acid (85) and a 7 per cent yield of the corresponding trans-1,3-cyclopentanediol (88).

Dimethyl cis-1,3-cyclopentanedicarboxylate (71) underwent normal cyclization to a mixture of the bicyclic products, cis-bicyclo[6.2.1]undecan-4-ol-5-one (73) and cis-bicyclo[6.2.1]undecan-4,5-dione (75), in xylene or dioxane solvent. The yield of the cis-acyloin-diketone (73 and 75) mixture was 10 per cent in xylene and 57 per cent in dioxane, demonstrating the superiority of the latter solvent. The mixture contained 85 per cent of the cis-acyloin 73 and 15 per cent of the cis-diketone 75. No abnormal products, analogous to those observed in the trans acyloin reactions, were detected. The cis-acyloin-diketone (73 and 75) mixture was found to decompose readily to the starting cis-dipropionic acid 52 upon standing. A mechanism, involving the initial formation of the radical-anion, cis-bicyclo[6.2.1]undecan-4,5-semidione (123), was postulated to explain the decomposition of the mixture.

Derivatives of the trans-bicyclo[6.2.1]undecane (36) system were postulated to be even more unstable than those (73 and 75) of the corresponding cis-bicyclic system (33) because of the higher strain energy associated with the trans ring juncture. The failure to isolate any trans-
bicyclic products, even in the attempted condensation of the trans-dibutyric ester 86 to the less strained trans-bicyclo[8.2.1]tridecan-5-ol-6-one (87), was, therefore, attributed to the instability of the trans-bicyclic products and to a large entropy barrier to cyclization in the trans case.

The cis-acyloin 23 was readily reduced to cis-bicyclo[6.2.1]undecan-4-one (111) with zinc and hydrochloric acid, and the cis-acyloin 23 and the cis-diketone 75 both reacted with Fehling's reagent to give 4-hydroxy-cis-bicyclo[6.2.1]decan-4-carboxylic acid (131).

The electron paramagnetic resonance spectrum of the semidione derivative (123) and the nuclear magnetic resonance spectrum of the quinoxaline derivative (132) of the cis-diketone 75 were measured. Possible conformations of the cis-diketone 75 were discussed in light of the spectral data.
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BIOGRAPHICAL SKETCH

Alfred Ernest Kober was born on December 25, 1940, at Somerville, New Jersey. He attended elementary schools in Cliffside Park, New Jersey, and in Lake Park, Florida. In June, 1958, he was graduated from Palm Beach High School in West Palm Beach, Florida. He received the degree of Associate of Arts from Palm Beach Junior College in June, 1960, and entered the University of Florida in September, 1960. In December, 1962, he received the degree of Bachelor of Science in Chemistry from the University of Florida. In January, 1963, he enrolled in the Graduate School of the University of Florida and since that time has pursued his work toward the degree of Doctor of Philosophy.

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This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of that committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council, and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

June 20, 1967

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