1967

Part I: Photoisomerization of tetra-O-methylpurpurogallin and the base catalyzed rearrangement of tri-O-methylpurpurogallin Part II: Oxidations with phenylhydrazines

Thomas Joseph Murphy
Iowa State University

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PART I: PHOTOISOMERIZATION OF TETRA-O-METHYLPUROGALLIN AND THE BASE CATALYZED REARRANGEMENT OF TRI-O-METHYLPUROGALLIN. PART II: OXIDATIONS WITH PHENYLHYDRAZINES.

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PART I: PHOTOISOMERIZATION OF TETRA-O-METHYLPURPUROGALLIN AND THE BASE CATALYZED REARRANGEMENT OF TRI-O-METHYLPURPUROGALLIN

PART II: OXIDATIONS WITH PHENYLHYDRAZINES

by

Thomas Joseph Murphy

A Dissertation Submitted to the Graduate Faculty in Partial Fulfillment of The Requirements for the Degree of DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

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Dean of Graduate College

Iowa State University Of Science and Technology Ames, Iowa

1967
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VITA

Thomas J. Murphy was born the second of four children to Hugh J. and Margaret R. Murphy on October 4, 1941, in Pittsburgh, Pennsylvania. His father died in 1955. He was graduated from St. Justin High School in June, 1959. That fall he entered the University of Notre Dame, from where he was graduated with a B. S. in chemistry, in June, 1963. He entered the graduate school of Iowa State University in the summer of 1963, majoring in organic chemistry. In August, 1967, he was granted the degree, Doctor of Philosophy from Iowa State University.
PART I: PHOTOISOMERIZATION OF
TETRA-O-METHYLPURUROGALLIN AND THE BASE CATALYZED
REARRANGEMENT OF TRI-O-METHYLPURUROGALLIN
HISTORICAL

Photochemical Reactions of Tropolones

There has been much work in recent years on the photochemistry of $\alpha,\beta$-unsaturated ketones. These compounds absorb ultraviolet light in a readily accessible part of the spectrum, and undergo a variety of interesting reactions. The tropolones are a class of unsaturated ketones whose photochemistry has received much attention. Colchicine (I), a natural product, was the first tropolone compound whose photochemistry was studied. Huebler (1), in 1865, noted that colchicine underwent a change on exposure to sunlight. Since that beginning, three photoproducts of I have been identified. The structures of the $\beta$- (III), and $\gamma$- (IV) isomers were deduced by Gardner (2). Chapman (3,4) proved the structure of the $\alpha$-isomer (II). It should be noted that all three photoproducts are derived by simple valence isomerization of the tropolone ring to bicyclo[3.2.0]heptadienones.

Chapman (5) reported that $\gamma$-tropolone methyl ether (V) yielded a single isomeric product VI upon irradiation in aqueous solution. Dauben (6) reported that $\alpha$-tropolone methyl ether and some derivatives yielded similar products on irradiation. Again, these simple tropolone systems yield photoproducts derived by simple valence isomerization of the starting material to the bicyclo[3.2.0]heptadienone system.
This seems to be the favored mode of reaction of photoexcited tropolone methyl ethers.

Forbes (7) reported that tetra-O-methylpurpurogallin (VII) yielded methyl 6,7,8-trimethoxy-1-naphthoate (VIII) on irradiation in aqueous ethanol. The photoproduct in this reaction is derived from ring contraction rather than from the expected valence isomerization. This photoisomerization is without precedent in tropolone systems. Because of the complexity of the rearrangement, it is difficult to write a satisfactory mechanism for this conversion. Of fundamental importance to any mechanism for this photoisomerization, is which carbon of VII becomes the carboxyl carbon of VIII.

Forbes (7) considered two mechanisms for this reaction. The first of these involved the initial formation of the diradical IX, which would, in an unspecified manner, yield VIII. Here the 1-carbon of VII would become the carboxyl carbon of VIII. The second mechanism involved valence isomerization to an oxabicyclo[1.1.0]butane intermediate X. The intermediate X would then isomerize to VIII. Here, carbon-2 of VII becomes the carboxyl carbon of VIII. Forbes pointed out that a carbon-14 labeling experiment could
distinguish between these two possibilities.

The oxabicyclobutane X was a novel postulate for that time, as no bicyclo[1.1.0]butane systems were then known, much less oxabicyclobutanes. Then Dauben (8) reported that 3,5-cholestadiene (XI) yielded the bicyclobutane XII on irradiation. Srinivasan (9) reported that butadiene yielded bicyclobutane and cyclobutene on irradiation. If an analogy may be drawn between a conjugated diene and an \( \alpha,\beta \)-unsaturated ketone, we might expect to find products derived from oxabicyclobutanes in the photochemical reactions of \( \alpha,\beta \)-unsaturated ketones.
Barltrop (10) proved the gross structure of tetra-0-methylpurpurogallin by synthesis. However, he was unable to distinguish between the tropolone isomers VII or XIII. Later work by Eschenmoser (11) showed VII to be the correct structure. The structure for the ester VIII was proposed by Perkin (12). He obtained this ester by methylation of the acid product obtained from base catalysed rearrangement of tri-0-methylpurpurogallin (XIV). Haworth (13) confirmed these structures by synthesis.

Base Catalyzed Ring Contraction of α-Tropolones

It has been shown in many systems (14) that α-tropolones and the corresponding methyl ethers, undergo base-catalyzed ring contraction to benzoic acid derivatives. This reaction
is illustrated by the conversion of colchicine (I) to allocolchicine (XV). The mechanism for this ring contraction has been presumed to be similar to that of the benzylic acid rearrangement.

In support of this mechanism, Doering (15) showed with carbon-14 labeling experiments, that 1,7-dibromotropone (XVI) yields o-bromobenzoic acid (XVII) on base catalyzed rearrangement. The 1-position of XVI, labeled with carbon-14, became the carboxyl carbon of XVII. This is consistent with the benzylic acid mechanism shown.

Tri-O-methylpurpurogallin (XIV), an α-tropolone methyl ether, undergoes this base catalyzed rearrangement to yield the expected acid product XVIII. This was shown by Perkin
(12). A benzylic acid mechanism for this rearrangement would predict that carbon-1 of XIV would become the carboxyl carbon of XVIII.
RESULTS

Photoisomerization of Tetra-O-methylpurpurogallin

The possibility that an oxabicyclobutane might be an intermediate in the VII to VIII conversion made a mechanistic study of this system particularly attractive to us. In order to try to elucidate the mechanism of this reaction, we undertook labeling studies. The first of these involved the synthesis of VII labeled in the 2-position with carbon-14. The photochemistry of this compound would give us information on the origin of the carboxyl carbon of VIII. This information is basic to a mechanistic understanding of this reaction.

The synthetic scheme for the synthesis of tetra-O-methylpurpurogallin-2\(^{14}\)C is outlined on Chart 1. All of the reactions used had been worked out for the tetra-O-methylpurpurogallin system (16-20). Diethylmalonate-2\(^{14}\)C (XIX) was used as the carbon-14 precursor. Two dilutions with non-radioactive compounds were made during the course of the synthesis.

There is a possibility that the carbon-14 label of the diethylmalonate starting material was all or partially present in the carboxyl carbons, the 1-position, rather than in the methylene carbon, the 2-position. Scrambling such as
Chart 1. Synthetic scheme for tetra-O-methylpurpurogallin-2-\textsuperscript{14}C
Overall Yield 0.3%
this of the carbon-14 label is ruled out by the fact that XX, obtained by the decarboxylation of XXI has the same specific activity, within experimental error, as XXI. If all the label were in the carboxyl carbons of XXI, one-half of it would have been lost on decarboxylation.

Labeled VII was irradiated in ethanol-water solution with a General Electric sunlamp. Ester VIII was isolated according to the procedure of Forbes (7). A Schmidt reaction was used to decarboxylate VIII. The carbon dioxide generated was trapped and counted. It contained all of the radioactivity of the ester VIII. Therefore, all of the radioactivity of VIII was in the carboxyl carbon. The presence of the carbon-14 label only in the carboxyl carbon of VIII indicates that there was no scrambling of the label during the synthesis or irradiation of VII.
We must also consider another mechanistic possibility. There are three cases in the literature (21-24), of intramolecular phenyl shifts upon irradiation. Therefore it is possible that, on irradiation of VII, an intramolecular oxygen to oxygen shift of a methyl group occurs to yield XIII or XXII. Either of these intermediates could go on to ester VIII. We decided to investigate the photochemistry of VII labeled in the carbonyl oxygen with oxygen-18 in order to gain information on the origin of the carbonyl in the ester product VIII. This information would allow us to rule out either X or XIII and XXII as possible intermediates in this reaction.

We hoped to prepare tetra-0-methylpurpurogallin carbonyl-\(^{18}\)O by exchange of the tropolone in a solvent containing water-\(^{18}\)O. After getting no oxygen-18 exchange in tetrahydrofuran-acid-water-\(^{18}\)O, and getting tropolone ether exchange in ethanol-acid-water-\(^{18}\)O, we finally were able to get VII labeled in the carbonyl oxygen with oxygen-18 by exchange of VII in methanol-sodium hydroxide-water-\(^{18}\)O. The position of the oxygen-18 label was checked by mass
spectroscopy. The M-28 peak in the mass spectra of tropolones has been attributed (25) to the loss of the carbonyl group as carbon monoxide. The M-28 peak in the mass spectrum of VII, (Table 1), shifted to M-30 in the mass spectrum of Table 1. The mass spectra of tetra-O-methylpurpurogallin

<table>
<thead>
<tr>
<th>% of Base</th>
<th>Tetra-O-methylpurpurogallin</th>
<th>Tetra-O-methylpurpuogallin</th>
<th>41 % Carbonyl-^{18}O</th>
</tr>
</thead>
<tbody>
<tr>
<td>m/e</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>278</td>
<td>3.2</td>
<td>72.6</td>
<td></td>
</tr>
<tr>
<td>276</td>
<td>100.0</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>0.7</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>248</td>
<td>20.8</td>
<td>35.9</td>
<td></td>
</tr>
</tbody>
</table>

oxygen-18 labeled VII, (Table 1). Therefore the oxygen-18 label was present in the carbonyl oxygen.

After getting no results with our first tropolone-^{18}O irradiations, we discovered that both VII and VIII exchanged their oxygen-18 labels with water in the solvent on irradiation. However, both were stable to exchange of their oxygen-18 label in the dark, and to chromatography on alumina. In order to perform our labeling experiments, we would have to go to anhydrous media for the irradiations.

The irradiation of VII was then attempted in anhydrous tetrahydrofuran. In rigorously dry tetrahydrofuran, no VIII could be detected by v.p.c. analysis after irradiation. Trace amounts of water in the irradiation, however, gave
trace amounts of ester VIII. Water is necessary then for the photoisomerization of VII to VIII, and the mechanistic scheme VII → X → VIII cannot be the full answer. However, we still would like to know if the two tropolone oxygens become equivalent or interconvert during the course of the reaction.

When VII is irradiated in methanol containing only 2.5% water, ester VIII can still be isolated, but with a yield reduced by about 50%. Tetra-O-methylpurpurogallin (VII) labeled in the carbonyl oxygen with oxygen-18, was irradiated in methanol containing 2.5% water (32% oxygen-18). The mass spectrum of the ester VIII obtained from this reaction showed oxygen-18 incorporation. The mass spectrum of unlabeled VIII, (Table 2), has an M-31 peak, which is attributed to the loss of methoxide. From the mass spectrum of the trideuterio compound XXIII, (Table 2), we were able to show that loss of

Table 2. Mass spectra of methyl 6,7,8-trimethoxy-1-naphthoate

<table>
<thead>
<tr>
<th>m/e</th>
<th>Ester VIII</th>
<th>Ester VIII 23% carbonyl-18O</th>
<th>XXIII (Trideuterio-methyl VIII)</th>
</tr>
</thead>
<tbody>
<tr>
<td>279</td>
<td>2.8</td>
<td>4.9</td>
<td>100.0</td>
</tr>
<tr>
<td>278</td>
<td>100.0</td>
<td>38.9</td>
<td>56.2</td>
</tr>
<tr>
<td>276</td>
<td>1.3</td>
<td>100.0</td>
<td>11.0</td>
</tr>
<tr>
<td>248</td>
<td>0.9</td>
<td>1.3</td>
<td>4.5</td>
</tr>
<tr>
<td>247</td>
<td>5.3</td>
<td>5.3</td>
<td>3.3</td>
</tr>
<tr>
<td>245</td>
<td>17.6</td>
<td>18.2</td>
<td>22.5</td>
</tr>
</tbody>
</table>
the ester methoxyl, contributes 84% to the M-31 peak of VIII. The mass spectrum of the oxygen-18 labeled photo product shows no loss of M-33, (Table 2). Thus none of the oxygen-18 label is in the ester methoxyl oxygen.

Direct evidence for the position of the oxygen-18 label was obtained by lithium aluminum hydride reduction of the oxygen-18 labeled photo product. The mechanism of the lithium aluminum hydride reduction, shown on the next page, demands that the carbonyl oxygen of VIII become the alcohol oxygen of XXIV. The alcohol XXIV obtained from the reduction, contained >90% of the oxygen-18 label of the VIII reduced. Therefore, the carbonyl oxygen of VII, or water, has become the carbonyl of VIII, and the oxygens of VII have neither interchanged, nor become equivalent. This rules out intermediates of the type XXII. These results are consistent with the initial formation of a ground state intermediate such as X, which would react with water to yield products, but they do not demand the intermediacy of X.

When VII was irradiated in anhydrous methanol, no VIII
could be isolated. Instead, a new photo product, XXV was isolated in good yield. The n.m.r. of XXV (Figure 1a), when compared to the n.m.r. of VII (Figure 1b), shows an additional methoxyl group, two protons on a saturated carbon and one less aromatic proton. The mass spectrum gives a molecular weight of 308. This fits for a methanol adduct of VII. Since we now have two equivalent methoxyls, the singlet of area six, it is probable that the methoxyl group has added at the 2-position. The decision between 1,2 and 1,4 addition is based on the mass spectrum of the adduct (Table 3), which has an intense m/e peak. This peak is
Figure 1. Nuclear Magnetic Resonance spectra

Top - Methanol adduct of tetra-O-methylpurpurogallin (XXV)

Bottom - Tetra-O-methylpurpurogallin (VII)
IR - 5.83 μm
UV - λm 293 ε = 4400
1m 250 ε = 28,000
Mass Spectrum
m/e % base
308 M+ 100
220 M-88 55
Table 3. Mass spectra of alcohol adducts of VII

<table>
<thead>
<tr>
<th>m/e</th>
<th>MeOH adduct</th>
<th>EtOD/EtOH adduct</th>
</tr>
</thead>
<tbody>
<tr>
<td>323</td>
<td>59.5</td>
<td>322 51.0</td>
</tr>
<tr>
<td>308</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>221</td>
<td>7.4</td>
<td>220 38.3</td>
</tr>
<tr>
<td>220</td>
<td>55.5</td>
<td>100.0</td>
</tr>
</tbody>
</table>

attributed to the loss of the relatively stable 1,1-dimethoxy-ethylene from the adduct. Structure XXV for the adduct best fits this data. Additional evidence for the identity of the m/e 220 peak in the mass spectrum of XXV, is obtained from the mass spectrum of the adduct (Table 3) formed in the irradiation of VII in deuterioethanol. This adduct loses a fragment of mass 103, 1-methoxy-1-ethoxy-2-deuterioethylene, from the m/e 323 parent ion, to give the m/e 220 peak. This experiment shows conclusively that alcohol adds 1,2, and that this same alcohol is lost in the fragmentation to yield the m/e 220 ion.

On further irradiation, XXV yields neither starting material VII, nor ester VIII. Forbes (26) has reported that the irradiation of VII in absolute ethanol yields the
trimethoxynaphthol XXVI. It is probable that XXV goes to XXVI on further irradiation.

Since deuterium is incorporated into the alcohol adduct XXV from solvent, it is possible that the formation of ester VIII would also show incorporation of deuterium from solvent. However, when VII is irradiated in deuterium oxide–ethanol, the VIII isolated contains <1% deuterium. The significance of this reaction, and the formation of the alcohol adduct to the mechanism of the VII–VIII isomerization will be discussed.

Base Catalyzed Isomerization of Tri-0-methylpurpurogallin

Tri-0-methylpurpurogallin (XIV), labeled in the 2-position with carbon-14, was synthesized as shown on Chart 1. It was rearranged and worked up according to the procedure of Forbes (7). Ester product VIII (15 dpm/mg; 6.7 mg) was decarboxylated via a Schmidt reaction to yield carbon dioxide which was trapped and counted. The carbon dioxide collected contained all of the radioactivity (107 dpm ± 5%) of the starting material. These results were checked by a second
rearrangement and further decarboxylations. Thus, in this reaction also, it is the 2-carbon of VII which becomes the carboxyl carbon of VIII. This result is not expected on the basis of the results obtained for 2,7-dibromotropone (XVI) (15), where the 1-carbon became the carboxyl carbon.

The following mechanism accounts for our observations. It involves base catalyzed addition of water to the 2,3-bond of XIV, ring contraction, and elimination of water. According to this mechanism, we should see incorporation of deuterium into VIII when the isomerization is run in deuterated media, unless the steps of addition, rearrangement, and elimination of water are each 100% stereospecific. When the reaction was run in deuterated ethylene glycol, the product VIII obtained, was deuteriated. The reaction was also run in deuterated ethylene glycol, and interrupted before the reaction had gone to completion. The starting material XIV isolated from this reaction was found to be deuteriated. Thus it seems as if the base catalysed rearrangement of this α-tropolone proceeds via a solvent adduct to give ester VIII, where the 2-carbon of VII has become the carboxyl carbon of VIII.

\[
\text{CH}_3\text{OH} \xrightarrow{\text{OH}} \text{CH}_3\text{OH} \xrightarrow{\text{CH}_3\text{O}} \text{CH}_3\text{O} \xrightarrow{\text{H}_2\text{O}} \text{XVIII}
\]

\[
\text{XIV} \xrightarrow{\text{OH}} \text{CH}_3\text{O} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{O} \xrightarrow{\text{CH}_3\text{O}} \text{XVIII}
\]
DISCUSSION

Photoisomerization of Tetra-0-methylpurpurogallin

We have found: 1) that carbon-2 of tetra-0-methylpurpurogallin becomes the carboxyl carbon of VIII; 2) that an oxygen to oxygen methyl shift does not occur; 3) that the tropolone carbonyl exchanges with solvent water on irradiation; 4) that water is a necessary catalyst for the reaction; 5) that an alcohol adduct can be isolated from the irradiation of VII in absolute alcohol; 6) that this adduct is not involved in the formation of ester VIII; 7) that deuterium from solvent is not incorporated into VIII; 8) and that water competes favorably with alcohol for an intermediate. Our mechanism for this reaction must account for these results.

A water adduct XXVII, similar to the methanol adduct XXII, is an obvious possibility as an intermediate in this reaction. However we can rule out such an adduct on the following grounds: 1) XXVII is a hemiketal and would be expected to readily hydrolyze and tautomerize to the tropolone XXVIII. A ferric chloride test for free tropolones on the crude photoreaction mixture was negative; 2) upon irradiation in deuterium oxide and ethanol, a deuterium atom would be picked up on the ring, unless the steps of addition, rearrangement and elimination were each 100% stereospecific. We have shown that deuterium is not incorporated into ester VIII.
Thus we have shown that XXVI is not an important intermediate in this reaction.
The mechanism shown on Chart 2, involving XXIX as the important intermediate seems to best fit all the data. The excited state formed on irradiation of VII may demote to form a ground state intermediate such as X, or it may add water and then demote to form the hydroxycyclopropanone hemiketal intermediate XXIX. If X is formed, it rapidly adds water to form XXIX.

In the case of alcohol as the irradiation solvent, XXX if formed, again either from addition of alcohol to an excited state or to the ground state intermediate X. When irradiated in dry, deuterioethanol, deuterium is incorporated into XXV steteospecifically in the 3-position. This is shown by the mass-spectrum (Table 3; page 20), and the n.m.r. which shows deuterium only in the 3-position. This 1,2 addition is readily explained by the intervention of the cyclopropyl ring in XXX.

The intermediates XXIX and XXX explain the apparent paradox of water. Namely that a small amount of water can compete favorable with alcohol to yield VIII, but the reaction in dry alcohol to yield XXV is much faster than when water is present, and VII is the product. Water seems to be much more efficient for trapping the reactive intermediate, but less efficient in yielding product. The explanation of this is that once XXIX is formed, it may lose water to go on to product VIII or lose water and return to VII. Either way there is no incorporation of a proton from solvent. However,
Chart 2. Mechanism of the photoisomerization of tetra-O-methylpurpurrogallin
XXX, when formed, cannot lose water and return to starting material or go on to ring contracted product, therefore it reacts via a third pathway which involves the opening of the cyclopropane ring and picking up a proton from solvent to give the isolable XXV. Water then reacts rapidly to form XXIX, but XXIX usually returns to starting material VII. Alcohol, on the other hand, reacts only slowly to form XXX, but XXX always gives product XXV.

We are left with a dilemma recently faced by others (27-30). Does solvent add to the excited state of VII or to the ground state intermediate X to give XXIX? We have attempted to trap X by quenching, with alcohol or water, irradiations performed in frozen glasses and by looking for new infra-red absorptions in irradiated, frozen glasses. In neither case were we successful.

We explain the isomerization of VII to VIII as proceeding via XXIX. Whether X also intervenes as an intermediate, we are unable to say. We have no evidence which excludes X, and we have no evidence which requires X.

What is the reason for this anomalous photochemical rearrangement of VII? If a model is made of VII, it is found that since the benztropolone system is planar and contains a seven membered ring, the carbonyl oxygen is pointed toward the 9-methoxyl group. This interaction is worse than the peri-interactions of naphthalenes, where the 1,8 groups are
parallel to one another. The steric strain between the 1,9-positions must be the deciding factor in the photochemistry of VII. Forbes (31) has shown that 9-desmethoxy tetra-0-methylpurpurogallin (XXXI) gives the normal valence isomerization products upon irradiation. Thus the steric and/or electronic effects of the 9-methoxyl group must be the deciding factor in this unique photoisomerization.

Base Catalyzed Ring Contraction of Tri-0-methylpurpurogallin

The lack of reactivity of the carbonyl in VII is remarkable. In trying to label the carbonyl with oxygen-18, we found that VII was inert to acid or base catalyzed exchange reactions. It would not exchange even though a seemingly easy pathway, shown below, was available. This pathway

should be favored by the relief of the carbonyl, 9-methoxyl
interaction with the formation of a tetrahedral carbon at carbon-1. Surprisingly, VII readily exchanged its carbonyl oxygen in acidic or basic methanol. It seems as if we have formed a solvent adduct, possible XXVII or XXV, which then exchanges with the water. Evidence for this comes from the fact that when exchanged in ethanol, the product is chiefly 2-O-ethyl-7,8,9-tri-O-methylpurpurogallin. When exchanged in deuteriated alcohol, the VII recovered is partially deuteriated.

This inertness of the carbonyl may also explain the anomalous base catalyzed ring contraction of XIV. Other tropolones, even hindered ones as colchicine (I), rearrange under relatively mild conditions (14). For I, these conditions are sodium methoxide in refluxing methanol for thirty minutes. XIV Gives only a poor yield of XVIII after three hours with potassium hydroxide in ethylene glycol at 160°.

It could be, that attack at the 2-position is a minor pathway, normally greatly overwhelmed by attack at the 1-position, but in XIV, due to the inhibition of attack at the
1-position, reaction via the minor pathway becomes significant.
EXPERIMENTAL

Instruments and Methods

All melting points were measured on a Kofler microscope hot stage equipped with a polarizer and are uncorrected.

All ultraviolet spectra were obtained in 95% ethanol, unless otherwise noted, on a Beckman Model DK-2A spectrophotometer.

All infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer.

All nuclear magnetic resonance (n.m.r.) spectra were taken on a Varian Associates Model HR-60 or A-60 spectrometer at 60 Mc. The HR-60 spectra were calibrated by the side band technique using the side band of tetramethyl silane as an internal standard. The chemical shifts values are reported in parts per million (p.p.m.), (6) units.

All mass spectra were taken on an Atlas CH-4 mass spectrometer at 70 electron volts (e.v.) unless otherwise noted.

All vapor phase chromatography (v.p.c.) measurements were made on a Aerograph Hy-Fi Model 600-c instrument. The column used was a five foot, 1/8 inch stainless steel column packed with 5% General Electric SE-30 on 60/80 mesh Chromasorb W. The instrument was operated with a flame ionization detector.

All elemental analyses were performed by Schwarzkopf
Microanalytical Laboratories, Woodside, New York or by C. F. Geiger, Ontario, California.

Experimental for the Photochemistry of Tetra-O-methylpurpurogallin

Preparation of tetra-O-methylpurpurogallin (VII)

Potassium hydroxide (30 g) was dissolved in water (15 ml) and to this was added immediately, 2,7,8-tri-O-methylpurpurogallin (XIV) (1 g) and dimethyl sulfate (3 ml). The solution was shaken for a minute, then additional dimethyl sulfate (3 ml) was added. The reaction was shaken vigorously and heated on a hot plate until the solution was almost colorless, at which time it was poured over ice, and concentrated ammonia solution (10 ml) added to react with the excess dimethyl sulfate. After stirring for about 20 minutes, the solution was made just barely acidic with hydrochloric acid and extracted with ether. The ether extracts were dried and the ether was removed with a rotary evaporator. The solid product was recrystallized once from cyclohexane, yield 0.90 g, mp 90-92° (lit mp 92°(7)).

Synthesis of tetra-O-methylpurpurogallin-2-¹⁴C

Tetra-O-methylpurpurogallin-2-¹⁴C was synthesized from methylene-¹⁴C diethylmalonate, as shown on Chart 1, using previously described reactions (16-20). The overall yield of the labeled product was 0.3% with specific activity of 45.7
dpm/mg.

Photoisomerization of tetra-O-methylpurpurogallin-2-\(^{14}\)C

Tetra-O-methylpurpurogallin-2-\(^{14}\)C (0.99 g, 45.7 dpm/mg) in 30% ethanol (333 ml) was irradiated for 165 hours with a General Electric Sunlamp. The reaction was worked up in the manner described by Forbes (7) giving methyl 6,7,8-trimethoxy-1-naphthoate (60 mg, mp 79.5-81.0\(^{\circ}\), 46.5 dpm/mg).

Degradation of methyl 6,7,8-trimethoxy-1-naphthoate

Methyl 6,7,8-trimethoxy-1-naphthoate (11.7 mg) and sodium azide (54.2 mg) were placed in a 3-neck flask equipped with a glass jacketed stirring bar, condenser, and pressure equilizing addition funnel. Nitrogen was passed through the flask and condenser and into a tube containing toluene scintillation solution (10 ml) and Packard Instruments Hydroxide of Hyamine 10-X solution (1 ml). With nitrogen passing through the flask, a solution of concentrated sulfuric acid (9 ml) and water (1 ml) was added. After three hours, the contents of the carbon dioxide absorption solution were transferred to a counting vial and immediately counted in a Packard Tri-Carb scintillation counter. Two decarboxylations of \(^{14}\)C-labeled methyl 6,7,8-trimethoxy-1-naphthoate using 21.7 mg and 11.7 mg gave labeled carbon dioxide which contained respectively 93 \(\pm\) 5% and 100 \(\pm\) 5% of the label.

Preparation of tetra-O-methylpurpurogallin carbonyl-\(^{18}\)O

A solution of sodium methoxide in methanol was prepared
by dissolution of sodium (5 mg) in absolute methanol (10 ml). Water (81% \( ^{18}O \), 80 mg) and tetra-O-methylpurpurogallin (50 mg) were added, and the solution was refluxed for 16 hours. The solvent was removed with a rotary evaporator, care being taken to remove all traces of solvent. The dried solid product was leached with dry cyclohexane, from which colorless crystals of tetra-O-methylpurpurogallin were crystallized (40 mg, mp 91.5-92°). The percentage of \(^{18}O\)-label and its position in the molecule were obtained from the mass spectrum (Table 1, page 14). The mass spectrum of the exchanged compound from this reaction showed 75% incorporation of oxygen-18 label into the carbonyl oxygen.

**Preparation of 2-O-trideuteriomethyl-7,8,9-tri-O-methylpurpurogallin**

7,8-Di-O-methylpurpurogallin (0.50 g) and sodium hydroxide (50 mg) were dissolved in deuterium oxide (10 ml). This solution was saturated with carbon dioxide and extracted with methylene chloride. The extracts were dried, and the solvent was removed with a rotary evaporator. The product obtained was added to a solution of a 50% excess of CD\(_2\)N\(_2\) in ether (100 ml), dioxane (100 ml) and deuterium oxide (10 ml), and allowed to stand at room temperature for 20 hours. The CD\(_2\)N\(_2\) solution was prepared by the addition of several 2 mg portions of phenol over a period of 1 hour to a solution of CH\(_2\)N\(_2\) in ether, dioxane, and deuterium oxide maintained at
0°. The solution was frequently swirled during this period. 2-0-Trideuteriomethyl-7,8-di-O-methylpurpurogallin was obtained by removal of the solvent with a rotary evaporator, and was recrystallized from ethanol. It was methylated with dimethyl sulfate as described above to yield 2-0-trideuteriomethyl-7,8,9-tri-O-methylpurpurogallin (340 mg, mp 88-91.5°).

**Irradiation of tetra-0-methylpurpurogallin carbonyl-\textsuperscript{18}O**

Tetra-0-methylpurpurogallin carbonyl-\textsuperscript{18}O (200 mg) was dissolved in absolute ethanol (8 ml), water (32% \textsuperscript{18}O, 250 mg) in a 22 x 175 mm Pyrex test tube. This solution was irradiated for 62 hours with a General Electric Sunlamp. After the irradiation, the solvent was removed with a rotary evaporator. 37.5% of the crude product was chromatographed on Woelm neutral alumina (activity 1). The column was eluted with benzene-chloroform, the ester product being the first major compound eluted. The product was recrystallized twice from cyclohexane (yield 4 mg, mp 80-81.5°, lit mp 81-82° (7)). The mass spectrum of the ester showed 21.7 ± 0.5% incorporation. The position of the oxygen-18 label in the ester was ascertained from the fact that both the labeled and unlabeled ester had an M-31 peak in its mass spectrum. This peak is due to loss of the methoxyl of the ester to yield the acylonium ion. That the M-31 peak is due predominately (84 ± 2%) to loss of the ester methoxyl and not to one of the other three methoxyl groups present in the molecule was determined from
the mass spectrum of trideuteriomethyl 6,7,8-trimethoxy-1-naphthoate (XXIII) prepared by irradiation of 2-O-trideuteriomethyl-7,8,9-tri-O-methylpurpurogallin, the synthesis of which is described above. The presence and relative intensity of the M-31 peak in the mass spectrum of the labeled ester indicates that the oxygen label present must be solely (+ 2%) in the ester carbonyl.

As an independent confirmation of the position of the oxygen-18 label, the remainder of the crude photo product was reduced with lithium aluminum hydride (300 mg) in ether. This reduction was worked up by adding successively, per mole of lithium aluminum hydride, water (10 ml), 20% sodium hydroxide (30 ml) and water (140 ml). The crude reaction product was chromatographed on Woelm neutral alumina (activity 1). The alcohol obtained was recrystallized twice from hexane (yield 0.5 mg, mp 78-81°, lit mp 85-86° (7)). The mass spectrum of this alcohol showed 19 ± 0.5% oxygen-18 incorporation and, with allowance for the oxygen-18 incorporation, agreed exactly with the mass spectrum of unlabeled material.

**Irradiation of tetra-O-methylpurpurogallin (VII) in deuteriated media**

Tetra-O-methylpurpurogallin (110 mg) was irradiated for 17 hours in ethanol (9 ml), deuterium oxide (21 ml) contained in a 22 x 175 mm Pyrex test tube. After the irradiation,
most of the alcohol was removed with a rotary evaporator, and
the remainder of the reaction mixture extracted with dichloro-
methane. The extract was dried, the solvent removed, and the
product chromatographed on Woelm neutral alumina (activity 1).
The ester product isolated was recrystallized twice from
cyclohexane. The mass spectrum of the product showed no
deuterium incorporation (<1%).

Tetra-O-methylpurpurogallin (108 mg) was irradiated as
above for 19.5 hours in methanol (10 ml) containing deuterium
oxide (22 ml). The reaction was worked up as above, and the
mass spectrum of the product showed no deuterium incorpora-
tion.

Irradiation of 2-O-trideuteriomethyl-7,8,9-tri-O-methylpur-
purogallin in deuteriated media

2-O-Trideuteriomethyl-7,8,9-tri-O-methylpurpurogallin
(118 mg) was irradiated as above for 17 hours in methanol
(10 ml) and deuterium oxide (22 ml). The reaction was worked
up as above, and the mass spectrum of the ester product showed
no deuterium incorporation (<1%) and no loss of the trideuter-
iumethyl group (<2%).

Control experiments of tetra-O-methylpurpurogallin (VII) and
methyl 6,7,8-trimethoxy-1-naphthoate (VIII)

Tetra-O-methylpurpuogallin (50% carbonyl-^{18}O, 20 mg) was
dissolved in ethanol (6 ml) and water (14 ml) and let stand
for 20 hours. The solvent was removed with a rotary
evaporator, and the product was recrystallized twice from cyclohexane. The mass spectrum of the product showed no loss of oxygen-18. Tetra-O-methylpurpurogallin (165 mg) was dissolved in absolute ethanol (10 ml) water (40% Oxygen-18, 100 mg), and irradiated in a 22 x 175 mm Pyrex test tube for 3.5 hours. The reaction was worked up exactly as the above irradiations. Recovered, unreacted starting material showed oxygen-18 incorporation.

Methyl 6,7,8-trimethoxy-1-naphthoate (VIII) (12 mg) was dissolved in absolute ethanol (8 ml) and water (20% oxygen-18, 186 mg) and let stand for 12 hours. A one ml sample was removed, evaporated, and recrystallized twice from cyclohexane. The mass spectrum of the product showed no oxygen-18 incorporation. The remainder of the solution was irradiated in a 22 x 175 mm Pyrex test tube for 19 hours. A v.p.c. analysis showed only the ester present after the irradiation. The solvent was removed and the product recrystallized twice from cyclohexane. The recovered ester showed oxygen-18 incorporation.

Both oxygen-18 labeled compounds were stable to the chromatographic work-up.

Irradiation of tetra-O-methylpurpurogallin (VII) in dry tetrahydrofuran

Tetra-O-methylpurpurogallin (VII) (133 mg) was added to a test tube, which had been previously flame dried and cooled,
and glass sealed to a vacuum manifold. At another outlet on the manifold, was affixed a flask containing analytical reagent tetrahydrofuran and solid lithium aluminum hydride. The manifold and the test tube were evacuated to 0.1 mm Hg pressure for one hour. Then tetrahydrofuran (1 ml) was distilled into the test tube by isolating the manifold from the pump, while maintaining the vacuum, opening the stopcock to connect the tetrahydrofuran flask to the manifold, and cooling the test tube in a Dry-Ice acetone bath. The test tube was then isolated from the manifold and the tetra-O-methylpurpurogallin was dissolved in the tetrahydrofuran by warming the test tube. After all of the compound had dissolved, the test tube was again evacuated and pumped on for one hour. This dissolution process was repeated one more time. Then tetrahydrofuran (6 ml) was distilled into the test tube which was cooled to Dry-Ice temperature, pumped to 0.1 mm Hg, sealed, removed from the manifold, and irradiated for 25 hours with a General Electric Sunlamp. After the irradiation the sealed tube was opened, and the composition of the product determined by v.p.c. analysis. The v.p.c. analysis showed no trace of the ester VIII.

Preparation of the methanol adduct of tetra-O-methylpurpurogallin (XXV)

Tetra-O-methylpurpurogallin (138 mg) was dissolved in methanol (8 ml) and water (0.2 ml), and irradiated for 5 hours
in a Pyrex test tube with a General Electric Sunlamp. The crude reaction mixture was chromatographed on Woelm neutral alumina (activity 1). The adduct (XXV), the first compound (50 mg) eluted from the column with benzene, was recrystallized four times from ether, mp 97-98\(^{\circ}\).

**Anal.** calcd. for \(C_{16}H_{20}O_6\): C; 62.32, H; 6.54. Found: C; 62.16, H; 6.73. **UV:** \(\lambda_{\text{max}}^{95\% \text{EtOH}}\) 251 m\(\mu\) (\(\epsilon = 25,900\)), 293 m\(\mu\) (\(\epsilon = 5,500\)). **IR:** 5.83 m\(\mu\). **NMR:** Figure 1a, page 19.

**Low temperature infrared studies of the irradiation of tetra-0-methylpurpurogallin**

The low temperature infrared cell of Wagner and Hornig (32) was modified to contain a solution cell of variable path length.

The cell was set up with two polished sodium chloride plates and a 1/32 inch Teflon spacer. A solution of tetra-0-methylpurpurogallin (0.4 mg/ml) in 9:6:1 methylcyclohexane: diethy ether:tetrahydrofuran was injected into the cell. Liquid nitrogen was added to cool the cell, and the cell was evacuated. When the solution had been thoroughly cooled, its infrared spectrum was taken, and the solution was irradiated for 10 hours, through a Pyrex filter with two General Electric sunlamps placed approximately 5 inches from the frozen glass. After the irradiation, the infrared spectrum was again taken, and no change was detected.
The irradiation of tetra-O-methylpurpurogallin (VII) in a rigid glass at -195°

A cell was constructed of 10 mm Pyrex tubing in the form of an H. One arm was sealed to a vacuum manifold. The tube was flame dried under vacuum, and tetra-O-methylpurpurogallin (VII) (2 mg) was added. After drying the sample, diethylether (2 ml) and methylcyclohexane (3 ml), which had been stored over lithium aluminum hydride in separate reservoirs affixed to the manifold, were distilled into the H-tube. The H-tube was sealed off, and the solution in the cell was thoroughly mixed and distributed equally between the two arms. The cross bar between the two arms was sealed, isolating the two arms.

The apparatus (Pyrex) described by Trecker and Henry (33) was used with the insert removed, as the irradiation vessel. Cooling water was circulated through the outer chamber, the next chamber was evacuated and the large inner chamber was filled with liquid nitrogen. The H-tube was immersed in the liquid nitrogen and irradiated with 8 General Electric sunlamps for 1 minute. After the irradiation, the cell was removed from the liquid nitrogen, and one of the arms was opened. Methanol (or water) was added. The addition was complete within 30 seconds after the end of the irradiation. The tubes were protected from ambient light and allowed to come to room temperature. After one hour, the second arm of the H-tube (control solution) was opened. Solvent was removed
from each solution with a rotary evaporator, and the residues were analyzed. No trace (<0.3%) of methanol adduct (XXV) (or ester (VII)) could be detected in the solution to which methanol (or water) had been added. The v.p.c. scans for the runs where methanol (or water) had been added were identical to those of the control.

Base Catalyzed Ring Contraction of Tri-O-methylpurpurogallin

Synthesis of 2,7,8-tri-O-methylpurpurogallin-2-\(^{14}\)C (XIV)

2,7,8-Tri-O-methylpurpurogallin-2-\(^{14}\)C was synthesized from methylene-\(^{14}\)C diethylmalonate, as shown on Chart 1, page 11, using previously described reactions (16-20). The overall yield of the labeled product was 0.4%, with specific activity of 403 dpm/mg.

Base catalyzed rearrangement of 2,7,8-tri-O-methylpurpurogallin-2-\(^{14}\)C (XIV)

2,7,8-Tri-O-methylpurpurogallin (XIV) (1 gm, 80.6 dpm/mg) and potassium hydroxide (3 gm) were dissolved in ethylene glycol (30 ml) and heated under nitrogen to 160° for three and one-half hours. The reaction was cooled and water (50 ml) was added. The reaction was then extracted with methylene chloride. These extracts were discarded. The reaction mixture was then neutralized with hydrochloric acid and extracted with ether and methylene chloride. These extracts were dried and the solvent removed with a rotary evaporator.
The residue was dissolved in 10% sodium hydroxide (30 ml) and heated for one hour with dimethyl sulfate (3 ml). This solution was extracted with ether and methylene chloride, the extracts dried and the solvent removed. The residue was chromatographed on Woelm neutral alumina (activity 1). The product was eluted with benzene and recrystallized from absolute ethanol. Yield 7 mg, mp 79–81°, 81.5 dpm/mg.

Rearrangement of 2,7,8-tri-O-methylpurpurogallin in deuteriated ethylene glycol

Tri-O-methylpurpurogallin (1 gm) and potassium hydroxide were dissolved in partially deuteriated ethylene glycol (30 ml). The reaction was run and worked up as above. The mass spectrum of ester VIII isolated from the reaction, showed the incorporation of deuterium (51% d₀, 36% d₁, 14% d₂).

Tri-O-methylpurpurogallin (XIV) (0.7 gm) and potassium hydroxide (3 gm) were dissolved in ethylene glycol (80% ²H₂, 30 ml). The reaction was heated to 160° for one-half hour. Water (30 ml) was added to the reaction mixture and it was extracted with methylene chloride. These extracts were discarded. The reaction mixture was neutralized with hydrochloric acid and extracted with methylene chloride. The extracts were recrystallized from 95% ethanol. The mass spectrum of recovered XIV showed incorporation of deuterium (41.4% d₀, 45% d₁, 11% d₂).
PART II: OXIDATIONS WITH PHENYLHYDRAZINES
Emil Fischer first prepared phenylhydrazine (34), and discovered that it gave crystalline derivatives with a number of aldehydes (35). Later he showed that sugars were oxidized by phenylhydrazine to vicinal dihydrazones, or osazones, derivatives (36). He was able to work out the stoichiometry of this reaction and showed that the sugar:phenylhydrazine ratio was 1:3, and that ammonia and aniline were the reduction products produced in the formation of the osazones (37).

Fischer (38) and Neuberg (39) reacted various sugars with 1-methylphenylhydrazine and other 1-substituted phenylhydrazines. In all cases they isolated the osazones, but no further oxidation products. It seemed to be tacitly assumed, probably based on the oxidations with phenylhydrazine that oxidation always stopped at the 2-position, and no attempts at further oxidation were reported.

Fischer was unable to offer any explanation of why oxidation stopped after only one carbon had been oxidized.
No progress was made on the problem until Fieser and Fieser (40) suggested that stable chelate rings, XXXII or XXXIII formed in solution and prevented further oxidation. They did not test their hypothesis, nor did they refer to the fact that 1-methylphenylhydrazine also gave osazones.

The Structure of Mixed Osazone A

Two mixed osazones of glucose with phenylhydrazine and 1-methylphenylhydrazine had been reported as the 1-phenyl-2-methylphenylosazones, mixed osazone A (XXXIV) (mp 193°), and the 1-methylphenyl-2-phenylosazone, mixed osazone B (XXXV) (mp 205°), (41). Mester (42) has shown that mixed osazone B is mixed osazone A contaminated with glucose phenylosazone.
In conjunction with some work on the structures of the osazones in solution, to be described later, it was necessary to know the structure of mixed osazone A. There are two structure proofs of mixed osazone A in the literature (42,43), neither of which is satisfactory.

The first structure proof of this compound (42) relies on the fact that glucosone-1-methylphenylhydrazone (XXXVI) reacts with phenylhydrazine to produce mixed osazone A. Grave doubt is cast on the validity of this structure proof by the evidence for hydrazone exchange reported by Robinson (44). In fact, we have been able to prepare mixed osazone A by each of the following four reactions. We have also found that a solution of the tris-methylphenylhydrazone of glyceraldehyde (XXXVII) in ethanol, water and acetic acid, exchanges with phenylhydrazine in less than a minute to produce the tris-1,3-
methylphenyl-2-phenylhydrazone of glyceraldehyde (XXXVIII). This demonstrates the ease with which these hydrazone compounds can exchange, and makes use of this type of reaction for a structure proof highly questionable.

The second structure proof depends on the formazan reaction (42). The formazan reaction is the reaction of the benzene diazonium ion with an aldehyde phenylhydrazone to yield a formazan product, IXL. Mester (42) states that the formazan reaction depends on two conditions; 1) the presence of a Schiff base, -CH=N-, and 2) the presence of a free, non-chelated, imino hydrogen on the phenylhydrazone.

Mixed osazone A gives no reaction with diazotized aniline in pyridine or in ethanol containing potassium hydroxide (42).
This indicates that mixed osazone A has structure XXXV, with the N-methyl group on the 1-hydrazone. However, in the same paper, Mester states that α-D-glucose phenylosazone fails to react in pyridine, but it does react in ethanol containing potassium hydroxide. It has since been shown by Mester (45) that glucose phenylosazone has structure XL in pyridine solution. Osazone structure XL fits Mester's two criteria for the formazan reaction, but it does not react. This fact makes Mester's use of this reaction, for a structure proof, questionable.

Formaldehyde Phenylhydrazone

The reaction of phenylhydrazine with aldehydes and ketones was developed by Fischer (34). The products of this reaction are usually hydrazones, as is shown below. However,

\[ R_1\ce{C=O} + H_2\ce{NN<^\phi} \rightarrow R_1\ce{C=NN<^\phi} + H_2O \]

when formaldehyde is reacted with phenylhydrazine, four
products $\text{XLI} \rightarrow \text{XLIV}$ can be isolated (46). None of these products is the formaldehyde phenylhydrazone. Compounds XLIII and XLII are usually reported as the formaldehyde phenylhydrazone (47,48) since they are readily obtained from the reaction of formaldehyde and phenylhydrazine. One source (49) reports the formaldehyde phenylhydrazone as being a liquid. However, no characterization of this liquid can be found in the literature. The melting point of compound XLI has been reported as being from 140-210° (47). Interestingly, repeated recrystallizations from ethanol give material which melts from 140-160°, with no apparent improvement on successive recrystallizations. However, recrystallization from ethanol containing some sodium ethoxide gives good crystals.
with melting point 210-211.5° (47). Compound XLIV is the glyoxal phenylosazone (50). It can be prepared in good yield from the reaction of phenylhydrazine and formaldehyde. This is the method of choice for the preparation of this compound.
RESULTS

The Alkazones

The Fiesers' postulated (40) that the further oxidation of the sugars is stopped by formation of chelate rings between the hydrazone groups of the osazones in solution. If this is true, then if one could prevent the formation of these chelates, one should be able to fully oxidize the sugars. Since the sugars are chelated through the N-H protons of the hydrazone groups, if one were to use a 1-substituted phenylhydrazine, which would have no N-H proton, oxidation of the sugars should proceed down the chain. Oxidations of sugars with 1-substituted phenylhydrazines had been attempted previously (38,39), but the only products reported were the osazones.

There are two methylphenylosazones reported for the three carbon sugars, mp 127-130° (39), and mp 147-148° (51). We began this work by preparing the osazone with melting point 127-130°. We hoped to be able to oxidize this further with phenylhydrazine or more methylphenylhydrazine. However, the n.m.r. spectra of this compound was quite different from that expected (Figure 2a). There was no \(-\text{CH}_2\text{OH}\) group, as would be expected for the osazone XLV. Rather, in the N-methyl region of the spectrum, there were two singlets, one of area six, the other of area three. The phenyl region integrated for 15
Figure 2. Nuclear magnetic resonance spectra

Top - Methylphenylpropazone (XXXVII)

Bottom - 1,3-methylphenylhydrazone-2-keto glyceraldehyde (XLVI)
$\text{CH} = \text{NNCH}_3\phi$

$\text{C} = \text{NNCH}_3\phi$

$\text{CH} = \text{NNCH}_3\phi$

7.62 ppm.  330 ppm

$\text{H} \overset{\text{C}}{=} \text{NNCH}_3\overset{\text{C}_2\text{H}_5}{}$

$\overset{\text{C}_2\text{H}_5}{\text{C}} = 0$

$\overset{\text{C}_2\text{H}_5}{\text{C}} = \overset{\text{NNCH}_3}{\text{C}_2\text{H}_5}$

7.63 ppm.  3.45 ppm
protons, and the aldimine singlet, just downfield from the phenyl region, integrated for two protons. Thus this compound must be the tris-methylphenylhydrazone of glyceraldehyde (XXXVII).

This is the first member of a new class of fully oxidized per-hydrazon compound. We suggest the name alkazone for this class of compounds to serve as the name osazone has served for that class of compounds. This first member of the alkazones XXXVII, would then be the methylphenylpropazone.

Following the procedures in the literature (51), we also prepared the glyceraldehyde methylphenyllosazone with melting point 147-148°. The very simple n.m.r. spectrum (Figure 2, page 55), and an infrared peak at 6.13 , led us to conclude
that this compound was the 1,3-dimethylphenyl-2-ketohydrazone of glyceraldehyde (XLVI).

We have been unable to prepare the methylphenyl osazone of glyceraldehyde. With the longer chain sugars, however, the methylphenylosazones reported can be prepared. The n.m.r. spectra of these osazones are in agreement with the reported structures.

The sugars, or their methylphenylhydrazones or osazones, yield the corresponding alkazones on further oxidation with 1-methylphenylhydrazine. The yield of the alkazone decreases with increasing chain length. The yield of the methylphenyl hexazone was about 2%.

Methylphenylbutazone (Figure 3a), prepared from erythrose in 55%, gives poly-morphic crystalline forms, mp 149-151°, and 158-160°. Both crystalline forms give the same n.m.r. and infrared spectra in solution. The same methylphenylpentazone (Figure 4a, page 61) was obtained in 39% yield from oxidation with methylphenylhydrazine of arabinose and xylose, two five carbon sugars differing in configuration at carbon-3. This pentazone shows no optical activity. The results of these two experiments are what one would predict from the pentazone structure XLVII. When finally characterized, the methylphenylhexazone was a yellow, high melting, highly insoluble compound. The n.m.r. spectrum (Figure 3b) of the hexazone in deuteriochloroform was run using a
Figure 3. Nuclear magnetic resonance spectra

Top - methylphenylbutazone
Bottom - methylphenylhexazone
Figure 4. Spin decoupling experiment

a. Top - n.m.r. of methylphenylpentazone
b. Left center
c. Right center
d. Bottom
The infrared (Figures 5, 6), ultraviolet (Figure 7) and mass spectra (Table 4) of the methylphenylalkazones were obtained. Spectral data for formaldehyde methylphenylhydrazone and glyoxal methylphenylosazone, the two trivial members of this alkazone family are included for comparison.

The six ultraviolet spectra (Figure 7) present an interesting study. The 2, 4 and 6 carbon methylphenylalkazones have qualitatively very similar ultraviolet spectra, differing only in absorption intensity. The chromophores are cross conjugated, so increasing the number of chromophores does not further extend the conjugation, it only increases the absorbance. Since these three compounds contain an even number of chromophores, these can pair-up into conjugated systems. From the similarity of the ultraviolet spectra, these pairs of double bond chromophores, are essentially non-interacting. The other alkazones, containing an odd
Figure 5. Infrared spectra

Top - Formaldehyde methylphenylhydrazone (XLIX)
Center - Glyoxal methylphenylosazone
Bottom - Methylphenylpropazone (XXXVII)
Figure 6. Infrared spectra
Top - Methylphenylbutazone
Center - Methylphenylpentazone (XIVII)
Bottom - Methylphenylhexazone
Figure 7. Ultraviolet spectra
Solvent: 95% Ethanol
Concentration: $1.5 \times 10^{-5}$ mol/L
Table 4. Mass spectra of the methylphenylalkazones

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<th>m/e % of Base</th>
<th>propazone</th>
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<th>pentazone</th>
<th>hexazone</th>
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<td>2.0</td>
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number of carbon-nitrogen double bond chromophores, cannot readily pair-up in such a simple manner. Their ultraviolet spectra reflect this.

Dr. Roy W. King made the astute observation that the two overlapping N-methyl groups of the methylphenylpentazone (Figure 4a, page 61), also seemed to be broadened. Expansion of the N-methyl region of the spectrum showed three sharp singlets and a broadened multiplet (Figure 4b). The aldimine
region, upon expansion, showed the two aldimine protons each split into unresolved multiplets, \((J = 0.9 \text{ cps})\) (Figure 4c). In a decoupling experiment, the aldimine protons were irradiated, causing the N-methyl multiplet to collapse to a doublet of two different N-methyl groups (Figure 4d). Thus the aldimine protons are coupled through five bonds to the N-methyl protons of the hydrazone groups. In the N-methyl phenylpropazone (Figure 2, page 55), and butazone (Figure 3, page 59), we were able to pick out the terminal N-methyl groups by their coupling to the aldimine protons.

We have shown that osazone formation can proceed further than the second carbon of a sugar by oxidation with 1-methyl-phenylhydrazine, and we have prepared and characterized the methylphenylalkazones of three to six carbons.

The Structure of Mixed Osazone A

It was important that the structure of mixed osazone A be known with certainty, but there still existed some doubt as to whether it was XXXIV or XXXV. Since we had found that long range coupling could be detected between an aldimine proton and the N-methyl group of a methylphenylhydrazone on the same carbon, we used this long range coupling to see if we could prove the structure of Mixed osazone A. The spin decoupling experiments could best be determined in deuterio-chloroform solution in which mixed osazone A was only slightly
soluble. Therefore we prepared the tetraacetate of mixed osazone A (XLVIII), which was readily soluble in deuteriochloroform. Upon expansion of the n.m.r. of XLVIII (Figure 8), the N-methyl group could be seen to be split (Figure 8b).

\[
\text{H}_3\text{C} - \text{N} - \phi
\]

\[
\text{H} - \equiv \text{N} - \equiv \text{N} - \equiv \text{N} - \phi
\]

\[
\text{(AcOHC)}_4 - \text{H}
\]

XLVIII

Unfortunately, the aldimine proton appeared to be buried in the aromatic multiplet. However, by irradiating 228 cps downfield of the N-methyl group, the N-methyl doublet collapsed to a sharp singlet (Figure 8c).

In a control experiment, the n.m.r. of glucose methylphenylosazone tetraacetate was run in deuteriochloroform (Figure 9a). It showed two distinct N-methyl groups, significantly one of them a sharp singlet, the other split into a doublet (\(J = 0.9\) cps) (Figure 9b). Thus only the 1-hydrazone group couples to the aldimine. Again, the aldimine proton was buried in the phenyl region of the spectrum. By irradiating 245 cps downfield from the coupled N-methyl group, the split N-methyl peak collapsed to a sharp singlet (Figure 9c). These spin decoupling experiments demonstrate beyond doubt
Figure 8. Spin decoupling experiment

a. Top – n.m.r. spectrum of mixed osazone A
b. Bottom left

c. Bottom right
H_2C=NNC=NHCH_3
C_6H_5
C=NNC_6H_5
(NHCOCH_3)_4

12.85  7.30  3.50  0.0  P.P.M.

IRRADIATE A
SCAN B
Figure 9. Spin decoupling experiment
   a. Top - n.m.r. of glucose methylphenylosazone
   b. Bottom left
   c. Bottom right
A \[ H=C=NNCH_3 \]
\[ C=NNCH_3 \]
\[ C=NNCH_3 \]
\[ (CHOCOCH_3)_4 \]

IRRADIATE A, SCAN B&C
that the methylphenylhydrazone group of mixed osazone A is on carbon-1, therefore mixed osazone A must have structure XXXV.

Formaldehyde Phenylhydrazone

The four products of the reaction of formaldehyde and phenylhydrazine $\text{XLI} \rightarrow \text{XLIV}$ were isolated. The glyoxal phenyllosazone (XLIV) was a well characterized compound (50). The reported structures of XLII and XLIII were confirmed by their n.m.r. spectra (Figure 10). Compound XLI turned out to be a relatively insoluble compound. It was soluble enough in dimethyl sulfoxide, however, to obtain a poor spectrum (Figure 11a). One can pick out an $A_2M$ multiplet, 4.5 p.p.m. downfield from tetramethylsilane, which is consistent with the methylene protons and the N-H protons splitting each other, as expected for structure XLI. However, when the n.m.r. spectrum of XLI is run in deuteriochloroform, a completely different spectrum (Figure 11b) is obtained. This spectrum has an $AB$ multiplet at 6.25 p.p.m. with $J = 11.3$ cps, and $\Delta \delta = 21.9$ cps. This is consistent with the n.m.r. expected for formaldehyde phenylhydrazone (XLIX). The methylene protons are chemically different, thus they split each other. The magnitude of the splitting seems large compared to the splitting usually observed for the methylene protons of a vinyl group, $J = 0-3.5$ cps. Actually it is intermediate to the terminal vinyl splitting with carbon-
Figure 10. Nuclear magnetic resonance spectra
Top - Compound XLII
Bottom - Compound XLIII
Figure 11. Nuclear magnetic resonance spectra
Top - Compound XLI
Bottom - Formaldehyde methylphenylhydrazone (XLIX)
carbon double bonds, and the splitting observed for the methylene protons of formaldehyde, \( J = 40 \text{ cps} \), with a carbon-oxygen double bond. These results are best explained by a monomer-dimer equilibrium which is solvent dependent. This would explain the difficulty one has in obtaining pure XLI by recrystallization.

Since XLIX was as yet uncharacterized, an attempt was made to prepare it. A 40\% solution of formaldehyde was mixed with neat phenylhydrazine, allowed to react, and the product steam distilled to yield a yellow viscous oil. This oil, in deuteriochloroform gave an n.m.r. spectrum identical to that of XLI in deuteriochloroform. The oil was not stable in glassware, but slowly dimerized to yield XLI. When XLIX was prepared in the presence of base, phenylazomethane (L) was also a product of the reaction.

The ultraviolet spectra of XLIX in different solvents presents an interesting study. In ethanol and cyclohexane, we find \( \lambda_{\text{max}} = 233, 271 \) and \( 293 \text{ m\AA} \), presumably due to XLI.
In acetonitrile and chloroform, we find $\lambda_{\text{max}} = 249 \, \text{m}$, presumably due to XLIX.
DISCUSSION

The sugar methylphenylosazones cannot form chelate rings in solution. We have shown that they can be further oxidized with methylphenylhydrazine to form the alkazones. This is consistent with the Fiesers' hypothesis (40) that the osazones form a stable chelate ring in solution which prevents further oxidation of the sugars.

There was an allied project concurrently in progress at Iowa State University under Dr. Orville L. Chapman, to determine the structures and to explain the mutarotation of sugar osazones in dimethyl sulfoxide solution. Dimethyl sulfoxide slowed the rate of amino and hydroxyl proton exchanges, producing sharp resonances and allowing spin-spin splitting of the hydroxyl protons to be observed (52).

The n.m.r. spectra of the osazones in dimethyl sulfoxide solution showed two N-H resonances. One N-H resonance was at quite low field, 12.2 p.p.m., the other at higher field, 10.7 p.p.m. In deuteriochloroform, the low field resonance remained essentially unchanged, while the higher field resonance moved further upfield to about 10.1 p.p.m. This implies that one of the N-H protons is intramolecularly hydrogen bonded, while the other is solvent bonded. The question is, which N-H hydrogen is hydrogen bonded? If it is the hydrogen of the C-1 hydrazone, the chelate should be XXXII. If it is the hydrogen of the C-2 hydrazone, the
chelate should be XXXIII. By analogy with the n.m.r. of mixed osazone A (XXXV), whose structure proof we have discussed, XXXIII was shown to be the correct structure of the osazones in dimethyl sulfoxide solution (53).

We found that the methylphenylpropazole (XXXVII) in water ethanol and acetic acid, rapidly exchanges with phenylhydrazine to yield a mixed osazone. The n.m.r. (Figure 12a) and elemental analysis of XXXVIII fit for the structure where one methylphenylhydrazone group has been displaced by a phenylhydrazone group. The n.m.r. in deuteriochloroform shows two different aldimine protons, and an N-H proton at 12.8 p.p.m. Upon expansion of the N-methyl region of the spectrum (Figure 12b), the N-methyl groups are seen to be coupled by 0.5 and 0.6 cps respectively. By irradiating the different aldimine protons separately (Figure 12c), the N-methyl proton were individually decoupled to give sharp singlets. Thus both methylphenylhydrazones are on terminal carbons, and the phenylhydrazone has chosen to substitute on the 2-carbon. This is what one would expect if the osazones had structure XXXIII, and this is further evidence for XXXIII being the structure of the osazones in solution.

Chapman (53) also found that the osazones equilibrated in solution between two structures, the chelate XXXIII and an open chain form LI. They found that the equilibrium ratio

\[ \text{XXX} \]

1 See pages 48 and 49, this thesis.
Figure 12. Spin decoupling experiment

a. Top - n.m.r. spectrum of 1,3-bismethylphenyl-2-phenylpropazone

b. Bottom left

c. Bottom right
of the chelate to non-chelate forms depends primarily on the size of the R group. When R = H or \(-\text{CH}_3\), the non-chelate form II is the only form present in solution. As the size of the R group is increased, the equilibrium shifts in favor of the chelate form XXXIII \((R = -\text{CHOHCH}_2\text{OH}, \text{ca. 80\% chelate})\).

Chapman (53) also showed that the base catalysed change in optical rotation, mutarotation, observed when a solution of osazone is allowed to equilibrate, is due to the equilibrium of the XXXIII chelate with the chelate II.

The implication of this work (53) is that chelate ring formation cannot be the sole answer to the oxidation of the sugars stopping at the osazone stage, since there is always open chain material present in solution able to be oxidized further. What is needed is an explanation of why this material does not oxidize further.

It may be a problem of slow kinetics, as there are one or more slow steps in the oxidation. Once begun, the oxidation proceeds at a slow pace unless one of the relatively
insoluble intermediates begins to precipitate. A precipitate effectively halts further oxidation by removing the substrate from solution. For example, with the five carbon sugar arabinose, by varying the media one uses for the oxidation with methylphenylhydrazine, one can isolate the hydrazone, osazone or pentazone in good yield. If allowed to stand, however, the hydrazone or osazone will slowly dissolve and oxidize until only pentazone can be isolated.

The oxidation of the first couple of carbons proceeds relatively easily, probably because of the relatively high concentration of reactants present. But as oxidation proceeds, many different intermediates build up in solution. The concentration of any one intermediate then, particularly the more fully oxidized ones, is correspondingly low. Thus the rate of oxidation is increasingly slowed for each successive carbon. With the longer sugars, more side reactions are possible and these side reactions have more time to proceed. They are able then, to siphon off a correspondingly larger amount of material. This is illustrated by the longer times necessary to isolate the higher alkazones, and their lower yields.

Why then does oxidation with methylphenylhydrazine ultimately give alkazones, while oxidation with phenylhydrazine gives only osazones? Possibly the phenylosazones are relatively less soluble or the rate of further oxidation
is very slow. Either, or both of these factors could slow
the further oxidation enough so that oxidation to the alkazone
is overwhelmed by side reactions, or it is too slow to be
observed. Possibly a large increase in the amount of
phenylhydrazine used in these reactions, and a longer reaction
time would increase the oxidation rate enough that further
oxidation of the osazones could be observed.
EXPERIMENTAL

Instruments and Methods

All melting points were measured on a Kofler microscope hot stage equipped with a polarizer, and all are uncorrected. All ultraviolet spectra were obtained on a Beckman Model DK-2A spectrophotometer in 95% ethanol, unless otherwise noted. All infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer.

All nuclear magnetic resonance (n.m.r.) spectra were taken on a Varian Associates Model HR-60 or A-60 spectrometer at 60Mc. The HR-60 spectra were calibrated by the side band technique using the side band of tetramethylsilane as an internal standard. The chemical shift values are reported in parts per million (p.p.m.), (δ) units.

All mass spectra were taken on an Atlas CH-4 mass spectrometer at 70 electron volts, unless otherwise noted. All vapor phase chromatography (v.p.c.) measurements were made on an Aerograph Hy-Fi Model 600-C instrument. The column used was a five foot, 1/8 inch stainless steel column packed with 5% General Electric SE-30 on 60/80 mesh Chromasorb W. The instrument was operated with a flame ionization detector.

All elemental analyses were performed by Schwarzkopf
Experimental for the Preparation of the Alkazones

Preparation of 1-methylphenylhydrazine

N-methyl-N-nitrosoaniline (27 ml) (54) was slowly added with stirring to lithium aluminum hydride (13 g) in diethyl-ether (250 ml) (55). After the addition was complete, the reaction was worked up by adding water (13 ml), 20% sodium hydroxide (10 ml) and water (45 ml). The granular precipitate was removed by filtration and washed with ether. The ether washings were added to the filtrate. The filtrate was dried over magnesium sulfate, and the ether removed with a rotary evaporator. The methylphenylhydrazine was used without further purification.

Preparation of the methylphenylpropazone (XXXVII)

1,3-Dihydroxyacetone (0.5 g), 1-methylphenylhydrazine (3.87 ml) and acetic acid (2.0 ml) were dissolved in 50% ethanol-water (10 ml). Within a minute, an oil began to separate, and it soon solidified. The reaction mixture was allowed to set for twelve hours, at which time it was cooled, and the solid was collected and recrystallized from 95% ethanol (yield 2.07 g, 93%, mp 124.5-127°). The n.m.r. of XXXVII is shown on Figure 2, page 55, the infrared is on
Preparation of methylphenylbutazone

Erythrose (0.5 g), 1-methylphenylhydrazine (3.87 ml), and acetic acid (2.0 ml) were dissolved in 50% ethanol-water (10 ml) and let stand at room temperature. Yellow crystals soon began to separate from the solution. After one day, the solution was cooled, and the crystals were collected and dried (yield 1.6 g, 72%). This product was recrystallized from absolute ethanol giving two crystalline modifications, mp 149-151° and 158-160°, which had superimposable n.m.r. and infrared spectra in solution. The n.m.r. of the methylphenylbutazone is shown on Figure 3, page 59; the infrared is on Figure 6, page 66; and the ultraviolet is on Figure 7, page 68.

Preparation of methylphenylpentazone (XLVII)

Arabinose or xylose (0.5 g), 1-methylphenylhydrazine (3.87 ml) were dissolved in 50% ethanol-water (10 ml) and let stand at room temperature. After two days, the red gum which had deposited on the bottom of the flask was collected and crystallized from boiling ethanol (yield arabinose 0.66 g, 30%, xylose 0.87 g, 39%, mp 150-152°). The n.m.r. of XLVII is shown on Figure 4, page 61; the infrared is on Figure 6,
Preparation of methylphenylhexazole

Fructose (0.5 g), methylphenylhydrazine (4.2 ml) and acetic acid (5 ml) were dissolved in 66% ethanol-water (10 ml). After five days, the precipitate which had formed was collected. It was recrystallized from pyridine. On standing, more material precipitated from solution and was collected (yield 40 mg, 2%, mp 262-264°). The n.m.r. of the methylphenylhexazole is shown on Figure 3, page 59; the infrared spectrum is on Figure 6, page 66; and the ultraviolet spectrum is shown on Figure 7, page 68.

Preparation of the 1,3-bismethylphenyl-2-phenylpropazone (XXXVIII)

Phenylhydrazine (0.10 g) was added to a saturated solution of methylphenylpropazone (XXXVII, 0.20 g) in absolute ethanol containing one drop of acetic acid. A yellow solid immediately separated. The solid was collected and recrystallized from absolute ethanol (yield 90%, mp 191-191.5°). The n.m.r. of XXXVIII is shown on Figure 12, page 86.

Anal. Calcd. for $C_{23}H_{24}N_6$: C, 71.84; H, 6.29; N, 21.86. Found: C, 71.86; H, 6.04; N, 22.08.
Preparation of mixed osazone A (XXXV)

Mixed osazone A was prepared from glucose phenylhydrazone and methylphenylhydrazone by the method of Percival (57), from glucosone methylphenylhydrazone and phenylhydrazine by the method of Henseke (43), and from glucose phenylosazone and methylphenylhydrazone and glucose methylphenylosazone and phenylhydrazine by the method of Votocek (41). The XXXV isolated from these reactions was characterized by melting point and they had infrared spectra identical with the infrared spectrum of an authentic sample.

Experimental for the Preparation of Formaldehyde Phenylhydrazone

Preparation of formaldehyde phenylhydrazone (XLIX)

Phenylhydrazine (10.8 g) was added to formaldehyde (7.5 g of a 40% aqueous solution). The reaction became warm. After ten minutes, additional water was added and the product was steam distilled. The distillate was extracted with ether, the ether solution was dried, and the ether was removed with a rotary evaporator, giving a pale yellow oil (bp 122-123° at 18 mm). The n.m.r. spectrum of XLIX is shown on Figure 11b, page 80; the infrared spectrum is on Figure 5, page 64.
Anal. Calcd. for C₇H₅N₂: C, 69.97; H, 6.70; N, 23.32.

Found: C, 69.91; H, 6.87; N, 23.33.

When the above preparation is carried out with potassium hydroxide (1 g) and the product distilled, a forerun of phenylazomethane (L) (bp 70° at 26 mm) is obtained. The infrared of this material is identical with that of an authentic sample of L prepared by the method of Cohen (58) from formaldehyde phenylhydrazone (XLIX).
LITERATURE CITED


ACKNOWLEDGMENTS

The author finds it difficult to express his gratitude to Dr. Orville L. Chapman for his guidance throughout the authors four years at Iowa State University. Dr. Chapman was able to guide, without directing, the author along the arduous road of a graduate career.

The author would like to acknowledge the help freely given by Drs. Kinstle, Wildman and King to the author on interpreting the labeling and spectroscopy results, upon which this whole thesis is based. The author would also like to thank Mrs. Yvette Vinson for the excellent mass spectra she was able to run for the author, always in record time, and Mr. Norman Heimer, a friend and colleague, who unselfishly gave of his time to teach the author to run the Beckman IR-12 and to fix the Packard Tri-Carb scintillation counter, which used to cease to function whenever the author entered the room.

The author would like to thank his parents and family for their sacrifices and encouragement on his behalf during his many years.

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"Where am I going, I don't know."

"Where am I heading, I ain't certain."

"All I know is I am on my way."

Alan J. Lerner