

THE SYNTHESIS OF COMPOUNDS  
RELATED TO PODOPHYLLOTOXIN

by

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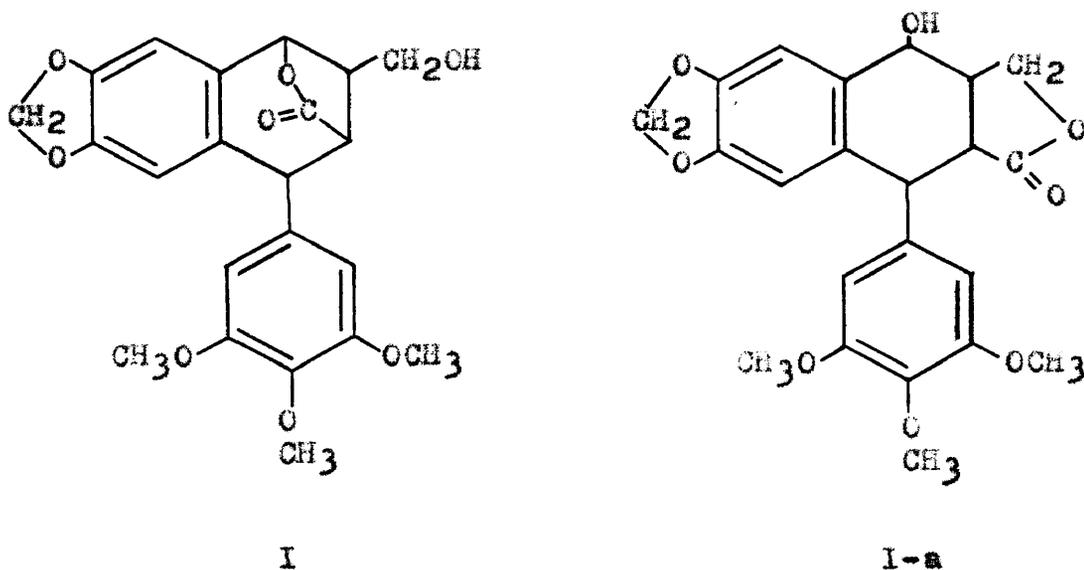
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## INTRODUCTION

Podophyllotoxin (I), a constituent of podophyllin resin, has been shown to have tumor damaging activity<sup>17,20,33</sup>. It has also been shown that the effect on normal cells is far less toxic, and that normal cells build up an immunity to the drug under normal dosage<sup>25</sup>.

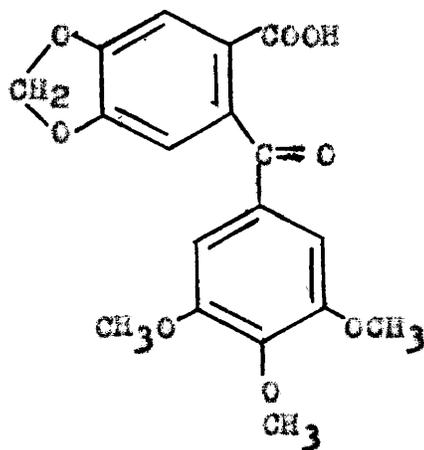


Although I is the accepted structure, considerable doubt has been cast upon the position of the lactone ring and of the hydroxyl group that is attached to the saturated ring. Recent work of Price<sup>35</sup>, at this institution, and of Hartwell and co-workers<sup>18, 19</sup>, at the National Institutes of Health, Bethesda, Maryland, tends to indicate that I-a might be the more probable structure, and that picropodophyllin, which has already been assigned structure I-a, is an optical isomer of podophyllotoxin and not a positional isomer, as was originally assumed.

A comprehensive survey of the structural studies on podophyllotoxin and of its chemistry has been published in the British Annual Reports on the Progress of Chemistry<sup>21,28</sup> and more recently reviewed by Sterling<sup>49</sup>. Price has compiled a similar study on 1-phenyltetralins so no expansive historical background will be presented in this thesis.

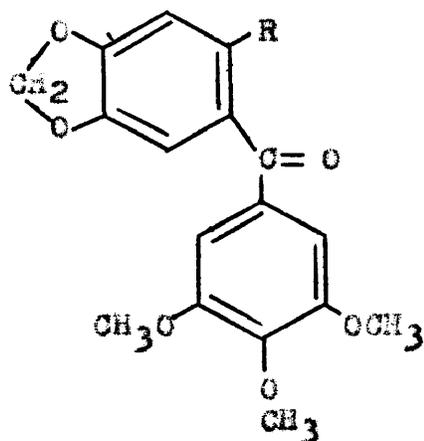
## DISCUSSION

Synthetic Work Planned. The present research has been directed toward producing compounds having a structure similar to podophyllotoxin, in hopes that one or more of them may also prove to have tumor damaging properties. Of equal importance, has been the preparation, in appreciable quantities, of 4,5-methylenedioxy-2-(3',4',5'-trimethoxybenzoyl)-benzoic acid (II), one of the intermediates required in the synthesis of podophyllotoxin which was outlined by Sterling<sup>49</sup>.



II

Earlier attempts to prepare compound II by oxidation of III, prepared by a Friedel-Crafts condensation of 3,4-methylenedioxytoluene and 3,4,5-trimethoxybenzoyl chloride, were failures<sup>36</sup>. Attempts to prepare the compounds, listed as III-a, from 3,4-methylenedioxyphenyl compounds, substituted in the 1 position with the corresponding R groups, and 3,4,5-trimethoxybenzoyl chloride gave no condensation product<sup>36</sup>.



III, R = CH<sub>3</sub>

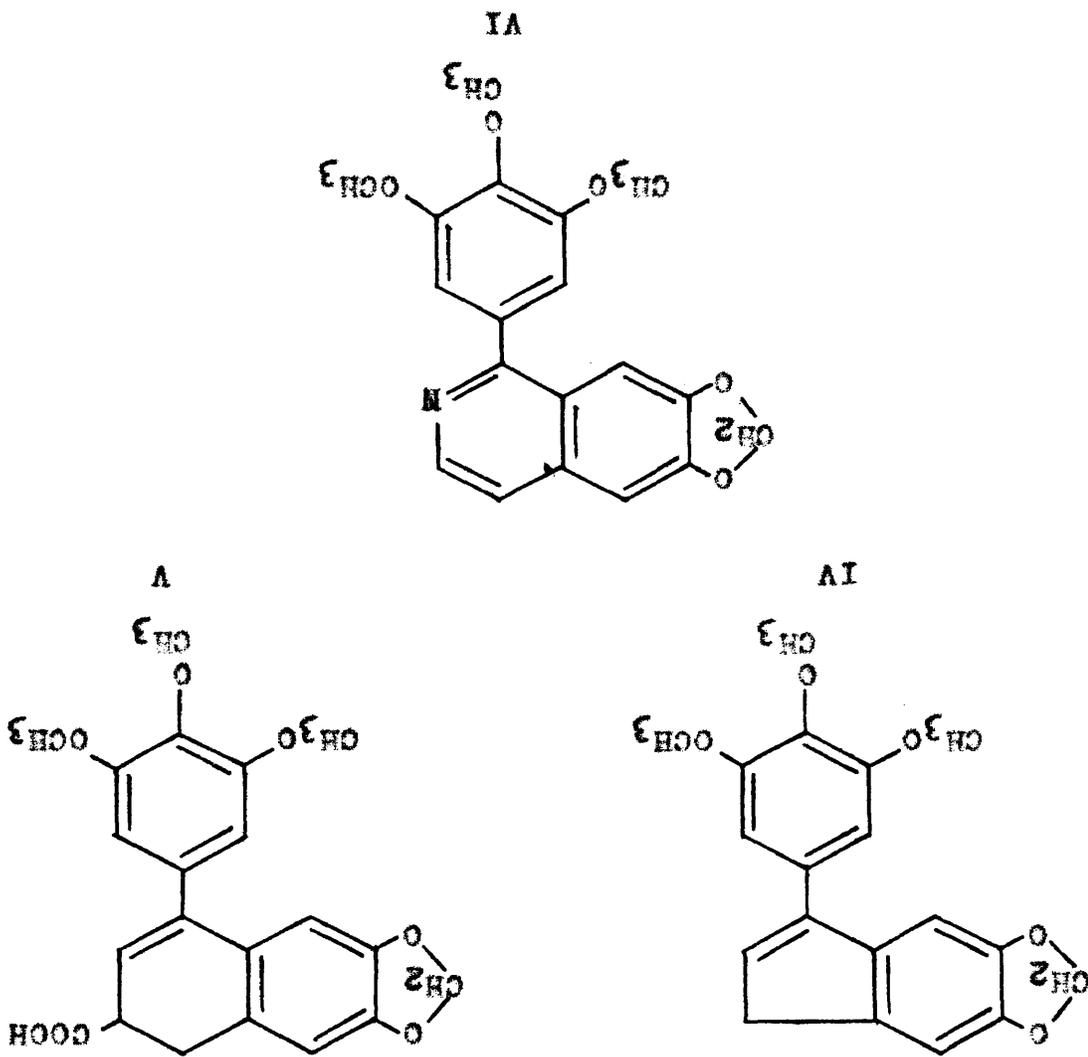
III-a, R = CH<sub>2</sub>OCOCH<sub>3</sub>,

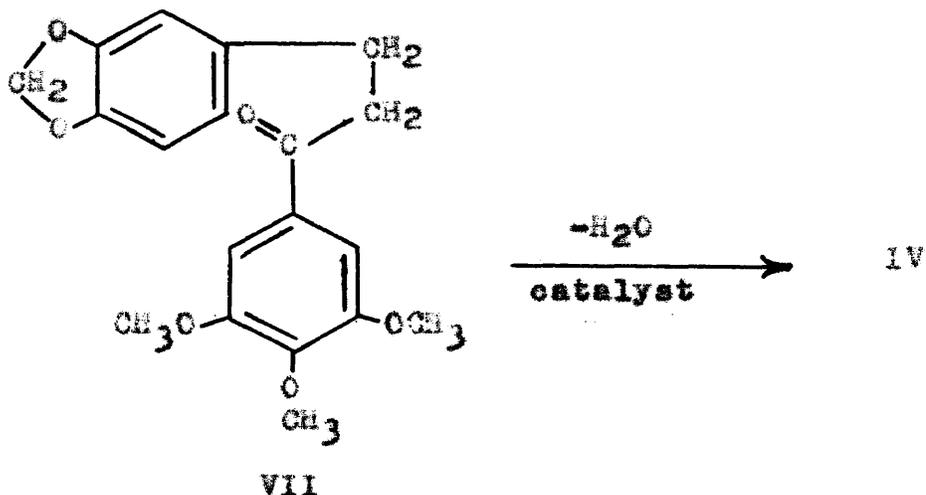
COOC<sub>2</sub>H<sub>5</sub>, CH(OC<sub>2</sub>H<sub>5</sub>)<sub>2</sub>,

CHO, CH<sub>2</sub>-CH=CH<sub>2</sub>

When this approach failed, other synthetic procedures were outlined which would satisfy both of the goals which were mentioned above. Three different procedures have been followed during this research in attempting to prepare compound II. The first was an attempt to prepare 5,6-methylenedioxy-1-(3',4',5'-trimethoxyphenyl)hydrindene-1 (IV). The second method involved a variation of the work done by Haworth and co-workers<sup>22</sup>. Our procedure would yield 6,7-methylenedioxy-1-(3',4',5'-trimethoxyphenyl)-3,4-dihydronaphthalene-3-carboxylic acid (V), instead of the aromatized naphthalene derivative prepared by Haworth. The third synthesis consisted of the preparation of 6,7-methylenedioxy-1-(3',4',5'-trimethoxyphenyl)isoquinoline (VI) and a series of derivatives of this basic structure. In all of the above syntheses, the final step would involve oxidative degradation of the appropriate ring to yield the keto acid (II).

5,6-methylenedioxy-1-(3,4,5-trimethoxyphenyl)hydri-  
 none-1 (IV). Using a variety of catalysts, attempts were  
 made to cyclize 3,4,5-trimethoxy- $\omega$ -(3,4,5-trimethoxy-  
 benzyl)acetophenone (VII) to the corresponding hydri-  
 none (IV). It was hoped that oxidative degradation  
 of the five membered acyclic ring would yield the desired  
 keto acid (II).





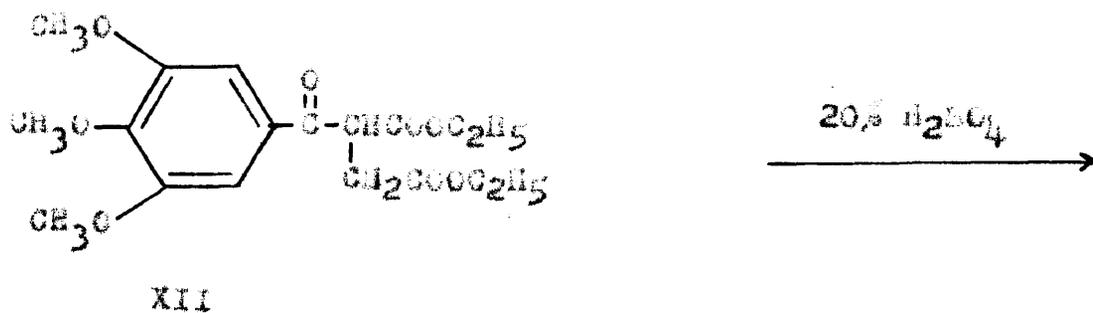
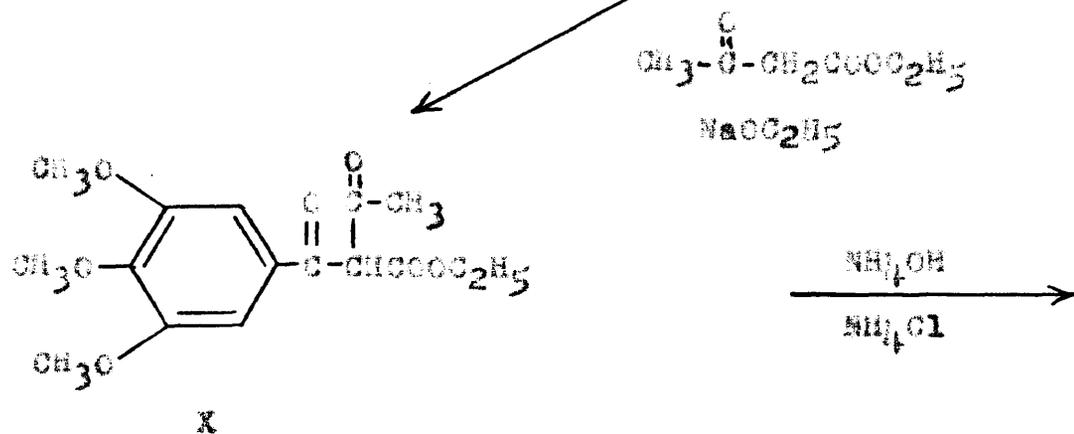
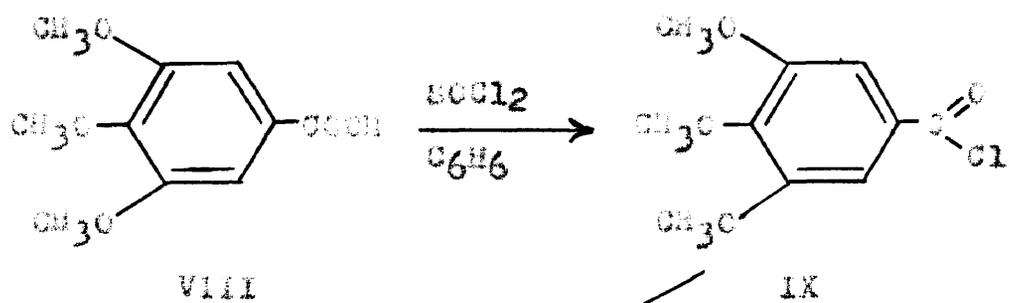
An attempt to use liquid hydrogen fluoride as a catalyst gave a carbonized residue, and no identifiable compounds were isolated. Cold concentrated sulfuric acid and *p*-toluenesulfonic acid in refluxing benzene gave black tars which would not yield any crystalline materials. Attempted cyclizations using phosphorous pentoxide in benzene, stannic chloride in carbon disulfide, and phosphorous oxychloride in toluene, yielded the starting material as the only identifiable product.

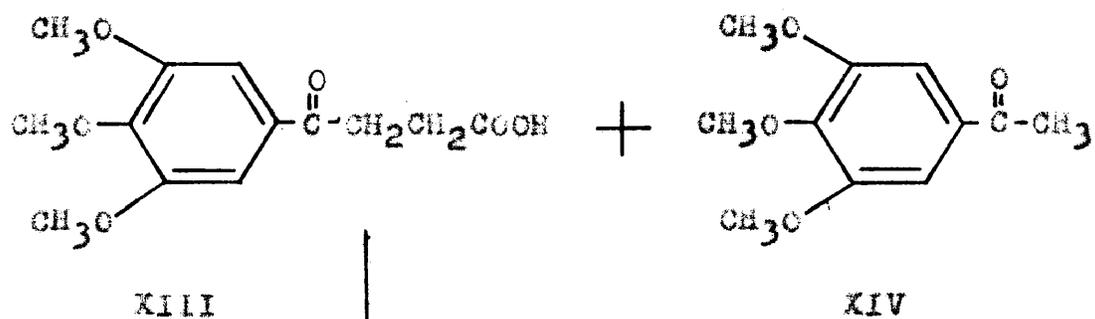
Phosphorous pentachloride in refluxing benzene gave a pale colored oil after removal of the phosphorous compounds and the solvent. This oil, which could not be crystallized, contained chlorine, and it was believed that the carbonyl oxygen may have been replaced by chlorine atoms, in a manner similar to that in which oxalyl chloride replaces the oxygen in carbonyl compounds with chlorine atoms as observed by Staudinger<sup>48</sup>. On this assumption, cyclization of the oil was attempted using stannic chloride as the catalyst in

carbon disulfide solvent. The only product isolated was a dark brown tar which could not be identified.

6,7-Methylenedioxy-1-(3',4',5'-trimethoxyphenyl)-3,4-dihydronaphthalene-3-carboxylic Acid (V). Since the closure of the five membered ring appeared to be infeasible, it seemed logical to attempt the closure of a six membered ring, in a manner analogous to that used by Haworth<sup>22</sup> in his structural studies on podophyllotoxin. The only modification of this synthesis would be the hydrogenation of a double bond so as to obtain a dihydronaphthalene derivative instead of the aromatized compound which Haworth prepared.

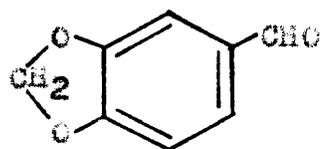
Trimethylgallic acid (VIII) was prepared by the method of Mauthner<sup>30</sup> and converted to the acid chloride (IX) using thionyl chloride and benzene as a solvent<sup>3</sup>. The acid chloride was then condensed with ethyl acetoacetate to yield ethyl  $\alpha$ -(3,4,5-trimethoxybenzoyl)acetoacetate (X)<sup>34</sup> and the latter hydrolyzed with ammonium hydroxide and ammonium chloride to remove the acetyl group and give ethyl 3,4,5-trimethoxybenzoylacetate (XI)<sup>34</sup>. Compound XI was treated with sodium ethoxide and then ethyl bromoacetate to yield diethyl  $\alpha$ -(3,4,5-trimethoxybenzoyl)succinate (XII)<sup>22</sup>. This compound was not isolated but was hydrolyzed and decarboxylated by refluxing with 20 per cent sulfuric acid to give  $\beta$ -(3,4,5-trimethoxybenzoyl)propionic acid (XIII)<sup>22</sup>. The yield of impure material in this step was 50 per cent of the theoretical amount as claimed by Haworth and co-workers. However, only a 50 per cent recovery of purified material was achieved



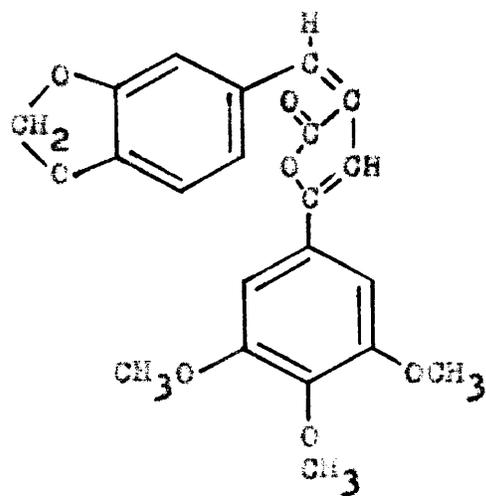


1) Prepare Na Salt

2)



,  $(\text{CH}_3\text{CO})_2\text{O}$

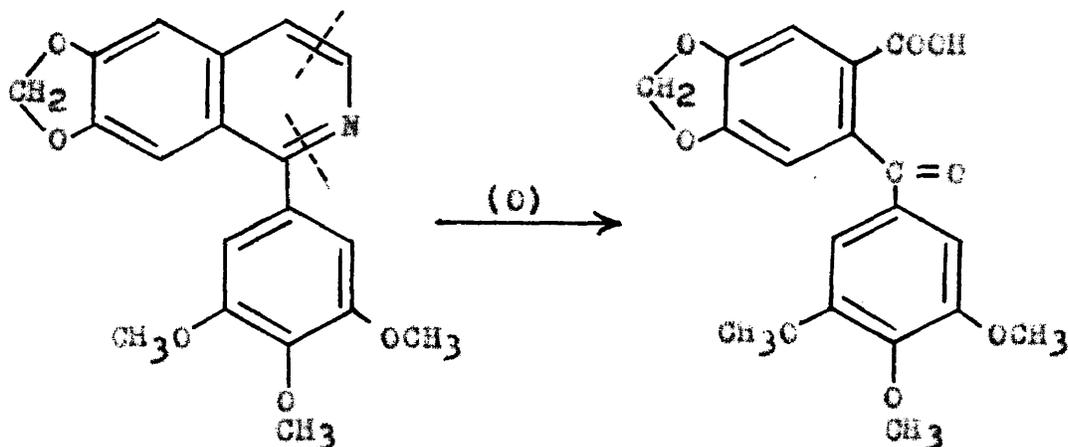


XV

by following their suggested recrystallization procedure, cutting the yield of pure material to 25 per cent. A considerable quantity of neutral material was obtained from the hydrolysis reaction. This proved to be 3,4,5-trimethoxyacetophenone (XIV) which was identified by its p-nitrophenylhydrazone and its oxime. The 2,4-dinitrophenylhydrazone was also prepared and analyzed. The potassium salt of XIII, when treated with piperonal and acetic anhydride, undergoes a modified Perkin reaction to yield the enol lactone of  $\alpha$ -(3,4-methylenedioxybenzal)- $\beta$ -(3',4',5'-trimethoxybenzoyl)propionic acid (XV)<sup>22</sup>. Once again the yield of impure material was 50 per cent of the theoretical amount but recrystallization again gives less than 60 per cent recovery of the pure material.

Since the overall yield was already below 5 per cent, and several more steps remained in the synthesis, this procedure was abandoned.

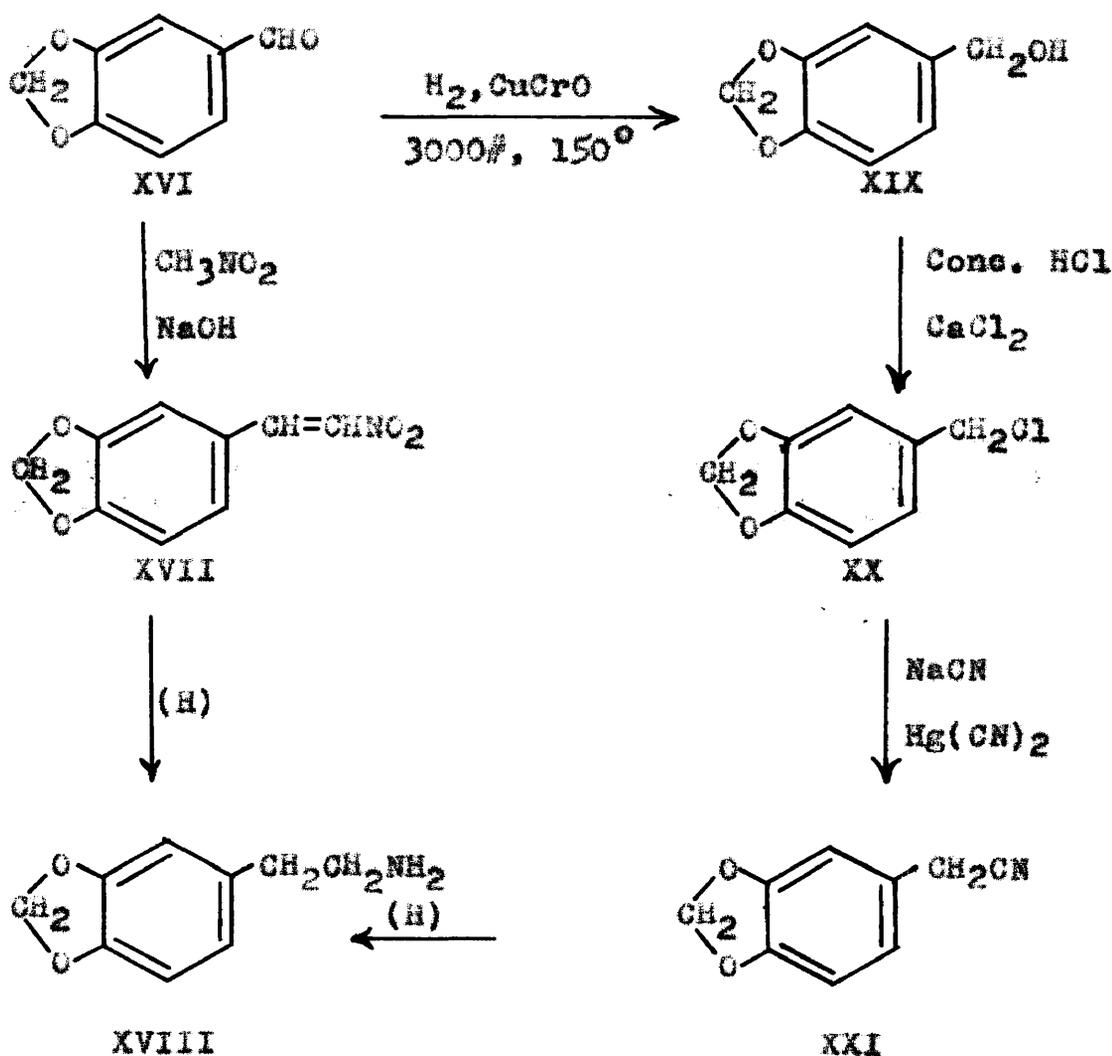
6,7-Methylenedioxy-1-(3',4',5'-trimethoxyphenyl)isoquinoline (VI). Another method of obtaining the desired carbon skeleton is through the synthesis of the isoquinoline VI. Oxidative degradation of the six membered heterocyclic ring could yield the desired keto acid (II).



The preparation of the intermediate homopiperonylamine (XVIII) was carried out by two different synthetic routes. When the first method, which consisted of the reduction of a nitrostyrene derivative, failed to give satisfactory yields, a second synthesis, based on the reduction of piperonyl cyanide, was used. The latter method gave good yields of the desired amine.

The first procedure was carried out in two steps. Piperonal (XVI) was condensed with nitromethane in alkaline solution to yield 3,4-methylenedioxy- $\omega$ -nitrostyrene (XVII)<sup>52</sup>. This was reduced over Raney nickel catalyst in dioxane solution to the desired homopiperonylamine (XVI) in 10 per cent of the theoretical amount. The amine reacted rapidly with carbon dioxide in the air to form a carbamate, and it was assumed that the vacuum distillation permitted carbon dioxide to react with the amine in the distilling apparatus and thus no more would distill. A second reduction, run under the same conditions, with the exception that the amine was distilled in an atmosphere of nitrogen, gave the same 10 per cent of the theoretical amount. Thus, it was obvious that the reduction was taking some course other than the desired one. The nonvolatile residue from the second reduction was dissolved in benzene and treated with 10 per cent hydrochloric acid. A tar formed and precipitated from the solution. The black tarry portion dissolved in acetone leaving a white residue which melted 261-262° after recrystallization from ethanol. This was later shown to be dihomopiperonylamine

hydrochloride. Other reductions carried out at room temperature and one atmosphere pressure using the methods of Kindler<sup>24</sup> and Schales<sup>40</sup> gave no yield of XVI. Repetition of the first procedure using Raney cobalt catalyst in place of the Raney nickel catalyst increased the yield to 26 per cent of the theoretical amount.



The second procedure gave much better results, although four steps are required in this preparation. Piperonal (XVI) was reduced over copper chromium oxide catalyst to piperonyl alcohol (XIX) by the method of Reeve and Sterling<sup>36</sup>. This

was treated with concentrated hydrochloric acid saturated with calcium chloride<sup>5</sup>. The impure chloride (XX), which was not isolated, was treated directly with an aqueous solution of sodium cyanide, using a mercuric cyanide catalyst<sup>27</sup>. This gave piperonyl cyanide (XXI) in a yield of 87 per cent of the theoretical amount, based on the alcohol. When mercuric cyanide was not used the yields were lower even with longer reaction time.

The reduction of the nitrile was studied using a variety of conditions and two different catalysts. Bills and Noller<sup>5</sup> reported a yield of 85 per cent using Raney nickel catalyst and alcoholic ammonia as the solvent. We have repeated this work, using the same procedure, and obtained a yield of 82 per cent of the theoretical amount. The results are compiled in Table I. All the reductions were run under the same conditions of temperature and pressure.

The use of cobalt catalysts for the reduction of nitriles to primary amines has been known to industry for more than ten years, as indicated by the many patents<sup>15,23,41,45</sup> which have been granted covering this subject. However, very little work appears to have been done in academic circles along this line. From the table, it can be seen that Raney cobalt, prepared by the method of Adkins and Billica<sup>1</sup> for W-7 Raney nickel, is far superior to the nickel catalyst under the same conditions. With Raney nickel, in the absence of ammonia, a large amount of the secondary amine is formed and the yield of primary amine is low. Using Raney cobalt with

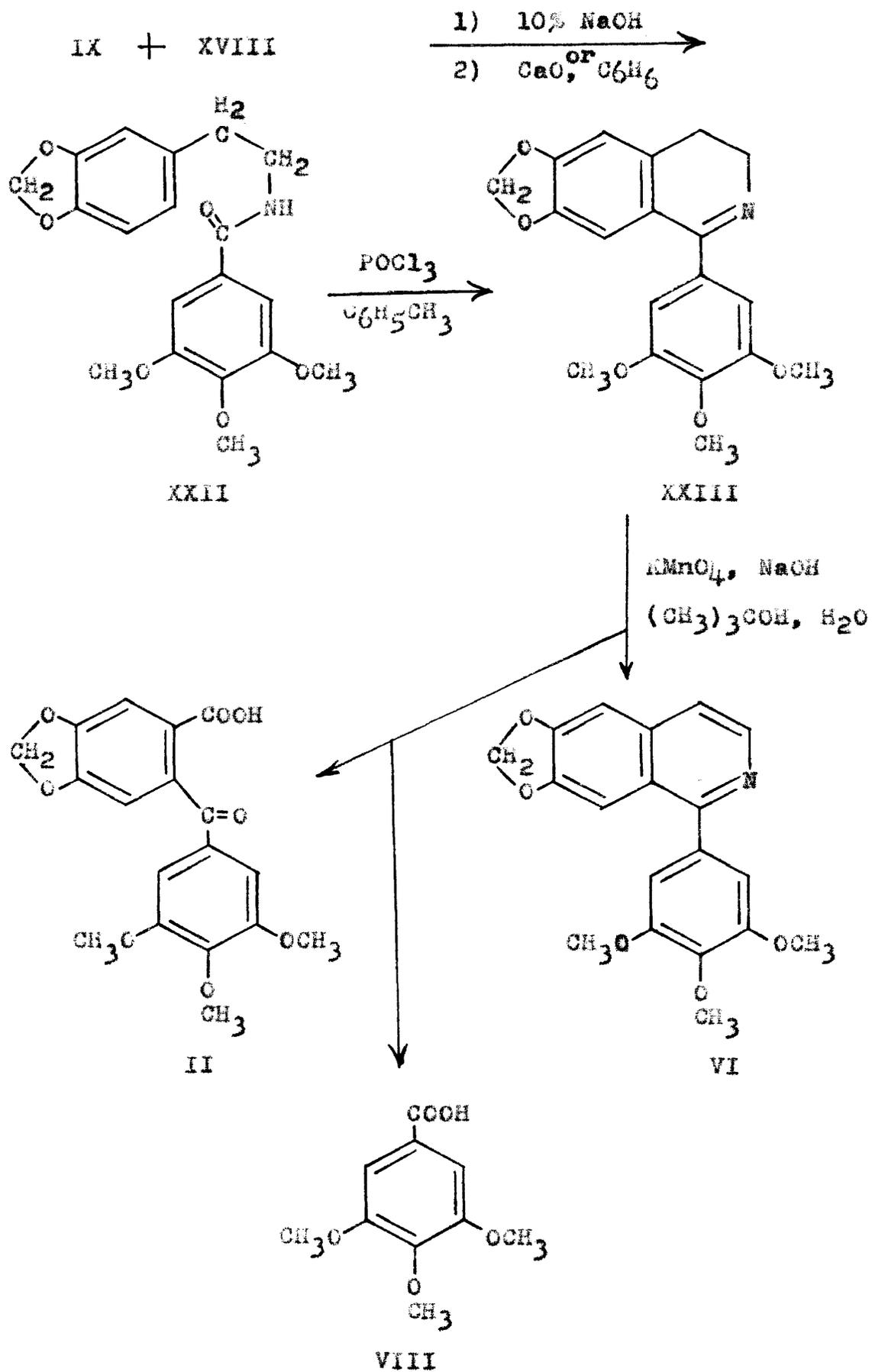
Table I

## Hydrogenation of Piperonyl Cyanide

<u>Catalyst</u>	<u>Solvent</u>	<u>Products</u>	<u>Yield</u>
Raney nickel	dioxane	homopiperonylamine	50%
		dihomopiperonylamine	25%
Raney nickel	ethanol-ammonia	homopiperonylamine	32%
Raney cobalt	dioxane	homopiperonylamine	79-87%
		dihomopiperonylamine	0-5%
Raney cobalt	ethanol-ammonia	homopiperonylamine	88%
Raney cobalt	anhydrous ethanol	homopiperonylamine	65-69%
		dihomopiperonylamine	10-15%

no ammonia the yield of primary amine increases considerably and the yield of secondary amine decreases. The yield of primary amine is greater if anhydrous dioxane is used as the solvent in place of anhydrous ethanol. In the presence of ammonia, Raney cobalt is again better than Raney nickel. It can be seen, that Raney cobalt without ammonia, using dioxane as the solvent, is as good as Raney nickel with ammonia. Thus, the use of Raney cobalt can eliminate the difficulties in the use of ammonia in carrying out these reductions, and still give good yields of primary amine. It might be noted that when ammonia was used, the reaction mixture had to be heated to a higher temperature (50-60° higher) before the reduction would start, than when no ammonia was used.

N-(3,4,5-trimethoxybenzoyl)homopiperonylamine (XXII) was first prepared by condensing XVI with 3,4,5-trimethoxybenzoyl chloride (IX) by a simple Schotten-Baumann procedure using 10 per cent aqueous sodium hydroxide<sup>43</sup>. The yields varied between 60 and 70 per cent of the theoretical amount. Another type condensation, as used by Slotta and Haberland<sup>46</sup>, was employed which gave better yields. The amine and acid chloride were dissolved in dry benzene and calcium oxide added to the mixture. Using this procedure, the yield was raised to 80 per cent of the theoretical amount. The amide (XXII) was cyclized by a Bischler-Napieralski<sup>6</sup> reaction, using phosphorous oxychloride in refluxing toluene, to the corresponding 1-(3',4',5'-trimethoxyphenyl)-6,7-methylene-dioxy-3,4-dihydroisoquinoline (XXIII) in 92 per cent of the



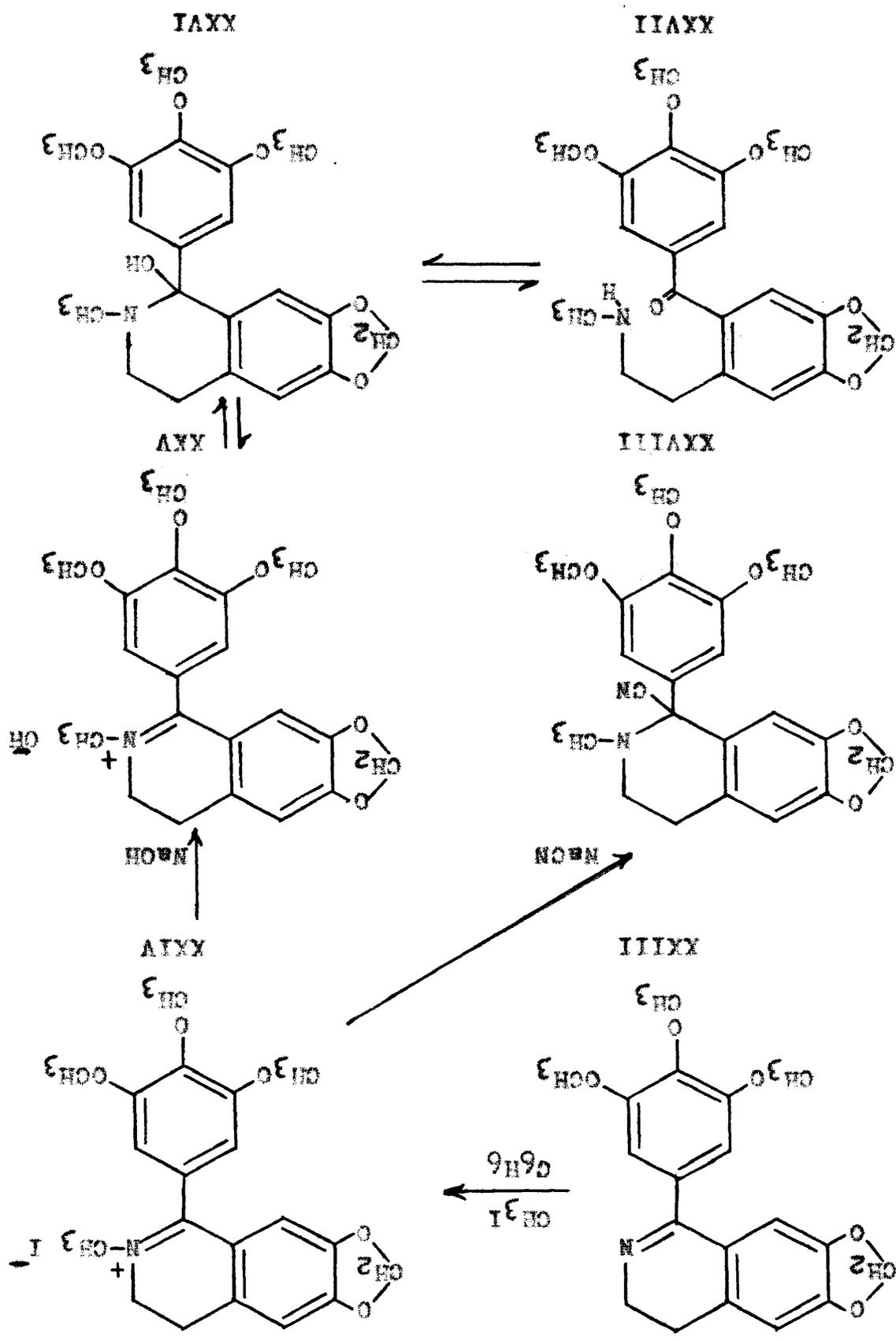
theoretical amount.

It was hoped that a direct oxidation of XXIII would lead to the keto acid (II) in good yield, by oxidation of the carbon to nitrogen double bond and degradation of the ethylamine side chain to a carboxyl group. Goss, Hanhart, and Ingold<sup>14</sup> have shown that the latter step occurs readily in  $\beta$ -phenethylamine compounds. In this case, however, competing reactions occur. Much of the dihydro compound is dehydrogenated to give the aromatized isoquinoline (VI). This stabilizes the heterocyclic ring and, in alkaline solution, the benzenoid rings are more readily attacked. The amount of potassium permanganate which is added to the reaction mixture is calculated to degrade compound XXIII to compound II, carbon dioxide, nitric oxide, and water. When the benzenoid rings are attacked, much of the oxidizing agent is destroyed by this competitive reaction. When compound XXIII is oxidized with the theoretical amount of potassium permanganate in a one to one tertiary butyl alcohol-water mixture under reflux, 17 per cent of the theoretical amount of the keto acid (II) is obtained, together with some trimethylgallie acid (VIII) and a smaller amount of unidentified acidic products. A considerable quantity of basic material, consisting of unchanged XXIII and the aromatized compound VI are also isolated. The 17 per cent yield would have been acceptable, but when the oxidation was run on a four times larger scale, the yield of keto acid dropped from 17 per cent to one per cent of the theoretical amount.

Oxidation procedures using chromic acid in acetic acid, lead tetraacetate in acetic acid, and nitric acid with vanadium pentoxide catalyst, gave none of the desired compound. The lead tetraacetate gave a quantitative recovery of the starting material.

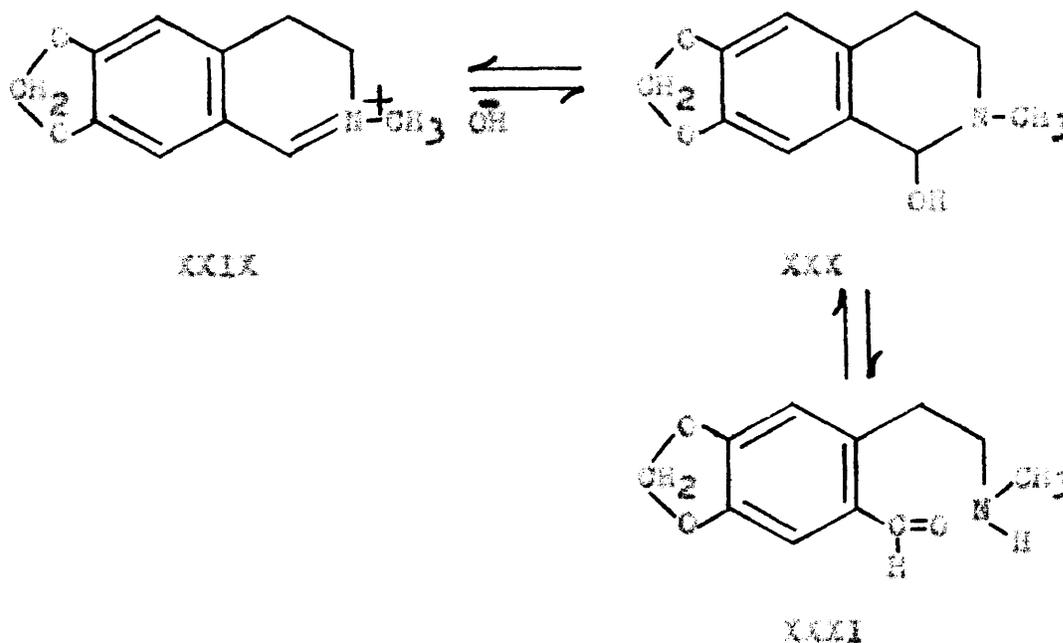
Potassium permanganate oxidations 1) at room temperature using one to one tertiary butyl alcohol-water solvent, 2) using an aqueous suspension of XXIII at 80°, 3) using vanadium pentoxide as a catalyst in the one to one tertiary butyl alcohol-water solvent, at reflux temperature, and 4) using 90 per cent tertiary butyl alcohol at reflux temperature, all gave much lower yields of the keto acid (II). On the basis of these experiments, all oxidations of the derivatives of XXIII were carried out under the conditions which gave the best yield with this compound. The one exception is the oxidation of VI, which was carried out in neutral solution using magnesium sulfate to maintain neutrality, as advised by Stevens and Robertson<sup>50</sup>. This gave no keto acid.

Compound XXIII was methylated using methyl iodide in benzene solution at room temperature<sup>10</sup>. Methylation with dimethyl sulfate, using the procedure of Bills and Noller<sup>5</sup>, gave materials which varied in melting point and analysis, between various runs. The methiodide (XXIV), however, was readily prepared in nearly quantitative yield and gave consistent melting points and an excellent analysis. Treatment of an aqueous solution of the methiodide with aqueous sodium hydroxide causes the pseudo-base (XXVI) to precipitate.



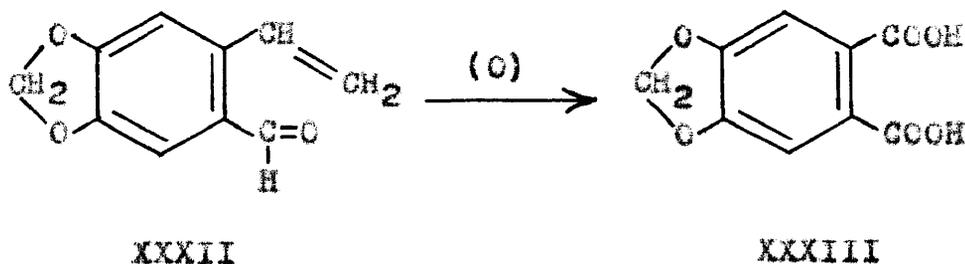
Oxidation of the pseudo-base gave 10 per cent of the theoretical amount of the keto acid but, once again, attempts to scale up the oxidation led to decreased yields.

The pseudo-base has a structure analagous to several of the naturally occurring isoquinoline alkaloids, one of which is hydrastinine (XXX).



Several investigators<sup>11,13,29</sup> have shown that this alkaloid can exist in three possible forms, the pseudo-base or carbinol form (XXX), the ionic ammonium form (XXIX) and an open chain carbonyl form (XXXI). The existence of the carbinol and ionic forms was shown by Dobbie and co-workers<sup>11</sup>, using adsorption spectra. The carbonyl form was identified by the preparation of an enil<sup>13</sup> and by base catalyzed condensation of the alkaloid with active methylene groups<sup>29</sup>. Exhaustive methylation of these condensation products and hydrolysis of the carbonyl derivatives gave the o-vinylaldehyde (XXXII)

which was readily oxidized to hydrastic acid (XXXIII).



It would appear that the same sort of ionic - carbinol - carbonyl equilibrium could exist as shown in compounds XXV, XXVI, and XXVII. Since the material precipitated by alkali was considered to consist of the non-ionic forms, it was added to give a more concentrated solution of the pseudo-base, which was only slightly soluble in pure benzene. Addition of excess methyl iodide gave a yellow compound, over a period of time, which proved to be identical with the methiodide (XXIV). This was explained by the fact that Dobbie<sup>11</sup> had found that alcoholic solutions of hydrastinine tended to exist largely in the ionic form. Here, a nucleophilic attack by the hydroxyl ion on the methyl iodide had caused an iodide ion to be generated and the methiodide had precipitated out of the benzene-alcohol solution.

Attempts to prepare carbonyl derivatives were failures. This is easily understood due to the benzophenone structure. Benzophenone is known to be unreactive toward carbonyl reagents, especially if there are any substituents in the positions ortho to the carbonyl. It was believed that the activating influence of the alkoxyl groups might overcome this effect and yield carbonyl derivatives of the compound,

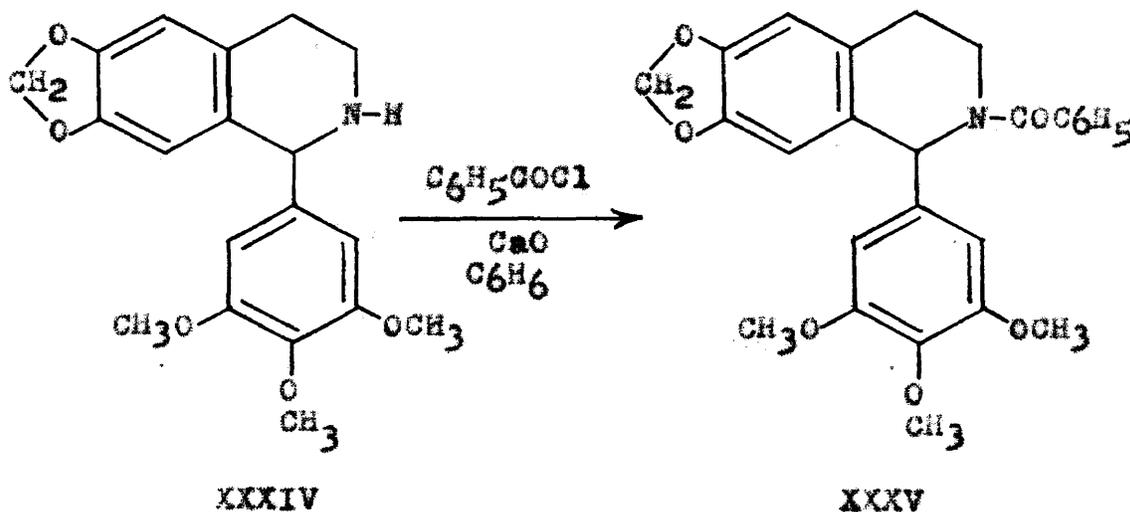
but this did not prove to be true. None of the desired products were obtained using the procedure of Freund<sup>13</sup> for the anil, the procedure of Liebermann<sup>29</sup> for the acetone condensation, and the procedure of Shriner and Fuson<sup>44</sup> for the 2,4-dinitrophenylhydrazone.

When these methods failed, a last attempt to open the heterocyclic ring was made by preparing the pseudo-cyanide (XXVIII), using sodium cyanide on the methiodide in aqueous solution<sup>16</sup>. This compound gave good analyses. An attempt to methylate it by the usual procedure gave inconclusive results.

When it appeared that an exhaustive methylation of the dihydroisoquinoline derivative (XXIII) could not be carried out satisfactorily, the heterocyclic ring was reduced to the tetrahydro stage. Compound XXIII was reduced using hydrogen at atmospheric pressure with platinum oxide catalyst in glacial acetic acid as the solvent<sup>2</sup>. A nearly quantitative yield of 1-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XXXIV) was obtained. Attempts to prepare XXXIV by high pressure hydrogenation of XXIII using Raney nickel as a catalyst in dioxane solution gave a mixture of products which could not be separated. In both of the high pressure reductions, the observed pressure drop was more than twice as great as the theoretical pressure drop calculated to reduce one double bond. The mixture of products must have been produced by reduction of one or both of the benzenoid rings, or portions thereof, as

well as the hydrogenation of the carbon to nitrogen double bond.

Oxidation of XXXIV in the usual manner gave no acidic products. Basic material was isolated from the oxidation and compound XXIII was identified as the hydrochloride. When this procedure failed to give the keto acid, it was decided that oxidation of an N-acyl derivative might prove to be better, as observed by Bamberger and Dieckmann<sup>4</sup> in the oxidation of tetrahydroisoquinoline. 1-(3',4',5'-trimethoxyphenyl)-2-benzoyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XXXV) was prepared from XXXIV and benzoyl chloride, using the procedure of Slotta and Haberland<sup>4,6</sup>.



Oxidation of XXXV gave a very small amount of the keto acid and a larger portion of neutral material which was not identified. An attempt to prepare an N-2,4-dinitrophenyl derivative of XXXIV, by following the procedure of Sanger<sup>39</sup> using 2,4-dinitrofluorobenzene and sodium bicarbonate, yielded a product which gave analyses that did not fit any reasonable

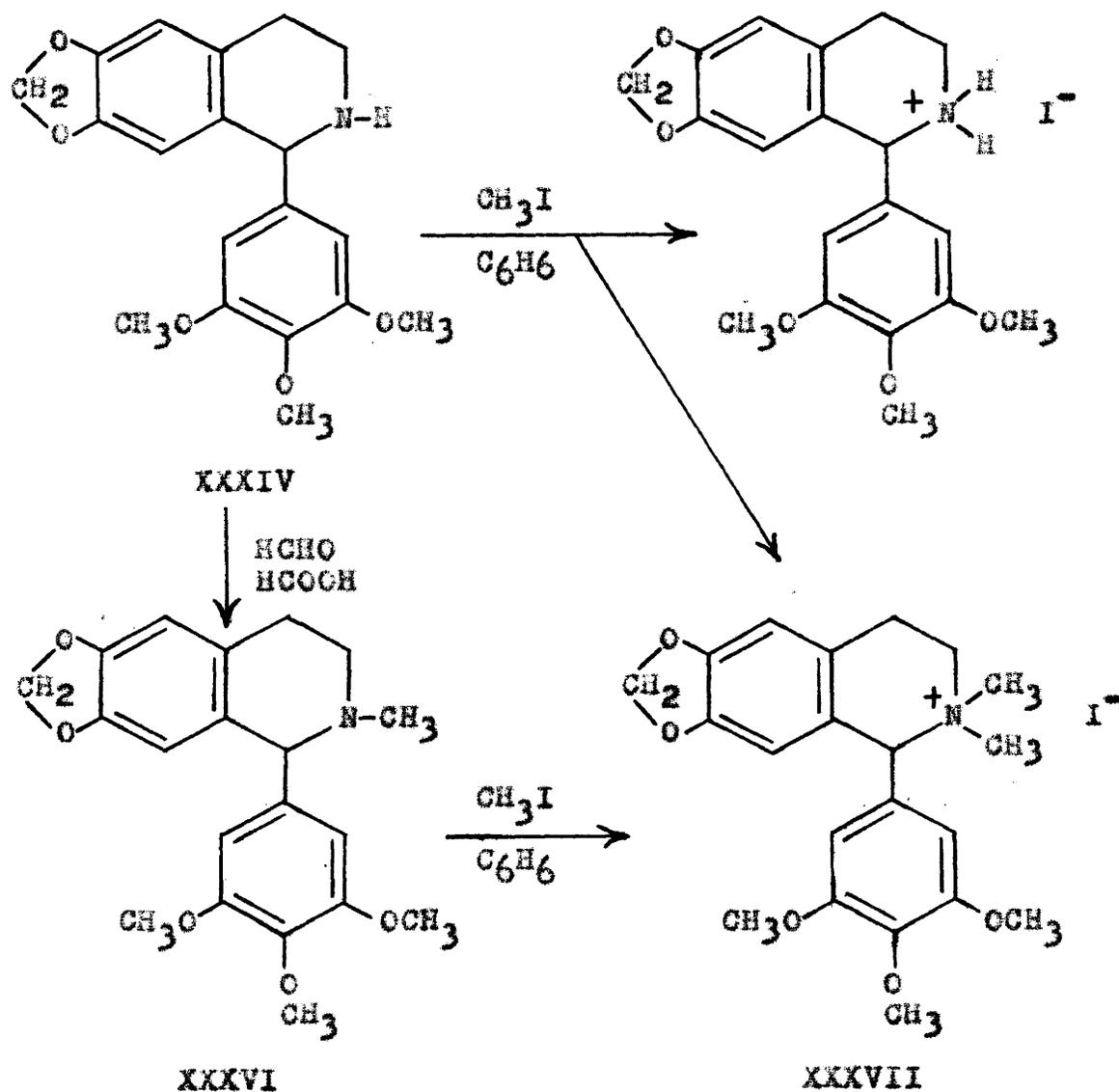
formula.

In order to carry out an exhaustive methylation of XXXIV, two methyl groups must be attached to the nitrogen atom. Attempts to methylate XXXIV using methyl iodide in a benzene solution, gave a mixture of products. It was assumed that the product would be the hydroiodide of 1-(3',4',5'-trimethoxyphenyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XXXVI). The yellow solid from the benzene solution was recrystallized from aqueous methanol as white needles which gave a sharp decomposition point and gave analyses for the hemi-hydrate of the expected compound. When the solid was dissolved in water and the solution made alkaline to precipitate the free tertiary base, the solid appeared to be compound XXIV from crystal form and melting point. The hydrochloride of this organic base, gave the same melting point and almost identical analyses as the hydrochloride of the tetrahydroisoquinoline (XXXIV). This seemed to indicate that if any methylation did occur, the hydrogen iodide was taken up by the secondary amine and the hydroiodide of the secondary amine precipitated from the solution, leaving the tertiary amine in solution. To prove that this was so, a much larger quantity of XXXIV was treated with excess methyl iodide and as the solid precipitated from the solution, it was filtered off periodically so that a series of six solid fractions was obtained. The various fractions were dissolved in water and treated with 50 per cent aqueous sodium hydroxide. The precipitate was recrystallized from ethanol. The first

fraction, after this treatment, proved to be the expected tetrahydroisoquinoline (XXXIV). The later fractions contained increasing quantities of a high melting compound which still contained iodine. This was believed to be the quaternary iodide (XXXVII) formed from XXVI, which remained in solution, and the excess methyl iodide. Fraction four was dissolved in ethanol and four volumes of ether were added. The white precipitate gave a good decomposition point, twelve degrees above that observed for the mixture described previously. It gave good analyses and the decomposition point agreed with that of 1-(3',4',5'-trimethoxyphenyl)-2,2-dimethyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolinium iodide (XXXVII) prepared by another procedure which gave only one product. A mixed melting point of the samples from the two sources showed no depression.

It was shown that the precipitation of the quaternary iodide from aqueous solution by the strong alkaline solution was a salting out effect. The same result was obtained by using a 50 per cent potassium iodide solution in place of the alkaline solution.

In order to get the intermediate tertiary amine (XXXVI), the methylation procedure of Clarke<sup>6</sup> was used. This involves treating the amine with formaldehyde and formic acid. The formic acid acts as a reducing agent and the formol derivative first produced is reduced by a disproportionation of the formyl ester, as shown below, to yield the N-methyl compound in 90 per cent of the theoretical amount. When



XXXVI is treated with methyl iodide in benzene, a quantitative amount of the quaternary iodide (XXXVII) is formed.



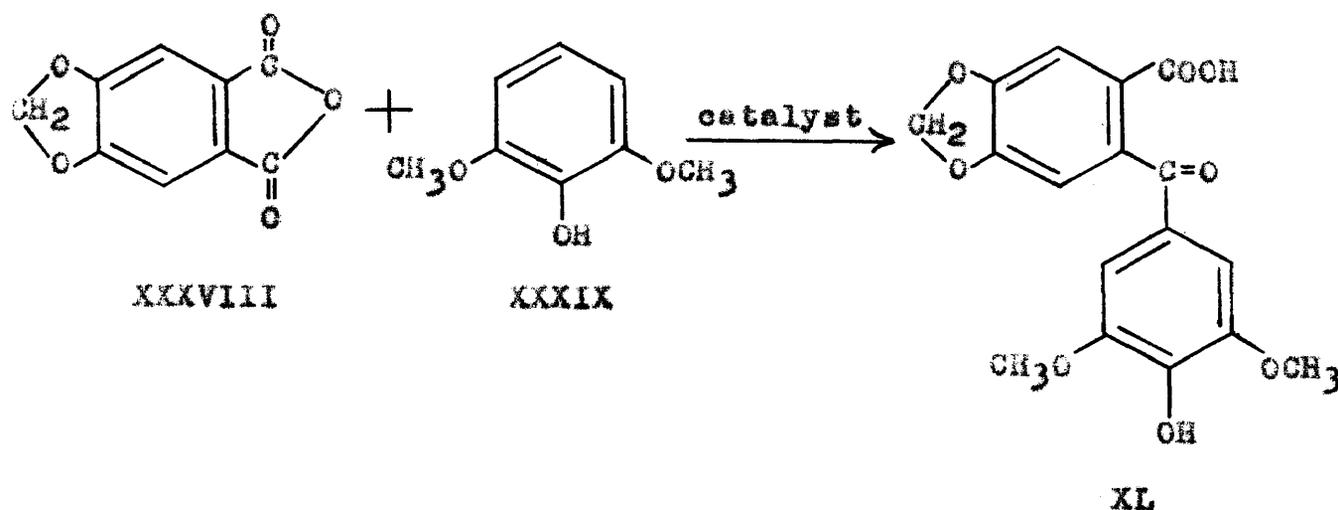
Oxidation of XXXVI could not lead to an aromatized heterocyclic ring, as in the case of the dihydro and

tetrahydroisoquinolines, without first removing the N-methyl group. When potassium permanganate oxidations were carried out, however, only a small amount of the desired keto acid was obtained. An appreciable amount of an alkali soluble compound containing nitrogen was obtained. After several recrystallizations, it gave analyses which would not fit any reasonable formula and is believed to be a mixture. While this solid was originally soluble in the alkaline reaction mixture after the manganese dioxide had been filtered off, it did not redissolve readily in alkali after precipitation with acid and drying.

Attempts to isolate the quaternary hydroxide were unsuccessful. When an aqueous solution of the quaternary iodide is treated with an equivalent amount of thalious hydroxide solution, thalious iodide precipitates, leaving an aqueous solution of the quaternary hydroxide. Evaporation of this solution in a desiccator over concentrated sulfuric acid or concentration of the solution under reduced pressure in an atmosphere of nitrogen, both led to glasses which could not be crystallized. A small portion of the glass was soluble in water and gave a weakly alkaline solution. The major portion was soluble in organic solvents. A carbon tetrachloride solution of the glass absorbed bromine rapidly and precipitated a yellow solid. A tertiary butyl alcohol solution reacted rapidly with potassium permanganate. This indicated a styrene derivative but time did not permit a complete exploration of this possibility.

Oxidation of the glass in one to one tertiary butyl alcohol-water solvent gave none of the desired keto acid, and only a small amount of neutral material. Direct oxidation of a solution of the quaternary hydroxide gave the same result. Another oxidation of the quaternary hydroxide was carried out after the solution was first refluxed for two hours, after removing the thalious iodide and before the potassium permanganate was added, in the hope that this might decompose the quaternary hydroxide. Again there was no recoverable amount of the keto acid.

An Alternative Friedel-Crafts Synthesis. Another possible preparation of the keto acid is through the Friedel-Crafts condensation of hydrastic anhydride (XXXVIII) and 2,6-dimethoxyphenol (XXXIX) to yield 4,5-methylenedioxy-2-(3',5'-dimethoxy-4'-hydroxybenzoyl)benzoic acid (XL). Methylation of the free phenolic hydroxyl group should yield the keto acid (II).



An initial attempt to prepare the condensation product, XL, has been made using stannic chloride as both the catalyst and solvent. This was unsuccessful.

## EXPERIMENTAL

All melting points are corrected.

Preparation of Piperonyl Alcohol (XIX). The method of Reeve and Sterling<sup>36</sup> was used in this preparation. Yields varied from 92 to 99 per cent. On two occasions the yields were 10 and 22 per cent. Since most of the reaction mixture would not distill, it was assumed that oxidation had occurred during distillation of the product. The piperonal was redistilled before reduction and the next reaction mixture distilled under nitrogen. The yield rose from 22 per cent to 92 per cent of the theoretical amount. All further reductions were run under these conditions.

Preparation of Trimethylgallic Acid (VIII). This procedure is the same as that outlined by Mauthner<sup>30</sup> with the exceptions that an extra portion of alkali was added and the yield has been increased. Two hundred and fifty grams (1.47 mole) of gallic acid were dissolved in a solution of 400 grams of sodium hydroxide in 2.5 liters of water, maintaining the temperature below 35°. Six hundred and seventy ml. of dimethyl sulfate were added over a period of three hours, maintaining the temperature below 35° for two hours and then allowing it to rise to 50° as the last 200 ml. of dimethyl sulfate were added. The mixture was heated under reflux for two hours and then 100 grams of sodium hydroxide in 150 ml. of water were added. After another two hours of heating, the solution was still strongly acid, so an additional 50 grams of sodium hydroxide in 100 ml. of water were added and

the solution heated for two more hours to insure the saponification of any ester that may have formed. The solution was acidified with 1:1 hydrochloric acid and the precipitated acid was filtered off. The solid was heated with 1.5 liters of water to remove any salts which may have coprecipitated and the tan colored acid filtered off and dried. The yield is 255 grams (1.20 mole), 82 per cent of the theoretical amount. M.p. 166-169°.

Preparation of Trimethylgalloyl Chloride (IX). The method of Asano and Yamaguti<sup>3</sup> was used in this preparation. One hundred and forty grams (.66 mole) of trimethylgallic acid (m.p. 166-169°) was dissolved in 650 ml. of dry benzene and 200 ml. of thionyl chloride was added. The mixture was refluxed for four hours and the solvents evaporated at water pump pressure. The acid chloride distilled at 138-139° at 2 mm. pressure and melted at 77-78°. The reported values<sup>3</sup> are 130° at 2 mm. for the boiling point and a melting point of 77-78°. The yield is 142.3 grams (.617 mole), 93.5 per cent of the theoretical amount. The yields in smaller runs ranged from 85 to 93 per cent.

Preparation of Ethyl  $\alpha$ -3,4,5-Trimethoxybenzoylacetate (X). The directions of Perkin and Weizmann<sup>34</sup> were followed except that the amounts were increased, using 0.76 mole of trimethylgalloyl chloride. The yield of material was about 35 per cent of the theoretical amount, with some deacetylation having taken place. M.p. 85-86°, (reported<sup>22</sup> 85°).

Preparation of Ethyl 3,4,5-Trimethoxybenzoylacetate (XI).

Continuing with the procedure of Perkin and Weizmann<sup>34</sup>, ethyl  $\alpha$ -3,4,5-trimethoxybenzoylacetate (X) was deacetylated in a yield of 91 per cent of the theoretical amount. The material melted 89-90° after successive recrystallizations from methanol and cyclohexane, whereas the reported<sup>34</sup> value is 95°.

<u>Analyses</u>	<u>Calculated for C<sub>14</sub>H<sub>18</sub>O<sub>6</sub></u>	<u>Found</u>
Carbon	59.57%	59.49% 59.69%
Hydrogen	6.43%	6.47% 6.53%
Methoxyl	43.97%	43.74% 44.34%

Preparation of 3,4,5-Trimethoxy- $\omega$ -(3',4'-methylene-dioxybenzyl)acetophenone (VII). The method of Sterling<sup>49</sup> was used but the yield was only 43 per cent of the theoretical amount as compared to 55 per cent reported by Sterling. M.p. 144.5-145.5°, (reported<sup>36</sup>, 146-147°).

<u>Analyses</u>	<u>Calculated for C<sub>19</sub>H<sub>20</sub>O<sub>6</sub></u>	<u>Found</u>
Carbon	66.25%	66.17% 66.12%
Hydrogen	5.85%	6.01% 5.95%
Methoxyl	27.00%	27.02% 26.88%

Attempted Cyclizations of 3,4,5-Trimethoxy- $\omega$ -(3',4'-methylenedioxybenzyl)acetophenone (VII) to 1-(3',4',5'-Trimethoxyphenyl)-5,6-methylenedioxy-1-hydrindene (IV).

1) Liquid Hydrogen Fluoride. Five grams (.0145 mole) of 3,4,5-trimethoxy- $\omega$ -(3',4'-methylenedioxybenzyl)acetophenone (VII) were placed in a copper flask and, after cooling to  $-10^{\circ}$  in an ice salt bath, 70 grams of anhydrous liquid hydrogen fluoride were added to the flask. The flask was permitted to warm up slowly to room temperature and the hydrogen fluoride allowed to evaporate. The residual solid was black and looked like coarse charcoal. The lumps melted on a hot plate, however, so they were crushed to a powder and extracted with various solvents. Benzene extracted a deep blue color but no solid could be obtained from the benzene solution. Ethanol gave a deep red colored extract but again only a small amount of tar could be obtained from the solution. The procedure was then abandoned.

2) Phosphorous Pentoxide. Three and four tenths grams (.010 mole) of compound VII were dissolved in 100 ml. of anhydrous benzene and 10 grams of phosphorous pentoxide were added. The solution was stirred and refluxed for three hours during which time the solution changed from colorless to pink to purple. The solution was cooled and filtered. Concentration of the benzene solution to 50 ml. gave 1.0 gram of starting material, m.p. and mixed m.p. with compound VII  $143.5-144.3^{\circ}$ . Further concentration and subsequent treatment with ethanol and water yielded another 1.0 gram of material,

melting 138-145°, which was mostly starting material.

3) Stannic Chloride. Compound VII (3.4 grams) (.010 mole) was dissolved in 125 ml. of carbon disulfide and added dropwise to a solution of 10 grams of stannic chloride in 50 ml. of carbon disulfide. This was refluxed for six hours and allowed to cool. On standing overnight, brown crystals came out which would not redissolve on heating the reaction mixture under reflux. The reaction mixture was treated with hydrochloric acid and ice water to destroy the stannic chloride and then excess 10 per cent sodium hydroxide added until all the stannic hydroxide redissolved. The carbon disulfide layer was extracted three times with water, then dried over calcium chloride. The carbon disulfide was evaporated and the residual yellow oil crystallized from ethanol. Two and five tenths grams were obtained, m.p. 141-144°, which showed no depression in mixed m.p. with compound VII.

4) Concentrated Sulfuric Acid. One and seven tenths grams (0.005 mole) of compound VII was added to 50 cc. of concentrated sulfuric acid cooled to -30°. The solution turned deep red immediately and then slowly to brown. The reaction was continued for one half hour at -15 to -30° and was then neutralized by slowly pouring into concentrated sodium hydroxide solution at -25°. The neutralization procedure was carried out entirely below 0°. The solid was filtered off and extracted with ether and benzene to remove any organic material from the sodium sulfate. Concentration of these solutions gave no crystalline products. The alkaline filtrate

was acidified and then extracted with benzene. The brown colored benzene solution gave only tars which could not be crystallized.

5) Phosphorous Pentachloride. Three and four tenths grams (0.01 mole) of compound VII were dissolved in 30 ml. of boiling benzene and a suspension of 6.0 grams (.03 mole) of phosphorous pentachloride in 30 ml. of dry benzene was added. The mixture was refluxed for one hour and then decomposed by adding 5 per cent ammonium hydroxide until neutral. The aqueous layer was extracted with benzene; the extract dried over magnesium sulfate and taken to dryness. The viscous oil would not crystallize from acetone, petroleum ether, ethanol, or carbon disulfide. Finally, the oil was dissolved in 25 ml. of carbon disulfide and added to a solution of ten grams of stannic chloride in 100 ml. of carbon disulfide. This was worked up as described for the stannic chloride procedure but yielded no crystalline products.

6) p-Toluenesulfonic Acid. Compound VII (5.16 grams) (0.15 mole) was added to a solution of 1.72 grams (.010 mole) of p-toluenesulfonic acid dissolved in 100 ml. of dry benzene. The refluxing benzene was passed through an azeotropic distillation trap but in 72 hours only one half of the theoretical amount of water came off and only black tars were isolated from the reaction mixture.

7) Phosphorous Oxychloride. One and seven tenths grams (.005 mole) of compound VII were heated under reflux with 20 ml. of phosphorous oxychloride in 25 ml. of toluene for 24 hours. The solution became deep purple in color. The

majority of the material was lost due to an accident in working up the reaction mixture, but the small amount recovered proved to be starting material, m.p.  $144-146^{\circ}$  after recrystallizing from ethanol.

Preparation of  $\beta$ -3,4,5-Trimethoxybenzoylpropionic Acid (XIII). Sodium metal (1.47 grams) (.064 gram atom) was dissolved in 50 ml. of absolute ethanol. Twenty grams (.071 mole) of ethyl 3,4,5-trimethoxybenzoylacetate (XI) and 100 ml. of ethanol were added. The ester slowly dissolved. The clear solution was cooled in an ice bath and 12.5 grams (.075 mole) of ethyl bromoacetate in 30 ml. of ethanol was added. No sodium bromide precipitated after 45 minutes in the ice bath, so the mixture was allowed to warm up to room temperature. After another hour, sodium bromide began to precipitate. The flask was warmed to  $40^{\circ}$  and maintained at that temperature in an oil bath for 24 hours. The reaction mixture was diluted 4 to 1 with water and extracted with three 250 ml. portions of ether. The ether was evaporated and the residual oil refluxed with 20 per cent sulfuric acid for 48 hours. The hydrolysis mixture was extracted with three 150 ml. portions of ether and the ether removed. The oil was heated with 60 ml. of methanol and 25 ml. of 10 per cent potassium hydroxide for 45 minutes. This was diluted 8 to 1 with water and extracted with three 200 ml. portions of ether to remove the neutral components. The aqueous layer was acidified and extracted four times with 200 ml. portions of ether. Evaporation of the ether gave 9.9 grams (.37 mole) of impure acid.

This, recrystallized from benzene, gave 5.4 grams (.0202 mole) of pure XIII, m.p. 119.5-121.5° (reported<sup>22</sup>, 121-122°), or 31.6 per cent of the theoretical amount, based on sodium metal. The neutral material was largely 3,4,5-trimethoxyacetophenone (XIV), m.p. 73-76° (reported<sup>7</sup>, 77°); p-nitrophenylhydrazone, m.p. 196-197° (reported<sup>31</sup>, 195-196°). The compound gives a deep red-violet 2,4-dinitrophenylhydrazone, m.p. 242.7-243.3°.

<u>Analyses</u>	<u>Calculated for C<sub>17</sub>H<sub>18</sub>O<sub>7</sub>N<sub>4</sub></u>	<u>Found</u>
Carbon	52.30%	52.23% 52.40%
Hydrogen	4.65%	4.73% 4.72%
Nitrogen	14.36%	14.35% 14.35%
Methoxyl	23.85%	24.08% 24.08%

Another run using 0.26 gram atom of sodium to 0.18 mole of ethyl 3,4,5-trimethoxybenzoylacetate gave none of the desired acid that could be isolated. The recovered acidic material, melting 155-165° after sintering at 145°, proved to be mostly trimethylgallic acid after recrystallizing from water, m.p. 169-170°.

<u>Analyses</u>	<u>Calculated for C<sub>10</sub>H<sub>12</sub>O<sub>5</sub></u>	<u>Found</u>
Carbon	56.60%	56.42% 56.73%
Hydrogen	5.70%	5.72% 5.82%
Methoxyl	43.87%	43.73% 43.86%

Preparation of  $\alpha$ -3,4-Methylenedioxybenzal- $\beta$ -3',4',5'-trimethoxybenzoylpropionic Acid (As the Enol Lactone) (XV).

Compound XIII (5.4 grams) was triturated with 10 ml. of water and neutralized with 10 per cent potassium hydroxide solution. All the acid went into solution. The solution was evaporated to dryness and the solid potassium salt pulverized. This was mixed with 6.5 grams of piperonal (XVI) and 13.5 ml. of acetic anhydride and heated on the steam cone under a reflux condenser for two hours. Addition of 200 ml. of water caused the liquid mass to slowly turn solid. The solid was filtered off, washed twice with water and three times with 50 ml. portions of methanol. The residue was dried in a desiccator. The yield of impure material was 4.0 grams (.01 mole) or 50 per cent of the theoretical amount. The material was recrystallized from methanol-chloroform as yellow-brown needles, m.p. 161-163.5° (reported<sup>22</sup>, 161-162°). The purified material weighed 2.2 grams (.0055 mole), 27.5 per cent of the theoretical amount. The following analyses were obtained for the lactone (XV).

<u>Analyses</u>	<u>Calculated for C<sub>21</sub>H<sub>18</sub>O<sub>7</sub></u>	<u>Found</u>
Carbon	65.95%	66.08% 65.86%
Hydrogen	4.75%	4.94% 4.96%
Methoxyl	24.35%	24.58% 24.38%

Preparation of 3,4-Methylenedioxy- $\omega$ -nitrostyrene (XVII).

The procedure outlined in Organic Syntheses<sup>52</sup> for  $\omega$ -nitrostyrene was followed in this preparation, with piperonal (XVI)

being substituted for benzaldehyde. The yield from a two mole run was 86 grams (23 per cent of the theoretical amount) after recrystallization from 95 per cent ethanol. M.p. 156-159° (reported<sup>26</sup>, 158-159°). The compound is light sensitive, changing from a bright yellow to a maroon color on exposure to sunlight. It can be stored for several weeks in a brown bottle without discoloration.

Preparation of Catalysts. The Raney nickel catalyst was prepared by the procedure of Adkins and Billica<sup>1</sup> for the W-7. Preparation of Catalysts. The Raney nickel catalyst was prepared by the procedure of Adkins and Billica<sup>1</sup> for the W-7<sup>1</sup> in the same manner, using a 40 per cent cobalt-60 per cent aluminum alloy in place of the nickel-aluminum alloy. The alloy was ground to pass a 100 mesh sieve before it was used in the preparation of the catalyst. The palladium oxide catalyst was first reduced in acetic acid as the solvent before the nitro compound was introduced. The platinum oxide catalyst was reduced in the reaction mixture.

Reduction of 3,4-Methylenedioxy-*o*-nitrostyrene (XVII).

1) Raney Nickel. Compound XVII (19.3 grams, 0.1 mole) was dissolved in 100 ml. of anhydrous dioxane by warming on a steam bath. The solution was placed in a 300 ml. steel hydrogenation vessel and about two grams of Raney nickel catalyst were added. Hydrogen was admitted to the vessel until a pressure of 2500 pounds per square inch was reached. The vessel was then rocked and heated to 125°. The theoretical amount of hydrogen was adsorbed in 30 minutes and there was no observed drop over the next 30 minutes. The vessel was

washed out with ethanol, and, after filtering off the catalyst, the solvents were removed at water pump pressure under an atmosphere of nitrogen. Homopiperonylamine (XVIII) distilled as a water white liquid from 154-156° at 22 mm. pressure, but only 1.9 grams (10 per cent of the theoretical amount) distilled from the mixture. The amine rapidly turned to a white solid in the air, forming a carbamate which melted 104-109° (reported<sup>9</sup>, 110°, not sharp melting). It readily formed a hydrochloride when dry hydrogen chloride was added to an ether solution of the amine. M.p. 206-207° (reported<sup>38</sup>, 207-208°). The nonvolatile residue was dissolved in benzene and treated with dilute hydrochloric acid. A black tarry solid precipitated. The tar was dissolved in acetone, leaving behind a white solid which recrystallized from water or ethanol and melted 261-262°. This showed no depression in melting point when mixed with an authentic sample of dihomopiperonylamine hydrochloride, m.p. 261-262°.

2) Raney Cobalt. The same procedure was followed as in the first reduction, except that the Raney nickel catalyst was replaced with an equal amount of Raney cobalt catalyst. The yield of primary amine was raised to 26 per cent of the theoretical amount, obtaining 4.3 grams of amine from 19.3 grams of the nitrostyrene.

3) Platinum Oxide. Compound XVII (10 grams, 0.05 mole) was dissolved in 130 ml. of anhydrous dioxane and three milliliters of concentrated sulfuric acid were added. The solution was placed in a shaker bottle together with 0.7 grams

of platinum oxide catalyst. The air was removed from the bottle by suction and the bottle was filled with hydrogen. The bottle was then shaken under one atmosphere pressure of hydrogen until no more hydrogen was absorbed. Only 76 per cent of the theoretical amount of hydrogen was taken up. The catalyst was removed by filtration and the solvent was distilled off under vacuum. The residue was taken up in ether and shaken with five per cent sodium hydroxide solution to remove the sulfuric acid. The ether solution was dried over anhydrous potassium carbonate and the ether distilled off. Nothing would distill out of the residue under reduced pressure with the oil bath at 225°. Heating with a direct flame caused rapid decomposition and no primary amine was isolated.

4) Palladium Oxide. Ten grams of XVII were dissolved in 200 ml. of glacial acetic acid. This was added to one gram of the reduced palladium catalyst and three milliliters of concentrated sulfuric acid were added. The mixture was shaken under one atmosphere pressure of hydrogen and 70 per cent of the theoretical amount of hydrogen was consumed. The product was worked up following the procedure of Kindler<sup>24</sup> but no primary amine was isolated.

Preparation of Piperonyl Cyanide (XXI). Piperonyl alcohol (XIX) (152 grams, 1.0 mole) was shaken in a separatory funnel with 250 ml. of concentrated hydrochloric acid. The hydrochloric acid layer was saturated with calcium chloride and the organic layer separated. The acid layer was extracted twice with 100 ml. portions of benzene and the mixed organic

layers were added over the period of an hour to a stirred solution of 175 grams (3.5 moles) of sodium cyanide and six grams (.025 mole) of mercuric cyanide in 265 ml. of water. The mixture was maintained at a temperature of 75 to 80° for seven hours and cooled to room temperature. Fifteen hundred milliliters of water were added and the layers were separated. The water layer was extracted with two 500 ml. portions of benzene and the mixed organic layers were washed once with 1000 ml. of water. The benzene was removed at water pump pressure and the nitrile distilled at 138-142° at 1-3 mm. pressure. The yield was 139 grams (86.3 per cent of the theoretical amount) of liquid which slowly solidified. It remelted at 38-40° and resolidified slowly in large cubic crystals. The literature reports the boiling point as 153-156° at 10 mm.<sup>42</sup> and 159° at 17 mm.<sup>32</sup> and the melting point<sup>32</sup> as 42° after recrystallizing from alcohol. A reaction run without using the mercuric cyanide catalyst gave a 76 per cent yield but the product contained a large amount of halide. Purification brought the yield to below 70 per cent.

A small amount of the nitrile was hydrolyzed by boiling with 20 per cent sodium hydroxide. Homopiperonylic acid (m.p. 126-128°, reported<sup>51</sup>, 129°) was isolated in 80 per cent of the theoretical amount.

Attempt to Isolate Piperonyl Chloride (XX). An attempt was made to distill the chloride after preparation from the alcohol by the described method. The benzene was removed at water pump pressure but nothing more distilled at two mm.

pressure even at a bath temperature of 225°. At this temperature the liquid in the distilling flask solidified and gave off copious quantities of white fumes. This solid was insoluble in water and all organic solvents, but a portion was scraped from the flask and washed by boiling with acetone and then with ethanol. The white fibrous material would not melt at 350° so was assumed to be 2,3,6,7-bis methylenedioxy-9,10-dihydroanthracene. This is reported by several investigators<sup>12,37</sup> who found that it did not melt at 360°. The following analyses were obtained.

<u>Analyses</u>	<u>Calculated for C<sub>16</sub>H<sub>12</sub>O<sub>4</sub></u>	<u>Found</u>
Carbon	71.64%	71.70% 71.74%
Hydrogen	4.51%	4.69% 4.61%

A considerable amount of the nonvolatile residue from the uncatalyzed nitrile preparation proved to be this compound.

Reduction of Piperonyl Cyanide (XXI).

1) Raney Nickel.

a) Ethanol-Ammonia Solvent. Piperonyl cyanide (71.8 grams, 0.446 mole), 40 ml. of absolute ethanol and 2 grams of Raney nickel catalyst were placed in a steel hydrogenation vessel and cooled in a dry ice-acetone bath. A graduate was placed in the cooling bath and 50 ml. of liquid ammonia were collected in it. The ammonia was placed in the vessel and the head and cap securely fastened. Hydrogen was admitted to the vessel at room temperature until a pressure

of 3200 pounds per square inch was reached. The vessel was shaken and heated to  $160^{\circ}$  before hydrogen uptake was noted. The pressure dropped rapidly and the temperature rose to  $170^{\circ}$ . The theoretical amount of hydrogen was absorbed in 15 minutes. The vessel was washed out with ethanol and the catalyst filtered off. The solvents were removed at water pump pressure and the amine was distilled at  $118-126^{\circ}$  from 2-10 mm. pressure. The water white liquid weighed 60.2 grams (.365 mole) or 82 per cent of the theoretical amount.

b) Dioxane Solvent. Piperonyl cyanide (42.0 grams, .261 mole) was dissolved in 100 ml. of purified dioxane and after placing the solution in the steel hydrogenation vessel with 2 grams of Raney nickel catalyst, the reduction procedure was carried out as above. The reduction started at  $100^{\circ}$  but the vessel was heated to  $150^{\circ}$  as the reaction proceeded. The theoretical amount of hydrogen was consumed in 12 minutes. The product was worked up as before and the amine distilled at  $136-139^{\circ}$  at 21 mm. pressure, but only 21.6 grams (50 per cent of the theoretical amount) could be distilled. The nonvolatile residue was dissolved in ether and dry hydrogen chloride was added to precipitate the amine. The pale tan precipitate was recrystallized from ethanol-water solvent after decolorizing with activated carbon. The white crystalline solid weighed 11.3 grams and melted and decomposed at  $255-258^{\circ}$ . After two more recrystallizations it melted  $261-262^{\circ}$ .

<u>Analyses</u>	<u>Calculated for <math>C_{18}H_{20}O_{1/4}NCl</math></u>	<u>Pound</u>
Carbon	61.82%	62.08% 62.08%
Hydrogen	5.73%	5.95% 5.74%
Nitrogen (Dumas)	4.00%	4.17% 4.14%

Since two moles of nitrile are required to form one mole of dihomopiperonylamine, the 11.3 grams or .0323 mole of amine hydrochloride represent .0646 mole of nitrile or 25 per cent of the starting material.

## 2) Raney Cobalt.

a) Methanol-Ammonia Solvent. The same procedure was followed as that for Raney nickel in 1-a with the exceptions that Raney cobalt catalyst was used in place of the nickel catalyst, and 61.5 grams of nitrile were used. The reaction proceeded more slowly and the theoretical amount of hydrogen was taken up in 90 minutes at 150°. The reduction began at 125° but since it was so slow, the higher temperature was used. The homopiperonylamine distilled at 123-126° at 8-10 mm. pressure and weighed 55.4 grams (88 per cent of the theoretical amount).

b) Dioxane Solvent. The same procedure was used here as in 1-b, with Raney cobalt replacing Raney nickel as the catalyst. In three runs, each using 70 grams of nitrile, yields of 79, 82, and 87 per cent of the theoretical amount were obtained. In each case the reduction started between 75 and 90° and was complete in 20 minutes, the temperature reaching 140° since heating was continued even after the

reduction started. The reduction which gave a 79 per cent yield of primary amine, also yielded about five per cent of secondary amine, isolated in the usual fashion.

c) Anhydrous Ethanol Solvent. The same procedure as in 2-b was followed except that anhydrous ethanol was substituted for dioxane as the solvent. In two runs of 70 grams each, the yields were 65 and 69 per cent of the theoretical amount. A total of 15 grams of dihomopiperonylamine hydrochloride was isolated from the combined nonvolatile residues from these reductions. This gives an average of 13 per cent of the starting material which was converted to the secondary amine.

Preparation of N-3,4,5-Trimethoxybenzoylhomopiperonylamine (XXII).

1) Aqueous Sodium Hydroxide<sup>43</sup>. Homopiperonylamine (XVIII) (62 grams, .375 mole) and 86.5 grams (.375 mole) of trimethylgalloyl chloride (IX) were added to a solution of 85 grams of sodium hydroxide dissolved in 600 ml. of water. The liter flask was placed in a shaking machine and agitated for two and one half hours. The fluffy white solid was filtered off and washed well with water. After drying, the solid weighed 95.4 grams (71 per cent of the theoretical amount) and melted 134-135.5°. A snow white solid melting 135.5-136° was obtained after two recrystallizations from 95 per cent ethanol.

<u>Analyses</u>	<u>Calculated for C<sub>19</sub>H<sub>21</sub>O<sub>6</sub>N</u>	<u>Found</u>
Carbon	63.50%	63.79% 63.57%
Hydrogen	5.89%	6.03% 5.91%
Nitrogen	3.90%	4.04% 3.97%
Methoxyl	25.92%	25.74% 25.98%

2) Calcium Oxide in Benzene<sup>46</sup>. Homopiperonylamine (102 grams, .616 mole) was dissolved in 600 ml. of dry benzene and 142 grams (.616 mole) of trimethylgalloyl chloride were dissolved in 600 ml. of dry benzene. The two benzene solutions were mixed with stirring, in a three necked flask which was equipped with a condenser and automatic stirrer. The solution immediately became a thick pasty mass which was still fluid enough to stir. Calcium oxide, which had been crushed to pass a 150 mesh sieve, was added in portions until a total of 55 grams had been added over a period of 90 minutes, maintaining the temperature of the reaction mixture between 75 and 80°. The suspension became much more fluid as the reaction proceeded. The mixture was filtered while hot and the benzene solution allowed to cool. The white solid which came down was filtered and dried, yielding 53.5 grams of the amide, m.p. 133.5-135.5°. Concentration of the benzene solution to 100 ml. yielded 18.4 grams, melting 130-134°. The original solid from the reaction mixture, containing calcium salts and the amide, was extracted with 1500 ml. of boiling

95 per cent ethanol and filtered. The filtrate, on cooling, yielded 61.6 grams of amide melting 135-136°. Concentration of the ethanol solution, eventually to 150 ml., gave another 42.7 grams of amide, m.p. 134-136°. The total yield is 176 grams (.490 mole) or 80 per cent of the theoretical amount.

Preparation of 1-(3',4',5'-Trimethoxyphenyl)-6,7-methylene-dioxy-3,4-dihydroisoquinoline (XXIII). One hundred and eighty grams (0.500 mole) of N-3,4,5-trimethoxybenzoylhomopiperonylamine (XXII) was placed in a three liter flask and 400 ml. of phosphorous oxychloride and 1000 ml. of dry toluene were added. The mixture was heated under reflux for three hours, the solution becoming a deep yellow-brown in color and some bright yellow solid precipitating. The solution was cooled to room temperature and poured into two liters of petroleum ether (b.p. 60-80°). After standing one half hour, the petroleum ether was decanted and the gummy solid was heated with 500 ml. of 95 per cent ethanol. Most of the solid went into solution and slowly came out as a bright yellow powder. The solid weighed 169 grams (.448 mole) (90 per cent of the theoretical amount), and melted 234-236° with decomposition. Addition of eight volumes of ether to the alcohol solution, after concentrating to 100 ml., gave an additional 3.5 grams, m.p. 233-235° with decomposition. A small portion was dissolved in hot water and the solution was made alkaline with sodium hydroxide. The white solid recrystallized from ethanol-water in fine white needles, m.p. 159.5-160°.

<u>Analyses</u>	<u>Calculated for C<sub>19</sub>H<sub>19</sub>O<sub>5</sub>N</u>	<u>Found</u>
Carbon	66.83%	66.91% 66.99%
Hydrogen	5.61%	5.66% 5.84%
Nitrogen	4.10%	4.17% 4.19%
Methoxyl	27.27%	27.02% 26.99%

A portion of the recrystallized free base was dissolved in absolute ether and dry hydrogen chloride was added. The bright yellow solid recrystallized from ethanol-ether as a fine powder, m.p. 235.5-236°.

<u>Analyses</u>	<u>Calculated for C<sub>19</sub>H<sub>20</sub>O<sub>5</sub>NCl</u>	<u>Found</u>
Carbon	60.41%	60.66% 60.75%
Hydrogen	5.34%	5.48% 5.50%
Nitrogen	3.71%	3.76% 3.75%
Methoxyl	24.65%	24.63% 24.74%

Oxidation of 1-(3',4',5'-Trimethoxyphenyl)-6,7-methylene-dioxy-3,4-dihydroisoquinoline (XXIII).

1) Potassium Permanganate.

a) 1:1 Tertiary Butyl Alcohol-Water Solvent at Reflux Temperature. Compound XXIII (6.2 grams, .018 mole) was dissolved in 150 ml. of tertiary butyl alcohol and 150 ml. of water were added. The solution was stirred and heated until

the solvent began to reflux, and five grams of solid sodium hydroxide and 11 grams of solid potassium permanganate were added. The heating and stirring were continued for 18 hours until all of the purple color was gone. The manganese dioxide was filtered off and washed well with hot water. To the filtrate was added 500 ml. of water and the milky suspension was extracted twice with 100 ml. portions of ether. The ether layer was evaporated to dryness. The basic material weighed 3.5 grams and melted 112-115°. This basic material was again dissolved in ether and dry hydrogen chloride was added. The yellow solid melted 245-248° with decomposition. After two recrystallizations from ethanol, the solid was nearly white and melted 252-253°. Analyses showed that this was 1-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxyisoquinoline (VI).

<u>Analyses</u>	<u>Calculated for <math>C_{19}H_{18}O_5NCl</math></u>	<u>Found</u>
Carbon	60.73%	60.80% 61.08%
Hydrogen	4.83%	5.07% 5.08%
Nitrogen	3.73%	3.87% 3.92%
Methoxyl	24.78%	24.75% 24.73%

The aqueous layer, after the ether extractions, was acidified by adding sulfur dioxide to the alkaline solution. As the solution became acid, a fluffy white solid was precipitated. This acidic material weighed 1.1 grams and melted

208-211°. Two recrystallizations from aqueous methanol gave 0.9 grams melting 215-216°. This is the keto acid (II) whose reported<sup>47</sup> melting point is 214-216°.

<u>Analyses</u>	<u>Calculated for C<sub>18</sub>H<sub>16</sub>O<sub>8</sub></u>	<u>Found</u>
Carbon	60.00%	60.32% 60.16%
Hydrogen	4.48%	4.81% 4.76%
Methoxyl	25.84%	25.87% 25.68%

After removing the keto acid, the aqueous layer was extracted twice with 100 ml. portions of ether. The ether was evaporated, leaving 0.3 grams of yellow solid melting 158-165°. After dissolving the solid in hot water and treating the solution once with activated carbon, a white solid crystallized on cooling and melted 166-168.5°. It showed no depression in melting point when mixed with an authentic sample of trimethylgallic acid, m.p. 169-170°.

When the procedure was repeated using 20 grams of XXIII, the yield of acidic material was less than two grams and melted from 179-186°. One recrystallization from methanol raised the melting point to above 200° but the recrystallized material weighed less than one gram.

b) 1:1 Tertiary Butyl Alcohol-Water Solvent at Room Temperature. The same procedure was used as in 1-a except that all the reactants were mixed at room temperature and the reaction proceeded at room temperature. All of the potassium

permanganate was consumed in 24 hours but no keto acid (II) was isolated, the main product being the aromatized isoquinoline (VI).

c) 1:1 Tertiary Butyl Alcohol-Water Solvent with Vanadium Pentoxide Catalyst. Procedure 1-a was repeated with two grams of vanadium pentoxide being added to the reaction mixture as a catalyst. The yields of the various materials were nearly the same as in 1-a, since 3.2 grams of basic material melting below  $120^{\circ}$ , 0.7 grams of keto acid melting  $213-215^{\circ}$ , and 0.9 grams of acidic materials melting  $155-165^{\circ}$  were obtained from 6.2 grams of XXIII.

d) 90 Per Cent Tertiary Butyl Alcohol Solvent. Compound XXIII (2.0 grams) was dissolved in 100 ml. of tertiary butyl alcohol and after heating until the solvent began to reflux, 3.5 grams of solid potassium permanganate and two grams of solid sodium hydroxide were added. The tertiary butyl alcohol did not dissolve the potassium permanganate so 10 ml. of water were added. The solution immediately became deep purple and the reaction proceeded slowly. The purple color disappeared after 48 hours of heating and stirring, but no keto acid could be isolated from the reaction mixture.

e) Water Solvent at  $30^{\circ}$ . Five grams of XXIII were finely powdered and made into a slurry with 10 ml. of water. This was diluted to a suspension in 300 ml. of water and heated to  $50^{\circ}$ . When this temperature was reached, 9.1 grams of finely powdered potassium permanganate and 2.0 grams of solid sodium hydroxide were added. The reaction mixture

was maintained between 80 and 90° for 16 hours until the purple color had disappeared. The manganese dioxide was filtered off and the filtrate acidified by the addition of sulfur dioxide. The acidic material, presumably the keto acid, weighed 0.22 grams and melted 205-211°. The manganese dioxide was heated with 150 ml. of ethanol to extract the basic materials and filtered. The ethanol solution was diluted with an equal volume of water and allowed to cool. A mass of fine white needles, which weighed 2.6 grams and melted 119-140°, was obtained. This was presumed to be a mixture of the dihydro and aromatized isoquinolines.

2) Chromic Acid in Acetic Acid. Two grams of XXIII were dissolved in 40 ml. of glacial acetic acid and heated to 60° in an oil bath. To this well stirred solution, a solution of three grams of chromic oxide in 150 ml. of glacial acetic acid was added from a dropping funnel over a period of two hours. The mixture was cooled to room temperature, diluted with water, and extracted with ether. The ether extract was washed with water and then extracted with sodium hydroxide solution. The alkaline solution was heated to remove the ether, and then acidified and extracted with ether. The ether was evaporated but there was no residue. The acetic acid solution was made basic and extracted with ether. This ether extract yielded 0.8 grams of starting material, melting 155-157.5°.

3) Lead Tetraacetate in Acetic Acid. Two grams of XXIII were dissolved in 55 ml. of glacial acetic acid and

heated to 60°. Fourteen grams of red lead ( $Pb_3O_4$ ) were added and the reaction mixture was stirred for four hours, maintaining the temperature at 60°. Some of the red lead did not go into solution. The solid was filtered from the mixture. The acetic acid solution was diluted with 300 ml. of water and extracted with ether. The ether was evaporated but no acidic residue was left. The acetic acid solution was made basic with sodium hydroxide and extracted with ether. This ether extract, on evaporating to dryness, yielded 2.0 grams of starting material, m.p. 157-158.5°.

4) Nitric Acid and Vanadium Pentoxide. Five grams of XXIII were pulverized and added to 100 ml. of water and 0.3 grams of finely powdered vanadium pentoxide. The suspension was heated to 70° and 25 ml. of concentrated nitric acid were added. Everything went into solution. The green solution was heated under reflux for 90 minutes and, after cooling to room temperature, diluted with 125 ml. of water. Less than 50 milligrams of solid precipitated from the solution. The solid was not readily soluble in sodium hydroxide solution and melted from 155-165°. This material was not identified. The solution was made basic and extracted with ether. An insignificant amount of brown solid material was obtained.

Preparation of 1-(3',4',5'-Trimethoxyphenyl)-2-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolinium Iodide (XXIV). Compound XXIII (21.7 grams, .0636 mole) was dissolved in 500 ml. of dry benzene and excess methyl iodide was added.

The solution was allowed to stand at room temperature overnight and the flask became solid with a yellow precipitate. The mass was broken up and filtered. The solid weighed 26.0 grams. The filtrate was returned to the flask and allowed to stand another 24 hours. Again the yellow solid was filtered off. This sample weighed 3.0 grams. After another 72 hours, 1.1 grams of yellow solid was obtained. The total yield is 30.1 grams (98 per cent of the theoretical amount), m.p. 222-223° with decomposition.

<u>Analyses</u>	<u>Calculated for C<sub>20</sub>H<sub>22</sub>O<sub>5</sub>NI</u>	<u>Found</u>
Carbon	49.70%	49.96% 49.97%
Hydrogen	4.59%	4.79% 4.83%
Nitrogen	2.90%	2.94% 3.02%
Methoxyl	19.26%	19.39% 19.18%
Iodine	26.26%	26.26% 25.77%

Attempts to methylate XXIII using dimethyl sulfate in benzene, followed by isolation of the methochloride, gave compounds with carbon analyses varying from 58.67 per cent to 60.70 per cent with a theoretical value of 61.29 per cent. Melting points varied from 220° to 228° with decomposition. Later evidences showed the chloride to be fairly hygroscopic, so this fact probably caused the poor results.

Both the iodide and chloride give the same pseudo-base when an aqueous solution of either is treated with aqueous

sodium hydroxide. The white solid melts 146-147° after recrystallizing from benzene.

Oxidation of the Pseudo-base of XXIV. The pseudo-base was prepared from 4.4 grams of XXIV dissolved in 100 ml. of water by adding excess 20 per cent sodium hydroxide solution. The white solid was filtered and washed and dissolved in 150 ml. of tertiary butyl alcohol. An equal amount of water was added and then procedure 1-a (p. 48) for the oxidation of XXIII was followed. The yield of keto acid was 0.4 grams (10 per cent of the theoretical amount) melting 210-212°. Recrystallization from methanol, after treating with activated carbon, gave almost 0.4 grams of pure white crystals, m.p. 214-216°.

Attempts to Prepare Carbonyl Derivatives of the Pseudo-base of XXIV.

1) Attempt to Prepare a 2,4-Dinitrophenylhydrazone. The procedure of Shriner and Fuson<sup>44</sup> was followed using 1.3 grams of XXVI and 0.75 grams of 2,4-dinitrophenylhydrazine in 50 ml. of ethanol. The solution was brown in color until the addition of the hydrochloric acid, when the color changed to a deep red-orange. No precipitate was observed even after 24 hours at room temperature. Concentration of the solution to 20 ml. gave a very small amount of a black solid which melted 138-140° after recrystallizing from ethanol. Addition of 50 ml. of water to the 20 ml. of alcohol solution after filtering off the black solid, gave a few red-orange crystals which melted 162-167°, but there was not enough to recrystallize.

2) Attempt to Prepare an Anil. The procedure of Freund and Becker<sup>13</sup> was followed. Two grams of the pseudo-base (XXVI) were triturated with 0.5 grams of aniline and a few drops of water. The mixture did not become an oil, as Freund observed using octarnine, but remained as a pasty mass. After mixing with 50 ml. of water the mixture was filtered and the solid washed well with water. The white powder melted 143-146° after recrystallizing from benzene and showed no depression in melting point when mixed with a sample of pure pseudo-base.

3) Attempt to Prepare a Derivative by Condensation with an Active Methylene Compound. The procedure of Liebermann and Kropf<sup>29</sup> was followed using acetone and the pseudo-base. One gram of the pseudo-base (XXVI) was suspended in 10 ml. of acetone and shaken after adding three ml. of saturated sodium carbonate solution. The compound did not go into solution, as was expected, and the only product which was isolated proved to be starting material.

Attempts to Methylate the Pseudo-base (XXVI).

1) Benzene-Alcohol Solvent. Compound XXVI was prepared from one gram of the methiodide (XXIV). The white solid was dissolved in a mixture of 90 ml. of dry benzene and 10 ml. of absolute ethanol. Excess methyl iodide was added and the solution became deep yellow. Crystals appeared after standing overnight. The yellow solid weighed 0.6 grams and melted 221-223° with decomposition. A mixed melting point with the methiodide (XXIV) showed no depression.

2) Benzene Suspension. Two grams of XXVI were slurried with 200 ml. of dry benzene. Only a very small amount went into solution. Excess methyl iodide was added and the solution became brown in color. The solid and solution slowly changed to a yellow color and, after allowing the mixture to digest for four days, the bright yellow solid was filtered off. It weighed 2.4 grams and melted  $195-198^{\circ}$  with decomposition. Recrystallization from ethanol gave 2.0 grams of a yellow powder melting  $217-219^{\circ}$  with decomposition. This showed no depression in melting point when mixed with a pure sample of the methiodide (XXIV), and gave a white solid, which melted  $143-145^{\circ}$ , when treated with sodium hydroxide. The white solid is the pseudo-base (XXVI).

Preparation of 1-(3',4',5'-Trimethoxyphenyl)-1-cyano-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (Pseudo-cyanide) (XXVIII). Compound XXIV (0.5 grams) was dissolved in 50 ml. of water and an aqueous solution of sodium cyanide was added. The white precipitate was washed and dried and weighed 0.4 grams, m.p.  $132-133^{\circ}$ . Two recrystallizations from 60 per cent ethanol raised the melting point to  $133-133.5^{\circ}$ .

<u>Analyses</u>	<u>Calculated for <math>C_{21}H_{22}O_5N_2</math></u>	<u>Found</u>
Carbon	65.96%	66.09% 66.21%
Hydrogen	5.80%	5.97% 6.11%
Nitrogen	7.33%	7.48% 7.52%
Methoxyl	24.35%	24.39% 24.09%

The pseudo-cyanide dissolved readily in benzene but no appreciable amount of precipitate was observed after 48 hours in the presence of excess methyl iodide.

Reduction of the Dihydroisoquinoline (XXIII) to 1-(3',4',5'-Trimethoxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XXXIV).

1) Raney Nickel Catalyst in Dioxane Solvent. Compound XXIII (22 grams, .0645 mole) was dissolved in 130 ml. of anhydrous dioxane and reduced under a pressure of 2500 pounds per square inch of hydrogen at 150°, using two grams of Raney nickel catalyst. A pressure drop of 870 pounds per square inch was observed, whereas the theoretical pressure drop would have been approximately 300 pounds per square inch. The catalyst was filtered off and the dioxane removed under reduced pressure in an atmosphere of nitrogen. The residual oil was dissolved in 100 ml. of ethanol and an equal volume of water was added. The white solid was filtered and dried, m.p. 81-88°. One recrystallization from aqueous ethanol raised the melting point to 89-96° and a second raised it to 92-97°. The purified sample was dissolved in ether and dry hydrogen chloride was added. The white solid hydrochloride was recrystallized twice from ethanol and melted 242-243° with decomposition. This gave the correct analyses for the hydrochloride of the tetrahydroisoquinoline (XXXIV).

<u>Analyses</u>	<u>Calculated for C<sub>19</sub>H<sub>22</sub>O<sub>5</sub>NCl</u>	<u>Found</u>
Carbon	60.09%	60.13% 60.04%
Hydrogen	5.84%	5.98% 6.03%
Nitrogen	3.69%	3.44% 3.45%
Methoxyl	24.51%	24.64% 24.61%

The final yield of material melting 92-97° was less than five grams or less than 25 per cent of the theoretical amount.

2) Platinum Oxide Catalyst in Acetic Acid Solvent<sup>2</sup>.

Compound XXIII (34.1 grams, 0.1 mole) was dissolved in 100 ml. of glacial acetic acid, and placed in a shaker bottle with 0.2 grams of platinum oxide catalyst. The reduction was run at one atmosphere pressure of hydrogen using a gas burette to measure the volume absorbed. The theoretical amount is 2485 ml., and 2517 ml. were taken up in two hours at 25°. The reaction was 90 per cent complete in one hour but the solution was still bright yellow. The yellow color persists until the reaction is more than 99 per cent complete but the final solution, after removal of the catalyst, was colorless. The solution was diluted with 600 ml. of water and neutralized with concentrated ammonium hydroxide. The gummy mass which precipitated solidified rapidly as the solution cooled. The solid was filtered, washed with water, and dried. The yield is 34.6 grams (100 per cent of theory). Recrystallization from ethanol yields fine white needles, m.p. 95-97°.

A second recrystallization of a small sample gave a melting point of 97-98.5°. The melting point is lowered by standing in air, presumably due to carbamate formation. A sample was dissolved in ether and dry hydrogen chloride added. The white hydrochloride melted 242-242.5° with decomposition without recrystallization and showed no depression when mixed with the analytical sample of the hydrochloride of the tetrahydroisoquinoline (XXXIV).

Oxidation of XXXIV. The tetrahydroisoquinoline (3.2 grams) was oxidized with potassium permanganate as in 1-a (p. 48). A few milligrams of acidic material, presumably the keto acid (II), melting 203-207°, was isolated and about one gram of basic material, melting 150-155°, which gave a yellow hydrochloride, melting 230-232° with decomposition. The basic material was shown to be the dihydroisoquinoline (XXIII), since the hydrochloride showed no depression in melting point when mixed with an authentic sample.

Preparation of 1-(3',4',5'-Trimethoxyphenyl)-2-benzoyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XXXV).

The tetrahydroisoquinoline (XXXIV) (5 grams, .0146 mole) was dissolved in 150 ml. of dry benzene and a solution of 2.05 grams (.0146 mole) of benzoyl chloride in 50 ml. of dry benzene was added with stirring and the mixture heated to 80°. Two grams of 150 mesh calcium oxide were added over a period of 40 minutes, and the hot suspension was filtered. The solid was readily soluble in dilute hydrochloric acid so was assumed to be composed of the inorganic salts. The

benzene solution was extracted with 10 per cent sodium hydroxide solution, then 10 per cent hydrochloric acid solution and washed with water. The benzene was removed under reduced pressure and the residual solid was dissolved in 30 ml. of ethanol. Addition of 30 ml. of water and cooling caused an oil to separate, which solidified rapidly when seeded. The solid was filtered off and dried and weighed 4.5 grams (.010 mole, 69 per cent of the theoretical amount). It melted 122.5-124.5° but two recrystallizations raised the melting point to 124.5-125°. This gave the correct analyses for the benzoate of the tetrahydroisoquinoline (XXXIV).

<u>Analyses</u>	<u>Calculated for C<sub>26</sub>H<sub>25</sub>O<sub>6</sub>N</u>	<u>Found</u>
Carbon	69.78%	69.96% 70.06%
Hydrogen	5.63%	5.65% 5.74%
Nitrogen	3.13%	3.23% 3.14%
Methoxyl	20.80%	20.93% 20.69%

Oxidation of XXXV. Two grams of the benzoyl derivative (XXXV) were dissolved in 75 ml. of tertiary butyl alcohol and 75 ml. of water were added. The oxidation was carried out with potassium permanganate as in 1-a (p. 48). Less than 50 milligrams of acidic material, presumably the keto acid (II), melting 203-207°, were recovered. Recrystallization from methanol, after treating with activated carbon, gave a small amount of white needles, m.p. 213-216°. Nonacidic

material, which melted slowly from  $55^{\circ}$  to  $125^{\circ}$ , was obtained but was not identified.

Reaction Between Methyl Iodide and Compound XXXIV in Benzene Solution. The tetrahydroisoquinoline (XXXIV) (34.3 grams, 0.10 mole) was dissolved in 300 ml. of dry benzene and a 10 per cent excess of methyl iodide was added. A yellow precipitate formed immediately and after 10 minutes the solid was filtered off (weight 12.5 grams, 25.8 per cent of the theoretical amount). The bright yellow filtrate was returned to the flask and allowed to stand 16 hours. The second solid fraction was filtered off (17.5 grams, 36.1 per cent) and the filtrate allowed to stand 24 hours. A third fraction (6.2 grams, 12.6 per cent) was filtered off and after five more days a fourth fraction (6.2 grams, 12.6 per cent) was filtered off. Five grams of methyl iodide were added to the filtrate and after 14 days the final sample (6.2 grams, 12.6 per cent) was removed. The total yield is 48.6 grams (100 per cent of the theoretical amount).

The first solid was dissolved in 200 ml. of water and 50 per cent aqueous sodium hydroxide was added. The white precipitate was dissolved in ethanol and two volumes of ether added. A very small amount of solid came out of solution so the ether was evaporated and an equal volume of water was added. The white needles which precipitated melted  $92-95^{\circ}$  and gave a hydrochloride melting  $240-241^{\circ}$ .

<u>Analyses</u>	<u>Calculated for <math>C_{20}H_{24}O_5NCl</math></u>	<u>Found</u>
Carbon	60.99%	60.08% 60.12%
Hydrogen	6.14%	6.09% 5.93%

The calculated values for  $C_{19}H_{22}O_5NCl$  are 60.09 per cent carbon and 5.84 per cent hydrogen. This indicated that the compound was the same as the starting material (XXXIV) and a mixed melting point of the two hydrochlorides showed no depression, conclusively proving the identity of the two compounds.

The fourth solid fraction was dissolved in 200 ml. of water and 50 ml. of 50 per cent sodium hydroxide solution were added. The white precipitate was dissolved in ethanol and an equal volume of ether was added. Short prisms crystallized from the solution. The material weighed 4.1 grams and melted 227-229° with decomposition. It still contained iodine. The solid was recrystallized twice more from ethanol and melted 233-233.5° with decomposition.

<u>Analyses</u>	<u>Calculated for <math>C_{21}H_{26}O_5NI_2</math></u>	<u>Found</u>
Carbon	50.50%	50.54% 50.42%
Hydrogen	5.25%	5.19% 5.28%
Nitrogen	2.80%	3.00% 3.02%
Methoxyl	18.64%	18.67% 18.72%
Iodine	25.42%	24.21% 23.92%

These analyses, and the fact that this compound shows no depression in mixed melting point with an authentic sample of the quaternary iodide (XXXVII), show that it is XXXVII.

The second fraction (17.5 grams) was worked up in the same manner as the others. This yielded 5.2 grams of the quaternary iodide (XXXVII), melting  $233-233.5^{\circ}$  with decomposition, and 4.5 grams of the tetrahydroisoquinoline (XXXIV), melting  $90-95^{\circ}$ .

Preparation of 1-(3',4',5'-Trimethoxyphenyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XXXVI).

The tetrahydroisoquinoline (XXXIV) (31.2 grams, .091 mole) was mixed with 52.5 ml. of 90 per cent formic acid and 21 ml. of formalin. The mixture was heated in an oil bath and the solid slowly dissolved. At  $50^{\circ}$  the solution was clear and carbon dioxide was bubbling off vigorously. The reaction mixture was maintained at  $50-60^{\circ}$  for 12 hours and then heated under reflux for four hours. The solution was diluted with 600 ml. of water and neutralized with ammonium hydroxide. The light tan precipitate weighed 29.9 grams (92 per cent of the theoretical amount) and recrystallized in white needles from ethanol, m.p.  $133-134^{\circ}$ .

<u>Analyses</u>	<u>Calculated for <math>C_{20}H_{23}O_5N</math></u>	<u>Found</u>
Carbon	67.20%	67.15% 67.24%
Hydrogen	6.49%	6.48% 6.51%
Nitrogen	3.92%	4.11% 4.18%
Methoxyl	26.04%	25.87% 25.96%

A small amount of the amine was dissolved in ether and dry hydrogen chloride added. The white solid melted 240-241° with decomposition after two recrystallizations from ethanol. A mixed melting point with the hydrochloride of the tetrahydroisoquinoline (XXXIV) gave decomposition at 230-235°.

<u>Analyses</u>	<u>Calculated for C<sub>20</sub>H<sub>24</sub>O<sub>5</sub>NCl</u>	<u>Found</u>
Carbon	60.99%	60.81% 61.07%
Hydrogen	6.14%	6.28% 6.33%
Nitrogen	3.56%	3.87% 3.31%
Methoxyl	23.63%	23.69% 23.54%

Oxidation of XXXVI. Using procedure 1-a (p. 48), 5.5 grams of compound XXXVI were oxidized. After filtering off the manganese dioxide, the tertiary butyl alcohol was removed under reduced pressure and the alkali insoluble material filtered off. The solid weighed 0.9 grams and melted 110-145° with decomposition but was not identified. The alkaline filtrate was acidified by adding sulfur dioxide and a powdery yellow solid precipitated. The acidic fraction weighed 2.4 grams and melted 188-198°. It did not readily redissolve in alkali. The material which did dissolve precipitated on the addition of hydrochloric acid and then redissolved when excess acid was added. The solid contained nitrogen. After two recrystallizations from alcohol, it melted 225-226° with decomposition.

<u>Analyses</u>	<u>Found</u>
Carbon	61.63% 61.40%
Hydrogen	5.22% 5.18%
Nitrogen	4.13%
Methoxyl	25.08% 25.29%

These analyses do not fit any reasonable compound, assuming that the methoxyl analysis is a measure of the molecular weight and that there are three methoxyl groups present in the molecule.

Two other oxidations were run using procedure 1-b (p. 50). Each gave 2.4 grams of neutral compounds, m.p. 206-215°, and 0.36 grams of acidic material, presumably the keto acid (II), melting 206-212°, from 5.5 grams of starting material.

Preparation of 1-(3',4',5'-Trimethoxyphenyl)-2,2-dimethyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolinium Iodide (XXXVII). Compound XXXVI (8.0 grams, .0224 mole) was dissolved in 400 ml. of dry benzene and excess methyl iodide was added. The solution remained colorless and a snow white solid precipitated from solution. After 18 hours, the white solid was filtered off and dried. It weighed 10.7 grams (95.5 per cent of theory) and melted 233-234° with decomposition. Another 0.6 grams was obtained by allowing the filtrate to stand for another 48 hours, making the total yield 11.3 grams (100 per cent of the theoretical amount).

Preparation of the Thallous Hydroxide Solution. Finely powdered barium hydroxide octahydrate (31.55 grams, 0.100 mole) and 50.48 grams (0.100 mole) of thallous sulfate were stirred in suspension in 500 ml. of water at room temperature for 20 hours. The insoluble salts were filtered off and washed well with water. The total volume of solution was more than 550 ml., and the solution of thallous hydroxide should have been about 0.36 normal. Titration with standard hydrochloric acid, using bromthymol blue as the indicator, gave an average value of 0.335 normal with an average deviation of five parts per thousand. Thallous chloride precipitated during the titration.

Attempt to Prepare the Quaternary Hydroxide from the Quaternary Iodide (XXXVII). Compound XXXVII (5.0 grams, 0.01 mole) was dissolved in 150 ml. of hot water and an equivalent amount of thallous hydroxide solution (29.9 ml.) was added. The thallous iodide was filtered off and the clear solution evaporated in a vacuum desiccator over concentrated sulfuric acid. The resultant glass could not be crystallized from water, ethanol, methanol, benzene, or petroleum ether. A solution of the glass in carbon tetrachloride gave an orange precipitate on the addition of bromine, m.p. 80-88°. The glass, dissolved in tertiary butyl alcohol, reacted rapidly with aqueous potassium permanganate.

If the solution of the quaternary hydroxide is concentrated under reduced pressure in an atmosphere of nitrogen,

the same glassy material is isolated and will not crystallize.

Oxidation of the Products Obtained by the Malleous

Hydroxide Treatment of XXXVII. The glass observed above was prepared from 5.0 grams of XXXVII by removing the water under reduced pressure. The semi-solid was dissolved in 100 ml. of tertiary butyl alcohol and oxidized according to procedure 1-a (p. 43). The neutral material weighed 0.60 grams and melted 227-228°. No acidic material was isolated by the usual procedure. Addition of a solution of cupric acetate gave less than 0.70 grams of a blue copper salt which was not identified.

Direct oxidation of the aqueous solution of the quaternary hydroxide solution gave no acidic material and 0.66 grams of neutral material, m.p. 229-233°. Two recrystallizations raised the melting point to 232-234°.

<u>Analyses</u>	<u>Found</u>
Carbon	61.46% 61.12%
Hydrogen	5.27% 5.31%
Nitrogen	4.64%
Methoxyl	25.23% 25.47%

These values are similar to those observed in the compound obtained in the acidic portion of the oxidation products of compound XXXVI, and again do not fit any reasonable formula, if the same assumptions are made.

Attempt to Prepare 4,5-Methylenedioxy-2-(3',5'-dimethoxy-4'-hydroxybenzoyl)benzoic Acid (XL). Hydrastic anhydride (XXXVIII) (3.84 grams, 0.02 mole) and 2,6-dimethoxyphenol (XXXIX) (3.08 grams, 0.02 mole) were mixed in a 50 ml. flask equipped with a reflux condenser fitted with a calcium chloride drying tube. Twenty milliliters of stannic chloride were added and the mixture was warmed to 110°. At this temperature, the reaction mixture darkened rapidly and became deep purple in color. After two hours, the mixture was added to a mixture of ice and hydrochloric acid to destroy the complex. The purple solution was extracted with ether. The brownish-green ether extract was shaken with dilute alkali, and all the color was removed from the ether layer, the alkaline layer turning deep blue. Evaporation of the ether layer left no residue. Acidification of the aqueous layer changed the color to purple but gave no precipitate. Evaporation of a colored ether extract gave a tar which dissolved in ethanol but would not crystallize. Activated carbon would not remove the color from the alcoholic solution or any of the aqueous solutions.

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