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THE SYNTHESIS OF 3,4,5-TRIMETHOXYPHENYLACETALDEHYDE (MESCALALDEHYDE)

A Thesis

Submitted to the

Faculty of Graduate Studies

in Partial Fulfilment of

the Requirements for

the Degree of

Master of Science

in the

College of Pharmacy,

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by

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I am very grateful for the financial assistance through the Saskatchewan Committee on Schizophrenia Research from the Department of National Health and Welfare, which made this work possible.

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INTRODUCTION

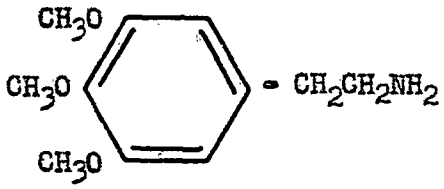
I. Survey of Research Problem

The problems of abnormal mental health have confronted the human race for many years. Early theories were based upon the belief that "spirits" which had taken over the body were the cause of such a condition. During certain periods of history such people were looked upon as human gods to whom the others looked for divine guidance. However, as civilization developed, it was realized that mental disabilities were due to some other, yet unknown, cause. As a result of this, no treatment was available for such a condition and very little understanding was given to such people. In recent years, however, this attitude has changed and the medical professions now regard people who have mental disabilities as patients who are suffering from a disease, which has a cause, and for which some treatment should be given. However, although this view is held, the cause of mental illness has not been fully determined and no satisfactory treatment has been found to fit all cases.

In Saskatchewan, the Department of Public Health, aided by the Federal Department of Health and Welfare has established a Saskatchewan Committee of Schizophrenia Research. The purpose of this committee is to carry out a thorough investigation of this phase of the mental health problem. One phase of their work deals with the biochemical aspect of schizophrenia. It has been known for some time that certain chemicals, if administered to a normal person will produce temporary symptoms, similar to those of schizophrenics. In fact, certain herbal mixtures have been

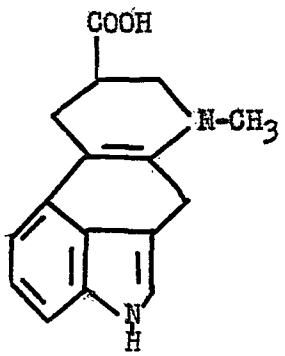
used by early man in religious ceremonies for the purpose of producing hallucinations and other psychic effects. An example is mescaline, which can be isolated from the mescal buttons of the dumpling cactus, Lophophora williamsii, and was used by the Indians of southwestern United States and northern Mexico. Due to the fact that mescaline and other chemicals produce a "model psychosis", an investigation of their biological activity was thought to be of interest and might contribute further to the knowledge regarding the cause of schizophrenia. It may be possible that certain hallucinogenic compounds* may function directly without chemical change, while others, by the processes of metabolism in the body, must be converted first to intermediates which have different structures and which produce the hallucinogenic effect.

The structures and names of certain chemicals that may be classified as hallucinogenic compounds are: (26, 27)



I

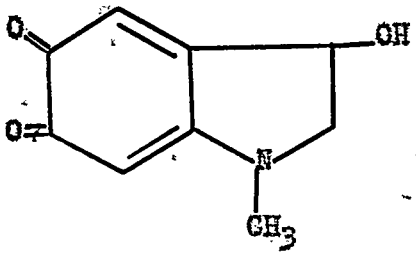
mescaline



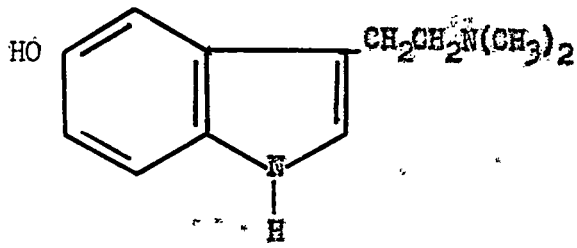
II

lysergic acid (as the N- ethyl and the N, N-diethyl amides)

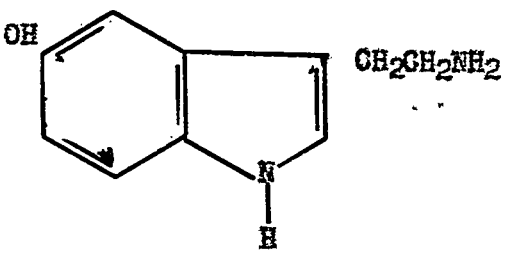
* A hallucinogenic compound will henceforth be used to refer to that compound which, if administered to a normal individual, will cause that person to have hallucinations similar to those observed in schizophrenic patients.



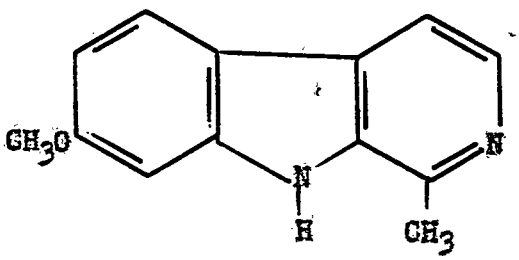
III
adrenochrome



IV
bufotenine

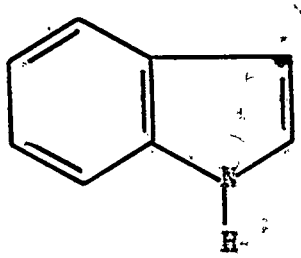


V
serotonin



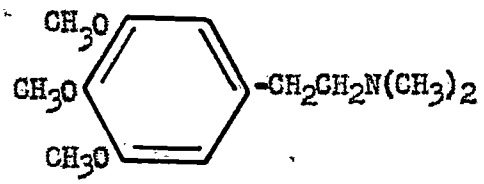
VI
harmine

It is interesting to note that with the exception of mescaline, and adrenochrome, each of the hallucinogenic compounds that are listed above has a benzopyrrole (indole, VII) ring structure.



VII
indole

From this observation it would appear that the presence of an indole nucleus may be characteristic of hallucinogenic compounds. Mescaline and adrenochrome, neither of which posses such a nucleus, could be converted to indoles by processes of cyclization, dehydrogenation and dehydration. The belief that this does happen is supported to some extent by the fact that the dosages required to cause similar hallucinogenic effects are: for mescaline, 500 mgm.; for adrenochrome, 5-10 mgm.; and for lysergic acid diethylamide, 0.1 mgm.. If the above processes are necessary to convert mescaline and adrenochrome to hallucinogenic compounds, the necessity of higher dosages may be attributed to the fact that the conversion is not quantitative. The assumption that mescaline must undergo a cyclization to become a hallucinogenic compound is supported by the fact that trichocerine, VIII, although related in structure to mescaline is not a hallucinogenic compound. (28)



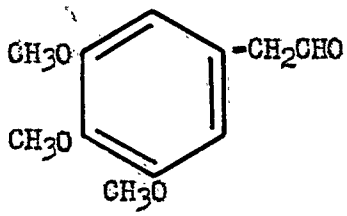
VIII

trichocerine

Trichocerine differs from mescaline in that it possesses a tertiary amino group which would render cyclization and dehydrogenation of the side chain

to an indole impossible.

It is possible therefore, that hallucinogenic compounds are characterized in structure by having either an indole nucleus or being capable of conversion to an indole nucleus. To help confirm this, it would be necessary to prove that mescaline did owe its hallucinogenic properties to the prior formation of such a structure* However, there is reason to believe that the metabolism of mescaline in the body may follow a much different path. It has been shown that mescaline can be deaminated by amine oxidase, an enzyme which deaminates a number of compounds including adrenaline and tyramine (1). If this should occur within the body, the hallucinogenic properties exhibited by mescaline may then be due to deamination of the amine and the formation of the aldehyde, 3,4,5-trimethoxyphenylacetaldehyde (mescalaldehyde; IX).



IX

3,4,5-trimethoxyphenylacetaldehyde
(mescalaldehyde)

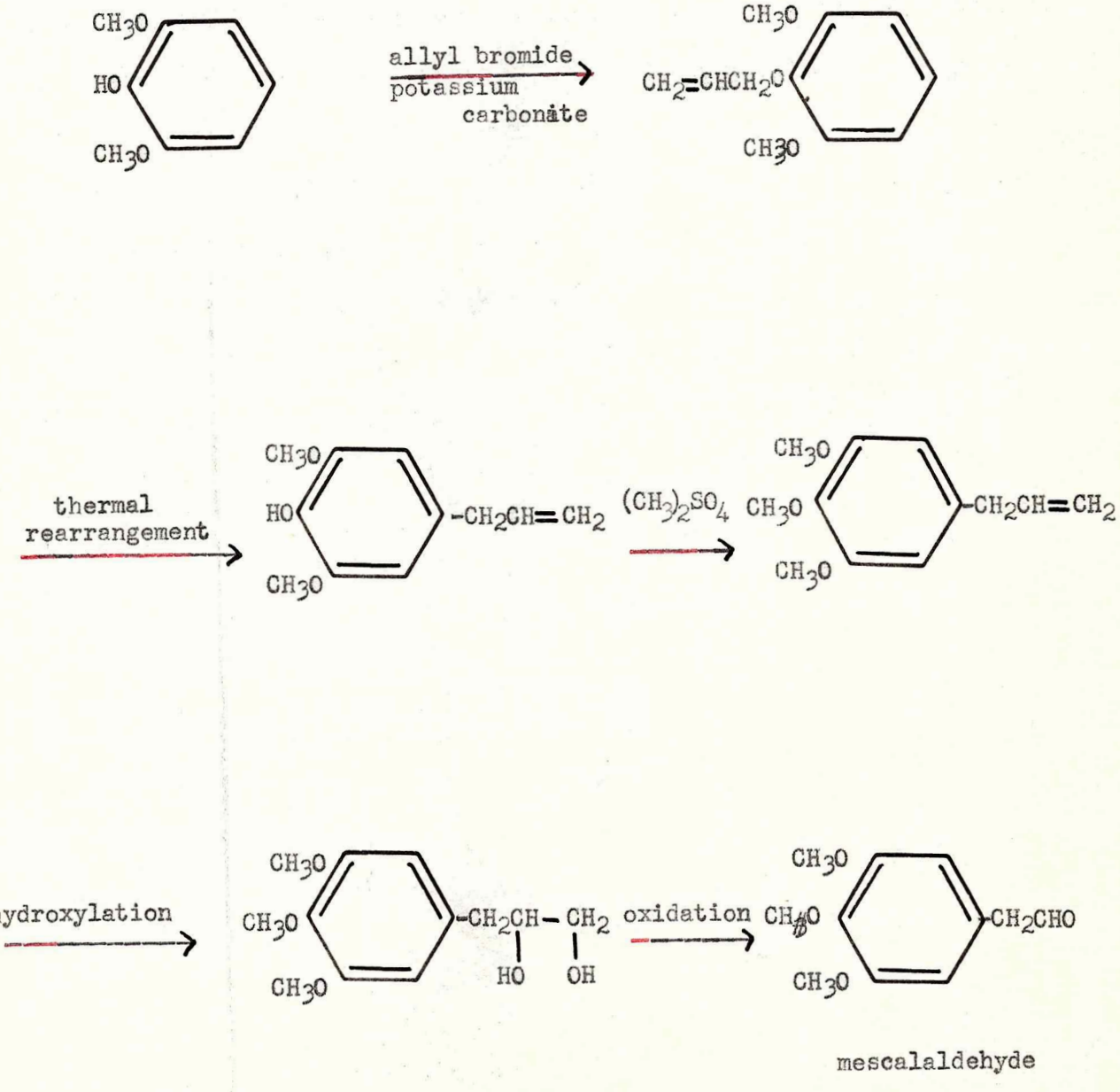
* A. Hoffer, Director of the Saskatchewan Committee on Schizophrenia reasearch, reports in a private communication that Dr. Harley-Mason has been unsuccessful in his attempts to cyclize mescaline.

It may be possible that one of the two mentioned paths of metabolism of mescaline may be responsible for its hallucinogenic effect. To obtain information as to which path, if either, is followed, tests which have been carried out on hallucinogenic compounds may be applied to the two possible metabolic intermediates of mesca_line. It has been shown that certain hallucinogenic compounds produce an inhibition in carbohydrate metabolism as well as an inhibition of the cytochrome system involved in oxygen uptake in brain tissue (1). If mescalaldehyde were the hallucinogenic compound formed from mescaline, one would expect the aldehyde to show a greater inhibition than is shown by mescaline. Another test involves the variable adsorption on wool of certain hallucinogenic compounds (1, 2). It has been found that the greater the affinity for wool, the lower the dosage required to cause a model psychosis. The adsorption on one gram of wool from solutions containing mescaline (500 mgm.) and lysergic acid diethylamide (0.1 mgm.) were zero and 2.6×10^{-3} respectively.* From these observations one would expect that if mescaline underwent deamination as part of its metabolism, then the adsorption of the aldehyde would be greater than that for mescaline, if this aldehyde were shown to be a hallucinogenic compound requiring a smaller dosage.

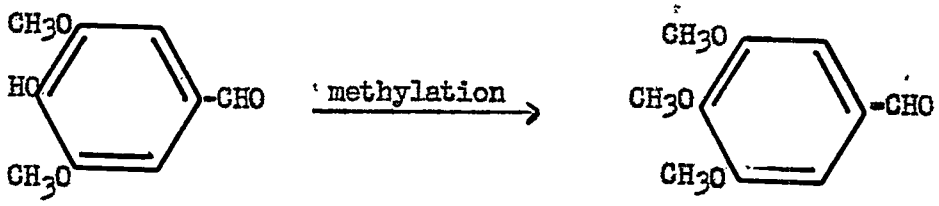
In order to study the action of mescalaldehyde it was necessary to effect its synthesis. A survey of the available literature revealed one synthesis of mescalaldehyde, by the ozonolysis of 3,4,5-trimethoxy-allylbenzene (3). As the equipment for this procedure was not readily available, other methods for the preparation of the required aldehyde were investigated. The following two synthetic procedures were selected.

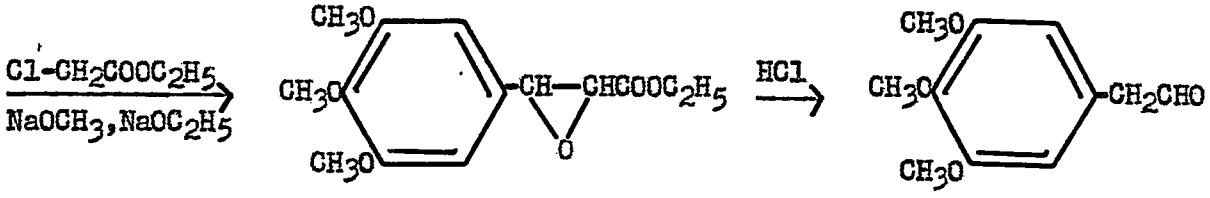
* The amounts given are dosages required for hallucinogenic activity and not concentrations.

(a)


CH3O
HO
CH3O
allyl bromide
potassium carbonate
CH2=CHCH2O
CH3O
thermal rearrangement
-CH2CH=CH2
(CH3)2SO4
hydroxylation
-CH2CH-CH2
HO OH
oxidation
-CH2CHO
mescalaldehyde

(b) By means of Darzens Glycidic Ester Condensation





mescalaldehyde

In order to determine the applicability of these methods of synthesis, preliminary work was undertaken using such compounds as would give rise to known intermediates. Therefore, eugenol was used for the first method of synthesis and anisaldehyde for the second.

II. Review of Synthetic Methods

A. Hydroxylation of Olefins

1. Using Potassium Permanganate (4,5,6,7,8). - Potassium

permanganate is a very powerful oxidizing agent, which can react in several different ways and which may yield quite different reaction products. This will depend upon whether it is used in limited amounts, or in excess or, again, whether it is used in strongly acid, neutral, or alkaline solution. Though aqueous solutions of potassium permanganate are chosen whenever possible, the fact that it is somewhat soluble in both dry acetone and dry pyridine greatly enlarges the scope of its applicability.

In the presence of a large excess of acid, potassium permanganate is reduced to a manganous salt

$$(MnO_4)^- + 5e + 8H^+ \longrightarrow Mn^{++} + 4H_2O$$

but in weakly acid, neutral, or alkaline solution it yields manganese dioxide.

$$(MnO_4)^- + 3e + 4H^+ \longrightarrow MnO_2 + 2H_2O$$

Since both acid and alkalies can effect other chemical changes during the course of the reaction, neutral conditions for the reaction are often desirable. If aqueous solutions are being used, neutrality can be secured by the addition of a suitable buffer, but if a solvent such as acetone is used, the addition of a neutral salt such as magnesium sulfate will control the alkalinity.

Dilute ice-cold solutions of potassium permanganate will promptly oxidize olefins to cis-1,2-diols.* This simple reaction is often used as a specific test for "unsaturation", but it is

* The terms cis and trans will be used to indicate the method of addition to the olefin.

important to remember that an excess of the reagent will oxidize glycols quite easily with the formation of acidic or ketonic products of greater stability.

$$R^1CH{=}CR^2R^3 \longrightarrow R^1CH(OH)-CH(OH)R^2R^3 \longrightarrow R^1COOH + R^2COR^3$$

Alkaline or neutral solutions are used to hydroxylate olefins. The general requirements for effective hydroxylations are:

(a) the use of very dilute (no greater than 1%) solutions of potassium permanganate.

(b) the use of a very dilute (0.1%) solution of the olefin.

(c) the maintenance of the reaction temperature below 15°C.

(d) the presence of a slight amount of alkali at the beginning of the reaction.

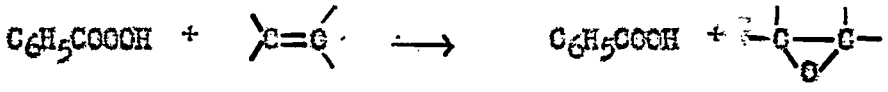
(e) the presence of suitable buffer to control the alkali that is formed in the course of the reaction.

(f) the reaction time should be short, in the order of five to ten minutes.

A major difficulty is the isolation of the glycol if it is soluble to any appreciable extent in water. "Salting out" of the glycol, combined with extraction using organic solvents seems to be the most satisfactory procedure to use in its isolation.

2. Using Organic Peracids (4,8) - The properties and reactions of the various organic peracids, RCO-O-OH, have been used for many years in the conversion of an olefin to its epoxide and thence to a trans-1,2-diol. This specific oxidation of an olefin was first

discovered by Prileshajew, who showed that perbenzoic acid, in cold, non-ionizing solvents such as chloroform, carbon tetrachloride, benzene, or ether, reacted as follows:



High yields of derivatives of ethylene oxide were formed. These could easily be separated, purified, and subsequently hydrolyzed by means of dilute acid to 1,2-diols. Many other peracids can be used in exactly the same way. Böeseken established that with solutions of peracetic acid the initial product was again the epoxide, though this was easily converted by hydrolysis to the glycol. If solutions of olefinic compounds in acetic or formic acids are treated with 20 - 30% hydrogen peroxide, in slight excess, the oxygen addition proceeds rapidly to give the monoesters, which can easily be saponified to obtain the diols. Under these circumstances the reaction proceeds via the initial formation of the organic peracid:

With formic acid, very little more than the theoretical quantity of hydrogen peroxide need be used.

In the use of performic acid for the conversion of olefins to glycols the olefins should be stirred at 40°C. with a solution of 30% hydrogen peroxide in aqueous formic acid (8).

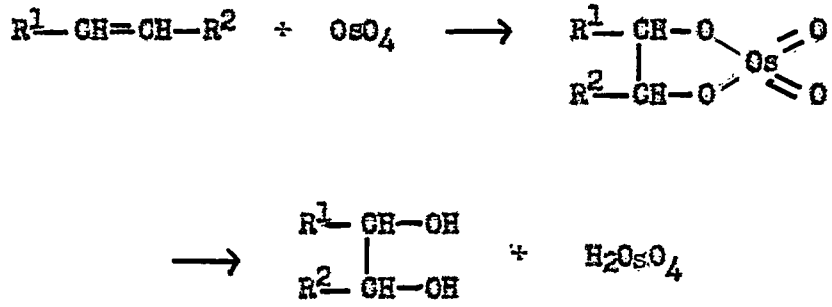
3. Using Hydrogen Peroxide (4).- Hydrogen peroxide, if used in excess in warm solutions, appears to be capable of slowly oxidizing

organic compounds of almost all types. However, it does seem to react preferentially with organic olefins to produce 1,2-diols. On account of its cheapness and its very low equivalent weight, hydrogen peroxide is often used in large excess. Under these conditions further oxidations may occur due to the free oxygen which is formed during the reaction.

Milas, Kurz, and Anslow have shown that although aqueous hydrogen peroxide reacts very slowly with cold solutions of unsaturated compounds, such substances can be hydroxylated more readily if their solutions in dilute hydrogen peroxide are irradiated with ultraviolet light of about 3000 Å wavelength. Similar oxidations can be effected very much more easily by treating olefinic substances with hydrogen peroxide in the presence of an acidic oxide of a metal such as osmium, vanadium, or chromium which forms an active peracid.

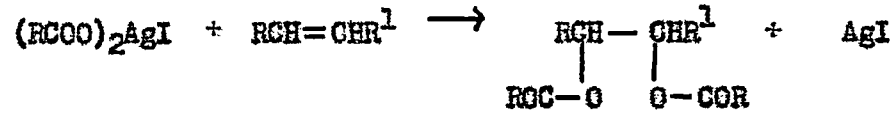
4. Using Osmium Tetroxide (4)- Osmium tetroxide is a reagent which can be used for the selective oxidation of olefins to cis-1, 2-diols. Its drawbacks are its cost, its high equivalent weight, its volatility, and its high toxicity. However, it will give at room temperature, high yields of clean reaction products, from which the osmium can easily be separated and recovered. The nature of its specific oxidizing action was disclosed in 1936 by Criegee. He found that in dry, inert solvents, osmium tetroxide reacted with olefins to give a yellow addition complex which could

be decomposed by heating with water, acetic acid, or alcoholic hydrogen chloride to give the corresponding cis-1,2-diol and osmic acid, H_2OsO_4.



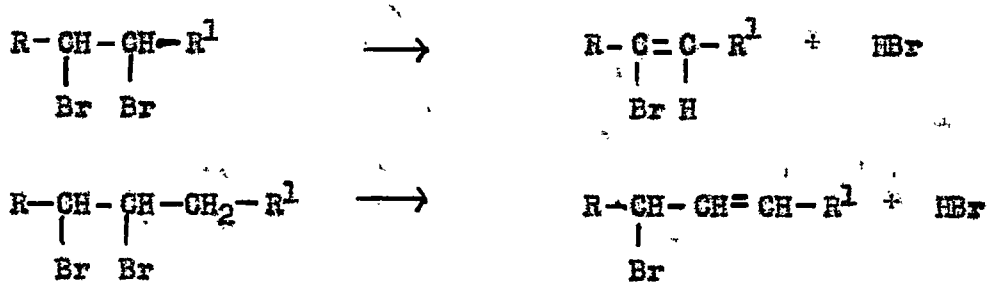
In carrying out such oxidations, it must be kept in mind that osmium tetroxide is a powerful oxidizing agent, and therefore alcoholic, phenolic, and amino groups must be protected.

5. Using the Prévost Reaction (4). - Prévost showed that silver salts of organic acids reacted with iodine to give complexes of the general formula $(RCOO)_2AgI$. These were slightly soluble in benzene, and these products readily reacted with olefins as follows to give the di-esters of trans glycols.



The reaction can be carried out quite simply by mixing a benzene solution of the olefin with two molecular equivalents of silver benzoate and then slowly adding two equivalents of iodine or of bromine. The addition occurs completely in the cold, but boiling mixtures can be used to speed the reaction. The resulting esters on hydrolysis yield the free 1,2-diols.

6. Using Vicinal Dihalide Derivatives (16). - The addition of a halogen such as iodine or bromine to an olefinic compound, followed by hydrolysis to the glycol is of little value. There is a possibility of further reactions taking place. During hydrolysis of the dihalide compound the following types of products may form:



B. Oxidative Cleavage of 1,2-diols

1. Using Periodic Acid (4, 7, 8, 9). - Periodic acid was first introduced as a reagent for the oxidation of 1,2-diols by Malaprade in 1928. He showed that free 1,2-diols react quantitatively , in neutral or dilute acid solutions, at room temperature in the following manner.

Fleury recognized that these oxidations ,which can be carried out with standardized solutions of paraperiodic acid, H_5IO_6, or with solutions of sodium metaperiodate, $NaIO_4$, in dilute sulfuric acid or sodium bicarbonate, were particularly valuable analytical procedures, since periodic acid can be estimated volumetrically.

Lemiux and Von Rudloff (7) have used periodic acid in conjunction with potassium permanganate to determine terminal methylene groups.

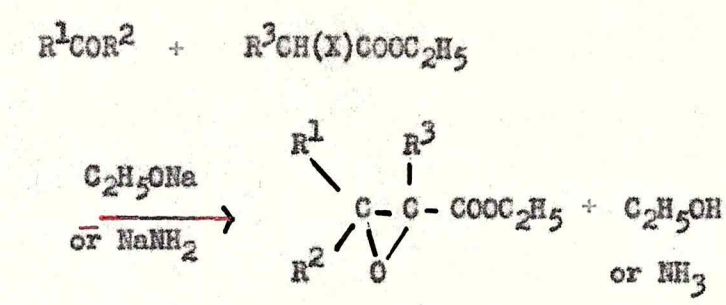
2. Using Lead Tetracetate (4,8,9). - Criegee showed that lead tetracetate reacted quantitatively with 1,2-diols to produce, by cleavage, a mixture of aldehydes or ketones without effecting any further degradation of these products.

$$R^1COR + R^2COR^3 + Pb(OCOCH_3)_2 + 2CH_3COOH$$

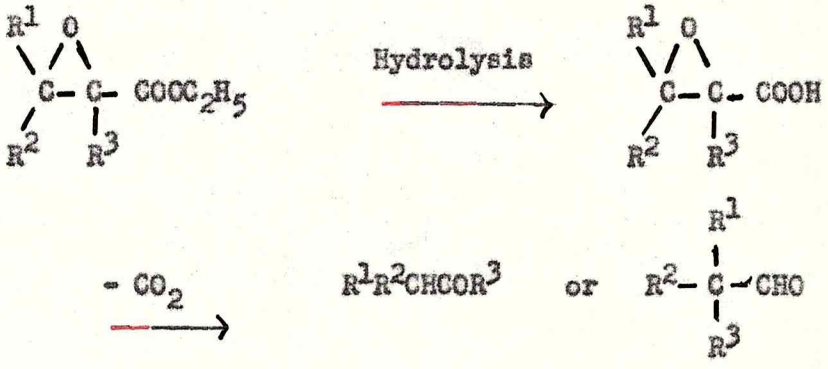
The solvent used for this reaction is usually glacial acetic acid, in which the lead tetracetate is readily soluble. However a suspension of the material in benzene can be used. Although the reagent is hydrolyzed rapidly by water, it can under certain conditions be employed in an aqueous medium. A lead tetracetate solution can be standardized by the use of sodium thiosulfate.

C. Darzens Glycidic Ester Condensation (8, 10).

The Darzens glycidic ester condensation involves the condensation of an aldehyde or ketone with an α-haloester to produce an α,β-epoxy ester (glycidic ester). The most frequently used condensing agents are sodium ethoxide or sodium amide.



The reactions are carried out under strictly anhydrous conditions preferably in an inert atmosphere at a temperature of 0°C. Hydrolysis of glycidic esters to acids, and decarboxylation of the acids yields ketones or aldehydes.

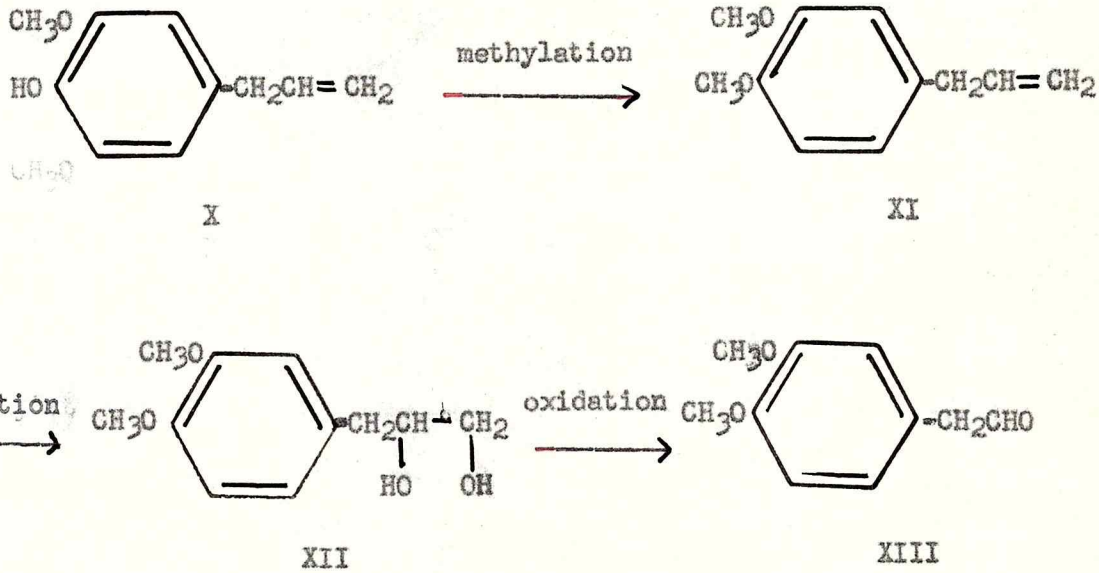


R^1 and R^2 may represent hydrogen or alkyl or aryl groups. If R^3 is hydrogen, an aldehyde always results; if a methyl group, methyl ketones are formed.

EXPERIMENTAL PROCEDURE AND RESULTS *

I. Synthesis of 3,4-Dimethoxyphenylacetaldehyde.

In order to study the hydroxylation of an olefin and the oxidative cleavage of the resulting 1,2-diol, the synthesis of 3,4-dimethoxyphenylacetaldehyde (XIII) was undertaken. Eugenol (X) was chosen as the starting material. The synthesis of 3,4-dimethoxyphenylacetaldehyde may be outlined as follows.



X XI XII XIII

A. Methylation of Eugenol

Eugenol (X)(150 gm.) was methylated according to the procedure of Mauthner (II); yield (140.5 gm.) (87%), b.p. $_{16}$ 140 - 150°C.

* All melting points are uncorrected.

B. Hydroxylation of Methyleugenol

1. Using Potassium Permanganate. - A total of seventeen hydroxylations of methyleugenol (XI) using potassium permanganate were attempted. The procedure that was most satisfactory is outlined as follows. Methyleugenol (15 gm.) (0.083 moles) was dissolved in water (75 ml.) and 95% ethanol (75 ml.) containing sodium hydroxide (2 gm.). The mixture was stirred in an ice bath and potassium permanganate (13 gm.) dissolved in water (1300 ml.) was added in one portion. The mixture was allowed to stand for fifteen minutes and then filtered to remove the manganese dioxide. The filtrate was then transferred to a film evaporator and concentrated to a volume of 400 ml.. This concentrate was extracted for twenty three hours with ether. The ether, after drying over anhydrous sodium sulphate, was removed by distillation. The crude product was recrystallized from benzene-petroleum ether (Skellysolve C): white crystals, 5.5 gm. (30.9%), m.p. 65 - 67°C., reported m.p. 65 - 67°C. (12).

Due to the extreme solubility of the glycol (XII) in aqueous solvents, its isolation presented a difficulty. The first reactions were attempted without isolation of the glycol, the reaction mixture being extracted with ether, the ether removed and the residue oxidized. These first reactions to produce the glycol gave a viscous, yellow oil as the product. A survey of the literature revealed that the desired glycol was a white crystalline solid with a melting point of 65 - 67°C. (12). It was noted

that on standing the yellow oil solidified. A mixture of benzene and petroleum ether (Skellysolve C) was found to be the most satisfactory solvent for the recrystallization of the glycol. The above oxidations were carried out in an aqueous solvent. As the yields of product thus obtained were low, other solvents were used in an attempt to increase the yield. A summary of the solvents and other conditions used are summarized in Table I. In each case, the yield was much lower than that reported in the literature (12). A higher yield of the glycol was obtained when the reaction mixture was made alkaline with sodium hydroxide (2 gm.) before hydroxylation. However, it was found that the extraction of the glycol from an aqueous solvent is very difficult and the higher yield that was obtained here may have been due to a more complete extraction. Large volumes of solvent were encountered in this procedure, and these were conveniently reduced to a smaller volume by the use of a film evaporator. Although higher yields were obtained by using ether as a solvent for extraction, benzene appeared to be as equally efficient. In using either solvent for extraction, even by means of a continuous liquid-liquid extractor, a long period of time still is required. The adjustment of pH by the use of borate buffers resulted in the formation of a white solid when the reaction mixture was concentrated. Extraction of this solid yielded no glycol and it was believed a complex between the glycol and boric acid had formed.

TABLE I

Hydroxylation of Methyleugenol Using Potassium Permanganate[2]

Run	Potassium Permanganate Concentration (%)	Solvent	Methyleugenol Concentration (%)	Solvent	Reagents Added	pH	Yield(%) of Glycol
1	0.9	water	8.9	water	-	-	-
2	1.0	water	8.9	water	-	-	-
3	6.5	acetone (70%)[1]	17	acetone	-	-	-
4	0.9	water	8.9	water	-	-	-
5	4.0	water	8.9	water	-	-	11.9
6	1.0	water	17	water	-	-	17.6
7	6.5	acetone (70%)[1]	17	acetone	-	-	16.0
8	1.0	water	6.0	ethenol (60%)[1]	NaOH	-	30.8
9	1.0	water	2.3	ethanol (50%)[1]	NaOH	-	30.9
10	0.6	water	1.0	ethanol (70%)[1]	Borate Buffer[3]	10	11.8
11	0.6	acetone (50%)[1]	1.0	acetone (50%)[1]	NaOH	-	-
12	1.0	acetone (50%)[1]	0.6	acetone (50%)[1]	NaOH	-	-
13	1.0	dioxane (50%)[1]	0.6	dioxane (50%)[1]	Borate Buffer[4]	9	-
14	1.0	acetone (50%)[1]	0.6	acetone (50%)[1]	Sodium Acetate[5]	8.9	-
15	1.0	acetone (50%)[1]	0.6	acetone (50%)[1]	$MgSO_4$[6]	6-7	-

Run	Potassium Permanganate Concentration (%)	Solvent	Methyleugenol Concentration (%)	Solvent	Reagents Added	pH	Yield(%) of Glycol
16	1.0	water	0.5	water	Phosphate Buffer[7]	7	18.0
17	1.0	water	0.5	water	-	-	-

1 - represents percentage of solvent in aqueous solution.

2 - all extractions were by the use of continuous liquid-liquid extractor, except runs 1, 2, 3, and 4 where a seperatory funnel was used for extraction. Ether was used as solvent for extraction in runs 1 to 9 and benzene for runs 10 to 17.

3 - Borate Buffer: M/5 boric acid (50 ml.), N/5 sodium hydroxide (43.9 ml.), water (106.1 ml.).

4 - Borate Buffer: M/5 boric acid (50 ml.), N/5 sodium hydroxide (21.3 ml.), water (128.7 ml.).

5 - Sodium acetate (8.9 gm.).

6 - Magnesium sulfate (12.0 gm.).

7 - Phosphate Buffer: Sodium dihydrogenphosphate (7.83 gm.), Potassium dihydrogenphosphate (9.0 gm.).

2. Using Performic Acid - The hydroxylation of methyleugenol was attempted using performic acid according to the procedure of Leaf and Neuberger (14). 30% Hydrogen peroxide (20 ml.) and formic acid (25 ml.) were mixed and allowed to stand at room temperature for one-half an hour. This was then added in three equal portions over a period of fifteen minutes to a stirred solution of methyl-eugenol (25 gm.) (0.14 moles) and formic acid (45 ml.). The temperature was maintained at 40 - 50°C. during the addition and then was maintained at 50 - 60°C. for one and one-half hours. The reaction mixture was then concentrated to 45 ml. by use of the film evaporator, made alkaline with NaOH (10 gm.) dissolved in ethanol (225 ml.) and refluxed for one and one-half hours. After the period of refluxing, the reaction mixture was cooled to room temperature, then acidified with dilute hydrochloric acid. Before acidification, brownish white crystals (6.6 gm.) were obtained. Acidification of the reaction mixture yielded clear crystals (4.6 gm.). Both products were inorganic in nature. Extraction of the reaction mixture yielded no glycol and it was concluded that hydroxylation had not occurred.

Since the above hydroxylation yielded no glycol the procedure of Ferron and L'Ecuyer (13) was followed. Methyleugenol (16.7 gm.) (0.15 moles), 98% formic acid (295 ml.), and 30% hydrogen peroxide (32 ml.) were placed in a round bottom flask. After a lag of approximately five minutes, the reaction began with a resulting rise in temperature. The reaction mixture was cooled on an ice

bath so that the temperature did not exceed 40°C.. This temperature of 40°C was maintained for two hours;after which the reaction mixture was transferred to the film evaporator and reduced in volume to a very viscous, black residue. This residue was dissolved in methanol (100 ml.) and saponified by refluxing for one hour with potassium hydroxide (40 gm.) dissolved in amixture of water (50 ml.), and ethanol (100 ml.). The reaction mixture was extracted with amyl alcohol (2 x 100 ml.). The amyl alcohol was washed with water (20 ml.) and dried over anhydrous sodium sulphate. The amyl alcohol was then distilled to leave a viscous, dark product. An attempt to extract the glycol with benzene was unsuccessful.

The above procedure was repeated starting with eugenol acetate (15.8 gm.) (0.75 moles) and molar equivalents of the other reagents. Before extraction, the solution was made acidic and ethyl acetate was used for the extraction. However the same viscous, dark product was obtained.

The above procedure appeared to be unsuitable for the preparation of methyleugenol glycol. Ferron and L'Ecuyer reported a high yield of methyleugenol glycol, using eugenol acetate as the starting material. The attempt to hydroxylate methyleugenol with performic acid was unsuccessful. If any hydroxylation had occurred, it was impossible to isolate the glycol from the reaction mixture.

3. Using Vicinal Dihalide Compounds. - An attempt to hydroxylate eugenol by means of formation of the dibromide, followed by hydrolysis was attempted. The procedure used was that outlined by Kaufmann, Rosenkranz and Lopez (16). Eugenol (25 gm.) (0.14 moles) was dissolved in ether (25 ml.) and the resulting solution was cooled in an ice bath. To this ether solution, bromine (15 ml.) was added with stirring. After the addition of the bromine, the ether layer was washed with water (15 ml.) and the water layer was extracted with ether. The two ethereal layers were mixed and dried over anhydrous sodium sulphate. Upon distillation of the ether a viscous, brownish-yellow oil (60 gm.) was obtained. The oil was dissolved in glacial acetic acid (300 ml.) and silver acetate (50 gm.) was added. ~~The mixture was refluxed for two hours.~~ After refluxing the mixture for two hours it was cooled and then filtered to remove the silver bromide that had formed. The filtrate was concentrated by use of the film evaporator and then extracted with ether. The ether was removed by distillation and the residue was dissolved in a solution of potassium hydroxide (18.2 gm.) and ethanol (325 ml.) and refluxed for two hours. Extraction of the reaction mixture yielded a viscous, brown product. No glycol was isolated.

C. Oxidation of Methyleugenol Glycol

The oxidation of methyleugenol glycol (XII) to 3,4-dimethoxyphenyl-

acetaldehyde (XIII) was accomplished by the use of both periodic acid and lead tetraacetate. The procedures that were followed are below.

1. Using Periodic Acid (17). - Methyleugenol glycol (XII) (5 gm.) (0.0226 moles) was dissolved in water (500 ml.). To this solution 0.54 molar periodic acid (75 ml.) was added and the mixture obtained was left at room temperature for seventeen hours. To the reaction mixture 20% lead nitrate (100 ml.) was then added to precipitate any excess periodic acid. This precipitate was removed by filtration and the filtrate was washed with water. The aqueous portions were then combined and extracted with ether. The ether layer was dried over anhydrous sodium sulphate and then removed by distillation. The crude 3,4-dimethoxyphenylacetaldehyde (XIII) (3.7 gm.) (87.1%) which was obtained, was distilled under reduced pressure, using a water aspirator. to yield 3,4-dimethoxyphenylacetaldehyde (XIII) (1.8 gm.) (40%); viscous yellow oil, semicarbazone m.p. 178 - 179°C., reported m.p. 180 - 181°C.(18). The low yield obtained above may be due to incomplete oxidation of the glycol or an inability to isolate the aldehyde without causing further oxidation or polymerization. To determine whether the oxidation had been completed and also the time interval necessary for oxidation to occur, analytical work involving the titration of unreacted periodate was used. The method used for this determination was as follows. Methyleugenol glycol (0.0001 moles)

was dissolved in water (50 ml.) and dry paraperiodic acid (0.0005 moles) was added to the aqueous solution of the glycol. After a definite time interval, potassium iodide (2 gm.) and dilute hydrochloric acid (10 ml.) were added and the liberated iodine was titrated immediately with 0.1 N sodium thiosulphate. The results that were obtained are given in Table II.

TABLE II

Oxidation of Methyleugenol Glycol using Periodic Acid

Run	Time (Mins.)	Periodic Acid Consumed (%)
1	2	83
2	2	90
3	2	90
4	10	107
5	10	107
6	20	103
7	20	101
8	30	108
9	30	107

The results found in the above table indicate that the theoretically required amount of periodate for the reaction had been used within a ten minute time period. The high percentages may be partially explained by further oxidations which may occur.

2. Using Lead Tetraacetate (13). - Methyleugenol glycol (XII)(1.9 gm.) (0.0094 moles) was dissolved in benzene (25 ml.) and placed in a three necked round bottom flask provided with a magnetic stirrer and a reflux condenser. The solution was refluxed and lead tetraacetate (4.1 gm.) (0.0094 moles) was added in small portions. After the addition of the lead tetraacetate was completed, the reaction mixture was refluxed for ten minutes. The reaction mixture was then cooled, filtered and the filtrate washed with water. The benzene was removed by distillation and further distillation in vacuo* yielded 3,4-dimethoxyphenylacetaldehyde (XIII) (0.8 gm.) (50%); semicarbazone m.p. 171 - 172°C., reported m.p. 180 - 181°C. (18).

The oxidation of methyleugenol glycol to 3,4-dimethoxyphenylacetaldehyde was accomplished using either periodic acid or lead tetraacetate. The yields obtained using these reagents were similar. It is possible that the yields are lowered in both cases by the distillation which may favor polymerization or further oxidation of the aldehyde.

D. Oxidation of Methyleugenol

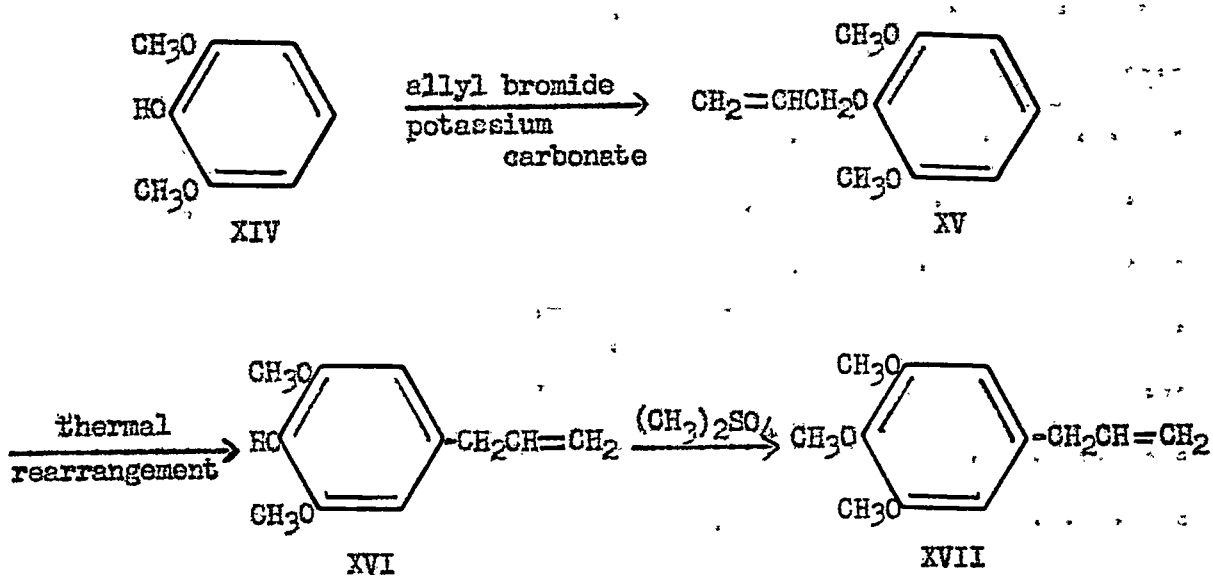
1. Using Nitrobenzene (15). - An attempt to synthesize the 3,4-dimethoxyphenylacetaldehyde using a nitrobenzene oxidation of methyleugenol was made. The following procedure was followed.

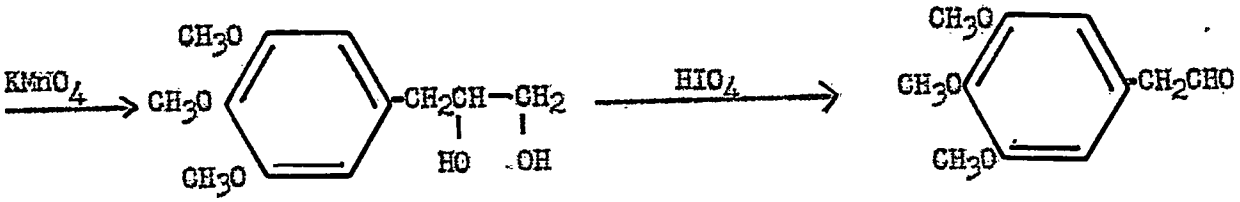
* Bath temperature during the distillation was 150 - 170°C, pressure ca 0.05 mm..

A mixture of methyleugenol (XI)(8.9 gm.) (0.05 moles), nitrobenzene (105 gm.), and 50% sodium hydroxide solution (60 ml.) were refluxed for three and one-half hours. After cooling, the two layers were separated and the alkaline layer was extracted with ether. Distillation of the ether yielded a yellowish oil which when dissolved in water and acidified yielded a light yellow crystals which left a residue on fusion indicating presence of inorganic matter. Nitrobenzene layer was extracted with 20% sodium bisulfite solution, but no bisulfite addition product was obtained. It was concluded that no aldehyde had been formed during the reaction.

II. Synthesis of 3,4,5-Trimethoxyphenylacetaldehyde (First Method)

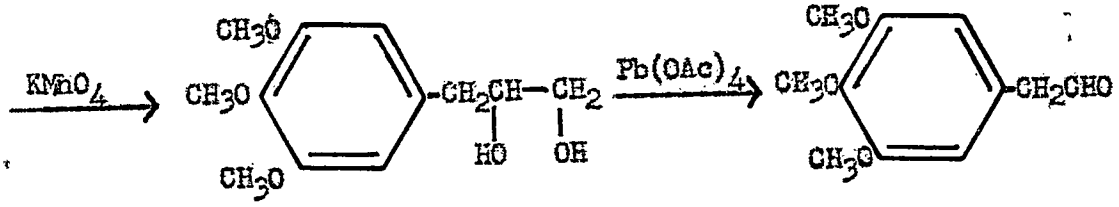
The conditions used for the synthesis of 3,4-dimethoxyphenylacetaldehyde from methyleugenol were applied to the synthesis of 3,4,5-trimethoxyphenylacetaldehyde from 3,4,5-trimethoxyallylbenzene.





XVIII XIX

or



XVIII XIX

A. Synthesis of 3,4,5-Trimethoxyallylbenzene (15). - 2,6-Dimethoxyphenol (XIV) (154 gm.) (1 mole), allyl bromide (121 gm.) (1.1 moles), anhydrous potassium carbonate (180 gm.) (1.3 moles) and anhydrous acetone (400 ml.) were placed in a two litre flask provided with a reflux condenser and a magnetic stirrer. After refluxing for eighteen hours, the reaction mixture was cooled and water was added to dissolve the potassium carbonate. The reaction mixture

was then extracted with ether. The ether layer was washed first with 10% sodium hydroxide and then with water. After drying the ether extract over anhydrous calcium chloride, the ether was removed by distillation. Further distillation under vacuum using a water aspirator yielded 2-alloxy-1,3-dimethoxybenzene (XV) (110 gm.) (56%); b.p. 180 - 195°C..

The 2-alloxy-1,3-dimethoxybenzene (XV) (110 gm.) (0.567 moles) was refluxed for two hours. Distillation of the reaction mixture yielded 4-hydroxy-3,5-dimethoxyallybenzene (XVI) (97.5 gm.) (90.1%); $b.p._{50}$ 172 - 174°C..

4-Hydroxy-3,5-dimethoxyallylbenzene (XVI) (50 gm.) (0.25 moles), and 10% sodium hydroxide (50 ml.) were placed in a one litre flask provided with a reflux condenser and magnetic stirrer. Dimethylsulphate (50 ml.) was added by the use of a dropping funnel. After this was added, the reaction mixture was refluxed for ten minutes and then a further addition of 10% sodium hydroxide (50 ml.) was made followed by dimethylsulphate (50 ml.). A final addition of sodium hydroxide (200 ml.) was made and the reaction mixture was then refluxed for one hour and then extracted with ether. The ether extract was washed with 10% sodium hydroxide and then with water. After drying over anhydrous calcium chloride, the ether was removed by distillation. Distillation under vacuum, using a water aspirator, of the residue yielded 3,4,5-trimethoxyallylbenzene (XVII) (48.3 gm.) (90.1%); b.p. 170 - 180°C..

B. Hydroxylation of 3,4,5-Trimethoxyallylbenzene

1. Using Potassium Permanganate - 3,4,5-Trimethoxyallylbenzene (XVII) (20.8 gm.) (0.1 moles) was dissolved in water (100 ml.) and ethanol (200 ml.). Potassium permanganate (5.5 gm.) dissolved in water (1100 ml.) was added in one portion with stirring; the reaction being carried out at a temperature below 15°C. After three minutes the manganese dioxide was removed by filtration and the aqueous portion was concentrated to a volume of 400 ml. by the use of the film evaporator and then placed in a continuous liquid-liquid extractor. Prolonged extraction using benzene, followed by removal of the benzene by distillation yielded crude 3-(3',4',5'-trimethoxyphenyl)propanediol-1,2 (XVIII). This was recrystallized from a mixture of benzene and petroleum ether (Skellysolve C), yield 12.2 gm., (52.59%); m.p. 83 - 84°C., Anal[E]. Calcd.for $C_{12}H_{18}O_5$: C,59.49; H, 7.488. Found: C, 59.48, H, 7.460. A survey of the available literature revealed no prior information for this compound.

C. Oxidation of 3-(3', 4', 5'-trimethoxyphenyl)propanediol-1,2.

1. Using Periodic Acid - 3-(3',4',5'-trimethoxyphenyl)propanediol-1,2 (XVIII) (6.4 gm.) (0.0266 moles) was dissolved in water (300 ml.). Paraperiodic acid (3.7 gm.) (0.03 moles) dissolved in water (200 ml.) was added through a dropping funnel. After a period of thirty minutes, 10% lead nitrate (100 ml.) was added and the

E - Analysis by Prairie Regional Laboratory, National Research Council, Saskatoon.

solution was filtered. The filtrate was extracted with ether (5 x 50 ml.) and then with benzene (1 x 50 ml.). The organic solvents were dried over anhydrous sodium sulphate and removed by distillation. Distillation *in vacuo*[*] of the residue yielded 3,4,5-trimethoxyphenylacetaldehyde (XIX) (1.85 gm.) (33.1%) as a viscous pale yellow oil[&]: semicarbazone m.p. 186 - 187°C., reported m.p. 188°C. (3).

2. Using Lead Tetraacetate - 3-(3',4',5'-Trimethoxyphenyl)propanediol-1,2 (XVIII) (5 gm.) (0.0238 moles) was dissolved in dry benzene (55 ml.) and placed in a three necked round bottom flask provided with a magnetic stirrer and a reflux condenser. The solution was refluxed and lead tetraacetate (9.3 gm.) was added in small portions. After the addition of the lead tetraacetate was completed, the reaction mixture was refluxed for ten minutes. The reaction mixture was then cooled, filtered and the filtrate washed with water. The benzene was removed by distillation and further distillation *in vacuo*[*] yielded 3,4,5-trimethoxyphenylacetaldehyde (XIX) (2.2 gm.) (50.9%); viscous pale yellow oil[&] , semicarbazone m.p. 186 - 188°C., reported m.p. 188°C. (3).

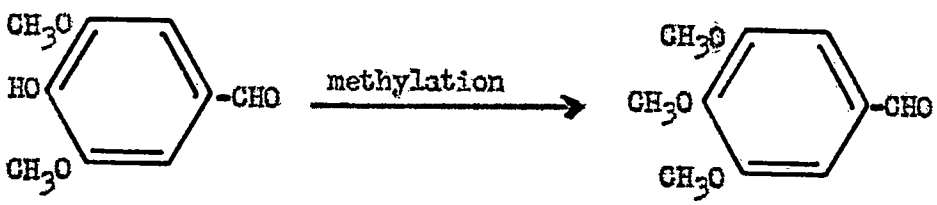
* Bath temperature during the distillation was 160 - 190°C., pressure ca (0.05 mm.).

& The aldehyde was reported in the literature as an oil. On seeding the oil obtained here with crystalline aldehyde obtained in a later procedure, this aldehyde was obtained in a crystalline form.

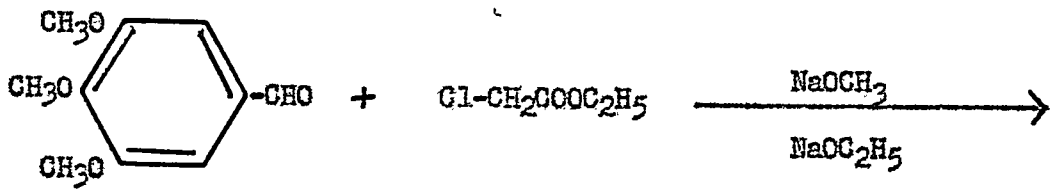
III. Synthesis of 3,4,5-Trimethoxyphenylacetaldehyde (Second Method)

A. Darzens Glycidic Ester Condensation

A second method for the attempted synthesis of 3,4,5-trimethoxyphenylacetaldehyde was the Darzens Glycidic Ester condensation of 3,4,5-trimethoxybenzaldehyde with chloro ethylacetate to form the glycidic ester of 3,4,5-trimethoxybenzaldehyde. Decomposition of the glycidic ester using dilute hydrochloric acid would yield 3,4,5-trimethoxyphenylacetaldehyde. To find the most suitable conditions for this reaction, the synthesis of p-methoxyphenylacetaldehyde from anisaldehyde using this reaction was attempted.



XX XXI



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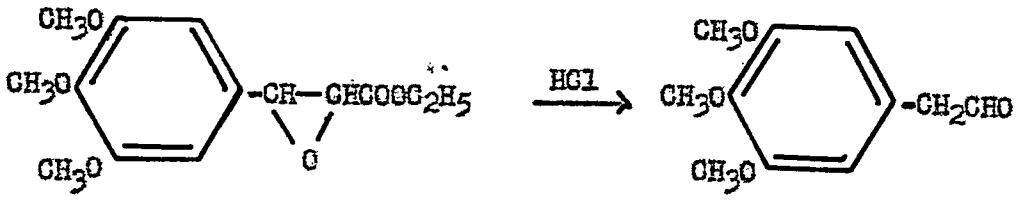

XXII XXIII

1. Using Anisaldehyde. - The procedure of Allen and Van Allen (19) for the preparation of hydratropaldehyde was used for the preparation of p-methoxyphenylacetaldehyde. Sodium amide was used as the condensing agent and the resulting glycidic ester was decomposed by acid hydrolysis. A viscous, yellow oil was obtained as a product; semicarbazone m.p. 136 - 140°C., reported m.p. 180 - 181°C.(21). It was concluded that the desired aldehyde had not been formed.

Lafefield's (20) procedure for the preparation of p-methoxyphenylacetaldehyde was followed. The aldehyde was isolated as the sodium bisulfite addition compound (82.7%). Decomposition of the bisulfite addition compound using sodium carbonate or dilute acid resulted in the formation of a product whose derivatives exhibited melting points which did not correspond to those for p-methoxyphenylacetaldehyde. It appeared that during