

Approval Sheet

John D. Sterling, Jr., Ph. D., 1949

Title of Thesis: The Dehydrogenation
of Benzyl Alcohol in the Liquid
Phase and The Synthesis of Inter-
mediates Leading to Anti-carcino-
genic Compounds

Thesis and abstract approved:

Wilkins Reeve

Professor in charge of thesis
Associate Professor in the
Department of Chemistry

July 20, 1948

**THE DEHYDROGENATION OF
BENZYL ALCOHOL IN THE LIQUID PHASE
and
THE SYNTHESIS OF INTERMEDIATES LEADING TO
ANTI-CARCINOGENIC COMPOUNDS**

by

JOHN D. STERLING, JR.

**Thesis submitted to the Faculty of the Graduate School
of the University of Maryland in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy**

1949

UMI Number: DP71128

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



UMI DP71128

Published by ProQuest LLC (2015). Copyright in the Dissertation held by the Author.

Microform Edition © ProQuest LLC.

All rights reserved. This work is protected against unauthorized copying under Title 17, United States Code



ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346

The author expresses his gratitude to Professor E. Wilkins Reeve for his encouragement and friendly criticism during the course of this work.

The author also wishes to express his gratitude to his wife for undertaking the typing of the manuscript, and to Mary H. Aldridge for doing the analytical analyses.

Table of Contents

	Page
General Introduction.....	1
Part I. The Dehydrogenation of Benzyl Alcohol in the Liquid Phase.....	3
Introduction.....	3
Discussion.....	4
Hydrogen Peroxide as a Hydrogen Acceptor.....	5
Vinyl Ethers as Hydrogen Acceptors.....	6
Diallyl Ether and 2-Ethylhexene-1 as Hydrogen Acceptors.....	7
Raney Nickel and Palladium Catalysts.....	11
Platinum Metal Catalysts.....	11
Other Hydrogen Acceptors.....	15
Experimental.....	15
Procedure Using Three-necked Flask.....	15
Procedure Using Hydrogenation Vessel.....	16
Preparation of Catalysts and Chemicals.....	17
Summary.....	18
Bibliography.....	20
Part II. Synthesis of Intermediates Leading to Anti-carcinogenic Compounds.....	22
Introduction.....	22
Chemistry and Pharmacology of Podophyl- lotoxin and Related Compounds.....	22
Characteristics of the Methylenedioxy Bridge..	34

	Page
Characteristics of the 3,4,5-Trimethoxyphenyl Group.....	35
Discussion.....	36
Synthetic Work Planned.....	36
3',5'-Dimethoxy-4'-trimethylgalloxy-2-methyl- 4,5-methylenedioxybenzophenone.....	38
3',4',5'-Trimethoxy-2-methyl-4,5-methylene- dioxybenzophenone.....	41
3,4,5-Trimethoxy- α -piperonylaceto-phenone.....	43
Experimental.....	47
Methylenedioxy Bridge Test.....	47
Piperonyl Alcohol.....	47
3,4-Methylenedioxytoluene.....	48
Trimethylgallic Acid.....	48
3',5'-Dimethoxy-4'-trimethylgalloxy-2-methyl- 4,5-methylenedioxybenzophenone.....	49
Trimethylgalloyl Chloride.....	51
3',4',5'-Trimethoxy-2-methyl-4,5-methylene- dioxybenzophenone.....	52
Oxidation Studies.....	54
Ethyl 3,4,5-Trimethoxybenzoylacetoacetate.....	56
Ethyl 3,4,5-Trimethoxybenzoylacetate.....	57
Piperonyl Bromide.....	58
3,4,5-Trimethoxy- α -piperonylaceto-phenone.....	58
Summary.....	60
Bibliography.....	62

GENERAL INTRODUCTION

The first part of this thesis deals with the catalytic dehydrogenation of benzyl alcohol in the liquid phase. The importance of aldehydes to the field of organic chemistry makes it desirable to find more successful and reproducible methods of synthesis. The experiments described in this part were carried out with the expectation of developing a successful synthesis of aldehydes by using common hydrogenation catalysts and hydrogen acceptors to dehydrogenate alcohols to the corresponding aldehydes.

The second part of this thesis deals with the synthesis of compounds which might have anti-carcinogenic activity. The compounds chosen for synthesis were those which would serve as intermediates in the preparation of compounds related to podophyllotoxin or even podophyllotoxin itself. Podophyllotoxin and related materials have been shown to have anti-carcinogenic activity.

PART I
THE DEHYDROGENATION OF BENZYL ALCOHOL
IN THE LIQUID PHASE

PART I. THE DEHYDROGENATION OF BENZYL ALCOHOL
IN THE LIQUID PHASE

Introduction

The preparation of aldehydes is often a difficult problem. Since the oxidation of alcohols containing more than four carbon atoms to aldehydes is usually unsatisfactory with the usual oxidizing agents, attempts have been made to remove the hydrogen of the alcohol group by means other than oxidation. It has been shown in previous work that alcohols can be dehydrogenated in both the liquid^{1,2,3} and vapor phases⁴. Vapor phase dehydrogenation is in general used as a method of preparing aliphatic aldehydes and ketones⁵.

Liquid phase dehydrogenation of alcohols has been carried out with Raney nickel catalyst at reflux temperatures and also at higher temperatures under pressure¹. Aliphatic secondary alcohols can be converted successfully to the corresponding ketones by refluxing the alcohol in the presence of Raney nickel catalyst². The method, however, gives poor yields in the case of aliphatic primary alcohols. The method is not satisfactory for the dehydrogenation of a carbinol group attached to an aromatic ring.

When the alcohol to be dehydrogenated contains other function groups which can react with hydrogen, this may occur. Thus dehydrogenation of allyl alcohol gives 82 per cent of the theoretical amount of propanal^{2,3}. Carbinol groups

attached to an aromatic ring give about equal amounts of hydrogenolysis product and aldehyde or ketone.

Since, as shown above, hydrogenation catalysts add as well as remove hydrogen, it should be possible under the influence of these catalysts to transfer hydrogen from an easily dehydrogenated to a readily hydrogenated compound⁶. Kindler and Peschke⁷ have used this principle to reduce cinnamic nitrile almost quantitatively to hydrocinnamic nitrile and *p*-chlorocinnamic acid to *p*-chlorohydrocinnamic acid by using tetralin as a hydrogen donator and palladium-black as the catalyst. Reeve and Adkins¹ have shown that primary aliphatic alcohols can be dehydrogenated in the liquid phase at 280° over copper chromium oxide catalyst in the presence of ethylene. The ethylene combines with the hydrogen formed by the dehydrogenation of the alcohol and thereby shifts the equilibrium so that the dehydrogenation reaction goes more nearly to completion. This method is not applicable to aromatic alcohols. In this thesis, compounds which force a dehydrogenation reaction to go more nearly to completion by combining with the hydrogen are called "hydrogen acceptors".

Discussion

The purpose of this research program was to study further the catalytic dehydrogenation of alcohols to aldehydes with the aid of a hydrogen acceptor, with the emphasis on aromatic alcohols and the use of catalysts which would be active around 100°. Benzyl alcohol was the aromatic alcohol chosen for study.

The first series of experiments were carried out to determine whether the dehydrogenation reaction occurred to an appreciable extent at temperatures below 100°. The following experiments indicate that dehydrogenation did take place to some extent at low temperatures. The reactions were performed using a three-necked flask.

TABLE I
Dehydrogenation at Low Temperatures

<u>Run No.</u>	<u>Catalyst</u>	<u>Hydrogen Acceptor</u>	<u>Alcohol</u>	<u>Length of Run</u>	<u>Temp.</u>	<u>Per Cent Carbonyl</u>
5	Raney nickel	none	Benzyl	3 hrs.	206°	1.6
6	Raney nickel	none	Benzyl	3 days	25°	trace
7	Palladium on carbon	none	Benzyl	3.5 hrs. 7 hrs. 67 hrs.	25° 25° 25°	0.8 1.9 12.4
10	Palladium on carbon	none	Benzyl	19 hrs. 42 hrs.	100° 100°	6.4 7.4

Hydrogen Peroxide as a Hydrogen Acceptor. Hydrogen peroxide is a readily available low molecular weight oxidizing agent, and it was thought that it might be used as a hydrogen acceptor. The experiments in Table II were performed in a three-necked flask using tertbutyl alcohol as a solvent.

The amount of aldehyde obtained was small. The reaction mixtures were titrated for acid content with 0.1N sodium hydroxide solution and no acid was detected. Apparently the difficulty was that the dehydrogenation was so much slower than

the rate of decomposition of the peroxide that the peroxide decomposed leaving only water in the reaction mixture. This would also tend to slow up the dehydrogenation.

TABLE II

Hydrogen Peroxide as Acceptor

<u>Run No.</u>	<u>Catalyst</u>	<u>Hydrogen Acceptor</u>	<u>Alcohol</u>	<u>Length of Run</u>	<u>Temp.</u>	<u>Per Cent Carbonyl</u>
1	Raney nickel	H ₂ O ₂	Benzyl	2 hrs.	30°	1
2	Raney nickel	H ₂ O ₂	Benzyl	2 hrs.	87°	2
3	Raney nickel	H ₂ O ₂	Benzyl	7 hrs. 11 hrs.	87° 87°	0.8 0.8
4	Raney nickel	H ₂ O ₂ (no solvent)	Benzyl	3 hrs. 6 hrs.	140° 140°	trace trace

Vinyl Ethers as Hydrogen Acceptors. It was next decided to use an unsaturated ether as a possible hydrogen acceptor. The first such compound tried was dihydropyran. A three-necked flask was used.

TABLE III

Dihydropyran as Acceptor

<u>Run No.</u>	<u>Catalyst</u>	<u>Mole* Hydrogen Ratio Acceptor</u>	<u>Alcohol</u>	<u>Length of Run</u>	<u>Temp.</u>	<u>Per Cent Carbonyl</u>	
8	Palladium on carbon	.7	Dihydro-pyran	Benzyl	6 hrs.	25°	4.3

* Ratio of the acceptor as compared to the alcohol.

This gave some carbonyl test; however, the unstability of the dihydropyran caused a variety of products to be formed, so its use was discontinued.

Vinyl isobutyl ether is commercially available, and it was tried as a possible hydrogen acceptor. The following experiments were performed using a three-necked flask.

TABLE IV
Vinyl Isobutyl Ether as Acceptor

Run No.	Catalyst	Mole Ratio	Hydrogen Acceptor	Alcohol	Length of Run	Temp.	Per Cent Carbonyl
19	Raney nickel	1.14	Vinyl isobutyl ether	Benzyl	18 hrs.	80°	10.5
20	Raney nickel	1.65	Vinyl isobutyl ether	Benzyl	5 hrs.	110°	9.0
21	Raney nickel with MgO	1.65	Vinyl isobutyl ether	Benzyl	5 hrs.	110°	trace
22	Raney nickel with MgO	1.65	Vinyl isobutyl ether	Benzyl	15 hrs.	80°	trace

The vinyl ethers were unstable and gave a mixture of products. In view of this and the poor yields, the work on vinyl ethers was discontinued.

Diallyl Ether and 2-Ethylhexene-1 as Hydrogen Acceptors.

Diallyl ether, the next candidate hydrogen acceptor studied, is commercially available. It has a boiling point of 95° making it convenient to carry out dehydrogenation reactions

at its refluxing temperature. It is more stable to acid than the vinyl ethers and the double bonds are readily reduced.

2-Ethylhexene-1 was also selected as a possible hydrogen acceptor. It is easily prepared by the dehydration of 2-ethylhexanol-1. It has a boiling point of 120° . The double bond is easily reduced.

An attempt was made to carry out all the experiments evaluating these two substances under similar conditions with the hope of obtaining a comparison between these hydrogen acceptors and between the different catalysts.

The first series of experiments were carried out in a three-necked flask, but it was soon found that it was easier to run the experiments in a closed hydrogenation vessel. This was selected for convenience; not for the use of high pressure. In some of the later experiments a glass liner was placed inside the steel vessel. The results are given in Table V.

Similar experiments were performed using palladium on carbon catalyst. The results are given in Table VI.

The experiments using Raney nickel catalyst indicated that the amount of aldehyde obtained was greater with diallyl ether than with 2-ethylhexene-1. There seemed to be no increase in aldehyde formed when the molar ratio of hydrogen acceptor was increased. In most cases the yield was not affected a great deal. In fact, the general trend was for the amount of carbonyl formed to decrease with a larger excess of hydrogen acceptor. The amount of aldehyde formed did not increase when the reaction was allowed to proceed for a long

TABLE V
Raney Nickel Catalyst

<u>Run No.</u>	<u>"Cat.* prep. no."</u>	<u>Acceptor</u>	<u>Mole Ratio</u>	<u>Alcohol</u>	<u>Length of Run</u>	<u>Temp.</u>	<u>Per Cent Carbonyl</u>	<u>Vessel</u>
14	1	Diallyl ether	0.9	Benzyl	15.5 hrs.	97°	21	3-necked flask
15	1	Diallyl ether	0.9	Benzyl	37 hrs.	97°	21.5	3-necked flask
16	1	Diallyl ether	0.9	Benzyl	11 hrs.	110°	25.6	bomb
17	2	Diallyl ether	1.33	Benzyl	22 hrs.	98°	16.7	bomb
31	3	Diallyl ether	1.33	Benzyl	22 hrs.	90°	7.8	bomb
30	3	2-Ethylhexene-1	1.7	Benzyl	11 hrs.	150°	4.9	bomb
28	3	2-Ethylhexene-1	1.5	Benzyl	24 hrs.	100°	1	bomb

* Catalyst preparation number

TABLE VI

Palladium on Carbon Catalyst

<u>Run No.</u>	<u>Acceptor</u>	<u>Mole Ratio</u>	<u>Alcohol</u>	<u>Length of Run</u>	<u>Temp.</u>	<u>Per Cent Carbonyl</u>	<u>Vessel</u>
11	Diallyl ether	0.9	Benzyl	7 hrs. 23 hrs.	97° 97°	trace 10.6	3-necked flask
12	Diallyl ether	0.9	Benzyl	24 hrs.	97°	14.5	3-necked flask
13	Diallyl ether	3.6	Benzyl	18 hrs.	97°	9.7	3-necked flask
23	Diallyl ether	1.8	Benzyl	24 hrs.	80°	trace	bomb
24	Diallyl ether	1.8	Benzyl	16 hrs.	110°	5	bomb

period of time. At the beginning of a run the amount of carbonyl increased until a certain amount of aldehyde was formed and then the formation of aldehyde stopped or increased very slowly.

Raney Nickel and Palladium Catalysts. The experiments with Raney nickel and palladium on carbon catalysts are rearranged in Table VII to show the effect of changing the catalyst and keeping the hydrogen acceptor constant.

This table gives a comparison between the nickel and palladium catalysts. Both seem to be effective as dehydrogenation catalysts under these conditions, but neither gave the yields expected in a preparative method. Nickel gave consistently somewhat better yields than did palladium.

Platinum Metal Catalysts. A series of experiments were then performed using different platinum metals under similar conditions. Diallyl ether and 2-ethylhexene-1 were used as hydrogen acceptors, and most of the experiments were run for 14 to 16 hours at 100°. The results are given in Table VIII.

The only catalyst that showed promise as a dehydrogenation catalyst under the conditions used was ruthenium. While ruthenium gave encouraging yields of aldehyde, it caused the diallyl ether to polymerize. This liquid polymer decomposed to give diallyl ether upon heating. Ruthenium and 2-ethylhexene-1 did not give an appreciable amount of aldehyde as did diallyl ether. When ruthenium and diallyl ether were used with 2-ethylhexanol-1 no appreciable amount of dehydrogenation took place.

TABLE VII

Diallyl Ether as the Hydrogen Acceptor

<u>Run No.</u>	<u>Hydrogen Acceptor</u>	<u>Mole Ratio</u>	<u>Alcohol</u>	<u>Length of Run</u>	<u>Temp.</u>	<u>Per Cent Carbonyl</u>	<u>Vessel</u>
14	Raney nickel	0.9	Benzyl	15.5 hrs.	97°	21	3-necked flask
15	Raney Nickel	0.9	Benzyl	37 hrs.	97°	21.5	3-necked flask
16	Raney nickel	0.9	Benzyl	11 hrs.	110°	25.6	bomb
17	Raney nickel	1.33	Benzyl	22 hrs.	98°	16.7	bomb
31	Raney nickel	1.33	Benzyl	22 hrs.	90°	7.8	bomb
11	Palladium on carbon	0.9	Benzyl	7 hrs. 23 hrs.	97° 97°	trace 10.6	3-necked flask
12	Palladium on carbon	0.9	Benzyl	24 hrs.	97°	14.5	3-necked flask
13	Palladium on carbon	3.6	Benzyl	18 hrs.	97°	9.7	3-necked flask
23	Palladium on carbon	1.8	Benzyl	24 hrs.	80°	trace	bomb
24	Palladium on carbon	1.8	Benzyl	16 hrs.	110°	5	bomb

TABLE VIII

Platinum Metal Catalysts

<u>Run No.</u>	<u>Catalyst</u>	<u>Hydrogen Acceptor</u>	<u>Mole Ratio</u>	<u>Alcohol</u>	<u>Length of Run</u>	<u>Temp.</u>	<u>Per Cent Carbonyl</u>	<u>Vessel</u>
32	Platinum on carbon	Diallyl ether	1.8	Benzyl	22 hrs.	100°	trace	liner
33	Platinum on carbon	2-Ethyl- hexene-1	1.7	Benzyl	19 hrs.	100°	trace	liner
34	Platinum on carbon	2-Ethyl- hexene-1	1.5	Benzyl	14 hrs.	100°	trace	liner
35	Rhodium on carbon	Diallyl ether	1.93	Benzyl	11 hrs.	100°	trace	liner
36	Rhodium on carbon	2-Ethyl- hexene-1	2	Benzyl	14 hrs.	100°	trace	liner
37	Ruthenium on carbon	Diallyl ether	1.8	Benzyl	16 hrs.	100°	16	liner
38	Ruthenium on carbon	2-Ethyl- hexene-1	2	Benzyl	16 hrs.	100°	trace	liner
39	Ruthenium on carbon	Diallyl ether	3.6	Benzyl	10 hrs.	100°	45.5	liner
44	Ruthenium on carbon	Diallyl ether	3	2-Ethyl hexanol-1	8-9 hrs.	100°	trace	liner
40	Iridium on carbon	Diallyl ether	1.8	Benzyl	16 hrs.	100°	trace	liner
41	Iridium on carbon	2-Ethyl- hexene-1	1.8	Benzyl	16 hrs.	100°	trace	liner
42	Osmium on carbon	Diallyl ether	1.8	Benzyl	16 hrs.	100°	trace	liner

TABLE IX

Other Hydrogen Acceptors

<u>Run No.</u>	<u>Catalyst</u>	<u>Hydrogen Acceptor</u>	<u>Mole Ratio</u>	<u>Alcohol</u>	<u>Length of Run</u>	<u>Temp.</u>	<u>Per Cent Carbonyl</u>	<u>Vessel</u>
25	Palladium on carbon	Cyclo- hexene	1.85	Benzyl	22 hrs.	150°	10.2	bomb
26	Palladium on carbon	Cyclo- hexene	1.85	Benzyl	45 hrs.	200°	1	bomb
27	Raney nickel	Cyclo- hexene	1.4	Benzyl	19 hrs.	100°	trace	bomb
29	Raney nickel	Diethyl maleate	1.0	Benzyl	20 hrs.	100°	none	bomb
18	Palladium on Raney nickel	Diallyl ether	1.33	Benzyl	22 hrs.	98°	10	bomb

Other Hydrogen Acceptors. Miscellaneous experiments were performed and are listed in Table IX. In experiment 27, when the reaction vessel was opened a rather large pressure was observed. This is presumed to be hydrogen. Upon distillation of the reaction mixture it was observed that the cyclohexene had been converted to benzene and cyclohexane.

Experimental

The reaction vessels used during these experiments were of three types: three-necked flasks, hydrogenation vessels without glass liners, and hydrogenation vessels with glass liners. The use of three-necked flasks had the advantage of allowing one to test for carbonyl at different time intervals without interrupting the experiment. With the mechanical stirrer, the equipment had the disadvantage of needing periodic attention which was impractical for the length of time required for some experiments. In addition, when diallyl ether was used as a solvent, the water cooled condenser was unable to prevent the diallyl ether from slowly escaping, even though the end of the condenser was plugged with cotton or connected to a drying tube. For these reasons the three-necked flasks were discarded in favor of the hydrogenation vessels.

Procedure Using Three-necked Flask. Benzyl alcohol (15 grams) and 0.75 grams of palladium on carbon catalyst were added to a 100 ml. three-necked flask. The flask was fitted with a mechanical stirrer and a reflux condenser protected by a calcium chloride drying tube. The reaction mixture was

stirred and heated to 100° . After 19 hours the stirring was stopped and the mixture cooled to room temperature. A 1 ml. sample was pipetted from the reaction mixture and the per cent aldehyde in the sample was determined by precipitating and weighing it as the 2,4-dinitrophenylhydrazone according to the procedure of H. A. Iddles¹¹. The per cent aldehyde present was 6.4. The stirring was continued and the reaction mixture heated at 100° for 42 hours at which time the stirring was discontinued and the reaction mixture cooled to room temperature. The per cent aldehyde in a 1 ml. sample was again determined and found to be 7.4.

Procedure Using Hydrogenation Vessel. Benzyl alcohol (10 ml., 0.0925 mole), 15 ml. (0.1235 mole) of diallyl ether and 1.5 grams of Raney nickel catalyst were placed in a standard American Instrument Company steel hydrogenation vessel having a capacity of 110 ml. The vessel was used as a reaction chamber by closing the hydrogen inlet tube with a fitted solid steel rod. The reaction was rocked at 98° in an American Instrument Company small rocker. The temperature was controlled by a Leeds and Northrup Co. Recording Micromax. After 22 hours the shaking was stopped and the reaction mixture cooled to room temperature, filtered with the aid of "Filter Cell", and the filtrate distilled through a 12 inch Vigreux column. The fraction distilling at $188-199^{\circ}$ was collected for analysis. The volume of this fraction was 7.5 ml. There was a 2.5 ml. residue remaining in the distillation flask. The per cent aldehyde based upon the original volume was 16.7.

The later experiments were carried out in a glass liner within the hydrogenation vessel. The liner was a closed glass ampule, fitted with a standard taper 19/38 removable top that just fit inside the hydrogenation vessel. A piece of Neoprene Rubber was placed at the top and bottom of the glass liner, and 5-7 ml. of the hydrogen acceptor was placed in the area between the liner and the closed hydrogenation vessel to keep the pressures on the inside and outside of the liner equal.

Preparation of Catalysts. The catalysts were prepared as described in the literature. Raney nickel was prepared by the method of Pavlic and Adkins⁸. Palladium on carbon was prepared by the method of W. H. Hartung⁹. The rest of the platinum metal catalysts were prepared by the method of A. A. Pollitt¹⁰.

Benzyl Alcohol. The benzyl alcohol was purified by distillation. The purified material gave a negative test for aldehyde.

Diallyl Ether. The diallyl ether was obtained from the Shell Chemical Corporation. It was purified by distillation.

2-Ethylhexene-1. The 2-ethylhexene-1 was prepared by the dehydration of 2-ethylhexanol-1 with aluminum oxide at 330-360°. The alcohol was passed over the hot aluminum oxide twice and converted to 95 per cent of the theoretical amount of 2-ethylhexene-1 having a boiling point of 117-120°/760 mm. pressure.

Cyclohexene. The cyclohexene was prepared by the

dehydration of cyclohexanol by aluminum oxide at 360° . A conversion of 90 per cent of the theoretical amount of cyclohexene was obtained. The cyclohexene had a boiling point of $81.5-82^{\circ}/760$ mm. pressure.

Vinyl Isobutyl Ether. The vinyl isobutyl ether was obtained from the General Aniline Co. It was purified by distillation.

Dihydropyran. The dihydropyran was obtained from Dr. G. F. Woods of the University of Maryland.

Summary

The conversion of alcohols into aldehydes and hydrogen is catalyzed by metallic hydrogenation catalyst at temperatures as low as 100° . The presence of a hydrogen acceptor removes the hydrogen formed and causes the equilibrium to shift and an increased amount of aldehyde to be formed. Even under optimum conditions, twenty-five per cent or less of the alcohol is converted to aldehyde. Accordingly, the method appears to be of little interest for the practical synthesis of aldehydes.

It was observed that in general, the reaction proceeded slowly until a certain amount of aldehyde was formed, and then very little or no more aldehyde was formed even though the reaction was continued for a longer period of time. One explanation of this phenomenon is that the aldehyde poisons the active centers of the catalyst. That is, as the aldehyde is formed it is adsorbed on the surface of the catalyst until finally the catalytic surface is completely covered by the

aldehyde and the alcohol cannot be adsorbed³.

If it is true that the reaction fails because the aldehyde is not satisfactorily desorbed by the catalyst, then it might be possible to continue the study along three possible paths:

1. Remove the aldehyde from the reaction mixture as it is formed.
2. Obtain a hydrogen acceptor which not only could be reduced by the hydrogen from the alcohol but also would displace the aldehyde from the surface of the catalyst.
3. Add a third component to the reaction mixture to displace the aldehyde from the surface of the catalyst by reacting with it or by being preferentially adsorbed.

Another possible, but less likely cause of failure may be that small amounts of water set free during the reaction poison the catalyst. For example, when benzyl alcohol is refluxed over Raney nickel catalyst a considerable amount of toluene and water are formed. Even though the amount of toluene and water formed was small under the conditions used in this research, this small amount of water could be sufficient to stop the dehydrogenation reaction by being strongly adsorbed on the catalytic surface.

Bibliography

1. Reeve, W. and H. Adkins, J. Am. Chem. Soc., 62, 2874 (1940).
2. Palfray, L. and S. Sabetory, Comptes Rendus, 208, 109 (1939).
3. Paul, R., Comptes Rendus, 208, 1319 (1939).
4. Bouveault, L., Bull. Soc. Chim., 3, 118 (1908).
5. Weggand, C, "Organic Preparations", Interscience Publishers, Inc., New York, 1945, p. 144.
6. Ibid., p. 25.
7. Kindler, K. and W. Peschke, Annalen, 497, 193 (1932).
8. Pavlic, A. A. and H. Adkins, J. Am. Chem. Soc., 68, 1471 (1946).
9. Hartung, W. H., J. Am. Chem. Soc., 50, 3370 (1928).
10. Pollitt, A. A., Chem. Age, 3, 200 (1920).
11. Iddles, H. A., A. W. Low, B. D. Rosen, and R. T. Hart, Ind. Eng. Chem., An. Ed., 11, 102, (1939).

PART II
THE SYNTHESIS OF INTERMEDIATES LEADING TO
ANTI-CARCINOGENIC COMPOUNDS

PART II. THE SYNTHESIS OF INTERMEDIATES LEADING
TO ANTI-CARCINOGENIC COMPOUNDS

Introduction

Chemistry and Pharmacology of Podophyllotoxin and Related Compounds. Podophyllin is a resinous plant extract which has long been used in India, Europe, and America as a powerful purgative, and was at one time believed to beneficially affect the liver¹. The drug is found in Podophyllum amodi, which is a small, herbaceous plant that grows abundantly in Northern India. The root, or more strictly, the rhizome extract of this plant is the source of the drug used in Indian medicinal practice. The American plant, Podophyllum peltatum, is employed in Europe and America. The active principle of the drug is the lactone podophyllotoxin; also present is the isomeric lactone picropodophyllin² and other substances.

Podophyllotoxin is a highly toxic compound which causes mucosal inflammation and gastroenteritis¹². It likewise involves the nervous system (in the cat) resulting in disturbance of coordination of the posterior extremities, rapidly increasing weakness, increased respiratory rate, violent colonic cramps and death in coma. The parenteral administration of podophyllin to chickens likewise results in nervous system involvement and damage to or complete degeneration of the cerebellar Purkinje cells and other nervous elements.

In 1947 it was reported that placental serum from a

patient previously treated for Condylomata acuminata with podophyllin caused severe damage to mouse tumor cells growing in roller tubes without affecting normal cells growing in the same tubes.

Later, more extensive biochemical work showed that podophyllin was significantly more damaging in vitro to mouse tumors than to normal embryonic mouse tissue including fibroblastic and epithelial elements. In vivo studies with tumor-bearing mice have confirmed the selective tumor damaging effects of podophyllin.

Podophyllotoxin, the constituent of podophyllin responsible for its purgative action, was first obtained pure by Kursten². He proved that three methoxyl groups are present in both compounds, which give the same hydroxy-acid¹, podophyllic acid. Podophyllotoxin crystallizes with a variety of solvents of crystallization and has the formula $C_{22}H_{22}O_8$ ³. Two non-phenolic hydroxyl groups are present in podophyllic acid and the lactones form a monoacetyl derivative. The acetyl derivative of picropodophyllin loses acetic acid, giving the unsaturated apopicropodophyllin. Borsche also treated podophyllotoxin with hydriodic acid in acetic acid and formed the acid, $C_{13}H_{10}O_4$, which is called podophyllomeronic acid (I).

Späth⁴ showed that one hydroxyl group was present in podophyllotoxin and picropodophyllin, and confirmed the suggestion that the isomeric lactones differ, owing to the participation of different hydroxyl groups in lactonization.

Soon after this Borsche⁵ proved the structure of the acid, podophyllomeric acid (I). It was fused with alkali to give phyllomeric acid (II). This was decarboxylated to give phyllomerol (III), which when distilled from zinc dust gave 2-methylnaphthalene (IV). Oxidation studies were carried out to aid in the proof of structure of these acids. Phyllomeric acid (II) was oxidized to 2,4,5-toluenetricarboxylic acid (V), which was oxidized to pyromellitic acid (VI)⁴. Pyromellitic acid was also obtained from the vigorous oxidation of phyllomeric acid (II).

Picropodophyllin and podophyllotoxin were both oxidized to trimethylgallic acid (VII) with hot permanganate^{4,5}. Hydrastic acid (VIII) was obtained by the oxidation of podophyllotoxin with alkaline permanganate⁶. By more careful oxidation of picropodophyllin with alkaline permanganate at 50° Späth⁷ was able to isolate the acid IX. The structure of this acid was proven by decarboxylation with copper-bronze to give ketone XIII. This ketone was synthesized in poor yield by the action of 1,2-methylenedioxybenzene (XI) with trimethylgalloyl chloride (XII) with the aid of aluminum chloride catalyst (page 29). The lactone X was isolated by Borsche⁸ from the oxidation products obtained from the oxidation of podophyllic acid and permanganate. Späth⁷ was also able to isolate this lactone from the oxidation of picropodophyllin with alkaline permanganate at 60°. He also converted the acid IX to the lactone X through reduction with zinc dust in alkaline methyl alcohol-water solution. The lactone obtained from this

reduction was identical with the lactone Borsche obtained from the oxidation of picropodophyllin. The isolation of the above degradation products indicates that podophyllin consists of two isomers which are lactones differing only as to the group that enters into the formation of the lactone ring. The isolation of trimethylgallic acid accounts for the three methoxyl groups present in the molecule, and the isolation of hydrastic acid indicates the presence of a methylenedioxy bridge in the molecule and its position with relation to other group attachments to that benzene ring. The isolation also of acid IX and the lactone X would indicate that the molecule has the general structure as outlined by formula XIV which also must contain a free hydroxyl and a lactone structure.

The isolation of podophyllomeronic acid (I) indicates that the hydriodic acid splits off the 3,4,5-trimethoxyphenyl group from either carbon one or four. It also would seem that the hydroxyl groups are not present on either the ring with the methylenedioxy group or on the 3,4,5-trimethoxyphenyl group. The carbon containing the 3,4,5-trimethoxyphenyl group cannot have a hydroxyl group since upon oxidation to give lactone X that carbon would be more easily oxidized than is indicated by the formation of this lactone. It also seems unlikely that carbon two or three could contain a hydroxyl since on those carbons it could not enter into lactone formation. By elimination, one hydroxyl must be on carbon

one; the 3,4,5-trimethoxyphenyl group must be on carbon four, and the other hydroxyl on the methylene group attached at carbon two. The structure of podophyllic acid is accordingly believed to be as indicated in formula XV.

This structure is also borne out by the dehydration and dehydrogenation work of Späth⁹. Both podophyllotoxin and picropodophyllin were heated at 230° with palladium to give a lactone $C_{22}H_{18}O_7$ melting at 266°. According to the proposed formulas the lactone would have the structure as indicated in formula XVI. This proposed formula was somewhat substantiated by Haworth¹⁰ when he synthesized lactone XVII and proved that it was different from the lactone XVI obtained by Späth. Both lactones, upon oxidation with permanganate, give the same dibasic acid XVIII.

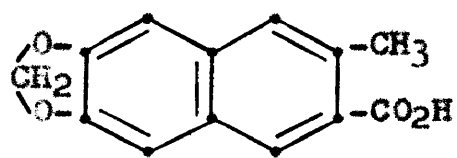
Lactone XVII was prepared by the following series of reactions (page 31). Ethyl sodio-3,4,5-trimethoxybenzoylacetate was reacted with ethyl bromoacetate in boiling alcoholic solution to give after hydrolysis β (3,4,5-trimethoxybenzoyl) propionic acid (XIX). The sodium salt of that was condensed with piperonal (XXX) in acetic anhydride solution to give XX. Acid XX was reacted with formaldehyde in alkaline solution to give XXI, which was cyclized by a mixture of acetic and hydrochloric acids to give XXII. After alkaline hydrolysis and lactonization the lactone XVII was obtained.

Later Haworth and Richardson¹¹ were able to synthesize the lactone XVI and found that it was identical with the lactone obtained by Späth from the oxidation of the natural

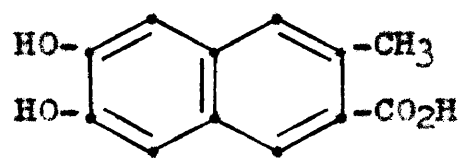
compound. Lactone XVI was synthesized by the following series of reactions (page 32). Safrole oxide XXIII was reacted with ethyl sodioacetoacetate to give XXIVa, which upon reaction with trimethylgalloyl chloride followed by hydrolysis with cold sodium hydroxide solution, gave XXVa. Compound XXVa was cyclized by treatment with hydrogen chloride in methyl alcohol solution to give the lactone XXVIa. This was dehydrated with potassium hydrogen sulphate at 180° to give the lactone XXVIIa. Upon treatment of this with either palladium-black or lead tetraacetate in acetic acid solution the desired lactone XVI was obtained which was identical with the one obtained by Späth from the oxidation of the natural product.

Lactone XXVIIa was oxidized to give acid IX which was identical with the acid Späth obtained from the oxidation of the natural product.

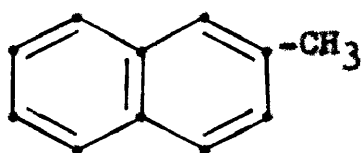
From this work it seems quite definite that podophyllic acid would have the structure XV. Podophyllotoxin and picropodophyllin are then given the formulas XXIV and XXV respectively. These structures seem quite logical since picropodophyllin seems to be the more stable of the two and its free hydroxyl is more easily removed by dehydration. These are the accepted formulas; however, they are not proven by synthesis.



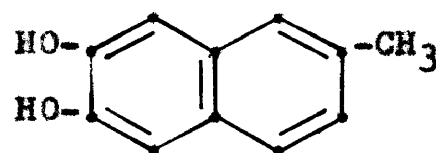
I



II



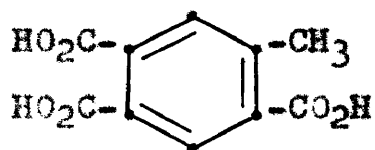
IV



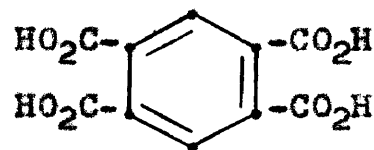
III



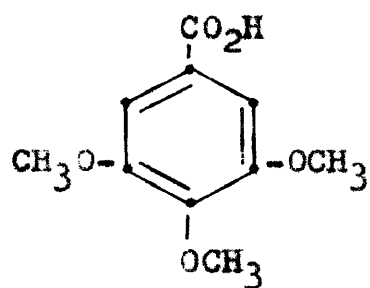
Oxidation



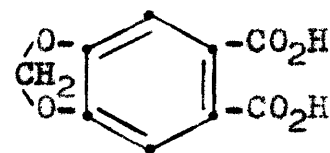
V



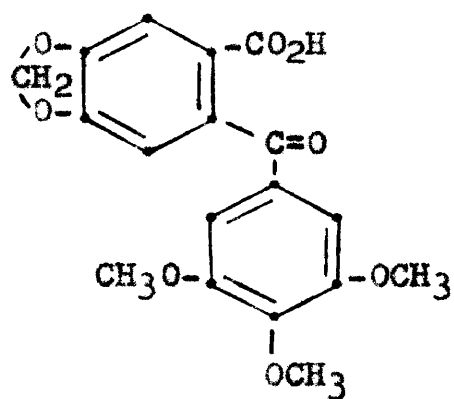
VI



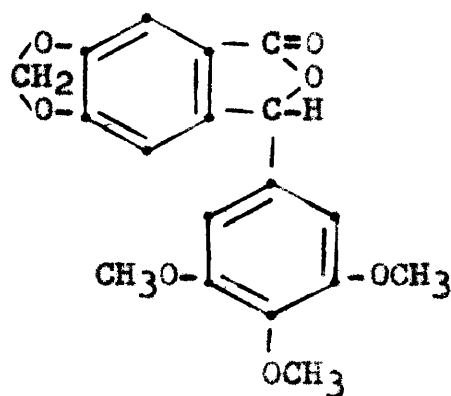
VII



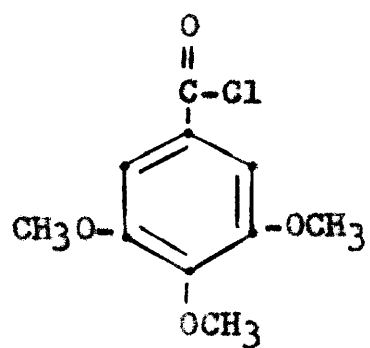
VIII



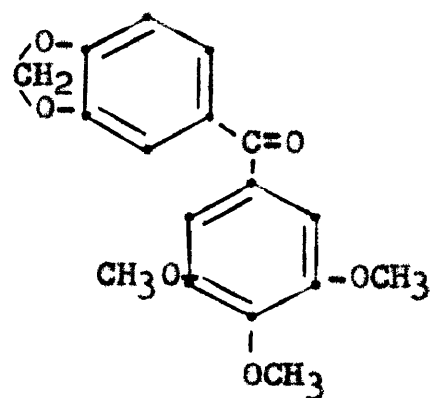
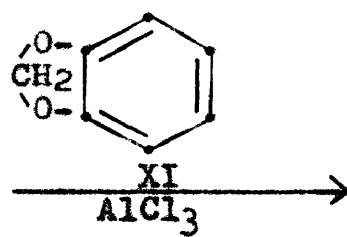
IX



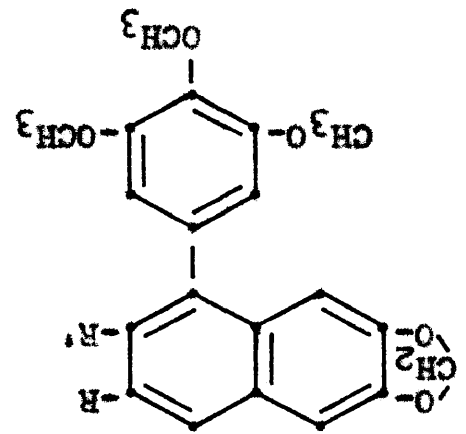
X



XII



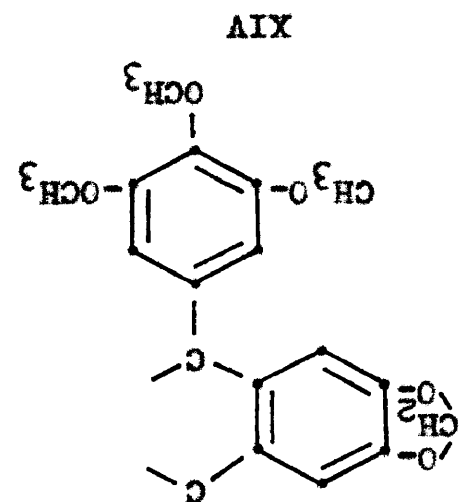
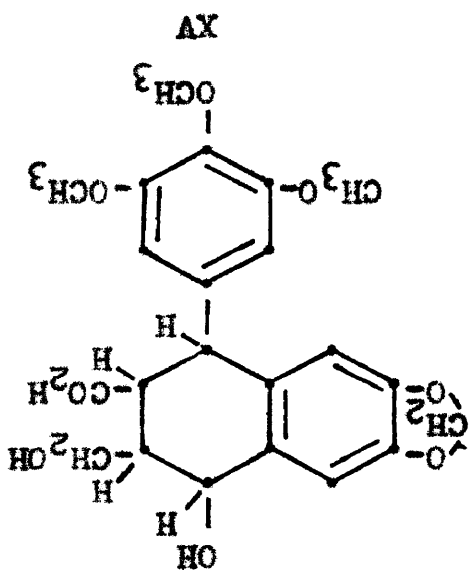
XIII

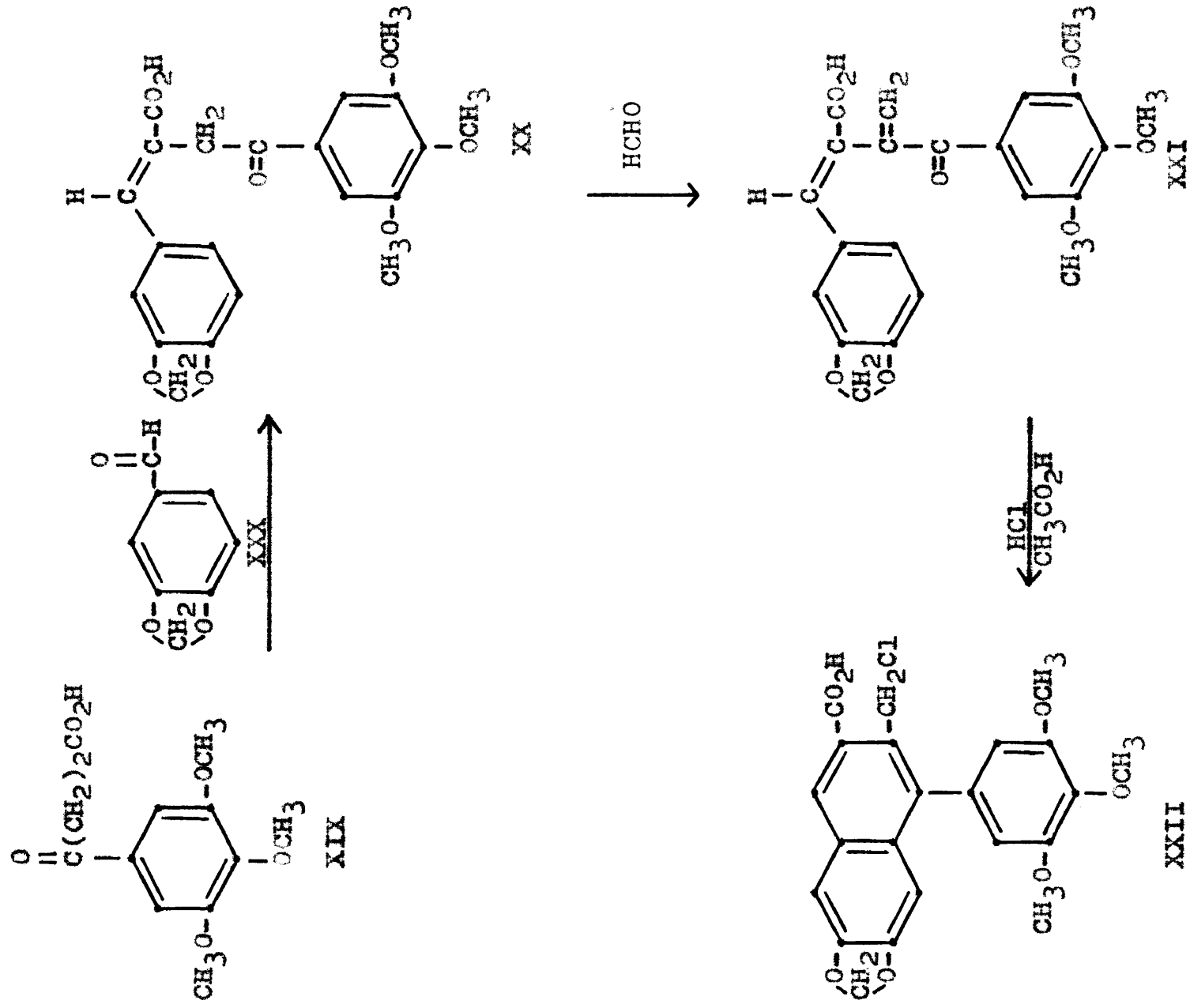


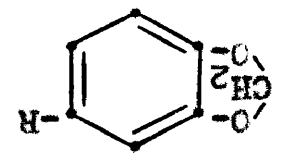
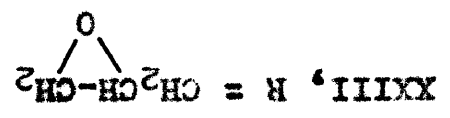
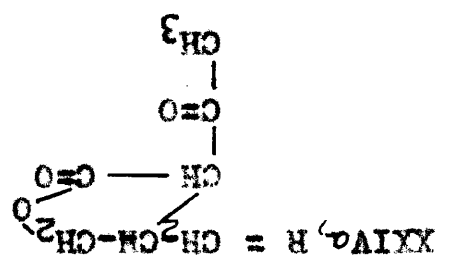
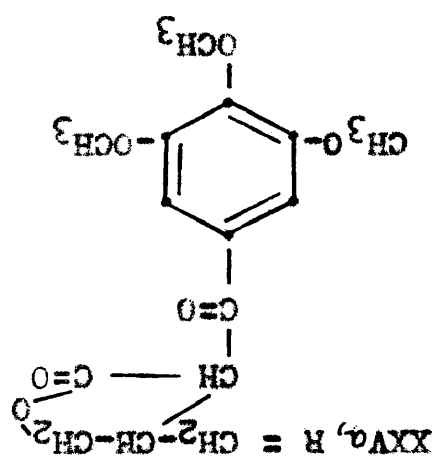
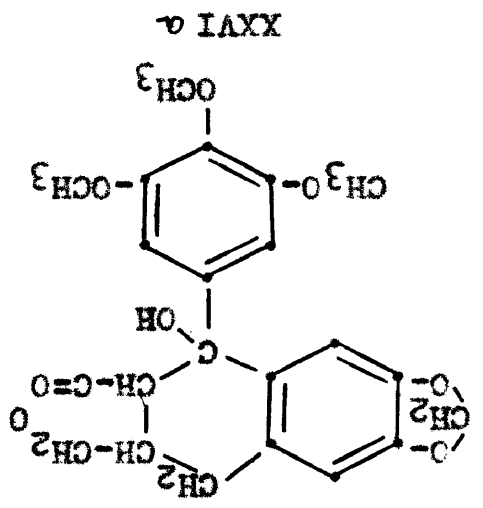
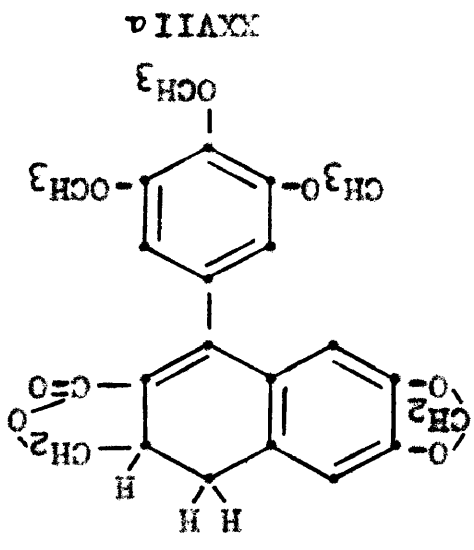
XVIII, $R=R' = \text{CO}_2\text{H}$

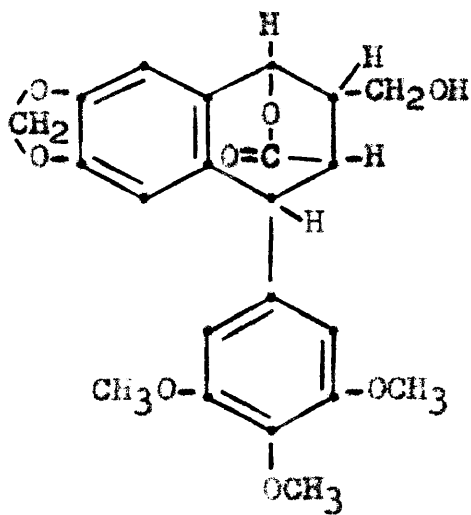
XVII, $R, R' = \text{C}=\text{O}$

XVI, $R, R' = \text{CH}_2$



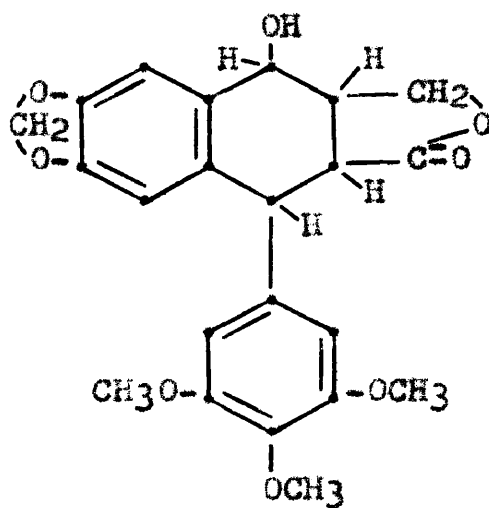






Podophyllotoxin

XXIV



Picropodophyllin

XXV

Characteristics of the Methylenedioxy Bridge. Since the purpose of this work was to synthesize compounds of similar structure to podophyllotoxin, the characteristics of the methylenedioxy bridge and the 3,4,5-trimethoxyphenyl group was an important consideration.

Compounds containing the methylenedioxy bridge react with concentrated acid¹³ to form insoluble, non-volatile polymers of a carbon-like appearance. These substances are usually formed by the liberation of formaldehyde which condenses with the phenolic parent substances.

Späth¹³ and Kafuku¹⁴ both found that methylmagnesium iodide ruptures the methylenedioxy bridge with the formation of the monoethyl ether of the dihydroxy compound and that this method could be used whenever the compound contains no other group that will react with methylmagnesium iodide.

Other acidic reagents such as aluminum chloride or aluminum bromide¹⁵ can be used to split the methylenedioxy bridge to the corresponding dihydroxy compound at room temperature with nitrobenzene as a solvent. Aluminum chloride is less reactive than aluminum bromide. This method leaves methoxyl and ester groupings practically intact.

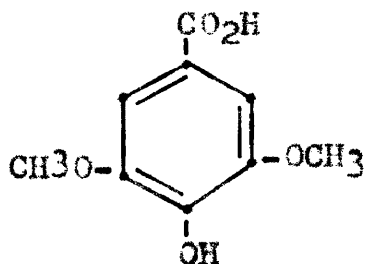
In contrast to the reactivity of the methylenedioxy bridge with acidic reagents, this group is stable toward basic reagents. This is in agreement with its acetal structure. Späth¹³ has shown that dihydrosafrole is scarcely attacked by sodium ethoxide at 175° or by sodium hydroxide at 200°.

The methylenedioxy bridge is stable when subjected to catalytic reduction^{13,14}. Safrole (XXXVIII) can be reduced to dihydrosafrole using Raney nickel and platinum or palladium on carbon. The group is also stable to reduction using copper chromium oxide catalyst which will be discussed later.

There are several qualitative^{18,19} tests for the methylenedioxy bridge. These methods are based upon the fact that concentrated sulfuric acid reacts to give formaldehyde which condenses with phloroglucinol or gallic acid to form a green or blue-green color. The methylenedioxy group can be determined quantitatively²⁰ by weighing the condensation product from the liberated formaldehyde and phloroglucinol.

Characteristics of the 3,4,5-Trimethoxyphenyl Group.

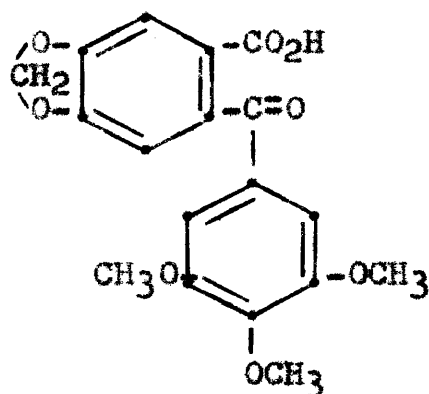
The 3,4,5-trimethoxyphenyl group is stable to alkali. The methoxyl groups can be split with acidic reagents, the center methoxyl being the one most easily split to the corresponding hydroxyl compound. Bogert and Coyne¹⁷ have employed this method to prepare syringic acid (XXVI) by treatment of trimethylgallic acid with concentrated sulfuric acid for six hours at 40°.



XXVI

Discussion

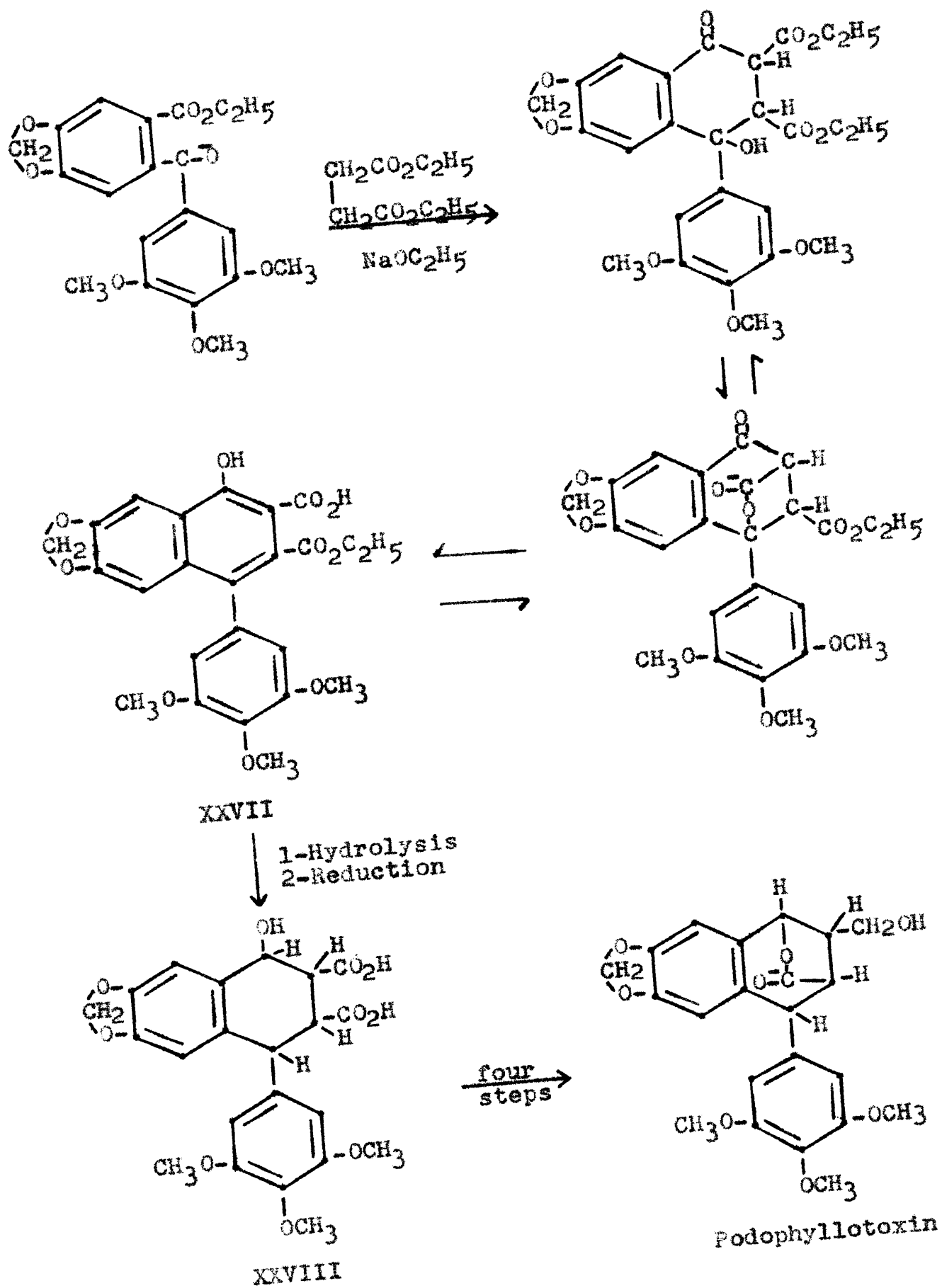
Synthetic Work Planned. The overall research program was planned in such a manner that compounds similar to podophyllotoxin could be prepared. These compounds might have anti-carcinogenic activity and could also serve as intermediates in the synthesis of podophyllotoxin itself. Since the acid IX had been obtained from oxidation studies of podophyll-



IX

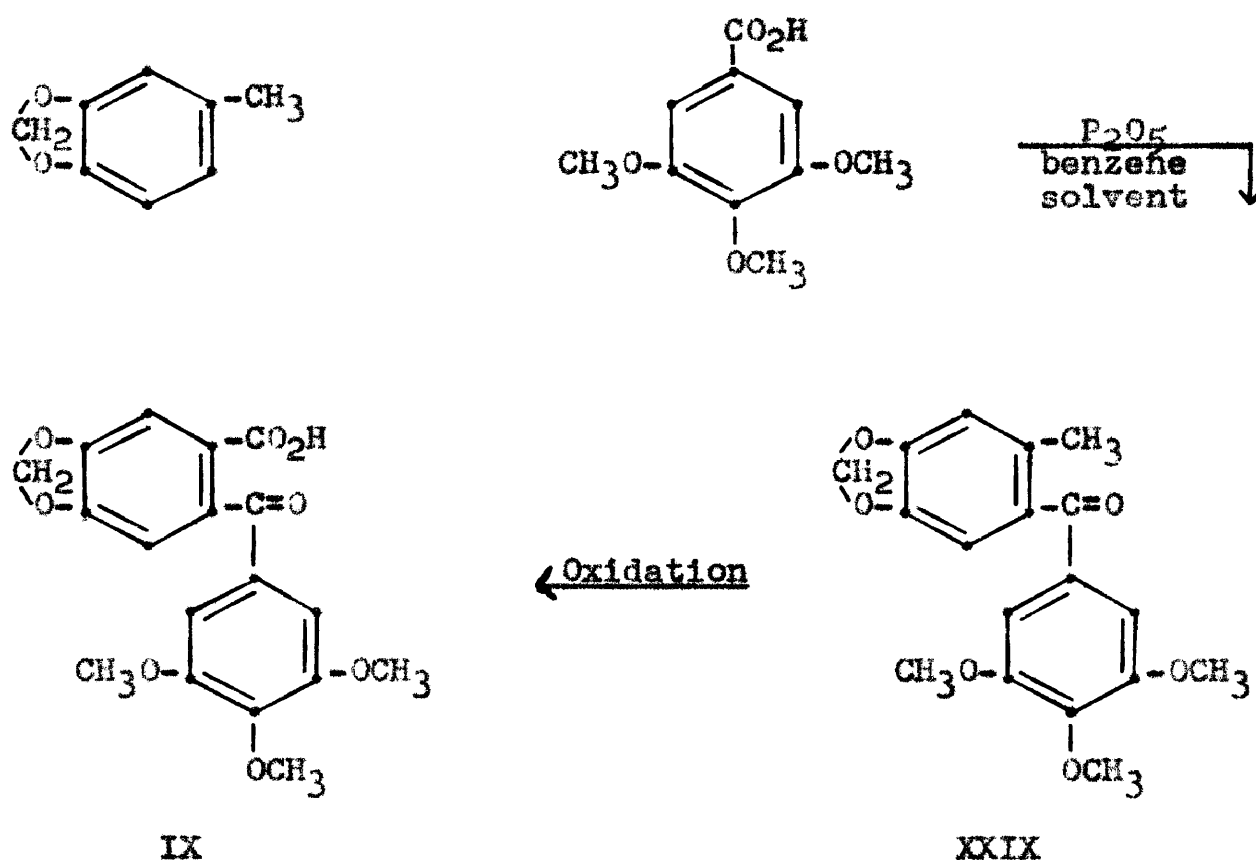
otoxin, it was decided to devise a synthesis of this compound which might be used in further synthetic studies. A series of reactions was outlined (page 37) starting with this acid which might lead to the synthesis of podophyllotoxin.

The first reaction of this series was one involving both a Stobbe and a Dieckmann condensation. The ethyl ester of acid IX is condensed with diethyl succinate. There are a few similar compounds which undergo the Stobbe condensation²¹. No examples have been found where both a Stobbe and a Dieckmann condensation occur. However, one example was found where a keto-nitrile reacted with diethylsuccinate to form a six membered ring²². Since the ester group will react more easily than the nitrile group in alkaline condensations, the above outlined reaction should take place. Compound XXVII upon hydrolysis and reduction should give the dibasic acid XXVIII. This dibasic acid is of interest since theoretically it could be derived from



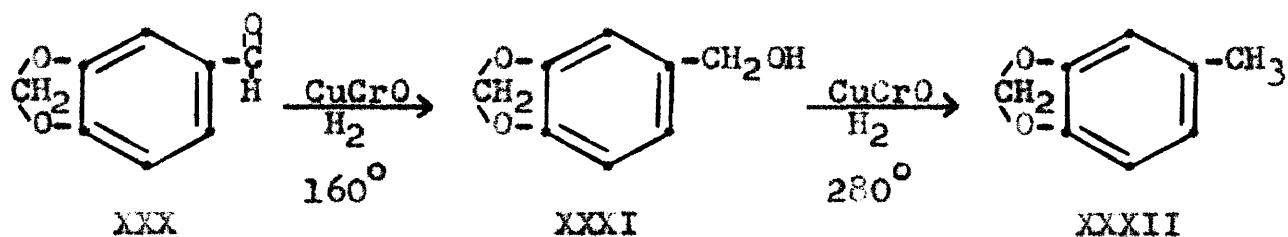
podophyllotoxin by the oxidation of the primary alcohol group. It should also prove of value as an intermediate for the synthesis of podophyllotoxin.

3',5'-Dimethoxy-4'-trimethylgalloxy-2-methyl-4,5-methylenedioxybenzophenone. The following synthesis of acid IX was undertaken.



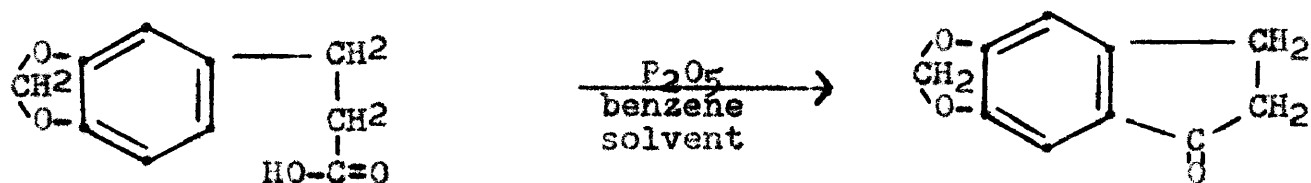
Trimethylgallic acid (VII) was prepared from gallic acid and dimethyl sulfate according to the method of Mauthner²⁵.

Piperonal (XXX) was reduced to piperonyl alcohol (XXXI) using copper chromium oxide catalyst. This was then reduced to 3,4-methylenedioxytoluene (XXXII) using the same catalyst but at a higher temperature.

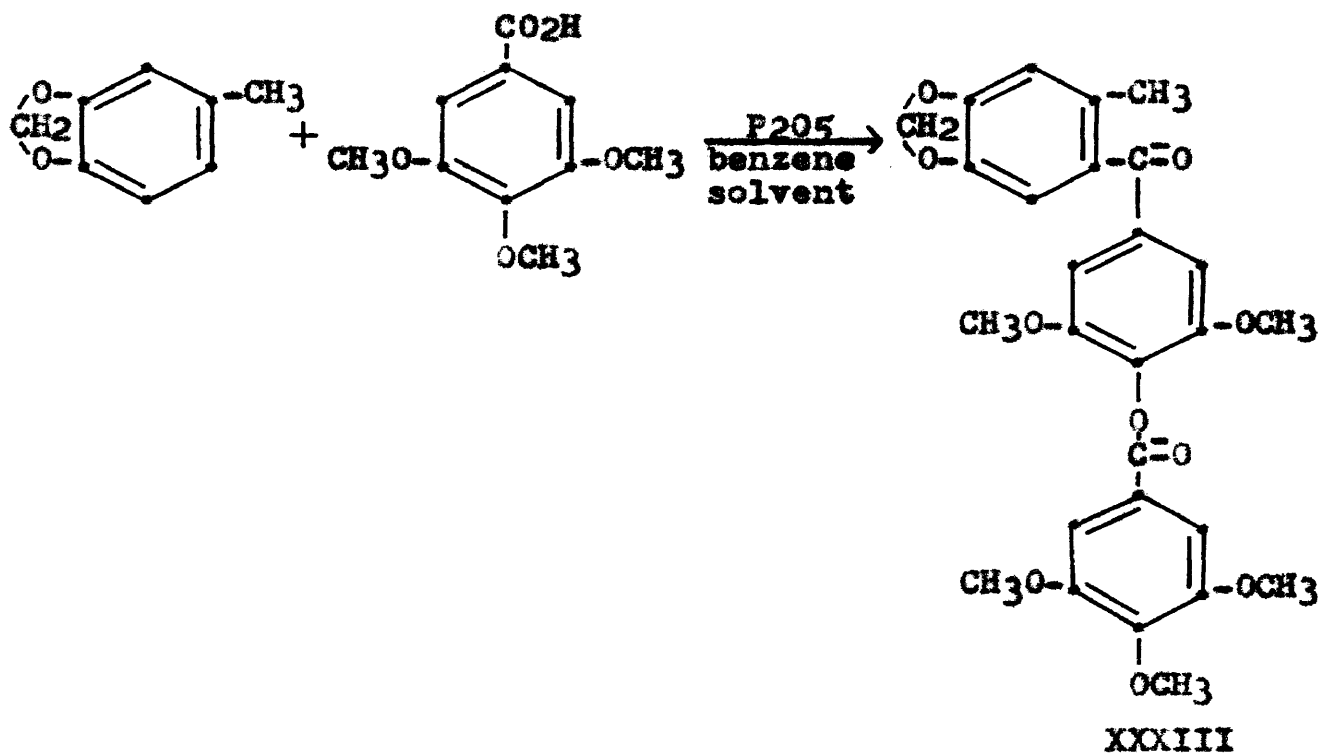


3,4-Methylenedioxytoluene had previously been prepared in thirty per cent yield by Wilhelm Schepss²³ by the electrolytic reduction of piperonal. It also has been prepared by Ashbinazi and Rabinovich²⁴ from 3,4-dihydroxytoluene. Methylene dichloride was reacted with 3,4-dihydroxytoluene in the presence of potassium hydroxide, bronze shavings and ethyl alcohol solvent to give sixty per cent of the theoretical amount.

The procedure followed in carrying out the condensation of 3,4-methylenedioxytoluene with trimethylgallic acid in the presence of phosphorous pentoxide was based upon the work of Kasolapoff²⁶ and Perkin and Robinson²⁷. The former condensed acetic acid with various aromatic ethers such as anisole and phenetole in refluxing benzene with phosphorous pentoxide and obtained sixty to eighty per cent of the theoretical amount of the expected aromatic ketones. Perkin and Robinson obtained 5,6-methylenedioxyhydrindone-1 in quantitative yield by the following reaction:



In view of the above successful use of phosphorous pentoxide in the preparation of related ketones, much time was devoted to trying to prepare ketone XXIX by this method. The product obtained was not the desired ketone but was mainly an ester formed by the replacement of one of the methyl groups of ketone XXIX by a 3,4,5-trimethoxyphenyl group. Considerable difficulty was encountered attempting to purify this material. It was partly purified by dissolving it in carbon tetrachloride and slowly adding this solution to stirring petroleum ether (b.p. 60-80°) which precipitated the compound as a tan colored solid. This was further purified by chromatographic absorption on an alumina column. The following reaction is believed to have taken place:



Correct carbon, hydrogen and methoxyl analyses were obtained for structure XXXIII. Upon oxidation highly colored

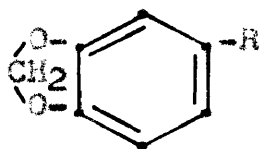
acetate of the corresponding carbinol. It was assumed the latter would be more easily oxidized than the methyl group. Most of the starting compound was recovered and a small amount of a dark brown alkali soluble material was obtained. Since the alkali soluble material no longer contained the methylenedioxy bridge, it appeared that the lead tetraacetate had attacked the molecule at this point.

Potassium ferricyanide often is a specific reagent for the oxidation of a methyl group to the corresponding acid^{31,32}. Many examples are known where a methyl group attached to a ring preferentially attacked by most oxidizing agents can be oxidized to the corresponding acid without affecting the ring. This reagent was reacted with the methyl compound XXIX using the method of Weissgerber³²; however, the starting compound was recovered in practically quantitative amount.

Since the methyl group in compound XXIX could not be oxidized to the corresponding acid, other methods of preparing the acid were considered. The stannic chloride catalyzed condensation of trimethylgalloyl chloride with substituted methylenedioxybenzenes should be applicable to the preparation of compounds other than XXIX. This condensation reaction is successful because the desired product has a ketone group which forms a complex with stannic chloride, precipitating it from the reaction mixture. This prevents the acid catalyst from splitting the methoxy groups or the methylenedioxy bridge.

Safrole (XXXVIII) was reacted with trimethylgalloyl chloride but no desired condensation product was obtained.

Piperonal (XXX), the ethyl acetal of piperonal (XXXV), ethyl piperionate (XXXVI) and piperonyl



XXX, R=CHO

XXXV, R=C(OC₂H₅)₂

XXXVI, R=CO₂C₂H₅

XXXVII, R=CH₂O₂CCH₃

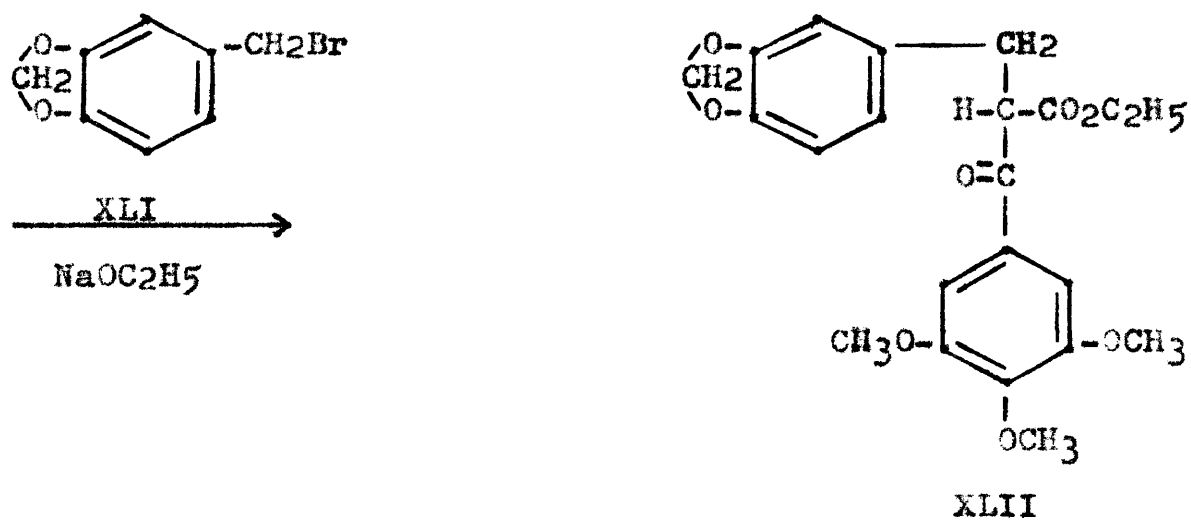
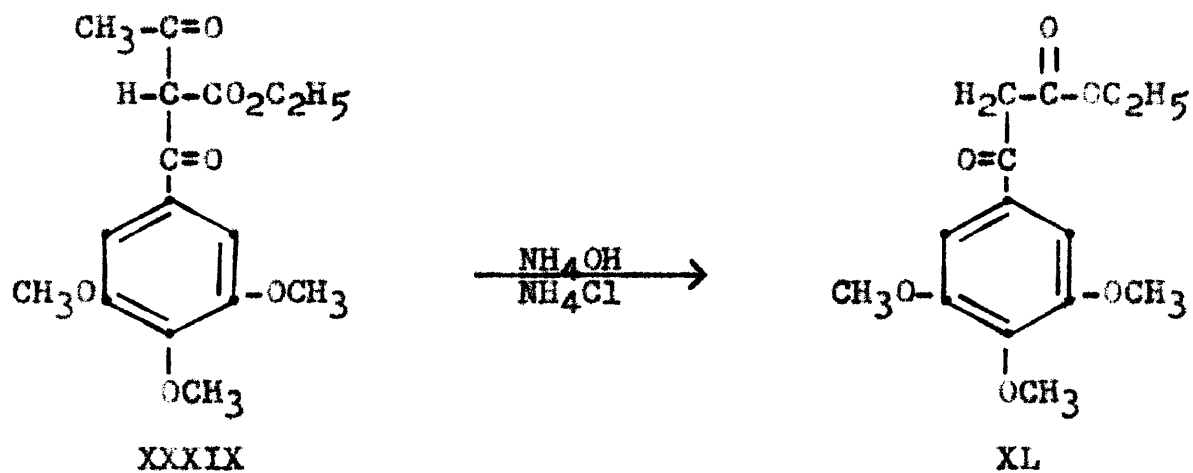
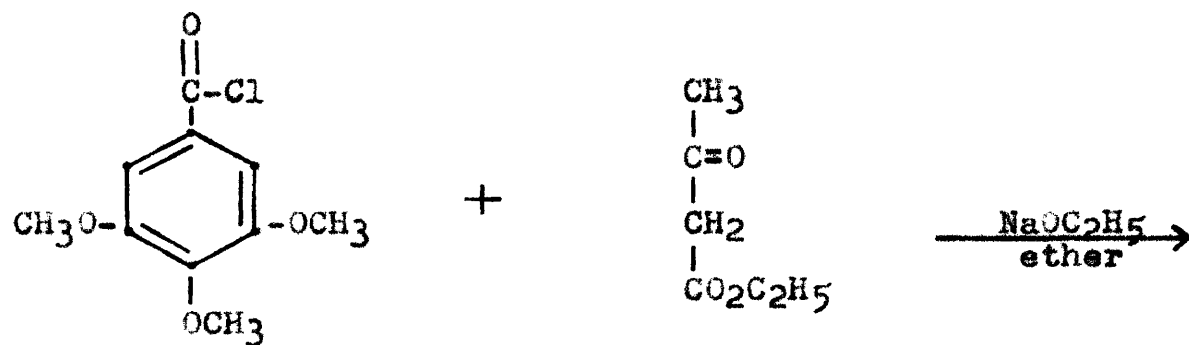
XXXVIII, R=(CH₂CH=CH₂)

acetate (XXXVII) all formed complexes with stannic chloride which were not soluble in carbon disulfide. The complexes between stannic chloride and XXXV and XXXVI were soluble in tetrachloroethane; however, the methylenedioxy bridge was readily split under such conditions.

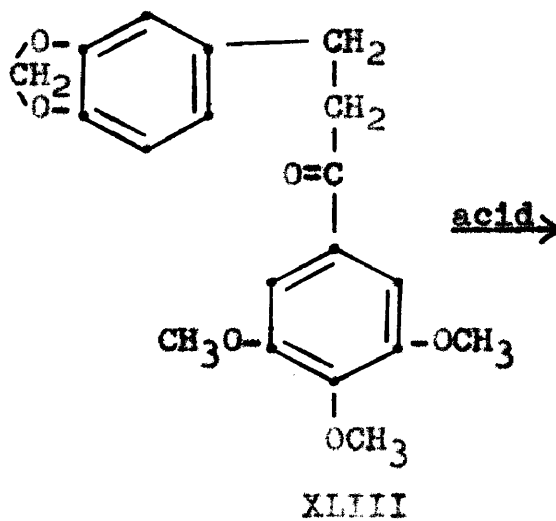
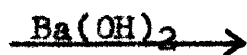
This method of condensation is not applicable in those cases where the acid chloride is to condense with a compound containing a doubly bonded oxygen, since the compound itself forms insoluble complexes with stannic chloride. The method should be applicable to condensations between trimethylgalloyl chloride and compounds such as 1,2-methylenedioxybenzene, anisole or phenetole. These reactions would be of interest because of the previous difficulty encountered in preparing these ketones^{33,34}.

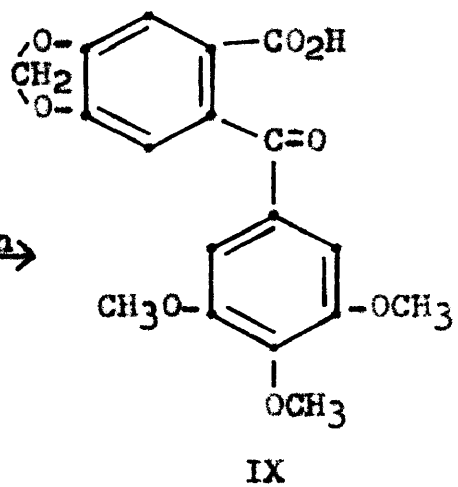
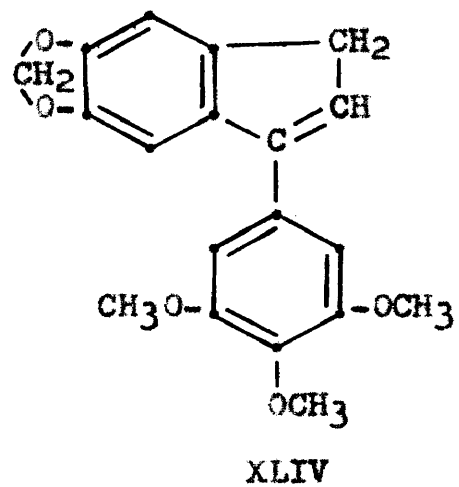
In view of the failure to prepare acid IX by methods involving the direct condensation of two component parts to form a substituted benzophenone, a more indirect synthesis was devised and one of the key intermediates (XLIII) synthesized. The synthesis is given on pages 44 and 45.

Ethyl 3,4,5-trimethoxybenzoylacetate (XXXIX) was prepared by the action of trimethylgalloyl chloride and ethyl acetoacetate using sodium ethoxide catalyst according to the



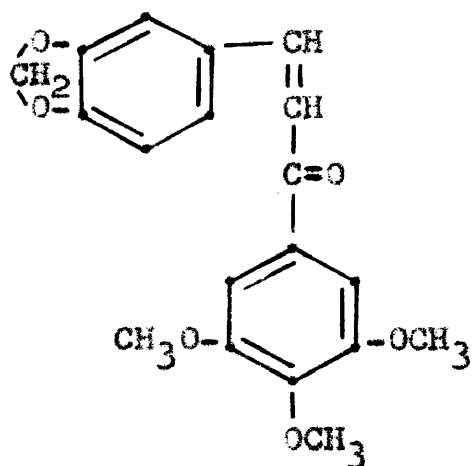
XLII



$$\xrightarrow{\text{acid}}$$


directions of Perkin and Weizmann³⁵. This was reacted with ammonium hydroxide solution to give ethyl 3,4,5-trimethoxybenzoylacetate (XL) also according to the directions of Perkin and Weizmann³⁵.

Piperonyl bromide, prepared by the method of Robinson and Robinson³⁶, was reacted with XL using sodium ethoxide catalyst to give compound XLII. Upon hydrolysis with barium hydroxide solution 3,4,5-trimethoxy- α -piperonylacetophenone (XLIII), having the melting point of 146-147 $^{\circ}$, was obtained. This compound had been previously reported by Bargellini and Monti³⁷. However, the melting point listed by them was 96-98 $^{\circ}$. They reported the preparation of the compound by the reduction of piperonylidene-3,4,5-trimethoxyacetophenone (XLV). The melting point of the unsaturated compound XLV listed by



XLV

Bargellini and Monti was 118-120 $^{\circ}$.

The melting point of this material was reported by Harding³⁸ to be 130-131 $^{\circ}$. In view of the differences in the reported melting points of the intermediate compound, the uncontrolled nature of their hydrogenation reaction, and the

lack of evidence that their ketone

was properly characterized, it is doubtful that they obtained ketone XLIII. The compound obtained during this research gave a positive ketone test with 2,4-dinitrophenylhydrazine and a positive test for the methylenedioxy bridge. It gave

the correct carbon, hydrogen and methoxyl analyses as demanded by formula XLIII.

Compounds XXXIII, XXIX and XLIII are to be tested for anti-carcinogenic properties.

Experimental

All melting points listed have been corrected.

Methylenedioxy Bridge Test.¹⁸ To 2 ml. of concentrated sulfuric acid was added three drops of an alcoholic solution of the substance to be tested and three drops of a 5 per cent solution of gallic acid. This solution was warmed on a steam bath and a dark blue-green or deep blue color indicated the presence of the group.

Piperonyl Alcohol (XXXI).^{39,40} Piperonal (90 g., 0.60 mole), 70 ml. of dioxane (purified by refluxing over sodium metal for two hours and distilling, the first fifth of the distillate discarded and the middle three fifths saved) and 5 grams of copper chromium oxide catalyst were placed in a hydrogenation vessel of approximately 300 ml. capacity. Hydrogen was introduced into the reaction vessel until the pressure was 3000 lbs./in.². The reaction vessel was then rocked and heated to 160°, at which temperature the reaction proceeded rapidly, and nearly the theoretical amount of hydrogen was absorbed in fifteen minutes. The temperature was then raised to 175° and the reaction continued until there was no further drop in the hydrogen pressure. The hydrogenation vessel was allowed to cool to room temperature, emptied, rinsed with 50 ml. of dioxane, and the combined fractions

filtered to remove the catalyst. The dioxane was removed by distillation at 30-40 mm. pressure and the product distilled at 6 mm. pressure. Ninety grams of piperonyl alcohol (98.5 per cent of the theoretical amount) which distilled at 125-128°/6mm. pressure was obtained. The literature gave the boiling point as 161°/20mm. pressure and the melting point as 51°.

3,4-Methylenedioxytoluene (XXXII)^{23,24}. Piperonyl alcohol (76 g., 0.5 mole), 60 ml. of dioxane and 4 grams of copper chromium oxide catalyst were placed in a 300 ml. hydrogenation vessel. Hydrogen was introduced into the reaction vessel until the pressure was 3000 lbs./in.². The reaction vessel was then heated and rocked at 280° until the theoretical amount of hydrogen was absorbed. The hydrogenation vessel was allowed to cool to room temperature, emptied, rinsed with 50 ml. of dioxane and the combined fractions filtered to remove the catalyst. The filtrate was shaken with anhydrous calcium chloride to remove most of the water, again filtered, and the dioxane removed by distillation at 30-40 mm. pressure. The product was fractionated at 12 mm. pressure. Fifty-eight grams of 3,4-methylenedioxytoluene (84.5 per cent of the theoretical amount) which distilled at 78-81°/12-14 mm. pressure was obtained. The literature gave the boiling point as 81-83°/11 mm. pressure.

Trimethylgallic Acid. (VII)²⁵. Sodium hydroxide (400 g., 10 moles) and 2.5 l. of water were placed in a 5-l. three-necked flask. The flask was fitted with a mechanical stirrer,

a stopper containing a "Bunsen valve" and thermometer which extended below the level of the liquid, and a 500 ml. addition funnel. The solution was cooled and stirred as the sodium hydroxide dissolved. After the sodium hydroxide solution had cooled to 35°, 250 grams (1.33 moles) of gallic acid was added by first placing the gallic acid in an Erlenmeyer flask and adding the acid through a rubber tube connected to one of the necks of the three-necked flask. Dimethyl sulfate (670 ml.) was added dropwise from the addition funnel over a two hour period. The temperature during the addition of the first 400 ml. was maintained between 35-38° by slight cooling. During the addition of the remainder of the dimethyl sulfate the temperature was allowed to rise to 48°.

After the addition of the dimethyl sulfate, the flask was fitted with a reflux condenser and the contents refluxed for two hours. A solution of 100 grams of sodium hydroxide in 150 ml. of water was then added, and the contents again refluxed for 2 hours to saponify the ester present. The reaction mixture was cooled and acidified with dilute hydrochloric acid; the trimethylgallic acid was filtered, washed with cold water and crystallized from water or dilute alcohol. Two hundred and twenty-five grams (79 per cent of the theoretical amount) of trimethylgallic acid was thus obtained.

3',5'-Dimethoxy-4'-trimethylgalloxy-2-methyl-4,5-methylenedioxybenzophenone (XXXIII). Trimethylgallic acid (26.5 g., 0.125 mole), sixty-eight grams (0.5 mole) of 3,4-methylenedioxytoluene and 500 ml. of anhydrous benzene were placed in

a 1-l. three-necked flask. The flask was fitted with a mechanical stirrer and a reflux condenser protected by a calcium chloride drying tube. The mixture was stirred and heated until all the trimethylgallic acid dissolved. Phosphorous pentoxide (60 grams) was then added and the mixture stirred and refluxed for six hours.

The reaction mixture was cooled, and the benzene layer decanted from the solid residue. The residue was washed with benzene and the combined benzene solutions washed with water, then with potassium hydroxide solution and again with water. The benzene solution was dried with anhydrous magnesium sulfate, and the benzene removed by distillation. The excess 3,4-methylenedioxytoluene was distilled at 5 mm. pressure and thirty-four grams were thus recovered. The residue was twice precipitated by dissolving it in 70 ml. of carbon tetrachloride and this solution slowly added to 800 ml. of stirring petroleum ether (b.p. 60-80°). A tan solid separated which was filtered and dried. Fifteen grams (48.5 per cent of the theoretical amount) of ester was thus obtained.

The compound could not be recrystallized but was further purified by chromatographic absorption on an alumina column. The compound did not have a definite melting point but the following behavior was quite characteristic:

105°-darkened

112°-started to melt

120°-red liquid

It gave a positive test for the methylenedioxy bridge. The following analyses were obtained:

	<u>Found</u>	<u>Theory</u>
Carbon	63.78% 63.50%	63.48%
Hydrogen	5.45% 5.30%	5.10%
Methoxyl	30.34% 30.25%	30.35%

Compound XXXIII was hydrolyzed with aqueous potassium hydroxide solution. Trimethylgallic acid was isolated from the hydrolyzed material by extraction with sodium hydrogen carbonate solution. The following analyses were obtained for the trimethylgallic acid:

	<u>Found</u>	<u>Theory</u>
Carbon	56.40% 56.56%	56.65%
Hydrogen	5.72% 5.94%	5.67%
Melting point	166-8°	167°

Compound XXXIII was also hydrolyzed with potassium hydroxide in methyl alcohol to give chiefly alkali soluble materials plus some methyl trimethylgallate. The following analyses were obtained for this ester.

	<u>Found</u>	<u>Theory</u>
Carbon	58.47% 58.63%	58.40%
Hydrogen	6.27% 6.34%	6.20%
Melting point	82-3°	82.5°

Trimethylgalloyl Chloride (XII)⁴. Trimethylgallic acid

(60 g., 0.283 mole) and 125 ml. of anhydrous benzene were added to a 200 ml. three-necked flask. The flask was fitted with a mechanical stirrer and a reflux condenser protected by a calcium chloride drying tube. This suspension was stirred and 55 ml. (90 g., 0.758 mole) of thionyl chloride was then added. The stirred suspension was heated at 60° for five hours after which time all the trimethylgallic acid had reacted and was in solution. The reflux condenser was then replaced with a downward condenser, and most of the excess thionyl chloride and benzene were distilled at 30 mm. pressure. The distillation was continued until 125 ml. of distillate had been collected. The residue was then transferred to a Von Braun distilling flask. The remainder of the solvent and excess thionyl chloride were removed by distillation at 30 mm. pressure. The product was then distilled. Fifty-five grams (84 per cent of the theoretical amount) was obtained which distilled at 130°/2mm. pressure. This product was pure enough for most purposes; however, it could be recrystallized from cyclohexane or petroleum ether (b.p. 60-80°) to give a white crystalline solid which melted at 77-80°. The literature gave the boiling point as 168-70°/14 mm. pressure and the melting point as 77-78°.

3',4',5'-Trimethoxy-2-methyl-4,5-methylenedioxybenzophenone (XXIX). 3,4-Methylenedioxytoluene (10 ml., 0.0835 mole), 50 ml. of anhydrous carbon disulfide and 4.5 ml. of anhydrous stannic chloride were placed in a 250 ml. three-necked flask. The flask was fitted with a dropping funnel, mechanical stirrer, and reflux condenser protected by a calcium

chloride drying tube. The reaction was cooled in an ice-water bath and 10 grams (0.0434 mole) of freshly distilled trimethylgalloyl chloride dissolved in 50 ml. of carbon disulfide was slowly added from the dropping funnel to the stirred solution. The reaction was stirred at ice bath temperature for 6 hours; as the reaction proceeded the product separated as a red complex.

To the reaction mixture was added 30 grams of ice-water mixture and 6 ml. of concentrated hydrochloric acid. The resulting mixture was extracted well with ether. The ether solution was washed with dilute hydrochloric acid, twice with water, dilute sodium hydroxide solution and finally with water. The ether solution was dried with calcium chloride, and the ether removed by distillation. The residue was refluxed with a solution of potassium hydroxide in methyl alcohol for 20 minutes. The resulting mixture was diluted and extracted with ether. The ether solution was washed with water, dried with calcium chloride, and the ether removed by distillation. The residue was crystallized from cyclohexane giving 6.2 grams (43.3 per cent of the theoretical amount) having the melting point of 108-110°. It gave a positive test for the methylene-dioxy bridge. The compound gave the following analyses:

	<u>Found</u>	<u>Theory</u>
Carbon	65.75% 65.45%	65.45%
Hydrogen	5.67% 5.55%	5.45%
Methoxy	27.87% 28.01%	28.15%

Oxidation of XXIX With Potassium Permanganate. Compound XXIX (0.5 g., 1.52×10^{-3} mole) was stirred with water at 80° . A saturated solution of potassium permanganate (0.6 g., 3.8×10^{-3} mole) was slowly added as it was reduced. After all the potassium permanganate had been added and reduced, the reaction mixture was cooled to room temperature and sulfur dioxide added until no more manganese dioxide remained. The solution was acidified with dilute sulfuric acid and filtered. The starting compound (0.4 grams, m.p. $108-110^{\circ}$) was recovered, and no alkali soluble materials were obtained.

This method was modified using excess oxidizing agent and purified acetone and tertbutyl alcohol as solvents, but no appreciable amount of alkali soluble material was obtained.

Oxidation of XXIX With Chromium Trioxide. Compound XXIX (0.557 g., 1.69×10^{-3} mole) was dissolved in 10 ml. of glacial acetic acid and placed in a 100 ml. three-necked flask and heated to 60° . The flask was fitted with a reflux condenser protected by a calcium chloride drying tube and a dropping funnel. The chromium trioxide (0.375 g., 3.72×10^{-3} mole) was dissolved in 25 ml. of glacial acetic acid, placed in the dropping funnel and added to the ketone solution over a 2 hour period. The reaction mixture was then cooled to room temperature, diluted with water and extracted with ether. The ether solution was extracted with sodium hydroxide solution. The sodium hydroxide solution was warmed to expel the dissolved ether, cooled and acidified. Only 0.06 grams of a dark brown precipitate was obtained. The starting compound

remained in the ether solution.

Oxidation of XXIX With Lead Tetraacetate²⁸. Compound XXIX (2.0 g. 0.006 mole) and 55 ml. of glacial acetic acid were placed in a 100 ml. three-necked flask. The flask was fitted with a mechanical stirrer and a reflux condenser protected by a calcium chloride drying tube. The mixture was heated to 60° and 5.3 grams of red lead (Pb₃O₄) added. The temperature was maintained until a negative test was obtained for the lead tetraacetate using moist starch-iodide paper.

The reaction mixture was diluted with water and extracted with ether. The ether layer was washed with sodium hydrogen carbonate solution, then with water and dried with calcium chloride. The ether was removed by distillation leaving an oil residue. This residue was warmed with a dilute alcohol solution of potassium hydroxide. After one-half hour the mixture was diluted with water, filtered, and the precipitate recrystallized from methyl alcohol. This gave 1.2 grams melting at 110-111°. A mixed melting point with the starting compound was 109-111° indicating that the starting compound had been unchanged.

The alkaline filtrate was acidified with dilute hydrochloric acid and a small dark brown precipitate was obtained. This material gave a negative test for the methylenedioxy bridge.

Oxidation of XXIX With Potassium Ferricyanide³². Compound XXIX (0.5 g.), 190 ml. of water, 75 grams of potassium ferricyanide and 5.6 grams of potassium hydroxide were placed

in a 1-l. three-necked flask. The flask was fitted with a mechanical stirrer and a reflux condenser. The reaction mixture was stirred for 24 hours at 80°, and then 30 grams of potassium ferricyanide and 5.3 grams of potassium hydroxide were added. After 36 additional hours, 15.5 grams of potassium ferricyanide and 2.5 grams of potassium hydroxide were added and the reaction continued for 36 more hours.

At the end of this period the reaction mixture was cooled to room temperature, acidified and extracted with ether. The ether solution was washed with water and dried with calcium chloride. The ether was removed by distillation leaving a residue which soon crystallized. The residue was extracted with warm potassium hydroxide solution and filtered. The alkaline filtrate was acidified but practically no precipitate was obtained indicating the absence of any organic acid. The alkali insoluble material was recrystallized from 80 per cent methyl alcohol yielding 0.4 grams of starting compound, m.p. 108-110°.

Ethyl 3,4,5-Trimethoxybenzoylacetoacetate (XXXIX)³⁵.

Sodium (9.2 g., 0.4 mole) was dissolved in 150 ml. of absolute alcohol. Ethyl acetoacetate (27 g., 0.208 mole) and 150 ml. of anhydrous ether were added to a 1-l. three-necked flask. The flask was fitted with a reflux condenser protected by a calcium chloride drying tube and a mechanical stirrer. Seventy-five milliliters of the sodium ethoxide solution was added to the stirred acetoacetic ester solution. Trimethylgalloyl chloride (23 g., 0.1 mole) was dissolved in

150 ml. of anhydrous ether and 75 ml. of this solution was slowly added to the ethereal solution of the sodium derivative of ethyl acetoacetate. After half an hour, half of the remaining ethoxide and half the acid chloride solution were added, and after 15 minutes the rest of these solutions was added. The stirring was discontinued and the reaction allowed to stand for 24 hours.

The reaction mixture was then filtered by suction, the precipitate washed with anhydrous ether and acidified with dilute hydrochloric acid. An oil separated which soon solidified. The solid was filtered and recrystallized from methyl alcohol. Twenty-six grams (76.5 per cent of the theoretical amount) of ethyl 3,4,5-trimethoxybenzoylacetoacetate was obtained having a melting point of 83-85°. The literature gave the melting point as 85°.

The purification with methyl alcohol was not necessary for hydrolysis with ammonium hydroxide.

Ethyl 3,4,5-Trimethoxybenzoylacetoacetate (XL)^{35,42}. The crude ethyl 3,4,5-trimethoxybenzoylacetoacetate obtained from the reaction of 23 grams (0.1 mole) of trimethylgalloyl chloride with ethylacetoacetate was shaken with 1.25 l. of water, 50 grams of ammonium chloride and 250 ml. of a 15 per cent solution of ammonia. A crystalline solid soon formed. The reaction mixture was warmed on a steam bath and then shaken for 15 minutes or until no more crystals separated from the solution.

The solid ester was filtered, washed with water and dried. Twenty-two grams (78 per cent of the theoretical

amount for the two steps) was obtained having a melting point of 90-92°. The ester was further purified by recrystallization from cyclohexane giving a melting point of 93-95°. The literature gave the melting point as 95°.

Piperonyl Bromide (XLI)³⁶. Piperonyl alcohol (10 g., 0.068 mole) was shaken with 50 ml. of concentrated hydrobromic acid. An oil formed which soon began to crystallize. After it had all crystallized, water was added and the additional precipitated bromide was allowed to crystallize. The bromide was filtered, dried between filter paper and recrystallized from petroleum ether (b.p. 30-60°). Fourteen grams (95 per cent of the theoretical amount) of piperonyl bromide was obtained. It was a white crystalline material melting at 47-49°. The literature gave the melting point as 49°. This bromide is unstable and should be used soon after it has been prepared.

3,4,5-Trimethoxy- α -piperonylacetophenone (XLIII).

Sodium (0.46 g., 0.02 mole) was dissolved in 50 ml. of absolute ethyl alcohol in a 100 ml. flask fitted with a reflux condenser protected by a calcium chloride drying tube. The alcohol solution was cooled with an ice bath and 5.64 grams (0.02 mole) of ethyl 3,4,5-trimethoxybenzoylacetate was added. Piperonyl bromide (4.5 g., 0.029 mole) was dissolved in 10 ml. of absolute ether and added to the cold alcohol solution. Sodium bromide soon began to precipitate. After ten minutes the ice bath was removed, and the reaction allowed to proceed until the solution was acid which was about one-half hour. The reaction mixture was diluted with

water and extracted with ether. The ether solution was dried with calcium chloride and the ether removed by distillation leaving a viscous oil. The oil was assumed to be chiefly XLI.

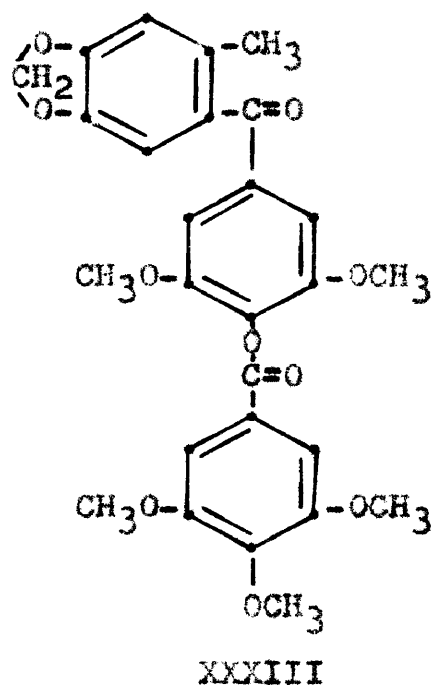
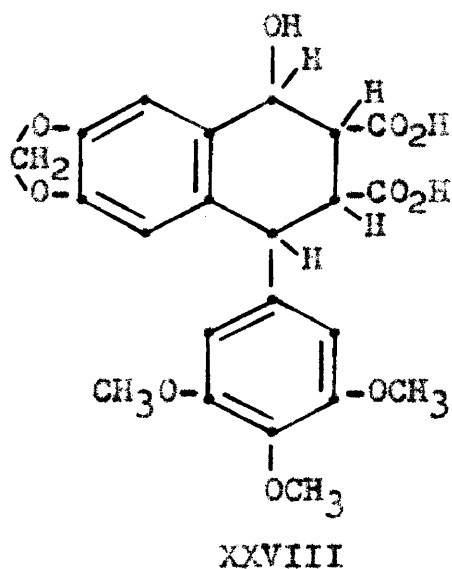
The ester group on compound XLII was removed by hydrolysis using barium hydroxide solution. The oil was dissolved in 400 ml. of methyl alcohol and this solution placed in a 1.5 l. Erlenmeyer flask. To this solution was added a solution of 45 grams of barium hydroxide octahydrate in 800 ml. of water. A white solid soon formed; the reaction mixture was allowed to stand for 12 hours. The solid was filtered and extracted with chloroform. The chloroform solution was dried with anhydrous magnesium sulfate and the chloroform removed by distillation. A white crystalline mass remained which weighed 3.8 grams (55 per cent of the theoretical amount for the two steps). This was recrystallized from methyl alcohol giving 3.4 grams having a melting point of 146-147°.

This gave a positive ketone test with 2,4-dinitrophenylhydrazine and a positive test for the methylenedioxy group. It was stable to both hot dilute alkali and acid. It gave the following analyses:

	<u>Found</u>	<u>Theory</u>
Carbon	66.94% 66.78%	66.27%
Hydrogen	6.18% 5.65%	5.83%
Methoxyl	26.47% 27.28%	27.03%

Summary

1. A discussion of podophyllotoxin and related compounds is given. A number of possible syntheses of compound XXVIII,



chosen because of its similarity to podophyllotoxin, have been investigated, and certain important intermediates prepared.

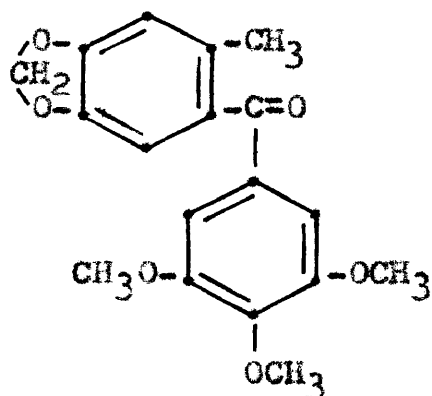
2. A synthesis of piperonyl alcohol by reducing piperonal using copper chromium oxide catalysts was developed.

3. A practical synthesis of 3,4-methylenedioxytoluene was developed involving the hydrogenolysis of piperonyl alcohol using copper chromium oxide catalyst.

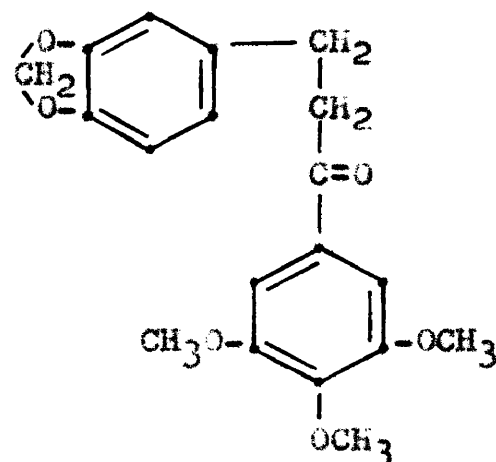
4. Compound XXXIII was prepared by the condensation of 3,4-methylenedioxytoluene with trimethylgallic acid using phosphorous pentoxide.

5. Compound XXIX was synthesized by condensing

trimethylgalloyl chloride with methylenedioxytoluene using stannic chloride catalyst. This is a new synthetic method of preparing methoxy and methylenedioxy substituted benzophenones. The reaction was shown to fail when the methyl group of the methylenedioxytoluene was replaced by an unsaturated or a negative group.



XXIX



XLIII

6. Oxidation studies demonstrated that the methyl group of compound XXIX could not be oxidized to the corresponding carboxylic acid. A variety of oxidizing agents were studied.

7. Compound XLIII was synthesized by an acetoacetic ester type synthesis. Physical properties do not agree with those reported by Italian workers who attempted its synthesis by another method and apparently obtained another material.

8. Compounds XXXIII, XXIX and XLIII are to be tested for anti-carcinogenic properties.

BIBLIOGRAPHY

1. Kursten, W. R. and J. A. Henry, J. Chem. Soc., 73, 209 (1893).
2. Kursten, W. R., Arch. Pharm., 229, 220 (1891); J. Chem. Soc., (Abstracts), 1133 (1891).
3. Borsche, W. and J. Niemann, Annalen, 494, 126 (1932).
4. Späth, E., F. Wessely, and L. Kornfeld, Ber., 65, 1537 (1932).
5. Borsche, W. and J. Niemann, Annalen, 499, 59, (1932).
6. Späth, E., F. Wessely, and E. Nadler, Ber., 65, 1773 (1932).
7. Späth, E., F. Wessely, and E. Nadler, Ber., 66, 125 (1933).
8. Borsche, W., J. Niemann, Annalen, 499, 62 (1932).
9. Späth, E., F. Wessely, and L. Kornfeld, Ber., 65, 1536 (1932).
10. Haworth, R. D., T. Richardson, and G. Sheldrick, J. Chem. Soc., 147, 1576 (1935).
11. Haworth, R. D. and T. Richardson, J. Chem. Soc., 149 348 (1936).
12. Ormsbee, R. A., I. Cornman, and R. E. Berger, Proc. Soc. Exp. Biol. and Med., 66, 586 (1947).
13. Späth, E. and H. Quietensby, Ber., 60B, 1882-90 (1927).
14. Kafuku, K., J. Pharm. Soc. Japan, No. 521, 609-24 (1925).
15. Mosettig, E. and A. Burger, J. Am. Chem. Soc., 52, 2988 (1930).

16. Arnold, R. T., N. Bortnick, and E. McMullen, J. Am. Chem. Soc., 64, 1410 (1942).
17. Bogert, M. T. and B. B. Coyne, J. Am. Chem. Soc., 51, 571 (1929).
18. Labat, J. A., Bull. Soc. Chim. Biol., 15, 1344-5 (1933).
19. Saechez, J. A., Andes Farm. Bioquim. 2, 141-53 (1931).
20. Gadamer, J. and Winterfeld, Arch. Pharm., 258, 148-67 (1920).
21. Haworth, R. and G. Sheldrick, J. Chem. Soc., 147, 636 (1935).
22. Johnston, W. S. and J. W. Peterson, J. Am. Chem. Soc., 67, 1366 (1945).
23. Schepss, W., Ber., 46, 2572 (1913).
24. Ashkinazi, Ya. B. and M. S. Rabinovich, J. Applied Chem., (U.S.S.R.) 10, 131-6 (1937).
25. Mauthner, F., "Organic Syntheses", John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. I, p. 537 (1946).
26. Kosolapoff, G. M., J. Am. Chem. Soc., 69, 1651 (1947).
27. Perkin, W. H. and R. Robinson, J. Chem. Soc., 91, 1084 (1907).
28. Cason, J., "Organic Syntheses", John Wiley and Sons, Inc., New York, N. Y., 21, 1 (1941).
29. Fieser, L. F., and E. B. Hershberg, J. Am. Chem. Soc., 60, 2542 (1938).
30. Ibid., p. 1893.
31. Brown, E. V., Iowa State Coll. J. Sci., 11, 227-9 (1937).
32. Weissgerber, R. and O. Kruber, Ber., 52, 352 (1919).

33. Frank, H. R., and D. S. Tarbell, J. Am. Chem. Soc., 70, 1276 (1948).
34. Späth, E., F. Wessely and E. Nadler, Ber., 66, 128 (1933).
35. Perkin, W. H. and C. Weizmann, J. Chem. Soc., 89, 1655-6 (1906).
36. Robinson, G. M. and R. Robinson, J. Chem. Soc., 105, 1463 (1914).
37. Bargellini, G. and L. Monti, Gazzetta Chimica Italiana, 44II, 28 (1914).
38. Harding, V. J., J. Chem. Soc., 105, 2796 (1914).
39. Carothers, W. H. and R. Adams, J. Am. Chem. Soc., 46, 1681 (1924).
40. Mastagli, P., Ann. Chim., 10, 281-377 (1938).
41. Asano and Yamaguti, J. Pharm. Soc. Japan, 60, 105-15 (1940).
42. Mauthner, F., J. Prak. Chemie, 82II, 278 (1910).

VITA

John D. Sterling, Jr.

Mantua-Sewell Road, Sewell, New Jersey

Ph. D., 1949

August 3, 1921

Latham, Missouri

Latham High School, Latham, Missouri

Central College, 1938-1942, B. A., 1942

Publications:

J. Am. Chem. Soc., 68, 1536 (1946) - "Synthetic Anti-malarials - Some Derivatives of 8-Aminoquinoline."

J. Am. Chem. Soc., 68, 1602 (1946) - "Synthetic Anti-malarials - the Preparation of Certain Derivatives of Sulfanilamide."

Positions held:

1942-1948 - University Graduate Assistantships and Fellowship, Anti-malarial Research Program, and National Institute of Health Grant.

1948 - E. I. du Pont de Nemours and Company (Inc.)
Jackson Laboratory
Deepwater Point, New Jersey